David Gozal
Leila Kheirandish-Gozal
Editors

Pediatric Sleep Medicine

Mechanisms and Comprehensive Guide to Clinical Evaluation and Management

Springer

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Many people, too many to enumerate, deserve appreciation for their contributions to this work. We will therefore simply thank our children Amin and Imran Gozal for being real troopers and for putting up with us during the many weekends and evenings during which we were busy working on the chapters rather than spending quality time with them.

This text is dedicated to several major figures and pioneers of our profession who unfortunately are not with us anymore, but whose legacy will last for many decades to come: Carole L. Marcus, Christian Guilleminault, Mariluz Alonso-Álvarez, and Joaquin Teran-Santos. To us, they were simply dearest of friends, and we terribly miss them!

Preface

It was back in 1980. I was in Jerusalem as a pediatric resident and was on call in the emergency room. It was a cold and dark winter night. At around 2:00 am, a woman arrived with her baby boy wrapped in her arms; there was a look of sheer terror and panic in her eyes. Her baby, who was healthy a few hours earlier, died of SIDS in his sleep. This was the first time in my life that I was exposed to a medical event that exclusively occurred during sleep, and it would guide the remainder of my career. I realized that while I had focused all my efforts to learn what happens when we are awake, I knew simply nothing about what happens when we sleep!

Many years later, a formidable ally joined me, and we have since partaken in the challenging task of unraveling sleep secrets in children, one at a time. Over the years, we have been fortunate to train and learn from many fellows along the way, and to interact in lively and sometimes heated discussions with many dear colleagues around the world, all for the simple objective of advancing a nascent field, that of pediatric sleep medicine.

As with every discipline that is still at an embryonic yet rapidly developing stage, what today is dogma will likely be wrong tomorrow. So many unknowns, so much more to be done! Over a drink one evening after a long day, Leila and I felt it would be useful to put together a book that summarizes and organizes the current knowledge basis of sleep in children. Still uncertain whether such effort would be worthwhile, we contacted some of our prospective chapter contributors, and their overwhelming positive responses convinced us that even if the overall result was going to be an incomplete and imperfect compendium, it would serve as the basis that informs anyone interested or dealing with children on what, why, and how to approach that huge portion of time that children spend asleep, and what can go well and what can go wrong then.

The authors are all experienced clinicians and researchers with considerable experience in the diagnosis, classification, and treatment of sleep and its disorders. We try to expose the science behind sleep and progressively address many of the intrinsic sleep disorders as well as a pragmatic selection of the multitude of pediatric conditions that can affect sleep integrity, quality, or quantity. This is the initial draft of what we hope will progressively evolve to become the go-to source for anyone wanting to learn and be informed about pediatric sleep medicine. With the help of our readers and with every future edition, we hope to refine the book and ultimately bring it to perfection. Till then, it is our ardent desire that this source will serve you well and help the children you care for achieve that ultimate stage of sleep: “sleeping like an angel.”

Columbia, MO, USA

David Gozal
Leila Kheirandish-Gozal

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Part I

Basic Introduction to Sleep

Normal Sleep in Humans

1

Saif Mashaqi and David Gozal

Introduction

Sleep is defined as a physiological, reversible, and recurrent behavioral state of perceptual disengagement from the surrounding environment and relative unresponsiveness to external stimuli. In Greek mythology, sleep was designated as *Hypnos* and the Latin equivalent of sleep is "Somnus." Hypnos is the God of Sleep. His brother is *Thanatos*, which is the God of Death. Both are the children of Nyx, "The Night," and Erebus, "The Darkness" [1]. Hypnos used to live in a big cave where the day and night met. Many poppy flowers, "which are the source of the narcotic opium," used to grow at the entrance of this cave. His bed was made of ebony wood. He is said to be a very gentle God and to help many humans who had sleep issues. As retribution for such favors, Hypnos owned half of their lives [2].

During sleep, several physiological changes affect different organs and systems in our body—such as cardiovascular, endocrine, respiratory, musculoskeletal, and gastrointestinal. The brain wave activities change with peculiar patterns and waves, which assume distinct different sleep stages when compared to the waking state. In this chapter, we review sleep architecture (including sleep stages) and the neurobiology of sleep, and describe the changes in sleep architecture and circadian rhythm that occur with age, from infancy to the elderly.

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Sleep Neurobiology: The Basics

The neurobiology of sleep has been the subject of intense study for more than a hundred years. In 1917, the Austrian psychiatrist and neurologist Constantin von Economo was the first physician to study the epidemic of Encephalitis Lethargica, "sleeping sickness," which affected more than five million people (between 1915 and 1926), with one-third of the patients succumbing in the acute stage of illness. Studying the autopsies of many of these patients, von Economo noticed that patients who had lesions within the posterior hypothalamus and rostral midbrain also manifested severe excessive daytime sleepiness while those who had evidence of damage to the anterior hypothalamus suffered from insomnia. Based on such findings, he formulated the hypothesis that the posterior hypothalamus contains wakefulness-promoting neurons and the anterior hypothalamus contains sleep-promoting neurons [3]. The easiest way to understand sleep neurobiology is to examine the neuroanatomy and the neurotransmitters that are operationally involved in wakefulness, then in non-rapid eye movement (NREM) sleep, and finally in rapid eye movement (REM) sleep.

Wakefulness

Wakefulness is maintained predominantly by a structure in the brainstem called the reticular formation (RF). A group of fibers traverse rostro-caudally through the midbrain, pons, and medulla, and form the diffuse ascending arousal system (DAAS). It seems that more rostral fibers are critical in wakefulness (e.g., rostral pons and midbrain) compared to the more caudal fibers (e.g., medulla). DAAS fibers consist of two types: *monoamine* neurotransmitter-releasing fibers and *cholinergic* fibers [4].

Monoamine fibers release monoamine neurotransmitters (such as norepinephrine, histamine, serotonin, and dopamine). Norepinephrine-releasing fibers originate from the

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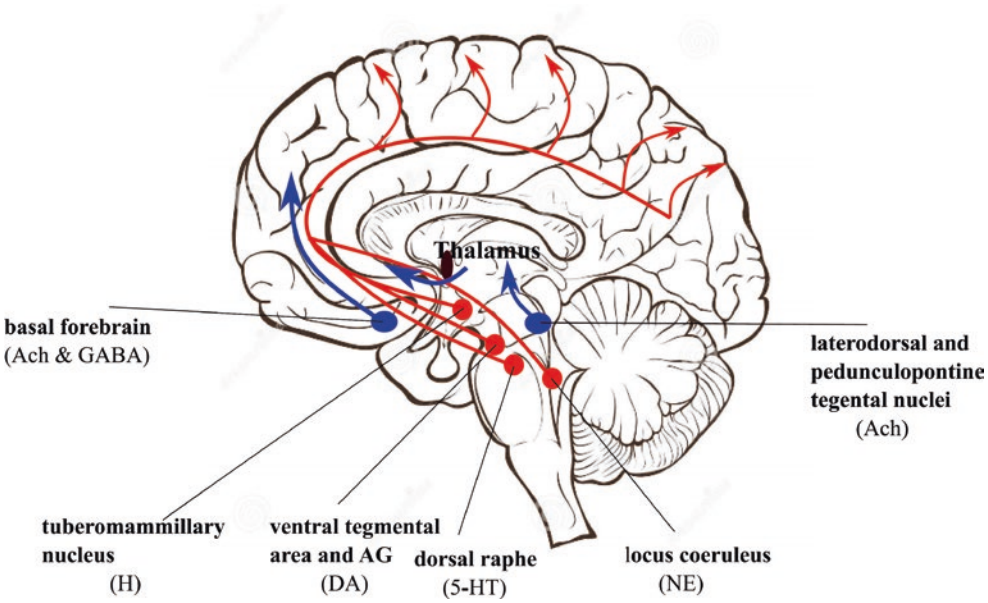

Fig. 1.1 Monoaminergic and cholinergic nerve fibers involved in the wake process and NREM sleep

locus coeruleus (LC) and fire at the highest intensity and frequency during wakefulness. Histamine-releasing fibers originate from tuberomammillary nucleus and play a critical role in the onset of wakefulness—this explains why antihistaminic agents, particularly the first generation of these compounds (e.g., diphenhydramine), induce sleepiness. Serotonin-releasing fibers originate from dorsal raphe nucleus. Serotonin plays a role in both wake and sleep and its role is very complicated due to the presence of many serotonin receptors (up to 15 receptor subtypes). Dopamine-releasing fibers originate from the ventral tegmental area and periaqueductal gray nuclei. Dopamine is the most common target clinically, and most of wake-promoting agents used in clinical practice work on dopaminergic pathways [5].

Cholinergic fibers release acetylcholine and gamma aminobutyric acid (GABA). They originate from the basal forebrain. Cholinergic neurons directly excite the pyramidal cells in the cortex, while GABAergic neurons inhibit the inhibitory neurons in the cortex, and subsequently cause excitation. Other cholinergic fibers originate from laterodorsal and pedunculopontine tegmental nuclei (LDT and PPT) and ascend to the thalamo-cortical area [5] (Fig. 1.1).

NREM Sleep

During wakefulness, there is a continuous excitation to the thalamo-cortical neurons that leads to regular tonic firing called "desynchronized EEG." In this process, continuous depolarization of the thalamo-cortical neurons takes place. As we transition from wake to NREM sleep, the EEG rhythm slows down and hyperpolarization of thalamo-cortical neurons takes place leading to high-frequency burst-pause firing

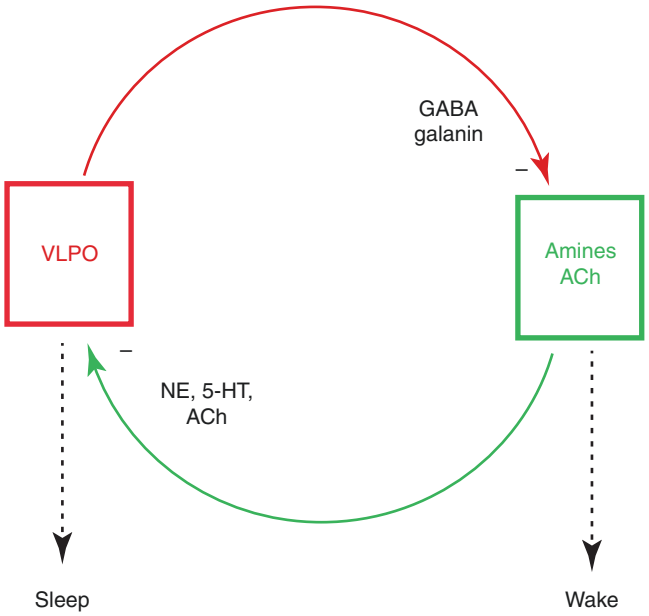

Fig. 1.2 The flip-flop switch mechanism that explains the bidirectional transition between wake and NREM sleep

"called synchronized EEG," and this transition from asynchronous to synchronous firing accounts for the slowing in the EEG rhythm from wake to NREM sleep (Fig. 1.2).

In order to maintain sleep and guarantee a rapid sleep onset, we need a system that will continuously suppress the monoamine fibers. The source of such inputs resides in the ventrolateral preoptic nucleus (VLPO) and median preoptic area (MnPO), located in the preoptic area of the hypothalamus. These are inhibitory nuclei and release GABA and galanin. VLPO and MnPO project inhibitory neurons to the monoaminergic neurons (NA, 5HT, DA, Ach) and to orexin-

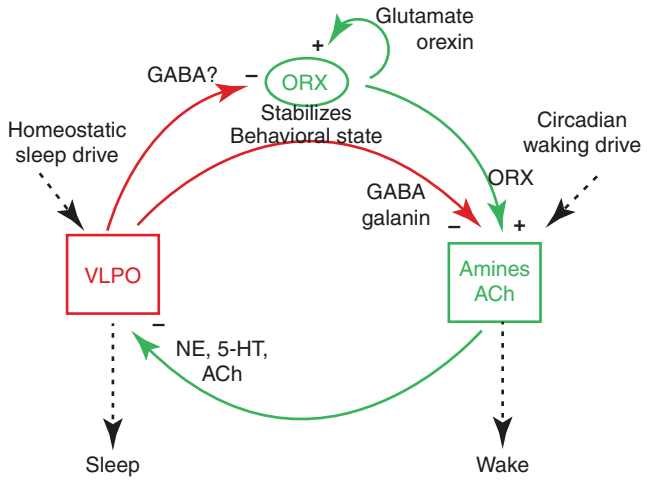

Fig. 1.3 Orexin as a regulator of the flip-flop switch mechanism

ergic neurons [6, 7] (Fig. 1.3). This creates a flip-flop circuit that switches on (initiates sleep) and switches off (initiates wake) [8].

To further fine-tune and stabilize this flip-flop circuit, a peptide called orexin (also termed hypocretin) is produced by hypothalamic neurons. It was described first as an appetite regulator and later as a sleep–wake cycle regulator. Orexin producing neurons are excitatory neurons that stimulate monoamine neurons and subsequently enhance wakefulness (Process C). At the same time, orexinergic neurons also exhibit an autocrine excitation pattern. With increasingly extended wakefulness, sleep pressure builds on to a point that VLPO and MnPO inhibitory neurons inhibit orexinergic neurons, and such processes enhance sleep propensity and onset (Process S: Fig. 1.4).

REM Sleep

REM sleep originates in the pons [9]. It was first described by the French neuroscientist and medical researcher Michel Jouvet (1925–2017) at the University of Lyon in France, and called it "sommeil paradoxale" (i.e., paradoxical sleep). In 1961, he categorized sleep into two stages, "telencephalic" (slow wave) sleep and "rhombencephalic" sleep (REM sleep), for the first time and mapped the area producing REM sleep in the brain [10]. Parallel work at the University of Chicago by Drs. Aserinsky and Kleitman led to nearly simultaneous discovery of rapid eye movements as a discrete state during sleep [11–13], and Dr. William Dement, then a graduate student, further elucidated the association of these events with dreams [14].

As mentioned earlier, in the LDT and PPT nuclei, cholinergic fibers originate and project to the thalamo-cortical area (excitatory neurons). From the same nuclei, another group of

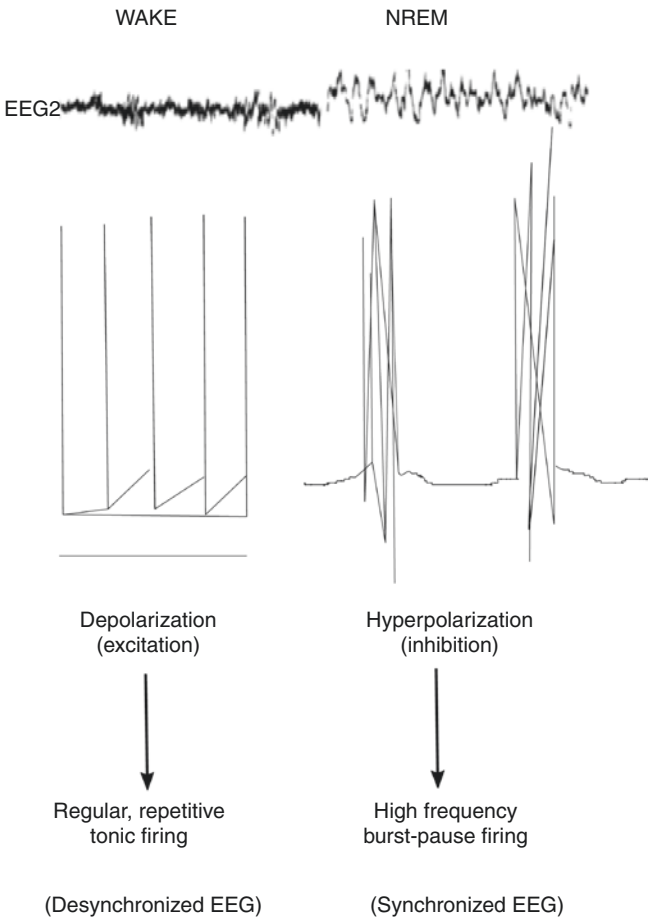

Fig. 1.4 The EEG rhythm in wake and NREM sleep (synchronized and desynchronized EEG)

cholinergic fibers descends downward to the ventral medial medulla (VMM) and pontine reticular formation (PRF) and subsequently induces muscle atonia [15] and rapid eye movements [16]. These neurons are called "REM-ON" neurons [4] (Fig. 1.5).

Sleep Architecture in Adults

Sleep is categorized into four stages: stage N1, stage N2, stage N3 (delta wave or slow wave sleep), and stage REM (rapid eye movement). This applies to all age groups except infants. They have a relatively different sleep architecture due to immaturity of many of the neural networks described above and therefore their sleep architecture will be discussed at the end of this chapter. The polysomnographic features of each sleep stage are based on The American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events (Version 2.6). Stage N1 is the first sleep stage. We spend about 5–10% of total sleep time in this stage [17]. This stage is characterized by slow eye movements

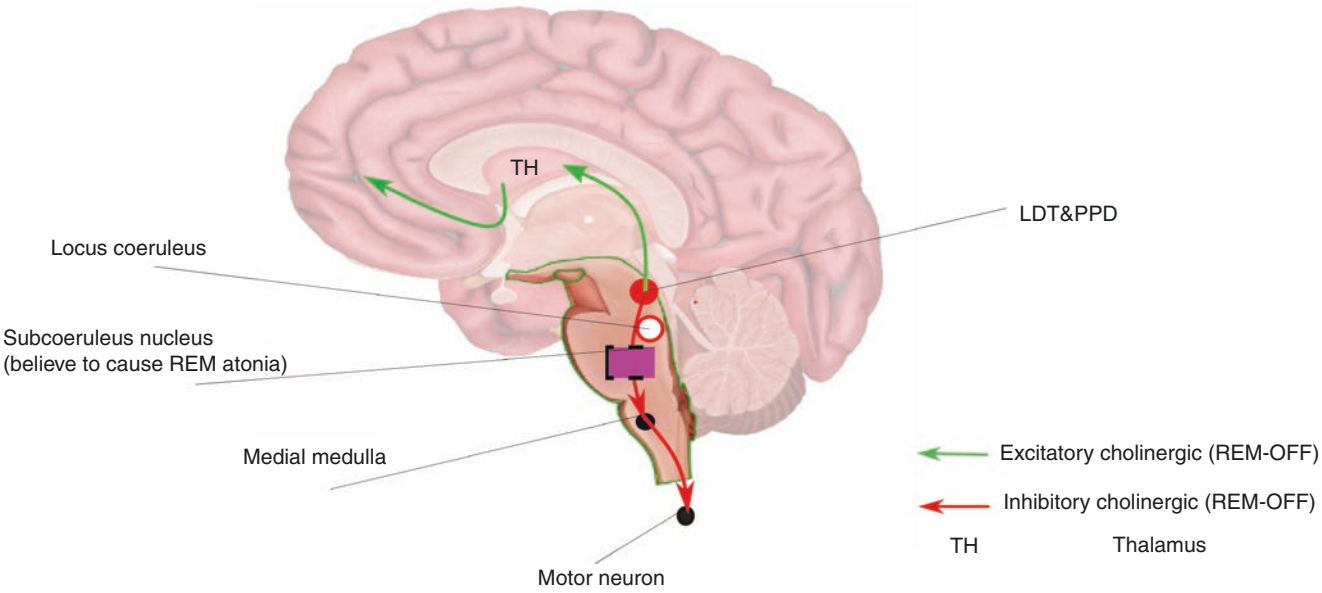

Fig. 1.5 The role of REM-ON nerve fibers in REM sleep and muscle atonia

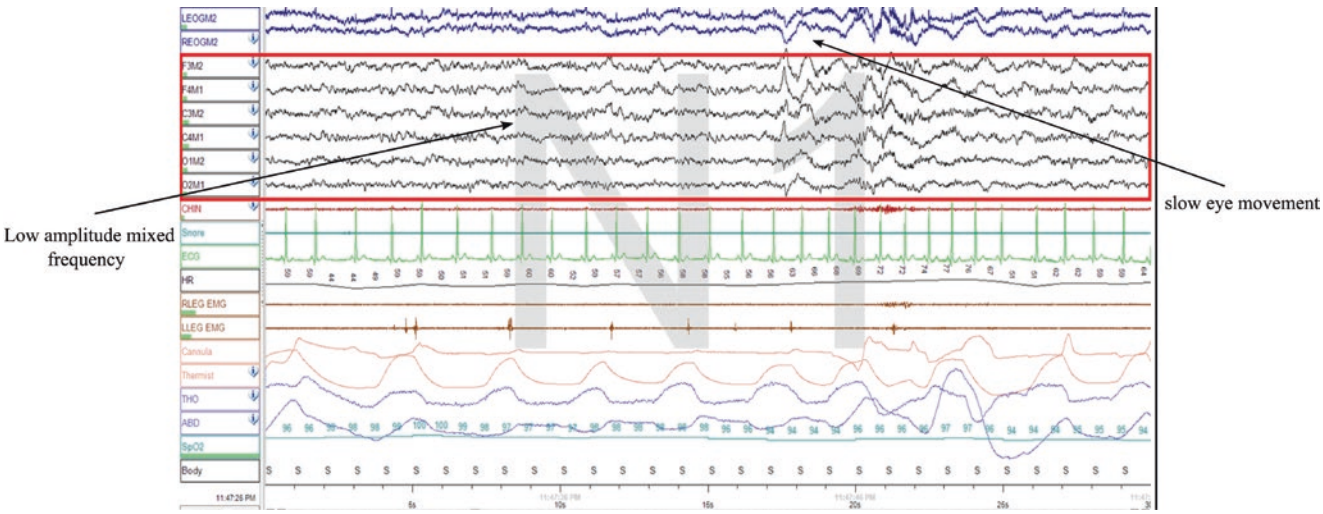

Fig. 1.6 The EEG and EMG characteristics of stage N1. (From Wikipedia, NascarEd, Creative Commons Attribution-ShareAlike 4.0 International [CC BY-SA 4.0]. Available at: https://www.wikiwand.com/en/Non-rapid_eye_movement_sleep)

(sometimes called rolling eye movements) on the electrooculogram (EOG), which are sinusoidal, regular, and conjugated movements lasting >500 msec. On electroencephalogram (EEG), the rhythm starts to slow down compared to alpha waves, "which are present during wakefulness with closed eyes." The frequency of the EEG rhythm is usually 4–7 Hz, with low amplitude forming the low-amplitude mixed-frequency pattern (LAMF). Sometimes, vertex sharp wave (V waves) can be seen during N1; however, this is not specific for N1 and can be seen in other sleep stages. The duration of this wave (i.e., the width) is <0.5 seconds. Stage N1 determines the onset of sleep (Fig. 1.6). Stage N1 is followed by stage N2, which is the predominant stage during sleep (45–50% of total sleep time) [17]. Stage N2 is characterized by two special waves (K-complex and sleep spindles). A K-complex is defined as a sharp negative deflection followed by slow positive component. The duration of K-complex is >0.5 seconds and K-complexes are more frequently seen in the frontal EEG derivations [18]. The history of K-complex is quite interesting. It was first described in a private laboratory built in a luxurious mansion in Tuxedo Park, New York. This laboratory was owned by Alfred Lee Loomis who graduated from Harvard Law School and worked as a corporate attorney and then became a bond trader for a while. He con-

solidated some of his money to build his private laboratory. He used silver leads to cover the scalp for EEG recordings [19]. In his ninth EEG paper in the early 1930s, Loomis described K-complex for the first time and remarked on the ability to evoke these complexes by external auditory stimuli. The exact physiological function of K-complexes is not totally clear to date. However, several papers after the initial Loomis publication agreed on at least one function for K-complexes. Indeed, Walter et al. [20], in 1953, described the K-complex as "a sign that sleep is deep and hard to disturb and seems to act as to muffle the arousal stimulus." Still, the question whether K-complex is "a sign of sleep arousals" [21–23] or "a sleep disruption protector" [24–26] has yet to be answered. The other feature of stage N2 is sleep spindles, which are distinct sinusoidal waves at a frequency range of 11–16 Hz. They are more distinctly recognizable in the central EEG derivations. Like K-complexes, the exact physiological function of sleep spindles is poorly understood. However, there is an evidence that sleep spindles play a role in the reinstatement of newly formed memories preparing for their integration into long-term memory during the sleep spindle refractory period. Memory reinstatement indicates the re-emergence of a newly learned-related neural activity. The sleep spindle refractory period blocks any further memories that subsequently reprocess and facilitate the integration of the new memory into the long-term storage [27] (Fig. 1.7). Following stage N2 comes stage N3, also termed slow wave sleep (SWS). This stage represents the deep stage of sleep and is characterized by the presence of delta waves. The frequency of delta waves is 0.5–4.0 Hz and the peak–peak amplitude is >75 μV. Delta waves are best observed in the frontal EEG derivations (Fig. 1.8). SWS constitutes 15–20% of total sleep time. Although K-complexes and sleep spindles are typical features of stage N2, they can be seen in stage N3. Stage N3—according to the AASM scoring system, which was introduced in 2007—replaced the previous Rechtschaffen and Kales scoring system that was introduced in 1968 and used stage 3 and stage 4 [28]. The last sleep stage is stage R (REM), which accounts for about 20% of total sleep time. This is usually referred to as the dream stage and is characterized by generalized muscle atonia (except the extraocular muscles and the diaphragm) manifesting as a low to virtually absent chin electromyography (EMG) amplitude. Stage R is characterized by rapid eye movements in the EOG derivations, which is defined as sharp deflections lasting <500 msec. REM can sometimes mimic blinking eye movements, which are seen during wakefulness. In the EEG derivatives, sawtooth waves (triangled and serrated waves with frequency of 2–6 Hz) are usually encountered and mainly in the central EEG derivations (Fig. 1.9). Stage R is often associated with transient muscle activity (TMA), which represent brief bursts of EMG tone lasting less than 0.25 sec and can be seen in the chin or the limb EMG derivations. TMAs are usually associated with the phasic phase of stage R (i.e., the rapid eye movement phase). The first stage R usually occurs within 90–120 min-

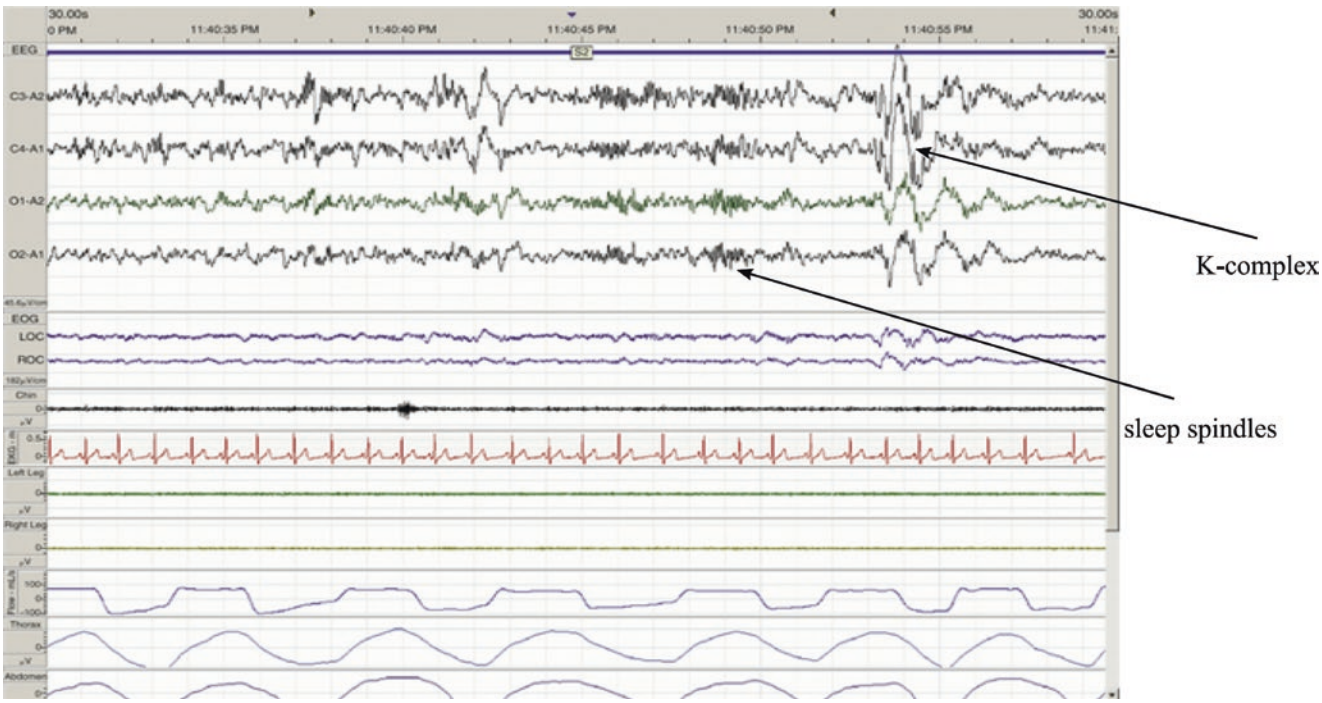

Fig. 1.7 The EEG and EMG characteristics of stage N2. (From Bahammam et al. [106]. Reprinted with permission)

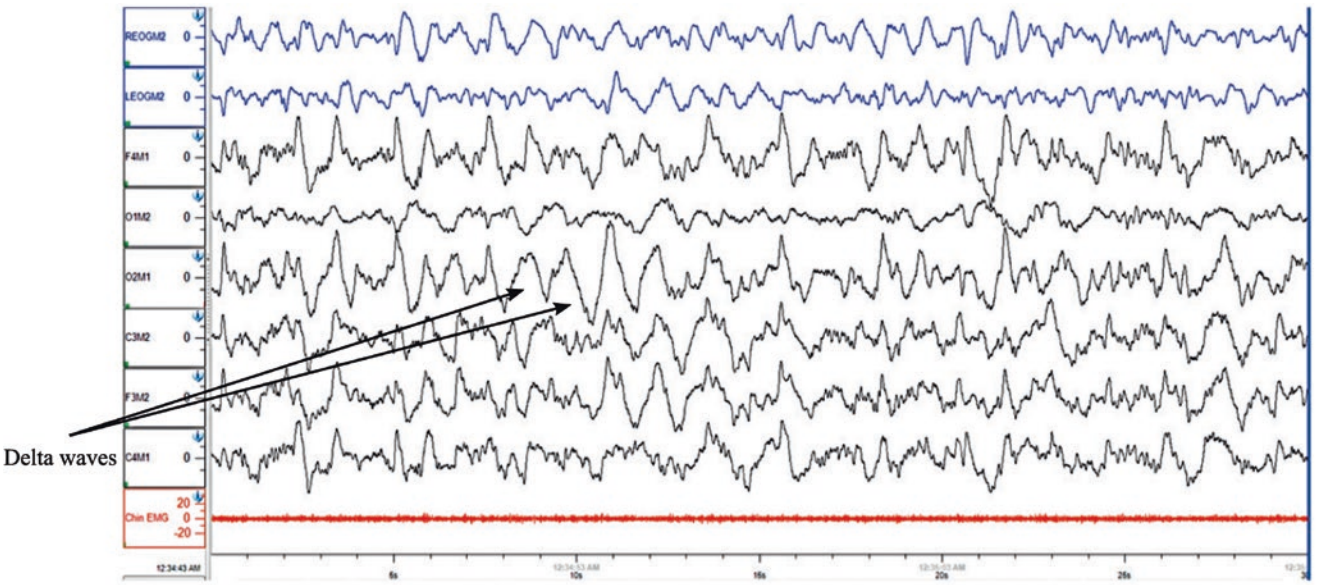

Fig. 1.8 The EEG and EMG characteristics of stage N3. (From Bahammam et al. [106]. Reprinted with permission)

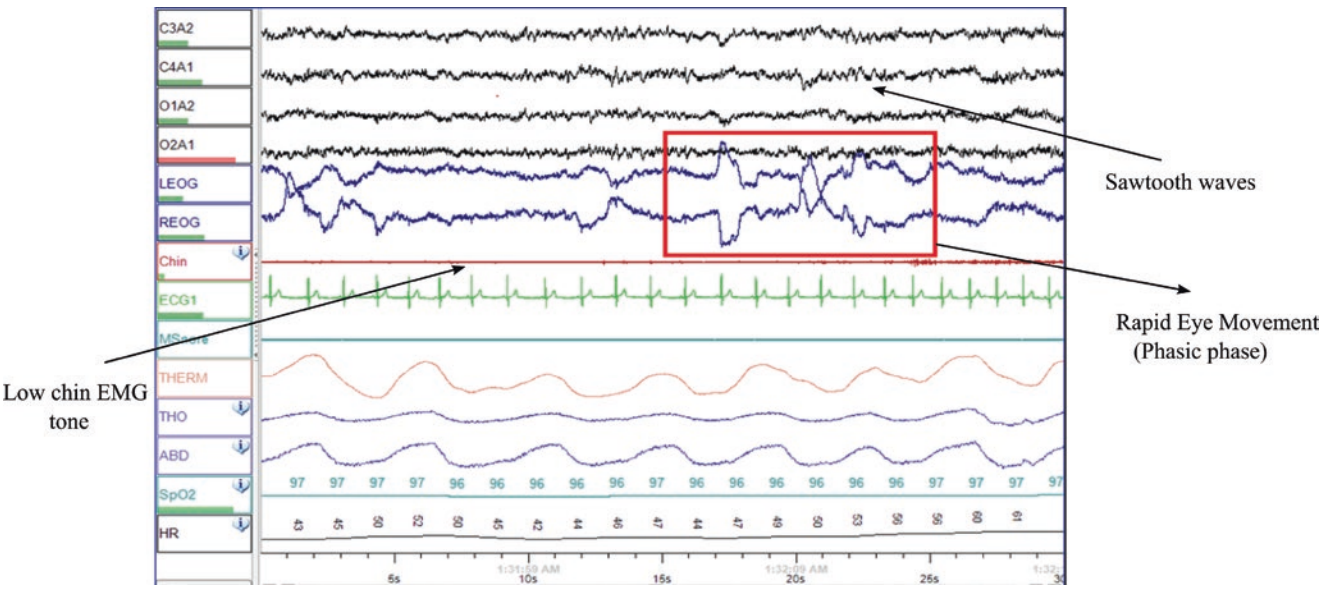

Fig. 1.9 The EEG and EMG characteristics of stage REM. (From Wikipedia, NascarEd, Creative Commons Attribution-Share Alike 3.0 Unported license. Available at: https://commons.wikimedia.org/wiki/File:Sleep_Stage_REM.png)

utes from sleep onset and most of REM cycles occur in the second half of the night compared to stage N3. The REM density—defined as the number of stage R per total sleep time—usually increases in later REM stages. All these stages mentioned previously are repeated as cycles during the night. Normally, there are 3–5 (REM and NREM) cycles per night [5].

Some of the sleep scoring data are summarized in Table 1.1 [29]. The table terms and concepts should also be very helpful to introduce some terms that will be used later in this chapter.

Table 1.1 Sleep recording data

Term	Definition
Lights out (hr:min)	The onset of recording
Lights on (hr:min)	The offset of recording
Total sleep time (TST) (min)	Time spent in all sleep stages (N1, N2, N3, R)
Sleep latency (SL) (min)	Time from light out to sleep onset (N1)
REM sleep latency (min)	Time from light out to first R
Sleep efficiency (%)	Total recording time/total sleep time
Wake after sleep onset (WASO) (min)	Total recording time – SL – TST

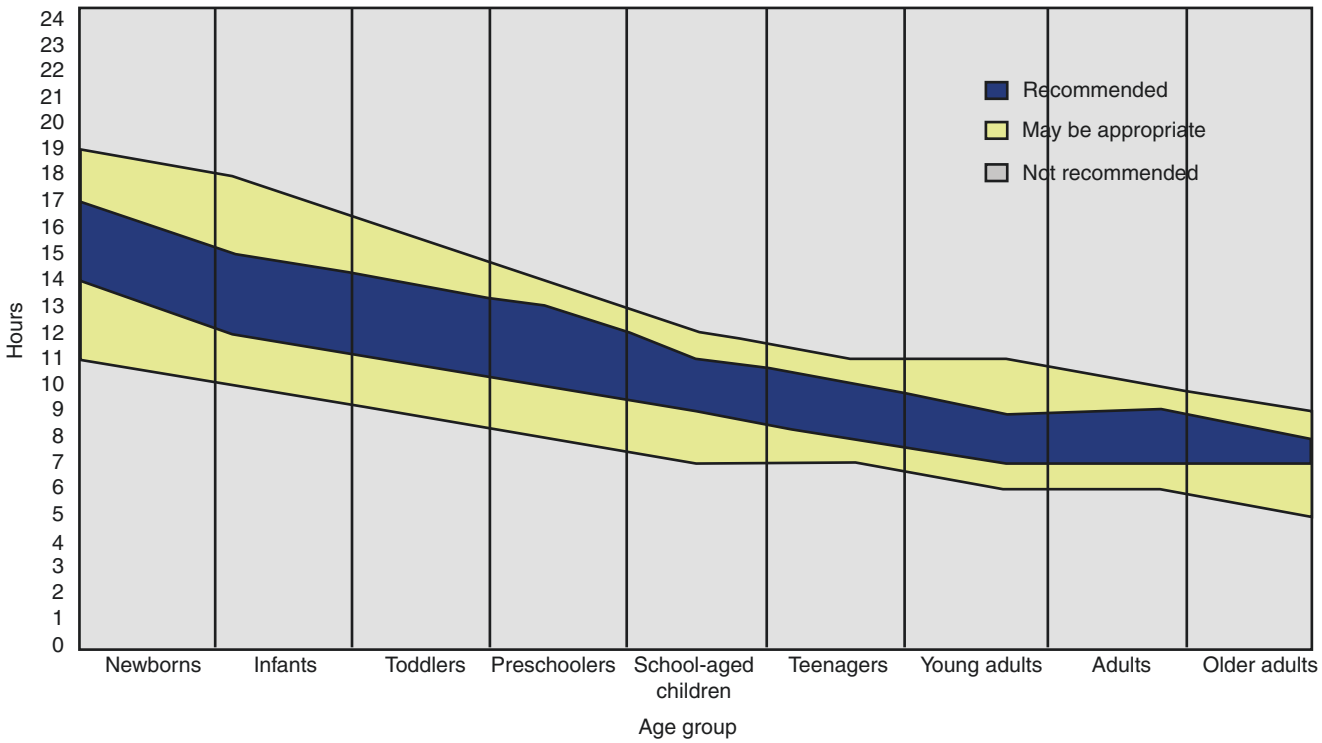

Fig. 1.10 Sleep hours needed in different stages of life. (From Hirshkowitz et al. [107]. Reprinted with permission from Elsevier)

Changes in Sleep Architecture with Age

The amount of sleep that we need is variable and changes according to age. In general, children need more hours of sleep compared to adults. Surprisingly, we still do not know the exact needs of sleep at any given age and therefore the estimates show a relatively wide range. According to the Consensus Statement of the American Academy of Sleep Medicine (AASM) regarding the recommended amount of sleep for pediatric populations, children between the age of 1 and 2 years need 11–14 hours every night while teenagers need 8–10 hours of sleep [30]. Adults on the other hand, need 7–9 hours of sleep every night. Getting less than 7 hours or more than 9 hours is associated with health risks [31]. However, please note that recommendations by a panel of experts and the National Sleep Foundation also issued a set of normative sleep duration based on post-natal age, which differ from those of the AASM, and as such some degree of latitude and common sense needs to be applied when interacting with parents and recommending the amount of sleep that a child may need at any given age (Fig. 1.10 and Table 1.2).

Table 1.2 Expert panel-recommended sleep durations in different age groups

Age	Stage	Recommended hours	Not recommended hours
0–3 months	Newborns	14–17	<11 >19
4–11 months	Infants	12–15	<10 >18
1–2 years	Toddlers	11–14	<9 >16
3–5 years	Preschoolers	10–13	<8 >14
6–13 years	School-aged children	9–11	<7 >12
14–17 years	Teenagers	8–10	<7 >11
18–25 years	Young adults	7–9	<6 >11
26–64 years	Adults	7–9	<6 >10
≥65 years	Older adults	7–9	<5 >9

Data from Hirshkowitz et al. [105]

Total Sleep Time (TST)

Total sleep time decreases with age. Several meta-analyses showed a linear decline in TST with age with an average of 10–12 minutes per decade [32]. In one trial where three groups (younger age, middle-age, and older age) were given the chance to sleep while being isolated of all time cues over 72 hours, spontaneous sleep was measured over 24-hour period and was the highest in the younger age group (10.5 hours), followed by middle-age group (9 hours), and finally lowest in the older age group (8 hours) [33]. It seems that TST is a predictor for longevity in adults. It is well established that sleeping less than 7 hours every night is associated with higher risk of cardiovascular diseases and obesity [34]. Similar findings have also been reported for children [35–50]. On the other hand, Burazeri et al. [51] noticed that 8 hours of sleep is needed for optimal health in Mediterranean population and those who slept more than 8 hours had double risk for all-cause mortality and triple risk of cardiovascular mortality. Since these numbers regarding TST are self-reported in most trials (few used polysomnography or at least actigraphy), we have to be cautious when we interpret these numbers in the elderly group who have a tendency to underestimate their sleep time or might have cognitive disorders that limit accurate reporting [52]. This might explain the plateau in TST decline with age beyond the age of 60 [53].

Sleep Initiation, Maintenance, and Sleep Efficiency

Sleep initiation usually becomes progressively delayed with age; however, the increase in the sleep latency (SL) is not one that can be explained by a simple linear correlation. There is a significant delay in SL between late teenage and the age of 30; then this delay plateau persists or is slightly reduced until the age of 50 years. Beyond the age of 50, SL continues to delay further. The same phenomenon applies to sleep maintenance, which worsens with age. A meta-analysis showed worsening of sleep initiation and maintenance as reflected by increases in wake after sleep onset (WASO) time and increases in the arousal index [32]. In another meta-analysis conducted by Ohayon et al., the increase in WASO time was estimated to be 10 minutes per decade between the age of 30 and 60 years [17]. Although there are more awakenings during the night in elderly people, they retain their ability to fall back to sleep as rapidly as young population. Similarly, sleep efficiency is decreased with age (mainly, between late teenage and young adulthood) [53].

Sleep Architecture

The most prominent change in sleep architecture with age is the reduction in SWS percentage, which subsequently leads to increases in stage N1 and stage N2 sleep. Ehlers et al. noticed decreases in SWS from 19% in early adulthood to only 3% in midlife [54]. However, no significant reductions in SWS percentage occur after the age of 60. Most of SWS percentage reduction affects the first NREM cycle and usually between the age of 20 and 40 [17]. Similarly, REM sleep decreases with age (mainly until late adulthood). After that, REM sleep starts to plateau or even slightly increase. In contrast with normal REM cycles distribution that tends to occur mainly in the second half of the night, REM sleep starts to shift to the first half of the night with age. At the same time, REM latency becomes shorter, which is expected secondary to higher prevalence of sleep-related and sleep-unrelated disorders with age, and which cause sleep fragmentation and enhance REM-rebound phenomenon [55]. Murphy et al. examined the stage at which sleep termination occurs and its relation with age. They concluded that younger adults tended to terminate sleep and woke up preferentially from Stage R compared to elderly who terminated sleep and woke up from NREM stages [56]. Another interesting observation is the gender-related sleep architecture changes with age. Redline et al. conducted a trial (Sleep Heart Health Study) where they obtained sleep scoring data from participants older than 37 years and divided them into quartiles. They concluded that the reduction in SWS percentage and REM percentage occurring with age is gender-related and mainly seen in males [57]. Similarly, the increase in stage N1 and stage N2 percentages that happens with age was predominantly in males [57].

Changes in Circadian Rhythm with Age

Normal Sleep–Wake Cycle: The Circadian Rhythm and Sleep Homeostasis

The sleep–wake cycle is under tight control from the master clock, which is located within the suprachiasmatic nucleus (SCN). The central clock is a collection of around 200,000 neurons located in the anterior part of the hypothalamus [58]. The word "circadian" means "about a day," which includes all the variations that happen within the 24-hour period [59]. Since the day–night cycle in humans is a little bit longer than 24 hours (~24.2 hours), other external stimuli called *zeitgebers* (i.e., time givers) entrain our circadian rhythm to within the 24-hour period [60]. The most important and common zeitgeber is light. Other zeitgebers include

temperature, food, and exercise [61]. Biological clocks are not just in the SCN. In fact, every single cell in our body has its own clock that works in a harmonious synchrony with the master clock [61]. For their discovery of the clock in essentially all biological systems, Jeffrey C. Hall, Michael Rosbash, and Michael W. Young were awarded the Nobel Prize in Physiology or Medicine in 2017.

Light activates photosensitive receptors in the retinal ganglion cells, which transmit the signal to the SCN via the retino-hypothalamic pathway [62]. In addition to regulating sleep–wake cycle in a circadian rhythm, SCN regulates the secretion of some hormones (such as melatonin and cortisol) and regulates the core body temperature. The release of these hormones and other hormones will be discussed in more details in the section of physiological changes in sleep. There are some markers that can be used to determine normal and abnormal circadian rhythms. The minimum core body temperature (CBTmin) is usually 2–3 hours before spontaneous wake up time (usually between 4:00 and 5:00 AM) [63]. The rise in melatonin level (dim light melatonin onset—DLMO) usually occurs 2–3 hours before typical bedtime [64]. Measuring these markers can be helpful sometimes to detect circadian problems in patients who suffer from phase-shift disorders.

The circadian rhythm is not the only regulator of the sleep–wake cycle. Sleep homeostasis is another critical factor that regulates sleep. Both the circadian system and sleep homeostasis lead to a fundamental model for sleep–wake regulation. This is called the Process C and Process S model. C stands for circadian and S stands for homeostasis. Sleep homeostasis simply implies that the more awake we are, the higher the sleep load or sleep pressure, and the higher the propensity to fall sleep. The interactions between both determine sleep onset and wake up times [65].

Phase Advance, Reduced Circadian Amplitude, and Less Adaptation to Phase-Shift

As we get older, progressive changes in the SCN develop, and result in phase advance in the elderly population. Older people tend to go to bed earlier than younger people (usually around 1 hour [66]). The phase advance does not include bedtime only, there is also advance in core body temperature and the secretion of melatonin and cortisol [67]. Monk et al. [68] compared a group of young healthy adults and a group of healthy elderly. Both groups had similar daytime social activities but despite that, the elderly group noticed more sleepiness (subjective and objective), and at an earlier time, compared to the young group. Using forced desynchrony, a technique of changing the circadian duration in an isolated environment without time cues, Dijk et al. [55] exposed young and elderly groups, and the older people had decreased sleep in all circadian phases compared to the young group.

Not only the circadian phase is advanced, the amplitude of the circadian rhythm (i.e., peak-to-trough) is reduced in older people. Vitiello et al. [69] concluded that minimum core body temperature is higher than the nadir temperature on the normal peak-to-trough temperature curve. Munch et al. [70] noticed that less melatonin and cortisol are secreted in older people during sleep compared to young people. Finally, the adaptation to phase change is decreased significantly in elderly population and that is reflected by more time needed to recover from shift work or jet lag, and more sleepiness and daytime dysfunction compared to younger population [71, 72]. Such studies have not been conducted in children for obvious reasons since they require extended periods of relative isolation, but the overall consensus is that the circadian system is robustly active and extremely adaptive already at term birth, and possibly even in pre-term infants. Indeed, in a recent study in premature babies exposed to phototherapy, the ultradian rhythm appeared to be independent of phototherapy, supporting the concept that sleep rhythms in these infants is principally driven by their internal clock [73]. However, it is also noteworthy that the circadian system of non-human primate infants is already responsive to light at very premature stages (equivalent to 21–23 weeks post-conceptional age in human fetuses) and that low-intensity lighting can regulate the developing clock in premature infants in the neonatal intensive care units. After term birth, there is also progressive maturation of the circadian system outputs, with pronounced rhythms in sleep–wake and hormone secretion generally manifesting very robustly after 2 months of age [74–76].

Sleep in Children

Sleep architecture and sleep schedules vary significantly in children (especially in infants) compared to adults. Based on this, we elected to discuss sleep changes in children in the following separate section, where variation in sleep architecture, schedules, and circadian rhythm are described in brief.

Infants: 0–1 Year

Sleep architecture is a little bit different in infants compared to other age groups. Sleep stages are simplified to three stages: W = wake, R = REM or previously called Active,

and N = NREM or also called Quiet. Stage W is characterized by crying, feeding, blinking, or scanning eyes. Breathing is usually irregular, and eyes are open in this stage. In stage N, movements start to be reduced compared to wake, eyes are closed, breathing starts to be regular, occasional startle and periodic sucking can happen, and there are no extraocular movements. In stage R, eyes are usually closed and rapid eye movements are present but sometimes they are absent, breathing is irregular, and movements are minimal [29].

About 65% of the 24-hour period is spent in sleep in the first few weeks of life. Due to the early expression of the circadian system, most of sleep occurs at night but sleep is extremely irregular and happens in many brief periods (i.e., polyphasic) [77]. The main external stimulus for the circadian system is hunger (likely driven by the high metabolic rates of infants), and light plays a role but its role is not as prominent [78]. At birth, most of sleep is spent in stage R (~50–60% and 15–20% in stage N, with the rest being indeterminate. With time, stage R starts to decrease and stage N increases (50–60% NREM and 25–40% R by the age of 1 year) [79]. By the age of 2–3 months, more maturation of the circadian system leads to increasing influence of light as a main zeitgeber for the regulation of the sleep–wake cycle [74]. Subsequently, more awakenings during the daytime and improved consolidation of sleep at night ensues. As we approach the first year of life, more sleep at night and less sleep during the daytime take place and less napping during the daytime [80]. Sleep onset latency shortens and fewer nocturnal awakenings are noticed, with a total of 10–12 hours of sleep at night and 2–3 naps during the daytime by the age of 6–9 months [81, 82].

Toddlers: 1–5 Years

In this stage, sleep continues to consolidate at night and decreases during the daytime and napping decreases, too. By the age of 1 year, bedtime is usually at 8:00 PM. Bedtime starts to delay with age and by the age of 5 years, bedtime is usually between 9:00 and 9:30 PM [83]. Ward et al. [84] evaluated napping time in children at different age groups in a daycare and concluded that 55% of children between the age of 3 and 5 years had one nap on three consecutive days, and 10% did not take any nap. By the age of 6 years, only 10% took naps [85]. Different factors influence daytime napping in children, such as cultural habits, family routines, and school schedule. Ethnicity seems to play a role too, whereby African American children tend to have a slower decline in their napping frequency through the pre-school stage compared to White Caucasian children [86].

Middle Childhood: 6–12 Years

In this stage of development, significant changes in sleep architecture occur, such as reduction in SWS and REM latency and increase in stage N2. TST starts to decrease, although most of these school-aged children get 10 hours of sleep and wake up spontaneously [17]. The change in sleep architecture is highly variable from child to child, and several factors play a role in structure (e.g., gender, ethnicity, socioeconomic status, and maternal education). Girls tend have better sleep efficiency, more SWS, and more stage N1 compared to boys of the same age [87]. Maternal education was noticed to influence shorter REM latency and less nocturnal awakenings [88].

A significant change that happens in these children is sleep onset delay, which decreases TST and leads to excessive daytime sleepiness in the morning. Sadeh et al. noticed a delay in sleep onset latency and bedtime—from 9:30 PM in second-grade to 10:45 PM in sixth-grade children [89].

Adolescents: 12–18 Years

The progression from childhood into adolescence is characterized mainly by further delay in bedtime and earlier rise time [90], which results in decrease in TST—from 10 hours in middle childhood to 7.5 hours in adolescence [91]. The phase delay that happens in adolescents is likely secondary to later bedtimes (e.g., due to homework, extracurricular activities, employment, TV watching), although intrinsic changes in the clock cannot be excluded. The trend toward phase delay continues in high school students and seems to be multifactorial. Delay in circadian rhythm and subsequent delay in the sleep homeostasis contribute partly to this process (for example, weekend rise time increases from 1.5 to 3 hours in childhood stage to 3–4 hours in high school) [92]. At this stage, sleep architecture is the same as childhood with reduced SWS, REM latency, and TST and increase in stage N2 [93].

Summary

With the development of technologies enabling multiparametric recordings of physiological signals, we have witnessed an explosion in our understanding of sleep, its structure, and the regulatory mechanisms that govern around a third of our lives. This is just the beginning of the short history of sleep as we know it, and much remains to be discovered in the upcoming years. If you wish to expand your reading into recent perspectives on the functions of sleep, we have added a few comprehensive reviews at the end of the reference list [94–104].

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Part II

Physiologic Regulation in Sleep and During Development

Control of Breathing During Sleep and Wakefulness in the Fetus, Newborn, and Child

2

Vincent Joseph, Aida Bairam, and John L. Carroll

Introduction

The main functions of the respiratory control system are to keep adequate tissue oxygenation and insure excretion of CO_2. To fulfill this, the system is able to respond to a variety of stimuli and modify the breathing pattern (amplitude and frequency of breathing), matching respiration with the metabolic needs. In addition to the sensors responding to increased muscular activity during exercise, or the intricate relations between the respiratory and the sleep/wake neuronal networks, a particular aspect of this system is that there is a constant monitoring of arterial blood gas levels by the peripheral and central chemoreceptors. Peripheral chemoreceptors are located at the bifurcations of the carotid arteries, while central chemoreceptors are found within the brainstem, and are respectively responding to low O_2 (hypoxia) and high CO_2 levels (hypercapnia). These sensors are constantly providing a "drive" to the groups of neurons that generate the respiratory rhythm; the intensity of this drive varies with the arterial pressures of O_2 (PaO_2) and CO_2 ($PaCO_2$). In a laboratory setting, it is possible to evaluate the intensity of these drives, or the chemoreflex functions, by different approaches that alter the levels of arterial blood gases. The typical responses to hypoxia or hypercapnia are an increased neuronal activity of the respiratory control system that is transferred to the spinal motoneurons of the phrenic nerve, thereby increasing minute ventilation in an attempt to restore the levels of arterial blood gases toward normal values. See Figs. 2.1, 2.2, and 2.3 for a simplified model of this system. One particular aspect of this system for sleep medicine emerges from the powerful drive provided by CO_2: if for any reason the $PaCO_2$ falls below a determined level (called the "apneic threshold"), breathing stops, and it is noteworthy that the difference between the eupneic and apneic CO_2 levels (also called the "CO_2 reserve") varies with age, being much smaller in newborns than in adults [1] (Fig. 2.3b). Hypoxic or hypercapnic exposures also result in activation of the sympathetic nervous system and might induce wakefulness when occurring during sleep.

When considering the physiology of this system for sleep medicine in a pediatric population, it is necessary to account for the interactions between sleep and breathing, and the developmental pattern of the respiratory control system. This developmental pattern can conveniently be separated in three main periods: fetal life, the early postnatal period (including the case of preterm birth, up to 1 year of age), and children. This chapter will briefly review the influence of sleep on the respiratory control system in the fetus and newborn, and how sleep exacerbates respiratory instabilities and apneas. We will then describe our current knowledge on the development of the respiratory control system during sleep based on studies from developing human and animal models. The influence of sex as a factor that modulates the regulation of breathing is also briefly discussed. Finally, we will describe respiratory control and the influence of sleep across the ages from early childhood through adolescence.

Influence of Sleep on the Respiratory Control System

The influence of sleep on the respiratory control system is a rich and fascinating field of research, tied to clinical and fundamental issues. It is clearly beyond the objectives of this chapter to provide a full overview. Several excellent reviews have been published over the years [2–4]. We will simply highlight the key elements that are pertinent to understand

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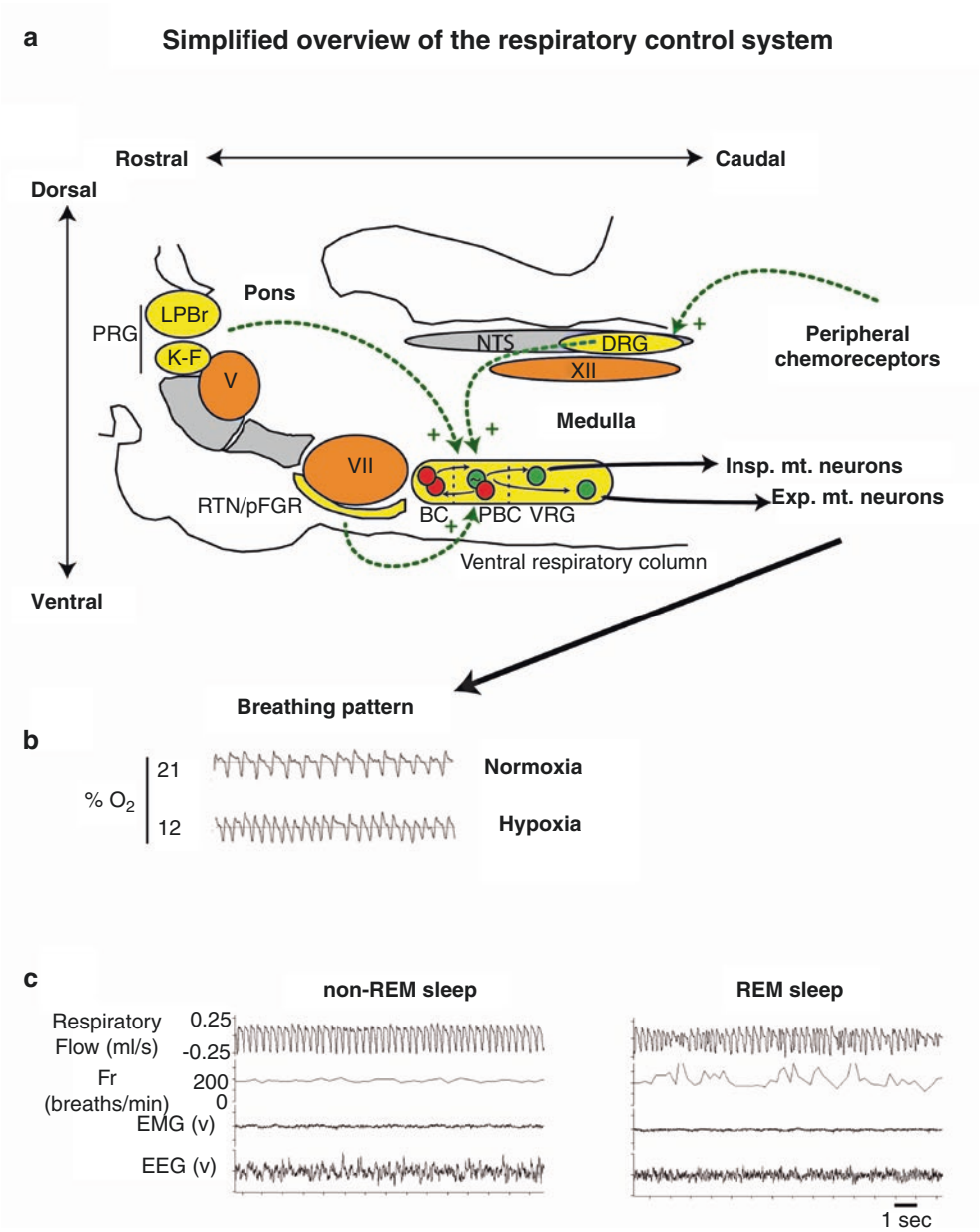

Fig. 2.1 (**a**) Sagittal view of the lateral medulla with the main groups of respiratory neurons (*yellow*) extending along the rostro-caudal axis up to the dorsal part of the pons. The Vth, VIIth, and XIIth motor nuclei are presented (*orange*) as anatomical landmarks. Groups of interconnected excitatory (*green*) and inhibitory neurons (*red*) are distributed along the ventral respiratory column. The microcircuit responsible for the generation of the breathing rhythm is localized in the PreBötzinger complex (PBC). The Bötzinger complex mostly contains expiratory neurons inhibiting inspiratory neurons of the PBC. Bulbospinal premotoneurons relaying inspiratory or expiratory drives to the spinal motoneurons are localized in the ventral respiratory group (VRG). Chemoreflex drives are provided by the peripheral chemoreceptors and their central projections to the dorsal respiratory group (DRG) of the caudal nucleus tractus solitarius (NTS), and by the central chemoreceptors of the retrotrapezoid nucleus/parafacial respiratory group (RTN/pFRG). The pontine respiratory group (PRG) includes the lateral parabrachial and Kölliker-Fuse nuclei (LPBr–K-F); it regulates the phase transition between inspiration and expiration, and is a relay of suprapontine afferents contributing to the respiratory drive. K-F also contains premotor neurons that control laryngeal muscles and upper airway resistances. The strength of the chemoreflex drives is dictated by levels of arterial blood gases. (**b**) Typical respiratory traces in normoxia and in response to hypoxia (recorded in a 10-day-old mouse, toward the end of the postnatal maturation of the respiratory control system). (**c**) Typical respiratory recording during non-rapid eye movement (non-REM) and REM sleep recorded in an adult mouse. Traces show the respiratory flow, respiratory frequency (breath-by-breath), electromyogram (EMG), and electroencephalogram (EEG). (Redrawn and adapted from Smith et al. [119] with permission from Elsevier. Respiratory traces adapted from Refs. [120, 121])

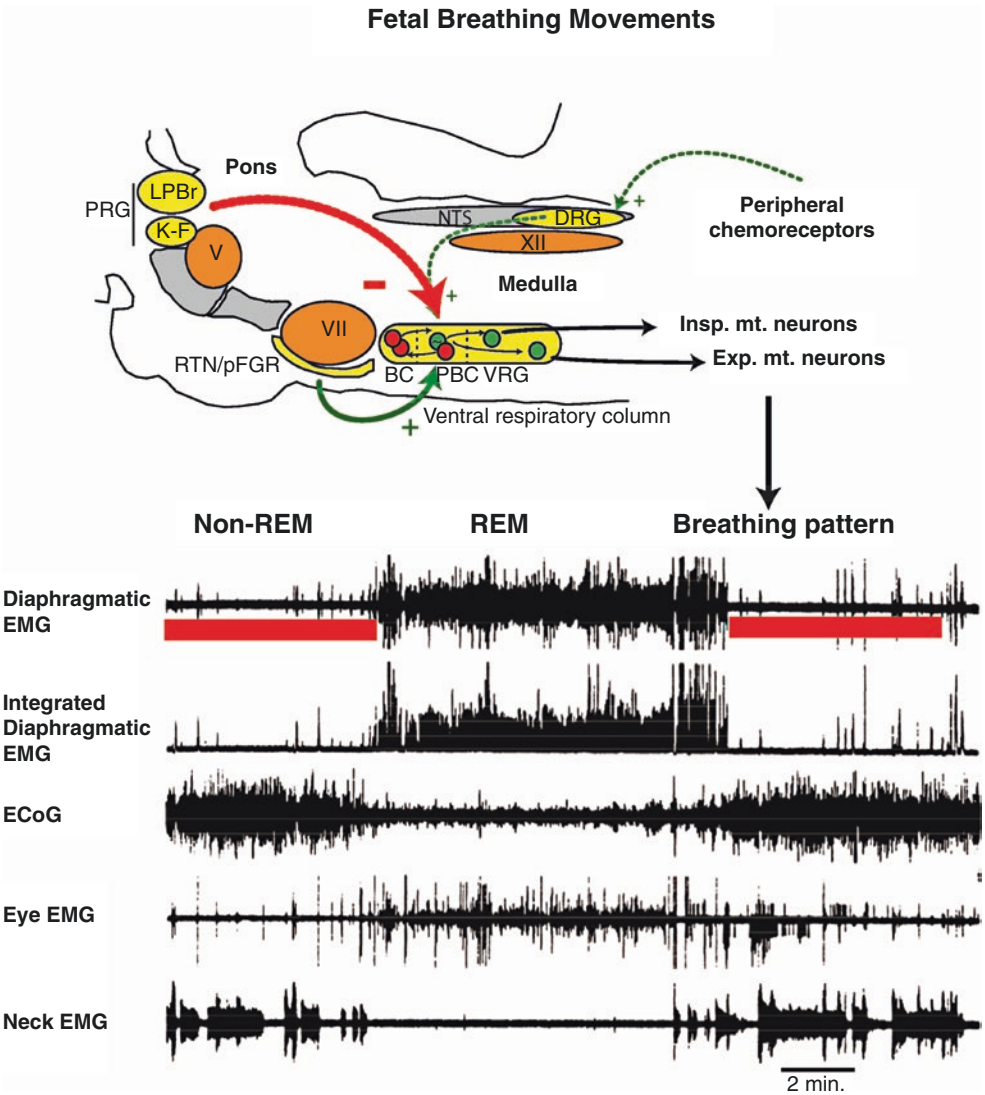

Fig. 2.2 Occurrence of fetal breathing movements during REM sleep in a near-term fetal lamb. (Recordings from Jansen and Chernick [11]. Reprinted with permission from The American Physiological Society). The pontine respiratory group exerts a potent inhibition on the activity of the respiratory neuronal groups of the ventrolateral medulla (*red arrow*). However, during REM sleep fetal breathing movements are visible. The pontine inhibition masks the effect of peripheral chemoreceptors during hypoxic exposures, but central chemoreceptor exerts a tonic activation (see text). See legend of Fig. 2.1 for further details

the intricate relationships. One of the most important drives to the respiratory control system arises from the wake-promoting neuronal networks localized in the medulla and hypothalamic nuclei. When the wake drive disappears during non-rapid eye movement (non-REM) sleep, ventilation is slightly reduced, and arterial levels of CO_2 increase by 2–8 mmHg. This reduced respiratory activity leaves the respiratory control system under metabolic regulation and even a transient and modest reduction in $PaCO_2$ that will have no consequence during wakefulness, will induce an apnea during sleep.

Furthermore, the resistance of the upper airway increases two- to fivefold during sleep. Recordings performed in rodents have shown that the activity of the XIIth cranial nerve, that innervates the genioglossus muscle, is decreased during non-REM sleep compared to wakefulness, and is completely suppressed during REM sleep, secondary to the withdrawal of excitatory inputs to the airway motor neurons [5]. During REM sleep, breathing is generally more variable, and the breathing pattern is influenced by non-metabolic stimuli [4]. Breathing frequency typically increases during periods of rapid eye movements compared to non-REM sleep, while tidal volume and minute ventilation are further depressed [6]. While some studies have shown that in apneic patients, the frequency of apneas is slightly higher during REM sleep than during non-REM sleep [7], others have not reported such differences [8].

Control of Breathing in the Fetus

In the fetus, respiratory exchanges occur through the placenta and the maternal respiratory system. However, fetal breathing movements (FBM), while limited, are nonetheless

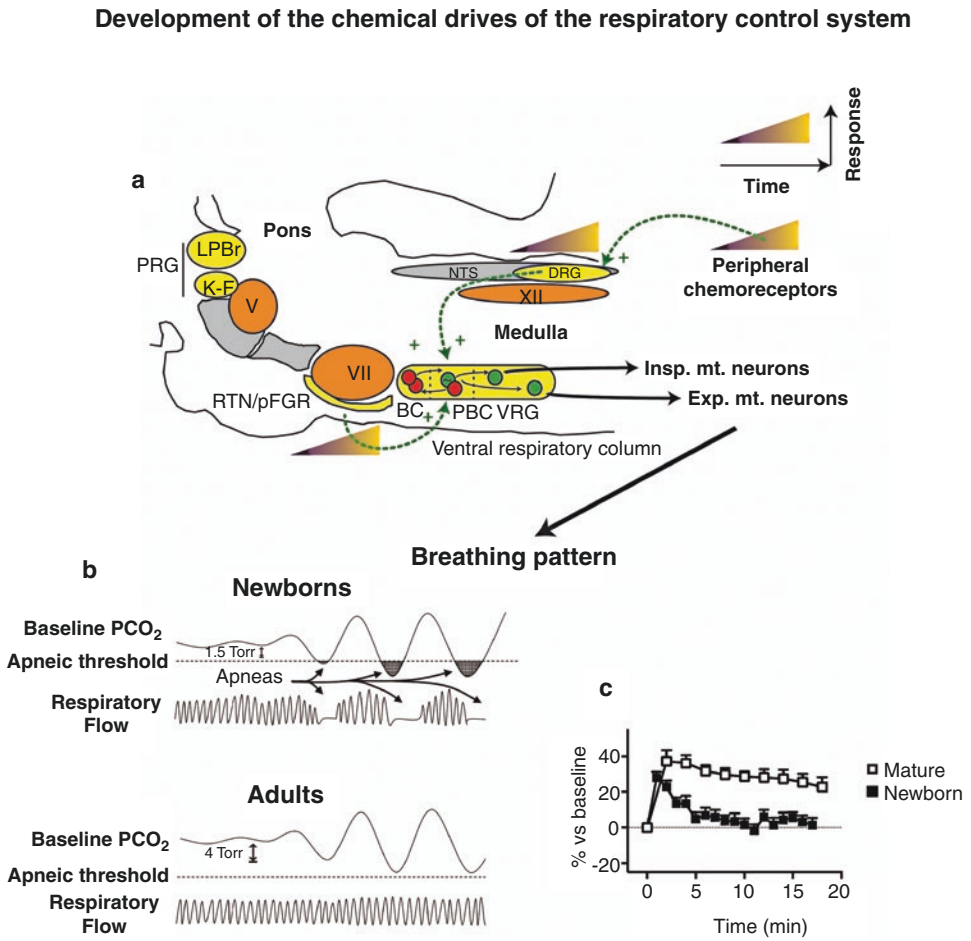

Fig. 2.3 (**a**) Schematic representation of the early postnatal maturation of the central and peripheral components of the chemoreflex drives to breath, showing general trends of increased efficiency with maturation. (**b**) Maturation of the central respiratory drives widens the "CO_2 reserve," driving eupneic breathing further away from the apneic threshold. (From Alvaro R [122]. Reprinted with permission from Springer Nature). (**c**) Postnatal maturation of the hypoxic ventilatory response in mice. Minute ventilation recorded by whole body plethysmography at postnatal days 3–4 (newborn) and 12 (mature). Graph shows percentage changes of minute ventilation (Tidal volume × Respiratory frequency) vs baseline value during a 20-minute exposure to 10% O_2. Note the sustained response in mature animals, and the biphasic pattern of the newborn, with a peak followed by a decline to baseline values. Data from Joseph & Bairam laboratories

observable in almost all mammalian species and have been particularly well studied in humans [9–11], lambs [12–14], and rats [15–17]. FBM play an important role in lung growth and respiratory muscle development [18], in particular for the diaphragm muscle, which develops concurrently with the establishment of the inspiratory drive in utero [16]. In humans, FBM can be detected by ultrasound as early as the 11th week of gestation [19]. At this early stage the FBM are continuous with a regular pattern, but they become clearly irregular and episodic in nature during the last trimester of gestation [9, 20, 21]; an episode of breathing can last 10–30 minutes with a mean frequency around 60/minute and is associated with increased body movements, decreased heart rate, and increased heart rate variability [10, 20, 22]. Between episodes, there is no breathing activity, and this "apneic" period might last up to 120 minutes [10, 20]. This developmental period of FBM is associated with the beginning of a clear differentiation of the low- and high-voltage electrocortical activity that are the signatures of sleep/wake states [23].

Interestingly, similar steps for the appearance of FBM and their association with cortical brain organization for sleep are observed in fetal sheep, which has been for many decades a powerful animal model to characterize the physiology of breathing before birth [11, 12, 14]. During the last 3 months of gestation, healthy non-anesthetized fetal lambs spend roughly 40% of their time in a state characterized by low-voltage electrocortical activity, with rapid eye movements (REM sleep state), 50% of the time is characterized by high-voltage electrocortical activity associated with non-rapid eye movements (non-REM sleep state) [12, 24], and the remaining time is classified as an undetermined state. In fact, the typical "wake" behavior (opened eyes with gross body and head movements) is only observed after birth [25]. FBM typically occur during REM sleep in fetal lambs [26], and in human [20], and are notably absent during non-REM sleep

[24, 25]. The isolated breaths during non-REM sleep are associated with body movements and can represent tonic diaphragmatic discharges rather than typical FBM [25].

The precise mechanisms explaining the absence of FBM during non-REM sleep remain unclear, but it is worth mentioning that sections through the upper pons or mid-collicular regions induce FBM independently of the state of electrocortical activity (REM or non-REM) [16, 27–29] (Fig. 2.2). Therefore, during non-REM sleep state, there is a powerful inhibitory pathway arising from the lateral pons and midbrain contributing to reduce the activity of the medullary respiratory rhythm generator.

Collectively, the pattern of fetal FBM during the course of gestation has been suggested to be an indicator of fetal health and nervous system development [30–32], providing information about the developmental course of the respiratory control system in utero [9]. Notably, an absence of FBM on ultrasound examination can be used to detect a short-term risk of preterm birth [33].

Regulation of FBM by Chemoreflex Drives

Hypoxic Drive and Peripheral Chemoreceptors

Fetuses live in a severe hypoxic environment with PaO_2 being low (about 25–30 mmHg) compared to after birth (55–70 mmHg) or standard levels beyond the postnatal period (95–100 mmHg). Despite this very low PaO_2, the activity of the peripheral chemoreceptors has been recorded in lambs and displays a functional response to hypoxia [34]. However, hypoxia [12, 13, 35], or experimental anemia [36], drastically inhibits the frequency and amplitude of the FBM, and also reduces the proportion of time in REM sleep state. A prolonged exposure to hypoxia for 24 hours inhibits FBM only during the first few hours of exposure [37]. After electrolytic lesion of the lateral pons, in a region corresponding to the lateral parabrachial and Kölliker-Fuse nuclei [29], hypoxic exposures increase FBM, showing the central origin of this inhibition (Figs. 2.1 and 2.3). Interestingly, inhibition of FBM in REM sleep state is stronger in fetus near term of gestation suggesting an age-dependent maturity of this central inhibitory pathway [12]. Finally, it is worth mentioning that hyperoxia has no effect on FBM or sleep state, indicating that fetal PaO_2 does not limit the normal expression of FBM [35].

Hypercapnic Drive and Central Chemoreceptors

In response to hypercapnia or hypocapnia during REM sleep, there are respectively an increased and a decreased incidence and amplitude of FBM [28, 38]. The response to hypercapnia is stronger in near term than in younger fetuses [13, 35, 39]. Interestingly, the effect of age and CO_2-concentration was evaluated in 30 human fetuses divided into 3 groups of 24–26, 28–30, and 32–34 weeks of gestation, while mothers breathed CO_2 at 2% or 4%. These fetuses show an age- and CO_2-concentration-dependent increase in FBM response, with higher responses at 32–34 weeks than 24–26 weeks of age [9].

Hence, in the fetus, the sensory mechanisms that underlie the responses to hypoxia and hypercapnia develop during gestation, and FBM are predominantly controlled by central mechanisms rather than by peripheral chemoreceptors (see Fig. 2.2). Although high CO_2 levels (hypercapnia) appear to be an important stimulus to regulate FBM, hypercapnia does not induce continuous breathing during non-REM sleep, further supporting the suggestion that central inhibitory mechanisms on the respiratory control system are strong during the fetal life. Maternal and intrauterine conditions can modify FBM pattern and several studies suggest that these factors can induce changes in the normal developmental course of the respiratory control system after birth, such as alteration of the ventilatory response to hypoxia [40], increased frequency of apnea [41], and disruption of the brainstem respiratory rhythm generation [42]. Different mechanisms have been proposed to explain such alterations in respiratory control in neonates born from stressed mothers, such as disturbances in neurotransmitter function (GABAergic and serotoninergic systems [41, 43] and enhancement in the neuro-inflammatory processes in the brainstem and spinal cord [42].

Control of Breathing in the Newborn

After the transition from liquid to gas breathing at birth, and once the continuous breathing pattern has been established (a topic not covered here), wakefulness and arterial blood gases remain the most powerful respiratory drives. As mentioned earlier, however, the "CO_2 reserve"—which represents the tolerance of breathing to a drop of $PaCO_2$ before an apnea occurs—is much smaller in newborn (about 1.0–1.3 mmHg in term and preterm neonates) than in adults (around 3.5 mmHg) [1] (Fig. 2.3b). With this small reserve, periodic breathing and apneas are commonly observed. In term infants at a mean age of 27 days, even a very small, spontaneous, increase in ventilation (frequency increasing from 32.8 to 33.9 breaths/min) can "precipitate" a decrease in $PaCO_2$ below the apneic threshold (from 39.7 to 38.7 mmHg) and initiate a sequence of periodic breathing or apnea [1]. In preterm neonates, the apneas during periodic breathing are typically associated with decreased arterial oxygen saturation [44, 45]; thus, this is a highly significant clinical concern exposing the newborn to intermittent hypoxia.

Postnatal development of the respiratory control system involves the peripheral and central chemoreceptors, the central integration pathways in the brainstem, and the effector muscles (respiratory diaphragmatic and intercostal muscles)

[46]. This maturation widens the CO_2 reserve, and consequently the newborns become less prone to exhibit recurrent apneas (Fig. 2.3). In humans, the maturity of the respiratory control system occurs progressively during the first year of life, in parallel with the maturation of sleep architecture [23, 47, 48]. The low- and high-voltage electrocortical activity in the fetus correspond in the newborn to active (AS) and quiet sleep (QS), respectively, and are considered as precursors of infant and adult REM and non-REM sleep. During the first postnatal year, there is a progressive increase in the proportion of time spent in AS and wakefulness, with a decrease in the proportion of time spend in QS [23, 49, 50].

Additional insight into mechanisms underlying ventilatory pattern instability during infancy can be derived from the concept of loop gain (LG), a dimensionless number that describes the stability of the respiratory control system [51]. When LG is low, respiratory control is stable and rapidly returns to a stable condition after a perturbation such as a sigh or movement. High LG indicates a tendency for breathing to become unstable and oscillate when the respiratory control system is perturbed. Calculation of LG from the ventilatory response to spontaneous sigh, in sleeping (QS) infants over the first 6 months of life, revealed low LG in 1–2 days after birth (stable), steadily increasing LG until ~4 weeks of age (increasing instability), followed by gradual fall in LG to a more stable level by 6 months of age (late postnatal stabilization) [51, 52]. Analysis of the components that comprise LG strongly indicated that early postnatal ventilatory pattern instability and subsequent stabilization reflect, in large part, maturation of peripheral chemoreceptor responses [51].

The contribution of the peripheral chemoreceptors to resting normoxic ventilation can be determined by suddenly exposing infants to hyperoxia while measuring the immediate response of minute ventilation within 15–30 seconds (the "hyperoxic test"). The sudden rise in PaO_2 silences the peripheral chemoreceptors, leading to sudden withdrawal of their input; the resulting drop in minute ventilation reflects the proportion of resting drive from the peripheral chemoreceptors. Using this approach, the contribution of the peripheral chemoreceptors to normoxic resting ventilatory drive in full-term infants during QS was found to be ~6% at 24 hours, ~25% at 10 days, ~40% at 10 weeks, and ~50% at 6 months [53, 54]. This remarkable developmental increase in peripheral chemoreceptor drive during the first 6 months of life is believed to be responsible, in large part, for the changes in LG noted above and the high degree of ventilatory pattern instability observed during infancy [51].

When LG is high, any disturbance affecting breathing (such as a sigh or body movement), will likely trigger periodic oscillations of ventilatory drive. Whether the respiratory control system oscillates with or without periodic apnea (periodic breathing) depends on the arterial PCO_2 and whether it dips below the apneic threshold as ventilatory drive oscillates [55]. A recent study using respiratory inductance plethysmography to record breathing in sleeping (QS) preterm infants at 36 weeks post-menstrual age confirmed that LG, determined from the ventilatory response to spontaneous sighs, strongly correlated with the percentage of periodic breathing [56]. This finding further unifies postnatal developmental changes in LG with numerous studies showing a low incidence of periodic breathing in the first days of life, an increase in periodicity until about 4 weeks of age, and a decline thereafter [57, 58]. A full discussion of LG and ventilatory pattern maturation are beyond the scope of this chapter. The reader is referred to a recent in-depth review of the numerous complex factors influencing ventilatory stability during infant development [51].

Regulation of Breathing in Neonates in Relation to Sleep, Chemoreflex Drives

Normoxic Breathing Pattern in Neonates in Relation to Sleep States

In newborns, it is generally accepted that minute ventilation is higher during AS, due to a higher respiratory frequency [59], and this contributes to a greater variability of arterial oxygen saturation [50] and of $PaCO_2$. Although apnea and periodic breathing are present in both AS and QS, their prevalence is higher in AS than in QS [60–62]. The frequency and duration of these apneic events are typically inversely proportional to the gestational age [49, 52, 63–65] and progressively decrease during the first year of life in either preterm or term infant [59, 62]. In preterm neonates, immaturity of the respiratory control system and exaggerated laryngeal chemoreflexes [66] greatly contribute to increase the frequency of apneas. Progressive development of these elements toward a mature phenotype contributes to a gradual reduction in apnea frequency [67] that becomes comparable to full-term infants near 1 month of corrected gestational age (44–46 weeks) [62, 68]. Interestingly, respiratory recordings performed in rats at 1, 4, 7, 12, 21, and 90 postnatal days illustrate this developmental sequence and the progressive establishment of a regular breathing pattern at rest, associated with a decreased apnea frequency [66, 67] (Fig. 2.4).

Hypoxic Ventilatory Responses (HVR) in Neonates in Relation to Sleep State

This response has been characterized in different mammalian species including in preterm and term human neonates [69–74]. The main feature of the hypoxic ventilatory responses (HVR) at this stage is its biphasic pattern, with an initial increase in ventilation, followed by a "roll-off" or inhibitory phase. During this inhibition, minute ventilation may decrease below the baseline normoxic level; the magnitude of this inhibition gradually decreases with age; see example from developing rats (Fig. 2.5). It is now under-

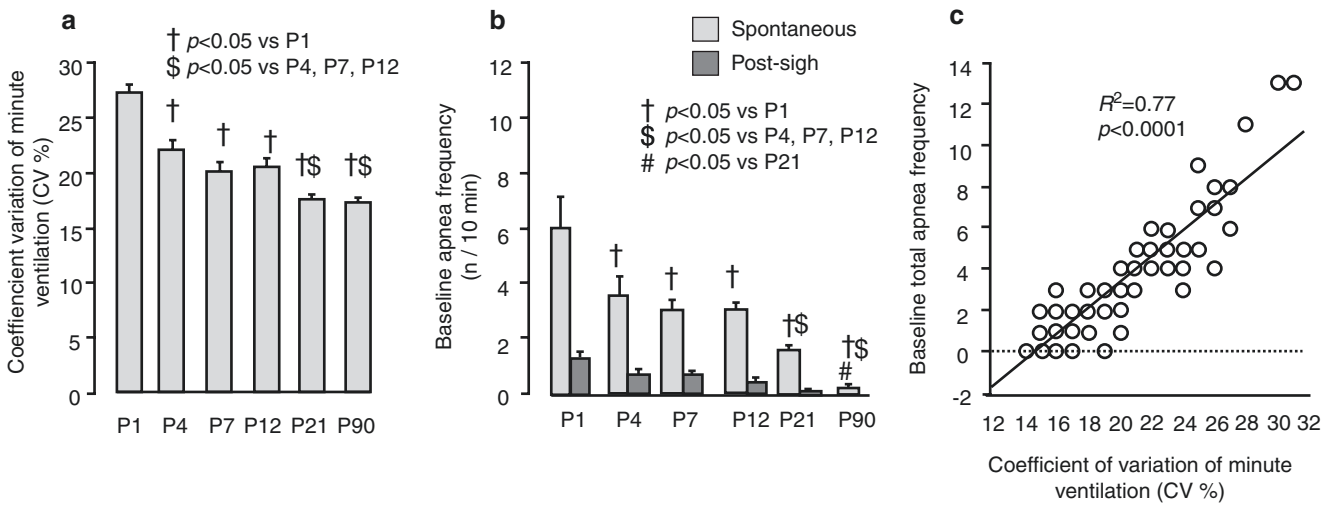

Fig. 2.4 Maturation of respiratory control in male rats between postnatal days 1 and 90 (P1–P90) illustrated by stabilization of the breathing pattern. (**a**) The coefficient of variation of minute ventilation (%) illustrates the variability of individual breaths around the mean for each rat. (**b**) Frequency of spontaneous or post-sigh apneas recorded at rest. (**c**) Positive correlation between the coefficient of variation and apnea frequency. (From Niane and Bairam [123], DOI: https://doi.org/10.4236/ojmip.2011.11001; and from Niane and Bairam [66]. Reprinted with permission from Springer Nature)

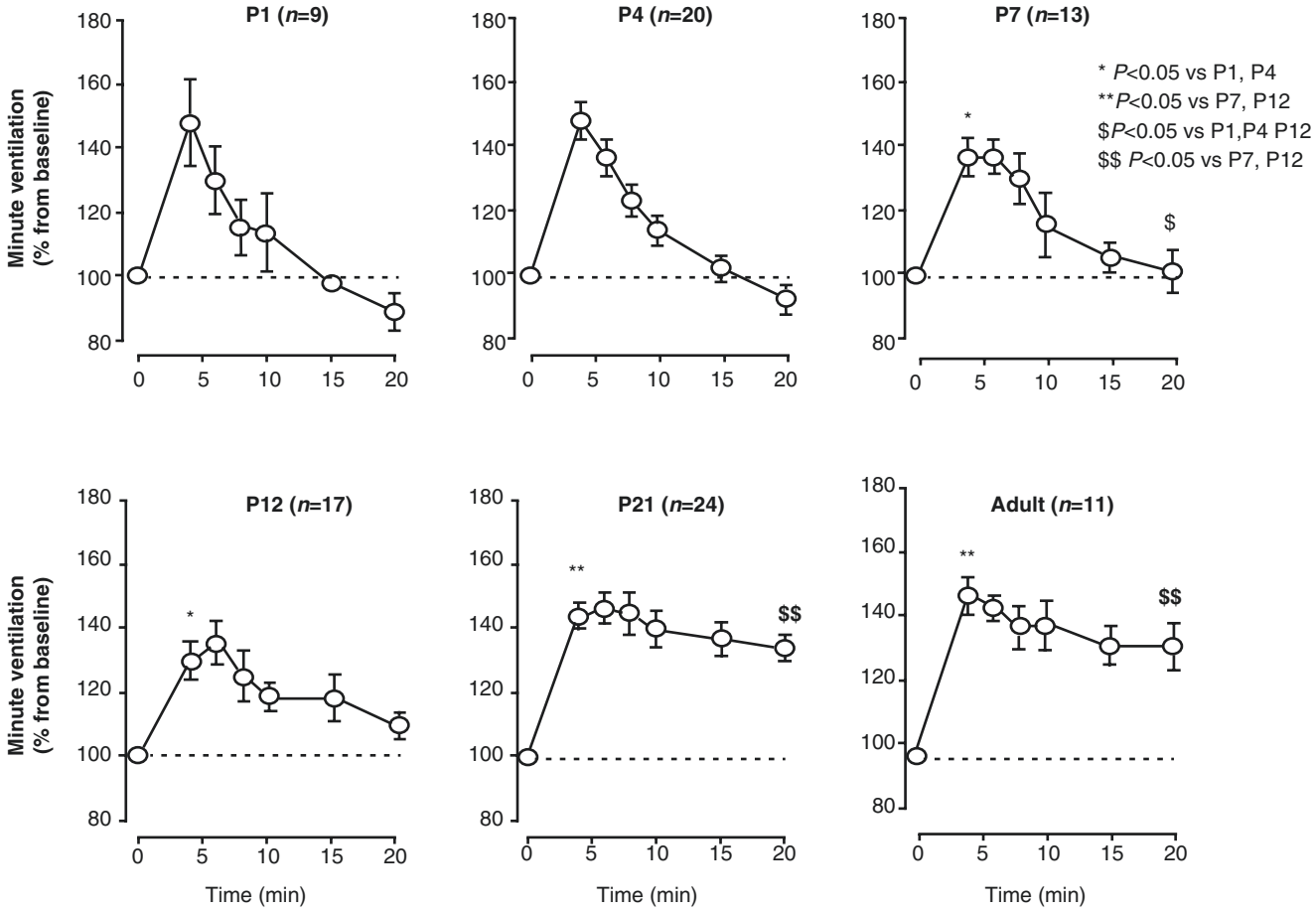

Fig. 2.5 Maturation of hypoxic ventilatory response in male rats between postnatal days 1 and 90 (P1–P90). Minute ventilation in response to moderate hypoxia (FiO_2 = 12%, 20 minutes) as percentage change from the baseline. Data are means ± SEM. Number of animal (*n*) indicated for each age group. (From Niane and Bairam [123]. DOI: https://doi.org/10.4236/ojmip.2011.11001)

stood that the initial phase of increase in ventilation results from stimulation of peripheral chemoreceptors (primarily located in the carotid bodies), while the late depressive phase is mediated by central inhibitory pathways under the control of mechanisms overriding the excitatory inputs from peripheral chemoreceptors (changes in metabolism, in cerebral circulation, and in inhibitory/excitatory neurotransmitters; Figs. 2.3c and 2.5) [72–75].

In relation to sleep state, studies in preterm and term infants showed that this biphasic response is present in both AS and QS [60] and persists until at least 6 months of age in infants born at term [76]. In humans, the sleep state did not affect the magnitude of the HVR [76, 77], but in lambs, ventilation during the late phase of a hypoxic test was higher in QS than AS [78], illustrating possible inter-species effects.

One study found that in infants born at term and that were followed at the age of 2–5 weeks, 2–3 months, and 5–6 months, hypoxic exposures during AS are systematically associated with arousal [76], while this occurs only in half of the infants during QS [76]. Arousal was related to a faster and deeper decrease in arterial oxygen saturation, suggesting that this awakening during hypoxia is a protective mechanism against further desaturation. Furthermore, during QS, and for the exposures that did not induce an arousal, the HVR was clearly following a maturational course that was not fully completed by 6 months of age since the older infants did not demonstrated a sustained HVR throughout the hypoxic exposure (15% O_2—5 minutes). This leads to the suggestion that significant development of the HVR occurs in QS [76], and that this developmental course is somehow masked during QS sleep. These developmental changes in the pattern of the hypoxic response with age are related to maturation of O_2-sensing mechanisms and establishment of functional synapses in peripheral chemoreceptors [73–75, 79–81], to a reduced central inhibitory mechanism, and to development of excitatory pathways during hypoxia [72, 74, 75, 82].

Hypercapnic Ventilatory Response (HcVR) in Neonates in Relation to Sleep State

Under normoxic conditions, ventilation is largely dictated by arterial PCO_2, which is sensed mainly centrally within the brainstem. Nonetheless, the contribution of the peripheral chemoreceptors to hypercapnic ventilatory response (HcVR) is estimated to be around 20–40% depending on the species studied [17, 82]. Although CO_2 responsiveness in term infants is nearly mature at birth [53, 83], it increases progressively after birth in preterm neonates [69, 83]. In newborn animal models, the response to hypercapnia undergoes maturational changes during the first 2 weeks of life, and this maturation involves both the central (brainstem) and peripheral (carotid body) sites [17, 75, 82, 84, 85]. Furthermore, an additive and/or synergistic interaction between hypoxia and hypercapnia is also age-dependent in human [53] and animal [17, 85] during the postnatal development. However, a particularity in response to hypercapnia in preterm is that CO_2 administered during periodic breathing increases minute ventilation and the respiratory frequency. Contrastingly, if administered during a regular breathing pattern, CO_2 increases tidal volume [61]. In addition, these responses were not affected by sleep state. The changes in CO_2 response with age involve cellular, molecular, and genetic modifications, as well as modifications in neurotransmitter patterns in a site-dependent manner [17, 69, 75, 80, 81].

Alteration of Ventilatory Chemoreflexes in Neonates by Chronic Intermittent Hypoxia

The succession of hypoxemic events associated with apneas and periodic breathing exposes the newborn infants to chronic intermittent hypoxia. It is increasingly recognized that apneic preterm infants have quantitative and qualitative impairments of the peripheral and central ventilatory control system that, in turn, favor further development of respiratory instabilities. Compared to non-apneic, apneic neonates have lower basal arterial oxygen saturation [86], lower ventilation, and higher breathing irregularities [45, 87–89]; a weak response to hypercapnia under normoxic [88, 90–92] or hypoxic conditions [1, 17]; and, alterations of the initial phase of the ventilatory response to hypoxia or hyperoxia [87, 88, 90, 93]. The mechanisms underlying these effects are related to an immature response to O_2–CO_2 interaction and to an elevated peripheral chemosensitivity to hypoxia [87, 88, 93]. The elevated peripheral chemosensitivity might further destabilize breathing by driving arterial PCO_2 below the apneic threshold in response to transient (and small) hypoxemic/hypercapnic events [70, 87, 88, 93, 94]. Altogether this participates in maintaining and increasing respiratory irregularities [45].

Similar to what is observed in preterm neonates, exposure to intermittent hypoxia in newborn rats enhances the carotid body chemosensory activity in response to hypoxia [95, 96] with greater magnitude than that observed in adult rats [97]. Exposure to intermittent hypoxia also decreases normoxic ventilation, increases the frequency of apnea [98, 99], and enhances the initial increase in ventilation in response to hypoxia [95, 99], while it reduces the late phase [99] and disrupts the ventilatory and chemoreceptor responses to O_2–CO_2 interactions [100]. Peripheral and central inflammatory reactions and production of reactive oxygen species in the central and peripheral nervous system have been proposed to mediate some effects of intermittent hypoxia on the breathing control system [101–104].

Sex and Control of Breathing at Neonatal Ages

The effect of sex in respiratory control before puberty and in neonates has not been adequately investigated, yet some data highlight, either directly or indirectly, its importance. The best example is that males are at higher risk for respiratory distress syndrome and sudden infant death syndrome [105], in which protective respiratory chemoreflexes are thought to be impaired. Suffocation accidents are also more often fatal in males than in females [106], and, finally, male neonates also develop more bronchopulmonary dysplasia and are less resistant to hypoxemic/ischemic cerebral injuries than females [107]. In a recent study, it has been found that treatment with caffeine for apnea in preterm infants is maintained for longer period in males than in females, indirectly suggesting a faster maturation of respiratory control in females than in males [108]. In this line of reasoning, experimental studies in newborn rats showed that males have more variabilities in respiratory frequency, tidal volume, and higher apnea frequency [41, 109]. Our understanding of such heterogeneity between males and females remains limited but some recent reviews discussed eventual underlying mechanisms [42, 109].

Respiratory Control in Older Children and Effects of Sleep State

Although respiratory control has been well studied in preterm and term infants, there are only a few studies in older children and very few that span the entire age range of childhood. There are even fewer studies that have examined the effects of sleep per se on respiratory control in older children and adolescents. In the following paragraphs, we describe normal ventilation and ventilatory responses to O_2 and CO_2 in older children. We do not address normal upper airway motor control or hypoxia and hypercapnia as stimuli for arousal from sleep, as these topics are addressed in Chaps. 4 and 36, respectively.

Respiratory Rate, Tidal Volume, and Minute Ventilation: Effects of Age and Sleep

Respiratory rate (RR) is highest during the newborn period and, in general, decreases with age during the first year of life [110] as breathing becomes more regular by about 8 months of age and the difference in RR between REM and non-REM sleep narrows [111]. A recent multicenter study of 209 healthy children ranging in age from 1 to 18 years confirmed that RR in quiet sleep is highest in infants and steadily

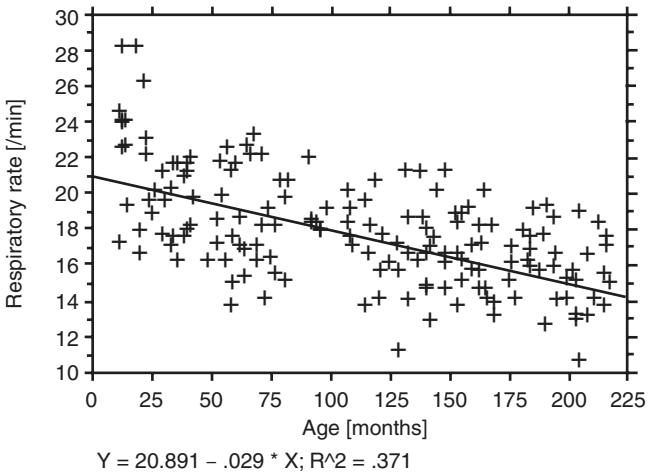

Fig. 2.6 Postnatal changes in respiratory rate during non-REM sleep. (From Scholle et al. [112]. Reprinted with permission from Elsevier)

decreases across the entire age spectrum [112] (Fig. 2.6). Specifically, RR in year 1 averaged ~22 breaths/min and by age mid-late adolescence average RR was ~15 breaths/min with a steady decrease over the age spectrum [112]. Interestingly, the variation in normal RR during quiet sleep was large, such that there was significant overlap in normal RR for 1- vs 18-year-old healthy subjects (Fig. 2.6). In normal, healthy adolescents, RR was highest during wakefulness, significantly decreased during stage 2 and 4 non-REM sleep, and intermediate in REM sleep [113]. Similarly, minute ventilation was highest during wakefulness, decreased about 8% during stage 2 and 4 non-REM sleep, and was intermediate in REM sleep. These changes in minute ventilation were entirely due to sleep-related changes in RR, as tidal volume (V_T) did not vary at all with sleep state [113]. As expected, the variability (coefficient of variation) for minute ventilation, V_T, and RR were all significantly higher during wakefulness and REM sleep compared to non-REM sleep in normal adolescents [113].

In the same study of normal adolescents, as RR slowed during non-REM sleep, inspiratory time (T_I) increased 25%, expiratory time (T_E) did not change, and T_I/T_{tot} did not change [113]. The increase in T_I in non-REM sleep, with no associated changes in V_T, resulted in a non-REM sleep-related 20% decrease in V_T/T_I (ml/s, mean inspiratory flow). In contrast to normal infants, which exhibit paradoxical inward rib cage motion (PIRCM) during REM sleep, PIRCM was not observed in any of the normal, healthy adolescents during REM sleep [113]. In a similar study of otherwise healthy adolescents diagnosed with moderate–severe asthma, paradoxical inward rib cage motion was observed during REM sleep in every subject, indicating that asthma alone can cause REM-sleep-related PIRCM in otherwise normal adolescents [114].

Ventilatory Response to Hypoxia and Hypercapnia: Effects of Age and Sleep

Beyond the first year of life, there are very few studies of ventilatory control in childhood and only one study spans the age range across the pediatric and adult age range. Hypoxic and hypercapnic ventilatory responses were studied in 59 healthy subjects ranging in age from 4 to 49 years [115]. Hypercapnic ventilatory responses (HcVR) were measured with a hyperoxic rebreathing method as described by Read [116] and hypoxic ventilatory responses (HVR) were measured using an isocapnic rebreathing method of Rebuck and Campbell [117]. Due to the very wide age and size range of the subjects, results were normalized by body weight [115]. The slope of the HcVR (normalized to weight) was highest in the youngest children, decreased with age until ~ age 10–15 years, and did not change thereafter. Similarly, the slope of the HVR (normalized to body weight) was greatest in the youngest children, decreased until ~ age 10 years, and remained unchanged thereafter in adults up to 49 years of age [115]. Although there is no consensus on the best approach to normalizing ventilatory response data, it is important to note that weight-normalized HVR and HcVR did not change between ~ ages 10 and 49 years, even though weight in a normal child nearly doubles between age 10 and 18. Another study of children 7–18 years of age found that the normalized (to body weight, surface area, or lean body mass) ventilatory response to CO_2 was highest in the youngest children, declined rapidly from age 7–8 to age 11–12, and then stabilized to age 18 [118]. However, the same study did not find differences in the hypoxic ventilatory responses of children from 7 to 18 years of age.

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Normal Respiratory Physiology During Wakefulness and Sleep in Children

3

John L. Carroll and Aida Bairam

Introduction

The thorax and respiratory muscles function together in a highly complex manner as the "respiratory pump" or "ventilatory pump." The obvious mechanical function of the respiratory pump is to generate the necessary pressures to expand the chest, inhale air, and fill the lungs for gas exchange at the alveolar-capillary interface [1]. The lungs, ribs, muscles, and other tissues exhibit mechanical properties including ability to stretch, resistance to movement, and tendency to recoil when stretched. Similarly, the intrathoracic airways can be characterized by their mechanical properties such as resistance to airflow, types of airflow such as smooth or turbulent, and pressures required to move air through large and small branching tubes in sufficient bulk to accomplish adequate gas exchange. These mechanical properties of the respiratory system determine the complex relationships between lung volumes, airway flows, and pressures generated by muscular effort [1]. The muscles that drive the respiratory pump are controlled by complex neural networks, which are in turn modulated to varying degrees by wakefulness, rapid eye movement (REM) sleep, nonrapid eye movement (NREM) sleep, arousal, and behavior.

Although practitioners of Sleep Medicine and the research literature tend to focus heavily on sleep and respiratory control, it is also important to understand how each component of the "respiratory pump," their complex interactions, and resulting respiratory system mechanics contribute to normal breathing and how these components are affected by sleep states. These aspects of normal respiratory physiology are highlighted in this chapter, with a focus on those most relevant to Pediatric Sleep Medicine. This chapter does not address normal respiratory control or upper airway function in depth, as these are covered in Chaps. 2 and 4, respectively.

As body size in humans increases approximately 20-fold between birth and early adulthood, all components of the respiratory pump undergo profound developmental, physiological and structural maturation. Maturation of the neural networks controlling respiratory pump components adds additional layers of complexity as the effects of sleep on respiratory pump function vary with age, especially during infancy.

Unfortunately, large knowledge gaps in the research literature covering this area make it difficult to characterize developmental changes in the effects of sleep on pulmonary mechanics. Although many studies exploring respiratory pump function in children have been performed *during* sleep, far fewer studies have examined the effects of sleep per se on pulmonary mechanics. Another difficulty involves the characterization of respiratory pump function over the entire childhood age range; most studies have been performed in term and preterm infants (birth to 1 year) with far fewer in older children and very few studies have characterized the effects of sleep on respiratory mechanics across the entire pediatric age range. Finally, the methods used in studies of sleep and respiratory mechanics vary between studies and have changed over time.

Lung Volumes

An understanding of standard lung volumes is important for understanding how sleep, respiratory muscle function, and development affect respiratory system mechanics. As illustrated in Fig. 3.1, traditional lung volumes include the volume of a single breath or tidal volume, the volume of gas left in the chest after maximum expiration, known as residual volume, and the inspiratory and expiratory reserve volumes (Fig. 3.1) [2]. Capacities are the sum of two or more volumes. All volumes and capacities shown in Fig. 3.1 are

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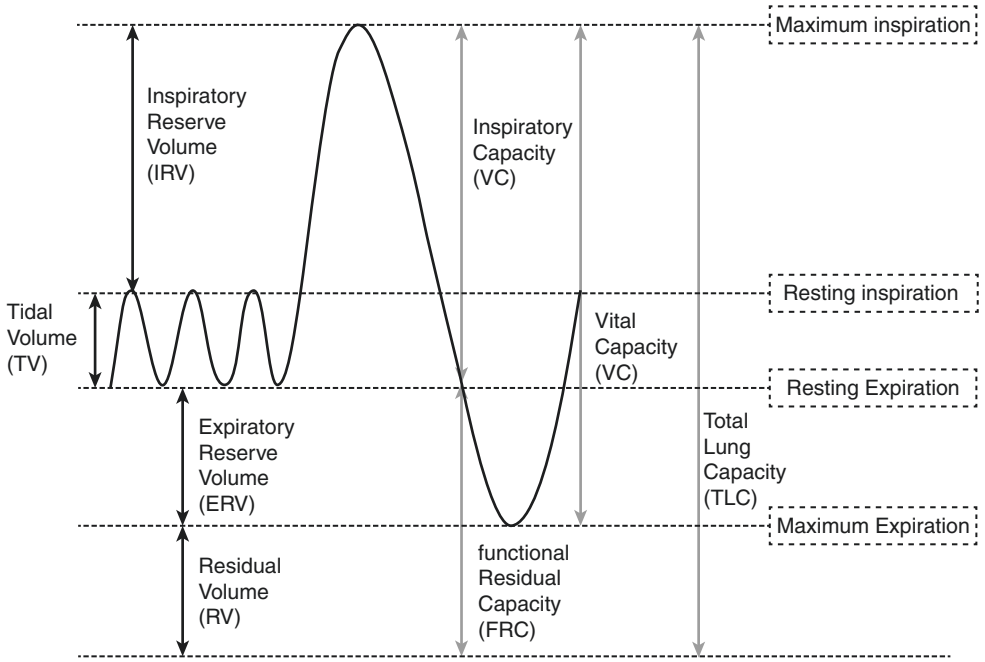

Fig. 3.1 Standard lung capacities and volumes. Black bars denote volumes. Gray bars denote capacities. (From Lutfi MF [2]. Open Access, Springer Nature)

determined by interactions of respiratory muscle strength, lung and chest wall compliance, upper and lower airway airflow, and respiratory control centers. Two of the pulmonary capacities shown in Fig. 3.1, tidal volume and functional residual capacity (FRC), are dynamically determined breath-to-breath and subject to modulation by behavior and sleep state (Fig. 3.1) as discussed below.

Chest Wall—Developmental Changes

The terms rib cage, thoracic cage, and chest wall all denote the structures surrounding the lungs, comprised of the spine, ribs, clavicles, and sternum and supported inferiorly by the hemidiaphragms and abdominal contents and by intercostal and other respiratory accessory muscles. The hemidiaphragms, intercostal, accessory, and abdominal muscles act in concert to rhythmically inflate the lungs and control the rate of lung deflation. Although the rib cage is often considered a structural component of the respiratory pump, in reality rib cage volume is heavily dependent on muscle function which is under constant neural modulation and therefore subject to modulation by sleep state (see below).

The cross-sectional shape of the rib cage differs in children compared to adults and changes during development. A study of children 1–18 years of age without respiratory disease, using chest radiographs and CT scans, indicated that the cross sectional shape of the chest during the first year of life is nearly circular and becomes more ovoid with age, achieving an adult ovoid shape by ~3–5 years of age with no change thereafter (Figs. 3.2 and 3.3) [3]. In addition, in the first months of life the dome of the left hemidiaphragm is at vertebral level ~T8, descends to ~T11 by age 3 years and

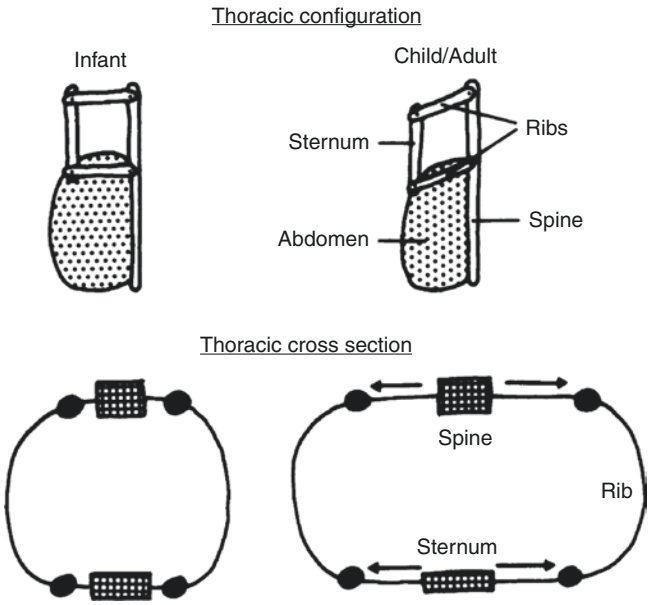

Fig. 3.2 Age-related changes in thoracic cage configuration and cross-sectional shape from infancy to childhood. Upper panel: Ribs in infants are relatively horizontal, without much potential for chest expansion by raising anterior rib cage. In older children and adults, ribs are down sloping, such that raising the anterior ribs expands chest volume. Lower panel: In infants, the cross-sectional shape of the chest is circular. With age, the chest becomes more ovoid. (From Openshaw P, et al. [3]. Reprinted with permission from BMJ Publishing Group Ltd.)

does not change thereafter [3]. The right hemidiaphragm is about a half vertebral space higher than the left at all ages. The ribs become more down-sloping, mainly by ~3 years of age (Figs. 3.2, upper panel). These are important changes that potentially affect gas exchange, work of breathing, and the ability of infants to increase chest volume under stress.

In older children and adults, contraction of the diaphragm normally lifts the anterior ribs to expand the chest. If the ribs are already horizontal, as they are during the first year, the ability to expand the chest by raising the anterior ribs is limited and diaphragm function is inefficient. Contraction of the hemidiaphragms with nearly horizontal ribs in infants results in increased distortion of the highly compliant infant rib cage instead of efficient chest volume expansion [4]. The combination of these factors, especially during the first few months of life as explained later in this chapter, results in less force output from the diaphragm, reduced expansion of the rib cage, and reduced air movement at a given level of neural ventilatory drive, compared to older children and adults [4].

The diaphragm, the major muscle of inspiration in mammals, is controlled by premotor neurons in the medulla, which output to phrenic motoneurons in the cervical spinal cord (C3–C6). Although the diaphragm muscle in mammals is active in the fetus and developed enough to sustain air breathing at birth, it is far from mature in newborns. All aspects related to diaphragm muscle structure and function, including composition of muscle fiber types, motoneuron properties and size, neuromuscular junction specialization, innervation ratios, and premotor control undergo normal pre- and postnatal maturation [5]. Several excellent reviews describe pre- and postnatal maturation of diaphragm motor units, endurance properties of the diaphragm, contractile properties and structure, respiratory accessory muscles, and other features beyond the scope of this chapter [4, 5].

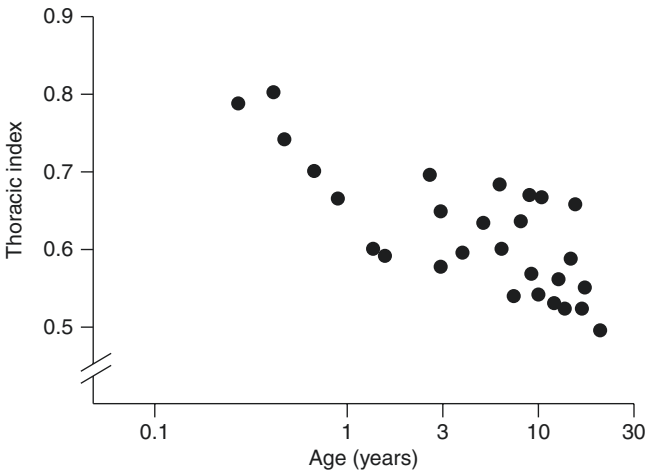

Fig. 3.3 Thoracic index (ratio of anteroposterior to lateral thoracic dimension) versus age. Lower index denotes more ovoid chest shape. No significant change after 5 years of age. Each point represents measurements of one subject. (From Openshaw P, et al. [3]. Reprinted with permission from BMJ Publishing Group Ltd.)

Lung and Respiratory System Compliance—Developmental Changes

For any elastic, expandable structure, compliance is defined as the change in volume produced by a given change in pressure and it can be measured for the lungs, the chest wall, or the lungs and chest wall together (total respiratory system compliance). For an expandable structure such as a balloon, the pressure–volume relationship is nonlinear; the balloon is easy to inflate initially but as it becomes more distended, more pressure is required to achieve a given increase in volume. The lungs have a similar, nonlinear pressure–volume relationship (Fig. 3.4, dashed line). The chest wall also has

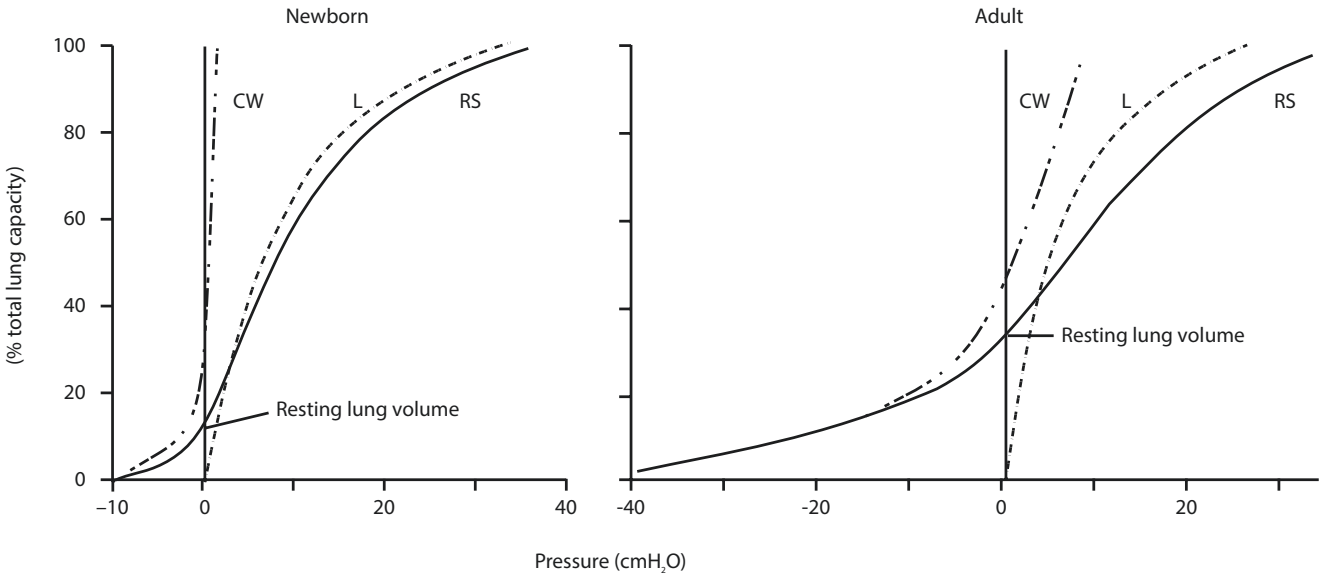

Fig. 3.4 Pressure–volume curves of the respiratory system. CW chest wall (dash-dotted line), L = lung (dotted line) and RS = respiratory system (L and CW combined, solid line). The chest wall exhibits high compliance in infancy while lung compliance varies little with age. (From Agostoni E, Mead J [7]. Reprinted with permission from Elsevier)

its own pressure–volume relationship (Fig. 3.4, dot-dashed line). The compliance of the respiratory system reflects the pressure–volume relationship of the lungs and chest wall combined (Fig. 3.4, solid line).

The lungs are stretched when expanded with air and tend to recoil inward due to their elastic properties. In contrast, the chest wall exhibits outward recoil due to its structure and elasticity; in the intact chest at rest, the chest wall is pulled inward by the elastic recoil of the lungs. When the outward recoil force of the chest wall is equal to the inward recoil of the lungs, the resulting resting lung volume (V_r), sometimes referred to as passive functional residual capacity (FRC) or elastic equilibrium volume [6], is determined entirely by passive respiratory system recoil properties.

As shown in Fig. 3.4, the passive resting lung volume is lower in the newborn compared to the adult, due to developmental differences in chest wall compliance [7]. Lung compliance, when adjusted for body size, changes very little with age [8]. The pressure–volume curve for the lungs is about the same in the newborn versus adult (Fig. 3.4, dashed line). In sharp contrast, the chest wall is much more compliant in newborns (Fig. 3.4, dash-dotted line), which means that it is less stiff structurally, elastic recoil is less and the soft, compliant chest wall can be distorted much more easily (i.e., retractions). Due to the lower outward elastic recoil of the newborn's chest wall, the point at which outward chest wall recoil is balanced by inward lung recoil occurs at a lower volume (Fig. 3.4, left panel). Given that the lungs are a major oxygen reservoir and metabolic rate (and therefore O_2 consumption) is relatively higher in infants, low lung resting volumes increase the probability of O_2 desaturation and may contribute to atelectasis [9, 10].

Numerous studies have examined the effects of age on lung, chest wall, and respiratory system compliance. Specific lung compliance at FRC (ml/cm H_2O/L-FRC) is about the same in an infant and an adult [11] and the relationships between lung volume and FRC or vital capacity were found to be remarkably constant across the age range from newborn to 15 years in healthy children (~0.057 ml/cm H_2O/ml FRC and ~0.035 ml/cm H_2O/ml VC, respectively) [12]. Compared to older children and adults, chest wall compliance is high in full-term infants and even higher in preterm infants. As result, chest wall collapsibility (instability) is high in preterm infants ~29 weeks postconceptional age (PCA) and mechanical chest wall stability steadily improves between 29 and 36 weeks PCA [13].

Lung or respiratory system compliance measurements made during continued breathing in the presence of airflow are termed "dynamic compliance." Compliance measured when breathing is paused, in the absence of airflow, is termed "static compliance." Static chest wall compliance was reported to be ~3 times greater than static lung compliance in 31–34 week healthy preterm infants 2–3 weeks of age [14]. In preterm infants, chest wall compliance correlates with the degree of prematurity, being highest (least stiff, most deformable) in the most preterm infants and decreasing with age (Fig. 3.5) [15]. A study of passive chest wall compliance in healthy children 2 weeks to 5 years of age also found that chest wall compliance was ~3 times higher than lung compliance in infants, but by approximately 2 years of age, stiffness of the chest wall had increased such that chest wall compliance equaled lung compliance, as in adulthood [16]. Total respiratory system compliance (combined lung and chest wall compliance) adjusted for body size (lung volume at FRC) was reported to decrease with age across the age range from ~2 to 18 years, likely due to gradually decreasing chest wall compliance given that lung compliance changes little with age [17].

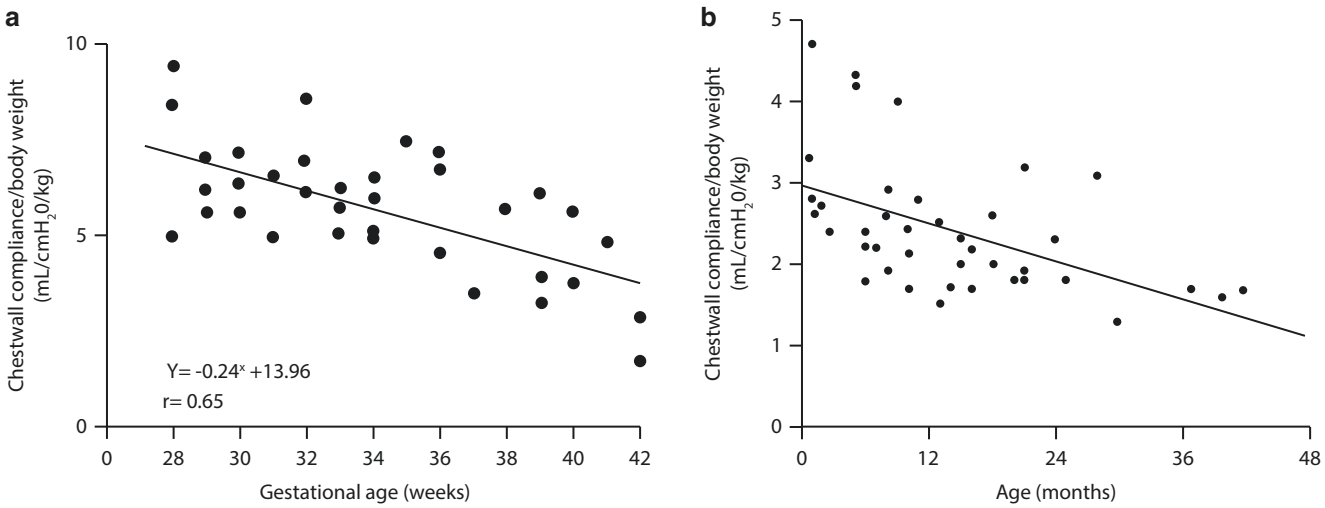

Fig. 3.5 Relationship of chest wall compliance (scaled to weight) versus gestational age. Each point represents one infant. (**a**: Data from Gerhardt T and Bancalari E [15]). (**b**: Data from Papastamelos C, et al. [16])

Importance of FRC

There are numerous important implications of the highly compliant, easily deformable chest wall in infants. A substantial (and variable) proportion of respiratory muscle energy is spent in stabilizing the chest wall instead of expanding the chest [16]. With low resting lung volumes, ventilation and even FRC (see Fig. 3.1) may be in the range of closing volume, increasing the likelihood of atelectasis and worsening ventilation/perfusion matching, both of which lead to hypoxemia [15]. In addition, smaller lung volumes reduce O_2 stores, resulting in a high probability for rapidly developing hypoxemia [18], a potentially important problem for infants, who are likely to have high rates of central apnea. A study of preterm infants ~36.6 weeks postconceptional age, spontaneously breathing on room air, found that the speed of O_2 desaturation correlated with FRC; lower FRC was associated with faster O_2 desaturation during central apnea (Fig. 3.6) [18]. This relationship, more rapid fall in O_2 saturation during apnea at lower lung volumes, holds true for all ages, including adults [19].

Contribution of Rib Cage Versus Abdomen to Tidal Volume—Effect of Sleep

Considering the highly deformable rib cage during the first year of life, it may be anticipated that the contribution of the rib cage to tidal breathing (tidal volume, Fig. 3.1) would be low in the newborn and increase with age. A study of healthy infants and children 1–26 months of age, using respiratory inductance plethysmography during supine quiet sleep, found that the percent contribution of the rib cage to VT generation was ~34% in the first 3 months, increasing to ~60% by 9 months, similar to adults and adolescents during quiet sleep [20]. A similar study of normal, near-term infants found that rib cage contribution to VT was ~34% during NREM sleep but dropped to 22% during REM sleep [21]. In normal adolescents 12–17 years of age, while sleeping supine, the rib cage contribution to VT was ~39% while awake, ~67% during NREM sleep, and ~33% during REM sleep [22]. The reduced contribution of the rib cage to VT during REM sleep was associated with a marked decrease in tonic and phasic intercostal muscle activity [22]. In adults, rib cage contribution to VT was found to be ~44% while awake and during NREM sleep, but decreased markedly to 19% during REM sleep [23]. Thus, across the age spectrum from infants to adulthood, the rib cage contribution to VT during REM sleep is about half of the rib cage contribution to VT during quiet (NREM) sleep. Due to their high chest wall compliance, infants during the first months of life are at high risk for hypoxemia, especially during REM sleep. Increasing chest wall stability (decreasing compliance) over the first year of life reduces the likelihood of low expiratory lung volumes and therefore of hypoxemia events associated with sleep [16].

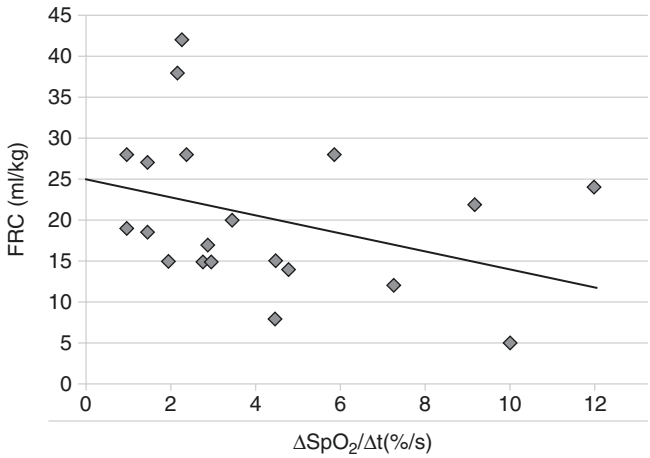

Fig. 3.6 Relationship between rapidity of desaturation and FRC in preterm infants ~30 weeks gestational age at birth, studied at ~36 weeks postconceptional age. Each point represents one infant. (Data from Poets CF, et al. [18])

Dynamic Maintenance of End-Expiratory Lung Volume

Passive resting lung volume (V_r), also termed passive or static FRC, is determined by matched opposing mechanical properties of the lungs and chest wall as discussed above. Infants maintain an end-expiratory lung volume (EELV) higher than the passive (V_r) and inhibition of respiratory muscle tone leads to a reduction in lung volume [23–26]. The term EELV, also termed dynamic FRC, refers to lung volume at end expiration during active breathing and encompasses other factors, beyond passive mechanics, that influence lung volume at the end of a tidal breath. In a study of full-term infants during quiet sleep, EELV was maintained higher than V_r by multiple mechanisms, including the use of upper airway muscles to increase expiratory resistance ("expiratory braking"), post-inspiratory inspiratory activity of the diaphragm (PIIA) to slow expiratory diaphragm relaxation and altering expiratory time relative to the expiratory time constant [27].

The expiratory time constant of the respiratory system reflects the compliance and resistive forces determining the speed of passive expiration. If expiratory time is long enough, passive exhalation to V_r can occur. However, during expiration, if the next breath (inspiration) is initiated before V_r is reached, then EELV remains elevated above V_r. Infants employ a dynamic combination of these mechanisms to keep EELV above the mechanically determined V_r [27–30].

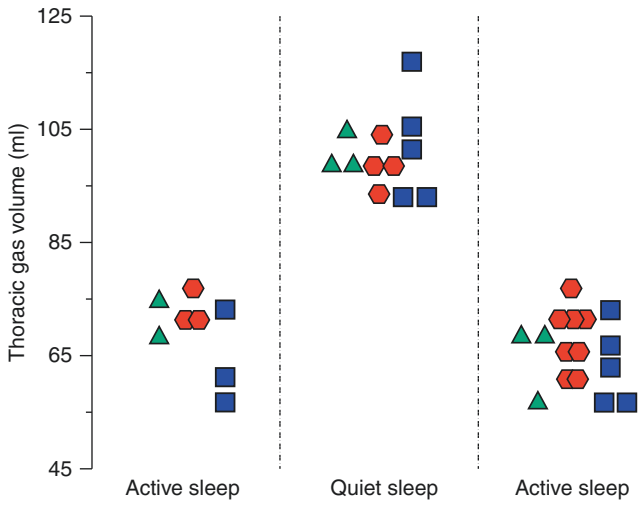

Fig. 3.7 Thoracic gas volume measurements from full-term infants in quiet versus active sleep. Each symbol-shape represents one infant, with 3–10 measurements per infant, per sleep state. (Data from Henderson-Smart DJ and Read DJ [31])

The maintenance of EELV higher than V_r is dependent on sleep state. In healthy full-term infants, end-expiratory lung volume was found to be ~30% higher in quiet sleep compared to active sleep (REM) (Fig. 3.7) [31]. Preterm infants also maintain EELV higher than V_r in a state-dependent manner. A study of healthy preterm infants ~32 weeks gestational age at 2–7 days of life reported that during NREM sleep EELV was maintained higher than V_r through a combination of PIIA (see above) and shortened expiratory time [29]. In sharp contrast, during REM sleep, EELV was similar to V_r due to a longer expiratory time and reduced expiratory laryngeal braking [29].

The benefits of dynamically maintaining EELV above V_r, including increased lung O_2 stores, improved maintenance of SpO_2 and prevention of atelectasis, may all be lost during central apnea. A study of preterm infants, 29 weeks gestational age and 8–21 weeks postnatal age, using intercostal muscle and diaphragm EMG and a measure of EELV (using magnetometers), found that during central apnea EELV decreased, which correlated with decreased tonic activity of the intercostal muscles and diaphragm. The drop in EELV during apnea was greater during NREM sleep, indicating that EELV is better maintained by intercostal muscle activity during NREM compared to REM sleep [26]. Another study of preterm infants (~30 weeks gestational age) studied at ~36 weeks postconceptional age found an ~23% drop in FRC for up to 2 minutes following an apneic pause [18]. Interestingly, sigh breaths restored FRC to pre-apneic values. Multiple studies confirm that lung volume decreases in infants during apneic pauses, indicating that infants can compensate while breathing for their naturally low passive V_r to some degree, although they do so less during REM sleep and during periods of irregular breathing [18, 27, 29, 32].

A large study of EELV during sleep in children aged 1 month to 8 years found that dynamically maintained, elevated EELV was the predominant pattern up to 6 months of age, 6–12 months was a transition period, and by 1 year of age end-expiratory lung volume was relaxed or passive, as in adults [33]. Older children and adults do not significantly maintain EELV above passive resting lung volume.

Paradoxical Inward Rib Cage Motion (PIRCM) During Inspiration

In infants, due to the high compliance of the chest wall, contraction of the diaphragm during inspiration results in chest wall distortion, costal margin retractions, and an overall inward motion of the anterior chest wall that limits expansion and limits the efficiency of inspiration [31, 34, 35]. This breathing pattern, known as "paradoxical inward rib cage motion," during inspiration (AKA "thoracoabdominal asynchrony," AKA informally as "paradoxing") is normal in newborns and during early infancy. The degree of PIRCM is greater in preterm compared to full-term infants.

PIRCM is more likely to occur during REM (active) sleep due to the normal muscle atonia characteristic of REM sleep. PIRCM during REM sleep is normal in full-term infants and is associated with more variable and lower PaO_2 [36]. It is, therefore, important for practitioners of Sleep Medicine to be aware of the developmental time course of normal PIRCM. A study of healthy infants and young children age 7–31 months, sleeping during afternoon naps, reported that sleep-related PIRCM decreased with age, being "absent" or "rare" by 3 years of age [37, 38] and PIRCM does not occur in normal adolescents during REM sleep [22]. Therefore, PIRCM in a child older than ~3 years suggests upper airway obstruction (assuming normal neuromuscular function) as in adults.

Normal Response to Respiratory Mechanical Loading During Sleep

The lungs, chest wall, and airways present volume-elastic and flow-resistive loads for the respiratory muscles during normal breathing. Supralaryngeal resistance increases during sleep in normal adults without significant changes in minute ventilation, tidal volume, or mean inspiratory flow, indicating that dynamic "load compensation" is a feature of normal breathing [39–41]. The elastic and resistive properties of lungs, airways, and chest wall are normal, intrinsic loads that the respiratory muscles must overcome to produce breathing movements. Chest wall and lung compliance provide elastic loads while frictional forces related to gas flow in airways provide flow-resistive loads [42]. "Loading" or "unloading" of the respiratory system refers to any mechani-

cal change that alters the forces that must be overcome by the respiratory muscles to maintain minute ventilation. Responses to altered loads involve changes in respiratory muscle function, timing, and respiratory control. Changes in load can be externally imposed in a variety of ways or imposed by lung, airways, and chest wall disease. Externally imposed resistive or elastic loads can be used experimentally to determine the ability of the respiratory system to compensate for increased loading.

Although many studies of increased respiratory system loading have been performed during sleep, the effects of sleep per se have not been a focus in most and differences in methodologies make it difficult to compare studies. Nonetheless, these studies are relevant given the abnormal loads to the respiratory system imposed by lung disease, neuromuscular, sleep-related breathing disorders, and equipment used to treat sleep and respiratory disorders. Excellent reviews are available summarizing the research literature on this topic [6]. The limited discussion here is intended to highlight key concepts as they may relate to sleep disorders in children.

Resistive Inspiratory Loading—Effect of Sleep

Flow-resistive inspiratory loads are typically imposed by having subjects breathe through a circuit (e.g., using a mask) with addition of resistors (for example, tubing with wire mesh of known resistance) in the inspiratory line. In a study of normal, awake adults, application of external graded inspiratory resistive loads did not significantly change VT, frequency, or minute ventilation in spite of a large drop in inspiratory flow rate [43]. VT was preserved by prolongation of inspiratory time, without an overall change in breathing frequency [43]. In marked contrast, inspiratory resistive loads applied during NREM sleep immediately resulted in a large drop in minute ventilation due to decreased tidal volume, resulting from inadequate prolongation of inspiratory time [43]. Similar results for adults have been reported by other investigators [44–46]. Responses to graded inspiratory resistive loading have been studied in healthy children ~9 years of age during REM and NREM sleep. Added inspiratory resistance during both NREM and REM sleep led to a large decrease in VT and minute ventilation, without a significant change in frequency or inspiratory time. However, the inspiratory time/total breath time ratio (T_i/T_{Tot}) increased due to shortening of expiratory time T_e [47].

The much higher chest wall compliance of full-term and preterm infants suggests that their ability to tolerate or compensate for resistive loads may be reduced compared to older children and adults. Especially in preterm infants, increased respiratory effort may simply lead to more chest wall distortion rather than preservation of tidal volume and minute ventilation. Inspiratory resistive loading was studied during NREM sleep in healthy full-term and preterm infants who did not have clinical evidence of lung disease [48]. Although these infants did not demonstrate visual evidence of paradoxical inward rib cage motion at rest, preterm infants exhibited more thoracoabdominal asynchrony as measured by respiratory impedance plethysmography (RIP) phase angle. In the full-term infants, addition of graded levels of inspiratory resistance did not affect minute ventilation, respiratory frequency, VT, or thoracoabdominal synchrony (RIP phase angle) [48]. In sharp contrast, in preterm infants (~31.6 weeks gestational age studied at ~35.5 weeks postconceptional age) inspiratory resistive loading caused significant reductions in VT, respiratory frequency and a marked reduction in minute ventilation as well as increased thoracoabdominal asynchrony. Although preterm infants may have sufficient respiratory drive to maintain minute ventilation during inspiratory resistive loading, their highly compliant chest wall and associated mechanical inefficiency reduces the ability to compensate [48]. Therapies such as continuous positive airway pressure (CPAP) or proportional assist ventilation (PAV) may achieve their effects in part via reduction in resistive forces (resistive unloading) [49, 50].

Elastic Loading—Effects of Sleep

Elastic work of breathing can be defined as the respiratory muscular work required to overcome elastic lung and chest wall forces during breathing. Respiratory elastic load is increased by lung and chest wall abnormalities such as hyperinflation (any cause), pulmonary fibrosis, cystic fibrosis, kyphoscoliosis, neuromuscular disease, and obesity [51–55]. In addition, some therapies, such as CPAP or PAV, ease work of breathing in patients with lung disease by reducing the elastic work of breathing (elastic unloading) [49, 50, 56].

A typical approach to elastic loading of the respiratory system involves breathing through a circuit such that the subject inspires from a closed volume reservoir (the size of the reservoir determines the magnitude of the elastic load) for one or multiple breaths. During wakefulness in adults, responses to an increased inspiratory elastic load are variable, but in general VT, minute ventilation and mean inspiratory flow (VT/T_i) are preserved and associated with increased neural respiratory drive that compensates for the load [57]. In contrast, sustained inspiratory elastic loading during NREM sleep results in decreased minute ventilation, VT and VT/T_i without compensation indicating that compensatory responses to elastic loading are sleep state-dependent [57].

In a study of full-term infants during quiet sleep, addition (for one breath) of an inspiratory elastic load immediately caused a marked reduction in VT, minute ventilation, and prolongation of T_i, without changing T_e [58]. Elastic loading

(for one breath) during expiration in full-term infants immediately resulted in prolongation of T_e, elevation of EELV, and reduced VT and minute ventilation [30]. A similar study of preterm infants 31 weeks gestational age and 8 days postnatal age found that graded inspiratory elastic loads caused a marked drop in VT and prolongation of T_i that correlated with the magnitude of the elastic load [59].

Full-term and preterm infants exhibit progressive load compensation when inspiratory elastic loading is prolonged for multiple breaths during NREM sleep [35]. Elastic load compensation was more effective in NREM versus REM sleep for both full-term and preterm infants. Increased rib cage distortion during REM sleep limited the infants' ability to compensate for the elastic load, resulting in disorganized, less effective compensatory increases in VT, and respiratory timing [35].

Responses to Respiratory System Loading—Complete Airway Occlusion

The extensive research literature on lung inflation and deflation reflexes, including the well-known Hering–Breuer reflex, is beyond the scope of this chapter. However, some aspects may be relevant here as respiratory cycle timing changes are a component of responses to respiratory system loading. Here we highlight several key points related to timing and mechanical responses to sudden airway occlusion (infinite elastic load) in infants and children.

Pulmonary slowly adapting stretch receptors (SARs) are afferent neural endings innervating the tracheobronchial tree, with fibers in the vagus nerves that provide input to the central respiratory pattern generator networks in the brainstem. The role of these sensory receptors in determining the depth, rate, and timing of each tidal breath was described by Breuer and Hering in 1868 [60]. Lung expansion progressively stimulates SARs, reflexively inhibiting inspiration and promoting expiration [61]. Hering–Breuer (HB) inflation reflexes can be elicited in multiple ways; airway occlusion at the end of expiration prolongs expiratory time, while airway occlusion at end inspiration prolongs inspiratory time. Multiple studies indicate that the HB inflation reflexes are more potent in infants during normal breathing compared to older children and adults [62]. Although HB inflation reflexes can be elicited from unsedated adults, large lung volumes are required (larger than normal tidal volume) [63]. In contrast, numerous studies show that HB reflexes are active during tidal breathing during infancy [30, 58, 60–64].

Total airway occlusion (for one breath) in healthy infants on days 2–3 of life during NREM sleep resulted in a marked increase in T_i without a change in T_e [58]. In same age full-term healthy infants, total expiratory occlusion (one breath) caused almost a doubling of T_e [30]. Full-term infants studied in NREM sleep during the first 3 days and again at 6 weeks of age, measuring T_e prolongation in response to end-inspiratory occlusion found that T_e was approximately doubled during occlusion at both ages, indicating that the newborn reflex response persisted to at least 6 weeks of age [65]. A subsequent study of full-term infants during NREM sleep measured the response to airway occlusion in a group of 30 infants at 4–8 weeks versus 1 year of age [66]. T_e prolongation in response to end-inspiratory airway occlusion was present within the VT range in all infants up to 1 year of age, although the magnitude was decreased in older infants.

In preterm infants, inspiratory airway occlusion has different effects depending on chronological age and gestational age at birth. In a study of preterm infants ~30 weeks gestational age at birth tested between 1 and 14 days postnatal age, when the airway was occluded (for one breath) at end expiration, the T_i of the following breath was increased 53%; the same maneuver in full-term infants prolonged the next inspiration by ~25% [32]. This and other studies suggested that HB inflation was strongest in premature infants [67]. In sharp contrast, other studies found that preterm infants have weak HB inflation reflexes that increase with gestational age. Preterm infants between 28.5 and ~40 weeks gestational age, studied at 2–4 days of age during NREM sleep using the same method (end expiratory airway occlusion), found that T_i was prolonged 44% in full-term infants after airway occlusion, 38% in ~37 weeks GA infants, ~20% in 32 week GA infants, and T_i was not prolonged at all following occlusion in 28.5 week GA infants [68]. Another study using end expiratory airway occlusion (for one breath) in infants 27 weeks gestational age to full term also found that preterm infants exhibited only a small T_i prolongation following inspiratory occlusion during the first week of life but after 14 days postnatal age the magnitude T_i prolongation even in the most immature preterm infants was the same as in term infants [69].

The numerous conflicting results from studies of airway occlusion in preterm infants are likely related to differences in postnatal age at the time of study, sleep state, or other methodological factors. The clearest data on the effect of prematurity derive from studies in which preterm and term infants of known gestational age were studied using identical methods. Taken together, available data suggest that respiratory timing effects of airway occlusion are smallest in the most preterm infants and increase with advancing gestational age (when postnatal age is controlled for). In addition, development of HB reflex activity appears to increase with postnatal age regardless of gestational maturity at birth. Several studies have examined the effects of sleep state per se on HB reflexes in infants with mixed results; in preterm infants prolongation of T_e by end-inspiratory occlusion was greatest during REM sleep [64] whereas in full-term infant's prolongation of T_i by end-expiratory occlusion was greatest during NREM sleep [70].

It is clear from the preceding description that studies using external mechanical loading or total airway occlusion must be interpreted with great caution. Most only studied patients in NREM sleep and very few have examined the effects of sleep per se. In some reports, postnatal age at the time of study was not carefully controlled, which may profoundly affect responses to airway occlusion in preterm infants. Occlusion or external respiratory loads may evoke compensatory effects, may stimulate multiple reflexes simultaneously, face or nasal masks may evoke yet other reflexes, and the negative pressure generated during inspiratory occlusion may stimulate negative pressure reflexes in the upper airway, all of which greatly complicate interpretation [71].

Summary

Practitioners of Pediatric Sleep Medicine may encounter patients of all ages, from infancy to adulthood. Over that time, body size increases 20-fold and all aspects of the respiratory system undergo maturational changes in structure and function while neural respiratory control is also undergoing development. The maturational time course of developing respiratory system components varies for each individual, and clinicians must interpret symptoms, signs, and laboratory data (e.g., from polysomnography) and prescribe respiratory equipment and treatments in the context of this development. Although the clinical diagnosis is often clear and straightforward, sometimes sleep-related respiratory problems do not fit a clear diagnosis or may fit several, overlapping possible diagnoses in a confusing way. The goal of this chapter was to provide a framework for understanding sleep-relevant aspects of normal pulmonary mechanics, how they might affect symptoms and physical findings, and how they change with age and the effects of sleep to the extent known. A better understanding of normal pulmonary mechanics may help the practitioner understand underlying mechanisms for sleep-related respiratory disorders, how respiratory equipment may affect breathing and perhaps aid in the interpretation of atypical findings on polysomnography.

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Upper Airway and Motor Control During Sleep

4

Jean-Paul Praud

Abbreviations

EMG	Electrical muscle activity
GG	Genioglossus muscle
NREM	Nonrapid eye movement
REM	Rapid eye movement
UA	Upper airways

Introduction

As part of the upper aerodigestive tract, the upper airways (UA) are an obligatory passage for breathing and feeding, two vital and competing functions. In order to meet the challenges imposed by these two functions, the complex UA anatomy consists in an array of muscles whose complex motor function is controlled by a number of cranial nerves and brainstem motor centers. A very fine coordination is needed not only between the more than 20 pairs of UA muscles, but also between the UA muscles and the thoracic respiratory muscles. Nutritive and non-nutritive swallowing must allow the transit of bolus through the UA toward the esophageal entrance while preventing lower airway aspiration. UA inspiratory function must direct the inspired air to flow into the larynx and the trachea while maintaining the floppy UA patent and preventing the air from inappropriately entering the esophagus. In the infant, UA expiratory function must often brake the expiratory airflow to maintain a sufficient amount of air into the lungs at end-expiration and continuously ensure an optimal alveolocapillary gas exchange. These few examples highlight the formidable task fulfilled by the UA motor function, which is further complicated in infants by the overall immaturity of the central nervous system controlling UA reflex and motor function.

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Sleep imposes further challenges to the UA, due to its inhibiting effect on UA reflex and motor function. Above all, the consequent increase in compliance of the pharyngeal tube can lead to obstructed sleep-disordered breathing in the presence of risk factors. This chapter briefly reviews the physiology of UA and motor control, providing information on the effect of sleep when available.

Anatomy of the Upper Airways

The UA span from the anterior nares and lips to the upper trachea (Fig. 4.1). They are part of the upper aerodigestive tract, which includes the nose, the pharynx, the lips, the oral cavity with the tongue, the larynx, the cervical esophagus, and the cervical trachea. The nose is an osteocartilaginous structure composed of the nasal passages, which communicate with the external environment via the anterior nares, and open into the pharynx posteriorly via the choanae. The pharynx is a muscular membranous tube comprised of three compartments: rostrocaudally, the nasopharynx extends from the choanae to the palate, the oropharynx extends from the palate to the hyoid bone, and the laryngopharynx (or hypopharynx) is situated inferiorly to the hyoid bone and behind the cricoid cartilage. The hypopharynx continues with the esophageal entrance and the cervical esophagus posteriorly to the larynx and the cervical trachea. The larynx is mainly a cartilaginous, more rigid structure with a cylindrical shape enclosing the vocal cords and situated at the entrance of the cervical trachea. Of note, the narrowest portion of the UA is at the level of the larynx, at the glottis and the cricoid/subcricoid region [1–3].

Finally, the hyoid bone is a U-shaped bone, which is part of the flimsy skeleton of the anterior face of the neck. While the suprahyoid muscles and ligaments suspend the hyoid bone to the skull and mandible, the thyroid cartilage and sternum are attached to the hyoid bone by the infrahyoid muscles and ligaments.

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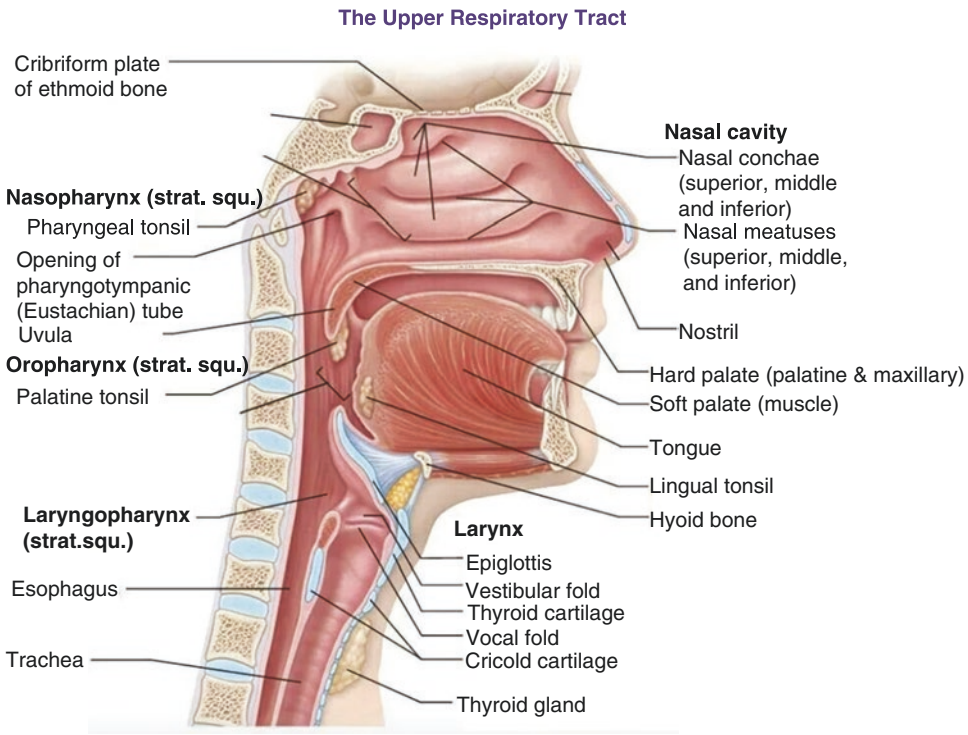

Fig. 4.1 Gross anatomy of the upper aerodigestive tract. (From: https://www.physio-pedia.com/images/e/ed/Upper_respiratory_system_2.jpg)

Maturational Anatomy of the Upper Aerodigestive Tract

Anatomically, a number of differences are present between the infant and adult UA. Besides the relatively larger size of the tongue in the oral cavity, which tends to encroach the pharyngeal lumen dorsally, a major difference in the infant resides in the highly rostral position of the larynx such that the epiglottis and the palate are superimposed. This configuration specific to early life in humans separates the upper aerodigestive tract in two compartments, one for breathing and one for feeding/swallowing. The consequences are at least twofold. On the positive side, this allows newborns and infants to feed and breathe at the same time, with the milk passing laterally to the larynx situated in the center. On a less positive note, this early life anatomy implies that many infants are preferential nose breathers up to at times 1 year of age [4]. Hence, any nasal obstruction (e.g., during a viral cold) can be responsible for respiratory distress in the first months of life. Of note, the relatively large tongue at this age also favors nasal breathing. On the contrary, descent of the larynx relative to the cranial base and the hyoid bone beginning around 6 months of age and believed to be needed for sound production through the oral cavity, allows for easier oral breathing after infancy, as during physical activity.

Innervation of the Upper Airway Muscles

Motor innervation of the more than 20 pairs of muscles surrounding the UA is complex and originates from the brainstem nuclei of cranial nerves V, VII, IX, X, and XII. The alae nasi dilator muscles are innervated by the facial nerve. Muscles of the soft palate are innervated by the pharyngeal plexus of the vagus nerve, with the exception of the tensor veli palatini muscle, which is innervated by the mandibular branch of the trigeminal nerve. The superior, middle, and inferior pharyngeal constrictor muscles are innervated by the pharyngeal plexus of the vagus nerve. Motor innervation also comes from the glossopharyngeal nerve for the stylopharyngeus muscle. All the intrinsic tongue muscles are innervated by the hypoglossal nerve except for the palatoglossal muscle, which is innervated by the vagus nerve. Motor innervation of all intrinsic laryngeal muscles is ensured by branches of the vagus nerve. More specifically, the recurrent laryngeal nerve provides motor innervation for all intrinsic laryngeal muscles but the cricothyroid muscle, which is innervated by the superior laryngeal nerve [5]. Innervation of the extrinsic laryngeal muscles comes from the trigeminal nerve, the facial nerve and the three first cervical nerves for the supra and infrahyoid muscles. Overall, the high number of brainstem centers and cranial nerves involved in breathing and lower airway protection explains the high

complexity of coordinating the action of the muscles of the upper aerodigestive tract between them as well as with the thoracic respiratory muscles. It follows that neural immaturity in the newborn, especially preterm, can be responsible for poor coordination between breathing and lower airway protection functions.

Motor Function of the Upper Airways

Motor Function of the Upper Airway Muscles During Breathing

The majority of the studies on UA motor function have assessed UA muscle electromyographic activity (EMG), most often using intramuscular electrodes. The relative invasiveness of the procedure explains that they have been performed exclusively in adults. The bulk of this section will hence summarize information obtained in adults. When available, the scarce information obtained via surface electrodes in children or infants will be given.

Alae Nasi Dilator Muscles Nasal resistance is responsible for ~50% of total airway resistance. By decreasing nasal resistance, contraction of the alae nasi dilator muscles augments inspiratory flow. Nasal flaring is a frequent sign of respiratory distress in infants, who are preferentially nasal breathers [6]. In adult humans, inspiratory phasic alae nasi dilator muscle EMG is observed during baseline ventilation and increases during hypercapnia [7]. Moreover, alae nasi dilator muscle EMG normally decreases from wakefulness to N2 sleep [8].

In healthy preterm infants, inspiratory alae nasi dilator EMG is three times more frequent in rapid eye movement (REM) than nonrapid eye movement (NREM) sleep (43% vs. 14% of breathing cycles, respectively) during room air breathing; presence of alae nasi dilator EMG leads to a 20% decrease in nasal resistance [9]. Hypercapnia increases alae nasi dilator EMG to similar levels in NREM and REM sleep. In all conditions, the onset of alae nasi dilator EMG precedes that of diaphragm EMG [10].

Palatal Muscles While a preferential site of UA narrowing during NREM sleep is at the level of the soft palate [11, 12], palatal muscle function with regard to respiration is unclear. Contraction of the levator palatini muscle promotes oral breathing. Phasic inspiratory and tonic expiratory levator palatini muscle EMG decrease from wakefulness to NREM sleep [12, 13]. Tensor palatini muscle contraction has unclear and variable respiratory effects, depending on the studies. By stiffening the soft palate, tonic contraction of the tensor palatini muscle might act synergistically to the levator palatini muscle; it has however been also reported to favor nasal breathing. A decrease in levator and tensor palatini muscle EMG has been related to increased upper airway resistance during sleep [14].

Genioglossus The genioglossus muscle (GG) is the main tongue protrudor and the largest muscle of the UA. Due to its easy access and its established role as a pharyngeal dilator, the GG EMG has been extensively studied as a model of UA dilator muscle function. In normal adult humans, phasic inspiratory and tonic expiratory GG EMG have been consistently shown during baseline ventilation, and both are increased in response to hypercapnia [14]. During NREM sleep, both phasic inspiratory and tonic expiratory GG EMG decrease compared to wakefulness, and a further inhibition is present in REM sleep [14, 15].

In normal children, a few studies have confirmed the presence of phasic inspiratory and tonic expiratory GG EMG, which decrease when going from wakefulness to NREM sleep and are further reduced in REM sleep (Fig. 4.2) [16, 17]. In sleeping adolescents without obstructive sleep-disordered breathing, a mild hypercapnic challenge tends to increase phasic inspiratory GG EMG. This increase is similar in obese and lean adolescents, as well as in NREM and REM sleep [18].

All results above were obtained using multimotor unit electrode recording. More recent studies in normal adults using single motor unit recording have yielded further information on the high complexity of GG EMG. Six different motor units can indeed be recorded. They are thought to be related to the efferent messages issued from the various components of the respiratory centers to premotor neurons of the hypoglossal nucleus. These include "inspiratory phasic and inspiratory tonic (the most abundant) units, expiratory phasic and expiratory tonic units, and tonic and other units" [19]. Hypercapnia recruits 33% more units, augments the firing rate of all units, and activates the inspiratory units earlier and for a longer time. Conversely, application of continuous positive airway pressure to reduce UA pressure receptor stimulation decreases the activity of all motor unit types [20]. At the transition from wakefulness to sleep, half of the phasic and tonic inspiratory GG motor units cease to discharge, while expiratory units continue to fire unaltered [21]. Moreover, compared to N2 sleep, phasic and tonic inspiratory GG motor units fire at a higher frequency and for a longer duration in N3 sleep, while the number of units is similar [22]. Furthermore, compared to N2 sleep, inspiratory and expiratory single motor unit GG EMG are reduced in REM sleep, especially in phasic REM; the number of active motor units is decreased, they fire at a lower frequency and for a shorter duration. In addition, single motor unit GG EMG suddenly decreases at hypopnea onset in phasic REM [23].

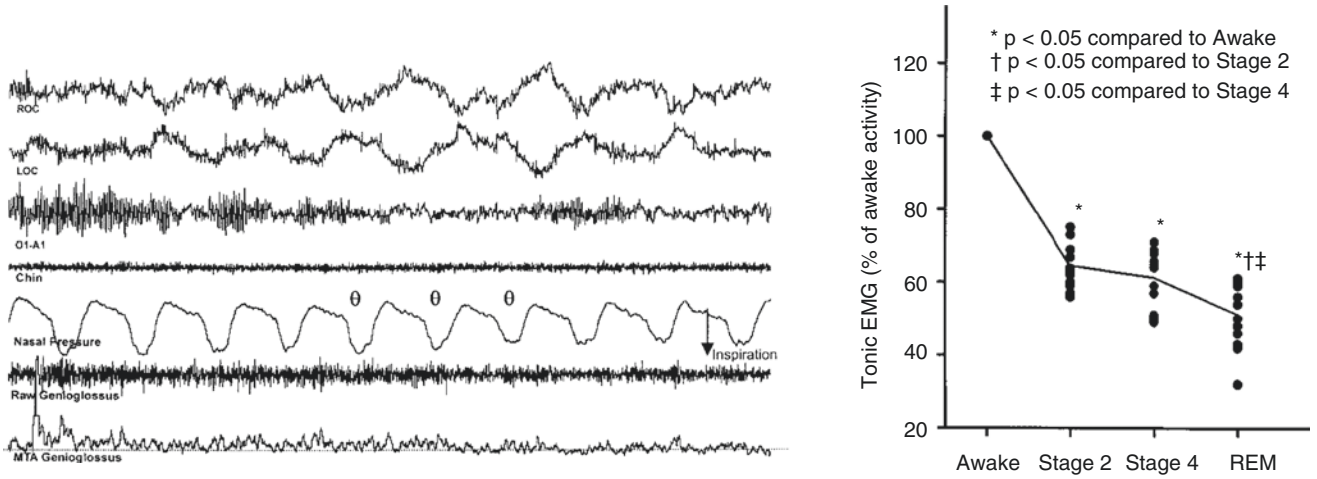

Fig. 4.2 Decrease in genioglossus muscle activity during sleep in children. Left panel: Genioglossus muscle electrical activity decreases at sleep onset (marked by the apparition of the three θ waves) in a normal 8-year-old child. From top to bottom: ROC and LOC: right and left electrooculogram; O1–A1: occipital channel of the electroencephalogram; nasal pressure (inspiration downward); chin: chin muscle electrical activity; raw and moving time average (MTA) electrical activity of the genioglossus muscle. (Adapted with permission from Katz and White [16]. Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society). Right panel: Progressive decrease in tonic electrical activity of the genioglossus muscle from wakefulness to NREM sleep, and from NREM sleep to REM sleep. EMG, electrical muscle activity expressed in percentage of wakefulness activity. (Adapted from Katz and White [17]. Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society)

Using ultrasound, movements of the inferoposterior part of the GG have been studied in normal adults lying supine during wakefulness. Results again underscore the complexity of GG function. Indeed, the GG moves anteriorly with inspiration during resting breathing. Conversely, with inspiratory loading, the anterior displacement of the GG decreases while inferior displacement increases. Finally, decreasing or increasing lung volume via variation of the pressure of an external rigid chamber does not alter GG displacement [24].

Pharyngeal Constrictor Muscles Pharyngeal constrictor muscles do not exhibit any respiratory-related activity during resting ventilation in awake or sleeping adult humans. Phasic expiratory activity is however observed with hyperventilation in response to hypoxia or hypercapnia during wakefulness only [25].

Our group has furthermore observed phasic inferior pharyngeal constrictor EMG in the post-inspiratory phase of the breathing cycle during baseline ventilation in newborn lambs [26]; it has been suggested that such post-inspiratory inferior pharyngeal constrictor EMG helps close the glottis, which is an important strategy in the neonatal period (see below) [27].

Laryngeal Muscles In adult humans, posterior cricoarytenoid muscles display phasic inspiratory EMG to dilate the glottis and facilitate airflow, as well as tonic expiratory activity; both inspiratory and expiratory EMG decrease from wakefulness to N3 sleep [28]. A further decrease in EMG is observed in REM sleep in adult cats [29], but not in dogs [30]. Similar to the other UA dilator muscles, the onset of phasic inspiratory EMG of the posterior cricoarytenoid muscle usually precedes that of the diaphragm [31]. Both hypercapnia and hypoxia increase the inspiratory and expiratory EMG [32].

In the neonatal period, a similar phasic inspiratory and tonic expiratory EMG of the posterior cricoarytenoid muscle is observed in nonsedated sleeping human newborns (no sleep staging) [33], as well as in dog pups [34] and newborn full-term and preterm lambs [35]. However, the inspiratory EMG of the posterior cricoarytenoid muscle does not always begin before diaphragm EMG in the human newborn, especially in the preterm, which may impede inspiration in conditions with hyperventilation [36]. As in adults, phasic inspiratory EMG of the posterior cricoarytenoid muscle increases in response to CO_2 breathing in sleeping preterm and full-term newborns; unexpectedly however, postinspiratory flow braking is increased [37–40].

Phasic respiratory contraction of the glottal constrictor muscles occurs in the postinspiratory phase of the breathing cycle; this is especially important in the neonatal period in order to retard expiratory flow and maintain a dynamic end-expiratory lung volume over the low passive functional residual capacity. The latter is related to the conjunction of a low lung compliance and a high chest wall compliance [41].

Contrary to initially believed, hypoxia does not enhance postinspiratory EMG of the glottal constrictor muscles [42, 43].

Suprahyoid Muscles Finally, phasic inspiratory and tonic expiratory activity of the suprahyoid muscles, especially the geniohyoid muscle, stiffen and increase UA diameter by moving the hyoid bone anteriorly and caudally. While tonic expiratory EMG of the geniohyoid muscle is similarly decreased in NREM and REM sleep, this is not the case for the phasic inspiratory EMG, which is not reduced during sleep in adult humans [14].

Upper Airway Motor Responses to Subatmospheric Intraluminal Airway Pressure

The importance of UA muscle responses to negative (= subatmospheric) airway pressure justifies further expanding on this matter. Despite the collapsibility of the pharyngeal tube, the UA do not close as long as the negative pressure applied to the UA remains above-5 cm H_2O in normal adult individuals. Reflex activation of UA dilator muscles is deemed highly relevant for maintaining UA patency in the presence of negative endoluminal airway pressure. While this neuromuscular response can be observed during tidal breathing in normal humans, it appears to be of crucial importance only when risk factors for UA closure are present. The balance between mechanical loading to the UA and neuromuscular response determines if the UA remain open. Hence, despite an identical decrease in airway size by enlarged tonsils, one child with a strong neuromuscular response can present with normal breathing while another will suffer from obstructive sleep-disordered breathing.

Features of the neuromuscular response to negative airway pressure in normal humans have been extensively reviewed by Horner [44] and will be briefly summarized herein. Various means to decrease airway pressure have been experimentally used, from brief negative pressure pulses to sustained application of negative pressure to the UA. While the response latency of the response to brief pressure pulses is between 30 and 50 ms, a sustained inspiratory partial or complete UA obstruction increases both phasic inspiratory and tonic GG EMG. The strength of UA muscle reflex activation in response to negative UA pressure is highly variable between individuals. Hence, an increase in the EMG of the GG, tensor palatini, levator palatini, and palatoglossus muscles is observed with a negative airway pressure somewhere below −4 to −15 cm H_2O in normal adult humans.

NREM sleep is responsible for increasing the response latency and decreasing the magnitude of GG activation. One study failed to find any response to nasal occlusion during REM sleep. The decreased neuromuscular response is due to a major reduction in the excitability of UA dilator motoneurons as well as decreased afferent input in response to a given decrease in airway pressure [45]. In children, application of negative pressure in the UA during NREM sleep also increases inspiratory GG EMG, although with a wide amplitude variability between subjects (Figs. 4.3 and 4.4) [46]. A similar increase in GG EMG is present in sleeping infants during the first two inspiratory efforts following airway occlusion [47].

Experiments in both animals and humans have contributed to our understanding of the neural pathways involved in

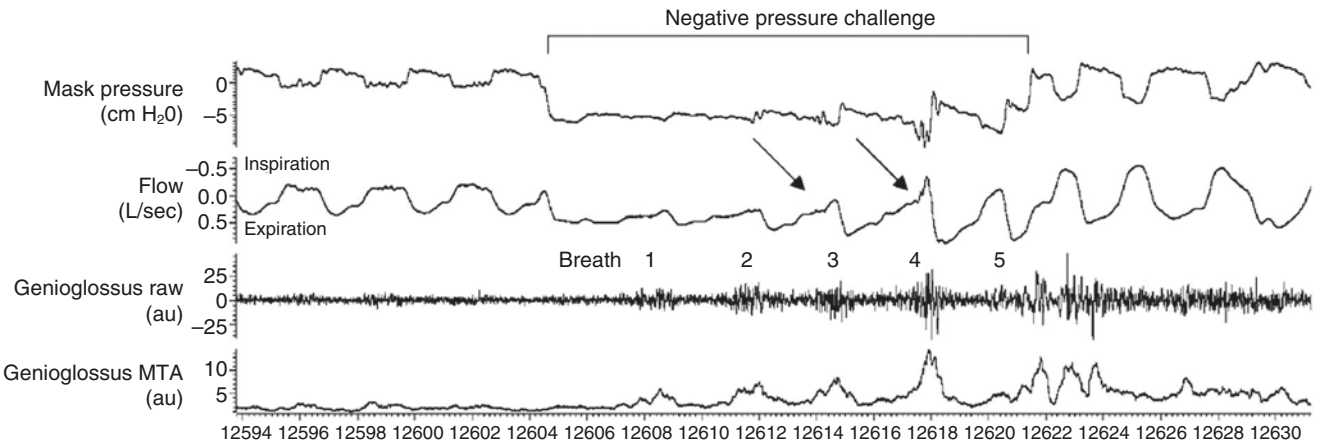

Fig. 4.3 Genioglossus response to negative intraluminal upper airway pressure in a normal child during sleep. The phasic electrical activity of the genioglossus muscle progressively increases during the first four breaths of the five-breath negative-pressure challenge to reestablish inspiratory flow (arrows). Genioglossus raw and MTA: raw and moving time average electrical activity of the genioglossus muscle. (From: Katz et al. [46]. Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society)

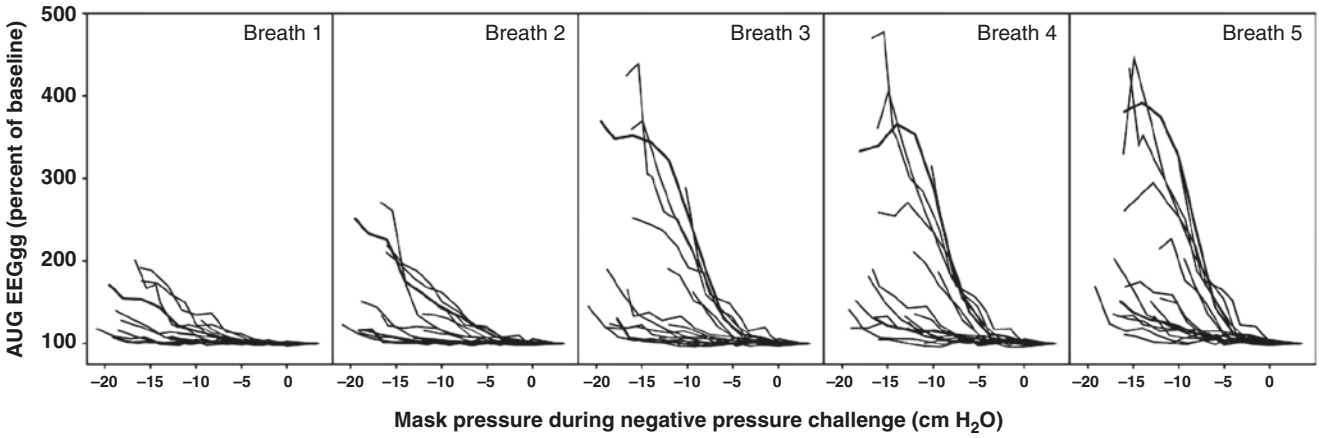

Fig. 4.4 Variability of genioglossus muscle response to a negative intraluminal upper airway pressure challenge in 19 normal children during N3 sleep. The graphs illustrate the area under the curve (AUC) of the inspiratory electrical activity of the genioglossus muscle (EMGgg) in response to progressively increasing negative-pressure challenges (from 0 to −20 cm H_2O). From left to right, the graphs present results obtained from the first (left graph) to the fifth (right graph) breath of the five-breath challenge. Note the important variability of the genioglossus muscle responses between individuals. (From: Katz et al. [46]. Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society)

the negative airway pressure reflex. Nasal and laryngeal mucosal mechanoreceptors are mainly involved via trigeminal and superior laryngeal nerve afferents, respectively. Conversely, oropharyngeal receptors do not appear to play an important role. Afferent input from slowly adapting bronchopulmonary receptors can also activate GG for airway pressure below −25 cm H_2O [48]. Following synaptic transmission in the nucleus tractus solitarius, the message is then transmitted to the hypoglossal motor neuron nucleus via premotor neurons located in the reticular formation lateral to this nucleus.

The viscoelastic properties of the UA and their potential to collapse in children have been reviewed by Katz [49]. No UA collapse was observed in normal sedated children using cine magnetic resonance imaging [50]. Moreover, endoscopic studies have shown that the UA endoluminal pressure must be at −7.4 ± 4.9 cm H_2O on average to collapse the UA in normal anesthetized and paralyzed children. This pressure is the passive critical closing pressure (passive Pcrit), and the obstruction occurs at the level of the soft palate, tongue and tonsils in normal children [51].

In theory, according to the tube law, a progressive decrement in negative transmural pressure increases the compliance of the floppy pharyngeal airway and is finally responsible for a rapid collapse as soon as the buckling point is reached [52]. In reality this is only true in passive conditions, that is, in the absence of UA muscle activity (paralysis). Recent results in adults show that the UA stiffen when UA diameter decreases, due to a progressive increase in UA muscle activity [53]. Similarly, in infants, the (passive) UA closing pressure measured postmortem with the neck in neutral position is only −0.7 ± 2 cm H_2O. The fact that such UA endoluminal pressure is normally observed with peak inspiratory flow in infants during eupnea indicates that UA muscle activity stiffens UA walls in the living infant [54]. In a living subject, active Pcrit is thus the result of both UA viscoelastic characteristics and UA dilator muscle activity.

Mechanisms of Increased Upper Airway Resistance to Breathing During Sleep

As already alluded to, sleep is responsible for a decreased activity of the UA dilator muscles, due to the loss of the "wakefulness stimulus." The normal resultant increase in UA resistance is responsible for a slight hypoventilation, manifested as an increase of 3–5 mm Hg in $PaCO_2$, as well as an increased dependence of ventilation on the strength of the CO_2 response [55]. In addition, the increase in UA resistance explains the presence of obstructive sleep-disordered breathing in subjects with risk factors, despite no sign of UA obstruction during wakefulness.

It is well demonstrated that the activity of the UA muscles, which maintains the UA open, is state-dependent. Hence, in children and adults, both tonic and phasic UA dilator muscle EMG decrease when transitioning from wakefulness to NREM sleep and are suppressed in REM sleep [17]. The neurobiological basis for this decreased activity during sleep has been particularly studied at the level of the hypoglossal motor center. The latter contains the

cell body of the motor neurons which innervate the tongue, including the GG, the major tongue protrudor. A number of neurotransmitters, which are traditionally known as involved in sleep-arousal mechanisms, can experimentally modulate motor neuron activity at the hypoglossal motor center [55]. This includes glutamate, GABA and glycine, acetylcholine, norepinephrine, serotonin, histamine, and orexin. While glutamatergic inputs are significantly involved in the wakefulness stimulus to hypoglossal motor neurons, studies in rodents have shown that noradrenergic and cholinergic inputs are the major mechanisms involved in the decrease in activity of hypoglossal motor neurons during sleep. Brainstem noradrenergic neurons, which project on motor neurons of the hypoglossal motor center, are located in several adrenergic centers of the brainstem (A1/C1, A5, A7, and subcoeruleus regions) [56]. Their activity decreases from wakefulness to NREM sleep and is further suppressed in REM sleep, paralleling the decrease in both tonic and phasic neuronal activity of the hypoglossal motor center during sleep. Brainstem cholinergic neurons, in turn, are mostly located in pontine tegmental nuclei and the intermediate reticular region of the medulla [56]. They are especially active in REM sleep. They uniquely suppress the activity of the hypoglossal motor neurons during REM sleep via binding to their pre- or postsynaptic muscarinic receptors. This in turn activates G-protein-coupled inwardly rectifying potassium channels (GIRK channels) that are expressed in hypoglossal motor neurons [15, 57]. Hence, the abolition of genioglossus muscle activity during REM sleep is considered to be due to cholinergic influences on hypoglossal motor neurons [15].

Control of Upper Airway Diameter During Central Apneas and Periodic Breathing

In NREM sleep, pharyngeal occlusion frequently occurs during spontaneous or hypocapnic (induced) central apneas and periodic breathing in normal adults (Fig. 4.5) [58–60]. Such decrease in UA diameter while in absence of central inspiratory drive indicates that other factors besides negative intraluminal pressure and UA muscle activity act on pharyngeal patency. These factors include the effects of lung volume, pharyngeal/peripharyngeal tissue volume and adhesive mucosal forces. The increase in lung volume during inspiration exerts a caudal traction of the UA, which stiffens the pharyngeal walls; in addition, the negative extraluminal pressure is transmitted to the peripharyngeal soft tissues during inspiration, thereby increasing the transmural pressure and in turn UA diameter. A decrease in lung volume has the opposite effect [61]. Moreover, an increase in peripharyngeal fat deposits decreases the UA transmural pressure and promotes pharyngeal closure. Vasodilation or vasoconstriction of the pharyngeal blood vessels decreases or increases UA diameter, respectively. Finally, adhesive mucosal forces can maintain the pharynx closed.

At the laryngeal level, tonic EMG of the thyroarytenoid muscle, a laryngeal constrictor, can be observed during spontaneous central apneas in normal adults [62], as well as in decerebrate cats (Fig. 4.6) [25].

The occurrence of apneas and bouts of periodic breathing is especially frequent during sleep in the neonatal period. The factors promoting pharyngeal closure appear preponderant at this age. Indeed, pharyngeal closure occurs in 40% of

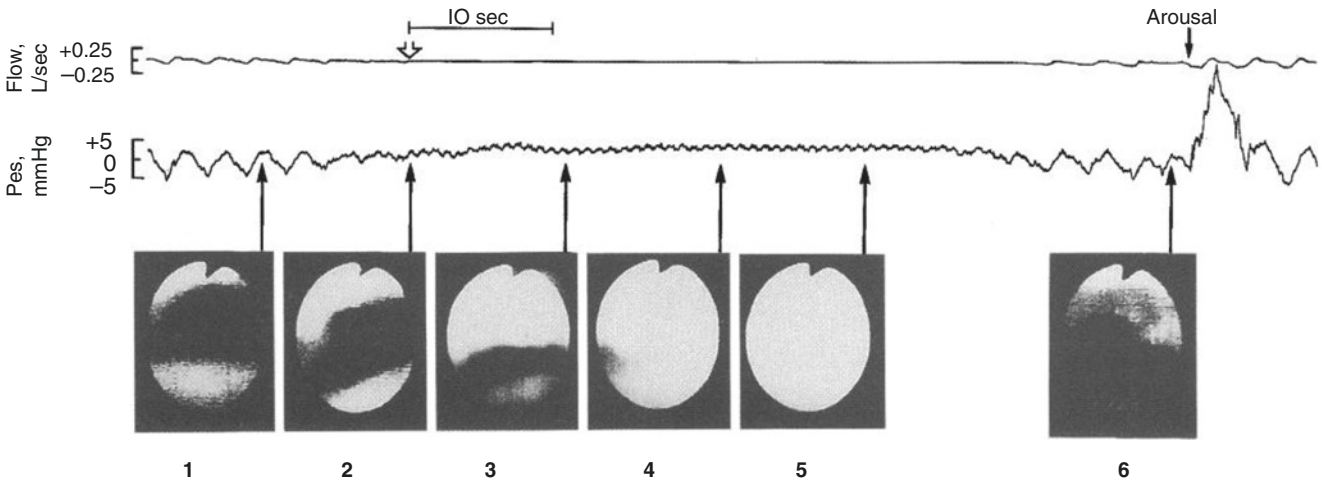

Fig. 4.5 Complete pharyngeal closure during central apnea in NREM sleep in an adult with central sleep apnea syndrome. From top to bottom: oronasal airflow (mask + pneumotachometer); esophageal pressure (Pes, pressure transducer-tipped catheter); endoscopic view of the oropharyngeal lumen with images 4 and 5 showing complete closure. (From Badr et al. [58]. Reprinted with permission from American Physiology Society)

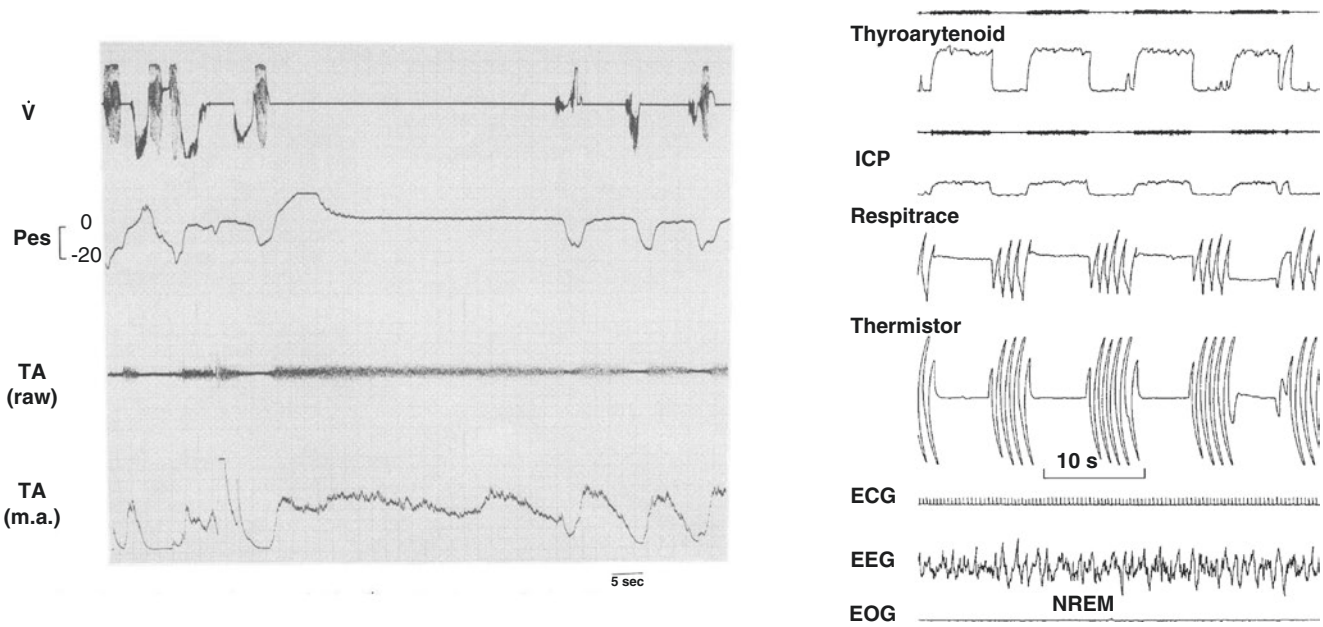

Fig. 4.6 Active laryngeal closure during an isolated central apnea and during periodic breathing. Left panel: Tonic electrical activity of the thyroarytenoid muscle, a laryngeal constrictor, in an adult during NREM sleep. V, oronasal airflow; Pes, esophageal pressure; TA (raw) and TA (m.a.), raw and moving time average electrical activity of the thyroarytenoid muscle. (From Insalaco et al. [62]. Reprinted with permission). Right panel: Tonic electrical activity of the thyroarytenoid muscle during a periodic breathing epoch during NREM sleep in a preterm lamb. Note that the lung volume during the apneic periods is maintained over the functional residual capacity (= inspiratory breath-holding), due to active complete laryngeal closure during the apneas. From top to bottom: thyroarytenoid, raw and moving time average electrical activity of the thyroarytenoid muscle; ICP, raw and moving time average electrical activity of the inferior pharyngeal constrictor muscle; Respitrace, lung volume variations (sum signal of the respiratory inductance plethysmography); Thermistor, nasal airflow (inspiration upward); ECG, electrocardiogram; EEG, electroencephalogram; EOG, electrooculogram. (From Renolleau et al. [68]. Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society)

isolated central apneas and periodic breathing in human preterm newborns, where a high proportion (~50%) of mixed and obstructive apneas is observed [63]. In addition to the overall immature control of breathing, incoordination of pharyngeal dilator muscles with thoracic respiratory muscles, increased pharyngeal compliance and narrow UA anatomy are blamed for the frequency of mixed and obstructive apneas in newborns.

Complete active laryngeal closure is also prominent at this age during central apneas and periodic breathing, as shown by fiberoptic observations in human preterm neonates [63] as well as EMG studies of the thyroarytenoid muscle (laryngeal constrictor) during central apneas in newborn mammals [64–67]. For instance, tonic thyroarytenoid muscle EMG is present throughout spontaneous central apneas in more than 90% of cases in NREM, including during periodic breathing, as well as in 75% of the central apneas in REM sleep in preterm lambs [68]. Of note, complete laryngeal closure during central apneas occurs well above functional residual capacity (Fig. 4.6); such inspiratory breath-holding limits postapneic desaturation in preterm lambs [69]. This tonic laryngeal closure during postnatal central apneas is reminiscent of what is observed in fetal life during prolonged absence of fetal breathing movements in NREM sleep-like state [70]. Such laryngeal closure during central apneas is not of reflex origin but rather corresponds to the basic breathing pattern of air-breathing vertebrates [71]. In 10–30% of the cases, glottal dilator EMG is also present in the last third of central apneas, together with a simultaneous decrease in lung volume [35].

A very different mechanism is responsible for the active laryngeal closure observed during central apneas triggered by laryngeal chemoreceptors stimulated by hypochloridic or acidic solutions [72, 73]. These fetal-type laryngeal chemoreflexes are observed in immature subjects, that is, primarily in preterm newborns, and include prolonged central apnea and bradycardia, forceful and sustained laryngeal closure, and hemoglobin oxygen desaturation [74]. More mature subjects present less vagally mediated responses, rather consisting in a short apnea and laryngeal closure, swallowing, coughing and arousal [75]. These laryngeal chemoreflexes correspond to a major lower airway protective mechanism aimed to prevent tracheal aspiration of offending solutions. Such reflexes have been shown to be present and of similar strength in NREM and REM sleep in preterm lambs [76]. Of note, several other lower airway protective reflexes originat-

ing from the esophagus or the upper aerodigestive tract are also present. The reader is referred to previous publications for more information on the latter [77–81].

Apnea and Non-Nutritive Swallowing Swallowing is a vital lower airway protective mechanism, which involves the very fine coordination of more than 20 pairs of muscles of the upper aerodigestive tract, including the pharyngeal, laryngeal, and esophageal muscles. Both nutritive and non-nutritive swallowing are of major importance. Non-nutritive swallowing safely clears saliva, UA secretions, and refluxed gastric content from the UA and prevents tracheal aspiration. The presence of laryngopharyngeal refluxes and regurgitations in virtually all infants during the first months of life explains why non-nutritive swallowing is even more crucial in infancy. While a detailed review on swallowing is clearly beyond the scope of the present chapter, the potential link between apnea and non-nutritive swallowing will be briefly reviewed.

Swallowing is a very potent inhibitor of breathing. During sleep, in adults as well as in children, the frequency of non-nutritive swallows decreases, being at its lowest during N3 state [82–85]. In newborns, the highest NNS frequency is during REM sleep [86]. Non-nutritive swallowing is associated with some neonatal apneas, mostly mixed, or obstructive [87–89]; this association is more frequent during REM sleep when non-nutritive swallowing occurs in bursts [90]. On the contrary, the occurrence of non-nutritive swallowing, even isolated, during the apneic phase of periodic breathing in NREM sleep is very rare [69]. The reason for the association between apneas and non-nutritive swallowing, either from peripheral (laryngeal chemoreflex stimulation) or central (reciprocal inhibition of the respiratory centers by the swallowing centers) origin, remains uncertain.

Concluding Remarks

The UA have a highly complex anatomy and motor function, which follow an extensive maturation during infancy and childhood. As part of the upper aerodigestive tract, the more than 20 UA pairs of muscles must be finely coordinated between them during breathing and swallowing, as well as with the thoracic respiratory muscles. Such coordination is not fully mature at birth, and both UA obstruction and impaired swallowing is frequent, especially in premature newborns. Throughout life, sleep takes its toll on UA dilator muscle activity and UA patency is at stake. Hence, in the presence of risk factors, UA obstruction can occur during sleep, especially when REM sleep-related mechanisms inhibiting UA dilator motor neuron centers are the most prominent. Decades of research on UA motor function during sleep have begun to reveal crucial information on these REM sleep-related mechanisms. This hopefully will lead to new treatments of obstructive sleep-disordered breathing in the near future.

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Endocrinology of Sleep

5

Dorit Koren

Abbreviations

AANAT	Arylalkyl amine N-acetyltransferase
ACTH	Adrenocorticotropic hormone (also known as corticotropin)
AgRP	Agouti-related peptide
ANS	Autonomic nervous system
AR	Androgen receptor
AVP	Arginine vasopressin
AVPN	Anteroventral periventricular nucleus
BMAL1	Brain and muscle Arnt-like protein-1
cAMP	Cyclic adenosine monophosphate
CLOCK	Circadian locomotor output cycles kaput
CNS	Central nervous system
CPAP	Continuous positive airway pressure
CRH	Corticotropin releasing hormone
CRY1/CRY2	Cryptochrome1/chroptochrome2
EEG	Electroencephalogram
ER	Estrogen receptor
FSH	Follicle stimulating hormone
FSHR	FSH receptor
GH	Growth hormone
GHD	Growth hormone deficiency
GHRH	Growth hormone releasing hormone
GnRH	Gonadotropin releasing hormone
GR	Glucocorticoid receptor
HPA	Hypothalamic-pituitary-adrenal
IGF-1	Insulin-like growth factor-1
LH	Luteinizing hormone
LHR	LH receptor
mRNA	Micro-ribonucleic acid
MT_1	Melatonin receptor 1
MT_2	Melatonin receptor 2
NPY	Neuropeptide Y
OSA	Obstructive sleep apnea
Per1/Per2/Per3	*Period1*/*Period2*/*Period3*
PVN	Paraventricular nucleus (of the hypothalamus)
REM	Rapid eye movement
SCN	Suprachiasmatic nucleus (of the hypothalamus)
SST	Somatostatin
SWS	Slow wave sleep
T2DM	Type 2 diabetes mellitus
T3	Triiodothyronine
T4	Thyroxine
TIDA	Tuberoinfundibular dopaminergic
TR	Thyroid (hormone) receptor
TRH	Thyrotropin releasing hormone
TSH	Thyroid stimulating hormone
VIP	Vasoactive intestinal peptide

Introduction

Humans exhibit physiological and behavioral rhythms that show distinct day-night variations, known as circadian rhythms, which are governed by circadian oscillators and generally entrained by environmental cycles of light and darkness. A number of biological systems follow a circadian rhythm, including the endocrine system. There are complex interplays between light-dark exposure, sleep, and the endocrine system—one well-known example is melatonin, which promotes sleep [1], but it is also noteworthy several of the sleep stages are accompanied by distinctive patterns of hormonal secretion [2, 3]. In the first part of the night, growth hormone secretion predominates [4–6]; later in the night, coinciding with the proportion of rapid eye movement stage of sleep, a marked upward slope in cortisol begins [7], although cortisol is less closely tied to sleep stages [8]. The relationships between hormones and sleep are complex and often reciprocal (especially vis-à-vis the hypothalamic-pituitary-adrenal axis). The temporal association suggests

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that there may be common regulatory mechanisms governing neuroendocrine hormone release and the neurophysiology of sleep, and that the relationship of sleep regulation, and the hormonal axes may be bidirectional. The goal of this chapter is to review the regulation of the endocrine system during sleep as well as the impact of various endocrine loops upon sleep initiation, maintenance, and architecture.

The Circadian System—A Brief Overview

There is a distinct day-night variation of human physiology and behavior: the optimal period for physical and mental performance for occurs during the daytime, while more regenerative activities are performed during the night. These circadian rhythms, which are produced by circadian oscillators, are synchronized primarily to environmental cycles of light and darkness. The synchronization is achieved by photoreceptors in the eyes relating signals to the suprachiasmatic nucleus (SCN) of the hypothalamus. In the SCN, a coupled population of neuronal circadian oscillators that function as the body's central clockmaker produce signals, which synchronize various independent peripheral circadian clocks of the body and drive rhythms of body temperature, feeding behaviors, activity, rest, and hormone production [9]. Some of the core clock genes regulating circadian rhythms include *Clock* (circadian locomotor output cycles kaput), *Cryptochrome* (*Cry1* and *Cry2*), *Bmal1* (brain and muscle Arnt-like protein-1), and *Period* (*Per1, Per2*, and *Per3*). These genes function in circadian feedback loops [10]. Of these, the proteins CLOCK and BMAL1 (encoded by the *Clock* and *Bmal1* genes respectively) form the main molecular enablers of these peripheral clock, although there are other independent molecular circadian oscillators as well [11]. The details of the circadian clock are explored in greater detail in other chapters in this book. A number of biological systems follow a circadian rhythm, produced by circadian oscillators, of approximately 24 hours; the endocrine system is one of these processes.

Interplays of the Endocrine System with Sleep and Circadian Rhythms

The endocrine system is a chemical messenger system comprised of glands. Historically, hormones were defined as secretions of these glands that entered the circulatory system targeting distant target organs, generally within the framework of feedback loops; a more inclusive and updated definition recognizes that hormones are chemical intracellular messengers, which may function locally as well as distantly [9]. Several of these loops are impacted by either sleep, light/dark exposure, or both.

Of note, mechanisms modulating sleep-wake homeostasis and those modulating circadian rhythms overlap extensively, and thus 24-hour studies of hormonal secretory patterns under standard conditions of nighttime sleep cannot easily differentiate between the two. To delineate the effects of the former, experimental sleep restriction/deprivation studies are often performed, while to examine the impact of the latter, sudden shifts of light-dark or sleep-wake cycles are often performed; the central circadian pacemaker typically takes several days to adjust to such large shifts, so the effects of circadian modulation can be observed outside of the context of sleep while effects of sleep at an atypical time can be investigated without the usual circadian impulses.

Hypothalamic-Pituitary Axes and Sleep

The Hypothalamic-Pituitary-Adrenal (HPA) Axis

The HPA axis works to provide a stress response of appropriate duration and magnitude in response to appropriate stimuli (e.g., illness). The HPA axis's function is governed by both positive and negative feedback mechanisms, both internal and external to the axis. Neural, endocrine, and cytokine signals in response to a daily circadian impulse or, if present, to a stressor converge to stimulate neurons within the paraventricular nucleus of the hypothalamus to secrete corticotropin releasing hormone (CRH) and arginine vasopressin (AVP) into the hypophyseal portal circulation system. Upon reaching the anterior pituitary, CRH and AVP bind to their cognate transmembrane receptors and trigger corticotroph cell synthesis and secretion of adrenocorticotropic hormone (ACTH). Rising levels of ACTH subsequently trigger production of glucocorticoid hormones (most notably cortisol) in the zona fasciculata of the adrenal gland [12, 13]. Cortisol and other glucocorticoids bind to the ubiquitous nuclear glucocorticoid receptor (GR) and activate the glucocorticoid signaling pathway. These glucocorticoids then exert pleiotropic and diverse physiological effects (both genomic and non-genomic), including regulation of cellular metabolism (mostly catabolic in nature) in hepatic, myocyte, and adipose tissue, influencing numerous central nervous system (CNS) functions, up- or down-regulating some 20% of the human leukocyte genome, maintaining cardiovascular tone, and modulating the human immune and inflammatory response [13–16]. Cortisol subsequently exerts an inhibitory effect upon the paraventricular nucleus (PVN) of the hypothalamus and upon anterior pituitary corticotrophs (but not on the SCN), in a classic negative feedback loop [17].

The HPA axis has one of the most distinct and elegant circadian rhythms in the body [18]. Typically, cortisol levels reach their nadir at around midnight; levels begin to slowly rise around 02:00–03:00, and reach their acrophase, or peak, at around 08:00–09:00, before beginning their slow decline

back down over the course of the day, to achieve a nadir once again at midnight [19, 20]. There is accumulating evidence that this cyclicity is mediated in large part by interactions of the HPA axis with the circadian clock system at multiple levels.

Hypothalamic Circadian Influence

A central pacemaker in the SCN of the hypothalamus controls the circadian release of CRH in the PVN, which in turn stimulates the release of ACTH and then cortisol. The release of CRH is pulsatile and circadian-dependent [21], in the absence of physiologic stressors that would upregulate the HPA axis. Lesions of the SCN central clock or elimination of its genetic components eliminate the rhythmicity of glucocorticoid secretion [22, 23]. Photic (light) signals from the SCN are transduced to the adrenal glands through the autonomic nervous system, and consequently induce adrenal cortical expression of the clock gene *Per1*; denervation of the adrenal gland abolishes this photo-stimulatory effect [24].

Circadian Activity of the Adrenal Glands

Accumulating evidence suggests that the adrenal gland contains a self-sustaining circadian clock whose activity (and resultant adrenal clock gene expression) seems to be independent of the HPA axis's stress-response [17, 25–27]—expression of the mRNA for three main clock genes of Per1, Per2, and Bmal1 display rhythmic oscillations with a 24-hour period, whose phase in one rat model did not differ between rats with intact pituitary glands versus those who had undergone hypophysectomy [28]. However, light exposure can still entrain this independent clock to the central circadian clock via activation of the SCN [24].

The adrenal circadian clock appears to influence adrenal cortical activity in a variety of ways. Numerous adrenal genes exhibit cyclicity of micro-ribonucleic acid (mRNA) production over the course of the day, and microarray analyses have revealed that 4–7% of these genes are expressed in a manner exhibiting circadian oscillation [23, 27]; gene enrichment analysis demonstrated that these gene transcripts are associated with several biological processes, including but not limited to steroid biosynthesis and cholesterol concentration [23]. In addition, the adrenal circadian clock regulates at which time intervals the adrenal gland can most effectively response to ACTH stimulation—that is, the sensitivity of the zona fasciculata to ACTH varies throughout the day, altering the rate of glucocorticoid production [13].

Circadian Rhythmicity of the Glucocorticoid Receptors and Their Actions

The rhythmicity of glucocorticoid receptor activity and actions is exhibited in a variety of ways. Mouse models have shown that GR expression oscillates in some peripheral tissues (brown and white adipose tissue), but not others (GR expression in hepatocytes and myocytes is not rhythmic) [29]. The cryptochrome proteins CRY1 and CRY2, which exert a light-*independent* inhibitory influence on the CLOCK-BMAL1 elements of the circadian clock [30], bind to the C-terminal GR domain and globally repress GR activation and consequent transactivation of target genes; indeed, in mice, loss of the genes encoding CRY1 and/or CRY2 lead to constitutively elevated levels of circulating corticosterone (the predominant murine glucocorticoid) [31]. These circadian influences described above are summarized in Fig. 5.1.

These circadian ties are important in health. Abrupt shifts of the sleep/wake and light/dark cycles, as occur in those who travel frequently over different time zones, will also perturb the HPA axis—while the onset of the change of the timing of the acrophase takes as little as a day, completing the shift of the onset of nocturnal cortisol rises takes up to 3 week [32]. Similarly, uncoupling of the sleep-wake cycle from the usual diurnal rhythm (e.g., rotating shift work), which is termed circadian misalignment [33], can lead to increased HPA axis activation and a blunting of the usual nocturnal cortisol decline. This increased HPA activation may partially underlie the association between rotating shift work and cardiometabolic risk, as well as increase in circulating levels of inflammatory markers, and a mild suppression of the immune system predisposing to common infections among other manifestations [34–38].

Thus far, the discussion has been limited to the interactions between the systemic and peripheral circadian clock systems and the HPA axis; we will next review the relationship of the HPA axis with sleep.

Influences of Sleep on HPA Axis

Physiology: In addition to circadian influences, sleep (especially slow wave sleep (SWS or N3)) also exerts an inhibitory influence upon HPA axis activity. Sleep onset tends to exert a mild inhibitory effect on cortisol output for a period of 1–2 hours, as evidenced by experimental studies of human sleep under a free-running condition (also known as temporal isolation) [39], in the setting of complete sleep-wake reversal [40], and in participants undergoing experiments of 3-hour sleep-wake cycle [41]. Cortisol levels typically decline during SWS [8, 40, 42], while awakening from sleep (both mid-sleep and the end of the sleep period) consistently induces a pulse of cortisol secretion [43].

Sleep duration and cortisol: Experimental sleep deprivation studies have served to illuminate the relationships between sleep and HPA axis activity. Sleep deprivation in animal models has been found to elevated release of hypothalamic corticotropin releasing factor (CRF, analogous to human CRH) but a *reduction* in CRF binding activity in the striatum and pituitary, suggesting decreased sensitivity to CRF under

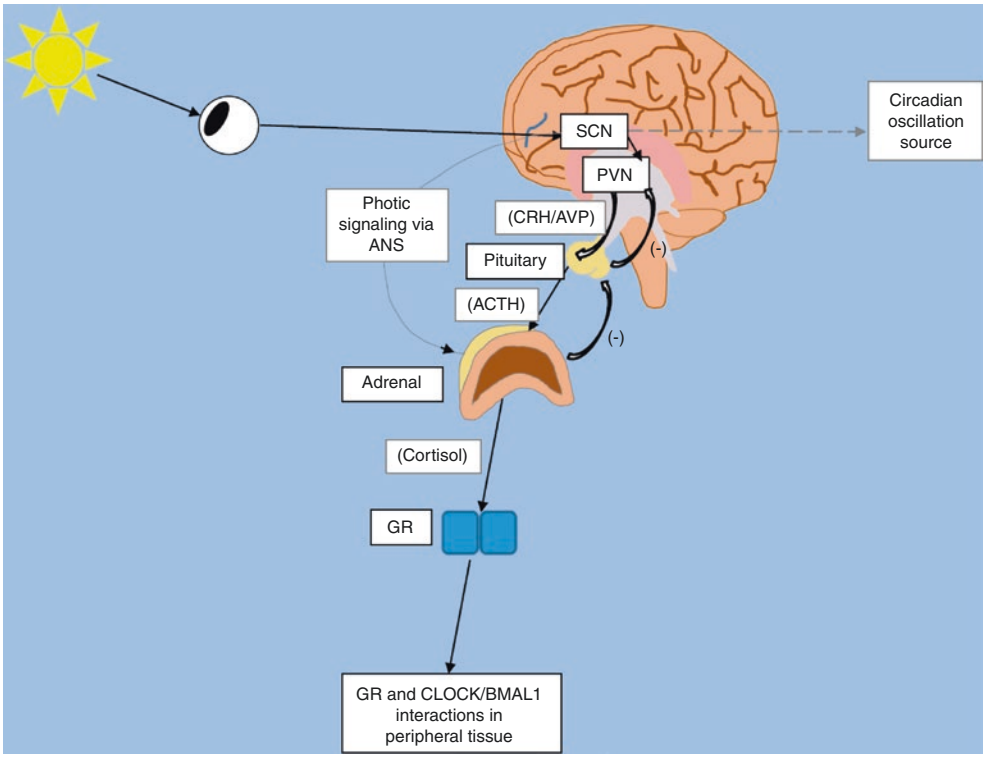

Fig. 5.1 Circadian influences on HPA axis. ACTH adrenocorticotropic hormone, ANS autonomic nervous system, AVP arginine vasopressin (also known as anti-diuretic hormone), BMAL1 brain and muscle arnt-like 1, CLOCK circadian locomotor output cycles kaput, CRH corticotropin releasing hormone, GR glucocorticoid receptor, PVN paraventricular nucleus of the hypothalamus, SCN suprachiasmatic nucleus of the hypothalamus

conditions of sleep deprivation [44]. Similarly, total or partial sleep deprivation significantly attenuates the normal nocturnal decline in HPA axis activity in both men and women [43, 45] and raises daytime ACTH levels [46, 47]. Longer partial sleep-deprivation studies (carried out over a week) in healthy volunteers led to elevation of evening cortisol levels as well [48]. Under conditions of sleep loss, the increased HPA axis activity leading to chronic sleep deprivation may also influence sleep quality, as elevated evening cortisol levels are likely to reduce sleep quality as discussed above [46].

A note of caution is advised in generalizing from experimental sleep studies, as data studies attempting to assess the association between long-term sleep duration and HPA axis activity in community-dwelling populations have yielded inconsistent results. In the Whitehall II study, the diurnal slope of cortisol secretion was flattened (with raised evening cortisol levels) and the cortisol awakening response was more pronounced in those with self-reported short sleep duration [49]. However, in two other community-based studies, no difference in cortisol levels were seen in those with self-reported or actigraphically measured short versus longer sleep durations [50, 51]. The Whitehall II study relied on self-reported sleep duration, which is not always accurate. One possible reason for the divergence in results between short-term experimental studies versus community-based studies may be adaptation of the HPA axis to chronic sleep deprivation. Supporting this, some studies have found that ACTH and cortisol responsiveness to exogenous CRH administration is blunted after experimental sleep restriction in both experimental rat models [52] and human volunteers [46], suggesting that there is a partial desensitization of the pituitary corticotrophs to CRH in the setting of chronic sleep deprivation and consequent increased CRH release [46].

Sleep architecture and the HPA axis: As reviewed above, cortisol secretion declines during SWS, although experimental suppression of SWS has not been shown to result in increased cortisol levels [53]. In addition, increased HPA activity, administration of exogenous systemic glucocorticoids, or (in animal models) intracerebroventricular administration of CRH results in lighter sleep and more frequent arousals/awakenings [54–56]. Also, administration of ACTH or synthetic analogs thereof in humans leads to prolonged sleep latency, decreased sleep duration, and lower sleep efficiency [57]. Similarly, administration of either continuous ACTH [57], or of exogenous glucocorticoids [58], significantly reduces rapid eye movement (REM) sleep duration.

Sleep fragmentation, obstructive sleep apnea, and HPA axis: While a detailed description of the impact of obstructive sleep apnea (OSA) upon the HPA axis is beyond the scope of this physiology chapter, no discussion of sleep and the HPA axis is complete without at least a brief mention of this condition. Repetitive arousals during sleep, leading to sleep fragmentation, significantly raise cortisol levels [59]. However, studies of cortisol levels in individuals with and without OSA have been inconsistent, with some showing

elevations in plasma cortisol levels between individuals with OSA versus controls and others finding no difference [60–62]. Studies of the impact of continuous positive airway pressure (CPAP) therapy and of CPAP withdrawal upon cortisol levels have similarly yielded contradictory results [60–63]. Some of the source of contradiction may reside in the methodology of HPA activity assessment—many studies rely upon single time-point cortisol measurement, which is not necessarily reflective of the full variation of HPA axis activity, as the studies performing more frequent measurements were more likely than studies that examined a single time-point cortisol level to report a reduction in cortisol levels with CPAP therapy. One exception to this generalization—a study examining the impact of 1 week of effective, full-night CPAP treatment in adults with OSA and type 2 diabetes mellitus (T2DM) upon multiple metabolic measurements found no difference in cortisol levels pre- and post-CPAP; cortisol was measured at 15–30 minute intervals throughout the night [64]. However, the divergence between this study's results versus other studies showing improvement lowering of cortisol levels with CPAP therapy may lie in the study population. The HPA axis may be disrupted in T2DM, with a flattened daytime cortisol slope and raised evening cortisol levels [65]; it is possible that in the setting of this pattern, the impact of CPAP therapy upon the HPA axis is blunted.

Thus, there is a clear bidirectional relationship between the HPA axis and sleep and circadian rhythms. It is thus unsurprising that numerous studies have established associations between insufficient sleep, disorders of sleep, circadian misalignment, and disorders of circadian rhythm with upregulation of the HPA axis and consequent predisposition to metabolic diseases; these connections will be explored at greater length in other chapters in this book.

Growth Hormone

Growth hormone (GH) is a single-chain peptide hormone secreted by pituitary somatotrophs, which are predominantly located in the lateral aspects of the adenohypophysis (anterior pituitary). GH secretion occurs in a pulsatile fashion and is stimulated by growth hormone releasing hormone (GHRH) and inhibited by somatostatin (SST). GHRH is produced in the arcuate nucleus of the hypothalamus, enters the portal venous system, and binds to a seven transmembrane G-protein-coupled receptor on the somatotrophs [66]; GHRH secretion is stimulated by numerous factors, including hypoglycemia, alpha2-adrenergic stimulation and hypothyroidism, and is inhibited by several factors, including insulin-like growth factor-1 IGF-1), somatostatin and activation of GABAergic neurons. SST is produced by specialized neuronal cells in the PVN and arcuate nucleus of the hypothalamus, is released via the median eminence into the adenohypophyseal portal venous system, and binds to a seven transmembrane G-protein couple-receptor (of which 5 subtypes have been identified in humans). SST secretion is stimulated by exercise, immobilization and elevated serum GH or IGF-1, and inhibited by hyperglycemia. Other stimulators of GH secretion include but are not limited to hypoglycemia and protein ingestion and ghrelin, which is a natural ligand for the GH secretagogue receptor; other inhibitors of GH secretion include hyperglycemia and elevated free fatty acids [67]. GH acts both directly through binding to its own receptors and indirectly by induction of insulin-like growth-factors (GFs), predominantly IGF-1 [68].

The association between GH secretion and sleep has long been recognized. In 1968, GH secretion peak was noted to occur with the onset of deep sleep and lasted for 1.5–3.5 hours, with delay of peak secretion seen if sleep onset was delayed or if participants were awakened for 2–3 hours and subsequently allowed to resume sleep [6]. Subsequent studies of adults have demonstrated that the most reproducible GH secretory pulse occurs soon after sleep onset [69], even if sleep onset is greatly delayed [70]; similar patterns are seen in children, though of note, GH secretory pulses are somewhat blunted in children with obesity [71]. Of note, the GH secretion seen at sleep onset appears to be primarily driven by GHRH (in the context of lower somatostatin levels as above) [72]. The GH secretory pattern in adults is sexually dimorphic. In adult men, daytime pulses are small [73], and in some men, the early-night GH pulse may be the only one observed over a 24-hour period [74], while women have a more continuous GH secretory pattern of more frequent pulses, with greater uniformity between the amplitude of daytime and nocturnal secretory pulses [73].

Experimental sleep deprivation studies in adults have found that sleep deprivation blunts the normal nocturnal GH secretion in most older men, but that men under age 24 were able to mount a robust nocturnal GH pulse [75] and (in another study of young adults) develop compensatory increases in daytime GH secretion [76] and in the nocturnal GH pulse the following night [77]. These data indicated a strong drive to maintain adequate GH secretion in the face of sleep adversity.

As discussed above, electroencephalogram (EEG) studies have shown that the peak of nocturnal GH secretion tends to coincide with the first SWS episode of the night in both adults [69] and children [78, 79], and GH activity generally associates with delta wave patterns on EEG (0.5–3.5 Hz of the EEG spectral power) [80]. Also, sophisticated studies that utilized deconvolution, a technique that allows the derivation of secretory rates from plasma concentrations of a hormone by accounting for the impact of its distribution and clearance, have more clearly demonstrated that GH secretory

activity coincides closely with episodes of slow wave activity [81]. The GH system may also influence sleep in its turn. Administration of medications that preferentially increases the duration or intensity of SWS (e.g., administration of oral gamma-hydroxybutyrate) also stimulates GH secretion [81]. Similarly, administration of ghrelin, an endogenous GH secretagogue, also stimulates SWS and increases slow wave activity [82]. More direct evidence has come from rabbit and rat studies, which have shown that intraventricular injection of synthetic GHRH and SST increases the proportion of the sleep period spent in SWS and in REM sleep, respectively [83]. Similarly, serial overnight administration of synthetic GHRH to human adult volunteers boosted the proportion of the night spent in SWS (and suppressed cortisol levels) while serial administration of SST led to a trend of increase in REM sleep density [7]. Thus, these data do support a bidirectional relationship between SWS and the GH axis.

However, the association between GH and SWS is not obligatory—a third of SWS episodes are not shown to associate with GH secretion [70], and GH secretion can occur during the daytime as discussed above. Also, experimental studies in which SWS was delayed led to disassociation of GH secretory peaks from SWS, as the GH peaks occurred closer the onset of sleep rather than to the occurrence of SWS [84]. Finally, several studies of sleep in growth hormone deficiency (GHD) also yielded conflicting results: the relationship between SWS and GH. One study of 8 young adults with severe GHD found a lower proportion of sleep spent in SWS and a longer total sleep duration compared to age-matched controls [85], but several other studies did not replicate this finding. A study of 10 children with GH deficiency and 13 age-matched controls found no difference in the percentage of the night spent in SWS between the groups [86], and a study of sleep in adults with pituitary GH deficiency found decreased total sleep time and increased sleep fragmentation, indicating poor sleep quality, but no difference in sleep stages compared to control adults [81]. More recently, a study found that children with GHD had significantly lower total sleep time and sleep efficiency than age-matched controls, less time spent in non-REM (NREM) stage 2 sleep and globally decreased EEG arousability as measured by a lower cyclic alternating pattern, but differences in SWS were not noted [87]. GH replacement also has not been shown to augment SWS—a study of 7 children with GH deficiency found that GH replacement was associated with a relative *decline* in the percent of sleep time spent in SWS [88], and a study of adults with GHD after 6 months of GH replacement found no difference in sleep duration or in the distribution of sleep stages after GH replacement [89].

These data suggest that the relationship between GH and SWS is not monotonic—that is, the temporal sequence, which SWS occurs relative to the start of the overnight sleep period may be a more potent and reproducible stimulus to GH secretion. However, data do suggest that interactions occur at the level of the hypothalamus, and that GHRH stimulation during a period of relatively low SST and CRH activity does appear to both stimulates GH secretion and predispose to deep sleep. However, the drive to maintain GH secretion is independent of sleep and maintained even in the setting of sleep deprivation.

The Hypothalamic-Pituitary-Gonadal/Ovarian (HPG/HPO) Axis

The human reproductive system is controlled by the hypothalamic-pituitary-gonadal (HPG) axis, which is referred to in women as the hypothalamic-pituitary-ovarian (HPO) axis. There is a circadian rhythm to the function of the HPG axis and reciprocal ties exist between sleep and reproductive function; as might be expected, these differ somewhat across the lifetime (as reproductive function changes) and also between men and women, as will be discussed in greater detail below.

Gonadotropin releasing hormone (GnRH) is secreted in a pulsatile fashion by hypothalamic GnRH neurons and plays the central coordinating role in this axis. GnRH cell bodies are typically located within the medial preoptic area (POA) as well as in the arcuate/infundibular nucleus of the hypothalamus, together forming a neuronal network that projects to the median eminence [90]. GnRH is secreted in a pulsatile fashion, enters the hypothalamic-hypophyseal portal system, and binds to the GnRH receptor on the anterior pituitary gonadotrophs. This in turn stimulates the synthesis and secretion of the gonadotropin hormones, luteinizing hormone (LH), and follicle stimulating hormone (FSH) in the anterior pituitary gonadotrophs. FSH activates its receptor, the FSH receptor (FSHR); in males, the FSHR is located in testicular Sertoli cells, and this binding stimulates spermatogenesis, a process that is also regulated by testosterone [91]. In females, the FSHR is located on ovarian granulosa cells and stimulates oocyte recruitment/follicular maturation [92]. LH binds to the LH receptor (LHR, also known as the LH/CGR as chorionic gonadotropins also binds to this receptor [93]), mainly expressed in testicular Leydig cells [94] and ovarian theca cells [95], and stimulates gonadal steroid secretion (testosterone, estradiol, and progesterone primarily). A surge of LH occurs mid-menstrual cycle and triggers ovulation [96].

There is a complex interplay of positive and negative feedback inhibition of GnRH, LH, and FSH secretion by gonadal steroids (predominantly estradiol and androgens, though progesterone also plays a role), modulated by the activities of other gonadal hormones, including follistatin, activin, inhibin A, and inhibin B [97, 98], as well as by gonadotropin inhibitory hormone (GnIH), which inhibits pituitary gonadotropin secretion [99].

Sleep exerts a profound effect on the HPG axis in both men and women, but in different ways. Prior to puberty and the activation of the GnRH pulse generator, there is minimal GnRH and consequently minimal LH and FSH secretion, and this is not synchronized with sleep. A hallmark of early puberty is the rise in LH secretory pulse amplitude in early sleep [100–102], most frequently seen in SWS [103]. Studies of LH secretory patterns in girls early in puberty found an increase in nocturnal LH pulse frequency as well as amplitude during peri-puberty [104] and early-mid pubertal phases (Tanner stages 2–3) [105, 106]. In both boys and girls, the overnight increase leads to a sleep-related rise in testosterone levels (in boys) or estradiol/progesterone (in girls) [107]. The patterns seen in early puberty are no longer seen by the end of puberty, however, and adult patterns differ between men and women; the patterns of the HPG axis will therefore be discussed separately for males and females.

Females: The pattern of early-sleep rise in LH pulse amplitude is abolished by later in puberty, and in adult premenopausal women, daytime and nocturnal LH pulse rate and amplitude vary by menstrual cycle phase [108]. During the early portion of the follicular phase of the menstrual cycle, the interval between LH pulses is greater during sleep (whether night-time or daytime sleep) than during wake, implying that sleep exerts an inhibitory impact on the GnRH pulse generator; this is confirmed by the observation that sleep interruption leads to an LH pulse [109]. However, LH pulse amplitude is greater during night-time sleep than wake, an augmentation that does not appear to occur during daytime sleep, and even during wake LH pulse amplitude appears to be greater in the evening hours, suggesting a separate interaction with time of day [109]. The latter observation may be in part attributable to the effect of melatonin, augments LH and FSH secretion during the follicular phase but not the luteal phase of the menstrual cycle [110]. The modulatory effect of sleep upon gonadotropin pulsatility is not as clear in the mid-late follicular phase, as nocturnal LH pulse amplitude is decreased and LH pulse frequency increased, but following ovulation, a nocturnal slowing of LH pulsatility and increase in pulse amplitude is again seen in the early luteal phase; this pattern is again abolished in the late luteal phase [111].

The menopausal transition in women is characterized by several sleep disturbances: sleep fragmentation and increased wake after sleep onset, somewhat tied to vasomotor symptoms ("hot flashes") [112]. Gonadotropin levels are tonically elevated in post-menopausal women, but do not show circadian variability between sleep and wake [111]. The causal role of gonadotropins in sleep disturbance is supported by the finding that administering long-acting GnRH agonists (which inhibit pituitary gonadotropin secretion) to premenopausal women leads to increased vasomotor symptoms and consequent sleep fragmentation [113], and conversely, hormonal replacement therapy with estrogens can improves sleep quality somewhat [114].

Males: The sustained rise in LH leads to a rise in testosterone levels during sleep in adolescent boys [115]. The fact that this is driven by sleep and not by light/dark exposure was shown by a sleep reversal experiment carried out by Boyar and colleagues, in which LH/testosterone levels were found to be higher in boys during daytime sleep than during nighttime [116]. In adulthood, the daytime pulse amplitude of GnRH increases and thus the diurnal rhythm is reduced or eliminated [111]. Thus, in adult men, no significant difference is seen between LH pulse frequency/amplitude between sleep and wake periods [117]; by contrast, testosterone levels achieve a nadir in the late evening, begin rising after sleep onset, and peak in the early morning hours [118]. As in adolescent boys, the rise in testosterone in adult men relates to sleep rather than time of day—the nocturnal rise in testosterone is blunted (and total androgen levels are lower) following sleep deprivation, and a sleep-related rise in testosterone is also seen if sleep takes place during daytime hours [119]. Thus, sleep itself rather than circadian timing drives the nocturnal testosterone rise. More specifically, the duration of latency to REM sleep may determine the degree of testosterone elevation—testosterone levels peak at the onset of the first REM episode [120], and as experimental sleep fragmentation suppressing REM sleep leads to attenuation of the sleep-related testosterone rise [121]. Of note, in men, the relationship between sleep and the HPG axis does not appear to be bidirectional—administration of GnRH agonists to suppress the HPG axis does not meaningfully alter sleep duration, though slow wave sleep duration may be somewhat diminished [122]. Finally, in older men, LH pulse amplitude is diminished and frequency increases, and while the circadian pattern of testosterone production is still seen, the amplitude of testosterone production is significantly lower [123] and no longer appears to relate to latency to REM sleep [124].

OSA: There is a well-known sexually dimorphic pattern of OSA prevalence: beginning in adolescence, far higher rates of OSA are seen in men than in premenopausal women (OSA prevalence increases in women after menopause) [128]. One of the proposed mechanisms to explain this disparity is the impact of sex steroid hormones. Sex steroids are known to impact ventilatory control, possibly via effects on central chemoreceptors: the hypoxia response declines in during sleep compared to waking in men but not in women, while men have a more significant ventilatory response to hypercapnia than do women [125]. Although testosterone is likely not the only mediator of this—proges-

terone seems to stimulate ventilation (somewhat variably) [126], especially in conjunction with estrogens [127]—higher androgen levels do seem to correlate with increased OSA risk. Women with obesity and polycystic ovary syndrome (PCOS), a state of hyperandrogenism, are at considerably higher risk of OSA than women with obesity but without PCOS [129]. Similarly, the prevalence of sleep-disordered breathing also rises in women after menopause [112], an increase that may be somewhat attenuated by estrogen replacement therapy [130]. Finally, while OSA can predispose to lower testosterone levels (hypogonadism), treatment of hypogonadal men with exogenous testosterone may induce or exacerbate OSA [131], and caution is therefore advised. A more detailed discussion of the relationship between sex steroids and sleep-disordered breathing is beyond the scope of this chapter.

The Hypothalamic-Pituitary-Thyroid Axis

The hypothalamic-pituitary-thyroid (HPT) axis regulates the production of thyroid hormone, which regulates metabolic function essential for normal brain development in childhood and maintaining normal homeostasis in adults by regulating the biological function of multiple tissues [132, 133]. Thyroid hormone exerts widespread impact on multiple tissues, regulating energy expenditure, food intake, cardiovascular function, hepatic function, bone turnover, and many other biological functions. Neurons in the PVN of the hypothalamus produce thyrotropin releasing hormone (TRH) from the precursor proTRH in a series of post-translational modifications [134]. TRH is then transported to the median eminence and thence released into the portal hypophyseal-portal circulation [135]. TRH binds to the type 1 TRH receptors on anterior pituitary thyrotropes [136], leading to the pulsatile release of previously synthesized TSH [137] and upregulating the synthesis of the two TSH subunits—the α-subunit (shared with FSH and LH, the other two anterior pituitary glycoprotein hormones) and the TSH-specific β-subunit [137]. TSH binds to its cell-surface receptor on thyroid cells (thyrocytes) and exerts tonic control of the production of thyroid hormones, thyroxine, and triiodothyronine (T3) [138]. Thyroid hormone binds to thyroid hormone receptors (TRs), a family of nuclear receptors found throughout the body, acting to regulate the transcription of multiple genes involved in numerous processes [134].

Much like the axes discussed above, the HPT axis also displays classic negative feedback inhibition. Thyroid hormone (primarily T3) binds to its nuclear receptor and inhibits pituitary TSH gene transcription, reduces TSH subunit secretion, and inhibits post-translational modification and release of TSH, and inhibits hypothalamic preproTRH production [134, 139].

Circadian Rhythmicity of the HPT Axis

The circadian rhythmicity of the HPT axis is less striking than that of other anterior pituitary hormones, but TRH and TSH levels do display some circadian variability [111, 140]. During the daytime, plasma TSH levels are typically lower and do not fluctuate significantly. There is a small but rapid rise in the pulsatile TSH secretion in the early evening hours, peaking at around the hour of sleep; TSH secretion declines later in the night until the morning is reached [141]. This diurnal variability of TSH secretion is likely influenced at least in part by cortisol (which peaks in the morning as noted above, and which suppresses TSH secretion somewhat [142]) and by the pineal hormone melatonin, which appears to upregulate pituitary thyrotrope response to TRH and thyrocyte response to TSH [143]. The wakefulness-promoting hypothalamic neuropeptide orexin may also play a role, as there is some evidence to suggest that it may modulate the HPT axis by mildly suppressing TRH and consequently TSH release; however, data on this connection are somewhat inconsistent and this requires further investigation [144]. Of note, neither the rise in TSH typically seen at the time of nighttime sleep onset nor the typical decline of TSH later in the night occurs during daytime sleep [111], suggesting that circadian influences outweigh those of sleep.

Sleep and the Thyroid

As above, the evening TSH peak appears to relate to circadian rhythmicity rather than to sleep. However, there does appear to be a reciprocal relationship between thyroid hormone and sleep: individuals with hypothyroidism tend to have prolonged sleep duration [145] and individuals with thyrotoxicosis have shortened sleep durations, with difficulties with initiating and maintaining sleep [146], together suggesting that thyroid hormone inhibits sleep and maintains wakefulness. Supporting this, TSH levels tend to decline during the first 20 minutes of SWS episodes [147]. Conversely, a distinct elevation of TSH and consequently of thyroid hormone levels is seen during total sleep deprivation [141, 145], and the normal circadian rhythmicity of the HPT axis is abolished [148], possibly due to the long half-life of thyroid hormone blunting the typical evening TSH rise. Similarly, in experimental conditions of rapid advancement of the darkness phase by 8 hours (simulating jet lag) led to conditions of daytime sleep, yielding failure of TSH to suppress, and consequently a rise in T4 levels rose. Of note, this upregulation of the HPT axis does not appear to occur during sustained partial sleep deprivation lasting 2 weeks [149]. The wakefulness promoting effect of the thyroid hormone in the short-term appears to be somewhat paradoxical when considering the circadian pattern of the HPT axis, as the levels of TRH and TSH are highest overnight at the time of sleep onset; however, there is a daytime occurrence of increased sleepiness, which coincides temporally with the nadir of

TRH and TSH levels, and a temporary decrease in sleepiness in the evenings, which tends to correspond temporally to the TRH/TSH peak [145]. Thyroid hormone may promote a wakeful state by a variety of mechanisms, including upregulating mitochondrial ATP production and subsequently stimulating synaptic velocity [145]. However, these effects are subtle, and may be primarily appreciated during either states of excess or insufficiency of thyroid hormone, or during states of prolonged sleep deprivation.

Prolactin

Prolactin a polypeptide hormone secreted in a pulsatile manner by anterior pituitary lactotrophs. It shares some structural homology with GH and with human placental lactogen. Prolactin's principal purpose in mammals is controlling lactation via stimulation of mammary cell differentiation and proliferation, but it exerts numerous other physiological effects [150], including but not limited to influencing reproductive function—elevation of prolactin inhibits the normal pulsatile secretion of GnRH and thus of pituitary gonadotropins, which in excess conditions can suppress the HPG axis in both sexes [151, 152].

Prolactin stimulation is unique among endocrine cells in that its secretion is under tonic *inhibition*: the basal secretory tone of pituitary lactotrophs is quite high. Dopamine secreted by hypothalamic tuberoinfundibular dopaminergic (TIDA) neurons enters the hypophyseal-portal circulation and subsequently binds to dopaminergic D2 receptors in lactotroph cell membranes, which activates intracellular signaling and acts to suppress the high basal secretory activity of pituitary lactotrophs by reducing prolactin exocytosis, prolactin gene expression, and lactotroph proliferation [153, 154]. Prolactin in turn regulates the hypothalamic dopaminergic neurons through "short-loop feedback"—increase in prolactin levels upregulates activity of the hypothalamic tuberoinfundibular dopaminergic neurons, and conversely a decrease in circulating prolactin levels lowers said neurons' activity [155]. Another known modulator of prolactin secretion is vasoactive intestinal peptide (VIP), which is secreted by neurons in the ventromedial and dorsal anterior nuclei of the hypothalamus and which enhances prolactin secretion [156].

Prolactin secretion demonstrates a strong circadian rhythm, with nadir levels around mid-day, rising rates of secretion in the early evenings hours and a notable rise during sleep (though amplitude of prolactin secretion is greater in women than in men) [157]. There is a clear causal relationship between sleep and prolactin—sleep interruptions and morning awakenings are associated with rapid declines in prolactin levels [111]. The cyclicity of prolactin secretion is likely significantly related to the rhythms of dopamine. TIDA neurons' dopamine release is rhythmic, and slightly out of phase with prolactin—dopamine secretion declines prior to the release of prolactin [158], enabling a near-doubling of prolactin levels overnight.

Beyond the basic association of prolactin secretion increase with sleep, the associations of prolactin secretion and sleep architecture are less consistent in the literature. As early as 1974, prolactin secretion was described to differ across sleep stages, with peaks during NREM sleep and nadirs during REM sleep described [159], and a later study of healthy young men further delineated this pattern and found that prolactin secretion was coupled to delta wave activity of SWS [160]. However, other studies cast this correlation into doubt. Another small study of healthy young men did not show a correlation between peak prolactin secretion amplitude and sleep stages (prolactin episodic fluctuations were randomly distributed across sleep stages) [161], another study of 8 young men and 2 women found that sleep disruption that caused selective SWS deprivation did not alter prolactin secretion [162]. Yet another study found that total rest duration (i.e., exposure to long dim periods of 14 hours rather than short ones of 8 hours) correlated with a greater prolactin rise [163]. Some of the differences in findings may relate to the age of individuals studied, given the known changes in sleep architecture over the lifespan (with decline in SWS proportion in later adult life [164]). A study of older adults (who spend less proportion of sleep in SWS) found that prolactin acrophase occurred ~3–4 hours after sleep onset, and unlike in younger adults, prolactin peak levels overnight were positively associated with total time spent in REM sleep rather than SWS [165].

Conditions of increased prolactin secretion also shed some insight upon the bidirectional relationship between prolactin and sleep. A study of post-partum lactating women (a state in which prolactin levels are naturally quite high) versus post-partum women who chose to formula-feed found a marked increase in time spent in SWS in the former group, although total sleep duration and REM sleep duration did not differ [166]. Similarly, a study of individuals with prolactinomas, pituitary adenomas producing excessive prolactin, has also found that individuals with prolactinomas had greater SWS duration versus controls, and that SWS was seen in these individuals in the second half of the night, but that REM sleep duration did not differ between groups [167]; the difference in SWS duration between those with prolactinomas versus controls was much more striking in younger individuals than in older individuals.

The association between prolactin and sleep is modulated by other circadian influences than sleep; thus, some of the nocturnal rise in prolactin is due to association with sleep and some to circadian influences, and only when the confluence of both sleep and proper circadian timing occurs is prolactin secretion maximized.

The Pineal Gland and Melatonin

The pineal gland is located in the mid-brain. Its principal function is to transduce retinal input of light and darkness into neuroendocrine signals, which impact whole-body physiology, principally via the rhythmic synthesis and release of the indoleamine hormone melatonin, known as the "hormone of darkness," from pinealocytes [168]; a process closely regulated by both circadian signals [169] and light exposure [168, 170].

The biosynthesis of melatonin in the pineal gland from its precursor L-tryptophan in a straightforward process of 4 sequential enzymatic steps; the rate-limiting step of melatonin synthesis is the conversion of serotonin to N-acetylserotonin, catalyzed by arylalkylamine N-acetyltransferase (AANAT, also called the "Timezyme") [171]. Post-ganglionic fibers from retinal cells convey signals, which lead to norepinephrine release, increased cyclic adenosine monophosphate (cAMP) production [172, 173], stimulating AANAT activity (said activity increases between 10 and 100-fold in the evenings and at night). Melatonin levels increase in parallel with AANAT; as melatonin has a short half-life due to rapid hepatic clearance [171, 174], the principal determinant of plasma melatonin levels is thus AANAT activity. Melatonin feeds back to modulate sleep and shift circadian firing rhythms in the SCN's central circadian clock in SCN via binding to its G-protein coupled receptors, melatonin receptors 1 and 2 (MT_1 and MT_2) in the plasma membrane [175, 176], which in turn activate secondary messenger systems and regulate the expression of clock genes [170]. The profile of melatonin secretion largely reflects that of the scotoperiod (period of darkness): during the daytime, light exposure inhibits melatonin production, and melatonin synthesis ramps up in the evenings beginning with the onset of dim light exposure, peaks overnight, and declines gradually thereafter [177]. Thus, melatonin effectively conveys a message of the state of "darkness" to the central circadian clock, subsequently inducing the soporific effect (the propensity to which typically occurs 2 hours after the onset of endogenous melatonin production [178]) as well as a nocturnal state of metabolism and physiologic functions [179].

The biosynthesis of melatonin is under the control of the central circadian rhythm generator in the SCN of the hypothalamus. Signals from the SCN are transmitted through the paraventricular nuclei (PVN) of the hypothalamus, the intermediolateral nucleus of the spinal cord, the superior cervical ganglion, and thence the pineal gland [180], and control the rhythmicity of melatonin biosynthesis; complete removal of the SCN abolishes this rhythmicity and leads to a significant daytime rise in melatonin levels by upregulating the establishing the central role of the SCN in the circadian rhythm of melatonin secretion [169]. A more detailed discussion of the role of melatonin can be found in other chapters in this book.

Endocrine Impact of Melatonin Action

In addition to impacting circadian rhythm, melatonin exerts several endocrine systems, notably glucose/insulin homeostasis and several hypothalamic-pituitary axes as detailed below (note that the impact melatonin upon either the HPA or HPT axes is quite inconsistent in the literature).

Insulin Secretion and Glucose Metabolism

Melatonin impacts glucose homeostasis and insulin sensitivity, but the directionality of the impact in the extant literature appears quite contradictory. In brown adipocytes, melatonin administration reduces the expression of the insulin-dependent GLUT-4 glucose transporter and thus reduces glucose uptake [181]. In rats, elevated melatonin levels are associated with higher glucose levels, and elevated insulin levels inhibit pineal melatonin synthesis in rat models [182]. Based upon these findings, a mutually inhibitory relationship between melatonin and insulin levels was long assumed. However, in human hepatocytes, melatonin *inhibits* hepatic gluconeogenesis [183], favoring lower glucose levels. Similarly, while variations in the *MTNR1B* gene (which encodes the melatonin MT_2 receptor) associated with greater type 2 diabetes risk, it is those variations associated with *decreased* melatonin sensitivity, which predict greater fasting glucose levels [184], impaired early insulin secretion, and increased risk of type 2 diabetes [185]. In addition, much attention has focused in recent years upon the impact of melatonin upon pancreatic islet cells, as MT_2 receptors are expressed on pancreatic glucagon-producing alpha-cells and insulin-secreting beta cells [186]; melatonin administration promote insulin secretion by sensitizing the cyclic AMP (cAMP) pathway and upregulating glucagon secretion, which exerts paracrine activity to stimulates beta-cell insulin secretion [186]. One possible explanation for the widely contradictory results in the literature may stem from disparate data sources. The majority of studies have been performed in rodents, which are nocturnal animals whose peak of melatonin synthesis coincides with their active "wake" phase. In diurnal animals such as humans, peak melatonin levels occur during the inactive "sleep" phase, which may explain why a different paradigm of the relationships between melatonin secretion and insulin secretion and glucose metabolism is seen [187].

Melatonin and Prolactin

The connection between melatonin and prolactin has been well-established in animal studies [188]. A study of young men found that rises in melatonin during the evening preceded temporally the rise in prolactin levels and similarly that the decline in melatonin secretion during the morning hours preceded the daytime decline in prolactin [189]. An experimental sleep deprivation study in young women found

that prolactin and melatonin levels did not rise during sleep deprivation under continuous illumination, but that both prolactin and melatonin levels did rise during conditions of sleep deprivation in a dark environment, clearly suggesting a circadian component. Indeed, administration of exogenous melatonin was found to stimulate prolactin release [190].

Melatonin and Growth Hormone

The greater frequency of GH pulses at night would seem to suggest a possible role for melatonin. This possibility has been explored through several mechanisms. In one study of children with GH deficiency, melatonin levels were found to be raised [191], suggesting the possibility of a compensatory mechanism. Several studies have shown that supraphysiologic exogenous melatonin plays a facilitative role in enhancing pituitary GH secretion in healthy young men [192, 193] and women [194]; this effect was attributed to a combination of enhanced response to GHRH and to inhibition of endogenous somatostatin release [194, 195]. However, though at least one study found no effect of melatonin upon GH secretion in humans [196], and there has not been significant examination of the impact of recombinant GH upon melatonin secretion; thus, this relationship remains to be further elucidated.

Melatonin and the HPG Axis

The amplitude of melatonin secretion varies widely between individuals, but also changes within individuals across the lifespan, decreasing substantially during puberty [197], a decline that cannot be entirely accounted for by increase in age or in body mass [198]. There is data in animal models to suggest that melatonin may inhibit GnRH secretion [199] and stimulate secretion of the inhibitory hypothalamic hormone GnIH [200]. This was historically taken to suggest a somewhat inhibitory effect of melatonin upon the central portion of the HPG axis [201]; however, no consistent inhibitory effect of exogenous melatonin administration upon gonadotropin or sex steroid levels has been demonstrated in the literature [202], and one study even found that exogenous melatonin enhanced LH secretion in women during the follicular phase but not the luteal phase of the menstrual cycle [203]; thus, the relationship of melatonin and the HPG axis in humans is not straightforward. Of note, elevated melatonin levels have been reported in adult men and women with hypogonadotrophic (central) hypogonadism and (for women) with functional hypothalamic amenorrhea [204], in which GnRH and gonadotropin levels are low, while *suppressed* melatonin levels have been reported in men with hypergonadotropic (primary) hypogonadism, in which gonadotropin levels are elevated [205], suggesting that GnRH itself (rather than sex steroid levels per se) may suppress melatonin secretion.

Globally then, melatonin is a hormone that exerts numerous endocrine and metabolic effects beyond the classical circadian impact; given the widespread use of high-dose exogenous melatonin supplementation, these metabolic and endocrine impacts should be clearly elucidated, with great care taken to distinguish between data derived from nocturnal animal models versus diurnal animal models and/or human data.

Summary

In this chapter, we have explored in great detail the associations between circadian rhythm, sleep and a number of endocrine systems, with special attention to the role of melatonin. An understanding of the normal physiology is a necessary underpinning to comprehending the pathophysiology when these delicate systems are disrupted. Historically, human behavior has been synchronized with the day-night cycle and the biological timing system, such that hormonal systems, which are modified by sleep and light exposure are exquisitely regulated. However, the advent of night-time artificial light exposure, shift work and resulting circadian misalignment, along with endemic chronic sleep restriction, can lead to dysregulation of the endocrine system in a manner that promotes the metabolic syndrome, type 2 diabetes, and cardiovascular risk.

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Thermoregulation and Metabolism

6

Véronique Bach and Jean-Pierre Libert

Introduction

Studies performed in animals have demonstrated that thermoregulatory responses are abolished during rapid eye movement (REM) sleep. In cats, Parmeggiani and Rabini [1] demonstrated that the body temperature change was not correlated with environmental temperatures in REM sleep—in contrast to the situation during non-REM (NREM) sleep. Similar results were obtained in kangaroo rats [2] and other mammals. These results suggest that a poikilothermic state operates during REM sleep—probably due to a transient, reversible inactivation of the central controller [3]. These observations led to several conclusions: (i) sleep and body thermoregulation are closely linked, (ii) the two processes interact, and (iii) REM sleep is characterized by a conflict between sleep needs and the maintenance of body homeothermia. As a result, partial or total REM sleep deprivation can be observed in animals sleeping in a cold or in a hot environment.

This functional conflict raises the question of whether thermoregulation during REM sleep is efficient in **humans** sleeping in a cool or warm environment. This question is of particular interest because of the longer duration of the REM episodes. This question was first addressed in adults and soon after in neonates. However, to the best of our knowledge, it has never been analyzed in older infants or adolescents. The studies performed in **adults** showed that in contrast to non-human mammals, thermoregulatory processes in REM sleep were depressed (but not abolished) in both cold [4] and warm environments [5].

This question is also of importance for the well-being of neonates, older babies, and infants when considering the paramount importance of sleep quantity and quality in neurodevelopment and good health in these more vulnerable populations. In the **neonate,** impaired thermoregulation during long episodes of REM sleep (lasting up to 1 hr) might be very harmful, since they can expose the child to significant, rapid heat exchanges with the environment at a time when the body's thermoregulatory capabilities are not fully efficient. This also represents a challenge for babies and older infants, even though the latter's thermoregulatory systems are more efficient. It is difficult to extrapolate the results obtained in adults to neonates or infants. Along with the difference in neural development, sleep and thermoregulation processes and rhythms develop progressively at these ages. In particular, there are marked differences between active sleep in neonates and REM sleep in adults. Moreover, because of the polyphasic nature of sleep (3- to 4-h sleep-wake cycles spread out across the 24-h period in neonates or with 1 or 2 daytime naps in babies and preschool infants), a single, long-lasting nighttime sleep period is not present yet, so that circadian processes and sleep pressure may act differently on sleep onset and maintenance than in adults.

This chapter reviews the functional interactions between sleep and thermoregulatory processes in neonates and infants, together with the implications of these interactions: thermoregulatory responses can differ according to the sleep stage, and sleep can be deteriorated or improved by a non-thermoneutral environment or by the manipulation of body temperatures.

Thermoregulation in Neonates and Infants

Basic Principles

Like adult humans, neonates and infants are homeotherms; they can maintain a constant body temperature despite changes in the surrounding environment. Homeothermia is achieved when the sum of metabolic heat production and heat loss from the body to the environment is nil.

Homeothermic organisms are able to control heat transfers and heat production through autonomic and behavioral responses in which the central nervous system has a leading

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role. The processes underlying these responses are not elicited in a specific range of air temperatures defined as the **thermoneutral range,** within which the body temperature (usually measured as the rectal temperature) is kept between 36.5 °C and 37.5 °C by merely changing the peripheral skin blood flow, and the metabolic heat production is minimal. In the adult, the thermoneutral range is defined by a narrow range of air temperatures (1–2 °C) and is also representative of the level of thermal comfort. In neonates, this temperature zone corresponds to optimal nursing conditions for vital functions and body growth. In premature neonates, the thermoneutral zone is narrower still; indeed, in very-low-birth-weight neonates, the width of the thermoneutral zone could be less than a single °C [6]. In infants, there is evidence that a narrow thermoneutral range is associated with delayed development of the central nervous system [7]. In neonates aged 3 months or less, the critical lower boundary of the thermoneutral zone varies greatly from one individual to another, and this variability is greater at the age of 3 months [8].

Above the upper boundary of the thermoneutral zone and below the latter's lower boundary, **thermoregulatory processes** are the only means of preventing body temperature changes. Although several hypotheses for the functioning of the thermoregulatory system have been put forward [9], most models are based on the fact that internal and peripheral warm and cold receptors transmit afferent information to a central controller, which integrates the information and triggers thermal responses by effectors through efferent signals. The central controller (though to be mainly located in the preoptic area and anterior hypothalamus) has a major role in both sleep regulation and thermoregulation; consequently, it is especially involved in the functional interaction between the two [for a review, see 10]. Neuronal activity of the warm-sensitive neurons in the preoptic area and anterior hypothalamus increases at sleep onset and decreases prior to awakening and during wakefulness [11]. Changes in skin or core temperature modulate the firing rate of these warm-sensitive neurons. Boulant and Hardy [12] have shown that skin temperatures have a strong impact on the activity of warm-sensitive neurons; this might be a sleep-promoting signal.

The **models** of thermoregulation are adapted from control system theory and are based on hypothalamic sensitivity and the concept of a reference value (i.e., a set-point value). The central controller might asses the difference (signal error) between the set point and the controlled temperature levels measured by thermal sensors, in a negative feedback process. The most widely accepted model was developed by Hammel et al. [13]. According to these researchers, the set-point value can be adjusted as a function of several factors, including skin temperature levels, alertness, circadian rhythms, sleep, and fever. Thermal responses (changes in vasomotor tone, shivering, non-shivering thermogenesis, sweating as described below) are mediated according to the sign of the signal error, in order to keep the controlled temperature within a narrow range. The intensity of these responses (defined as a gain, i.e., the slope of the relationship between the thermal response and the controlled temperature) can be constant, since the responsiveness of the hypothalamic structures is only modified when changes in skin temperature reset the set-point value. Other studies describe the central controller's contribution as an increase in the gain of the thermoregulatory function in response to skin temperature signals, without any change in the set-point temperature [5, 14, 15]. Although the validity of these various concepts of thermoregulation control is still subject to debate, they do explain a lot of observations.

As temperatures are not regulated uniformly from one body region to another, the **concept of a single, regulated temperature** of 36.5–37.5 °C remains questionable. This uniform temperature is not the overall body temperature. The body can be divided into two parts: a core including organs such as the lungs, heart, abdominal organs and brain (whose temperature is almost constant at between 36.5 and 37.5 °C) and a peripheral "shell" corresponding to skin layers (whose temperature is highly variable). In the adults, the skin can be divided into "hot" regions (above 36.5 °C) where the large arteries are close to the surface (such as the cheeks and the inguinal region), "warm" regions (above 33.5 °C, the skin of the limbs), and "cold" regions (below 33.5 °C, such as the extremities). Indeed, blood flow is controlled and regulated differentially in each body region. In preterm neonates (postnatal age: 28 days; body mass: 2300 g) nursed at thermoneutrality in a closed incubator, the regional thermal profile is less heterogeneous than in the adults. The highest skin temperatures are measured at the nape of the neck (37.05 °C), whereas the lowest values are recorded over the upper arms and feet (35.53 and 35.54 °C, respectively) [16]. The thermoregulatory system's output results from the spatial integration of these various temperatures. Although this thermal heterogeneity generates variations in the afferent nervous information sent to the central controller, most models consider that the core or internal temperature (measured as the rectal, esophageal, axillary, or tympanic temperature) is the sole controlled variable.

In contrast to children and adults, neonates are particularly at **risk of thermal stress**. They have less efficient thermoregulatory responses, and relatively greater body heat losses to the environment—notably as a result of a high surface-area-to-body-volume ratio (0.8, 0.6 and 0.2 cm^{-1} in premature neonates, term neonates, and children weighing 20 kg, respectively) [17]. Neonates have less insulation from subcutaneous tissue, which increases thermal conductance and constitutes a further disadvantage when faced with cold. Moreover, the convective and evaporative heat transfer coefficients in neonates are greater than those in adults (promoting heat loss), as a result of the strong curvature of the body

segments. The more immature the neonate, the larger the body heat losses. Comparing two mannequins representing small neonates of 900 and 1800 g, Elabbassi et al. [18] showed that the overall dry heat loss by convection, conduction, and radiation was 20.4% higher for the smaller mannequin.

Hence, neonates can become rapidly hypothermic; in addition to their disadvantageous physical characteristics, their thermoregulatory processes are not fully efficient and the energy available for maintaining body temperature is limited—increasing morbidity and mortality rates.

Thermoregulatory Parameters and Sleep Stage Effects in the Thermoneutral Range

The thermal responses controlled by hypothalamic structures differ from one sleep stage to another. This can be observed even within the thermoneutral range.

Oxygen consumption is greater in REM sleep than in NREM sleep in full-term neonates—at least during the first week of life [19–21], at 2 or 3 weeks of age [22], and 3–4 months of age [8, 23]. The situation for preterm neonates is subject to more debate, since the sleep stage difference in oxygen consumption was not always statistically significant—perhaps because the babies were more premature (33–35 weeks of gestation, studied between 3 and 17 days of age) [24].

In full-term babies aged 5 hr. to 7 days, **skin blood flow** (measured at the forehead) is greater (by 28%) during REM sleep than during NREM sleep (scored using behavioral criteria); this results (at least in part) from greater autonomic nervous system activity during REM sleep [25]. In full-term 3-day-old neonates, overall **body heat loss** was found to be greater during REM sleep; however, **water loss** did not differ significantly, except when specifically considering the transition from NREM sleep to REM sleep (it was higher in REM sleep) [20].

In a study of infants aged 2–26 weeks, nighttime **body temperature patterns** showed periodic ultradian oscillations with a period of approximately 1 hour; these oscillations might reflect alternating REM and NREM sleep stages [26]. The esophageal temperature is higher during REM sleep in preterm neonates reaching term [27]. A significant decrease in rectal temperature had already been observed during the REM-NREM transition in full-term neonates but not in preterm neonates reaching term [28]. With a larger sample size, the same group of researchers evidenced sleep stage differences in rectal and skin temperatures in both preterm and full-term neonates [29]. Richard [30] observed that the increase in axillary temperature due to mother–infant bed-sharing was mostly restricted to NREM sleep, and further suggested an explanation based on infant homeostasis, rather than passive body heating by mother heat-flux. In the study by Ammari et al. [31], however, skin temperatures and thermal gradients were similar in REM and NREM sleep stages.

Body temperature **patterns** during a given episode of sleep also differ from one sleep stage to another. During NREM sleep, the esophageal temperature and the mean skin temperature both decrease over the course of the episode. In contrast, both temperatures increase significantly during REM sleep episodes. Oxygen uptake decreases during episodes of REM sleep but only when the latter is followed by an episode of NREM sleep [27]. This explains why the direction of the sleep state change (i.e., REM to NREM, or vice versa) may be relevant, and might explain also the discrepancies reported in the literature. The direction of the sleep state change has rarely been studied, however.

In preterm and term neonates, the **variability** of all the following thermoregulatory parameters is always greater in REM sleep: rectal but not skin thoracic temperatures [29], forehead blood flow [25], respiratory rate [32], metabolic activity [19]). This results from the predominant parasympathetic activity during NREM sleep (during REM sleep, parasympathetic activity decreases and sympathetic activity increases) [33].

Physiological Adjustments to Cold, and Sleep Stage Effects

When exposed to a cold environment, **peripheral vasoconstriction** occurs first, and directs venous blood from the peripheral skin layers to the deeper venous network. This process (which takes place within a few minutes) increases the insulating value of peripheral tissues, increases the internal-to-skin temperature difference, and decreases body heat losses (by convection, radiation, and conduction) to the surroundings. Distal skin regions contain arteriovenous anastomoses, which are primarily innervated by the sympathetic nervous system. As a result, vasoconstriction is more pronounced at the extremities than on the trunk; hence, the distal-to-proximal skin temperature gradient (DPG) increases. This difference is often considered to be an early marker of thermal stress [34, 35]. Lindqvist et al. [36] have observed that in neonates, vasomotricity is controlled more by the sympathetic system than by the parasympathetic system.

Brück et al. [37] reported that the thermoregulatory modulation of vascular tone is mature and functional in full-term neonates. In preterm neonates (weight <1000 g), this control is absent at birth but develops over the following 2–3 days [38]. However, there is evidence to show that the peripheral vasomotor responses of very premature infants are impaired during the first few hours after birth [39, 40], even though

their arteriovenous anastomoses are functional [41]. Knobel et al. [40] pointed out that hypothermic small neonates (weighing 800 g) did not exhibit peripheral vasoconstriction during the first 12 hours of life. Taking into account Lyon et al.'s report [38] that peripheral vasoconstriction only occurred in neonates aged over 5 days, Knobel et al. [40] assumed that the increase in peripheral vasoconstriction capacity as a function of postnatal age was due to neuronal maturation. However, it has been observed that peripheral vasoconstriction can occur in body extremities (the hand, foot, and calf regions) in premature and term neonates [42]. Berg et al. showed that a fall in the air temperature of 4.5–8 °C decreased the peripheral blood flow by 36% [42]. In neonates with a gestational age of 33–36 weeks, peripheral vasoconstriction in the foot was combined with a release of vasomotor tone on the trunk [43], which limited the efficiency of this mechanism in response to cold exposure. The heat loss response to cold stress is age-dependent, since the rate of blood flow in the arteriovenous anastomoses begins to decrease during childhood [41]. Several studies have shown that in the cold, cutaneous vasoconstriction is greater in prepubertal infants than in adults [44–46]. A similar finding was reported by Tsuzuki et al. [47], who showed that the local skin temperatures at the hands and feet were greater in children (aged 15 months to 3 years) than in the mothers (aged 29 to 40 years), as a result of greater vasoconstriction.

Although the initial thermoregulatory response to cool exposure is peripheral skin vasoconstriction, there are few data on the effects of sleep stage on this process in a cool environment.

In a second response to cold exposure, **metabolic heat production** is increased through non-shivering thermogenesis (NST). This metabolism thermal response mainly involves the brown adipose tissue (BAT). However, organs such as the liver or the brain (due to their high metabolic heat production) and tissues such as white adipose tissue also contribute to metabolic heat production. Given its large mass and relatively high oxygen consumption, the brain can warm the body. White adipose tissue not only provides free fatty acids to organs involved in thermogenesis but also produces heat directly. The metabolism in BAT is controlled by sympathetic innervations, and this tissue can produce a significant amount of heat. Most of the BAT is located in the thoracic, cervical, and paravertebral regions. The tissue's location and ample blood supply mean that the generated heat warms the spinal cord, the heart, and the thorax as a whole—making it possible to increase cold resistance. At between 22 and 29 weeks of gestation, the BAT constitutes the majority of the neonate's fat stores. At birth, a neonate weighing 3000 g has 40 g of BAT (about 11% of the body's fat). However, the amount of BAT increases by a factor of 1.5 between the third and fifth weeks of life. Clarke et al. [48] have demonstrated that lambs delivered by cesarean section had a lower level of thermogenic activity (by 50%) in the BAT than those born vaginally; the level was similar to that of a fetus after 145 days of gestation. This was probably because the postpartum level of guanosine 5′-diphosphate (GDP) did not rise in these animals. Recent studies have suggested that BAT may have a key role in sleep promotion, and that this organ may be influenced by the interaction between sleep and body temperature [49].

Heat can also be generated through **shivering thermogenesis**. This thermal response to cold exposure appears progressively with age, and does not exist in the neonate—except when cold exposure is very strong [50]. Classically, shivering is induced by the cooling of the skin. However, a drop in the internal temperature drop can also induce shivering thermogenesis, even when the skin temperature is normal or elevated. Shivering thermogenesis involves two pathways. The first is muscle activity; this consists of rapid rhythmic, muscle contractions, starting in the scapular region. Synchronization with the antagonistic muscles makes it possible to combine the shivering with body movements. In neonates, shivering cannot be the major process in heat production, since the skeletal muscle system is not mature. The second pathway results from a transfer of energy chemical processes related to the stimulation of cellular metabolism by sympathetic activation and thyroid hormones.

As reported by several researchers [44, 45], metabolic heat production in response to cold exposure is greater in prepubertal infants than in adults. Combined with more efficient peripheral vasoconstriction, children can maintain similar [45] or higher body temperatures [44] than adults.

When exposed to a cool environment (an air temperature 3–5 °C below thermoneutrality), metabolic heat production increases in both 1-week- and 3-month-old infants [8]. Even premature infants (33–35 weeks old) were able to increase their oxygen consumption in all sleep stages [24]. All the literature data argue in favor of active, efficient thermoregulation during REM sleep in neonates.

Although the metabolic response to cooling varies widely from one neonate to another, it is usually assumed to be more intense during REM sleep than during NREM sleep in full-term neonates from the first week of life [20, 51] until the age of 3 months [8]. However, this difference is subject to debate [19, 24].

Since the thermal response during REM sleep is at least equivalent to (or more intense than) that recorded during NREM sleep, the sleep-stage-specific differences in oxygen consumption as observed at thermoneutrality are increased on cool exposure [52].

When the **cool thermal load was prolonged** (75 hr., thermoneutrality—2 °C, at 37 weeks of postconceptional age), the esophageal temperature difference between REM and NREM sleep disappeared, whereas oxygen consumption increased less in REM sleep (by 20%) than in NREM sleep

(by 33%); furthermore, the inter-sleep stage difference was no longer present at the end of the cool exposure [53].

In **individual neonates,** we observed a negative correlation between oxygen consumption on the one hand and the esophageal and skin temperatures on the other hand when exposed to cool challenge [22]. In 5 of the 9 neonates, the metabolism increased when body temperatures decreased—demonstrating that closed-loop regulation (suggestive of a classical non-shivering thermogenesis response) is fully operative during REM sleep. Unfortunately, the small number of NREM sleep episodes prevented us from directly assessing this relationship in NREM sleep and thus probing potential sleep stage differences in the regression line's slope (the gain of the response) and the intercept (the set point) [22].

Physiological Adjustments to Heat, and Sleep Stage Effects

In warm environments, the main heat loss responses are the release of the skin vasomotor tone and evaporative skin cooling (due to sweating).

There are few published data on the changes in peripheral blood flow in premature and low-birth-weight neonates exposed to hot environments—partly because the latter are less frequently encountered than cool conditions in nursing care. Likewise, sleep-stage effects on these responses have not—to the best of our knowledge—been analyzed in older infants. It is commonly accepted that the skin blood flow response to a rise in body temperature decreases with age [54, 55]. The higher peripheral blood flow and reduced cardiac output observed in young infants [56] increase the cardiovascular strain during heat exposure.

For preterm neonates, the heat loss by evaporation occurs by **transcutaneous water loss**. The skin is highly permeable because the epidermal barrier to water diffusion has not fully developed.

Active thermal sweating does not operate in the neonate before 37 weeks of gestational age [57], except when the body temperature is very high (i.e., rectal temperature ˃37.9 °C [58]. In mature neonates, thermal sweating occurs successively on the forehead, trunk, and limbs. Foster et al. [59] found that (i) the sweat gland density is higher in neonates than in adults but (ii) the maximum sweat output per gland in the neonate after intradermal injection of acetylcholine is only one-third that found in the adult. Likewise, the sweating rate response in prepubertal children is lower than in adults, despite a higher sweat gland density [60] and independently of the gender [61]. Lower sweating rates with ageing are mainly attributed to a decrease in sweat output per gland [62] and/or a higher threshold for sweating onset [63]. However, a possible age-related decrease in the hypothalamic set-point temperature for sweating (i.e., from premature infants to adults) cannot be ruled out [64].

When measuring water loss in neonates, it is difficult to discriminate between transcutaneous water loss and active sweating; this is especially problematic in preterm neonates. In a closed incubator, Okken et al. [65] reported a water loss rate of 1.04 ± 0.24 $mL.kg^{-1}.hr.^{-1}$ for preterm neonates (body mass: 1520 g; gestational age: 31 weeks; postnatal age 13 days) nursed under thermoneutral conditions. This water loss can lead to hypothermia and dehydration if appropriate preventive measures are not taken. Transcutaneous water loss decreases with postnatal age, as a consequence of the increase in the keratin content of the epidermis stratum corneum [66]. Thus, Wu et al. [67] showed that insensible water loss through the skin and respiratory tract in premature neonates can be four times that measured in term neonates. An old study performed on children aged from 5 months to 4 years found that the sweat rate was higher at sleep onset than during wakefulness [68]. Unfortunately, this work did not include a sleep stage analysis. Some recent studies [20] (but not others [8, 22]) have found a sleep stage effect on **water loss** at thermoneutrality.

In a slightly warm environment (thermoneutrality +2 °C, +0.23 °C for the esophageal temperature, and + 0.33 °C for the skin temperature), evaporative skin water loss in preterm neonates increased significantly (+66%) but there were no sleep state differences. Individual positive regressions between water loss and esophageal and skin temperatures measured during REM sleep episodes suggested that controlled, active process were operating—in line with what was observed in a cool environment [22].

Despite the differences in the thermoregulatory responses observed between adults and prepubertal infants, the respective **body temperatures** do not differ when they are exposed to heat stress [69, 70].

Behavioral Thermoregulation

As with autonomic regulation, behavioral regulation keeps the body temperature as constant as possible by acting on the external environment through various strategies. These involve the motor system and the creation of a microenvironment that protects the organism against fluctuations in the external thermal environment (i.e., avoidance reactions). Behavioral regulation precedes autonomic regulation and can be considered as an anticipatory avoidance reaction triggered by the peripheral perception of thermal stress. Indeed, behavioral regulation requires peripheral and internal temperature sensitivities and a central nervous component that partly overlaps with the autonomic regulation pathway. The motor effectors are different, however, and are stimulated via corticospinal and mesencephalic pathways. The

mesencephalon is significantly involved in avoidance reactions. Thus, neonates can increase thermogenesis through muscle activity [22]. **Body movements** can also reflect discomfort upon cool exposure, interrupt sleep continuity, and induce sleep stage changes or awakenings. As expected, body activity increases when preterm neonates are exposed to a cool environment [71]; this often leads to the infant waking up [8]. Increased body activity is more pronounced in 1- to 3-month-old full-term babies than in younger ones, whatever the sleep stage [8, 51]. In preterm neonates, we have observed concomitant increases in the frequency and mean duration of body movements but only during REM sleep, which is already characterized at thermoneutrality by greater durations and frequencies of body movement. Four of the 9 neonates exhibited a positive individual correlation between oxygen consumption and internal temperature (but not skin temperature), which reflected greater body movements while sleeping in response to a lower internal temperature [22]. It is not clear how effective this process really is because the motor system is not well developed [72], and some studies have not observed this increase in body movement in response to cold [73].

When faced with cold or heat challenges, neonates can assume postures that change the skin surface area exchanging heat with the environment. Harpin et al. [58] showed that neonates were less active and adopted a relaxed "spread-eagle" position when exposed to a hot environment (an incubator air temperature of up to 39.9 °C). This behavioral thermoregulatory response is also observed in some immature infants (˃30 weeks of gestational age). Using a mannequin representing a neonate with a weight of 3300 g and a surface area of 0.23 m^{-2}, Wheldon et al. [74] showed that the skin surface area for heat exchange increased from 0.48 for a fetal position (as observed in cold conditions) to 0.57 for a relaxed position and 0.76 for a spread-eagle position. The heat transfer coefficient for convective heat exchanges (promoting radiant and convective heat losses with the environment) respectively increased from 4.0 to 5.4 $W.m^{-2}.h^{-1}$.

With the exception of neonates nursed naked in an incubator (i.e., neonates requiring a highly controlled environment), clothing insulation is also a relevant component of behavioral thermoregulation. More mature infants usually sleep clothed, which considerably reduces heat loss but can increase the risk of body overheating. In sleeping adults wearing pajamas and covered by two cotton sheets and a single woolen blanket, Candas et al. [75] showed that the air temperature of the microclimate inside the bed was respectively 28.6, 29.6, and 29.7 °C for room temperatures of 16, 19, and 22 °C. The creation of an approximately thermoneutral microenvironment in the bed helps to protect the sleep stage structure [76].

Sleep Is Influenced by Non-thermoneutral Conditions

The impact of non-thermoneutral conditions on sleep has mainly been studied in neonates or older babies, given their greater vulnerability (especially regarding thermoregulation), the relevance of sleep for neurodevelopment, the risk of sudden infant death syndrome, and their relative inability to alert their parents when ambient conditions are harmful.

Sleeping in a Cool Environment

Although the disruption or continuation of the sleep cycle in neonates cannot strictly be described as an alternation between a homeothermic state and a poikilothermic state (in contrast to what is observed in adult animals and, partly, adult humans), sleep can be disturbed by cool exposure even when the latter does not elicit thermal responses.

The first impact concerns **sleep duration and continuity**. Cold exposure (by as much as 4 °C below thermoneutrality) increases the frequency of awakening in **preterm neonates** [43, 77]. Similarly, moderate cool challenges (1.5 °C below thermoneutrality) reduced the total sleep time (by a mean ± standard deviation of 20 ± 44 min) and the longest sustained sleep period, and increased intrasleep wakefulness [78]. These modifications were observed even though thermoregulation was only slightly elicited (vasodilation only, evidenced by a greater internal vs. skin temperature difference and no increase in oxygen consumption). Final spontaneous awakening was earlier (by 21 ± 41 min), and intrasleep wakefulness was longer [27].

Older infants (3- and 4-month-old) also woke up earlier when lightly clad in cool rooms, though their body temperatures were not low [8, 79]. However, 14-week-old Finnish infants slept longer (with an increase of 92 min during the daytime nap, as defined by behavioral criteria) outdoors in northern winter conditions (air temperature between −25.9 and 2.2 °C) than indoors (20.5–26.7 °C). Despite this observation, outdoor sleeping duration was shortened when the skin temperature cooling rate (but not the mean, maximal, or minimal value of any skin temperature) was large or when the outdoor air temperature was low. This apparent contradiction could be explained by the clothing and sleeping bag used in the prams, which restrained the infants' movements. The researchers suggested that outdoor sleeping makes it possible to sleep swaddled without overheating. They concluded that sleeping outdoors is beneficial as long as the skin temperatures do not fall too much [80], in line with the studies cited below.

As regards **sleep architecture,** NREM sleep appears to be particularly sensitive to cool thermal stress; indeed, the

latter can induce partial or even total NREM sleep deprivation [51]. Cool exposure reduces the total duration of NREM sleep and increases the total duration of REM sleep in full-term neonates [8, 51] and preterm neonates [22, 27, 78, 81–84]. In preterm neonates, NREM sleep episodes are less frequent, and the longest NREM sleep episode is shorter [82, 84]. Preferential switching from NREM sleep to REM sleep is observed [78]. Thus, neonates exposed to cool environment favor REM; this leads to greater expenditure of metabolic energy for thermoregulatory needs rather than energy conservation (which would be greater during NREM sleep but might compromise body homeothermia). This pattern is even observed for low-magnitude thermal stress.

Decrease of the ambient temperature or the core body temperature is associated with a greater amount of REM sleep [8, 22], which decreases the NREM/REM sleep ratio and/or the number of transitions from NREM sleep to REM sleep [19]. REM sleep episodes were more frequent but less frequently followed by an NREM sleep episode, and more frequently followed by wakefulness [27, 78]. It is noteworthy that the effects of cold exposure on REM sleep episodes differ according to an episode's outcome: REM sleep episodes followed by NREM sleep were shortened (by 17 ± 28 min, on average) and less frequent, whereas REM sleep episodes followed by wakefulness were lengthened. The outcome of REM sleep in neonates is not related to a specific body temperature value at the time of the sleep stage transition. In contrast, a low esophageal temperature at the beginning of the REM sleep episode and/or a progressive rise in this temperature enhance the transition towards wakefulness [27].

This switching from NREM sleep to REM sleep is relevant from a thermoregulatory viewpoint. Interestingly, neonates exhibiting the greatest increase (by 41%) in metabolic heat production during NREM sleep did not switch into REM sleep [51]. Moreover, the modification of NREM sleep and REM sleep was less frequent in 3-month-old infants because most of them woke briefly at the beginning of the cooling procedure [8]. Consistently, the shorter NREM sleep episodes [51] and the longer REM sleep episodes observed in 1-week-old, full-term neonates [8] were not statistically significant in 3-week-old preterm neonates [27].

In another study, a 5 °C difference in the incubator air temperature between daytime and nighttime did not lead to sleep disturbances; however, this might have been due to a nycthemeral effect blunting the temperature effect and/or a small sample size [85].

During **chronic cool exposure** (75 hr., 2 °C below thermoneutrality, 37 weeks postconceptional age), the neonates' sleep structure and duration did not improve (and continued to deteriorate, in fact) after thermal adaptation (as inferred by greater metabolic heat production during the last exposure than during the first cool exposure) [53]. Hence, protective mechanisms for maintaining body temperature do not interact with sleep mechanisms—in contrast to the situation in adults [86].

Sleeping in a Warm Environment

A warm environment (thermoneutrality +2 °C, +0.23 °C for esophageal temperature, and + 0.33 °C for skin temperature) did not induce any sleep differences in full-term neonates aged 2 or 3 weeks, although the sweating rate was increased (by 66%). Only the body movement frequency fell [22]. Franco et al. [87] did not observe any sleep differences between 11-week-old term infants sleeping at 28 °C and those sleeping at 24 °C, despite some intergroup differences in the body temperature pattern. Likewise, Brück et al. [81] did not observe any sleep modifications.

In a study performed in an earthquake shelter, school children (mean age: 11 years) claimed that heat was the most frequent cause of sleep disturbances. However, it is difficult to determine whether sleep disturbances (as assessed by actigraphy) are due to thermal discomfort and/or a sweaty feeling, rather than other factors (noise, stress, etc.) [88].

Impacts of Thermal Transients on Sleep

Neonates nursed in a closed incubator are often exposed to transient air temperature changes when the incubator door is opened or during a thermal overshoot after the door is closed. A decrease in the air temperature (from 24–27 °C to 18–21 °C over a 20 min period) during an episode of NREM sleep promotes the transition to REM sleep. This switch to a sleep stage associated with higher oxygen consumption was not observed when the latter had increased greatly during the preceding NREM sleep episode. When the air temperature decreased during an REM sleep episode, half of the neonates did not enter NREM sleep [51]. Few of the older (3-month-old) infants remained in the same sleep stage before and after transient cool exposure [8].

During progressive cooling, the REM sleep/NREM sleep ratio decreased in preterm neonates but increased in full-term neonates. Conversely, during a heating transient, the REM sleep/NREM sleep ratio decreased [89].

Sleeping at Thermoneutrality

The above-mentioned studies observed sleep disturbances in a non-thermoneutral environment. Sleep disturbances are observed as soon as (or sometimes even before) thermoregulatory processes are solicited. Indeed, sleep appears to be more sensitive to thermal stress than thermoregulatory

parameters are. Kapas and Szentirmai [49] suggested that sleep duration is optimal when the organism does not need to invoke functions that require wakefulness. Thermoregulation is one of these functions, along with other activities related to energy metabolism (feeding, muscle activity, etc.). On the basis of studies of animals and adult humans, one can conclude that (i) sleep in general and REM sleep in particular are optimal within the thermoneutral range, and (ii) the REM sleep duration could be considered as a marker for thermoneutrality. In neonates, NREM sleep appears to be the most sensitive sleep stage, and is be reduced by exposure to a non-thermoneutral environment [27].

It has been observed that adults regulate sleep in phase with the circadian body temperature rhythm. Sleep occurs during the period where the core temperature is relatively low. In particular, increased sleepiness and habitual sleep onset occur when the core temperature is decreasing. Conversely, the likelihood of awakening increases as the core temperature increases in the morning. Distal (foot and hand) skin temperatures vary in the opposite way to the core temperature.

In 1938, Magnussen (cited in [90]) suggested that vegetative sleep preparedness starts around 100 min before sleep onset. The first step is skin vasodilation; this is particularly pronounced on the distal regions with the greatest vasomotricity (due to arteriovenous anastomoses [for a review, see 91]), which increases the heat losses to the environment and thus decreases the core body temperature. Bedtime and sleep onset usually occur just after or close to the most rapid decline in core temperature. However, the core body temperature decrease is probably a consequence of the distal skin heat loss, which initiates sleep per se [92]. In mechanistic terms, it is hypothesized that increased distal skin temperature stimulates the discharge of warm-sensitive neurons in the preoptic area and anterior hypothalamus. This induces a downwards shift of the set-point value for the vasomotor tone, and thus facilitates and improves sleep. Among various candidates (the core body temperature, the melatonin level, the heart rate, the subjective sleepiness rating…), the **DPG** (a marker of the vasomotor tone) is the best predictor of sleep onset [93].

As a result, many changes (including sympathovagal changes) occur at least 30 min before sleep onset [94]). These changes are linked to sleep per se (rather than to lights-off) and have a role in initiating sleep.

Interestingly, the **relationship** between simultaneous changes in sleep propensity and body temperature rhythms is causal relationship. Several studies in adults have shown that experimentally induced distal vasodilation promotes sleep (see below). This raises the question of whether the causal relationship also operates during development in infants, whose sleep is polyphasic and whose circadian rhythms are less tightly controlled.

Temperature Circadian Rhythm in Infants and Its Relationship to Sleep

Body temperature rhythm per se is one of the first circadian rhythms to appear in babies. According to Bueno and Menna-Barreto [95] the endogenous circadian system that regulates body temperature may be functional as early as 29 weeks of gestation. Longitudinal studies show that the temperature rhythm becomes more robust between birth and the age of 3 months [96], and that the rhythm at 6 months of age is already similar to that observed in young adults [97]. The rhythm increases in amplitude between 7 months and 7 years of age, and achieves an adult-like pattern at the age of 7 years [98].

Discrepancies in the literature data regarding the age at which the circadian body temperature rhythm appears can be attributed to high interindividual variability and the fact that the emergence of circadian rhythms depends on many environmental parameters (light levels, hospital vs. home differences, etc.), care-related parameters (the feeding schedule, etc.) and/or the mother and baby's characteristics (maturation, intra-uterine growth, prematurity, etc.) [for a review, see 96]. These researchers concluded that sleep and circadian rhythms are already coupled in infants but that their time course of development is not necessarily comparable [96].

Body Temperature Rhythm According to Sleep

Even though Richard [30] has suggested (on the basis of anthropological data) that the "normal" sleep temperature profile (defined here as mother-baby co-sleeping) does not include a large drop in core temperatures at sleep, most researchers have demonstrated that the core temperature is higher when the baby is awake and falls with sleep [99]. In a study of *3–4-month-old babies* sleeping at home, Wailoo et al. [100] observed that the rectal temperature (which was above 37 °C before the baby was put in its cot) fell by 0.8 °C over the following hour. The temperature then stabilized and rose slightly after 5 hr. Similarly, Tsogt et al. [101] observed a mature, diurnal temperature change pattern in 3-month-old infants: a fall in core temperature and an elevated peripheral temperature during the night, that is, probably after sleep onset (although sleep was not measured). The opposite pattern was observed later in the night, that is, probably before early awakening. This is observed by the age of 6 weeks, regardless of whether sleep occurs during the day or the night [102]. The older the baby, the greater the fall in rectal temperature after sleep onset [103].

In preterm infants aged 9 days, we observed similar results [104]. Foot and hand distal temperatures increased (by 0.38 °C and 0.15 °C, respectively) during the 20 min before nocturnal sleep onset (as determined by polysomnography), leading to a greater DPG (by 0.52 and + 0.30 °C/20 min,

respectively). During the same period, the abdominal skin temperature (often considered as a marker of the core body temperature) did not vary significantly. In contrast to older infants and adults, the increase in distal temperature stopped after sleep onset. Differences in sleep between neonates, older infants, and adults might account for this specificity; in neonates, REM sleep appears first after sleep onset (and is characterized by an increase in sympathetic tone), whereas the autonomic balance in older infants and adults is in favor of parasympathetic tone and thus NREM sleep after sleep onset.

When considering the 30 min periods before and after sleep onset (as assessed by actigraphy) in *4-month-old term babies*, the distal temperatures (but not the proximal temperatures) increased gradually until 10 min after sleep onset and then stabilized. The DPG rose by 0.075 °C/min during the 30 min before sleep onset. However, 7 of the 43 babies did not exhibit a similar pattern, and their distal temperature remains high for up to 45 min after sleep onset. Interestingly, the value of the DPG was correlated with the distal temperature rather than the proximal skin temperature—emphasizing the importance of the distal segments [91].

Abe and Kodama [91] found a lack of individual stability in the pre-sleep body temperature pattern in babies *aged 4–9 months*. In contrast, Lodemore et al. [105] observed that full-term babies developed mature temperature rhythms (defined here as the age at which the trough rectal temperature fell below 36.6 °C during the nighttime sleep) at a mean age of *11.1 ± 2.5 weeks*. This change occurred abruptly (over 1 or 2 days) and was permanent—suggesting that the endogenous mechanism of temperature control was physiologically altered. Lodemore et al. demonstrated that the transition to mature temperature rhythms results from a complex interaction between intrinsic and extrinsic factors, including breast feeding, speed of weight gain, sex, and a supine sleeping position. The noticeable interindividual variability in the time needed to achieve a mature rhythm was associated with the appearance of longer nighttime sleep.

It is generally assumed that because a baby's body temperature pattern does not depend on the ambient temperature or the thermal insulation (clothing or wrapping), it is internally driven and controlled. However, Franco et al. [87] demonstrated that the rectal temperature fell more rapidly and reached a lower trough value when *11-week-old term* babies slept at 24 °C, relative to 28 °C. Moreover, the mature diurnal temperature pattern was not found in *3-month-old* **babies** with traditional Mongolian swaddling, even though this higher degree of thermal insulation did not induce any thermal stress [101]. In contrast, Petersen et al.'s [99] study of 12- to 22-week-old babies did not report any significant effect of the thermal insulation used (which was probably lighter than Mongolian swaddling) on the core temperature level and rhythm—except for the combination of a prone position, heavy swaddling, and a warm room. In the latter situation, body temperatures tended to increase more rapidly at the end of the night but there was no impact on morning awakening. Interestingly, the decrease in core temperature was greater in babies not fed before sleep [106].

Wrist, shin, and foot temperatures show opposite trends (relative to the rectal temperature) [26] and have a one-hour phase advance [95]: these distal skin temperatures increase rapidly over the first hour after sleep onset, and decrease during or shortly before or after awakening. In contrast, the skin temperature measured on the abdomen only rose slightly or remained stable during the first part of the night in 3- to 4-month-old babies [100].

The fact that a **baby's** body temperature pattern is in **phase with its placement in a cot** (and presumably sleep onset) rather than with time of the day, suggests that circadian rhythms do not have a major role at this age. However, a circadian influence is still present, as indicated by a lower fall in rectal temperature during a daytime sleep episode than during a nighttime sleep episode of similar duration [106].

Body Temperatures and Sleep Onset

In infants (5–12 years of age), Murphy et al. [107] observed that a distal (calf) skin temperature and a proximal (subclavicular region) skin temperature increased before bedtime. The distal temperature continued to increase after bedtime, whereas the proximal temperature began to fall slightly. In 6- to 12-year-old infants sleeping in their natural settings, McCabe et al. [108] reported increases in skin temperatures (on the back, neck, foot, and subclavicular region but not the forehead) from 1 hour before the reported bedtime to 2 hours afterwards. The changes were greater for the distal temperature than for the others, and all the changes were reproducible from one night to another. When considering the temperature change around sleep onset (as assessed by actigraphy), the DPG (T_{feet}—$T_{subclavicular}$) started to increase 1 hour before sleep onset and continued to do so until 90 minutes after sleep onset. However, the trend for a decrease in the core tympanic temperature from 1 hour before bedtime (the first measurement) to bedtime (the second measurement) did not reach statistical significance but was consistent with literature data in adults. Except for the abdominal temperature, none of the skin temperatures significantly varied before morning awakening.

In a study of preschool children (mean age: 4 years) and their mothers, Okamoto-Mizuno et al. [109] found that proximal temperatures might have a greater role than the foot distal skin temperature—probably as a result of more rapid redistribution of the blood to the proximal regions than to the distal regions at the wake-sleep transition. This discrepancy is unlikely to be due to age-related differences because studies performed in both younger and older populations have

evidenced the major role of distal temperatures in prompting the core temperature decline before sleep onset.

Murphy et al. [107] reported that the DPG increased (i.e., distal temperatures rose towards proximal temperatures) before and after sleep onset in *5- to 12-year-old infants*. These researchers defined a specific criterion (DPG0°) as the time at which the DPG first crossed 0 °C. In line with the literature data on adults, the study's results showed that the shorter the time to reach DPG0°, the shorter the sleep onset latency. Interestingly, some of the infants in Murphy et al.'s study had pediatric bipolar disorder; these children displayed both thermoregulatory changes and sleep onset difficulties—suggesting that thermoregulation and emotion regulation share some neural circuits.

In contrast to the results in adults, the value of the DPG at sleep onset in *4- to 9-month-old infants* was not correlated with rapid sleep onset and could therefore not accurately predict the sleep onset latency. For example, babies with a high DPG (getting close to 0) did not always fall asleep quickly, since the sleep onset latency ranged from 4 to 68 min. However, Abe and Kodama [91] observed that babies with a DPG value that remained low over the first 15 min after lights off were unlikely to fall asleep rapidly (i.e., within half an hour).

Since there are no easily measured, reliable markers of sleep propensity in neonates with polyphasic sleep, we sought to determine sleep propensity indirectly by studying the duration of the wakefulness episode [110]. This duration was analyzed as a function of body temperatures in 9-day-old preterm neonates. Our results showed that the duration of wakefulness was significantly shorter when distal (foot, hand, and thigh) temperatures measured at the end of the wakefulness episode were high. This was not the case for proximal skin temperatures at any time point or for both distal and proximal skin temperatures at the beginning of the wakefulness episode. Therefore, sleep onset was related to distal skin vasodilation during the wakefulness episode. Our study was also the first to find that regional skin temperature homogeneity (measured over the entire body, including distal and proximal parts of the body) promoted sleep onset: the more homogeneous the skin temperatures, the shorter the wakefulness episode.

Another aspect is **sleep maintenance**. In a study of babies *during the first 6 months of life)*, Lodemore et al. [102] reported a negative correlation between the trough rectal temperature during the first 4 hours after bedtime and the time to first disturbance of the parents. Hence, the time to first disturbance was an indirect way of analyzing the duration of maintained sleep. The researchers suggested that body temperature and sleep rhythms were associated but could not determine whether the relationship was causal (i.e., whether temperature changes predisposed to longer sleep or vice versa, or whether the two rhythms matured simultaneously but independently).

Impacts of Thermal Manipulations Within the Circadian Body Temperature Range

In adults, the relationship between sleep and body temperature rhythms is causal, since experimentally modifying the body temperature influences sleep. Interestingly, several studies have shown that sleep can be promoted by slight manipulations of the body temperatures (i.e., those producing changes that remain within the everyday circadian range). These manipulations are designed to induce or strengthen skin vasodilation (especially distal vasodilation), increase heat loss, and to achieve a "completely relaxed, one-compartment body" state (i.e., when DPG = 0 °C, i.e., disappearance of the thermoregulatory shell [111] and homogenization of the skin temperatures, as already observed in preterm neonates [110]).

As a result, pre-sleep thermal manipulations capable of promoting distal vasodilation (a hot-water bottle [112], wearing a thermosuit [113], wearing socks [114], etc.) or nonthermal manipulations (lights off, lying down [115, 116], a spicy meal, physical exercise, cognitive and physical relaxation, etc.) were capable of (or might be capable of) increasing sleepiness, reducing sleep onset latency, and improving sleep maintenance [10, 117] in healthy men, older adults with insomnia [118], and adults with narcolepsy [119]. In particular, it has been proven that subtle skin warming—although perceived as slightly uncomfortable by the subject—reduces sleep onset latency [113]. Promoting pre-sleep relaxation and reducing anxiety when retiring for bed is also of value in decreasing sympathetic nervous system activity and, in turn, promoting skin vasodilation prior to sleep onset [120]. The same may hold for hypnotics (benzodiazepine [121] and temazepam: [122, 123]); the induced skin vasodilation might contribute to the drugs' hypnotic effects. Likewise, melatonin secretion is the signal that induces selective vasodilation in the distal skin segments [93, 124].

In a Japanese study, Nakamura Ikada et al. [125] carefully analyzed the temperature and humidity values in the **infant's** bed, as well as the infant's skin temperatures. The researchers found differences according to the season and the environmental conditions (bedding, clothing, etc.). They recommended avoiding the use of waterproof sheets (especially during humid seasons), and bedding and coverings made for adults but that are not thermally appropriate for infants. Unfortunately, the study did not include an actigraphic analysis, and so the impact of these conditions on the infant's sleep quality and quantity could not be assessed.

In a study that compared **4-year-old preschool children** with their mothers, significant correlations were observed between sleep parameters and a proximal temperature (the chest) but not a distal temperature (the foot): the higher the

proximal temperature, the lower the amount of wakefulness (the total duration and the episode duration) and the mean activity (measured using actigraphy) and the higher the sleep efficiency index. This was not observed in the mothers [109]. The major role of proximal temperature suggested by this study is not, however, in line with almost all the other studies performed in infants, whatever their age. It should be noted that in contrast to most studies in this field, Okamoto-Mizuno et al.'s study was performed in the absence of thermal constraints.

In **babies aged 4–9 months**, Abe and Kodama [91] suggested that interventions that decreased the DPG at lights off (e.g., a relatively low ambient temperature) could help to stabilize the DPG pattern from one night to another. It has also been found that increasing daytime exposure to light and maximizing the light-dark difference within a 24-hr period may promote circadian entrainment (and thus sleep) in 2- to 10-week-old babies [126]. In the same study, however, attempts to shorten the sleep onset latency (with lights off, and darkening the room during the night) did not exert a significant effect.

Lastly, the decrease in core temperature at sleep onset was found to be greater in babies not fed before sleep [106]. Therefore, lengthening the interval between the last feed and bedtime might shorten sleep latency.

To the best of our knowledge, and beyond the above-cited observational studies, the use of deliberate thermal manipulation within the circadian body temperature range (in order to improve sleep) has never been studied in neonates or older infants; this would be of great interest.

Conclusion

In contrast to adults, the neonate's thermoregulatory system is fully operative during REM sleep in both cool and warm conditions—at least in the range of environmental temperatures usually studied. The maintenance of efficient thermoregulation in REM sleep protects the neonate from long periods of poikilothermy that would otherwise occur. This is of particular relevance, since REM sleep episodes can be long. Moreover, the thermoregulatory system not only helps to prevent REM sleep deprivation but also favors this sleep stage (i.e., preferential switching from NREM sleep to REM sleep, and a greater relative duration of REM sleep). As a result, REM sleep (of importance in neurodevelopment) appears to be a well-protected sleep stage.

The lack of data on thermoregulatory responses in older infants or adolescents prevents us from saying whether the transition from the neonatal thermoregulatory characteristics (greater efficiency, and a longer duration of REM sleep when exposed to a cool environment) to the adult thermoregulatory pattern (poor efficiency, and partial REM sleep deprivation in cool or warm environments) occurs at the same time as the transition to adult sleep characteristics and rhythms.

All the literature data indicate that distal skin vasodilation is part of "sleep preparedness" in infants (from preterm neonates to older children)—much as is observed in adults, and despite the many infant vs. adult differences in sleep structure, rhythm, neural maturation, thermoregulatory function, and thermoregulatory centers. It is important to note that distal skin vasodilation occurs even when most of the environmental and behavioral parameters that have been demonstrated to have a major role in the pre-sleep increase in vasodilation and sleepiness in adults (lying down, cognitive relaxation, body relaxation, reduced light intensity, etc.) cannot fully operate in babies and preterm neonates. This observation opens up interesting perspectives for further research, for example, whether it would be possible to improve sleep through thermal or nonthermal manipulations that induce distal skin vasodilation.

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Sleep and Immunity

7

Carmen T. Gómez de León and Jorge Morales-Montor

Introduction

Sleep is a physiological process that has been proposed to have restorative and regulatory properties [1, 2]. Sleep has garnered particular interest in recent years due to its potential influence on the immune system. Many studies have demonstrated that total sleep deprivation and rapid eye movement (REM) sleep deprivation modify various components of the immune system, such as the percentage of cell subpopulations (e.g., CD4+, CD8+, and NK) and cytokine levels (e.g., IFN-g, TNF-a, and IL-1) [3, 4]. Also, conversely, sleep patterns are altered during the immune response, suggesting that sleep and the immune response are linked through bidirectional communication [5].

Sleep can be defined as a state of immobility resulting from the decreased ability to respond to external stimuli and is distinguished from coma and analgesia because it is rapidly reversible. Further, when deprived of sleep the organism tends to recover, depending on the extent and duration of sleep loss. The existence of this "rebound" after sleep deprivation suggests that sleep is not simply a period in which activity and alertness decline, it is a vital process that modulates various physiological functions [6].

Sleep has specific electroencephalographic (EEG) patterns in mammals and birds, which divide the sleep process into several stages. In addition, electromyograms (EMGs) and electrooculograms (EOGs) are used to differentiate the phases of sleep. Based on these parameters, several stages of sleep have been proposed: wakefulness, light sleep (two stages), slow-wave sleep, and rapid eye movement (REM) sleep, each of which has specific electrical patterns [7, 8]. Based on the classification of sleep stages, a hypnogram can be constructed describing the number of episodes, duration, rhythmicity, and latency of overnight sleep. Sleep patterns differ between species and during ontogeny and are altered in sleeping disorders (dyssomnia) or when a medical, psychiatric, or neurological disease develops [8, 9]. During sleep, important processes occur in endocrine function in mammals, for example, the rise in the levels of hormones such as prolactin and growth hormone [9, 10]. On the contrary, cortisol levels decline, observing an increase before wake up, which demonstrates the existence of a connection between sleep and other physiological events [9–11]. Studies on total sleep deprivation and REM sleep deprivation suggest that sleep has an important function in memory consolidation, learning, and neuronal plasticity [11–14]; although it has also been proposed to be a mechanism to conserve and recover energy [1].

The Function of Sleep

One of the crucial questions in the sleep study is: what is the function of sleep and particularly what is the role that REM sleep plays in the organism? Various theories have been postulated about its function that have been divided into three large groups that involve different types of sleep functions; the first group includes theories that propose sleep as a mechanism to conserve energy; a second group establishes sleep as a facilitator of learning and memory through the generation of changes in brain plasticity and synaptogenesis; and the last group proposes sleep as a process of restoration of various cellular components and biosynthesis of macromolecules [14]. Despite the various theories that explain the existence of sleep, its functions in mammals remain unclear. Some other studies suggest that duration of sleep may be related to the protection against oxidative stress, whereas previous studies have shown a phylogenetic correlation between sleep time and metabolic rate [15]. A high metabolism is linked to a greater number of biochemical changes, several of which have been related to sleep control. A high metabolic rate results in the generation of high levels of reactive oxygen species (ROS) by the mitochondria, and this

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generation of ROS has been linked to aging [16]. On the other hand, it has been shown that sleep deprivation in the rat produces an increase in oxidative stress; interestingly, it was found that the most noticeable changes occurred in a region of the brain with higher rate of protein synthesis and presumably of the generation of ROS. So, one of the theories is that at higher metabolic rates longer periods of sleep are required to disrupt ROS-induced damage in brain cells, and thus facilitate the synthesis and activity of molecules that protect brain cells against oxidative stress [15].

The argument that sleep has a vitally important function is compelling as lack of sleep in rodents and flies can cause death faster than food deprivation [17]. On the other hand, the amount and nature of sleep are related to age, body size, and ecological variables, such as whether animals live a terrestrial environment or aquatic environment, their diet, and the safety of the place where they sleep. Sleep can be an effective process that performs certain functions, but variations in sleep expression indicate that these functions may differ between species [18].

Diverse evidence suggests that REM sleep and non-REM sleep have distinct functions; most theories suggest that non-REM sleep plays an important role in energy conservation, while REM sleep is involved in the recovery of nervous system, learning, neuronal plasticity, and synaptogenesis [14].

It has been proposed that REM sleep is a state of periodic brain activation during sleep that can participate in recovery processes and emotional regulation [19]. Physiologically, it has also been observed that during this stage important processes occur in mammalian endocrine function, as it is during this stage that the highest levels of hormones such as prolactin and growth hormone are reached, in comparison to decreased cortisol, and it is right to wake up when it reaches its maximum levels [10], which could show the existence of sleep interactions with phenomena typical of other physiological systems.

Sleep Deprivation

Sleep deprivation consists of either a complete lack of sleep over a certain period of time or a reduction in optimal sleep time. A chronic reduction in sleep time or fragmentation of sleep leads to sleep cycle disruption and may have consequences similar to those observed by acute sleep deprivation, such as alterations in cognitive functions, attention, and operating memory. Sleep deprivation for several days is usually performed in extreme situations or under experimental conditions [20].

In humans, clinical symptoms of sleep deprivation or restriction usually include an increase in reaction time to any stimulus, distraction, disturbances in attention and concentration, as well as difficulty in memorizing the new information. Higher stress level is observed; tiredness, drowsiness and irritability increase; decreased effectiveness and motivation when working [20]. Total sleep deprivation in rats causes their death over a period of approximately 3 weeks, presenting a physical deterioration, with ulcerations on the skin, tail, and legs; alterations in motor and postural coordination (ataxia); increases in food intake accompanied by considerable weight loss and increased energy spent [21]. Acute sleep deprivation impairs the integrity of cognitive processes, such as attention, learning, and memory. This deterioration is accompanied by a change in brain metabolic activity [22]. Sleep restriction, which consists of decreased sleep time, is observed as the most common form of deprivation in humans. Restriction and sleep disorders have been associated with a wide range of health consequences, including an increased risk of hypertension, diabetes, obesity, depression, heart attack, and stroke [23].

Immune System

The primary function of the immune system is to defend the body from infections due to pathogens, to external chemical and biological agents (nonpathogens) or self-transformed cells through early innate immunity and subsequent adaptive responses [24].

Innate immunity is the first line of defense; Its two primary functions are to isolate and destroy invading pathogens through inflammatory processes and to recognize and process antigens to trigger acquired immunity [25]. Both types of immunity include cellular and biochemical mechanisms that are designed to respond quickly to infections and accurately distinguish between native and foreign materials [24, 25].

In innate immunity, for example, foreign pathogens are recognized by pattern recognition receptors (PRRs), which are encoded in the germline, have broad specificity for detecting molecular structures that are unique to such organisms, and are evolutionarily conserved. These unique molecular patterns in pathogens are known as pathogen-associated molecular patterns (PAMPs) [26]. PAMPs are generally components of the bacterial cell wall, such as lipopolysaccharide (LPS) and peptidoglycan. Other important PAMPs include β-glucan (a cell wall component of fungi) and viral nucleic acids (DNA and RNA), all of which have specific structural characteristics [26]. There are various receptors that recognize PAMPs, the most extensively studied of which are toll-like receptors (TLRs), comprising 13 types that recognize a wide range of PAMPs. TLRs bind to molecules, such as large lipopeptides in bacteria and mycoplasma [27]. NLRs form another group of PRRs that act as intracellular sensors that detect viral DNA and RNA

[28]. The activation of TLRs by their bacterial ligands induces an inflammatory response that stimulates macrophages, which produce proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), interferon-gamma (IFN-γ), and interleukin-6 (IL-6), which coordinate local and systemic inflammatory immune responses [29]. TNF-α and IL-1β are triggered in the local endothelium to induce vasodilatation and increase permeability of blood vessels, promoting the recruitment of serum proteins and leukocytes to the site of infection. IL-1β and IL-6 together, interacting to hepatocytes, activate them to produce acute phase proteins that activate complement and opsonize pathogens, to be phagocytosed by neutrophils and macrophages [29]. TLRs are expressed in other effector cells of the innate immune system, such as neutrophils, monocytes, NK cells, and γδ T cells [29], which can co-express more than one type of TLR. Phagocytic leukocytes, such as eosinophils, basophils, and mast cells, are the principal effectors of innate immunity, the main function of which is to ingest and kill pathogens [30]. Other types of phagocytes participate in these processes, acting as antigen-presenting cells (APCs) and generating antigenic peptides that activate specific immune responses particularly foreign antigens that are partially degraded by T lymphocytes [31].

Recognition of antigens by the adaptive immune system is mediated by specific receptors. These receptors are also encoded in the germline, and through somatic recombination, random combinations of segments of these genes can generate a large and diverse repertoire of receptors with high specificity [32]. The resulting products are clonally distributed in antigen-specific T and B lymphocytes, which express receptors that are specific for one antigen, and specific populations are selected to expand in response to the pathogen [32]. T cells recognize peptides through the T-cell receptor (TCR), which triggers different mechanisms that will determine the fate of the T cell. There are two chief groups of conventional T cells: T helper (Th) cells that express the CD4 co-receptor and cytotoxic T lymphocytes that bear CD8 [31, 32]. Both cell types recognize an antigenic peptide that must be complexed to the major histocompatibility complex class II (MHC II) molecules, whereas B cells recognize the antigen by binding to a 3D molecular determinant (epitope) [31, 32]. In turn, certain Th cells interact with B cells, through which the latter produce large amounts of immunoglobulin or antibody. Every B cell produces antibodies, with a unique specificity, that neutralize and destroy the antigen [32]. Innate and acquired immune responses require a network of molecules that signal and orchestrate them [31]. These molecules (cytokines) are synthesized by all classes of immune cells and many other cell types. Generally, cytokines act as proinflammatory, regulatory, or anti-inflammatory molecules and can be classified depending on the subtype of lymphocytes that produced them, as Th0, Th1, Th2, Th3, or Th17, although the actual classification is broader and more complex [33, 34]. Cytokines participate in innate and adaptive immune responses [34]. Th1 cells and activated macrophages primarily secrete IFN-γ and other cytokines that mediate the response against intracellular pathogens and induce B cells to synthesize IgG2 antibodies. Th2 cells preferentially respond to multicellular parasites and produce IL-4, IL-5, and IL-13 [35], which modulate the function of eosinophils, basophils, and mucosal epithelial lymphocytes. IL-5 specifically instructs lymphocytes to produce IgE antibodies. Th17 cells induce cell types, such as epithelial cells, to produce IL-17 and chemokines that recruit neutrophils to the site of infection and are involved in the response against extracellular bacteria and fungi [33]. The differentiation of Th cells into various lineages is controlled by master transcription factors, the expression of which is regulated by cytokines that are produced and governed by APCs in response to activation by PAMPs. Thus, the adaptive immune response results in antigen-specific activation that is orchestrated by the innate immune response.

Sleep, Brain, and Immune System

The brain is linked to the immune system, and similar interactions occur during sleep, wherein brain activity changes, resulting in the putative "awake brain" and "sleeping brain." There is evidence that the expression of molecules, such as neurotransmitters, hormones, and cytokines, is modulated while the subject sleeps, and human studies have described changes in the serum levels of some of these components during sleep; specifically, the secretion of IL-1β, IL-10, IL-12, and TNF-α by monocytes and dendritic cells peaks during sleep, independently of circadian rhythms (Fig. 7.1). This behavior may be directly related to sleep, because when the animal is deprived of the rhythmicity of these cytokines [36–38], the changes in expression wane. Also, blood levels of monocytes, T cells, and NK cells follow a clear circadian rhythm regarding the sleep–wake cycle [36]. Notably, other neuroendocrine mediators, such as prolactin, cortisol, and norepinephrine, also exhibit circadian rhythms, but their secretion pattern is more related to the sleep–wake cycle, and all of these compounds modulate the immune response [39]. Conversely, certain cytokines affect sleep, such as IL-1β, which, when administered intracerebroventricularly to rabbits and rats, increases the duration of non-REM sleep (Fig. 7.1). This effect is abolished when IL-1β antagonists are given [40]. Administration of the cytokines TNF-α and IFN-α has the same effect as IL-1β [40, 41].

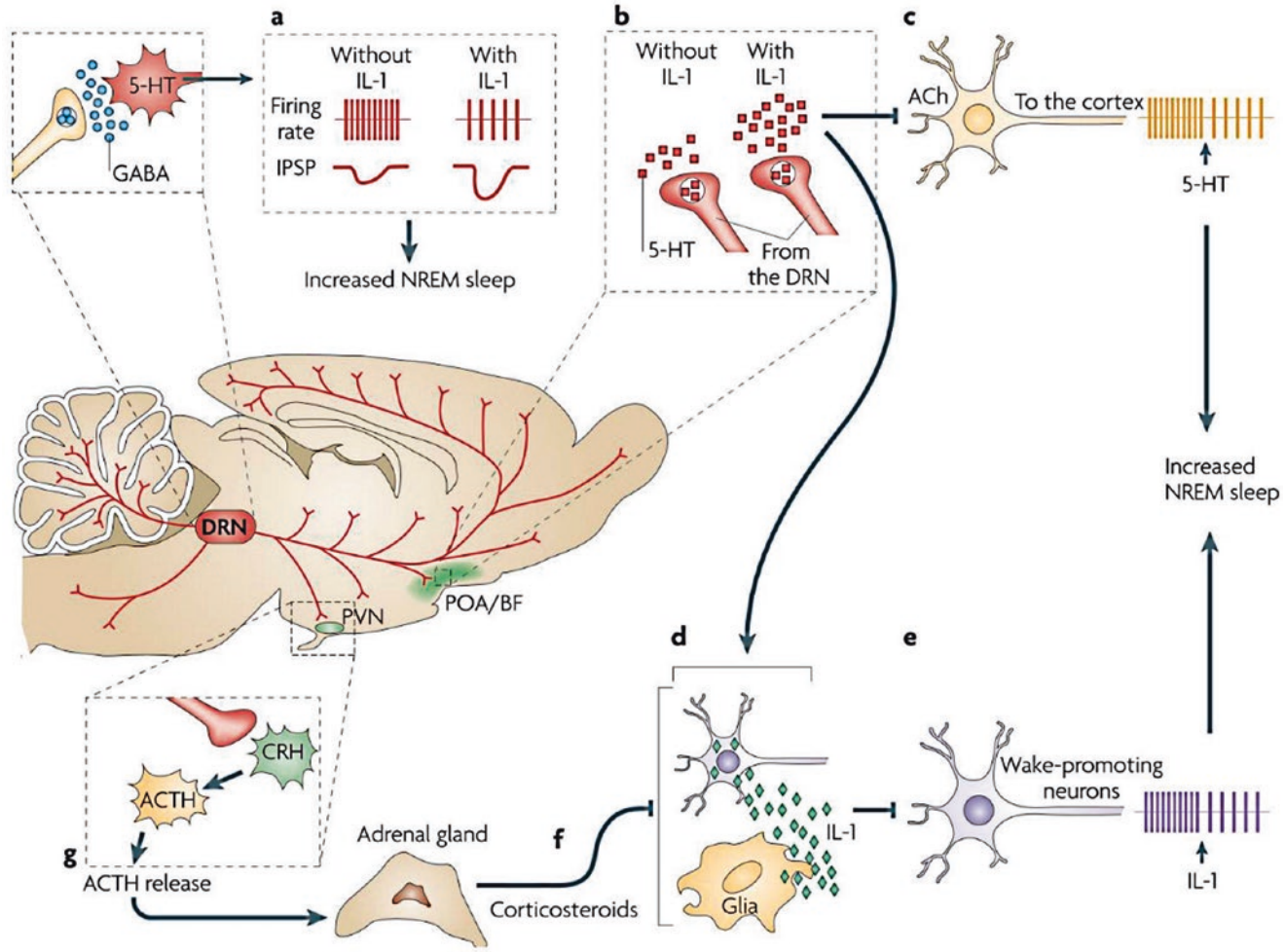

Fig. 7.1 Interaction of IL-1 with serotonin in NREM sleep regulation. IL-1 and serotonin (5-HT) interact at different sites in the brain to regulate NREM sleep. Interactions between IL-1, serotonin, and GABA are shown that are important during NREM sleep regulation. In the core of dorsal raphe nuclei (DRN), IL-1 microinjections promote NREM sleep; IL-1 reduces the rate of firing of active serotonin neurons in wakefulness through increased inhibitory effects of GABA. (**a**) In the preoptic hypothalamic area and the basal brain stem region (POA/BF), IL-1 stimulates the secretion of 5-HT; (**b**) 5-HT inhibits cholinergic neurons involved in cortical activation; and (**c**) stimulates the synthesis of IL-1; (**d**) while inhibiting wakefulness-promoting neurons and active sleep-promoting neural populations in POA/BF. In POA/BF, IL-1 is subjected to a potent inhibitory homeostatic control of corticosteroids secreted by the adrenal cortex (**f**). Corticosteroids in turn depend on the activity of the hypothalamus–pituitary–adrenal axis, which is activated by the serotonergic system (**g**). IPSP inhibitory postsynaptic potential, Ach Acetylcholine, ACTH adrenocorticotropic hormone, CRH corticotropin-stimulating hormone, IPSP inhibitory post-synaptic potential, PVN paraventricular hypothalamus nucleus. (From Imeri L, Opp MR. [51]. Reprinted with permission from Springer Nature)

The Role of Sleep in Regulating the Immune System

In recent decades, various works have shown that sleep seems to be associated with the regulation of the immune system and immune response, and that lack of sleep induces vulnerability to develop certain disorders [42].

In this respect, some authors propose that sleep participates in the phase of the formation of immune memory, making the comparison with the consolidation of neurobehavioral memory [12–14], in which the information is transferred from a short to long term in the acquisition, in a similar way sleep can participate in the acquisition of immune memory, as well as the recovery phase and in the immunological synapse by recruiting cells to the antigen presenters to be presented to the T helper lymphocytes [43].

Other work provides evidence that the concentration of circulating immune cells and cytokines are subject to sleep regulation, as higher or lower systemic levels are reached during sleep, depending on the cell population and the interleukins [42–44]. Cell populations, such as neutrophils, monocytes, and NK cells, present their lowest blood levels

during sleep, an opposite behavior is observed in B lymphocytes, T cytotoxic, and T helper cells, which reach their highest levels during sleep [45]. Similarly, IL1-O is known to reach its minimum blood levels during sleep, while TNF has a contrary behavior, reaching its maximum concentrations during the night. It should be noted that sleep regulation on cell concentration at the systemic level may differ from the regulatory effect it exerts on their cytokine production or secretion [46].

About the regulatory effect that sleep can have on the immune system has emerged an interesting but unproven idea, which addresses that the dream has evolved to play an important role in protecting animals against parasitic infections [47]. This theory is derived from the clinical observation of close physiological relationship between sleep and the immune system. This relationship suggests that species that have evolved to longer sleep duration seem to be able to increase investment in their immune systems and be better protected against parasites [47].

To prove this possibility, the authors made a comparative analysis among 26 species of mammals, of their sleep characteristics, confronting them with different parameters of their immune system [47]. According to the authors, there is a strong correlation between the increases in sleep duration in different mammals with the increase in immune defenses measured through the number of circulating immune cells [47]. It observed a positive correlation between the amount of both non-REM sleep and REM sleep with the number of cells in the white formula, while cells of the red formula had no significant variation [47]. Neutrophils that account for about 47% of white blood cells that rank as the first line of defense against pathogen attacks, themselves increased in relation to the increase in sleep [48]. Similarly, lymphocytes that account for about 44% of white blood cells, and which are related to acquired immunity, also increased at the same time in the 26 species of mammals studied [47, 48]. In addition, both eosinophils and basophils that together add up to about 6% of white blood cells also have this positive correlation. On the other hand, the number of pathogens that can infect each species studied was determined, it was found that the relative infection state had a negative correlation respect to total sleep time, that is, as sleep time increased the relative infection state decreased [47]. Just as this study provides new information about sleep, it also opens up questions. For example, only monocytes, which are about 5% of white blood cells, did not present a positive correlation with the amount of sleep. So, we would have to try to explain both the positive relationship of the amount of sleep with most of immune cells and the lack of this correlation with the monocytes. Why don't these cells behave like the rest of their sleep peers?

Effect of Sleep Deprivation on the Immune System

As mentioned above, humanity has repeatedly observed how sleep deprivation makes us more vulnerable to infectious agents. However, few research groups have addressed this issue and the lack of information available is surprising. In addition, man is the only species that can voluntarily suppress his sleep, which would have some experimental advantages compared to studies in animals, to which he is forced to stay awake. In this context, the alterations that can occur in the immune system are of great importance when there is a modification in sleep or when it is deprived. In this respect, the first works were reported in humans by Palmblad and collaborators in 1976 [49]. In this first study, eight women were completely deprived of sleep for 77 hours in circumstances that simulated a battlefield. A blood sample was taken before, during, and after deprivation. The authors found no changes in leukocytes, monocytes, or circulating lymphocytes, but in interferon production and phagocytic activity [49].

Subsequently, other work showed that sleep deprivation resulted in decreased lymphocyte blastogenesis, and an increase in IL-1 and IL-2 levels, while a decrease in NK cell activity was observed during sleep deprivation [50]. In a study published by the Dinges group in 1995 conducted on private youth for 64 h, a significant increase in the percentage of NK cells, granulocytes, and monocytes was observed, while observing changes in IL-1 and IFN levels [42]. Other studies in which rats were selectively deprived of REM sleep reported an increase in total leukocytes and IgM systemic at 96 h of deprivation [39].

Furthermore, another group reported an increase in plasma levels of IL-1, IL-6, IL-10, TNF, and IL-17 when subjects were deprived of sleep in a period of 72 h [4]. These findings suggest that REM sleep deprivation involves changes in immune system modulation, perhaps increasing inflammatory processes or favoring the type of cellular response. However, little is known about the effect that sleep deprivation can have when an immune response to an infection develops, although empirically it is known that in infectious processes the sleep pattern is modified, indicating that it may be regulating the generated response [51]. Little has been studied about the relationship between sleep and immune response modulation, particularly in parasitic type infections, as well as possible mechanisms that are mediating this phenomenon [51]. REM selective sleep deprivation studies conducted in rats, as detailed in previous paragraphs, are regularly contaminated with a stress component that is inherent in the deprivation technique. Although changes have been made to reduce this component, there is still con-

troversy in this regard. Moreover, when it comes to assessing the immune response, this controversy is even more relevant, given the marked effect of stress on the immune system. Therefore, the strategy of comparing the effects of REM sleep deprivation with some stressor that causes the usual response has occasionally been used [52].

Immune System Effect on Sleep

In general, infectious diseases, mental disorders, and physical conditions are associated with drowsiness and fatigue. After being stimulated, innate immune system cells secrete inflammatory cytokines that induce the synthesis of a different cytokine profile characteristic of each disease, including sleep disorders [39]. Proinflammatory cytokines synthesized in the periphery by the immune system reach the brain through nerves or blood and regulate sleep. The details of the interaction between sleep and an immune process have not been so widely studied, much less the effects of various types of infections on it have been clarified; however, there is evidence of a close direct and two-way relationship between them [39].

The list of cytokines and chemokines that have been studied in laboratory animals or humans that suggest an alteration or that affect sleep include: IL-1, IL-2, IL-4, IL-6, IL-8, IL -10, IL-13, IL-15, IL-18, TNF, TNF-α, IFN-1, INF-α, and macrophage protein (also known as CCL4) [1–5, 51]. Of these, only two substances, IL-1 and TNF, have been studied enough to claim that they are involved in the physiological (i.e., spontaneous) regulation of sleep. Evidence of a role for IL-1 and TNF in physiological sleep regulation has been derived from electrophysiological, biochemical, and molecular genetic studies [53, 54]. For example, when IL-1 was administered intravenously or intracerebroventricularly in rabbits, it resulted in an increase in NREM sleep time of approximately 60–70% [55]. The same effect has been observed with the administration of two other interleukins, such as TNF and IFN, although the effect of these two may be mediated by IL-1, as receptors for IL-1 have been found in several structures of the brain, in addition to the existence of immunoreactive hypothalamic neurons to this cytokine. Interestingly, IL-1 exerts effect on the serotonin system, involved in regulating sleep at different levels [55, 56].

The above mentioned evidence supports the existence of an interaction between components of the immune system and sleep. In this context, the alterations that can occur in sleep when there is an immune response are of great relevance. In this line of research, it is known that systemic levels of TNF-α present a circadian rhythm that coincides with sleep–wake rhythm [57]. In addition, secretion of IL-6 is negatively related to the amount of nighttime sleep. Consequently, decreased secretion of IL-6 is associated with good nighttime sleep and a feeling of well-being the next day. Since treatment with IL-6 causes drowsiness and fatigue, it is proposed that this cytokine has direct action on the central mechanisms of sleep [58].

Evidence collected over the past few years also suggests that these cytokines are synthesized directly by brain cells that also express specific receptors for them. In this respect, cytokines are also known to be de novo synthesized and secreted by neurons and glia, and that there are immunoreactive neurons for IL-1 and TNF located in regions of the brain that are involved in the regulation of sleep–wake, such as the hypothalamus, hippocampus, and brainstem [51]. Even more, IL-1 and TNF receptors are also present in various areas of the brain, such as the choroid plexus, hippocampus, hypothalamus, brainstem, and cortex, and are expressed in neurons and astrocytes [59].

In this context, IL-1 and TNF increase the non-REM (NREM) sleep in several species (rat, mouse, monkey, cat, rabbit, and sheep), regardless of the administration route. NREM sleep that initiates as a result of IL-1 or TNF administration has some physiological sleep characteristics in the sense that it remains episodic and is easily reversible when the animal is stimulated. Although IL-1 usually causes NREM sleep fragmentation, the magnitude and duration of its effects depend on dosage and time of administration: very high doses suppress NREM sleep in rodents but, if IL-1 is administered before the dark phase of the light–dark cycle, NREM sleep increases [60]. In addition, the antagonists of these cytokine systems also attenuate the increase in NREM sleep caused by excessive food intake or acute temperature elevation, which are associated with increased production of IL-1 or TNF. Consistently, knockout mice that lack the receptor to IL-1 and the receptor for TNF, both type 1, spend less time in NREM sleep than control mice [60, 61].

Taken together, evidence suggests that IL-1 and 5-HT systems participate in reciprocal interactions that contribute to NREM sleep regulation. IL-1 improves 5-HT axonal release and stimulates IL-1 synthesis, while inhibiting wakefulness promoting neurons. IL-1 also inhibits serotonin-wake-active cell bodies in the dorsal raphe nuclei. Therefore, IL-1 exerts opposite effects on the serotonin cell bodies and axon terminals. These effects complement each other, and both contribute to the same functional result, NREM sleep enhancement [51].

Sleep During Infection

The above mentioned evidence supports the existence of an interaction between components of the immune system and sleep. In this context, the alterations that can occur on sleep when there is an immune response are of great relevance. In this respect, a wide variety of infectious diseases have been

linked to sleep disorders, particularly it has been documented that infectious agents such as viruses or parasites are capable of infecting the CNS thus generating such disorders, either by the effect of the immune response generated against the infection or by direct effect of the pathogen [62]. One of the first diseases in which alterations in the sleep pattern was described was lethargic encephalitis. Lethargic encephalitis is a CNS disorder characterized by pharyngitis, followed by the presence of sleep disorders including drowsiness, sleep inversion, or insomnia [62]. Some recent studies have associated this disease with an autoimmune pathology, although its etiology is not known for certain [62].

Most of the pathogens that cause this type of sleep disorders are viruses. In particular, patients infected with the virus such as human immunodeficiency (HIV) (which also affect the CNS) suffer alterations such as fatigue and sleep disorders from the asymptomatic stage [39]. Reports show disruption of the physiological organization of sleep, which can appear from the early stage and progress throughout infection in both adult and child individuals [39]. These reports described the decrease in REM sleep, delta wave sleep or SUN, and can progress as the disease progresses to subsequently have shortened total sleep time and reduced sleep stage two, while increasing wakefulness [39].

Since sleep disturbances appear from an early stage in infection, it has been proposed that these alterations are caused by direct infection in the CNS; some peptides of the virus may be involved [39]. Studies with cats infected with the feline variety of the virus show alterations similar to those found in HIV-infected or AIDS patients [39], so these models are a good experimental strategy to elucidate the mechanisms by which this infection causes sleep pattern alterations; these alterations may be performed by the direct action of virus components on the CNS or by the action of immune system in response to the virus infection.

Patients infected with other types of viruses such as rabies, hepatitis C, or chickenpox have similar symptoms, such as reduced REMS and total sleep time. However, it has not been possible to differentiate whether these disorders are caused by the virus itself or as a consequence of the immune response generated to counteract it [39]. In this respect, some studies propose that sleep disturbances may be caused by the continued exposure to cytokines of innate immune system, such as the case of IFN-α, proposing that these cytokines reduce sleep continuity and induce a consistent pattern with insomnia and alertness [5]. Other infectious agents can cause sleep disturbances indirectly by affecting other systems such as respiratory or endocrine, but not the centers involved in sleep regulation; however, most infectious processes, particularly during the acute phase, coincide in altering the sleep pattern, usually causing an increase in the duration of SUN and decreased wakefulness and/or REM sleep [39]. This alteration that can be observed in a generalized way during an infectious process could be a mechanism of the organism to adapt to these circumstances; forcing the greatest energy supply to the immune system, so it can be able to eliminate the infection (Fig. 7.2).

It has also observed that substances associated with bacterial infections are able to induce sleep [63]. Among these substances are the components of the cell wall of bacteria. In this respect, it is known that muramyl peptide is capable of inducing an excess of SUN when administered in rabbits, rats, and cats [63], while LPS and antigen A produce an increase in both the amount of SUN and its amplitude while

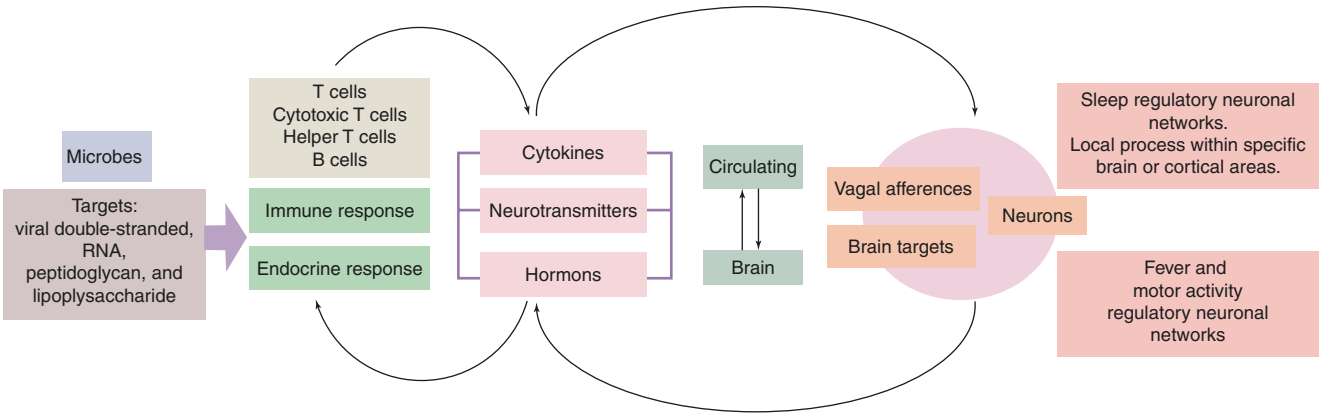

Fig. 7.2 Interactions during infectious processes. It is shown the immune response resulting from the invasion of a pathogen with the consequent secretion of immune mediators, such as interleukins and cytokines, which is accompanied by the response at the endocrine level and the nervous system. Secreted substances can find their targets at the systemic level or they can cross the blood–brain barrier to reach their receptors in different neural structures, or may have a modulation via vagal, in order to modulate the response mechanisms aimed at maintaining homeostasis. This modulation can also be used by pathogens to ensure the establishment of the infection, completing its life cycle and ensuring its offspring. (From Ibarra-Coronado EG, et al. [39]. Creative Commons Attribution 3.0 Unported (CC BY 3.0). Available at https://www.hindawi.com/journals/jir/2015/678164/)

suppressing REM sleep when administered in rabbits via intracerebral ventricular and intravenous [64]. In humans, Salmonella abortus endotoxin produces a noticeable diminution of both wakefulness and REM sleep, accompanied by an increase in NREM sleep, in addition to causing disturbances during the day, mainly daytime sleepiness [50].

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Sleep and the Gastrointestinal System

8

Hari P. R. Bandla

Sleep Related Changes in Upper Gastrointestinal Physiology

Sleep has a profound influence on the physiology of upper gastrointestinal tract and these state-dependent dynamic changes lead to marked alteration of esophageal and gastric function. There is reduction in upper esophageal sphincter pressure, decreasing from 40 mm during wakefulness to 10 mm with sleep onset [1]. The circadian rhythm of basal gastric acid secretion peaks between 8.00 pm and 1.00 am [2]. Sleep disrupts gastroenteric function leading to delayed gastric emptying [3]. There is a marked decrease in swallowing during sleep (an average of 2 swallows per hour during total sleep time) with almost no deglutition during stages 3 and 4 [4, 5]. Along with decreased deglutition frequency during sleep, saliva production was found to be essentially absent [4, 6]. Normal saliva production and deglutition are vital mechanisms in the process of esophageal acid clearance, a pivotal defense mechanism against the development of GERD-related symptoms and inflammation. Thus, sleep hinders the normal clearance mechanisms and leads to prolonged acid clearance time [7]. A summary of these changes is listed below.

Sleep related changes in upper gastrointestinal physiology
Fall in upper esophageal sphincter tone
Reduced swallow frequency
Decreased salivary secretion
Prolonged acid clearance time
Delayed gastric emptying

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Sleep and Gastroesophageal Reflux: Sleep Is a Vulnerable State for GERD

Gastroesophageal reflux (GER), the retrograde passage of gastric contents into the esophagus, is a normal physiologic process that occurs in all age groups. The main protective barrier for GER is the lower esophageal sphincter (LES), which consists of a 2–4 cm high-pressure zone at the level of the gastroesophageal junction. The LES operates as a dual sphincter mechanism consisting of a ring of thickened circular muscle and the diaphragmatic crura. The LES receives cholinergic innervation and the crural diaphragm receives bilateral phrenic nerve innervation. The occurrence of a vagally mediated and transient LES relaxation (TLESR) constitutes the primary mechanism for GER; these TLESRs events are brief, are not related to weak lower esophageal sphincter pressure, and occur independent of swallowing [8]. Esophageal clearance factors are important defensive mechanisms that neutralize the acid refluxate and minimize acid exposure to esophageal and extra-esophageal structures. These include salivation and primary peristaltic contractions triggered by saliva-stimulated swallowing. In addition, salivary bicarbonate also neutralizes the acid refluxate [9]. When awake, GER is most likely to happen in the post prandial period when there is abdominal distention and TLESR. These episodes are short and are rapidly cleared as the acid mucosal contact enhances salivary flow also stimulates a higher frequency of swallowing. However, the swallow frequency and salivary production are almost nonexistent during stable sleep [4, 5], and sleep related reflux events will occur predominantly during arousals and awakenings and, if recurrent in sufficient frequency, can lead to mucosal injury as a result of impaired clearance mechanisms.

A pediatric based survey has estimated that vomiting, a common symptom GER, occurs in 50% of infants in the first 3 months of life, in 6% of 4-month-old infants, and in 5% of 10–12 month old infants [10, 11]. Most episodes of GER last <3 minutes, occur in the postprandial period, and cause few or no symptoms. However, a subset of children develops

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pathologic gastroesophageal reflux disease (GERD) which is associated with plethora of gastrointestinal and extra gastrointestinal symptoms. These symptoms include feeding difficulties, failure to thrive, heartburn/chest pain, dystonic posturing, and recurrent respiratory symptoms of coughing, stridor, and wheezing. The estimated prevalence of GERD in infants 0–23 months, children 2–11 years old, and adolescents 12–17 years old is 2.2–12.6%, 0.6–4.1%, and 0.8–7.6%, respectively [12, 13]. It is important to realize that in healthy persons, sleep is relatively free of GER events.

However, given the dynamic changes in sleep as they relate to alteration in clearance mechanisms, it is not surprising that many patients experience frequent nighttime symptoms of regurgitation, heart burn, insomnia, and poor quality of sleep. These symptoms cumulatively grouped as a distinct diagnostic entity as "Sleep Related Gastroesophageal Reflux" in International Classification of Sleep Disorders (ICSD) [14]. Essential features of this diagnosis include heartburn, substernal burning, chest discomfort, coughing, choking, or unexplained excessive day time sleepiness, even in the absence of typical reflux symptoms. Sleep related GER is also associated with sleep onset and sleep maintenance insomnia, early morning awakenings, sleep disturbances, arousals, unrefreshing sleep, daytime dysfunction. A national random sample telephone survey to estimate the prevalence of frequent GERD and nocturnal GERD concluded that over all prevalence of frequent GERD was 14% and nocturnal GERD was 10%. Seventy four percent of those with frequent GERD symptoms reported nocturnal GERD symptoms [15]. Similarly, in a Gallup survey of 100 adults conducted on behalf of the American Gastroenterological association, 79% respondents had nighttime symptoms and 40% reported that these nighttime symptoms diminished their ability to function well the next day [16]. Despite the fact that GERD is common in children of all ages, the exact prevalence of nighttime symptoms and sleep disturbance in children has not been well studied, and there is paucity of information and minimal research on the bidirectional relationships of GERD and sleep in pediatric population. Indeed, the recently published clinical practice guidelines on Pediatric Gastroesophageal reflux did not specify any sleep-related symptoms [17]. A questionnaire-based study identified infants and young children with pathologic reflux, compared with population norms, as having a greater prevalence of nighttime awakenings, delayed onset of sleep during the night, and greater prevalence of daytime sleep [18]. Another large-scale cross-sectional study on Japanese junior high school students found that problem behaviors in adolescents are associated with some sleep problems, including sleep bruxism, as well as several lifestyle and food habits and GERD symptoms [19]. In another study of snoring obese children without evidence of OSA, simultaneously performed polysomnographic and MII-pH studies concluded that acid GER caused increased arousals and awakenings sleep interruptions [20]. Assessing the impact of GERD treatment in improving the sleep quality in adolescents, 8 weeks of esomeprazole improved the sleep dysfunction domains of quality of life in a prospective randomized controlled study [21].

GERD and OSA: Bidirectional Relationship?

In patients with obstructive sleep apnea, the increased collapsibility of the upper airway leads to progressive increases in respiratory effort during periods of heightened upper airway resistance, thereby generating very large intrathoracic pressure swings. Such intrathoracic pressure swings may promote reflux of gastric contents into the distal esophagus. With the impaired clearance mechanisms that characterize the sleep state, such reflux episodes can be prolonged, leading to increased mucosal damage and thus symptoms of esophagitis. Such effects can be compounded by the supine position during sleep, and these effects can be further multiplied by the concurrent presence of obesity, a common comorbid condition in patients with obstructive sleep apnea. Thus, from a physiological perspective, it is natural to assume that three pathophysiological consequences in the relationship with GERD and OSA are present, namely a) gastroesophageal reflux is estimated to occur with higher degree of prevalence in patients with obstructive sleep apnea, b) there will be temporal relationship between respiratory events and reflux parameters, and c) the severity of OSA will correlate with the severity of GERD.

The frequency of nocturnal GER in adult patients with obstructive sleep apnea ranges from 54% to 76%, and application of nasal CPAP resulted in marked improvement of nocturnal GER [22]. One study found that five of six patients with OSA who underwent pH monitoring had markedly abnormal nocturnal GER, and that application of CPAP reduced GER frequency [23]. Graf and coworkers found that 11 of 17 patients with OSA had abnormal GER but failed to establish a temporal relationship, as well as any other relation between GER and the severity of OSA [24]. In addition to these small studies, Ing and colleagues compared nighttime pH monitoring results in patients with AHI <5/ hrTST (n = 41) to those with and AHI index >15 /hrTST (n = 63). Patients with AHI >15 /hrTST experienced more GER events, and nasal CPAP reduced GER in both groups suggesting a nonspecific effect [25]. Additionally, CPAP reduced the mean duration of reflux episodes, as well as the total percentage time of reflux in six non OSA patients with GER, further confirming the non-specific effect of CPAP in reducing nocturnal GER [26]. Unfortunately, few studies are available in children on this specific issue. In a small sample of otherwise healthy children referred to sleep laboratory to

rule out OSA, a high prevalence of GER was observed in children with OSA [27]. In addition, and similar to the aforementioned studies in adult patients, no time-based or severity-based relationships emerged between OSA events and reflux episodes [27]. In another small series of 18 children with obstructive sleep apnea, gastroesophageal reflux was frequent and occurred in 41% children. However, no temporal relationship was observed between the respiratory events and reflux events and furthermore, there was no correlation between the severity of OSA and the presence and severity of GERD [28].

Laryngopharyngeal Reflux: LPR

Extraesophageal symptoms are common in patients with GERD. The principal protective barrier for the prevention of extraesophageal reflux is the Upper Esophageal Sphincter (UES), a zone of high pressure that includes the cricopharyngeus muscle. Due to sleep related changes in the decrease of upper esophageal sphincter tone in combination with prolonged clearance time, sleep state may promote proximal retrograde migration of gastric contents breaching the UES with the resultant pharyngolaryngeal injury. Recent studies in adults have identified that the etiology, pathogenesis, clinical manifestations, and the treatment of these symptoms are indeed unique, and significantly differs from conventional GERD, being actually viewed as a variant. Thus, the term LPR (laryngopharyngeal reflux) has been coined to describe this separate entity, and the abundance of publications in the recent literature justifies its consideration and discussion [29]. Indeed, while GERD represents the digestive manifestations of the disease, LPR represents the upper airway manifestations of this disease process. Hoarseness, dysphonia, sore throat, and dysphagia are common symptoms. Although GERD symptoms can be present in patients with LPR, symptoms related to LPR are exclusively extraesophageal, predominantly laryngopharyngeal in majority of cases, with no associated GI symptoms [30].

Although extraesophageal reflux and its associated laryngopharyngeal symptoms are well characterized in adults, recent reports seem to indicate that a similar presentation spectrum also occurs in children. Indeed, chronic rhinitis and rhinosinusitis and laryngeal disorders have been reported in children associated with laryngopharyngeal reflux [31]. Furthermore, an increased prevalence of GER has been associated with the presence of increased risk for adenoidal hypertrophy in young children [32]. This association strongly supports the role of chronic chemical irritation and ensuing inflammation resulting from GERD and promoting lymphoid hyperplasia in the upper airway, thus contributing to adenotonsillar hypertrophy. The putative role of extraesophageal reflux as a cause of adenotonsillar hypertrophy leading to OSA has been highlighted by a recent publication of a case report. A 7-year-old child with adenotonsillar hypertrophy and OSA had severe GERD confirmed by 24 hr. pH probe monitoring. This patient also had an endoscopically confirmed diagnosis of laryngopharyngeal reflux (Fig. 8.1). The adenotonsillar hypertrophy and laryngeal changes improved significantly with acid suppression therapy, and such changes were also associated with ameliorations in overnight polysomnographic findings [33]. Intuitively, one can propose that a subset of patients with OSA is likely to present with LPR, and that appropriate treatment of LPR may decrease the severity of OSA. Given that the treatment for OSA in children is surgical, it is imperative to look for evidence of GERD in general, and LPR in particular, in an effort to minimize the need for invasive surgical treatments.

While the diagnosis of GERD is based on well-established criteria based on 24 hr. pH probe monitoring, similar criteria are not present for defining LPR, and the diagnosis is often challenging and based on empirical assumptions, usually by incorporating the symptoms and upper airway endoscopic findings. Endoscopic abnormalities are often localized in regions of the larynx, particularly involving the posterior laryngeal wall, the arytenoid cartilages, interarytenoid areas, and the posterior third of the vocal cords. Although adding a hypopharyngeal sensor in the context of the conventional dual pH probe recording may increase the diagnostic yield of LPR, demonstration of reflux events can be best achieved by multichannel intraluminal impedance (MII) studies. Symptom-based diagnosis has low diagnostic specificity and laryngoscopic findings have low sensitivity. In addition, only 40% of patients with laryngeal findings attributed to LPR have objectively confirmed reflux events measured by MII pH [34]. Treatment is often lengthy, usually requiring 2–6 months administration of high dose, twice daily, acid suppression therapy [35].

Many of the published studies have investigated relationships between OSA and GERD, but very few studies have explored the relationship between LPR and OSA. It has been hypothesized that the causal relationship between LPR and OSA is actually bidirectional. The swings in negative intrathoracic pressure related to repetitive obstructive apneas promote reflux of gastric contents into the esophagus. Proximal migration of the refluxate into the laryngopharyngeal structures is promoted by sleep-related decrease in the clearance mechanisms, as well as by the sleep-associated decrease in upper esophageal sphincter tone, Over time, the pharyngeal inflammation related to LPR may then contribute to the progression of OSA by enhancing the collapsibility of the upper airway, likely mediated by the activation and propagation of local inflammatory and sensory neuropathic mechanisms [36] (Fig. 8.2). Indeed, significant improvements in the severity of OSA have been reported in adults by implementation of an aggressive anti-reflux therapy regimen [37].

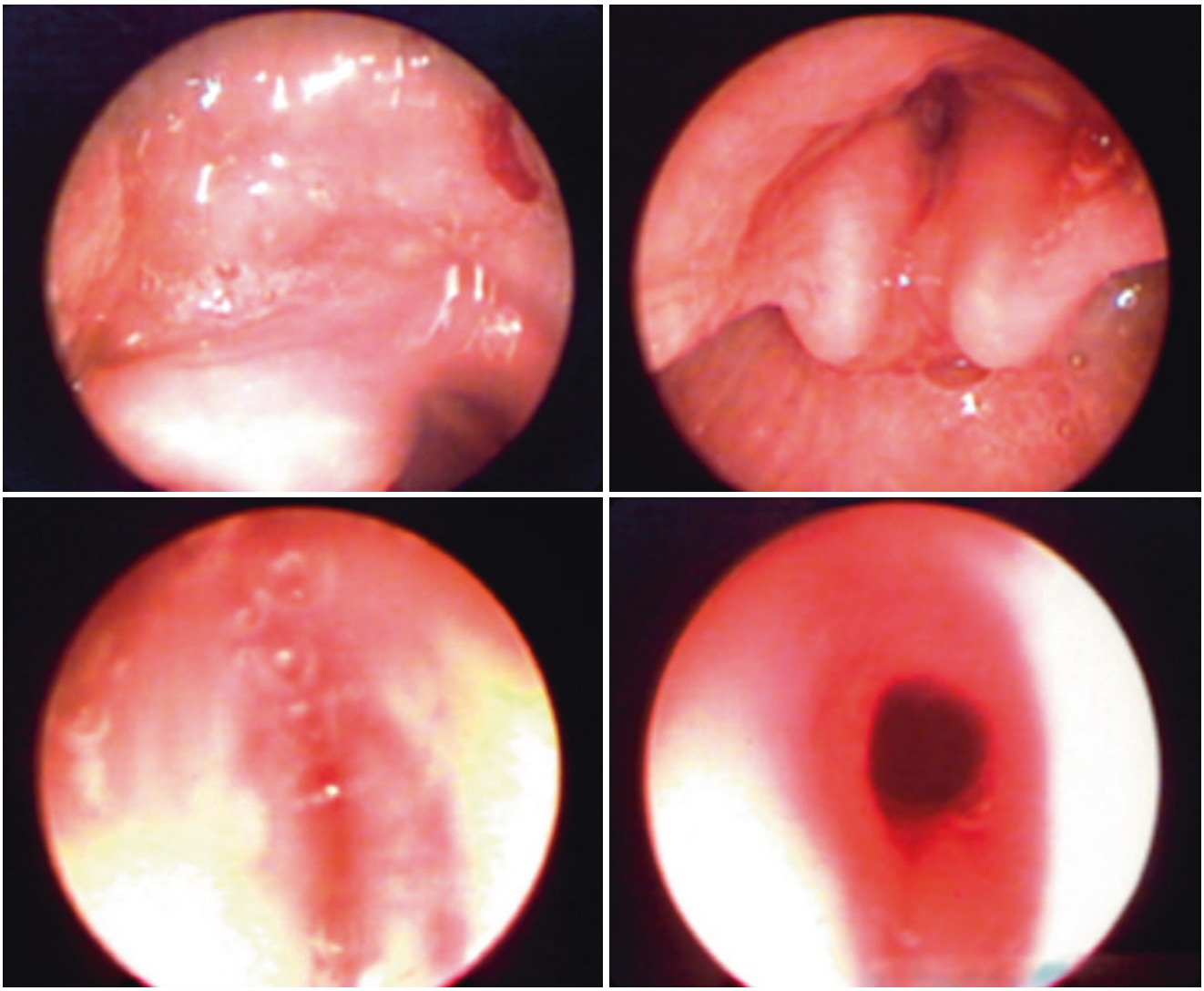

Fig. 8.1 Laryngopharyngeal Reflux. Endoscopic view of Laryngopharyngeal reflux reveals thickened epiglottis, posterior glottic swelling, and almost complete obstruction of the larynx with grade 3 subglottic stenosis. (From Stapleton and Brodsky [33]. Reprinted with permission from Elsevier)

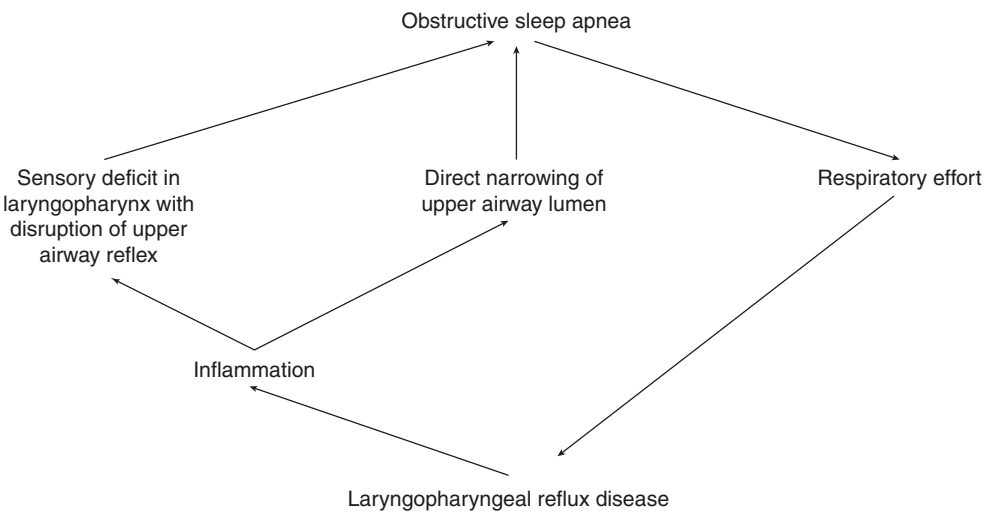

Fig. 8.2 Schematic drawing of the relationship between OSA and LPR disease. (From Eskiizmir and Kezirian [36]. Reprinted with permission from Elsevier)

Modulation of Cardiorespiratory Events in Neonates and Infants: Role of Sleep and GER

Protective Airway Reflexes

For better understanding of the interrelationship between GER and cardiorespiratory events in neonates and infants, it is important to recognize two important airway protective reflexes, namely the laryngeal chemoreflex and the esophago-glottal closure reflex. Active glottic closure is involved in both reflexes, and plays an important role in preventing aspiration, but can potentially promote apnea. The laryngeal chemoreflex is elicited by stimulation of laryngeal mucosal receptors by various liquids and the esophago-glottal closure reflux is elicited by distension of the proximal esophagus [38–40].

Apnea of Prematurity (AOP)

The estimated prevalence of GERD is about 10% in sick infants in the Neonatal Intensive Care Unit (NICU) [41]. Pre-term infants are at increased risk for GER partly because of their large fluid intake in addition to the age-specific supine position. A causal relationship between AOP and GER has long been suspected due to the observations that AOP occurs more frequently in the immediate post-prandial period and that the apneic episodes are more likely to occur after episodes of regurgitation, Consequently, the laryngeal chemoreflex has been suggested as the possible mechanism. These observations have been supported by animal studies wherein stimulation of laryngeal chemoreceptors with various liquids, milk formula, and acidic fluids can provoke a prolonged and fatal apnea [42]. The hypothesis on this causative linkage has been also been confirmed in human preterm infants [38]. Such assumptions led to widespread use of anti-GER medications in the newborn nursery with an expectation that this will reduce the frequency and severity of the apneic episodes. Few earlier studies have shown an association between regurgitation and apnea. Nine pre-term infants and one term infant showed a 14-fold increase in prolonged apnea frequency immediately following regurgitation [43]. However, in a subsequent study, no relationship between the occurrence of GER and apneas was identified in a study of 20 premature infants with a concurrent history of persistent AOP [44]. Furthermore, GER treatment did not reduce the frequency of apnea in 132 premature infants <36 weeks of gestational age [45]. A proposed explanation for the lack of such association between apneas and reflux events was that it was nonacid reflux, undetectable by conventional pH monitoring, that operated as the culprit for AOP causation. This led to implementation of novel diagnostic MII techniques for detection of both acid and non-acid reflux events [46]. However, in a study of 19 preterm infants, using MII technology in conjunction with cardiorespiratory monitoring, Poets et al. concluded that both reflux and apneic events are common, but that no temporal relationships can be identified between cardiorespiratory events and GER [47]. As neonates sleep 80% of the time, it is likely that sleep state might modulate the frequency and severity of these events. To identify the role of sleep in the modulation of GER and to define the spatio-temporal characteristics of GER, respiratory events, and sleep state, Jadcherla et al. have performed concurrent polysomnography with pH impedance study in a group of neonates who are hospitalized in NICU. There were 18 neonates who were hospitalized with apparent life-threatening events, apnea, desaturations, bradycardia, cyanosis, and stridor, with mean post menstrual age of 41 weeks at the time of study. A total of 317 GER events during 16 hours of polysomnography were analyzed. The study concluded that (1) frequency of impedance positive events were significantly less during sleep, (2) proximal migration of refluxate is also significantly less during sleep, and (3) frequency of respiratory symptoms were significantly decreased during sleep [48].

Brief Resolved Unexplained Event (BRUE) (Apparent Life-Threatening Event: ALTE)

Apparent Life-Threatening Events are frightening episodes in infants characterized by a combination of apnea, color change, abnormal muscle tone, choking, and gagging that require an intervention by the observer [49]. In 2016, the American Academy of Pediatrics (AAP) released a clinical guideline for practitioners recommending that the term ALTE be replaced by Brief Resolved Unexplained Event (BRUE) [50]. The aim was to allay the anxiety to the caregivers brought about by the use of the term ALTE, as well as to give practitioners clear management guidance by stratifying such infants into high- and low-risk groups. In patients with ALTE, apnea is the most frequently reported symptom, and 60–70% of patients with ALTE will also manifest the presence of recurrent regurgitation or emesis. Thus, GER has been suspected as a causative factor for ALTE. Indeed, up to 40–80% of patients with ALTE have abnormal pH monitoring studies. However, despite such associations, efforts to document a temporal relationship between ALTE and GER by simultaneous polysomnographic and pH probe studies have failed to convincingly demonstrate the occurrence of this process. Indeed, 14 infants with abnormal GER scores and a history of apnea did not show a temporal relationship between reflux and apneic events, the latter being considered

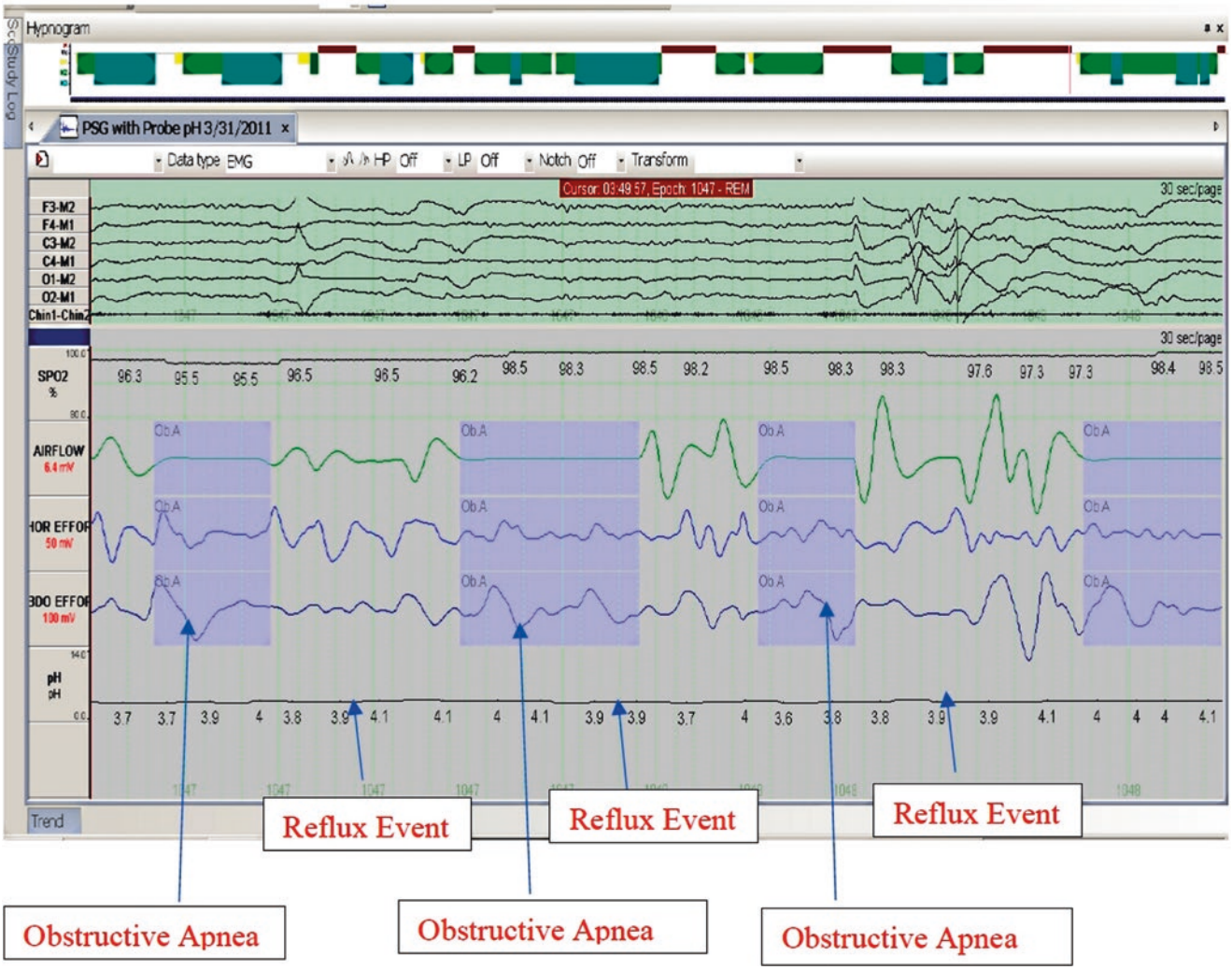

Fig. 8.3 Temporal relationship between obstructive events and reflux events

as a manifestation of more general developmental delay [51] (Figs. 8.3 and 8.4). In another study of 20 infants with ALTE with no clinical symptoms of emesis, no correlations between duration, lowest value of esophageal pH, and the number of apneas or duration of apneas could be found [52]. Even in patients with proven GER and ALTE, no relationship between GER and obstructive episodes in terms of frequency, duration, or temporal occurrence was detected [53]. Although it is often stated that gastroesophageal reflux is the most common cause of a brief resolved unexplained event or apparent life-threatening event, a recent literature search of multiple cross-sectional observational studies concluded that there are very few data to support the hypothesis of cause and effect [54]. Thus, based on the current evidence, in the majority of infants, GER is not related to ALTE, although a clear temporal relation based on history, observation or testing may occur in individual infants.

Thus, both GER and apneic episodes (central/obstructive) are common in vulnerable infants in specific age groups, but there is an apparent lack of temporal relationships between the apneic events and GER. Several plausible reasons for the lack of such relationship could include (1) methodological issues such as small cohort size, selection bias, different methods for the diagnosis of apnea and GER, (2) the two conditions may share a common causative mechanism, and (3) different mechanisms for airway obstruction other than laryngeal closure with regurgitation may be operational.

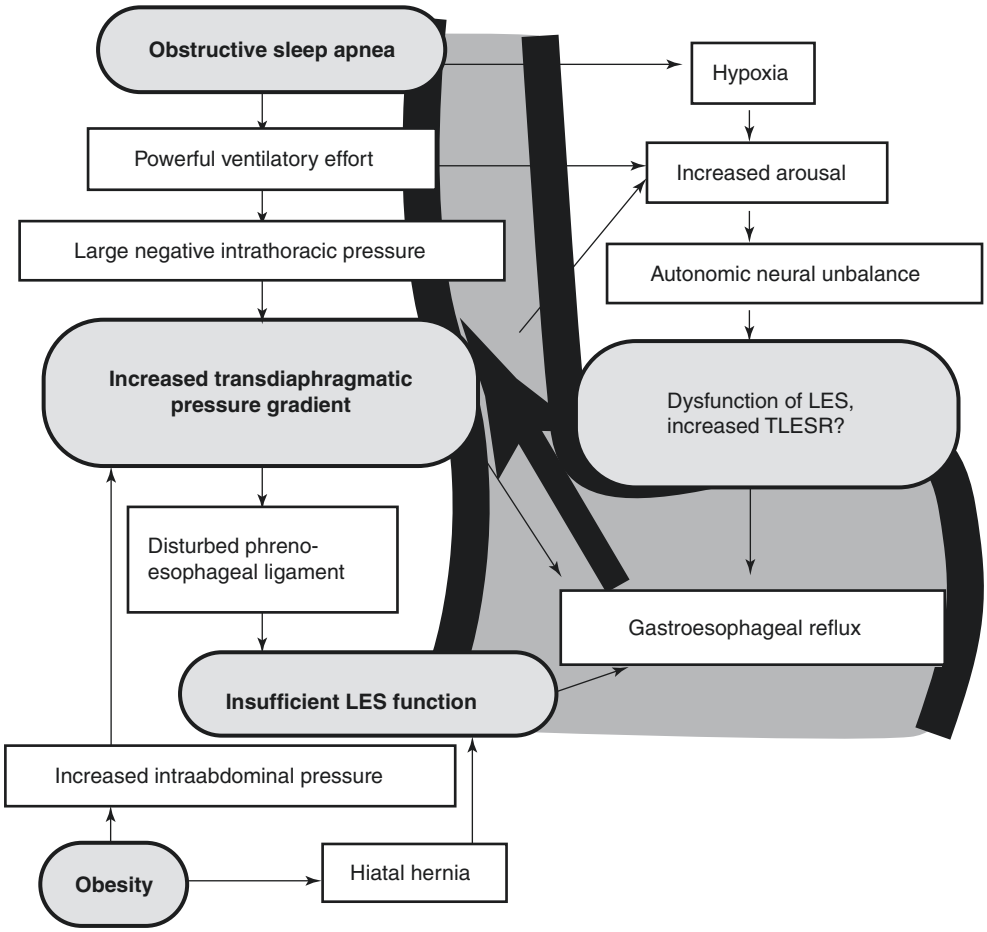

Fig. 8.4 Possible mechanisms for the relationship between obstructive sleep apnea syndrome (OSAS) and gastroesophageal reflux disease (GERD). The mechanisms of the specific linkage between OSAS and GER are not fully elucidated, but possible explanations include the generation of large negative intrathoracic pressures, insufficient lower esophageal sphincter (LES) function, increased arousals, autonomic neural unbalance, and obesity predisposing to both conditions. TLESR transient lower esophageal sphincter relaxations. (From: Mizuta et al. [55])

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Circadian Rhythms in Children

9

Lorenzo Tonetti

Endogenous Origin of Circadian Rhythm: The Circadian Timing System

Circadian rhythms, which present a period of around 24 hours, are endogenously generated by the circadian timing system. The circadian timing system is composed of an input pathway, the biological clock, and the output pathway. The input pathway through photoreceptors detects and transmits information from the retina to the biological clock, which is anatomically localized in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. The biological clock then transmits its outputs to other brain areas, generating circadian rhythms, which are entrained to the 24-hour cycle by so-called Zeitgebers or synchronizers. Among the environmental synchronizers, the dark/light cycle is commonly acknowledged as the most powerful for the human species. However, at different levels, other synchronizers can be detected. For example, school start time and melatonin represent examples of social and biological synchronizers, respectively.

Although in humans the fetal SCN has been recognized at an early stage (i.e., around mild gestation) [1], at gestational term it is still largely immature. The SCN undergoes an intensive development during the very first few months of postnatal life [2]. This means that at birth circadian rhythms are still not apparent; furthermore, environmental variables during early postnatal life could importantly affect the emergence and consolidation of these rhythms.

Examples of Interactions Between Circadian Timing System and the Environment

Preterm Birth

Each milestone of the development of the circadian timing system is modulated not only by biological mechanisms, but also by interaction with the environment. One example of such interaction is represented by the preterm birth. Indeed, it has been shown that preterm infants are characterized by the earlier appearance of a 24-h sleep/wake rhythm (i.e., one of the most widely investigated circadian rhythms) compared with full-term infants (e.g., [3]). A possible explanation of this result is that the earlier and more regular exposure of preterm infants to environmental signals such as light (e.g., the cycled light conditions) [4] and social time cues (e.g., regular feeding pattern) [5] in the neonatal care unit plays a primary role in the earlier appearance of a 24-h sleep/wake rhythm. Interestingly, results from research into the relationship between preterm birth and circadian preference suggest an association between preterm birth and an early imprinting of the SCN. Although circadian preference will be presented later in the chapter, it can basically be described as a continuum with evening types (those who prefer to perform mental and physical activities later in the day and would rather stay up late at night and wake up late in the morning) and morning types (those who show a preference toward early bedtime and get-up time, as well as to performing demanding activities in the morning) at the extremes and intermediate-types (no clear preference toward morning or evening activities) in the middle [6]. Previous studies [7, 8] have shown an association between preterm birth and morningness preference, that is, a preference toward an early phase of the sleep/wake cycle, which could be related to an early imprinting of the SCN in preterm born children [9].

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Chrononutrition

Another example of interaction with the environment that could modulate the development of the circadian timing system is represented by human milk as a potent form of chrononutrition [10], which may have been shaped by evolution in aiming to transmit information to the infants regarding the time of day. It is interesting to observe that human milk differs in its composition according to the time of day. In particular, during the daytime human milk is composed of higher levels of activity-promoting amino acids and cortisol [11], which could increase alertness. On the contrary, during the nighttime, the levels of such activity-promoting factors decrease concurrently with an increase in the levels of melatonin [12] and tryptophan, which could improve sleep and the consolidation of sleep/wake rhythms. Since breastfeeding is not always possible, knowledge regarding chrononutrition has been applied to the development of dissociated milk formulas with daytime and nighttime components, which mimic the aforementioned circadian variations in human milk. It is interesting to observe that experimental evidence seems to point out that the administration of this dissociated formula milk helps the consolidation of the sleep/wake rhythm in infants [13, 14]. In line with these observations, the study by Cohen Engler and colleagues [15] pointed out that infants who were exclusively breastfed showed a trend toward longer nocturnal sleep duration compared with those exclusively fed with artificial formula milk that was not dissociated into daytime and nighttime components.

Photoperiod at Birth

Photoperiod at birth represents another example of an environmental factor that could interact with and modulate the development of the circadian timing system. Indeed, it is known that annual changes in daylight occurring during the early stages of development could affect the development of the SCN, the anatomical structure that is accountable for the generation and entrainment of circadian rhythms [9]. It is thus possible that a phenomenon similar to an imprinting could happen during a sensitive stage of development immediately after birth, with the first 3 months of life suggested as a critical time for the development of sleep/wake rhythm in humans [16]. An interesting study in mice showed that perinatal photoperiod has an imprinting-like effect on the mammalian circadian clock [17], with those developing in a long photoperiod (16 hours of light and 8 hours of dark) presenting shorter circadian periods compared with those perinatally exposed to a short photoperiod (8 hours of light and 16 hours of dark). Bearing in mind that mice are nocturnal animals, these data point out that mice exposed to a long photoperiod present a phase advance of the circadian timing system while those exposed to a short photoperiod show a phase delay. Season of birth is considered a useful marker of the perinatal photoperiod, with autumn and winter associated with decreasing and short photoperiods, while being born in spring and summer is connected with increasing and long photoperiods. During the developmental age, Touchette and colleagues [18], examining mostly Caucasian children aged between 4 and 6 years, highlighted a trend in wake-up times that were delayed in those born during spring-summer compared with those born in autumn–winter. The effects of season of birth have also been investigated with reference to circadian preference [19]. On the whole, most of the studies in Caucasian children (e.g., [20]), adolescents (e.g., [20, 21]), and young adults (e.g., [22]) found a consistent pattern of results with a higher prevalence of evening types among those born in seasons with long photoperiods, and a higher prevalence of morning types among those born during short photoperiod seasons, in line with the results observed in mice by Ciarleglio and colleagues [17]. This pattern of results could be usefully interpreted according to the photoperiod at birth hypothesis [23], with people born during long photoperiods setting their internal clocks according to longer days compared with those born during short photoperiods. As a result, the former should show a phase delay (i.e., tendency toward eveningness) compared with the latter (i.e., tendency toward morningness). Natale and Di Milia [24] successfully tested this hypothesis by assessing the relationship between season of birth and circadian preference in Caucasian university students living in the northern (Italy) and southern (Australia) hemisphere. They found an inverse relationship between hemispheres, in the direction of a higher prevalence of morning types among those born during seasons with short photoperiods and a higher number of evening types among those born during long photoperiod seasons. While the previously reviewed studies investigated Caucasian populations, works on Asiatic children [25], young adults [26], and adults [27] failed to point to a significant effect of season of birth on circadian preference. These discrepant findings could be explained within the framework of differences between these populations in ocular photosensitivity [28] and polymorphisms of circadian clock genes [29]. As regards the circadian clock, previous studies in mammals have clarified that its functioning is grounded on a genetic-based negative feedback loop mechanism (see [30], a review). The first description of a negative feedback loop mechanism of the Period gene in drosophila by Hall, Rosbash, and Young was awarded with the Nobel Prize for Physiology or Medicine in 2017 [31]. In mammals, several circadian clock genes have been identified, such as Clock, Per1, Per2, and Per3. Although specific polymorphisms of circadian clock genes have been associated with a higher risk of diseases like multiple sclerosis [32], for example, or with the higher probability of being a morning type [33], genetic

contribution is not enough to completely explain human behavior as shown in this second paragraph about the environmental effect on the still-developing circadian timing system.

Emergence and Consolidation of Circadian Sleep/Wake Cycle

The emergence and consolidation of the circadian sleep/wake cycle in human infants represents an important developmental task that attracts the attention not only of parents, as expected, but also of psychologists, chronobiologists, and pediatricians. Although several studies have been carried out, the last word has yet to be said regarding the age of emergence and consolidation of the sleep/wake cycle in humans. While the emergence of a difference in activity between night and day, which could mirror the sleep/wake cycle, has already been observed in the first month of life [34, 35], the consolidation of this rhythm is thought to occur later, within the third month of life [16] or in the second half of the first year [34, 36, 37].

Circadian Sleep/Wake Cycle and the Two-Process Model of Sleep Regulation

The organization of the sleep/wake cycle circadian rhythm can be usefully understood within the framework of one of the still prevalent theoretical models in the area of sleep research, that is, the two-process model of sleep regulation [38, 39]. This model posits the existence of a circadian (C) process and a sleep (S) or homeostatic process that continuously interact during the 24 h cycle to auto-regulate sleep. The C process varies according to the time of day with a sinusoidal trend, reaching the acrophase at around 17:00–18:00 h and the nadir at around 04:00 h. The S process exponentially increases its value in relation to the lengthening of wake and sleep starts when a critical value is reached, that is, when the S process comes close to the upper threshold of the C process. During sleep, the value of the S process decreases in relation to the increase of hours of sleep reaching the level observed during previous wake. The awakening occurs when the S process reaches the lower threshold of the C process. Slow-wave activity during NREM sleep is considered the main marker of the S process while the rhythms of body temperature and melatonin, which are inversely coupled, are considered the main markers of the C process. While the anatomical substrate for the S process is yet to be clearly identified, the C process is generated at the level of the SCN by the endogenous circadian clock [40]. It is possible to suggest that a unique anatomical reference center may not be necessary for the S process because such a process is more pervasive in comparison to the C process. Indeed, while the C process can be viewed as an orchestra conductor who coordinates several musicians, potentially explaining the reason why an anatomical substrate has been disclosed, the S process triggers some retroactive feedback servomechanisms, aimed at keeping the internal environment constant, and thus reducing the need for a single reference center.

Developmental Changes According to the Two-Process Model of Sleep Regulation

Looking at the two-process model from a developmental perspective, it could be supposed that the S process may be preponderant over the C process in early life, with electroencephalographic markers of the S process appearing in the very first few months of life [41]. It is possible that the prevalence of the S process over the C process at birth could be due to the high sleep requirement in infants, which could be evolutionarily adaptive bearing in mind the potential role played by sleep at this stage of life in, for example, long-term memory consolidation [42] and cortical development [43]. Furthermore, in line with a possible earlier appearance of slow-wave sleep [44], it could be supposed, generally speaking, that from a phylogenetic point of view the S process may be preponderant over the C process in early life because homeostasis is an intrinsic basic of living beings, aimed at avoiding the possible interference of the environment. When growing up, the need for sleep decreases [45] and slow-wave activity (a marker of the S process) also decreases, particularly during puberty [43] and adolescence [43]. In line with these data, Jenny and colleagues [46] have shown that the accumulation of homeostatic sleep pressure was slower in post-pubertal adolescents compared with pre-pubertal children. This maturational change in the S process during adolescence seems to allow for the appearance of a preponderant C process. Indeed, the C process, which aims to help the S process to gradually tune with environmental changes, undergoes a progressive development that is completed at the end of adolescence [47], a period of life that is characterized by the circadian timing system's higher sensitivity to light [48]. During this precise stage of life, a phase delay in the circadian timing system [49], which has mainly been thought to be prompted by pubertal maturation, has consistently been reported, not only in humans but also in other mammalians (e.g., rhesus monkey) [50, 51]. While the C process seems prevalent in adolescence over the S process, aging is associated with a weakening of the C sleep regulation process, as pointed out by Cajochen and colleagues [52], leading to less consolidated sleep. Supporting this hypothesis, some experimental evidence has highlighted the possible neural substrate of this age-related decline in the C process

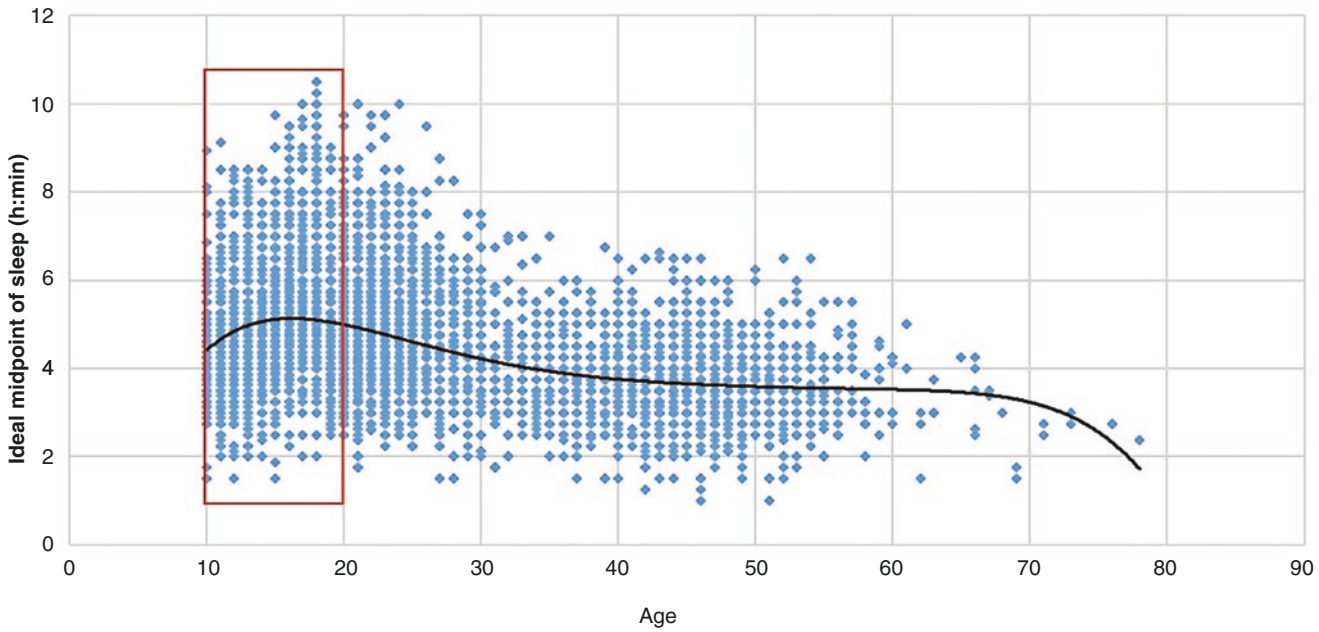

Fig. 9.1 Variation of the ideal midpoint of sleep across the human life span. Datapoints refer to an overall number of 11.418 persons aged between 10 and 78 years, of whom 7.225 were females and 4.193 males. The ideal midpoint of sleep reported here derives from the administration of questionnaires aimed at measuring circadian preference in several studies carried out by the research group coordinated by Professor Vincenzo Natale at the Department of Psychology of the University of Bologna (Bologna, Italy)

of sleep regulation. In particular, Nakamura and colleagues [53] showed a degradation of neural activity rhythms at the level of the SCN with aging in mice, in line with postmortem studies in humans [54].

Individual Differences in Circadian Rhythm

Individual differences in both circadian and homeostatic sleep regulation [55] can separately contribute to the emergence of circadian preference [19], which is commonly acknowledged as one of the most robust individual differences in circadian rhythm. Although measurement of circadian preference through biological markers (e.g., through the recoding of body temperature) is preferable because it is more accurate, this kind of assessment is often impracticable in large-scale studies due to the high cost. For this reason, the assessment of circadian preference is commonly carried out through questionnaires, with the Morningness-Eveningness Questionnaire (MEQ) [56] being the most widely used questionnaire throughout the world. A variant of the MEQ for children and adolescents is available; this questionnaire has been successfully validated through objective external criteria such as monitoring of body temperature and actigraphic recording of sleep/wake cycle [57]. In the MEQ the use of open questions concerning the subject's ideal bedtime and get-up time allows researchers to compute the ideal midpoint of sleep, that is, the clock time that splits the interval between the ideal bedtime and get-up time in half. The ideal midpoint of sleep is commonly acknowledged as a reliable marker of sleep timing preference because it is more strongly correlated with the overall score of the MEQ [58]. A later ideal midpoint of sleep points to a preference toward eveningness, while an earlier ideal midpoint of sleep points out a preference for morningness. From a developmental point of view, as can be observed in Fig. 9.1, morningness is more prevalent than eveningness during childhood. A shift to higher prevalence of evening types has been consistently observed in adolescents of different nationalities, leading to the supposition that mainly biological factors (e.g., pubertal maturation) may be involved in this shift. The maximum tendency toward eveningness is reached at around 20 years of age [47, 59] and afterward, a shift toward morningness preference begins, leading to a higher prevalence of morning types in adulthood [47, 59, 60]. The end of the shift toward eveningness combined with the beginning of the shift back toward morningness at around 20 years of age has been proposed as a biological marker of the end of adolescence [47].

Conclusions

Although the development of the circadian sleep/wake cycle is yet to be fully understood, the two-process model of sleep regulation provides a useful theoretical framework that allows us to derive some conclusions.

In early life the S process may be preponderant over the C process due to the latter being less "mature". Indeed, the C process may be programmed to help the S process to gradually tune with the environment. The example of prematurely born infants could support the view of the gradual development of the C process, which is completed at the end of adolescence and becomes preponderant over the S process. Indeed, preterm infants' early interaction with a sui generis environment that is characterized by a more regular temporal pattern (e.g., the regular pattern of feeding in neonatal care units) [5] may result in a reinforcement of the C process. This reinforcement of the C process could lead to the early consolidation of the circadian sleep/wake cycle in prematurely born infants [3].

As already pointed out, the topic of the emergence and consolidation of the sleep/wake cycle in infants attracts the attention of several figures, such as parents, psychologists, chronobiologists, and pediatricians. Parents, in particular, should be aware of the potential positive outcome of circadian milk as a powerful form of chrononutrition [10], which seems to be a highly promising strategy to produce an early consolidation of the sleep/wake cycle [14]. Furthermore, parents should consider that "immersing" their babies into the environmental rhythmicity could promote a circadian development that is in harmony with the environment. Indeed, light is able to act on the circadian timing system even when infants are sleeping [61]. Moreover, parents should also be aware of the importance of the regularity of meals to favor a harmonious development of the C process with the environment. For example, it has been shown that skipping breakfast, an adjustable risk factor, is associated with a higher body mass index [62]. Indeed, skipping breakfast, apart from producing a lower satiety level that could explain a higher food intake, negatively affects the clock gene expression, leading to an increase in the postprandial glycemic response [63]. Since the S process is preponderant in early life, concurrently with strategies aimed at facilitating the appearance of the C process, it should be opportune to protect the homeostatic mechanisms. For example, sleep deprivation in children, the effects of which could be more detrimental than those observed in adults in which the two processes work equally, should be avoided through interventions of sleep hygiene [64] aimed at protecting the S process.

An example of another intervention on the C process that would be possible to carry out would involve adolescents. As previously highlighted, a phase delay of the circadian timing system occurs in adolescence [49] that in some cases could lead, along with other factors, to the so-called delayed sleep phase disorder (DSPD) [65]. It is known that DSPD has higher prevalence among adolescents and has several negative outcomes on health and social life [65]. A potential intervention aimed at counteracting the negative effects of DSPD is represented by light therapy, which is commonly acknowledged as an effective treatment of circadian rhythm sleep disorders [66], with light acting as a key regulator of the C process.

In spite of the phase delay in the circadian timing system that commonly occurs during adolescence, school start time (a social synchronizer) does not change according to this biological phase delay. The lack of synchrony between the biological and social clock is the so-called social jetlag [67] that reaches its maximum extent during adolescence [68]. Social jetlag has been associated with several negative outcomes, such as obesity [68] and poor academic performance [69]. One potential intervention aimed at reducing social jetlag consists in acting on the C process by delaying school start time. A systematic review [70] has shown that delaying school start time by between 25 and 60 minutes can decrease daytime sleepiness and depression.

To sum up, within the theoretical framework of the two-process model of sleep regulation, two macro-categories of interventions can be suggested: on the one hand, the interventions on the S process are mainly protective/collaborative, while, on the other hand, those on the C process are mostly educative. The interventions on the S process could be more effective if carried out in the family context, for example, the role of parents is of primary importance in order to help children to practice good sleep hygiene, thus reducing the risk of sleep deprivation. To this end, formative activities specifically addressed to parents could be devised. As regards interventions on the C process, the role of society should also be taken into account with, for example, legislative interventions aimed at delaying school start time, since this tactic has proved to be effective at reducing some consequences of social jetlag. A future research task would be to provide data concerning both types of intervention.

To conclude, this chapter has shown that, by examining the developmental changes of the sleep/wake cycle according to the two-process model of sleep regulation, some interventions can be scheduled in order to consolidate the sleep/wake rhythm in early life or to prevent/solve some issues due to the maturational changes of sleep regulation processes.

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Part III

Sleep Mechanisms: Developmental Aspects

Developmental Aspects of Sleep

10

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Introduction

Sleep is a dynamic process that undergoes remarkable changes in architecture (duration and pattern) during development. In altricial species including humans, babies are born with immature neural networks for sleep-wakefulness (S-W) and several other higher brain functions. In the human foetus, brain networks mature as the conceptional age progresses. Rats and mice, the commonly used animal models also exhibit similar patterns. Thus, research on these models provides the conceptual framework for understanding S-W patterns during human foetal development.

After the landmark discovery of REM sleep, understanding about sleep has progressed immensely in the last 66 years. The initial challenges were to understand the neural substrates of NREM and REM sleep, with the majority of studies conducted in adult animals employing a variety of classical tools and techniques ranging from lesion, stimulation, single unit studies etc., and more recently, optogenetics and chemogenetics. Involvement of discrete brain nuclei in the regulation of different components of sleep are reported elsewhere [1–5]. In this chapter, developmental aspects of sleep only are addressed, laying emphasis on species differences and similarities.

In comparison to adults, relatively fewer experimental studies are carried out on the developmental intricacies of sleep in the newborn. It is always challenging to study the brain of the newborn due to its small size, delicate fragile nature, and underdeveloped body functions. Adding to it are the difficulties in getting ethical clearance for such studies. Nonetheless, a few studies had provided insights into ontogenetic aspects of sleep [6–12]. Moreover, the developmental aspects of sleep were also obtained from animal studies involving sleep restriction and effects of other stresses such as smoking, drugs and alcohol treatments during pregnancy.

Developmental Profile of Sleep

Development of sleep profile occurs in parallel to cognitive and physical growth. Sleep pattern in human neonates and infants is polycyclic [7–9, 11]. Moreover, adult features of NREM and REM sleep are not observed during early development. So, the terms such as quiet sleep (QS) and active sleep (AS) are used, and they are considered as precursors of NREM and REM sleep respectively [6, 7]. Foetuses and newborns exhibit spontaneous cyclic alterations in AS and QS, which could be identified with the help of physiological and behavioural state recordings in polysomnography. Diverse criteria and events such as body movements, respiration, heart rate and muscle tone are used for classifying sleep stages before the appearance of clear-cut differentiation in EEG [13–15]. The patterns of brain activity during AS and QS begin to change *in utero* and continue postnatally in human and other mammals [16]. In all mammals studied to date, the amount of AS remains much higher during early periods of development; conversely, the amount of QS and wakefulness continues to be lower during this time. The ultradian, circadian and homeostatic sleep regulatory mechanisms also undergo important modifications during the neonatal period [8, 17].

The exact timing for the emergence of well-defined sleep states is still a matter of debate. As per Curzi-Dascalova and group [18], distinct AS and QS with alternating periods of continuous and discontinuous background EEG patterns occur by 27–30 weeks of gestation in human foetus, while others believe that the organization of different stages of sleep occurs only after week 32 of gestation

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[14–16]. In sheep, on the other hand, the neocortical EEG does not show slow wave activity until 115–120 days of conception [19]. In guinea pigs, it occurs after 50 days of gestation [20], and it continues till postnatal developmental day 12 in rat pups [21].

Sleep of human newborns is distributed approximately equally across the day and night. Human neonates sleep most of the time (85%), out of which half the time is spent in short episodes of AS during the initial months. After a few weeks of life, episodes of sleep and wakefulness become longer, with sleep consolidating towards the nighttime resulting in the development of nocturnal sleep pattern. By 12 weeks of age, 50–75% of infants sleep through the night [22] and 90% of them sleep throughout the night at 6 months of age [23]. The AS/REM sleep decreases gradually from birth until puberty in the human.

Newborn rats also show relatively shorter bouts of sleep episodes than the adults [7, 11]. In these newborns, AS constitutes a substantial period of time (about 70%) and they spent comparatively lesser time in QS (about 10%) as shown in Fig. 10.1. This pattern continues for about a week and then slowly AS begins to reduce while the percentage of QS rises. After about 10 days, the dramatic reduction in AS is achieved while QS is increased exponentially. Also, the bouts of AS become shorter while the length of QS increases. While the percentage of AS in the normal full-term human babies is approximately 50% [6, 10] it is higher (approximately 70%) in rats. Albeit species differences, higher percentage of AS is found in immature newborns [7]. In human babies, the percentage of AS decreases approximately by 30% in the first year of life [6, 24], which is similar to the decrease observed from postnatal day 15 in rat pups. Thus, the sleep parameters display age-dependent development. The lower percentage of QS in comparison to AS in the pup indicates that the neural mechanisms for QS develop comparatively later [25]. Progressive increase in the bout duration of QS and reduction in the number of cycles (bout frequencies) with the progression in age are attributed to the influence of the developing forebrain mechanism and its interaction with the other brain regions [26]. The early prominent behavioural events in rats during AS in the initial postnatal days 1–7 include rapidly occurring myoclonic twitches and the jerky limb movements, expressed against a background of muscle atonia. The myoclonic twitches and the subsequent hippocampal neocortical communication probably assist in the development of the cortical neural networks and somatosensory responses [27, 28].

Stressed Maternal Conditions Leading to Malformed S-W and Neurobehavioural Development in the Newborn

Recent studies have provided robust evidences that sleep restriction, intake of alcohol, drugs and smoking during pregnancy alter the *in utero* development of brain networks thereby disrupting cognitive development [11, 12, 29–39]. The studies that involved controlled experimental sleep restriction during the last trimester of pregnancy provided insight into brain plasticity for sleep networks in growing neonates. Restriction of REM sleep (REMSR) for 22 h per day by classical platform method, or deprivation of both

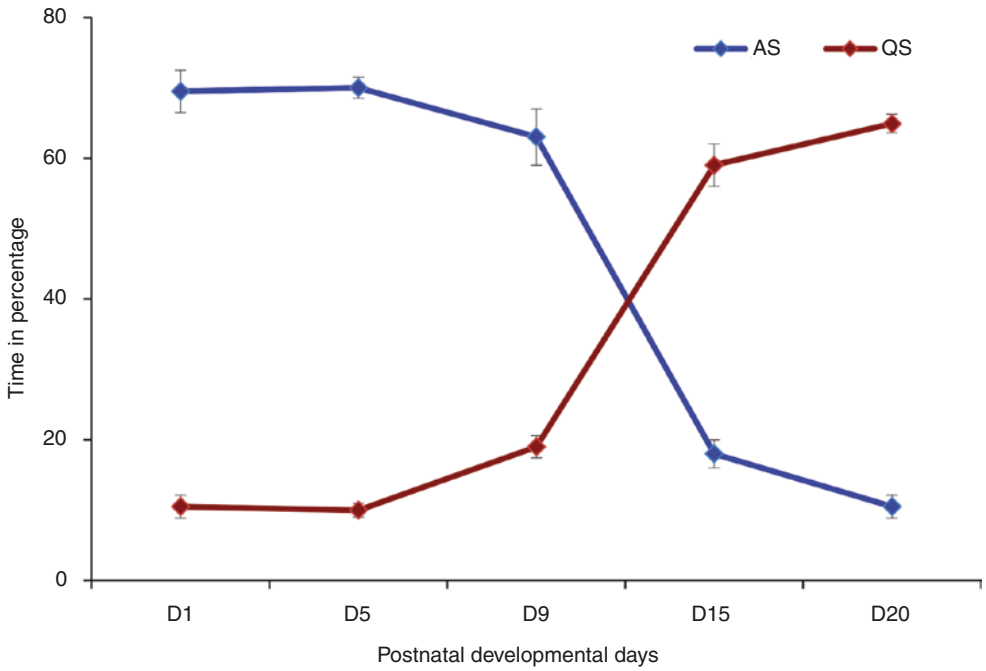

Fig. 10.1 Changes in sleep during postnatal days. Changes in active sleep (AS) and quiet sleep (QS) in percentage during postnatal developmental days (D) in rat pups

Table 10.1 Depiction of changes in sleep parameters by increase (+) or decrease (−) in total sleep-restricted group and REM sleep-restricted group, in comparison to values in control group, on five postnatal days

Parameters	Total sleep-restricted group					REM sleep-restricted group				
	D1	D5	D9	D15	D20	D1	D5	D9	D15	D20
AS %	++	+	++	−	NS	++	++	++	NS	+
QS %	−	−	−	++	NS	−	−	−	+	NS
AS (Freq)	−	−	−	NS	+	−	−	−	+	++
QS (Freq)	−	−	−	NS	NS	−	−	−	NS	−
AS (Dur)	++	++	++	+	−	++	+	++	−	−
QS (Dur)	NS	NS	NS	+	++	NS	NS	NS	++	++
S-W C Dur	++	++	++	+	+	++	++	++	++	+
AS latency	NS	NS	NS	NS	NS	NS	NS	NS	−	−

NS implies no significant change, ++/−− shows changes at $p < 0.001$ and +/− at $p < 0.01$ level

REM and NREM sleep, that is, total sleep restriction (TSR) for 5 hrs per day by gentle handling method, during 15–20 days of pregnancy not only affected the natural ontogenetic development of sleep *in utero* but also delayed and disrupted development of S-W [11, 12]. Compared with age-matched control, pups from both groups of sleep-restricted dams displayed a higher percentage of AS and a lesser percentage in QS. In Table 10.1, alterations in AS and QS in pups from sleep-restricted dams are shown in comparison with the data of control pups.

Longer duration of the S-W cycles in neonates and infants of sleep-restricted mothers indicated vulnerability of this parameter during foetal development. Reduced S-W cycles were observed in pre-term babies (younger than 30 weeks gestational age) as compared with the control group [40]. The circadian rhythms in these pre-term neonates are also less robust as they exhibit a multitude of ultradian frequencies while full-term neonates show a distinct circadian frequency depicting fast initial adaptation in the first week of life to a 24 h day [17, 41]. In altricial species where babies are born immature (e.g., human babies born between 27 and 37 weeks), AS is high at the time of birth [42, 43]. Experimental studies have shown that full-term pups of sleep-restricted dams also display immature patterns of sleep at the time of birth [11, 12]. This clearly indicates that maternal sleep restriction during the last term of pregnancy delays the maturation of S-W *in utero*. This may not be due to maternal stress during sleep restriction, as infants of mothers who consumed alcohol, showed reduction in the AS and increase in wakefulness [32, 33]. Mothers exposed to cigarette smoke during pregnancy (passive smoke) had babies with impaired arousal patterns and were more susceptible to sudden infant death syndrome [30, 31].

Sleep restriction of dams resulted in depression-like symptoms in the offspring, later in life [38]. Recording of ultrasonic vocalizations showed that pups of sleep-restricted dams had subtle changes in the behaviour even during the early developmental days, which are equivalent to the days of childhood in humans [36]. In addition to the prenatal factors, the postnatal factor can also contribute to the altered patterns in sleep. Post-parturition maternal separation leads to increased total sleep time, increased REM sleep and higher percentage of NREM sleep episodes in the offspring [44, 45]. REM sleep-restriction of rats during the third term of pregnancy produces reduced parental care by these mothers, during the three postnatal days [36]. This may result in long maternal separation of the offspring during these crucial days, which could contribute towards sleep alterations. Neonates are most vulnerable to physical separation from dams as they have poor capacity to thermoregulate during the initial postnatal days. Thus, some contribution from the postnatal care cannot be ruled out, in addition to prenatal factors, in the observed effects of maternal sleep restriction.

Body weights of pups of the sleep-restricted mothers were normal till weaning, but it was reduced after weaning [39]. Effective parenting during the initial developmental period can diminish the stress response in human infants [46]. These findings suggest that the offspring with immature S-W networks would probably require extended maternal care for an optimal growth of brain. Non-invasive neonatal sleep evaluation can provide useful information about the brain development in neonates.

Pups of REM sleep-restricted mothers had reduced REM sleep latency during postnatal days 15–20. This could probably be taken to indicate depression-like traits. Early onset of REM sleep is observed in the clinical conditions of depression and narcolepsy [47, 48]. In addition, the impaired sleep regulation including altered sleep homeostasis, reduced REM latency, reduced slow-wave sleep and increased REM duration are commonly observed in depressed patients [49–51]. *In utero* exposure to valproic acid also elicits sleep behaviour in infant rats similar to children with autism spectrum disorders with less time spent in NREM sleep [52]. Moreover, reduced REM latency and diminished NREM sleep also featured in the sleep patterns in the offspring when their mothers were restrained during pregnancy [53].

Maternal Sleep Restriction Affecting Neural Development in the Newborn

In general, the AS mechanisms located in the brainstem are the first to mature, whereas those for the expression of QS develop comparatively later [25]. All the same, QS is also affected by maternal sleep restriction. The reduced QS percentage in the pups of REM sleep-restricted dams indicated suppression of QS organization. Moreover, the immature nervous system lacks inhibitory control over the AS/REM sleep; the persistence of higher level of AS/REM sleep until postnatal day 20 probably indicated the existence of the

immature brain [6]. A greater amount of QS observed in the infants of depressed mothers is considered as a conservation-withdrawal phenomenon [54] since information processing for both auditory and visual stimulation are altered in depressed individuals during deep sleep [55]. In addition, decreased wakefulness (both % and duration) probably indicate a delay in natural development of wake-promoting regions in the brain, including locus coeruleus that contribute to the developmental transition in the S-W pattern [11, 56]

During development, longer durations of S-W cycles may be taken as early signs of altered neurodevelopment. Decreased transitions between sleep and wake stages, due to longer bouts of these stages, indicate high risk development [57]. Transitions between QS and wakefulness are influenced by neuromaturation in infants [58]. The structural composition of sleep is altered with prolonged AS in children with central nervous system disorders [59]. Thus, apparently, any sleep restriction during pregnancy affects normal neuromaturation of the baby.

It must be emphasized that mothers during normal pregnancy also experience sleep loss, especially REM sleep loss, due to disrupted sleep during last term of pregnancy [60–63]. Considering that sleep is normally compromised to some extent during late pregnancy, further disruptions of sleep would result in prenatal stress to mothers. The stress hormone corticosterone is elevated in REM sleep-deprived rats [64]. Various studies involving prenatal stress protocols in rats have indicated neurobiological alterations due to disruption of circadian rhythms, varied corticosterone secretion and changes in hypothalamic–pituitary–adrenal (HPA) axis as in people suffering from depression [65, 66]. Aberrations in the cortisol rhythm are reported in depressed patients [67]. The prenatally stressed rats showed increased plasma corticosterone levels with increased amounts of REM sleep and light slow-wave sleep with slight decrease in the deep slow-wave sleep [68]. In humans, the HPA axis is strongly regulated by social or parental buffering during the first year of life [46]. The optimal maternal care help in normalizing the S-W profile of the neonates. Sleep changes in pups born to REM sleep-restricted dams during postnatal days 15 to 20 mimic the trend found in patients with depression. Patients with depression also exhibit dysfunctions in HPA axis and circadian rhythmicity [69] and abnormalities in sleep profile [70].

Circadian rhythms for S-W develop around 2 months of age in human babies [71]. Since melatonin is one important hormone for sleep regulation, maintenance of an optimal maternal circadian rhythmicity via the suprachiasmatic nuclei would be essential to program the foetal melatonin cycle. Chronodisruption and disturbed melatonin cycles have a negative impact on the maturing foetal oscillators, which may contribute to psychological and behavioural problems in the offspring [72]. Preterm infants, deprived of exposure to normal maternal melatonin cycle for some time, show delayed development of the circadian rhythm. Studies in rodents have shown that maternal rhythms, when disrupted during pregnancy alter the postnatal circadian rhythms in the offspring [73].

Micro-Architecture Based on Differences in Development of EEG Bands

Power spectral analysis is a well-established method to understand the power distribution of different EEG frequency bands of the developing brain. Such analysis performed during postnatal days 15 (D15) and 20 (D20) during QS and AS sleep provided an interesting insight into the development of these bands. In control pups, during QS, delta power decreases from D15 to D20, whereas powers in theta, alpha, beta bands increase (Fig. 10.2a, b). Such developmental decrease in delta power and an increase in beta power are reported during the first month of life in human babies [74]. However, pups born to REMSR dams exhibited lower delta power than controls on D15, while there was high power on other frequencies (beta and theta) in the QS traces (Fig. 10.2a). Besides this, the delta power did not decrease during D20, rather it remained higher, but beta, alpha and theta powers decreased significantly (Fig. 10.3b). During AS, there were higher delta power and lesser theta and beta power on D15. On the other hand, higher theta power and lower alpha, beta powers on D20 reflected imbalance and delay in the development of networks involved in EEG (Fig. 10.2c, d). Similar trends are observed in preterm foetal growth restricted neonates [75]. Alterations in cortical structure and organization can reduce the percentage of delta power [76]. Decreased delta powers during slow wave sleep are also evident in depressed patients [49] with increased high-frequency activity [77], which may be considered as markers for susceptibility to stress and psychiatric disorders. We had also reported a similar pattern in the pups that were born to the total sleep-restricted dams [12]. During the first year of life in a human baby, significantly lower spectral powers are observed in beta, alpha and delta bands during AS than in QS, and lower theta in AS than in QS after 5 months of age indicate normal maturation of quiet sleep EEGs [78]. The premature babies exhibit higher frequency and larger amplitude of beta activity and improved inter- and intrahemispheric relationships compared with full-term newborns. In human neonates, high density EEG (non-invasive) can be used to assess brain maturation in infants who are at the risk of neurodevelopmental deficits.

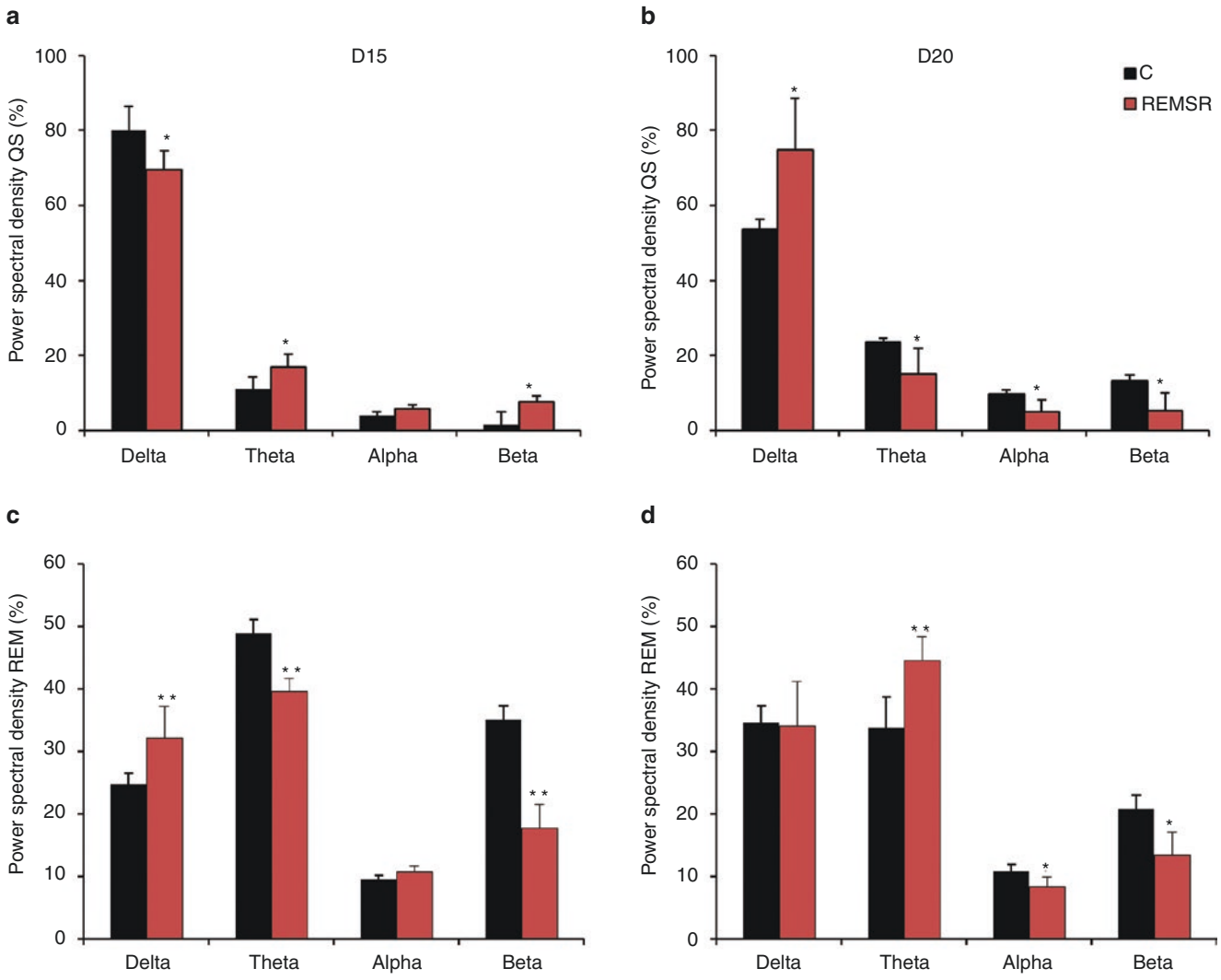

Fig. 10.2 Power spectral analysis of different EEG bands in QS (**a**, **b**) and AS (**c**, **d**) on day 15–16 (D15) and day 20–21 (D20) of pups born to control, REMSR dams. Y axis represents the power analysis in percentage of QS sleep and X axis represents the various frequency bands. Data expressed as mean ± SD. The level of significance is $*p \leq 0.05$

Clues From Modelling of Distribution Patterns of S-W Bouts During Development

The mechanisms that bring about the different stages of sleep and wakefulness in the infant brain remain unclear. It is still not very clear whether the timing of sleep depends on the time spent awake. Mathematical models are used to predict the precise developmental accounts of the neural foundations of sleep [79]. In human adults, sleep bouts follow an exponential distribution, whereas wake bouts follow a power-law distribution and similar patterns are true in adult rats, cats and mice [79]. Exponential processes imply probabilistic state changes typically governed by a constant rate of change over time. Similar dynamics in sleep-wakefulness architecture may benefit in understanding the mechanisms involved in disease conditions [80]. Power law distributions are thought to arise from multiple components of a system interacting in a complex manner.

We also tested the generalizability of the S-W bout distribution from postnatal days 1–20 in pups born to total sleep-restricted dams (Fig. 10.3). The duration of sleep bouts exhibits exponential distributions similar to previous reports [11, 26, 79]. Illustration of reduced slope in the log-survival plots for bout durations of sleep in the TSR group on all the studied postnatal days (PNDs) not only highlighted a delay in the development of sleep networks but also depicted the

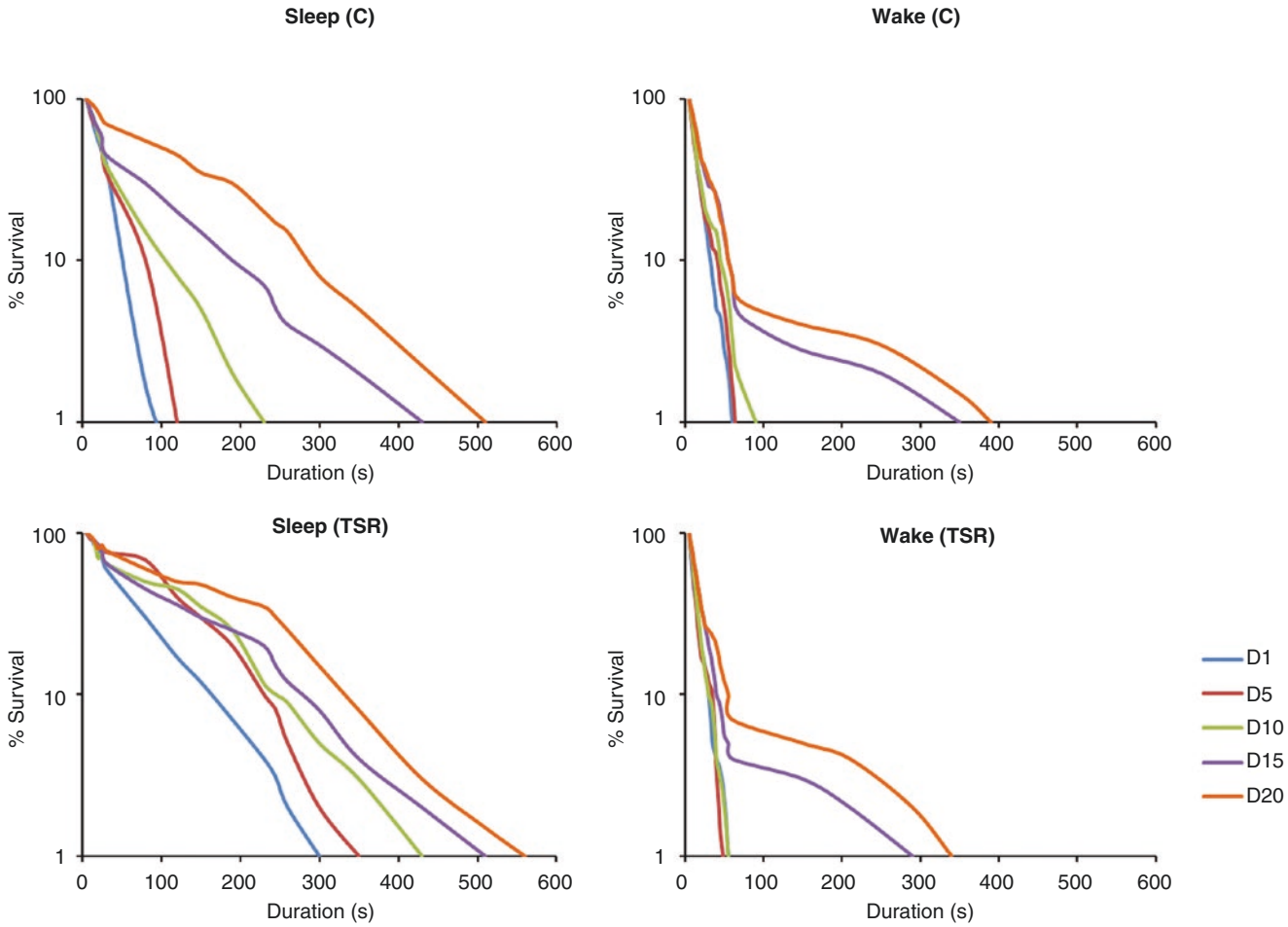

Fig. 10.3 Survivor plots for sleep and wake bout duration in control and TSR groups on different developmental days. Log-survivor plots of sleep and wake bout distributions for rats on D 1, 5, 10, 15, and 20 for the control (**a**, **b**), TSR (**c**, **d**). Each plot was constructed from pooled data. The Y axis represents the survival percentage of bout duration and X axis represents the duration in seconds

vulnerability of sleep maturation process. Strikingly, due to underdeveloped wake networks during early PNDs 1–10, the survival plots for wakefulness were least altered. But during PNDs 15 and 20, compromised development of wakefulness could be noticed. Such a distribution suggested that a sleep bout works as a stochastic process with a constant probability of transition into wakefulness; the transition probability decreases through development, leading to longer episodes of sleep. Wake bouts in very young rats also follow an exponential distribution during initial development (postnatal days 1–10) but the distribution of wake bouts followed power law from postnatal day 15 onwards. After the third week of development, the probability distribution indicated that an already lengthy wake bout is likely to persist a little longer. Sleep and wake bout lengths show no memory for the duration of any previous episode, so that transitions between these states resemble an alternating renewal process [26]. These modelling studies helped in studying sleep architecture, bout fragmentation and associated disorders.

Detection of sleep changes in neonates may be of great clinical significance and can be viewed as early markers of psychobehavioural disorders. The presence of decreased QS during early postnatal days 1–10 and comparatively increased AS during all postnatal developmental days in the offspring of REM sleep-restricted mothers suggest slowing of the maturational process.

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Humoral and Other Sleep-Promoting Factors

11

Éva Szentirmai and Levente Kapás

The idea that circulating "humors" may be the ultimate cause of sleep dates back to ancient scientists and philosophers, but only at the beginning of the last century was the concept first addressed experimentally. With the advance of experimental techniques and the discovery of the first hormone, secretin, the search for humoral sleep factor(s) appeared to be technically possible and theoretically justified. Kuniomi Ishimori in Japan and Henri Pieron in France independently demonstrated that injection of brain extracts or cerebrospinal fluid (CSF) from sleep-deprived dogs to non-sleep-deprived recipients causes robust increases in behavioral sleep [1, 2]. Pieron named the putative sleep-inducing substance "hypnotoxin." Schnedorf and Ivy reproduced Pieron's findings which gave further support to the hypnotoxin theory and inspired further search for the elusive sleep factor [3]. Kornmüller in 1961 and Monnier in 1963 used parabiotic cats and rabbits and demonstrated that thalamic stimulation of the donor elicits increased cortical slow-wave activity and sleep in the recipient animals [4, 5]. These experiments led to the isolation of delta sleep-inducing peptide (DSIP) [6]. A Japanese group led by Shojiro Inoue extracted a sleep-promoting substance from the brainstem of sleep-deprived rats in the early 1970s, and later they identified one component as uridine and another component as the oxidized form of glutathione (reviewed in [7]).

The above attempts led to the identification of substances with variable and generally modest effects on sleep, and the field all but gave up on pursuing their further investigation. One series of studies, however, left a lasting effect on sleep research. In the late 1960s, Pappenheimer and his coworkers undertook a series of studies on extracting sleep-promoting substance, which was initially found in the CSF of sleep-deprived goats [8], subsequently in bovine and rabbit brains and CSF, as well as in human urine (reviewed in [9]). The somnogenic component of the sleep-promoting material was identified as muramyl peptides [10]. Since muramyl peptides are bacterial cell wall fragments, not produced by eukaryotes, there was a general skepticism about their physiological role as endogenous sleep-promoting substances. Their identification as somnogenic substances, however, led to further investigation of their actions and to the important discovery that proinflammatory cytokines, endogenous peptides produced mainly by macrophages exposed to bacterial cell wall components, possess strong sleep-promoting activities. Furthermore, the recent recognition of the microbiota as a source of brain signaling and the recognition that products of the intestinal bacteria translocate to the internal environment of the host put the possible relevance of bacterial products in sleep regulation in a new perspective.

Proinflammatory Cytokines

It has been known since the 1950s that systemic infections and administration of components of bacteria, such as endotoxin, elicit fever through the stimulation of the production of a circulating pyrogen, which was called "endogenous pyrogen" at that time. Two lines of evidence suggested that the endogenous pyrogen could also be a sleep-inducing factor. One, in addition to fever, acute systemic infections are also characterized by increased sleepiness. Two, cell wall components of bacteria that elicit sleep also stimulate the production of endogenous pyrogen by immune cells.

In the 1980s, three laboratories characterized the sleep effects of purified endogenous pyrogen obtained from the supernatants of macrophages or astrocytes activated by heat-killed bacteria. Krueger and coworkers demonstrated that intravenous and intracerebroventricular (icv) administration of purified endogenous pyrogens induce prolonged increases in non-rapid eye movement sleep (NREMS) and fever in rabbits [11]. The effects were attributed to interleukin-1 (IL-1), which was the only known endogenous pyrogen at that time, but the actual structure of the active component of the injected sample was unknown. Tobler and coworkers demonstrated that icv administration of astrocyte-derived endogenous pyro-

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gen elicits fever and enhanced slow-wave activity of the electroencephalogram (EEG), a measure of sleep intensity [12]. In cats, icv administration of purified human IL-1 caused dose-dependent changes in sleep, the lower doses being somnogenic, while higher doses wake-promoting [13].

Subsequent studies using recombinant IL-1 confirmed that central or systemic administration of IL-1 induces NREMS in rabbits [14], rats [15], and mice [16]. Circulating IL-1β acts on a peripheral target to induce sleep as evidenced by the effectiveness of vagotomy to block the somnogenic actions of moderate doses of systemically administered IL-1β [17, 18]. However, when high doses of IL-1β are administered peripherally or directly into the cerebral ventricles or brain tissue, it also has the potential to act on central sleep-promoting mechanisms. The site of the central actions is unclear, but the locus ceruleus [19], dorsal raphe [20], prostaglandin D2 (PGD2)-sensitive basal forebrain region [21], and median preoptic area [22] have been suggested, along with growth hormone-releasing hormone-receptive [23] and serotonergic mechanisms [24, 25]. The role of prostaglandins in IL-1β-induced fever has been well established, but their contribution to its somnogenic actions is controversial [26, 27]. Extensive evidence indicates, however, that sleep increases in response to IL-1β are not a direct consequence of its pyrogenic actions (reviewed in [28]).

In the second half of the 1980s, it became apparent that IL-1 is not the only endogenous pyrogen. White blood cells that are activated by components of the bacterial cell wall secrete other bioactive peptides into the circulation that induce fever and have complex effects on immune functions (reviewed in [29]). Screening of these peptides revealed that interferon α2 (IFNα2) [30] and tumor necrosis factor-α (TNFα) [14, 31] also have NREMS-promoting properties.

TNFα, similarly to IL-1β, is a proinflammatory cytokine with multiple target sites and complex effects on immune functions and metabolism. Its primary source is the immune cells, such as macrophages, dendritic cells, and T lymphocytes, but it is also expressed in the brain by microglia, astrocytes, and neurons [32–34]. After the identification of TNFα as another endogenous pyrogen produced by activated white blood cells [35], it was soon established that systemic or central administration of TNFα induces inflammatory responses, including sickness response characterized by increased sleep, fever, and loss of appetite (reviewed in [36]). The NREMS-promoting effects of TNFα are mediated by the TNF receptor 1 [16] and have been described in rabbits, sheep, mice, and rats [14, 16, 26, 31, 37]. TNFα production also correlates with sleep-wake activity. In rats, hypothalamic levels of TNFα mRNA and TNFα protein are higher during the rest phase [38, 39], and sleep loss elevates TNFα mRNA expression in the cerebral cortex and basal forebrain [40].

Similarly to IL-1β, vagotomy blocks the sleep-promoting effects of systemically administered TNFα pointing to a peripheral site of action [41, 42]. Direct delivery of TNFα into the brain also induces NREMS, possibly acting in the locus ceruleus [19], the preoptic region [43], and the PGD2-sensitive, sleep-promoting zone of the basal forebrain [21]. Nitric oxide and prostaglandins have an established role in mediating the sleep effects of TNFα [26, 44, 45]. While the role of increased secretion of proinflammatory cytokines in sleep responses to systemic infections and inflammatory processes is widely accepted, their contribution to the regulation of sleep-wake activity under healthy conditions appears to be less clear. The role of endogenous TNFα in sleep regulation was first studied by using anti-TNF antibodies, TNF-binding protein, and fragments of TNF receptor 1. The general outcome of those experiments was that molecules that bind to and neutralize endogenous TNFα decrease the time spent in NREMS, which pointed to the possibility that TNFα may contribute to the maintenance of spontaneous sleep (reviewed in [46]). Subsequent advances in TNFα biology revealed further complexities in TNFα biochemistry that may necessitate the reinterpretation of the initial findings. TNFα is a transmembrane protein which can function in its membrane-bound form, or it is proteolytically cleaved with the subsequent release of the trimeric soluble TNFα, which is the form of TNF present in the extracellular environment, including the plasma (reviewed in [34]). Antibodies and receptor fragments which were used in sleep studies (e.g., [47, 48]) not only bind and neutralize soluble TNFα molecules but also are ligands for membrane-bound TNF and may, in fact, trigger increased TNFα secretion (reviewed in [49]).

The role of endogenous TNFα in sleep regulation has also been addressed by using mouse strains with deficient TNF signaling. Studies with TNF receptor-deficient mice led to disparate findings on their sleep behavior. Both reduced and unchanged NREMS were reported in TNF receptor 1 knockout (TNF R1 KO) mice [16, 50] and TNF R1 and R2 double-KO mice [51, 52]. TNF R2 mice had decreased rapid eye movement sleep (REMS) but normal amounts of NREMS [50]. Deficiency of the receptor ligand, as demonstrated in TNFα KO [53] and TNFα and lymphotoxin-α double-KO mice [50], does not result in reduced NREMS. Regarding REMS, somewhat consistent results have been obtained in experiments using exogenous TNFα administration and in studies on spontaneous sleep in KO models. Icv or systemic injection of TNFα suppresses REMS in mice, rats, and rabbits [14, 41, 54], while REMS is increased in both TNF R1 and R2 double-KO mice [51] and in TNFα KO mice [53]. This suggests that endogenous TNFα may have a tonic REMS-suppressive activity.

Acute and chronic sleep loss or sleep fragmentation results in a proinflammatory state manifested as increased expression of IL-1β and TNFα and activation of NF-κB signaling in the brain and elevated circulating proinflammatory cytokine levels (e.g., [55–61]). Sleep rebound after sleep deprivation is attenuated by a TNF receptor fragment and anti-IL-1β antibodies [62, 63] and in TNF R1 and IL-1 R1 double-KO mice [64] suggesting a possible role for proinflammatory cytokines

in response. Studies using TNF receptor and ligand KO models, however, did not confirm that TNF signaling is necessary for these rebound responses [50, 53].

In summary, TNFα and IL-1β have the potency to increase NREMS acting on both peripheral and central targets. A few cytokine-sensitive brain sites have been identified, but additional studies will be required to construct a comprehensive map of the central targets. Attempts to acutely neutralize soluble TNF and IL-1 and the constitutive KO models all have their limitations. To gain a clear picture of the role of endogenous cytokines in maintaining spontaneous sleep will require the use of inducible KO models or pharmacological approaches that do not have the potential to stimulate the release of proinflammatory cytokines. Three of the endogenous pyrogens, IFNα, TNFα, and IL-1β, show striking similarities in their effects on body temperature and NREMS. Endogenous prostaglandins provide a unifying mechanism for the pyrogenic actions of these molecules [29]. The identification of similar unifying mechanism for their somnogenic actions would provide a valuable insight into fundamental mechanisms of sleep regulation.

Adipokines

In addition to its role in energy storage, the white adipose tissue is also recognized as an endocrine organ. Hormones secreted by the adipose tissue are collectively referred to as adipokines. Adipokines, such as leptin, adiponectin, and resistin, have diverse effects on metabolism by acting on multiple tissues, including the brain (reviewed in [65]). Leptin is a 167-amino acid peptide produced by white adipose tissue in proportion to the amount of body fat, thereby reflecting the status of long-term energy stores. The most widely recognized action of leptin is its potency to reduce body weight by decreasing food intake and increasing energy expenditure, but leptin may also provide a link between metabolism and the regulation of sleep. Systemic or icv administration of leptin increases NREMS in rats, suggesting that leptin released from the adipose tissue may be a sleep-promoting molecule [66, 67]. Obesity, however, leads to increased sleep in rats and mice independently of leptin as shown by increased sleep amounts in obese rodents with deficient leptin signaling [68–71]. A major source of circulating TNFα is the white adipose tissue; thus TNFα is often regarded as an adipokine. Within adipose tissue, macrophages account for nearly all TNFα production [72]. Circulating TNFα concentration rises with increasing obesity and correlates with insulin resistance [73]. Increased sleep observed in obese rodents may be linked to enhanced production of TNFα [68–70, 74, 75].

In addition to adipokines, lipolysis itself may result in the production of sleep-promoting signals. In nocturnal rodents, the feeding period (dark phase) is characterized by lipogenesis, while in the rest phase (light), when feeding is minimal, lipolysis provides the main energy source. By using sequential infusions of lipolytic and lipogenic hormones, the lipogenic and lipolytic phases can be reversed in these nocturnal animals, which leads to the complete reversal of the sleep-wake cycles to a diurnal pattern [76]. Further, restricting feeding to the light period also causes the reversal of the lipolytic and lipogenic phases with the concomitant reversal of the sleep-wake pattern [77–80]. In addition, strong lipolytic signals, such as IL-1β, TNFα, epinephrine, β3-adrenergic receptor (β3-AR) activation, and 2-deoxy glucose, all enhance NREMS [14, 37, 53, 81–83].

Gastrointestinal Hormones

The relationship between sleep and energy balance has long been recognized. In general, feeding and positive energy states facilitate sleep, while fasting and negative energy balance induce wakefulness (e.g., [74, 84–86]). This relationship pointed to the possible role key metabolic organs as well as satiety and orexigenic hormones in sleep signaling. The best characterized satiety hormone is cholecystokinin (CCK), a product of the "I" enteroendocrine cells of the small intestines, which is produced postprandially in response to dietary fat and protein, and its systemic administration suppresses feeding [87]. The actions of ghrelin, a product of the X/A-like cells of the gastric mucosa, are the opposite of those of CCK. Ghrelin secretion increases under conditions of negative energy balance, such as starvation and cachexia, and declines under conditions of positive energy balance, such as feeding and obesity [88]. Ghrelin is the only known peripheral hormone that stimulates feeding [89]. In addition to their gastrointestinal sources, ghrelin and CCK are also produced by neurons in the brain, and their receptors are widely expressed both in the periphery and the central nervous system [87, 90]. Ghrelin and CCK have antagonistic actions not only on feeding but also on sleep. CCK was first identified as a sleep-inducing hormone in cats; two pioneering studies demonstrated that feeding or intraduodenal administration of fat elicits sleep, and the sleep-inducing effects were reproduced by the iv administration of CCK [91, 92]. Subsequently, NREMS-promoting effects of systemically injected CCK were also described in rats [93, 94], rabbits [95], and mice [96]. CCK elicits the complete behavioral sequence of satiety, and its effects are indistinguishable from the signs of naturally occurring postprandial state [97, 98]. REMS amounts are not affected by CCK in intact animals, but in para-chlorophenylalanine-induced insomniac cats, CCK restores REMS [99], and in normal rats, CCK increases REMS frequency [100] and decreases REMS latency [98].

Studies using CCK2 agonists and CCK1 receptor antagonist indicate that CCK2 receptor activation is not sufficient, but CCK1 receptor activation is necessary for the somnogenic effects of CCK [101–103]. Spontaneous sleep of

CCK1 receptor-deficient rats is not altered, suggesting that the activation of the receptor is not required for maintaining baseline sleep [104], but pharmacological blockade of CCK1 receptors abolished feeding-induced sleep, indicating a role for CCK in postprandial sleep increases [105].

Central administration of ghrelin triggers the dark onset syndrome, the behavioral sequence characteristic of the first hours of the active period in nocturnal rodents, including long bouts of wakefulness and increased feeding activity [106, 107]. In microinjection studies, the lateral hypothalamus, medial preoptic area, and hypothalamic paraventricular nucleus were identified as potential target sites for the wake-inducing actions of ghrelin [106]. It has been proposed that a hypothalamic circuit, containing ghrelin – orexin – neuropeptide-Y neurons, forms a shared mechanism for both the orexigenic and wake-promoting effects of orexigenic signals [108].

The extent to which peripheral ghrelin-sensitive targets are also involved in the wake-promoting actions of the hormone is unclear. In rats and mice, systemic administration of ghrelin induced both wakefulness [109] and sleep [110] or had no effect on vigilance [107]. In humans, intravenous administration of ghrelin also led to inconclusive findings. The most potent known synthetic agonist of the ghrelin receptors, hexarelin, suppressed deep sleep [111], whereas ghrelin itself was either wake- or sleep-promoting or had no effect depending on the gender of the subjects and the treatment paradigm [112–115]. Ghrelin receptor KO mice or mice with the deletion of the GHRL gene that encodes the peptide preproghrelin, a precursor to ghrelin and obestatin, have more fragmented sleep, but the amount of sleep and the rebound sleep response after sleep loss do not show any alteration suggesting that ghrelin signaling is not key to maintaining baseline sleep or to homeostatic sleep responses [116, 117]. Ghrelin signaling, however, plays a role in arousal responses to several physiological stimuli. Exposure to novel environment or fasting suppresses sleep in mice, a response that is absent in ghrelin receptor KO animals [117]. Furthermore, ghrelin plays a role in integrating sleep and thermoregulatory responses to metabolic challenges. In response to fasting at low ambient temperatures, wild-type mice enter short torpor bouts, but preproghrelin knockout mice develop protracted hypothermia associated with reduced sleep, which culminates in a marked drop in body temperature to near-ambient levels [118]. The sleep promoting effects of proinflammatory stimuli, such as lipopolysaccharide, are accentuated in preproghrelin KO mice suggesting that ghrelin-associated arousal circuits may have a role to balance sleep-wake activity in inflammatory conditions [119].

Prolactin

Circulating levels of most pituitary hormones show 24-h rhythms and thus correlate with sleep-wake cycles, and exogenous administration of some of these hormones affects sleep under certain conditions. These findings, while suggestive, do not necessarily indicate a role for a hormone in the regulation of sleep. The most complete set of evidence that a pituitary hormone may be a physiological modulator of sleep, mainly REMS, and therefore could be considered a humoral sleep factor has accumulated for prolactin. Plasma prolactin levels increase after sleep onset, independent of the time of the day when sleep occurs, suggesting that prolactin secretion is regulated by sleep-wake activity rather than circadian factors (reviewed in [120]).

Exogenous administration of prolactin induces selective REMS increases in rats and rabbits [121–123]. Stimulation of prolactin secretion by vasoactive intestinal peptide or by prolactin-releasing peptide and the induction of hyperprolactinemia by transplanted pituitary grafts led to increases in REMS [123–125]. Anti-prolactin antibodies suppress REMS in rats [126, 127]. In mutant hypoprolactinemic rats, REMS is suppressed during the light period [128]. Prolactin-deficient transgenic mice have reduced amounts of spontaneous REMS and diminished REMS rebound after sleep deprivation [129].

Increased circulating prolactin levels correlate with enhanced REMS amount in pregnancy/pseudopregnancy and during recovery after exposure to certain stressors, thus suggesting that prolactin may play a role in REMS responses in these conditions [130–133]. In fact, ether stress-induced REMS is diminished after anti-prolactin antibody treatment or in prolactin KO animals [129, 134].

Sleep Signaling by Metabolic Organs

The findings that phase shifts in metabolic processes greatly influence the diurnal distribution of sleep and wakefulness and that positive and negative energy balances affect sleep the opposite way suggested that signals from key metabolic organs may play a role in sleep regulation. Adipose tissue plays a central role in the interplay between nutrition, energy balance, and sleep. Two types of adipose tissue with fundamentally different functions exist. White adipose tissue is responsible for storing excess energy in the form of fat, whereas brown adipose tissue (BAT) dissipates energy as heat. The tightly regulated balance between the activities of the two fat tissues is critical in maintaining metabolic homeostasis [135]. BAT controls energy balance via regulated (adaptive) heat production. The thermogenic property of BAT is conferred by the tissue-specific presence of uncoupling protein 1 (UCP-1). UCP-1 is a H^+ transporter on the inner mitochondrial membrane of brown adipocytes [136]. The thermogenic activity of the BAT is regulated by the sympathetic nervous system through β3-ARs expressed by brown adipocytes. Stimulation of BAT by β3-AR agonists elicits robust sleep increases [53, 81, 137], which is absent or attenuated in UCP-1 KO mice [81] indicating that thermogenic activation of BAT promotes sleep. The somnogenic actions

of BAT activation are independent of changes in core body temperature and are mediated by capsaicin-sensitive afferents arising from the organ [81]. Systemic inflammation or warm ambient temperature-induced sleep and rebound sleep increases after sleep loss are abolished or attenuated in UCP-1 KO mice indicating that BAT-derived somnogenic signaling plays a role in sleep responses to systemic inflammation and thermoregulatory challenges, and it is required for the full activity of homeostatic sleep regulation [54, 138].

In the immune system, macrophages provide a significant source of sleep-inducing signals. After demonstrating the sleep-inducing effects of endogenous pyrogen(s), several studies focused on the role of macrophages in sleep responses during clinically manifest infections. It was determined that macrophages play a role in the production and metabolism of somnogenic substances, inflammatory cytokines, after microbial challenge [139, 140]. Subsequently, it was demonstrated that macrophages also play a role in sleep signaling under physiological conditions. Depletion of the peripheral macrophage pool by clodronate-containing liposomes suppresses rebound sleep responses after sleep loss in mice and macrophage-depleted animals unable to maintain normal sleep amounts when exposed to moderately cold temperatures. These findings indicate that in the absence of an inflammatory challenge, under normal physiological conditions, macrophage function/signaling is required for maintaining normal sleep [141]. The lack of alternatively activated (M2) macrophage subpopulation leads to similar deficiencies in sleep as the complete macrophage deficiency, which suggests a central role for M2 cells in sleep signaling [142].

The liver has a central role in the regulation of metabolism and immune defenses. It harbors about 80% of the body's macrophage population and is responsible for removing circulating microbial molecules, such as endotoxin and other products of the microbiota or intruding pathogens. The first direct evidence about the role of liver in sleep signaling came for studies demonstrating that local, passive warming of the organ results in increased NREMS [143]. Depletion of liver macrophages diminishes feeding-induced sleep [144] and recovery sleep responses after sleep loss [141]. More recently it was demonstrated that the hepatoportal region contains a sleep-promoting viscerosensory mechanism which is sensitive to butyrate, a short-chain fatty acid, a product of the intestinal microbiota [145]. This finding suggests that products of the intestinal microbiota, after translocating from the gut lumen to the portal circulation, may enhance sleep by acting in the hepatoportal region (Fig. 11.1). Consistent with this notion are the

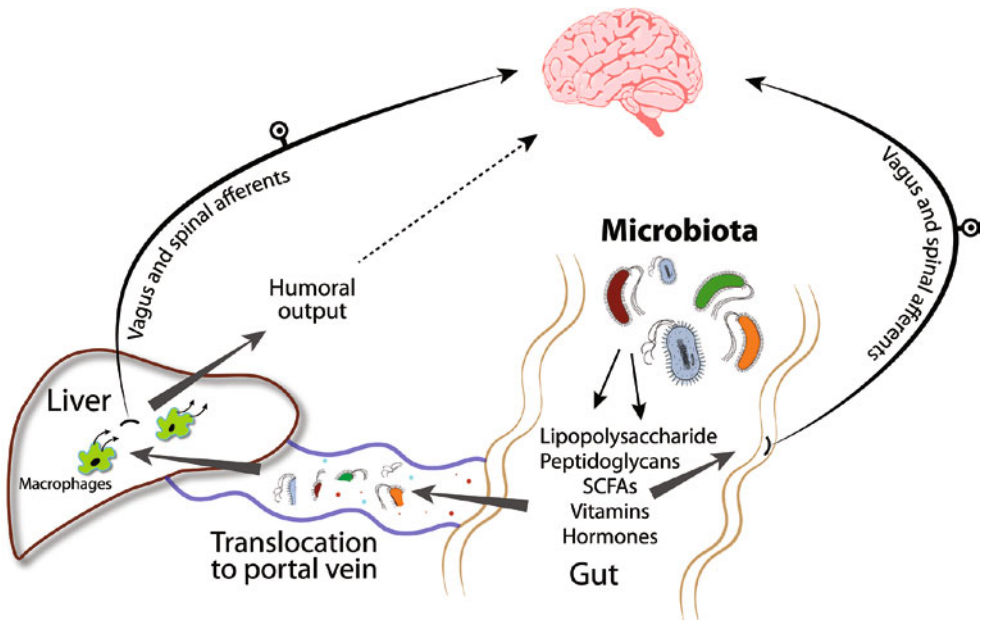

Fig. 11.1 Hepatoportal viscerosensory sleep signaling. The effects of commensal bacteria on extra-intestinal organs, including the brain, are explained by the exchange of microbial molecules to virtually all tissues of the body. Bacterial translocation is defined as the migration of viable bacteria or bacterial products from the intestinal lumen to the portal circulation. During bacterial growth, division, and death, components of bacterial cell wall are released and translocated through the intestinal microcirculation to the portal blood in biologically significant quantities. Fragments of the bacterial cell wall, such as lipopolysaccharide, and bacterial metabolites, such as short-chain fatty acids, are detected in the portal and systemic circulation even under physiological conditions [155–157]. Low doses of intraportally, but not systemically, administered short-chain fatty acids and lipopolysaccharide induce robust sleep increases, indicating that the hepatoportal region is a privileged site for the somnogenic actions of microbial products [145, 158]. Portally circulating microbial molecules reach the liver, which may act directly on hepatic afferents or may activate liver macrophages and other hepatic cells to secrete bioactive molecules, such as prostaglandins and tumor necrosis factor-α. These secretory products may reach brain sleep circuits through the systemic circulation, or they may also act on local sensory nerves

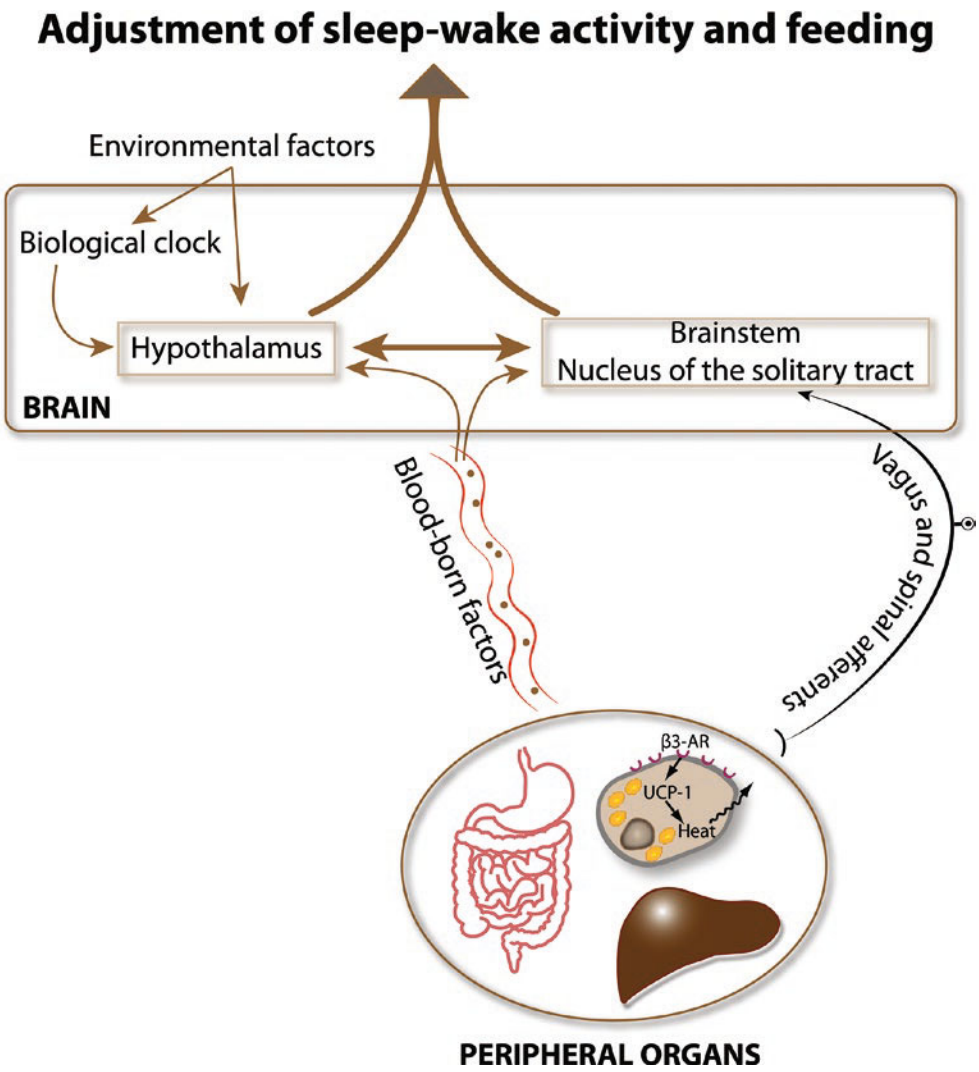

Fig. 11.2 Integration of peripheral sleep-promoting signals with core sleep circuits in the brain. Metabolic tissues, such as the brown adipose tissue, and the liver as well as cells of the immune system and intestinal bacteria generate sleep-promoting signals. Somnogenic signals may be carried to core sleep circuits of the brain by the circulation or by the activation of neuronal afferent pathways. The hypothalamus, where the best characterized sleep circuits are located, and the brainstem, where visceral afferent systems project, are likely targets of peripherally produced sleep-inducing signals

findings that the depletion of the intestinal microbiota results in decreased sleep in rats and mice [146, 147].

It has been proposed that somnogenic signals for the liver reach core sleep circuits of the brain via sensory vagus innervation. The role of vagus in peripheral sleep signaling has been known for long. For example, stimulation of the vagus elicits EEG synchronization and complete sleep cycles [148–150]. Vagotomy attenuates or abolishes the sleep-promoting actions of systemically administered lipopolysaccharide, IL-1β, and TNFα [17, 18, 41, 42, 151].

Conclusions

For long, it has been thought that sleep is of the brain, by the brain, and for the brain [152]. In light of the recent advances in the field and after careful reinterpretation of old findings, this notion needs revision. Sleep is a complex behavior, in which the entire organism, including the brain, participates. Core circuits of sleep regulation, just like core circuits of all behavioral manifestations, are located in the brain. These circuits receive extensive ascending somatic and visceral inputs from metabolic organs and the immune and endocrine systems through humoral and neural pathways (Fig. 11.2). The significance of these inputs is to help align the timing and intensity of sleep behavior with the actual metabolic status of the body. Sleep loss and misalignment between sleep and the circadian system have a negative impact not only on the brain but on the function of metabolic organs and immune system [153, 154].

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Part IV

Measurement of Sleep

Survey Tools and Screening Questionnaires to Pediatric Sleep Medicine

12

Abdullah AlNabhani and Colin M. Shapiro

Introduction

This chapter provides information on selected pediatric sleep-related questionnaires. These questionnaires can be used to assess sleep habits, daytime sleepiness, breathing difficulties, or parasomnias.

Adolescent Sleep-Wake Scale

Aim and Description This scale is designed to be a general sleep quality assessment tool for adolescents. It consists of five dimensions: going to bed, falling asleep, maintaining sleep, reinitiating sleep, and returning to wakefulness.

Age Adolescents 12–18 of age.

Administration It takes around 20 min to complete the questionnaire. It is a self-reported instrument that consists of 28 items. A Likert-type scale of six points is used to assess the adolescent's sleep behaviors during the last 30 days [1].

Reliability and Validity The scale has good internal consistency across its samples (Cronbach's α for the instrument's subscales ranged from 0.60 to 0.81), while the full scale possessed a reliability of $\alpha = 0.80$ [2].

Language/Translation English and Italian languages.

Availability The scale can be obtained from an article published by the authors [2].

Scoring Each of the five sleep behavior domains is calculated as the mean subscale. The overall sleep quality score can be obtained by averaging the score of the five subscales. There are tips as to how to interpret the questionnaire results by LeBourgeois and her colleagues [2]. Higher scores are indicative of better sleep quality, so it is preferable to use this instrument as a compression between different participants (research setting) or to compare between different clinical visits for a single patient.

Developer Name and Contact
A published copy can be found in a study by LeBourgeois and colleagues [2].

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Behavioral Evaluation of Disorders of Sleep (BEDS) (Fig. 12.1)

Aim and Description The scale was developed by Schreck et al. in 2003 [3]. The developers recommended using it for research purposes [4]. The scale was designed to be used for *primary school children*. It consists of 28 items that cover 4 different sleep problems: expressive sleep disturbances (e.g., screaming, sleepwalking), sensitivity to the environment, disoriented awakening, and apnea/bruxism. It screens distorted sleep behavior for the past 6 months.

Age Children between 5–12 years.

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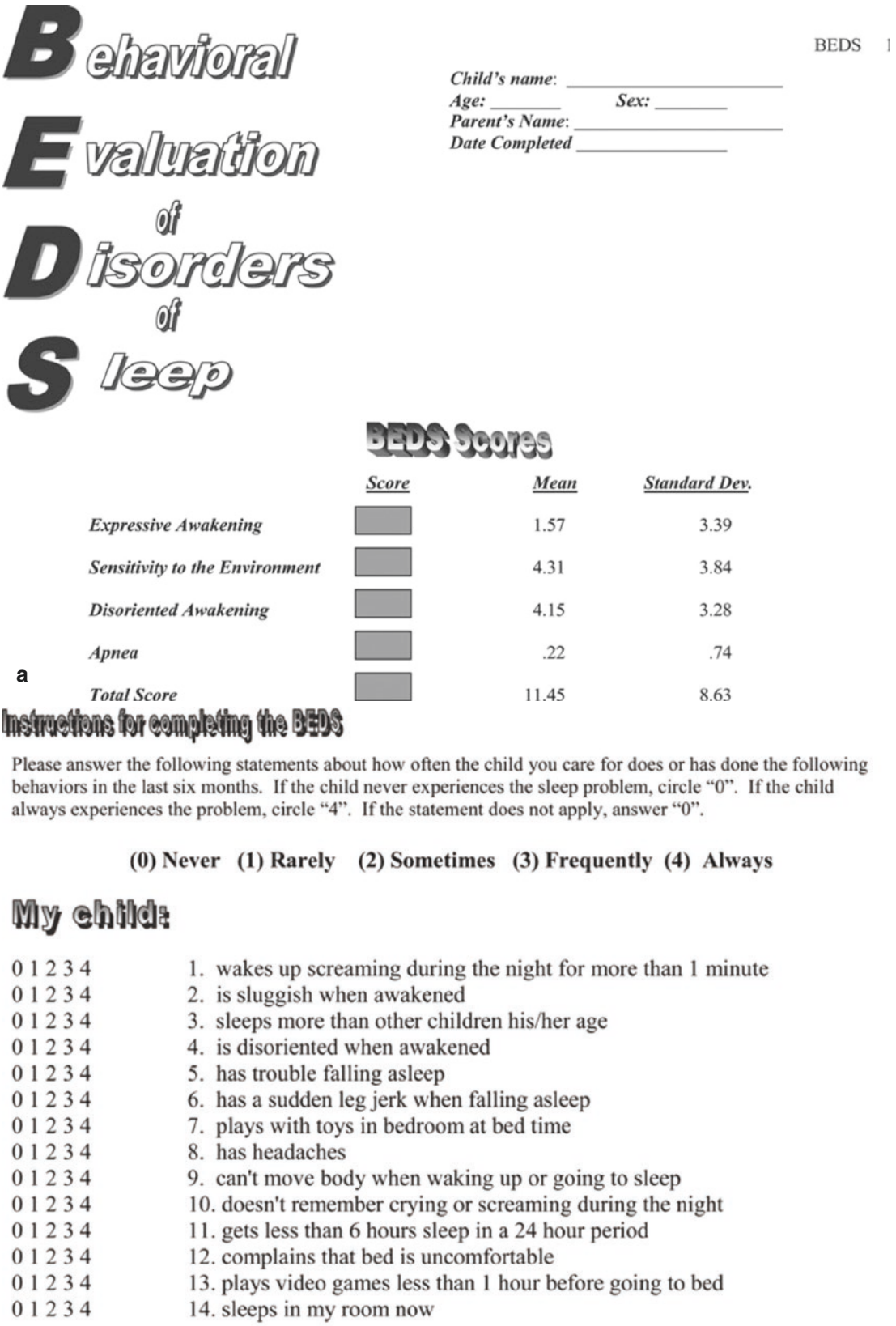

Behavioral Evaluation of Disorders of Sleep

BEDS 1

Child's name: _____
Age: _____ *Sex*: _____
Parent's Name: _____
Date Completed _____

BEDS Scores

	Score	Mean	Standard Dev.
Expressive Awakening		1.57	3.39
Sensitivity to the Environment		4.31	3.84
Disoriented Awakening		4.15	3.28
Apnea		.22	.74
Total Score		11.45	8.63

a

Instructions for completing the BEDS

Please answer the following statements about how often the child you care for does or has done the following behaviors in the last six months. If the child never experiences the sleep problem, circle "0". If the child always experiences the problem, circle "4". If the statement does not apply, answer "0".

(0) Never (1) Rarely (2) Sometimes (3) Frequently (4) Always

My child:

0 1 2 3 4	1. wakes up screaming during the night for more than 1 minute
0 1 2 3 4	2. is sluggish when awakened
0 1 2 3 4	3. sleeps more than other children his/her age
0 1 2 3 4	4. is disoriented when awakened
0 1 2 3 4	5. has trouble falling asleep
0 1 2 3 4	6. has a sudden leg jerk when falling asleep
0 1 2 3 4	7. plays with toys in bedroom at bed time
0 1 2 3 4	8. has headaches
0 1 2 3 4	9. can't move body when waking up or going to sleep
0 1 2 3 4	10. doesn't remember crying or screaming during the night
0 1 2 3 4	11. gets less than 6 hours sleep in a 24 hour period
0 1 2 3 4	12. complains that bed is uncomfortable
0 1 2 3 4	13. plays video games less than 1 hour before going to bed
0 1 2 3 4	14. sleeps in my room now

Fig. 12.1 (**a**–**e**) Behavioral Evaluation of Disorders of Sleep (BEDS)
Scoring: Parents are asked to use a five-point scale to rate the frequency of certain sleep behaviors exhibited by their child (0 is "never," while 5 is "always"). Higher scores indicate more severe sleep issues. (From Shahid et al. [1]. Reprinted with permission from Springer Nature)

c

0 1 2 3 4 15. watches horror and/or action movies/TV show before bed
0 1 2 3 4 16. wakes up screaming during the night and cannot be calmed down
0 1 2 3 4 17. engages in violent behaviors while asleep (hits, kicks, punches, tackles)
0 1 2 3 4 18. takes frequent naps during the day
0 1 2 3 4 19. stops breathing during sleep
0 1 2 3 4 20. needs me to read before falling asleep
0 1 2 3 4 21. takes a day to "catch-up" on sleep
0 1 2 3 4 22. needs something to eat before falling asleep
0 1 2 3 4 23. can not be awakened when sleep walking
0 1 2 3 4 24. needs a night light to fall asleep
0 1 2 3 4 25. sleeps better in a place other than own bed
0 1 2 3 4 26. talks in sleep without knowing it
0 1 2 3 4 27. complains of jaw pain
0 1 2 3 4 28. requires medicine to help sleep
0 1 2 3 4 29. has no problem sleeping, when it is quiet outside
0 1 2 3 4 30. will stay in bed unless I get him/her up
0 1 2 3 4 31. has frequent skin rashes
0 1 2 3 4 32. is sleepy during the day

d

(0) Never (1) Rarely (2) Sometimes (3) Frequently (4) Always

0 1 2 3 4 33. sleeps longer or shorter on weekends than weekdays
0 1 2 3 4 34. complains that room is not dark enough to sleep
0 1 2 3 4 35. wakes up screaming and sweating during the night
0 1 2 3 4 36. needs a pacifier to fall asleep
0 1 2 3 4 37. walks in sleep
0 1 2 3 4 38. goes to bed at different times
0 1 2 3 4 39. has nightmares
0 1 2 3 4 40. acts out dreams
0 1 2 3 4 41. screams during the 2nd half of the night
0 1 2 3 4 42. wakes up crying at night
0 1 2 3 4 43. watches TV in bedroom
0 1 2 3 4 44. wakes up screaming approximately two hours after going to sleep
0 1 2 3 4 45. drinks soda/caffeine before bed
0 1 2 3 4 46. rocks body in sleep
0 1 2 3 4 47. has problems/been upset since a new adult moved into the home
0 1 2 3 4 48. sleep walks about 2 hours after going to sleep
0 1 2 3 4 49. does homework less than 1 hour before going to bed or in bed
0 1 2 3 4 50. has problems/been upset since a divorce or separation in the family
0 1 2 3 4 51. eats 1 hour before going to sleep
0 1 2 3 4 52. sees flashes of light when first going to sleep
0 1 2 3 4 53. does not remember walking in sleep
0 1 2 3 4 54. slept in my room as an infant
0 1 2 3 4 55. is afraid of falling, at bedtime
0 1 2 3 4 56. bangs head in sleep
0 1 2 3 4 57. stalls at bedtime
0 1 2 3 4 58. exercises before bed
0 1 2 3 4 59. looks at books or reads in bed
0 1 2 3 4 60. seems depressed
0 1 2 3 4 61. complains that room is uncomfortable
0 1 2 3 4 62. has problems/been upset since moving to a new home or school
0 1 2 3 4 63. wakes up during violent behaviors
0 1 2 3 4 64. throws temper tantrums at bedtime
0 1 2 3 4 65. has problems/been upset since the death of a family member, friend, or pet
0 1 2 3 4 66. frequently has an upset stomach
0 1 2 3 4 67. rocks head in sleep
0 1 2 3 4 68. wets bed
0 1 2 3 4 69. is not awake when screaming at night

Fig. 12.1 (continued)

e

(0) Never (1) Rarely (2) Sometimes (3) Frequently (4) Always

0 1 2 3 4	70. sleeps worse after eating certain foods/beverages
0 1 2 3 4	71. is irritable
0 1 2 3 4	72. reacts slowly when awakened
0 1 2 3 4	73. will sleep for 6 hours or longer at a time
0 1 2 3 4	74. cries easily
0 1 2 3 4	75. needs something to drink before falling asleep
0 1 2 3 4	76. is awakened by loud noises (trains, traffic, etc.)
0 1 2 3 4	77. speaks slowly when awakened
0 1 2 3 4	78. chooses own bedtime
0 1 2 3 4	79. is under emotional stress
0 1 2 3 4	80. is sad
0 1 2 3 4	81. complains of aches, pains, or sore eyes
0 1 2 3 4	82. has difficulty breathing during sleep
0 1 2 3 4	83. wakes up screaming in the 2nd half of the night
0 1 2 3 4	84. is afraid of noises in the night
0 1 2 3 4	85. actively plays before bed
0 1 2 3 4	86. sleeps in inappropriate places
0 1 2 3 4	87. grinds teeth at night
0 1 2 3 4	88. takes medicine during the day that makes him/her sleep worse
0 1 2 3 4	89. wakes up during the night to eat
0 1 2 3 4	90. needs to rock to sleep
0 1 2 3 4	91. seems anxious or scared
0 1 2 3 4	92. needs a toy, stuffed animal or doll to go to sleep
0 1 2 3 4	93. needs a blanket to fall asleep
0 1 2 3 4	94. sleeps poorly without medicine at night
0 1 2 3 4	95. is afraid to fall asleep
0 1 2 3 4	96. takes naps without being told
0 1 2 3 4	97. snores
0 1 2 3 4	98. eats in bed
0 1 2 3 4	99. has a new sibling
0 1 2 3 4	100. sleeps less than other children his/her age
0 1 2 3 4	101. drinks more than 1 glass of water awakening
0 1 2 3 4	102. teeth are smooth
0 1 2 3 4	103. falls asleep before being put to bed
0 1 2 3 4	104. rubs eyes
0 1 2 3 4	105. becomes pale or blue during sleep
0 1 2 3 4	106. is limp or stiff during sleep
0 1 2 3 4	107. sleeps on a mattress that is less than 3 inches thick

Supplementary Questions

108. How many hours does your child typically sleep per night? _____

109. How many hours has your child slept in the last 24 hours? _____

110. How many hours does your child typically nap during the day? _____

111. Do you think your child has a sleeping problem? YES NO

Fig. 12.1 (continued)

Administration It takes around 10 min to complete the survey by parents or caregivers.

Reliability and Validity The internal consistency for the BEDS items was $\alpha = 0.82$.

Language/Translation English language.

Availability **P**ermission is needed to use the scale. The contact address of the author is provided in the developer name section.

Scoring The higher the score, the more severe the sleep problem. Each component has five answers where "0" means the child does not experience the problem or the statement does not apply. A "4" means the child always experiences the problem. Then you add the scores of each component and the total score.

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Brief Infant Sleep Questionnaire (BISQ)

Aim and Description BISQ consists of 13 items that screen the duration of sleep, sleep settling, sleepwalking, and sleep arrangements during the past 1 week. It is a tool that can be used for clinical and research purposes.

Age Children between 0–3 years of age.

Administration It takes 5–10 min to complete the questionnaire by child's parents or caregivers [5].

Reliability and Validity It has high test-retest correlation ($r > 0.82$). The questionnaire is also reliable in collecting sleep data for a large sample of children via the Internet [5].

Language/Translation English, Portuguese, Nibali, Indonesian, Turkish, Spanish, and Chinese languages.

Availability The questionnaire is available in the article published by the author [5].

Scoring If the child spends more than 1 h in wakefulness each night, receives less than 9 h of sleep during 24-h period, or wakes more than three times a night, he or she needs further evaluation by a sleep specialist.

Developer Name and Contact
Dr. Avi Sadeh died on September 19, 2016.

Center for Epidemiological Studies Depression Scale for Children (CES-DC) (Fig. 12.2)

Aim and Description Recognizing depression in children with sleep difficulties is very important in a comprehensive assessment of distorted sleep. Up to 75% of children with major depressive disorder reported sleep disturbances such as insomnia (50%) or hypersomnia (10%) [6]. The Center for Epidemiological Studies Depression Scale for Children (CES-DC) is a useful tool for screening depression. It consists of 20 items that assess adolescent responders how they have felt for the past 1 week. A Likert-type scale that ranges from "not at all" to "a lot" was used. Of 20 items, only 2 address sleep disturbances. This scale is useful in conjunction with other sleep scales as it focuses more on depression, which can be a reason of sleep disturbances.

Age Can be used for patients 6–23 years of age.

Administration CES-DC is a simple scale that usually needs less than 8 min to complete. Younger children might need assistance from their parents or caregivers.

Reliability and Validity The effect size estimate of 0.72 was significantly different from zero. The sensitivity is around 80%. It is useful as a screen for major depressive disorder and dysthymia [7].

Language/Translation English, German, Chinese, Turkish, Persian, and Spanish languages.

Availability Free of charge. Can be downloaded for free from https://www.brightfutures.org/mentalhealth/pdf/professionals/bridges/ces_dc.pdf.

Scoring To ensure participants' attention and to avoid random answering, questions 4, 8, 12, and 16 were constructed positively, while the remaining items were negative. Children who response "not at all" get zero, where "a lot" scores 3 points. For items 4, 8, 12, and 16, the scores are inverted, i.e., "not at all" gives 3 points and "a lot" scores 0. A cut point of 15 points suggest depression and warrants more detailed assessments for depression.

Center for Epidemiological Studies Depression Scale for Children (CES-DC)

Number _____

Score _____

INSTRUCTIONS

Below is a list of the ways you might have felt or acted. Please check how *much* you have felt this way during the *past week*.

DURING THE PAST WEEK	Not At All	A Little	Some	A Lot
1. I was bothered by things that usually don't bother me.	____	____	____	____
2. I did not feel like eating, I wasn't very hungry.	____	____	____	____
3. I wasn't able to feel happy, even when my family or friends tried to help me feel better.	____	____	____	____
4. I felt like I was just as good as other kids.	____	____	____	____
5. I felt like I couldn't pay attention to what I was doing.	____	____	____	____

DURING THE PAST WEEK	Not At All	A Little	Some	A Lot
6. I felt down and unhappy.	____	____	____	____
7. I felt like I was too tired to do things.	____	____	____	____
8. I felt like something good was going to happen.	____	____	____	____
9. I felt like things I did before didn't work out right.	____	____	____	____
10. I felt scared.	____	____	____	____

DURING THE PAST WEEK	Not At All	A Little	Some	A Lot
11. I didn't sleep as well as I usually sleep.	____	____	____	____
12. I was happy.	____	____	____	____
13. I was more quiet than usual.	____	____	____	____
14. I felt lonely, like I didn't have any friends.	____	____	____	____
15. I felt like kids I know were not friendly or that they didn't want to be with me.	____	____	____	____

DURING THE PAST WEEK	Not At All	A Little	Some	A Lot
16. I had a good time.	____	____	____	____
17. I felt like crying.	____	____	____	____
18. I felt sad.	____	____	____	____
19. I felt people didn't like me.	____	____	____	____
20. It was hard to get started doing things.	____	____	____	____

Fig. 12.2 Center for Epidemiological Studies Depression Scale for Children (CES-DC). (From Weissman et al. [31]. Reprinted with permission from Wolters Kluwer Health, Inc.)

Scoring:
0 = "Not At All"
1 = "A Little"
2 = "Some"
3 = "A Lot"
However, items 4, 8, 12, and 16 are scored in the opposite order:
3 = "Not At All"
2 = "A Little"
1 = "Some"
0 = "A Lot"

Children's Morningness-Eveningness Scale (Fig. 12.3)

Aim and Description Ten items and a multiple-choice scale that assess the circadian rhythm in children.

Age Children in 4th, 5th, and 6th grades (10–12 years of age). Spanish version can be used from 12 to 16 years of age [8]. Italian version is for children from 11 to 5 years of age.

Administration Up to 5 min, very easy to administer.

Reliability and Validity The Spanish version of the scale has reliability (α = 0.70) and an internal consistency of α = 0.82 [8]. The English version was also validated [9].

Language/Translation English, Spanish, French, Japanese, German, Turkish, Italian, Kannada, Korean, and Thai languages.

1*. Imagine: School is canceled! You can get up whenever you want to. When would you get out of bed? Between…

a. 5:00 and 6:30 am
b. 6:30 and 7:45 am
c. 7:45 and 9:45 am
d. 9:45 and 11:00 am
e. 11:00 am and noon

2. Is it easy for you to get up in the morning?

a. No way!
b. Sort of
c. Pretty easy
d. It's a cinch

3*. Gym class is set for 7:00 in the morning. How do you think you'll do?

a. My best!
b. Okay
c. Worse than usual
d. Awful

4*. The bad news: You have to take a two-hour test. The good news: You can take it when you think you'll do your best. What time is that?

a. 8:00 to 10:00 am
b. 11:00 am to 1:00 pm
c. 3:00 to 5:00 pm
d. 7:00 to 9:00 pm

5*. When do you have the most energy to do your favorite things?

a. Morning! I'm tired in the evening
b. Morning more than evening
c. Evening more than morning
d. Evening! I'm tired in the morning

6*. Guess what? Your parents have decided to let you set your own bedtime. What time would you pick? Between…

a. 8:00 and 9:00 pm
b. 9:00 and 10:15 pm
c. 10:15 pm and 12:30 am
d. 12:30 and 1:45 am
e. 1:45 and 3:00 am

7. How alert are you in the first half hour you're up?

a. Out of it
b. A little dazed
c. Okay
d. Ready to take on the world

8*. When does your body start to tell you it's time for bed (even if you ignore it)? Between…

a. 8:00 and 9:00 pm
b. 9:00 and 10:15 pm
c. 10:15 pm and 12:30 am
d. 12:30 and 1:45 am
e. 1:45 and 3:00 am

9. Say you had to get up at 6:00 am every morning: What would it be like?

a. Awful!
b. Not so great
c. Okay (if I have to)
d. Fine, no problem

10*. When you wake up in the morning how long does it take for you to be totally "with it?"

a. 0 to 10 minutes
b. 11 to 20 minutes
c. 21 to 40 minutes
d. More than 40 minutes

Fig. 12.3 Morningness-Eveningness scale for children. A score is derived by adding points for each answer: a = 1, b = 2, c = 3, d = f, e = 5, except as indicated by *, where point values are reversed. The maximum score is 42 (maximal morning preference), and the minimum is 10 (minimal morning preference). (From Carskadon et al. [9]. Reprinted with permission from Oxford University Press)

Availability Can be downloaded free of charge. Scale and scoring can be downloaded from this website:
http://www.sleepforscience.org/contentmgr/showdetails.php/id/93.

Scoring The score is obtained by adding the points of each answers where a = 1point, b = 2 points, c = 3 points, d = 4 points, and e = 5 points. Items indicated by * (items 1, 3, 4, 5, 6, 8, and 10) have reversed value to ensure the participant's attention. Score that is indicative of morning preferences is between 10 and 42, where 42 is the maximum morning preference and 10 is minimal morning preference. Less than 10 indicates evening preference [9].

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Children's Sleep Habits Questionnaire (CSHQ)

Aim and Description The questionnaire consists of 45 items to be completed by parents or caregivers. It covers most common sleep disturbances that occur in children and was designed for children 4–12 years of age. It covers these domains: "bedtime behavior and sleep onset; sleep duration; anxiety around sleep; behavior occurring during sleep and night wakings; sleep-disordered breathing; parasomnias, and morning waking/daytime sleepiness" [10].

Age Children between 4 and 12 years of age.

Administration It takes parents or caregiver around 15 min to complete the questionnaire.

Reliability and Validity The whole CSHQ internal consistency was 0.68 for the community sample and 0.78 for clinical sample. Test-retest reliability fell between 0.62 and 0.79, sensitivity was 0.80, and specificity was 0.72.

Language/Translation English, Spanish, Chinese, Hebrew, Portuguese, and Dutch languages.

Availability Information is not available. Please contact the developer address in developer name section.

Scoring Parents are asked to fill the Likert-type scale that has three options for each item. Parents are asked to recall the child's typical behavior in recent weeks and then start filling the scale. Items are rated on a three-point scale: "usually" if the sleep behavior occurred five to seven times/week, "sometimes" for two to four times/week, and "rarely" for zero to one time/week. Some items were reversed in order to consistently make a higher score indicative of more disturbed sleep [10].

Developer Name and Contact
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Cleveland Adolescent Sleepiness Questionnaire (CASQ) (Fig. 12.4)

Aim and Description A self-administered instrument that consists of 16 items measuring daytime sleepiness of adolescents in various settings like riding a vehicle, at school, or at home.

Age Adolescent age from 11 to 17 years.

Administration It takes around 7 min to complete the scale. It is available in pencil-paper format.

Reliability and Validity Goodness-of-fit measures for the final 16-item scale structure ranged from good to excellent. The internal consistency was good (α = 0.89). There was some evidence that the CASQ's had construct validity as there was a correlation between CASQ, two other measures of daytime sleepiness, and sleep parameters [11].

Language/Translation English and Brazilian Portuguese languages.

Availability The original article does have a copy of the questionnaire. Permission from the authors is needed for commercial use [11].

Scoring Higher score means higher sleepiness. Each 16 items uses 5-point Likert-type scale where the option "almost always" receives 5 points and "never" receives 1 point.

a

Cleveland Adolescent Sleepiness Questionnaire

Today's Date: (fill in) __ __ / __ __ / __ __

What is your age? (fill in years) _____ **What is your sex? (check one)** 1. Female 2. Male

We would like to know about when you might feel sleepy during a usual week. For each statement, mark the circle under the response that best fits with how often it applies to you. It's important to answer them yourself – don't have people help you. There are no right or wrong answers. For example, if we asked "I sleep with a pillow," and the response that best fit how often you sleep with a pillow was "often," you would mark the item as follows:

EXAMPLE	Never (0 times per month)	Rarely (less than 3 times per month)	Sometimes (1-2 times per week)	Often (3-4 times per week)	Almost every day (5 or more times per week)
I sleep with a pillow	○	○	○	⊗	●

Sleepiness Questions

	Never (0 times per month)	Rarely (less than 3 times per month)	Sometimes (1-2 times per week)	Often (3-4 times per week)	Almost every day (5 or more times per week)
1. I fall asleep during my morning classes	○	○	○	○	○
2. I go through the whole school day without feeling tired	○	○	○	○	○
3. I fall asleep during the last class of the day	○	○	○	○	○
4. I feel drowsy if I ride in a car for longer than five minutes	○	○	○	○	○
5. I feel wide-awake the whole day	○	○	○	○	○
6. I fall asleep at school in my afternoon classes	○	○	○	○	○

Fig. 12.4 (**a**, **b**) Cleveland Adolescent Sleepiness Questionnaire (CASQ). (Courtesy of Jim Spilsbury, PhD, MPH. Used with permission)

b	Never (0 times per month)	Rarely (less than 3 times per month)	Sometimes (1-2 times per week)	Often (3-4 times per week)	Almost every day (5 or more times per week)
7. I feel alert during my classes	○	○	○	○	○
8. I feel sleepy in the evening after school	○	○	○	○	○
9. I feel sleepy when I ride in a bus to a school event like a field trip or sports game	○	○	○	○	○
10. In the morning when I am in school, I fall asleep	○	○	○	○	○
11. When I am in class, I feel wide-awake	○	○	○	○	○
12. I feel sleepy when I do my homework in the evening after school	○	○	○	○	○
13. I feel wide-awake the last class of the day	○	○	○	○	○
14. I fall asleep when I ride in a bus, car, or train	○	○	○	○	○
15. During the school day, there are times when I realize that I have just fallen asleep	○	○	○	○	○
16. I fall asleep when I do schoolwork at home in the evening	○	○	○	○	○

Fig. 12.4 (continued)

Developer Name and Contact
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Pediatric Daytime Sleepiness Scale (PDSS) (Fig. 12.5)

Aim and Description A self-reported, short, and quick questionnaire that is used to measure daytime sleepiness. It consists of eight items.

Age Children age 11–15 years.

Please answer the following questions as honestly as you can by circling one answer only:

1. How often do you fall asleep or get drowsy during class periods?
Always Frequently Sometimes Seldom Never

2. How often do you get sleepy or drowsy while doing your homework?
Always Frequently Sometimes Seldom Never

*3. Are you usually alert most of the day?
Always Frequently Sometimes Seldom Never

4. How often are you ever tired and grumpy during the day?
Always Frequently Sometimes Seldom Never

5. How often do you have trouble getting out of bed in the morning?
Always Frequently Sometimes Seldom Never

6. How often do you fall back to sleep after being awakened in the morning?
Very often Often Sometimes Seldom Never

7. How often do you need someone to awaken you in the morning?
Always Frequently Sometimes Seldom Never

8. How often do you think that you need more sleep?
Very often Often Sometimes Seldom Never

Scoring	4	3	2	1	0

*Reverse score this item

Fig. 12.5 Pediatric Daytime Sleepiness Scale (PDSS). (From Drake et al. [12]. Reprinted with permission from Oxford University Press)

Administration A paper-and-pencil questionnaire. It takes around 5 min to complete.

Reliability and Validity The developers found the internal consistency (Cronbach's alpha) for the final eight-item scale was 0.80 [12].

Language/Translation English, Chinese, Turkish, Spanish, Korean, Brazilian Portuguese, French, Italian, German, Dutch, Finnish, and Russian languages.

Availability Free usage for clinical use or small research study, but permission is needed for large studies (like pharmaceutical research study). A copy can be obtained by contacting the author, Dr. Christopher L. Drake.

Scoring A Likert scale format that has five options per item. A response of "never" has 0 point, "seldom" 1 point, "sometimes" 2 points, "often" 3 points, and "always" 4 points. Item #3 has reverse scoring to ensure attention and honesty in response. A higher score indicates more daytime sleepiness.

Developer Name and Contact

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Pediatric Sleep Questionnaire (PSQ)

Aim and Description It contains two validated scales. The first relates to sleep-related breathing disorders (SRBDs) such as obstructive sleep apnea, and the second covers restless legs/periodic leg movements (RLS/PLMS). In general, the scale covers a wide range of sleep problems including breathing difficulties, snoring, daytime sleepiness, hyperactivity, inattention, obesity, and nocturnal enuresis.

Age Children 2–18 years of age.

Administration It takes around 10–15 min to complete. Majority of the questions are multiple-choice type. There are sections that have open-ended questions addressing medical and medication histories.

Reliability and Validity The test specificity was 0.87 and its sensitivity was 0.81–0.85. Its internal consistency was 0.66–0.89 (snoring scale, 0.86; sleepiness scale, 0.66; behavior scale, 0.84; and SRBD scale, 0.89.), and a test-retest reliability was 0.66–0.92 [13].

Language/Translation English, Chinese, Greek, Hindi, Spanish, and Turkish languages.

Availability Free of charge. The applicant needs to sign an agreement first. To download the questionnaire, go to the following website address:

http://inventions.umich.edu/technologies/3766_pediatric-sleep-questionnaire-designed-as-research-screen-for-symptoms-of-obstructive-sleep-apnea-and-other-sleep-disorders-in-children.

A copy of the questionnaire is also available in the published paper by the authors [13].

Scoring "Yes" and "No" answers have a score of 1 and 0, respectively. A 0 point is also considered for answers with "does not apply" and "applies just a little" and 1 point for "applies quite a bit" and "definitely applies most of the time" answers [14].

Developer Name and Contact

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Pictorial Sleepiness Scale Based on Cartoon Faces (Fig. 12.6)

Aim and Description A self-reporting questionnaire that can be used with children, illiterate patients, and people who do not speak English.

Age Valid for 4–73-year-old patients.

Administration Paper-and-pencil scale. It is self-administered and takes less than 5 min.

Reliability and Validity The scale was correlated with Karolinska Sleepiness Scale ($P < 0.05$), Stanford Sleepiness Scale ($P < 0.04$), and visual analog scale measuring sleepiness ($P < 0.0001$). The questionnaire can measure sleepiness, uncontaminated by pain, anger, or happiness [15].

Language/Translation English language.

Availability Developers published the article in their paper. Permission is needed for usage.

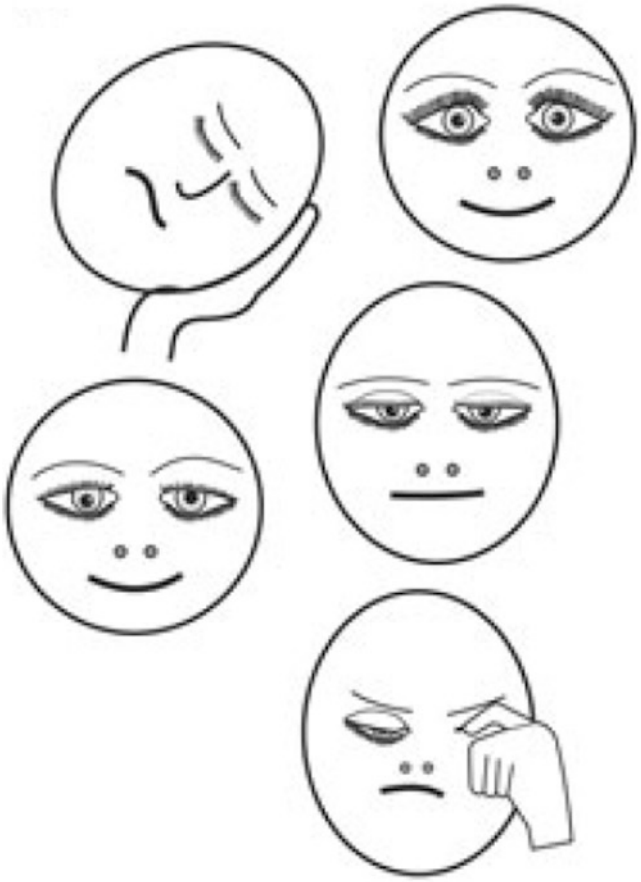

Fig. 12.6 Pictorial Sleepiness Scale Based on Cartoon Faces. (From Maldonado et al. [15]. Reprinted with permission from Oxford University Press)

Scoring Five faces that show the level of sleepiness the patient subjectively feels. The participant chooses a face that represents their level of sleepiness.

Developer Name and Contact

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School Sleep Habits Survey (Fig. 12.7)

Aim and Description This questionnaire consists of 63 items that screen sleep-related problems in *high school children*. It assesses sleep-wake cycle and daytime function [16]. The questionnaire starts with some data identifying the child: age, date of birth, sex, and grade at school. Then it assesses the availability of parents at home, sleep schedule, daytime sleepiness, performance at school, mood, any medical conditions the child has, medication, ADHD, and its treatments if available.

Age Children from age 9 to 19 years or at school grades 4–12.

Administration Self-reported scale. It is available in paper-and-pencil format. It takes around 20–25 min to complete it.

Reliability and Validity The internal consistency of sleep-wake subscale is 0.75, sleepiness subscale is 0.70, and mood scale is 0.79 [17].

Language/Translation English.

Availability Can be downloaded for free from Science Sleep Research Lab website: http://www.sleepforscience.org/contentmgr/showdetails.php/id/93.

Scoring The questionnaire assesses respondent's sleep history for the past 2 weeks. A different method of scoring is used for each section. A higher score indicates more sleep difficulties.

For the section that evaluates sleepiness in different situations, an answer of "no" gives 1 point, and "both struggled to stay awake and fallen asleep" gives 4 points. Higher total score implies greater sleepiness. The sleep-wake problem behaviors scale consists of 10 different items with maximum score of 50. A response of "everyday" means 5 points and "never" has 1 point. The depressive mood scale consists of six items, where an answer of "not at all" carries 1 point and 3 points for "somewhat too much."

Developer Name and Contact

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Sleep Disorders Inventory for Students (SDIS): Children's Form (SDIS-C) and Adolescent Form (SDIS-A)

Aim and Description There are two versions of SDIS: the children form (SDIS-C) and adolescent form (SDIS-A). The former consists of 30 items, the latter 35. The SDIS screens six different sleep disorders and five different parasomnias. The sleep disorders are obstructive sleep apnea, behavioral insomnia of childhood or delayed sleep phase syndrome, narcolepsy, periodic limb movement disorder/restless legs

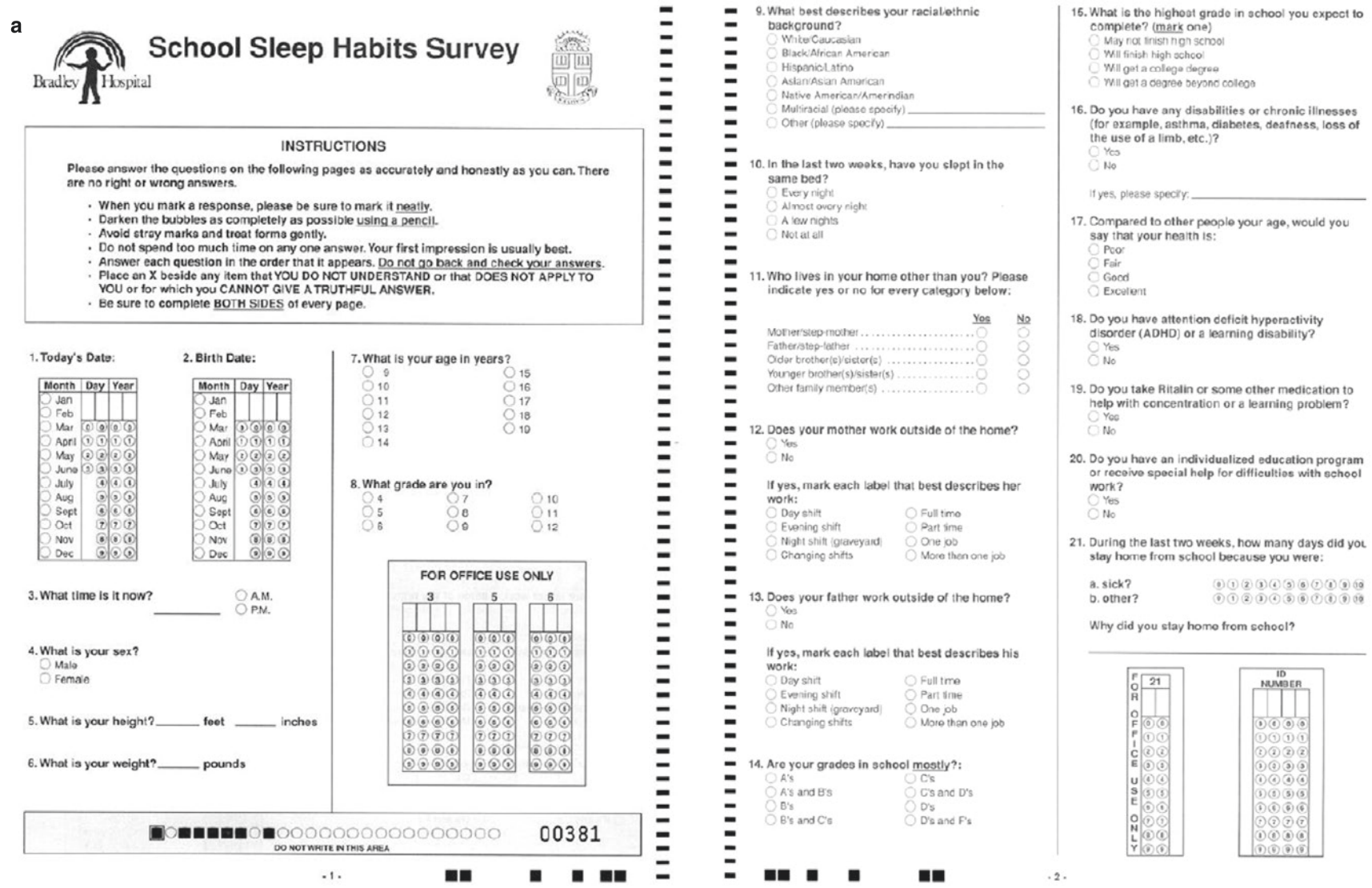

Fig. 12.7 (**a**–**d**) School Sleep Habits Survey. (From http://www.sleepforscience.org/research/instruments.php. Courtesy of Mary A. Carskadon, PhD. Used with permission)

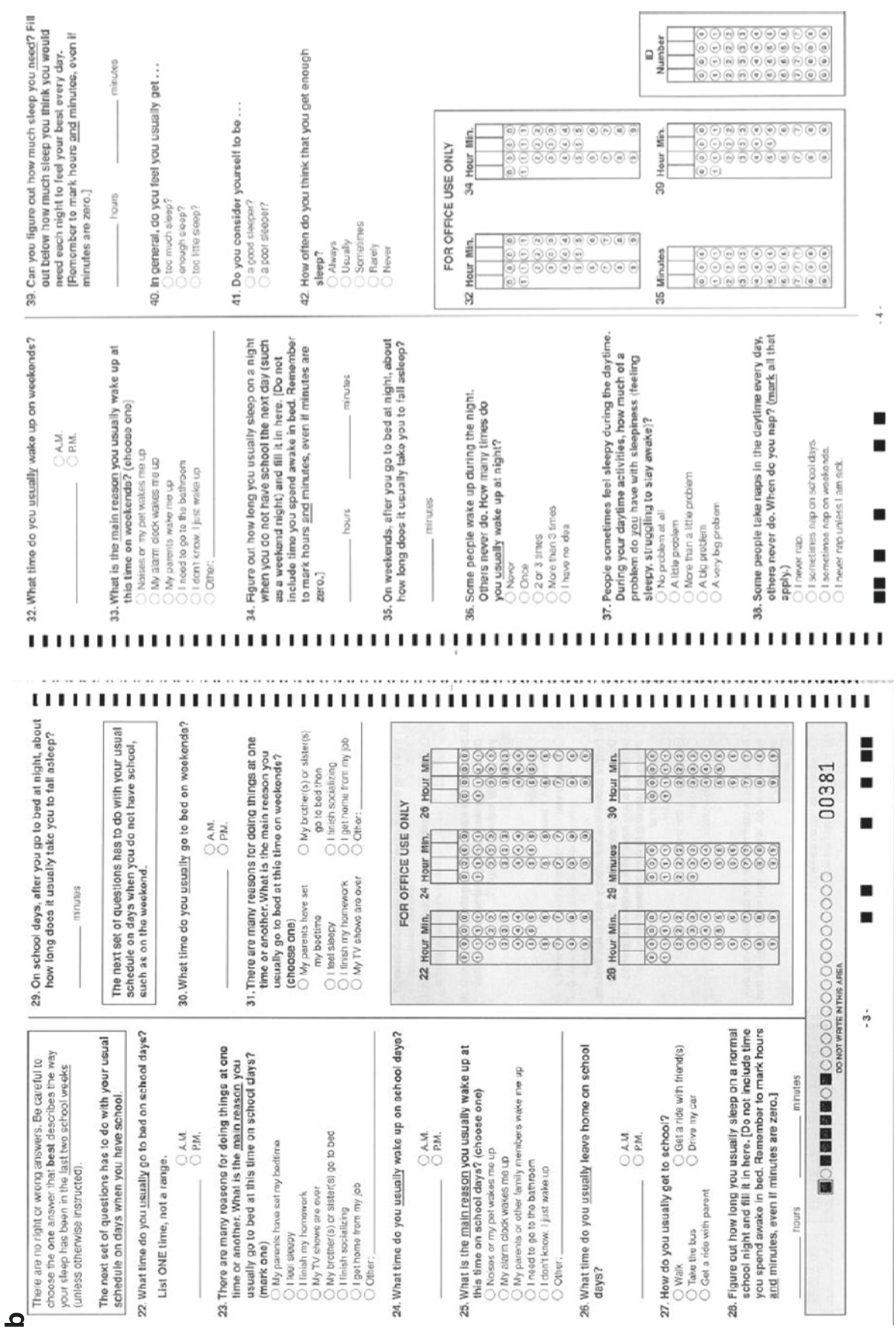

Fig. 12.7 (continued)

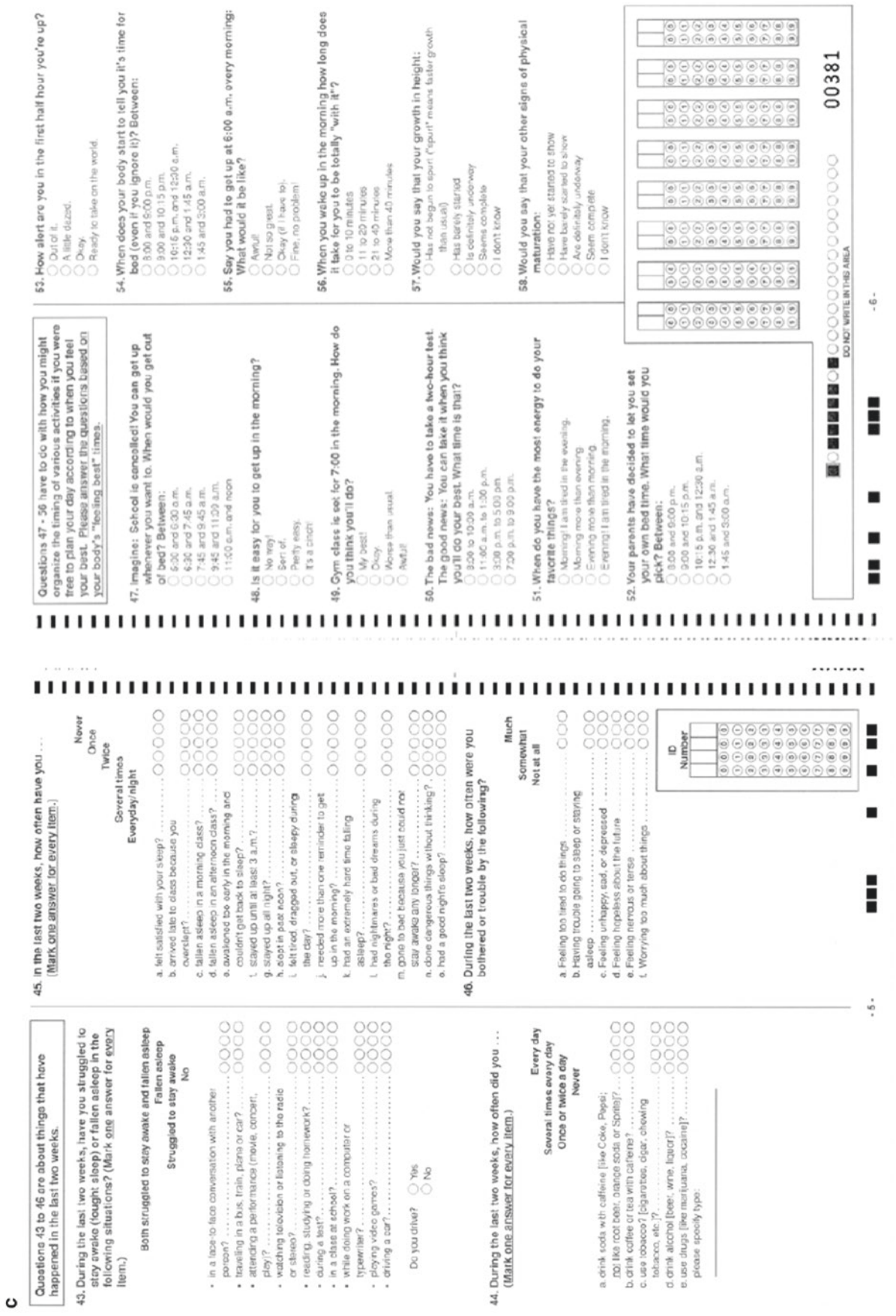

Fig. 12.7 (continued)

d

59. During the last week, did you work at a job for pay? (If no, skip to number 60.)
○ Yes ○ No

What kind of job? _____

How many days did you work at the following times?
in the morning before school 0 1 2 3 4 5
in the afternoon after school 0 1 2 3 4 5
in the evening on days that you have school . . 0 1 2 3 4 5
on the weekend 0 1 2

How many hours did you work at your paying job this week?
during the school week: _____ hours
during the weekend: _____ hours

During the last two weeks, have you struggled to stay awake (fought sleep) or fallen asleep at your job?
○ no ○ struggled to stay awake
○ fallen asleep ○ both struggled to stay awake and fallen asleep

If you did not have your job, would you go to bed:
○ earlier than you do. ○ the same as you do.
○ later than you do.

If you did not have your job, would you wake up:
○ earlier than you do. ○ the same as you do.
○ later than you do.

60. During the last week, did you engage in organized sports or a regularly scheduled physical activity? (If no, skip to number 61.)
○ Yes ○ No

What kind of sport? _____

How many days did you practice at the following times?
in the morning before school 0 1 2 3 4 5
in the afternoon after school 0 1 2 3 4 5
in the evening on days that you have school . . 0 1 2 3 4 5
on the weekend 0 1 2

How many hours did you practice this week?
during the school week: _____ hours
during the weekend: _____ hours

During the last two weeks, have you struggled to stay awake (fought sleep) or fallen asleep during practice?
○ no ○ struggled to stay awake
○ fallen asleep ○ both struggled to stay awake and fallen asleep

If you did not have your sports activity, would you go to bed:
○ earlier than you do. ○ the same as you do.
○ later than you do.

If you did not have your sports activity, would you wake up:
○ earlier than you do. ○ the same as you do.
○ later than you do.

61. During the last week, did you participate in organized extracurricular activities? (For example, committees, clubs, volunteer work, musical groups, church groups, etc.) (If no, skip to number 62.)
○ Yes ○ No

What kind of activity? _____

How many days did you participate at the following times?
in the morning before school 0 1 2 3 4 5
in the afternoon after school 0 1 2 3 4 5
in the evening on days that you have school . . 0 1 2 3 4 5
on the weekend 0 1 2

How many hours did you participate this week?
during the school week: _____ hours
during the weekend: _____ hours

During the last two weeks, have you struggled to stay awake (fought sleep) or fallen asleep during this participation?
○ no ○ struggled to stay awake
○ fallen asleep ○ both struggled to stay awake and fallen asleep

If you did not have your organized activity, would you go to bed:
○ earlier than you do. ○ the same as you do.
○ later than you do.

If you did not have your organized activity, would you wake up:
○ earlier than you do. ○ the same as you do.
○ later than you do.

62. During the last week, did you study/do homework?
○ Yes ○ No (If no, skip to number 63.)

How many days did you study at the following times?
in the morning before school 0 1 2 3 4 5
in the afternoon after school 0 1 2 3 4 5
in the evening on days that you have school . . 0 1 2 3 4 5
on the weekend 0 1 2

How many hours did you study this week?
during the school week: _____ hours
during the weekend: _____ hours

During the last two weeks, have you struggled to stay awake (fought sleep) or fallen asleep during studying?
○ no ○ struggled to stay awake
○ fallen asleep ○ both struggled to stay awake and fallen asleep

If you did not have your homework, would you go to bed:
○ earlier than you do. ○ the same as you do.
○ later than you do.

If you did not have your homework, would you wake up:
○ earlier than you do. ○ the same as you do.
○ later than you do.

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53. Below are some ways that people get hurt or injured. If you answer Yes in the first column to any item, please fill in an answer to each of the follow-up questions. IN THE PAST 6 MONTHS:

	Were you injured this way?		IF YES, then: Were you treated by a doctor or nurse for the injury?		Did this injury limit your physical activity?		Had you been drinking alcohol or using drugs at the time of the injury?		Where did the injury occur? H = home W = work S = school O = other
	Yes	No		Yes	No	Yes	No	Yes	No	
A. By being in a physical fight with someone?	Y	N	If Yes:	Y	N	Y	N	Y	N	H W S O
B. By getting cut?	Y	N	If Yes:	Y	N	Y	N	Y	N	H W S O
C. By a gun, BB gun, or pellet gun?	Y	N	If Yes:	Y	N	Y	N	Y	N	H W S O
D. By being hit by something, like a rock or glass?	Y	N	If Yes:	Y	N	Y	N	Y	N	H W S O
E. By nearly drowning?	Y	N	If Yes:	Y	N	Y	N	Y	N	H W S O
F. By falling?	Y	N	If Yes:	Y	N	Y	N	Y	N	H W S O
G. By being burned by fire, chemicals, electricity, or hot liquids?	Y	N	If Yes:	Y	N	Y	N	Y	N	H W S O
H. By an animal bite or serious insect bite?	Y	N	If Yes:	Y	N	Y	N	Y	N	H W S O
I. While driving a car, truck, or bus?	Y	N	If Yes:	Y	N	Y	N	Y	N	H W S O
J. While riding in a car, truck, or bus?	Y	N	If Yes:	Y	N	Y	N	Y	N	H W S O
K. While riding a bicycle, skateboard, rollerblades, or rollerskates?	Y	N	If Yes:	Y	N	Y	N	Y	N	H W S O
L. While riding a moped, motorcycle, all-terrain vehicle (ATV), or snowmobile?	Y	N	If Yes:	Y	N	Y	N	Y	N	H W S O
M. During a team sport, athletic activity, or exercise?	Y	N	If Yes:	Y	N	Y	N	Y	N	H W S O
N. By being hit by a moving vehicle while walking?	Y	N	If Yes:	Y	N	Y	N	Y	N	H W S O
O. By drinking or eating a dangerous substance?	Y	N	If Yes:	Y	N	Y	N	Y	N	H W S O
P. By being physically attacked?	Y	N	If Yes:	Y	N	Y	N	Y	N	H W S O
Q. Injured in some other way?	Y	N	If Yes:	Y	N	Y	N	Y	N	H W S O

If yes to Q, please describe how you were injured: _____

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Fig. 12.7 (continued)

syndrome, and excessive daytime sleepiness (a serious symptom of sleep disorders). The parasomnias are bed-wetting (enuresis), sleep or night terrors, sleep talking (somniloquy), sleep walking (somnambulism), and teeth grinding. The SDIS is a valuable screening tool as it screens wide range of sleep complains in children.

Age Sleep Disorders Inventory for Students (SDIS): Children's Form (SDIS-C) – children age 2–10 years. Sleep Disorders Inventory for Students: Adolescent Form (SDIS-A) – children age 11–18 years.

Administration It takes 15–20 min to complete the forms. The children's version is completed by parents or guardians. The adolescent's form is also completed by parents and guardian, but it is advised to include the adolescent during administration for better accuracy. The forms are available as online version and the results can be obtained immediately.

Reliability and Validity The scale internal consistency is 0.91 for children form and 0.92 for adolescent form. The sensitivity of children form is 0.82 and adolescent form is 0.81. The specificity of children from is 0.91 and adolescent form is 0.95. The content validity is 0.94 [18].

Language/Translation English and Spanish languages.

Availability The forms need to be purchased from Child Uplift Inc. from their website: http://www.sleepdisorderhelp.com/.

Scoring Majority of the items are Likert-type, which has seven points. Some items are answered by "yes" and "no" format. The scoring is done by computer, and it gives T-scores, percentiles, and categorizations of sleep into normal, caution of sleep disorder, or high risk of a sleep disorder.

Developer Name and Contact

Child Uplift, Inc. http://www.sleepdisorderhelp.com/
Mailing Address: P.O. Box 146, Fairview, WY 83119
Email: childuplift@aol.com
Phone: 307-248-0825 or 307-248-0226

Tayside Children's Sleep Questionnaire (TCSQ)

Aim and Description A ten-item scale that assesses disorders of initiating and maintaining sleep (DIMS) in children.

Age Children between 1 and 5 years of age.

Administration It takes less than 5 min to administer the scale. It is completed by parents or guardians. It is available in a paper-and-pencil format.

Reliability and Validity The developers found internal consistency of 0.85 [19].

Language/Translation English language.

Availability A copy of the questionnaire is available in the paper published by the authors. Permission is needed to use it.

Scoring The first nine items are used in the scoring. The last item is mainly concerned with parental or guardians' perceptions of the child's sleep pattern. The scale assesses initiating and maintaining sleep for the past 3 months. Each item has five-point Likert-type scale where "behavior happens every night" gives 4 points and "behavior never occurs" gives 0 point. A cut point of 8 was chosen by developers to indicate problems in initiating and maintaining sleep in children [19].

Developer Name and Contact

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Teacher's Daytime Sleepiness Questionnaire (TDSQ)

Aim and Description It is a ten-item scale that is used by *schoolteachers* to assess sleep difficulty manifestations in elementary school children.

Age Children between 4 and 11 years of age.

Administration It takes less than 5 min for a schoolteacher to complete the questionnaire. It is available in a paper-and-pencil format.

Reliability and Validity The scale internal consistency is 0.80 [20].

Language/Translation English.

Availability It is available in the paper that is published by the author [20]. Permission is needed for usage.

Scoring Each item has three-item Likert-type scale. A response of "never or rarely" has 1 point and "usually" has 3

points. Total score then is calculated, and higher score indicates higher daytime sleepiness.

Developer Name and Contact
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Adolescent Sleep Habits Survey

Aim and Description A structured questionnaire that has sets of open-ended and multiple-choice questions. It is a useful tool to gather demographic, familial, and medical histories, along with information about sleep habits, schedules, and behaviors [21].

The questionnaire has three versions. Two are self-reporting (differ only in male- or female-related developmental milestones), and the third one is intended for the adolescent's parents or guardian to complete [22].

Age Children from grade 4 to grade 12.

Administration Each version requires 25 min on average to complete. All versions consist of 61–65 questions. The two self-reported versions focus more on personal sleep preference and habits, while the parents' or caregivers' version addresses their observations of the patient (e.g., snoring) and developmental history.

Reliability and Validity The psychometric properties of the test were not analyzed. It can be considered as qualitative method to gather history that helps the sleep specialist go through wide range of sleep and developmental histories [22].

Language/Translation English language.

Availability Permission is needed from the author for usage.

Scoring The interpreter needs basic background in sleep medicine as it has plenty open-ended questions. There is no scoring system for the survey.

Developer Name and Contact
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BEARS Sleep Screening Tool

Aim and Description An easy and quick pediatric screening tool that was designed to be used mainly in the *primary care sitting* [23]. The tool consists of five items. The components of the tool are gathered in the test acronym BEARS: *b*edtime issues, *e*xcessive daytime sleepiness, night *a*wakenings, *r*egularity and duration of sleep, and *s*noring. The parents or caregivers are asked if the child has problem in each section. If yes, the clinician should gather more information. The scale also increases the attention and promotes treatment in primary care. For these reasons, it is very useful for family physicians and GPs [23].

Age Children between 2 and 12 years of age.

Administration It takes the GP or primary care physician less than 5 min to administer.

Reliability and Validity According to Owens et al. [23, 24], the amount of sleep information gathered by physicians increased by two- to tenfold. The test was not validated psychometrically [23, 24].

Language/Translation English and Spanish languages [25].

Availability Permission is needed from the author to use the tool. The contact detail is provided in the section of developer name below. A copy of the scale is published in the study by the authors [23].

Scoring No scoring is needed. The physician should be familiar with different sleep disorders and made recommendations or refer the patient to a specialized sleep clinic.

Developer Name and Contact
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Obstructive Sleep Apnea-18 (OSA-18)

Aim and Description The questionnaire consists of 18 items grouped into 5 subscales: sleep disturbance, physical symptoms, emotional symptoms, daytime function, and caregiver concerns. OSA-18 is a helpful tool to measure the impact on health-related quality of life.

Age 6 months–12 years.

Administration It takes around 5–10 min to complete the survey by parents or caregivers.

Reliability and Validity The OSA-18 questionnaire showed poor validity in detecting and predicting pediatric OSA, especially severe apnea. It should not be used as a predominant diagnostic tool. The sensitivity of OSA-18 (when total score is ≥80) was only 32%, indicating a high risk of missing children with severe obstructive sleep apnea [26].

Language/Translation English, Greek, Chinese, and Thai languages.

Availability Permission is needed from the author to use the tool. A copy of the scale is published in the study by the authors [27].

Scoring Each item is scored using a Likert-type scoring system. The caregiver is asked about the frequency of list of symptoms for the last 4 weeks. Each item has a score from 1 to 7 points where (1) none of the time, (2) hardly any of the time, (3) a little of the time, (4) some of the time, (5) a good bit of the time, (6) most of the time, and (7) all of the time. The sum of all points is called total symptom score (TSS) and it ranges from 18 to 126 points.

A (TSS) ≤ than 60 indicates a small impact on health-related quality of life. A score from 60 to 80 indicates moderate impact, and TSS ≥ 80 indicates severe impact [27].

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IF SLEEPY/I SLEEPY/I'M SLEEPY Questionnaires

Aim and Description An eight-item questionnaire that can be used as a screening tool for pediatric OSA. The items were constructed in a Yes/No format. The questionnaire is completed by parents/caregivers, and there is a version of the questionnaire where children aged 7 and above can complete it as well. The IF SLEEPY questionnaire has modified versions called I SLEEPY and I'M SLEEPY.

In I SLEEPY, in the second item, the F question ("Does your child **F**idget/Is he hyperactive?") was removed as hyperactivity is not specific to OSA. In I'M SLEEPY, the second question ("Does your child **F**idget/Is he hyperactive?") was changed to M: body mass index. A positive point is added if the child's BMI percentile is equal to or above 85%. Including the BMI in I'M SLEEPY improved its sensitivity compared to IF SLEEPY and I SLEEPY.

Age Children aged 3–18 years.

Administration It takes parents or caregivers around 5 min to complete the questionnaire. The same time is needed for the children's section (age 7 and above).

Reliability and Validity The parent version of IF SLEEPY has a sensitivity of 78% and a specificity of 40% as a screening tool for high-risk OSA (AHI ≥10). The children's version of IF SLEEPY has sensitivity of 45% and a specificity of 52% as a screening tool for high-risk OSA.

The I SLEEPY questionnaire has sensitivity and specificity of 76% and 55%, respectively, for high-risk OSA. The children's version of I SLEEPY has a sensitivity of 39% and a specificity of 63%. For I'M SLEEPY (parents), the sensitivity is 82% and specificity is 50%. The children version of I'M SLEEPY has a sensitivity and a specificity of 47% and 58%, respectively [28].

Language/Translation English.

Availability Free of charge. It is available in the paper published by the authors [28].

Scoring Any "yes" answers count as 1 point. A score equal to or more 3 indicates high risk of OSA.

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IF SLEEPY Questionnaire: Parent's version. Answer Yes/No

- I – Is your child often Irritated or angry during the day?
- F – Does your child often Fidget and/or is hyperactive?
- S – Does your child usually Snore?
- L – Does your child sometimes have Labored breathing at night?
- E – Ever noticed a stop in your child's breathing at night?
- E – Does your child have Enlarged tonsils and/or adenoids?
- P – Does your child have Problems with concentration?
- Y – Does your child often Yawn or is often tired/sleepy during the day?

IF SLEEPY Questionnaire: Children's version (age 7 and above). Answer Yes/No

- I – Are you angry a lot?
- F – Is it difficult for you to sit quietly? Do you feel that you always have to be "on the move"?
- S – Do you snore at night?
- L –Did your parents or a friend tell you that your breathing is "difficult" at night?
- E – Did your parents or a friend tell you that you stop breathing at night?
- E – Do you have problems with your tonsils or adenoids (glands inside your mouth)?
- P – Is it difficult for you to focus (at school or at home)?
- Y – Do you feel tired or sleepy a lot?

I SLEEPY Questionnaire: Parent's version. Answer Yes/No

- I – Is your child often Irritated or angry during the day?
- S – Does your child usually Snore?
- L – Does your child sometimes have Labored breathing at night?
- E – Ever noticed a stop in your child's breathing at night?
- E – Does your child have Enlarged tonsils and/or adenoids?
- P – Does your child have Problems with concentration?
- Y – Does your child often Yawn or is often tired/sleepy during the day?

I SLEEPY Questionnaire: Children's version (age 7 and above). Answer Yes/No

- I – Are you angry a lot?
- S – Do you snore at night?
- L –Did your parents or a friend tell you that your breathing is "difficult" at night?
- E – Did your parents or a friend tell you that you stop breathing at night?
- E – Do you have problems with your tonsils or adenoids (glands inside your mouth)?
- P – Is it difficult for you to focus (at school or at home)?
- Y – Do you feel tired or sleepy a lot?

I'M SLEEPY Questionnaire: Parent's version. Answer Yes/No

- I – Is your child often Irritated or angry during the day?
- M – Body Mass index above 85%?
- S – Does your child usually Snore?
- L – Does your child sometimes have Labored breathing at night?
- E – Ever noticed a stop in your child's breathing at night?
- E – Does your child have Enlarged tonsils and/or adenoids?
- P – Does your child have Problems with concentration?
- Y – Does your child often Yawn or is often tired/sleepy during the day?

I'M SLEEPY Questionnaire: Children's version (age 7 and above). Answer Yes/No

- I – Are you angry a lot?
- M– Filled in by the doctor: body mass index above 85%?
- S – Do you snore at night?
- L –Did your parents or a friend tell you that your breathing is "difficult" at night?
- E – Did your parents or a friend tell you that you stop breathing at night?
- E – Do you have problems with your tonsils or adenoids (glands inside your mouth)?
- P – Is it difficult for you to focus (at school or at home)?
- Y – Do you feel tired or sleepy a lot?

Obstructive Sleep Apnea-5 (OSA-5) (Table 12.1)

Aim and Description A five-item questionnaire that was developed from OSA-18. The aim is to screen quickly for pediatric sleep-disordered breathing (SDB). Each item is scored using Likert-type answers. The questionnaire checks for frequency of symptoms during the last 4 weeks.

Age 2–18 years of age.

Administration It takes less than 5 min to complete the questionnaire. It can be completed by the parents/caregivers, or by children who are able to read and understand the questions.

Reliability and Validity The sensitivity is 79%, and specificity is 35% if a total score of 5 or higher was used to diagnose OSA (AHI > 1). If it is used to detect moderate to severe OSA (AHI ≥ 5), the sensitivity is 82% and specificity is 32% [29].

Language/Translation English.

Availability A copy of the questionnaire is available in the paper published by the authors. Permission might be needed for commercial use [29].

Scoring Each item is scored from 0 "None of the time" to 3 "All of the time." Total score can range from 0 to 15. A score ≥ 5 indicates OSA. The higher the score, the more likelihood of sleep-disordered breathing.

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Table 12.1 OSA-5

	During the past 4 weeks, how often has your child had...	None of the time	Some of the time	Most of the time	All of the time
1	Loud snoring?	0	1	2	3
2	Breath holding spells or pauses in breathing at night?	0	1	2	3
3	Choking or made gasping sounds while asleep?	0	1	2	3
4	Mouth breathing because of a blocked nose?	0	1	2	3
5	Breathing problems during sleep that made you worried that they were not getting enough air?	0	1	2	3

From Soh et al. [29]. Reprinted with permission from Elsevier

Conclusion

It is worth mentioning that these questionnaires and scales are not meant to replace clinical assessment by sleep specialists or GPs. The best outcome can be achieved from questionnaires in conjunction with a detailed history and clinical examination. There are other scales that address anxiety, fatigue, or behavioral difficulties in children and have components that address sleep difficulties. These scales were not included in this chapter (except the Center for Epidemiological Studies Depression Scale for Children (CES-DC) but can be useful. A paper published by Spruyt and Gozal [30] has a detailed review on pediatric sleep questionnaires that were available up to 2011. We listed below examples of questionnaires that are not discussed here (Table 12.2). A more

Table 12.2 Brief list of pediatric sleep questionnaires that were not discussed in detail in this chapter

No	Questionnaire	Age	Administered by
1	Children's Sleep Status Questionnaire (CSSQ)	0–5 years	Parent
2	Sleep and Settle Questionnaire (SSQ)	6-week-old infants	Parent
3	Infant Sleep Questionnaire (ISQ)	12–18 months	Parent
4	Parental Interactive Bedtime Behavior Scale (PIBBS)	12–19 months	Parent
5	Maternal Cognitions about Infant Sleep Questionnaire (MCISQ)	12.9–16.8 months	Parent
6	Bedtime Routines Questionnaire (BRQ)	2–8 years	Parent
7	Children's Sleep Wake Scale (CSWS)	2–8 years	Parent
8	Children's Sleep Hygiene Scale (CSHS)	2–8 years	Parent
9	Obstructive Sleep Disorders 6-Survey (OSD-6)	2–12 years	Parent
10	Maternal Attitudes Scale	36–68 months	Parent
11	Family Inventory of Sleep Habits	3–10 years	Parent
12	Children's Chronotype Questionnaire (CCTQ)	4–11 years	Parent
13	Children's Sleep Habit Questionnaire -preschool and school ages (CSHQ)	4–12 years	Parent
14	Sleep-Related Breathing Disorders scale (SRBD)	5–12.9 years	Parent
15	Hong Kong Children's Sleep Questionnaire (HK-CSQ)	5–15 years	Parent
16	Missouri Children's Behavior Checklist (MCBC)	5–16 years	Parent
17	Sleep Questionnaire by Simonds and Parraga	5–20 years	Parent
18	Children's Sleep Behavior Scale (CSBS)	6–12 years	Parent

(continued)

Table 12.2 (continued)

No	Questionnaire	Age	Administered by
19	Sleep Behavior Questionnaire (SBQ)	6–14 years	Parent
20	Sleep Disturbance Questionnaire for School aged Children (SDQC)	6.5–14.10 years	Parent
21	Sleep Disturbance Scale for Children (SDSC)	6.5–15.3 years	Parent
22	Pediatric Sleep Disturbance Questionnaire (PSDQ)	7–20 years	Parent
23	Sleep Habits Questionnaire	7.2–12.7 years	Parent/self
24	Dysfunctional beliefs about sleep	8–10 years	Self
25	Dream Content Questionnaire for Children (ChDCQ)	9–13 years	Self
26	Adolescent Sleep Wake Scale (ASWS)	12–18 years	Self
27	Adolescent Sleep Hygiene Scale (ASHS)	12–18 years	Self

Data from Spruyt and Gozal [30].

detailed list is available in the paper by Spruyt and Gozal [30] that can be found online. Some clinics gather a number of questionnaires in a booklet and ask the parents, children, and adolescents to complete them before the clinical interview. This method saves time and empowers the parents to verbalize their children's sleep problems.

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Pediatric Patients with Sleep Complaints: Initial Interview and Diagnostic Planning

13

Jyoti Krishna

Introduction

> If you don't know where you are going, you might wind up someplace else. –Yogi Berra

Sleep is part of our very existence, the very fiber of our being, the fringes of which we are only now beginning to explore using modern scientific tools. Yet, sleep presents an enigma that has been the subject of human thought since time immemorial [1–3]. Disruptions in both the external and internal environmental milieu within which the human organism exists can affect sleep in complex ways which may then present as a perturbation in a clinically palpable and often measurable fashion. While detailed descriptions of various sleep disorders are presented elsewhere in this book, the purpose of this chapter is to give the 10,000-foot view with due recognition of Yogi Berra's pithy insight. For, if one is well familiar with normal human sleep, the spectrum of diagnostic possibilities and available assessment tools, one is less likely to "wind up someplace else!"

Over the past three decades, the field of pediatric sleep medicine has matured sufficiently to where the snoring child with large tonsils is less frequently referred for a tertiary-level sleep apnea consultation. With well-publicized clinical guidelines now in place, such "bread and butter" cases of obstructive sleep apnea (OSA) are increasingly screened and investigated by primary care providers who utilize direct-to-lab polysomnography and subsequently make the necessary referral to the ENT surgeon for adenotonsillectomy [4]. At the same time, burgeoning public awareness of restful sleep as a sine qua non for healthful living has resulted in the ever-increasing complexity of patients directly referred for consultation to the pediatric sleep specialist. Such patients regularly present with complaints like "never slept well," "cannot sleep," "will not sleep," "tired in the day," "restless sleep," or "sleeping too much." When asked if any interventions have been tried, the distraught parent often has the familiar response that they "have tried everything" alluding often to a plethora of Internet resources and self-help books they have already consulted before arrival. They frequently then go on to list a series of dietary, behavioral, pharmaceutical or environmental interventions that have been gleaned from best-selling books, mobile apps or well-intentioned general physicians. They often conclude their opening remarks with the conviction that if only their child "could sleep well, all the (child's school, behavior, and mood) problems would be better." They typically then look the present sleep expert expectantly for the magic solution to the malady.

Screening for Sleep Disorders

A variety of questionnaires have been developed to assess sleep disorders and their associated effects on daytime behaviors and mood. Their psychometric properties have been tested with varying degrees of rigor. Some are designed for primary care practitioners to screen for the presence of sleep problems (e.g., BEARS screen) [5], while others are more useful for research purposes (e.g., Pediatric Sleep Questionnaire) [6, 7]. There are those questionnaires that have been modified for children from their adult versions (Epworth sleepiness scale) [8, 9], and those that are specific for certain types of sleep disorders like restless legs syndrome [10]. While the psychometrics of many of these tools have been discussed recently [11], no single tool is applicable to the entire age-spectrum of pediatrics, nor does any provide reliable diagnostic power. Thus, their utility is often limited to screening and research, leaving the burden of final diagnosis on the clinician.

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The Two Major Presenting Problems: Insomnia and Hypersomnia

Start Simple

The current edition of the International Classification of Sleep Disorders lists over 60 distinct diagnostic entries including sleep-related medical and neurological disorders [12]. Mechanistically, we may conceptualize sleep problems to be the result of reduced total sleep time in a 24-hour day, sleep that is of poor quality or interrupted for a variety of reasons, problems resulting from circadian misalignment of day-night rhythms, or overwhelming intrinsic sleepiness that is independent of the other mechanisms [13]. Broadly, these mechanisms may operate alone or in combination and eventually result in the two broad sets of presenting sleep complaints, namely poor or interrupted sleep at night (insomnia) and excessive tiredness or sleepiness in the day (hypersomnia) (Fig. 13.1). The key to a successful clinical outcome lies in a carefully elicited history analyzed in the context of the biological, behavioral, and social milieu of the patient.

Age Matters

A working knowledge of common ages of presentation of various sleep disorders is useful since many disorders occur

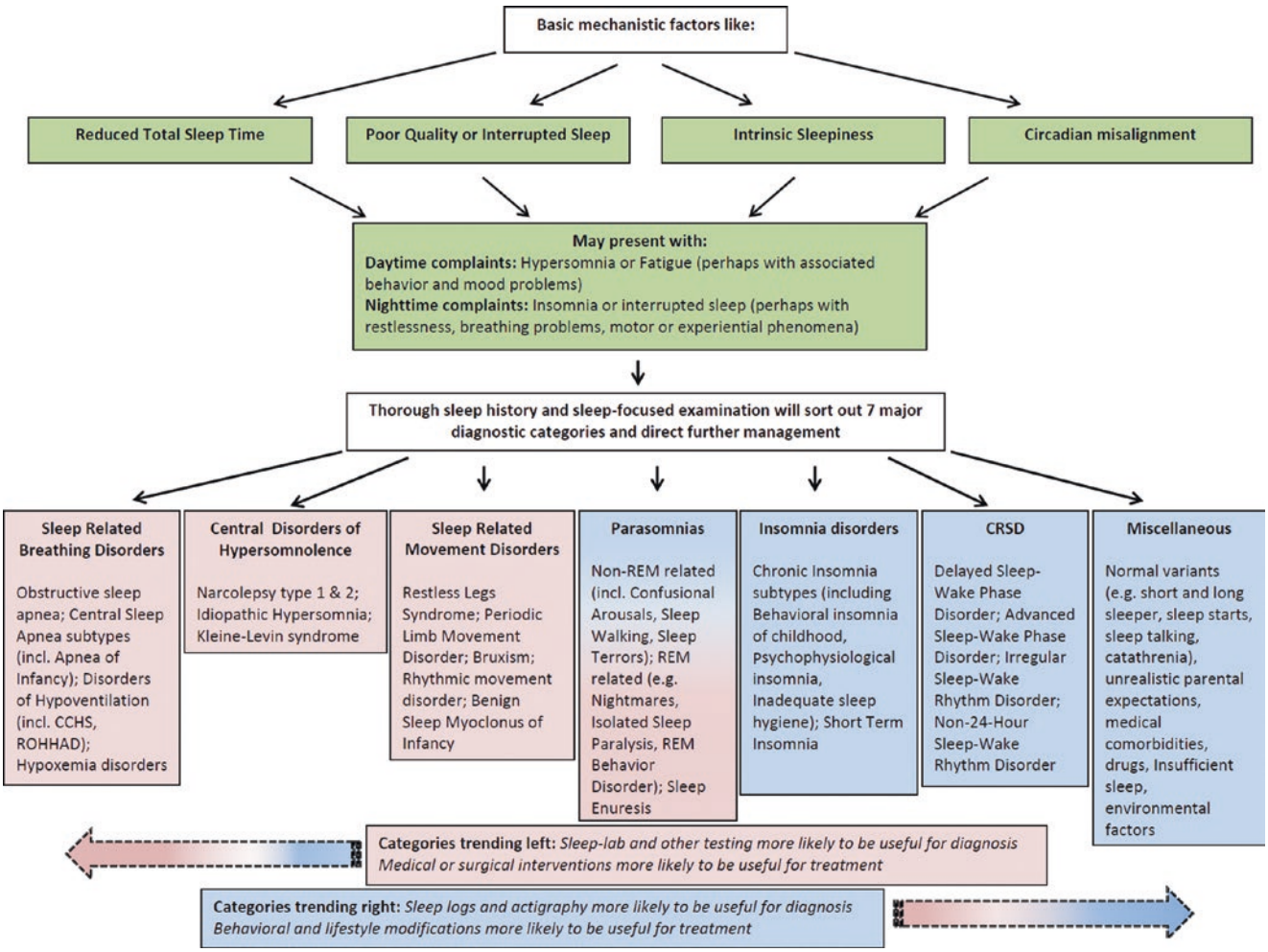


Fig. 13.1 Approach to pediatric sleep disorders. This concept diagram is presented for broad illustrative purposes only. Commonly encountered entities are listed. For a comprehensive list of sleep disorders please refer International Classification of Sleep Disorders (ICSD-3) [12]. Arguably, the initial presentation is often complex with considerable overlap between diagnostic and therapeutic choices. The graded color scheme in the boxes listing the seven major diagnostic categories attempts to denote the likelihood that the child will need in-lab sleep testing with medical or surgical interventions rather than more conservative management. Note, several entries in the Miscellaneous box may be reassigned to other boxes per ICSD-3 (e.g., Normal Variant subtypes; Insufficient Sleep). For brevity, the official nomenclature has not been used for many entries (e.g., bruxism). *CCHS* congenital central hypoventilation syndrome, *ROHHAD* rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation, *REM* rapid eye movement, *CRSD* circadian rhythm sleep disorder

only at developmentally appropriate times [12]. Thus, among parasomnia disorders, confusional arousals and sleep terrors commonly occur in the toddler or preschooler, whereas sleep walking is generally seen in the school aged child. By definition, bedwetting should not be considered pathological before the age of five. On the other hand, sleep-related hallucinations and isolated sleep paralysis are most likely to occur in adolescence.

Sleep-related breathing disorders can occur at any age. Apnea of prematurity generally resolves quickly with advancing age. In otherwise healthy children, obstructive sleep apnea secondary to adenotonsillar hypertrophy generally appears around the time when these tissues are most exuberant relative to the rest of the upper airway viz. preschool or early school years [14]. Of course, co-morbidities such as obesity, craniofacial structural abnormalities, neurological or metabolic conditions can blur these boundaries.

Similarly, insomnia disorders may occur at any age. Discounting co-morbid conditions, the common subtypes seen in the typically developing infant or preschooler are the behavior insomnia disorders such as sleep onset association disorder and limit setting sleep disorder [12]. Contrast this to the preschool child whose fertile imagination may invoke bedtime fears and result in problems settling at night, or the teenager whose insomnia is more likely to be from circadian rhythm misalignment, inadequate sleep hygiene or psychophysiological factors [12].

Hypersomnia complaints are less common in the younger child than in late childhood and teenage years when narcolepsy and the delayed sleep phase type of circadian rhythm sleep disorder occur most frequently [12]. As a corollary, unusual daytime sleepiness in the prepubertal school-going child should raise red flags [15].

The First 5 minutes

What Is the Chief Complaint at Night?

As elsewhere, the typical sleep clinic visit begins with a broad open-ended question aimed at eliciting chief complaints. Nighttime symptoms are usually forthcoming very early in the interview. Quick preliminary questions should simply probe the presence or absence of snoring, perceived sleep-related breathing problems, restless sleep or excessive body movements, unusual behaviors during sleep, inconsistency of sleep wake times, difficulty initiating or maintaining sleep and excessive daytime sleepiness. Positive answers can then be dealt with in detail during the rest of the interview while negative responses may be set aside.

What Else Is Going On in the Day?

Reciprocal interactions between daytime behaviors and sleep are well known. Developmental, psychiatric and behavioral problems such as ADHD, mood and conduct disorders, school tardiness or falling grades and the trajectory of body weight should be ascertained [16, 17].

Supporting Data?

The growing public awareness of the importance of sleep for overall health has spawned a variety of wearable tracking devices. It is common to see parents nervously enquiring about desaturations on their baby's nocturnal oxygen monitors or restless sleep noted on a wearable activity tracker. Parents may have brought along a video or audio recording of worrisome nocturnal events. Giving them a chance to present this data early on in the visit provides the satisfaction that they have been heard. Besides, it certainly may be useful to guide the remainder of the interview and aid diagnostic planning.

The Sleepy Seven

Thus, the first few minutes of the visit will often serve to broadly sort the problem(s) at hand into one or more of the seven major categories (Fig. 13.1). In each of these areas, symptom onset, evolution, frequency, severity as well as any precipitating, perpetuating and relieving factors should be elicited. Some general principles and common scenarios will now be presented to serve as a rough guide.

Sleep-Related Breathing Disorder

Parents or friends may report symptoms of snoring, witnessed apneas, gasping or choking in sleep, or restless sleep. They may recall unusual sleeping positions possibly to optimize airway patency (e.g., hyperextended neck, sleeping propped up) [4]. The patient may complain of night sweats or morning headaches. Questions regarding the upper airway such as recurrent tonsillitis, nasal allergies, history of a broken nose or deviated nasal septum may be useful. Bedwetting may be overrepresented among children with obstructive sleep apnea (OSA) [18]. A history of prior upper airway surgery like tonsillectomy, orthodontic or craniofacial interventions, or use of intranasal steroids may be helpful. Premature birth or central nervous system disorders such as Chiari malformation may suggest increased risk for central sleep apnea [19].

Hypersomnia

Hypersomnia can be the result of poor sleep quality at night from a plethora of causes and may have nothing to do with true central disorders of excessive daytime sleepiness such as narcolepsy or idiopathic hypersomnia. Nevertheless, if sleepiness is severe, questions directed toward symptoms of narcolepsy such as cataplexy, hypnagogic or hypnopompic hallucinations, and sleep paralysis should be asked. Often there is a history of sudden weight gain in children with narcolepsy [20]. Children with narcolepsy often report feeling refreshed after naps unlike those with idiopathic hypersomnia where long hours of unrefreshing sleep is more common [12]. Rarely, cyclical symptoms of sleepiness lasting several days interspersed with several weeks to months of normalcy in a teen may suggest the Kleine Levin syndrome especially if the episodes also involve changes in behavior and appetite [12]. Precipitating causes for central hypersomnia such as head trauma or exposure to certain types of influenza vaccination may be evident [21]. Sleepiness should be distinguished from lethargy, lack of energy or fatigue whose causes may be myriad. Mood disorders may be comorbid or may mimic central hypersomnia and should be part of the differential diagnosis [12].

Sleep-Related Movement Disorders

Excessive movements and "wild" restless sleep are frequent complaints. While restless sleep may be the result of severe sleep apnea or parasomnia, limb movement disorders often are the cause. The bedsheets of such patients are often described to be in disarray in the morning. Restless legs syndrome (RLS) is usually a clinical diagnosis in the older child or teen where the history suggests symptoms of discomfort, funny feelings or paresthesia in the legs, worsening of symptoms toward the evening, temporary relief of symptoms with limb activity, and return of symptoms when the activity is stopped [12]. In younger children or those with limited language skills, these criteria may be difficult to establish, and it might be necessary to look for comorbid periodic limb movements (PLM) on a polysomnogram to support the diagnosis [22, 23]. A history of iron deficiency, caffeine consumption or use of SSRI medication is often present [23]. Of course, excessive motor activity in sleep always needs to be distinguished from seizure activity or parasomnia in the appropriate clinical context. Rhythmic movements (e.g., head banging) are common in younger children and generally abate by school age but may be severe enough to cause injury in some [12, 24]. Benign sleep myoclonus involving limb and truncal jerks in the infant may be frightening to the observer but thankfully rare and self-limited [25]. Leg movements ("pseudo-PLMs") may be seen in untreated OSA and often the newly described Restless sleep disorder may need to be considered [26].

Parasomnia

Parasomnia disorders are common in childhood whose timing relative to the sleep period often helps distinguish non-REM parasomnias (which occur earlier in the night when deep sleep is more likely) from REM parasomnias (which usually occur later in the night when dream sleep is more common). The evolution of behaviors during the event, status of the eyes (open or closed), clarity of thoughts upon awakening, recall of events the next morning, stereotypy, as well as other semiology may help distinguish the various types of parasomnias from each other and from seizure disorder [27]. It is vital to ascertain the safety of the home environment and define any potentially dangerous spots (e.g., sleeping in upper bunkbed, access to stairs, sharp knives) and identify any past injurious behaviors.

Primary enuresis is distinguished from secondary enuresis by the absence of dry nights for a six-month period in a child who is older than 5 years [12]. A history of snoring and sleep disordered breathing should be sought [18]. Details of urination including the quality of the urinary stream, daytime urgency, frequency, dysuria, renal disorders, patterns of fluid consumption (including caffeinated beverages), and abnormal genital anatomy are useful. Constipation may be present and need to be addressed. Such historical details will help distinguish monosymptomatic from non-monosymptomatic bedwetting and guide management [28].

Insomnia

Insomnia can present as difficulty falling asleep, staying asleep, and/or early morning awakening. Behavioral insomnia of childhood is typically seen in the younger child [12]. The limit-setting subtype includes stalling bedtime by making excuses and is seen in families where parental boundaries are not respected by the child. Typically, daytime limiting setting problems are evident as well. In contrast, increased need for parental attention at night suggests problems with self-soothing. The fact that the child needs to be fed, held, rocked or massaged until sleep ensues suggests negative sleep associations. Conversely, a toddler who sleeps easily and with less fuss when under the watch of a specific caretaker, say, a no-nonsense nanny, reinforces the suspicion that behavioral insomnia is involved.

Older children may be able to describe their inability to "shut the brain off," bedtime worries, clock-watching or need for stimulus (e.g., TV) to "help fall asleep." In some, a history of better sleep on weekends or when away from home

might support psychophysiological insomnia. Consistently easier sleep onset at a later clock-hour should raise the possibility of a circadian disorder (see next section). On the other hand, younger children may be described to be upset, fearful, getting a second wind after a certain hour, or they may simply remain "wound up" until a late shift working parent finally arrives home.

Reasons for waking up in the middle of the night should be clarified. These may include hunger, a full bladder, fears, environmental discomfort, a crying sibling, or even the entry or exit of a pet from the bed. It is also important ask about the behaviors once sleep has been interrupted. How long does it last? Does the child try to go back to sleep on his/her own? Does the child leave the bed and wander the house? Does he/she turn on the TV or electronics again? Does the child go seeking the parent aiming to co-sleep, or head to the kitchen for a snack?

It will be evident to the reader from the sample of given scenarios that several permutations and variations are possible and that a detailed history is very important in patients with insomnia since the key to a solution often lies within that narrative. It is also important to note that insomnia may be secondary to other sleep disorders (e.g., OSA, PLMs), mood disorders, medical conditions, drugs or illicit substances [12, 29].

Circadian Rhythm Sleep Disorder

This is one subset of sleep disorders that is commonly misdiagnosed. Most frequently seen in the pediatric sleep clinic is the Delayed sleep-wake phase disorder (DSWPD), which is an extreme manifestation of a natural delay in the biological clock that often occurs in many teens around the onset of puberty [17]. It may present in a variety of ways. Sometimes, it presents as insomnia with a substantial delay in sleep onset as late as early morning hours. Tardiness for morning classes is frequent. Those who do reach school on time often report feeling foggy or slow in the morning and academic performance suffers. Often, there is a history of well-meaning physicians having tried sedatives (for insomnia) or stimulants (for daytime hypersomnia). Very frequently, the story is additionally complicated by poor sleep hygiene practices, low motivation and lack of parental supervision. The latter may occur for a variety of reasons not the least of which is the teenager exerting their independence and spending time at home sequestered in their own bedroom surrounded by electronics [30]. Therefore, the teen presenting with insomnia at night and sleepiness in the day should raise suspicion for DSWPD and/or inadequate sleep hygiene.

Miscellaneous

This category lists a variety of conditions that may co-present with other well-defined sleep disorders. Of these, components of good sleep hygiene should be routinely confirmed. Specific questions about the bedroom environment including the mattress, extraneous noise, ambient light, and temperature control are useful. Importantly, the presence of electronic media, clocks, pets, and use of caffeine need to be queried. Care must be taken when enquiring about caffeine since misconceptions about the caffeine content of beverages are common. The practice of this author is to ask for the names of the drinks consumed rather than superficially enquire if caffeine is being consumed or not [31]. A list of current medications and clinical co-morbidities should be reviewed since poorly controlled systemic diseases (e.g., eczema or asthma) may prevent good sleep [32, 33]. Medication side effects may disrupt sleep as well. For example, some anti-depressants may worsen symptoms of restless legs and PLMs [34].

The Bedroom and Bedtime Routines

A description of the sleeping area is vital [29]. How many bedrooms are there in the home relative to the size of the family? What is the location of the child's bed relative to the parental bed? Are there habitual sleeping areas other than the bed (e.g., the living room couch)? What about the presence of other siblings in the room, or bedroom sharing with parents? Does the teenager spend most of his or her time in the basement with electronics to keep him or her company and scant exposure to direct daylight? On the contrary, do later sunsets in the summer lead to too much light in the bedroom (especially common in subtropical regions)?

It is beneficial to assess bedtime routines. The timing of any evening medications, dinner, bath, snack, and bedroom habits should be noted. Is there quiet story-time or horse play right before bed? What is the method of putting the child to bed? Do parents follow a predictable pre-bedtime routine, lovingly tuck the child in, and walk away while the child is still awake or do they linger to rub the child's back or co-sleep until she falls asleep? Who else is involved in the bedtime routines? Do all adult caregivers enforce the same bedtime rules? Is the child dividing time between two or three homes (e.g., divorced parents and babysitter)? Does the child migrate to the parental bed at night?

No sleep history should be considered complete without comparing sleep-wake timings on weekdays with weekends or extended breaks from school. Late nights on weekends commonly forebode problematic Monday mornings.

Current and Past Interventions

It is a good idea to always ask the family what interventions have been tried thus far. Have over the counter or prescription medications been used? Have any behavioral changes been made? How long and with what consistency were these techniques enforced? Was the help of a behavioral expert taken? What about adenotonsillectomy or orthodontics? Were any of these interventions even partially helpful or not at all?

Family and Social History

Certain sleep disorders may run in families [12]. It is common to see obstructive sleep apnea cluster in families not because of an identifiable genetic anomaly but rather from the fact that respiratory control characteristics, facial anatomy, dietary habits, and the resulting body habitus is likely to be similar. A parental history of partial arousal parasomnias is frequent and such a history may serve to reassure parents that their child too will likely outgrow the problem just like themselves. RLS and narcolepsy may have a genetic basis as well [35, 36].

The social history certainly informs decision making. For instance, a family of 5 living in a 2-bedroom apartment will need a very different interventional approach for behavioral insomnia than a family with more commodious homes. Parental work hours may impact regular bedtime routines, family dietary habits may influence obesity management and personal beliefs may prevent surgical intervention. The availability of transport and medical insurance may all play into management decisions as well.

The Physical Examination

For most experienced clinicians, "examination" begins from the moment of entry into the patient's room. Observation of the interpersonal behaviors during history taking often provide clues to the possible social dynamics at home including limit setting issues (e.g., the child running around unchecked), media use (e.g., the teen who glances at his cell phone between questions), as well as the family's dietary patterns (e.g., the caffeinated soda and chips in the overweight parent's hand).

Anthropometrics and vital signs should be routinely documented. An elevated body mass index and large neck circumference may be a setup for sleep apnea [37, 38]. An elevated blood pressure may be seen with sleep apnea [4]. The general exam might clearly suggest a malformation (e.g., Pierre Robin sequence) or a genetic syndrome (e.g., Down syndrome or Prader-Willi syndrome) with their attendant complications including sleep disordered breathing and hypersomnia [12].

Commonly, systemic examination initially focuses on the upper airway. Attention to adenoids facies, oral breathing, tonsillar size, crowding of the upper airway and oropharynx, macroglossia, misaligned dentition, deviated nasal septum, nasal turbinate hypertrophy, micrognathia, cleft palate and craniosynostosis are worth mentioning. Thyromegaly or acanthosis nigricans may be apparent in the neck. The neurological exam may confirm peripheral neuropathies associated with secondary RLS [39]. Myopathies and scoliosis increase risk of hypoventilation or sleep apnea [40]. Intracranial pathology (brain tumor) may impact respiratory control or cause hypersomnia [41]. The presence of a vagal nerve stimulator may result in sleep-disordered breathing [42]. Asthma may reciprocally interact with OSA or cause sleep problems by itself [43]. Hypertension may occur with untreated OSA [4]. Presence of bedwetting should direct attention to a genitourinary examination looking for any abnormalities of the external genitalia and correlates of renal disease [28].

Decision-Making

Know What Is Normal

Remarkable anatomic and physiologic changes occur in the various organ systems of the developing child and sleep is no different. It behooves the sleep expert to have a working knowledge of the distribution of sleep stages within the major sleep period (ultradian rhythm), the distribution of sleep periods within the 24-hour day (circadian rhythm), as well as age-appropriate daily sleep requirements [44–46]. It is always wise to bear in mind that there is a statistical spread around the commonly quoted sleep requirements (Fig. 13.2). Napping is commonly seen in infants and toddlers. The typical preschooler commonly gives up naps by 5 years of age.

When Only Hand Holding May Be Needed

Worried parents often resort to the Internet for answers to their child's sleep concerns. However, many find it difficult to navigate the vast material available on-line. Even materials from reputable sources may not be extrapolated readily to a particular child's situation or parents may be biased due to a worrisome family medical history. Accordingly, a few scenarios that for most part need reassurance only, are presented here.

Anxiety about seizures or apnea in may arise for a neonate displaying rapid eye movements, facial grimaces, sighs

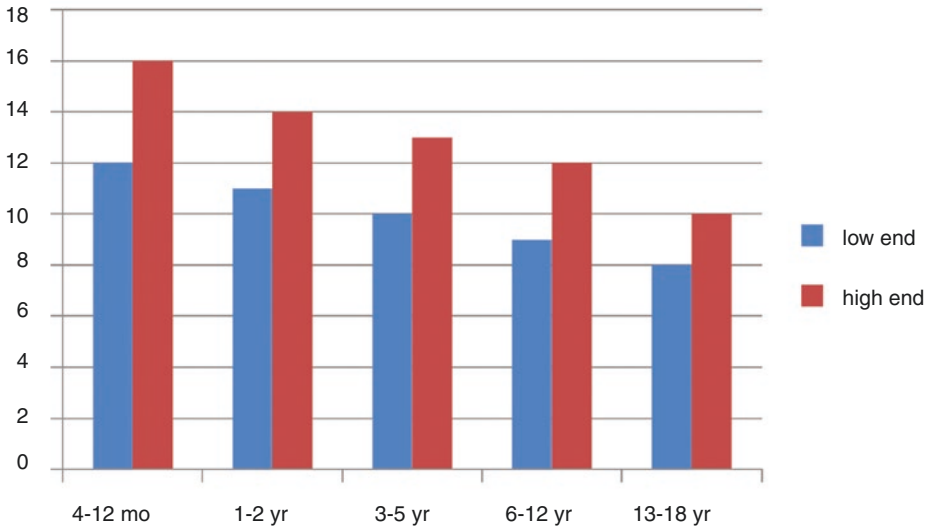


Fig. 13.2 Recommended daily sleep duration in children and teens. Recommended range of daily amount of sleep for pediatric populations (hours/day) are shown [45]. The lower end (blue bars) and upper end (red bars) reduce with age. These data are useful in estimating if a particular child is getting sufficient sleep on a regular basis

and muscle twitches soon after sleep onset. Parents may also see brief limb jerks in older children as they fall asleep. All other things being normal, knowledge of sleep-onset REM in neonates with its attendant facial, ocular and limb movements, benign sleep myoclonus of infancy, and hypnic jerks in the older child will guide the sleep physician to offer reassurance [47, 48].

Not uncommonly, a heretofore healthy and normally sleeping 6-month-old may suddenly appear to unlearn all her sleep training and resume intermittent awakening through the night. Such night wakings are a well-known developmental phenomenon [49]. Educational tools aimed to help the parent avoid the trap of reinforcing the behavior and spiraling into a true behavioral condition due to entrenchment of unhelpful sleep associations is usually all that is needed.

Most 5-year-olds should be able to stay awake through the full school day with only a single sleep period occurring at night. However, there certainly are a few 5–6-year-olds who may not be yet ready to give up their precious afternoon siesta such that watchful waiting may be preferred over an expensive and laborious hypersomnia work-up [50].

Similarly, in otherwise healthy children, recurrent isolated sleep paralysis (without hypersomnia), sleep talking, and the occasional non-injurious partial arousal parasomnias usually require no investigation or intervention [12].

Investigative Decisions

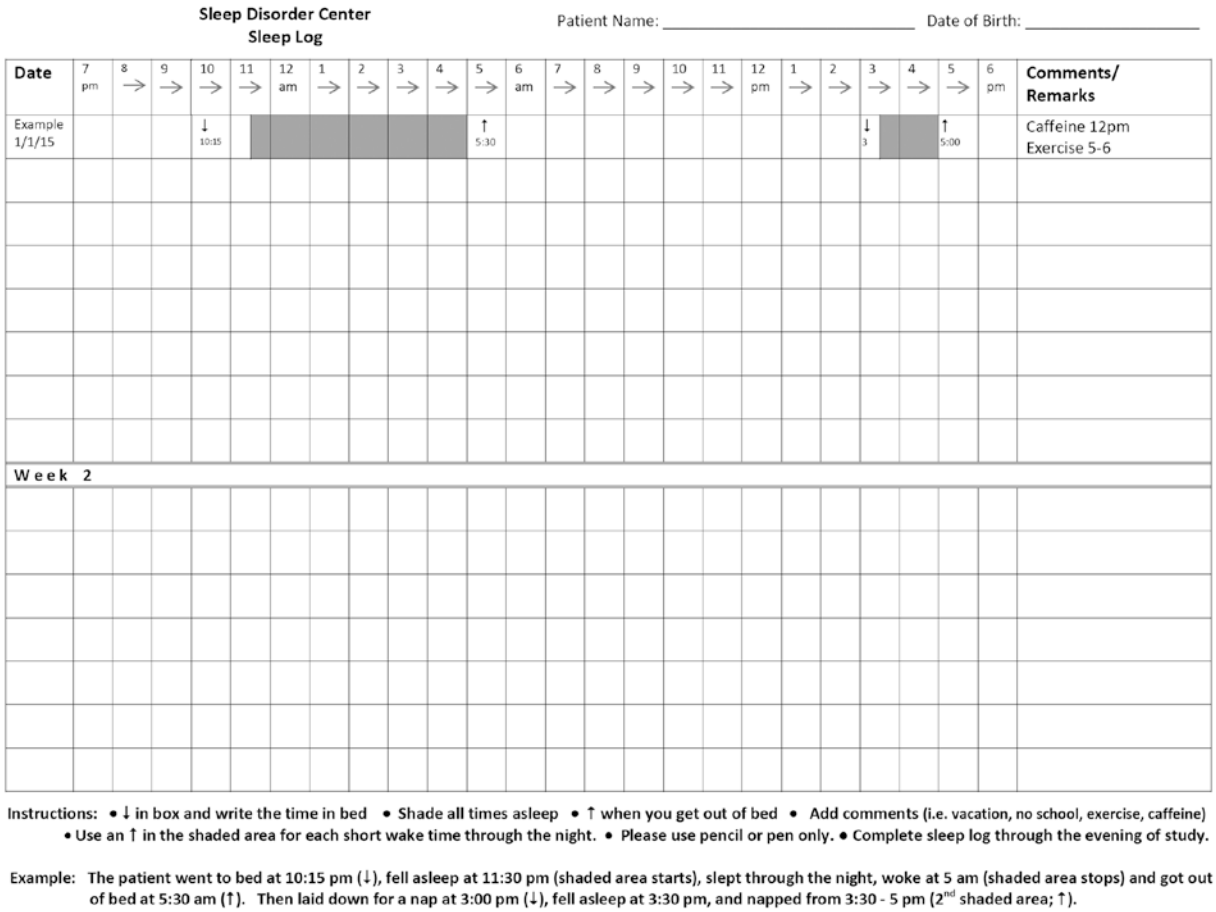
Assuming true pathology is suspected, the initial decision rests upon choosing between the polysomnogram (PSG), multiple sleep latency test (MSLT), actigraphy and sleep diary (Fig. 13.3). These tools are summarized in Table 13.1. The maintenance of wakefulness test (MWT) is rarely used in pediatrics. Depending on the clinical context, ancillary tests may include blood tests, cerebrospinal fluid analysis, genetic testing and radiological imaging (Table 13.2). Several guidelines exist to help with this decision [4, 51, 52]. Based on these guidelines, an overview of the tools is briefly highlighted below and also mentioned in Fig. 13.1.

Sleep-Related Breathing Disorder

Suspected sleep-disordered breathing is the single most common indication for a diagnostic PSG. The PSG is also used to assess response of sleep-disordered breathing to treatment (e.g., tonsillectomy, mandibular distraction, weight loss, Chiari decompression). A variant aimed at optimizing non-invasive respiratory support is commonly known as a positive airway pressure (PAP) titration study.

Hypersomnia

The MSLT is useful if common causes of excessive daytime sleepiness (e.g., insufficient sleep, inadequate sleep hygiene, circadian rhythm disorder) have been clinically eliminated and narcolepsy is suspected. This test is ideally run after adequate preparation including adherence to a stable sleep-wake routine for several days prior to the test. Medications that may interfere with the test need to be judiciously curtailed in advance. Typically, a PSG is coupled to run on the prior night to document adequate sleep time and eliminate the possibility that other untreated sleep disorders (e.g., OSA) may exist.



Sleep Disorder Center
Sleep Log

Patient Name: _____ Date of Birth: _____

Date	7 pm	8 →	9 →	10 →	11 →	12 am	1 →	2 →	3 →	4 →	5 →	6 am	7 →	8 →	9 →	10 →	11 →	12 pm	1 →	2 →	3 →	4 →	5 →	6 pm	Comments/ Remarks
Example 1/1/15				↓ 10:15							↑ 5:30										↓ 3		↑ 5:00		Caffeine 12pm Exercise 5-6
Week 2																									

Instructions: • ↓ in box and write the time in bed • Shade all times asleep • ↑ when you get out of bed • Add comments (i.e. vacation, no school, exercise, caffeine)
• Use an ↑ in the shaded area for each short wake time through the night. • Please use pencil or pen only. • Complete sleep log through the evening of study.

Example: The patient went to bed at 10:15 pm (↓), fell asleep at 11:30 pm (shaded area starts), slept through the night, woke at 5 am (shaded area stops) and got out of bed at 5:30 am (↑). Then laid down for a nap at 3:00 pm (↓), fell asleep at 3:30 pm, and napped from 3:30 - 5 pm (2nd shaded area; ↑).

Fig. 13.3 Sample 2-week sleep log. A 2-week work sheet used to log sleep at the author's sleep center is presented. The sleep log is mailed ahead of time to be filled-in by all prospective patients who are then asked to bring it for the initial visit. Logs are also required to be submitted prior to MSLT testing and are useful for interpretation of test data. They are used extensively by the center's behavioral sleep psychologist, often over extended periods, to formulate and track therapy

Table 13.1 Primary tests for evaluating sleep disorders

Polysomnogram (PSG)
• Indicated for assessing sleep related breathing disorders before and after surgical intervention, for titrating noninvasive respiratory support (e.g., CPAP), for assessing periodic limb movements, and for evaluating narcolepsy (paired with MSLT next day)
• Records limited EEG (frontal, central, occipital), EOG, chin and leg EMG, limited lead ECG, pulse oximetry, capnography, oro-nasal airflow, upper airway sounds including snoring, thoraco-abdominal respiratory effort and continuous video to provide comprehensive sleep data
• The data are scored using standard criteria to report sleep stages, arousals, body position, apnea-hypopnea count, periodic limb activity, observed parasomnia, cardiac rate and dysrhythmias, EEG abnormality, O_2 and CO_2 status, and pertinent video graphed behaviors throughout the night
• PSG with expanded EEG is a variant using the full EEG lead array to screen for epileptiform activity
Multiple sleep latency test (MSLT)
• Indicated for assessing daytime sleepiness where the ability to fall asleep is measured over five 20-minute naps spaced 2 hours apart throughout the day following a prior night PSG.
• Records limited EEG (frontal, central, occipital), EOG, chin EMG, limited lead ECG, and continuous video to provide daytime sleep data
• The data are scored by standard criteria to report the average time of sleep onset and presence of sleep-onset REM sleep periods
• MWT is a variant that is rarely used in pediatrics. It tests the ability to stay awake in the day measured over four 40-minute quiet periods labeled "naps" in a relatively boring low light environment
Actigraphy
• A wristwatch-like device with an accelerometer to measure rest-activity cycles as a surrogate for sleep-wake
• Captures data over days to weeks to assess and follow insomnia and circadian rhythms
• Data are usually combined with sleep diaries
Sleep diary
• A systematic pictorial or graphic log maintained prospectively by the parent or child (if old enough) to record daily bedtimes, sleep and wake times, sleep quality and special circumstances that impact sleep.
• Usually logged for 1–2 weeks or longer and useful for initially assessing insomnia and circadian rhythms disorders, concretizing uncertain history, documenting sleep-wake patterns and following the effect of interventions. Often used in conjunction with actigraphy.

Legend: *CPAP* continuous positive airway pressure, *EEG* electroencephalogram, *EOG* electrooculogram, *EMG* electromyogram, *ECG* electrocardiogram, *MSLT* multiple sleep latency test, *REM* rapid eye movement, *MWT* maintenance of wakefulness test

Table 13.2 Ancillary tests used in the sleep clinic

Presentation	Test	Remarks
Obstructive sleep apnea	Lateral X-ray of neck	To assess adenoidal hypertrophy
Central sleep apnea	MRI of brain	For brainstem abnormalities or other intracranial disease
CCHS	PHOX2B gene mutation	Diagnostic and prognostic value
Narcolepsy	HLA type for narcolepsy; CSF hypocretin	Available in limited laboratories
Hypersomnia unspecified	Urine drug screen; CBC; CMP; TSH	Drug screen may be considered with MSLT
Sleep enuresis	Urinalysis	A good initial single test
RLS, PLMD	Ferritin, serum iron, TIBC, CBC	Asseses iron stores and anemia
Obesity	Fasting lipids, CMP, TSH	Initial metabolic screening

Legend: These tests are among the more commonly considered in the author's practice. This list is not designed to be exhaustive and ultimately the tests ordered will depend on the case presentation and the differential diagnosis that it generates. *CCHS* congenital central hypoventilation syndrome, *RLS* restless legs syndrome, *PLMD* periodic limb movement disorder

Sleep-Related Movement Disorder

The diagnosis of RLS in the older child or teen may be straightforward but it may need to be supported with the demonstration of PLMs on a PSG in the younger child whose history may not be as persuasive. Restless or "wild sleepers" may have periodic limb movement disorder (PLMD) without RLS or restless sleep disorder [26].

Parasomnia

Uncomplicated partial arousal parasomnias generally do not require a PSG, but a PSG with expanded EEG may be run if parasomnia is atypical or has elements that may suggest the possibility of seizures. On the contrary, a PSG is almost always needed to document the absence of muscle atonia during dream sleep if REM sleep behavior disorder (RBD) is suspected.

Insomnia

It is often unnecessary to do a PSG for simple insomnia. Behavioral therapy with attention to sleep hygiene are usually the initial interventions. On the contrary, refractory insomnia may merit a PSG especially if a secondary cause (e.g., OSA or PLMs) is suspected to interrupt sleep.

Circadian Rhythm Sleep Disorder

A good clinical history with sleep logs and actigraphy are commonly the only tools needed to diagnose this subset of disorders.

Parting Thoughts

Before the initial interview is brought to a close, it is crucial to set goals and understand limitations of both investigations and treatment. That the PSG will be diagnostic for all sleep problems is a myth best dispelled at this time. Parents often believe if only their child could sleep "deeply" or "get sufficient dream sleep" they will be better. While there may be an element of truth in these statements, setting achievable goals and mutual expectations goes a long way in establishing an optimal, if not ideal, clinical outcome.

Since sleep disorders often cluster in families simply due to shared lifestyles (e.g., unhealthy diet, poor sleep habits), it is often clinically very satisfying to be able to impact the whole family while evaluating a child from the household. This author can happily recall several examples where a child's diagnosis and/or optimistic attitude positively impacted the sleep habits, CPAP use or dietary compliance of a parent or sibling with the same disorder.

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14 Best Practices for Accommodating Children in the Polysomnography Lab: Enhancing Quality and Patient Experience

Sally Ibrahim, Jennifer Stone, and Carol L. Rosen

Introduction

In 2005, our Rainbow Babies and Children's Hospital sleep team wrote a paper published in the second issue of the brand-new Journal of Clinical Sleep Medicine entitled "Making polysomnography more 'child friendly:' a family-centered care approach" [1]. The inspiration for that manuscript were children with sickle cell anemia who were participating in a National Institute of Health-sponsored study that included research sleep studies as part of study assessments [2]. The lead author for that paper was a dedicated Child Life Specialist who applied her profession's principles that help children cope with hospital procedures to improve coping with the polysomnography (PSG) procedure. The approach emphasized respect for the family, psychological preparation, adaptation of laboratory routines to the needs of the family, substitution of child-friendly terminology for medical jargon, coping strategies for the child and family during the procedure, positions of comfort, utilization of distraction and medical play, modeling behavior for the parent, and continuous praise and reassurance for the child. These techniques were applicable to children of all ages with a broad range of comorbidities. Implementation of this approach has minimized the burden of PSG for the child, boosted the confidence of the sleep technologist, improved study quality for the interpreting physician, and increased patient and family satisfaction. With these techniques, sleep centers have been able to successfully welcome children into their diagnostic facility, helping the field of pediatric sleep medicine to grow and flourish. This chapter provides an updated review of those techniques with additional guidance to clinicians and their sleep teams about the best practices for a quality pediatric PSG experience.

Indications for Polysomnography in Children

Polysomnography (PSG) is an essential diagnostic tool in the evaluation of pediatric respiratory and non-respiratory sleep disorders and indications are summarized in Table 14.1 [3–5]. PSG is most commonly performed for respiratory indications in children with suspected obstructive sleep apnea (OSA). The prevalence of OSA is 1–4% in the general pediatric population and higher in those with comorbidities such as obesity (up to 44.6%) [6, 7]. The most common risk factor for OSA in children is adenotonsillar hypertrophy and adenotonsillectomy (AT) is the first line of therapy for that problem. Other risk factors for sleep disordered breathing include obesity; genetic, craniofacial, and neuromuscular disorders; and other chronic medical conditions. The 2012

Table 14.1 Indications for polysomnography in children

Respiratory indications	Non-respiratory indications
OSA diagnosis	Periodic limb movement disorder
Following AT in children with pre-operative moderate-severe OSA or residual symptoms	Restless legs syndrome in children who require supportive data
PAP titration	
Central apnea and hypoventilation	Prior to mean sleep latency test to evaluate excessive somnolence and to quantify sleepiness
Sleep-related hypoxemia/ hypoventilation due to other disorders	
BRUE with clinical evidence of oSDB	Frequent parasomnias, spells, or nocturnal enuresis that may be secondary to oSDB
Prior to decannulation in select protocols	

AT adenotonsillectomy, *PSG* polysomnography, *OSA* obstructive sleep apnea, *oSDB* obstructive sleep disordered breathing, *PAP* positive airway pressure, *BRUE* brief resolved unexplained event

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American Academy of Pediatrics (AAP) clinical practice guideline, which focused on typically developing children, recommends PSG and/or specialist referral in the evaluation and management of OSA symptoms [8]. The 2019 American Academy of Otorhinolaryngology clinical practice guideline for adenotonsillectomy recommends PSG prior to surgery in specific populations: younger age (<2 years), obesity, Down syndrome, craniofacial abnormalities, neuromuscular disorders, sickle cell disease, or mucopolysaccharidoses [9]. Two patient populations – those with Down syndrome [10–12] and Prader–Willi syndrome [13] – deserve special mention because they are at especially high risk for OSA, benefit from treatment, and are commonly referred for PSG evaluation in both pediatric and adult age groups. For these reasons, today's sleep laboratories should be willing and able to accommodate their unique intellectual, developmental, and behavioral needs of these patient groups.

For children with suspected residual OSA post-AT or who are not candidates for AT, positive airway pressure (PAP) titration studies can help identify optimal treatment pressures. In some children, especially those who are very young or with intellectual or developmental disabilities, PAP must be introduced with mask desensitization techniques prior to scheduling a titration study [14]. Providing pediatric-friendly lab services, pediatric-specific PAP titration protocols, and mask interfaces tailored for children are described in a 2010 best practices guideline from American Academy of Sleep Medicine (AASM) [14].

Other respiratory PSG indications include more complex types of sleep disordered breathing such as central sleep apnea and/or hypoventilation. PSG is also valuable in assessing residual OSA and likelihood of successful decannulation in children with tracheostomy [15]. In patients with chronic lung disease (CLD), PSG may be a more appropriate test than oximetry to evaluate nocturnal hypoventilation and hypoxemia if there are concerns about ventilation during sleep [16]. For centers with available pediatric pulmonary expertise and respiratory therapy support, PSG may identify sources of unexplained nocturnal desaturation in patients with more complex respiratory conditions using ventilatory support and allow for adjustment their settings [4]. Finally, for infants with symptomatic apnea, PSG may aid in characterizing the presence and severity of the sleep disordered breathing. However, PSG has no predictive value in the recurrence of a Brief Resolved Unexplained Event (BRUE; formally known as apparent life-threatening event/ALTE) or future risk of SIDS [17].

In general, when the indication for a pediatric PSG is non-respiratory, formal sleep medicine consultation (rather than direct referral for testing) is strongly suggested. This consultation will help ensure that the testing is appropriate and that the need for additional preparation, sensors, or testing (e.g., limb leads, full EEG montage, multiple sleep latency testing, need to modify usual wake/sleep schedule) has been planned for. Non-respiratory indications include overnight PSG combined with daytime mean sleep latency testing (MSLT) to help diagnose central hypersomnolence disorders like narcolepsy, which typically presents in childhood or adolescence. Sleep laboratories must strongly consider the effects of puberty, a child's usual wake/sleep schedule, and regularity of sleep patterns prior to testing when scheduling and interpreting this testing [18]. PSG is also utilized in the diagnosis of periodic limb movement disorder (PLMD), supporting the diagnosis of childhood restless legs syndrome (RLS), and in children with parasomnias or in characterizing the nature of sleep-related movement disorder [18].

Most sleep laboratories are oriented toward adults with more than half only performing studies in ages ≥13 year and very few dedicated solely to pediatrics (1.3%) [19]. There is opportunity for labs to include pediatric sleep services, especially given the downturn in lab-based studies for adults. Sleep laboratories that conduct studies in children will need to have a pediatric and family-centered environment. The remainder of this chapter will outline how to perform a quality pediatric PSG and care for pediatric patients coming to the lab with special attention to the family-centered approach, a pediatric friendly environment, and preparatory strategies for best practices and optimal patient experience.

A Family-Centered Approach

The family-centered care approach is favored when performing sleep studies in children. The family-centered care approach recognizes the role of family to promote the typical patterns of living and includes the parent to garner emotional, social, and developmental support through a procedure. A *family-centered* sleep lab prioritizes preparation for the PSG procedure: education about why it is being done, what to anticipate on study night, and what everyone's role is in the procedure (patient, parent, technologist; see Fig. 14.1).

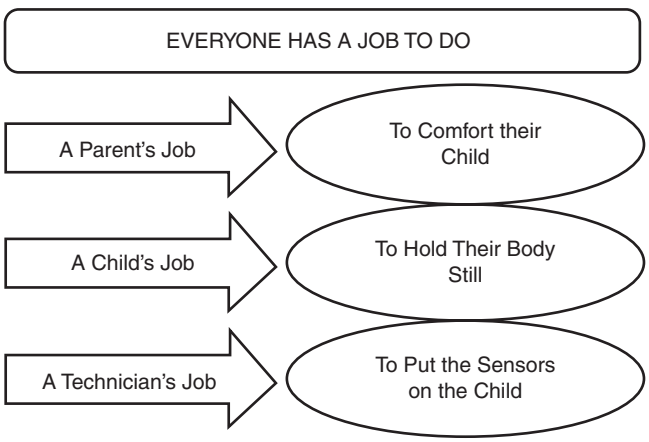

Fig. 14.1 The family-centered approach to a Sleep Study Hook-up. Talk about your team approach to the parent/guardian in helping to support their child through the procedure … what is everyone's role?

A family-centered lab works to create an experience that reduces the challenges of the procedure. Both children and their caregivers may feel uncomfortable and respond accordingly when uninformed about the PSG procedure and when in an unfamiliar environment. A *child-friendly* approach to PSG delivers age and developmentally appropriate care that empowers the child to remain calm, minimizes discomfort, and empowers the family caregiver to participate in the shared goal of a positive patient experience on their night away from home. Involvement of caregivers through preparation beforehand and participation during PSG is key to a family-centered sleep lab. The goal of using this care approach is to create the least amount of trauma for the child and caregiver while obtaining the best quality procedure [1].

Preparing the Sleep Lab for Children and Families

A number of strategies are available to help prepare children and families for the PSG procedure. These are summarized in Table 14.2 and are discussed in greater detail below.

Table 14.2 Summary of strategies to promote psychological readiness and sleep procedure tolerance for children and families

Pre-procedure sleep strategies	Preparatory phone call Pre-procedure sleep lab visit What to expect document, book, video, or other preparation tool available on virtual platforms (e.g., website) Scheduling materials with preparation information such as items to bring for the sleep study Pediatric specialist or advocate available to discuss procedure and pre-procedure planning Nurse educator in the sleep clinic or available to non-sleep referrals Child-life services when available and needed
Strategies on the night of the sleep study	Conduct the sleep study according to children's bed times Introduce the lab with pediatric friendly staff Use of child-friendly language and a family centered approach Pediatric lab equipment, sensors, parent/caregiver sleep accommodations, and staff readiness to accommodate children Adjust the order of the hook-up and place sensors after sleep if needed Use of modeling, play, distraction techniques, and other methods to help children tolerate the procedure When available, a child-life specialist to attend the hook-up for more anxious/complex children

Scheduling and Considerations in the Pediatric Sleep Study Orders

The PSG scheduling team will need additional guidance about workflow for pediatric patients. The ordering clinician and/or the medical director who reviews the PSG order needs to consider the age and the presence of any behavioral, sensory, developmental, or intellectual problems that indicate a need for additional preparation or staffing. Some children will require extra hook-up time or pre-procedure consultation with the pediatric sleep team to best plan the logistics for the study night. The study goals of the PSG must be clear, for example, is the purpose diagnostic, PAP treatment, or other respiratory goals, such as titrating oxygen therapy? Pediatric sleep studies include CO_2 monitoring [20], so optimal sensor approach (end-tidal, transcutaneous, or both) need to be specified in the PSG order and appropriately sized sensors available. If PAP therapy is considered or needed, scheduling a "split-night" study in a pediatric patient may require extra time for mask fit at the start of the study. Staff will need to be trained to deliver a "child-friendly" introduction to PAP equipment. For younger children or children with developmental, intellectual, significant behavioral or sensory problems, a successful trial of PAP mask sensitization at home prior to scheduling the treatment PSG may be required. If the PSG procedure is ordered for non-respiratory sleep disorders, such as central hypersomnolence disorders, parasomnias, movement disorders, or paroxysmal events, then additional sensors, special observations, or extra testing are usually required. The level of medical complexity in a child that can be safely accommodated will be informed by the location of the sleep laboratory, its resources, and the training of the technical and on-call medical staff. These issues must be individually determined by each sleep center and are beyond the scope of this chapter.

Medical History Information Needed for Planning

The general health, current medications, sleep, and social information including usual wake/sleep schedules or habitual co-sleeping should be confirmed by scheduling staff to quickly identify pertinent medical conditions, behavior/developmental concerns, or other issues that signal the need for a more intensive pre-PSG preparedness. A child who is on multiple psychotropic medications or hypnotics for sleep at night is clue that the child may have more challenging behaviors and needs additional time for medical review and hook-up. If the child was seen in by a sleep medicine clinician, this information should be included in that consultation

in the electronic health record. If the child is directly referred from a non-sleep clinician, extra efforts to establish these data will be required. The timing of the study should be around the child's usual sleep and wake schedule to allow sufficient time for PSG set-up and families to settle into the room close to the time they are accustomed to. At least 1 hour should be devoted to cooperative children, with more time anticipated for children with special needs or other accommodations. The sleep lab should coordinate these studies with the technical staff who are most comfortable with children and families [1].

For labs that are associated with a children's hospital, child life professionals may be available to help with children with developmental, mental, and behavioral challenges. Child life service integration in the child health delivery system is considered a quality benchmark [21] and has been shown to reduce parent reported stress and help normalize the experience [22]. A child life program provides guidance toward appropriate aesthetics and distraction items and identifies potential sources of stress (e.g., equipment that beeps and smells). Child life provides psychological preparation before and during procedures with information and reassurance, as well as encouragement for children to plan and cope with their procedures. In the ambulatory setting, child life services may aid in making a pediatric-friendly sleep lab in a variety of ways. One is in making the sleep laboratory child and family friendly with preparatory material. Another option is to educate the technical staff on how to implement coping strategies to decrease anxiety. If available, the child life specialist can be scheduled to be present for the PSG hook-up on a case-by-case basis.

PSG Planning and Preparatory Education for Families

Pediatric sleep laboratories that provide preparation prior to a procedure lessen anticipatory anxiety and procedural distress as well as increase caregiver satisfaction [1]. Caregivers and children alike will commonly and repeatedly inquire about the "who, what, where, when, and why" of PSG. Preparation can be accomplished through face-to-face discussion, telephone conversation, or electronic communication, and supplemented by written materials such as handouts, brochures, or pamphlets. Many sleep centers utilize their website to promote PSG preparation and provide additional opportunity for caregivers to view pictures, videos, and educational materials that serve to ease anxiety surrounding the procedure [1]. A center can designate a sleep lab delegate or pediatric care liaison that aids in preparation before, during, and after scheduling the study. However, all staff members, from the scheduler to the technician, should be prepared to answer common questions from families with confidence and consistency.

Families should receive a confirmation letter that indicates their scheduled arrival time, appointment timespan, general logistics (e.g., parking, what to bring), and supplementary preparatory material [1]. Several weeks may separate the initial order and actual procedure, so the letter should serve as an all-encompassing guide to their upcoming appointment in the sleep lab. Confirmation letters can also provide opportunity to clarify and reinforce all prior descriptions or discussions about the sleep lab and can include additional resources for caregivers such as directions to visit the website to view pictures and videos. A list of what to bring is helpful, encouraging caregivers to pack overnight needs, especially transitional objects or items that foster familiar sleep associations. Children who use comfort items for sleep, such as a stuffed animal, are more likely to sleep [23]. Furthermore, the lab should encourage parents to bring usual night-time equipment according to their child's sleep routines, such as toiletry items (e.g., toothbrush, toothpaste, overnight diapers) and a favorite bedtime story.

Emotional Preparation

Preparation for a sleep study procedure in a child is necessary for best outcomes – both from a psychological standpoint and for the accuracy of information obtained. Emotional preparation builds confidence and can take many forms. This behavioral intervention, sometimes call psychoeducation, provides specific information on what happens during the medical procedure. The aim is to build trust, reduce uncertainty, enhance coping strategies, minimize distress, and optimize outcomes [24]. Children who are more prepared for a procedure are more likely to use coping strategies that decrease anxiety as well as increase their cooperation [25]. Accompanying parents who can unintentionally transmit their medical anxiety to their children also need emotional preparation. In a study of an outpatient procedure involving electroencephalogram (EEG), the group of parents that received detailed psychoeducation prior to the procedure and had helped with distraction/played during the procedure showed decreases levels of anxiety and distress [24]. Similarly, the PSG hook-up requires attention to the planning of distraction techniques that will be used during the procedure [1].

This type of preparation for a PSG can take many forms, depending on lab resources and staffing. Using visual tools demonstrating the hook-up procedure is a form of psychoeducation. One example is the Snoring Puppy book, which uses cartoon pictures to tell a story of a puppy going to the sleep clinic and laboratory [26]. Labs may choose to make their own literature or have pictures of a hook-up that help

the families understand the procedure. Modeling, especially live peer modeling, can be a useful tool in easing the anxiety in children undergoing procedures, for example, a video of a similarly aged child undergoing a hook-up can be a tool that prepares children for a sleep study [25]. These resources can be used in sleep clinic prior to the procedure, or readily available on a virtual platform such as the clinic/hospital website.

Pediatric sleep laboratories should consider a pre-visit phone call to the sleep laboratory, especially in more complex cases. These phone calls may help to prepare for the sleep study, answer any questions about the sleep study and how to prepare, as well as ease any anxiety regarding the sleep study. Conversation about past experience with procedures and coping strategies informs preparation. Addressing barriers to knowledge gaps and addressing common misperceptions supports readiness. These calls may also re-assess sleep wake times and ensure proper scheduling and staffing for the sleep study [1]. Table 14.3 provides language and questions to consider during a preparatory phone call. Alternatively, a sleep technologist can aid in a pre-visit to the sleep lab for those with highest apprehension. The pre-sleep lab visit may help comfort all who are involved to prepare for the night in the sleep lab, especially in those with special needs or behavioral challenges. In patients who received a pre-lab visit, nearly all reported that it was helpful [27]. Providing this option to families is an excellent way to psychologically prepare for a sleep study [1].

In the sleep clinic setting, a pediatric sleep nurse can be instrumental in helping families with psychoeducation and guiding preparatory measures for a sleep study. A sleep nurse can coordinate the PSG for children with complex care, such as those who require interventions at night and how to prepare for these during the study. Nursing educators can promote education within a sleep clinic and provide adequate preparation for the sleep study. When clinically indicated, the sleep nurse can help coordinate additional care needs with the child-life specialist and sleep laboratory staff for optimal psychological readiness.

Table 14.3 Talking points for the pre-study preparation phone call

Questions to consider	Does your child take any medications at night for sleep or other medication to help with behavior or mood? "*Reminder – make sure to take your usual daytime medications and bring your nighttime medications on the study night, unless advised otherwise by our medical director – I will check.*" What do you already know about a sleep study? How do you think your child will do during the hook-up and through the night? Has your child had prior hospitalizations, tests or surgeries? Such as an EEG, imaging studies, etc.? If so, how did they manage? How do they respond when asked to hold still? For example, during a haircut? What has helped your child manage hard things in the past? What are your child's interests? What is your child's typical bedtime routine and how do they typically fall asleep? Is there anything more you would like to share with me about your child that would be helpful for us to know in order to make this a positive experience? Consider offering a tour of the sleep lab: "Do you think your family coming in for a tour of the bedroom will help your child be prepared? We can allow them to look at the sensors and place them on a doll/stuffed animal"
Describing the PSG set-up	Describe step-by-step what will happen Use child-friendly wording without medical jargon in your descriptions and explanations and encourage families to talk with their children the same way Talk about your "team approach" with the parent/guardian in helping to support their child through the procedure … what is their role? Debunk some common misperceptions: (will this hurt?/will you have to cut my hair?, I'm going to get tangled in those wires, what if I have to use the bathroom, when can I take the stickers off, will it hurt?, will you know my dreams?)
Encourage preparation	Discuss coping strategies for their child Discuss preparation techniques the parent can use at home with their child Offer phrasing the parent/guardian can use with their child to verbally prepare them for their experience *before they* arrive Bring familiar items from home which will offer comfort Plan food, meds, and which parent will stay Encourage the parent and child to put "fun" stickers with strings attached on a doll or stuffed animal Encourage the parent to talk positively with their child about their upcoming "sleepover" … it is an *adventure* that they will have together; pack a suitcase together Prepare a written description (with appealing pictures) of the set-up that can be mailed to the family to reinforce the information discussed Explain that cancellation will be needed for illness

Special Needs Populations

Children with trisomy 21 and Prader–Willi syndrome are examples of children with neurodevelopmental disabilities who are at increased risk for sleep disordered breathing [8, 28], have more limited ability to cooperate with the PSG procedure, but who greatly benefit from a child- and family-centered care approach in the sleep laboratory. Children with autistic spectrum disorder (ASD) are another special needs group who are at increased risk for a range of sleep disorders and commonly referred for diagnostic testing [29]. These children frequently have comorbid anxiety, sensory sensitivity and difficult with new procedures, and can be offered desensitization prior to PSG [30]. Children with ASD have a preference for visual cues. Stories and books can provide a brief intervention to foster predictability. One desensitization

protocol involves an introduction to the equipment and the PSG process using a book at the initial visit [31]. With this approach, children with ASD are able to successfully complete a PSG when needed, after appropriate desensitization procedures. When labs do not have formal desensitization protocols, offering assistance to families to identify what works for their child, supply sensors for practice and offering photos for a story book may prepare for the procedure.

Families of children with special needs may have complex bedtime routines, including tube feeds and diapering that require information regarding the limitation of the outpatient sleep setting. There may be misconception of extra supplies being available, like in an inpatient setting. Helping families prepare by thinking through the night-time routines and bringing necessary medical supplies with them to this ambulatory procedure will support a successful study. Finally, when there is considerable comorbid anxiety, mood disturbance, or previous trauma in an older child, a cognitive-behavioral preparation may be needed. This approach directly reduces the patient's anxiety/fear and also trains them to use cognitive-behavioral coping strategies to reduce anxiety before and during the procedure [25]. A sleep or health psychologist may be needed to intervene and provide coping skills for the procedure.

Physical Set Up, Protocols, Staffing

Sleep lab design and staff readiness are imperative to welcoming children and their caregivers to the lab and vital to delivering family-centered care. Considerations include alterations to scheduling hours, attention to the physical set up of equipment, fluctuations in staffing for children with special needs, and adjustments to sleep laboratory protocols. Special arrangements for furniture should be identified in advance, such as utilizing a crib for infants and young toddlers or a bed with side rails that can be padded for active or positional sleepers. Be prepared for families who habitually co-sleep with their children. The lab space should allow for safety (e.g., no sharp-edged furniture and electric outlets should be plugged), ample space for movement around the child, comfortable sleeping accommodations for the accompanying parent, side tables for equipment, and storage for personal belongings. Not uncommonly, parents may need an electric outlet for their personal nocturnal PAP therapy or charging their cellular device. Children with sensory impairments will benefit from modifications to visual stimuli (e.g., dimmer lights, soothing wall décor), auditory stimuli (e.g., PSG equipment silence capability, allowance of home sound machines for sleep), and tactile stimuli (e.g., optional bedding or linen alternatives, thermostat adjustments). Physical disabilities (e.g., ambulatory vs. wheelchair-bound, ventilator-dependent, tube-fed) should also be considered when setting up the family-centered sleep lab, and extra bedside tables, equipment poles, and room for overnight storage should be readily available for use [1]. Child-friendly labs that accommodate children with very challenging behaviors may need access to "bubble-top cribs" and hospital bed zipper enclosures.

Careful consideration to the sleep hours of the child and subsequent lab staffing needs to take place prior to the appointment in order to have the most optimal sleep study and quality data collection, as well as patient and family experience. However, staff training and lab protocols should allow for modifications to the PSG procedure schedule of events in real time to address any unanticipated needs of children (e.g., breast- or bottle-feeding before, during, after placing sensors, movement breaks, positioning for comfort, time for consoling, habitual co-sleeping). Scheduling and staffing to accommodate the unique sleep periods of children at different ages, as well as anticipating the potential for additional time once present in the lab, are considerations built into the established protocols of a family-centered, child-friendly sleep lab. Table 14.4 summarizes how to make units ready for pediatric studies.

Table 14.4 Preparing your unit for children

Environment and equipment	Scheduling and staffing	Lab oversight
Comfortable and child-friendly Sleep accommodations for parent Options for co-sleeping Child safety (e.g., electric plugs) Noise level, background white noise Pediatric emergency equipment CO_2 monitoring Pediatric sized sensors Pediatric sized masks Pediatric "champion" available to help families plan for a sleep study Sleep study preparation guides Visual guides to explain PSG	Match to usual sleep times for children (longer shifts may be needed) Consider technologist to patient ratios. 1:1 ratio may be needed for hook-up only, then revert to 2:1 for Age < 6 years Comorbidity (e.g., autism, challenging behavior, non-ambulatory) Consider 1:1 tech to patient ratio for the entire procedure for: Challenging nighttime behaviors Non-invasive respiratory support, tracheostomy patients, PAP titration for the child with limited ability to cooperate	Training technical staff on pediatric sleep studies Family-centered atmosphere Pediatric policies, protocols, and procedures Pediatric scoring knowledge Calibration of CO_2 Ensure order processes that identify challenging patients using clinical clues to offer pre-planning Accommodations for a pre-planning phone call or visit Maintain quality controls

During the Procedure

Technologist Considerations: Initial Greeting and Hook-Up

Children coming to the laboratory necessitate attention to their developmental age. Accordingly, age-appropriate greetings and interventions to ease the burden of the procedure can be implemented. Technologists should be aware of "towering over" small children, so when greeting them, getting down to eye-level when possible can be less intimidating. Technologists need to have a warm and friendly demeanor when engaging with children. Their use of age/developmentally appropriate language is needed to introduce the lab and the sensors they will be using. Recommended "child-friendly" language for describing sleep lab sensors is summarized in Table 14.5 [1].

The PSG hook-up involves the entire team (child, parent, and technologist). The technologist can encourage everyone to "help" with the overnight stay. The child can be encouraged to help with the hook-up by putting on fun stickers over the sensors. Praise with each step keeps the patient encouraged and engaged. Making the hook-up child-friendly can also be as simple as changing the sequence of placing leads (e.g., starting low and working toward the head and face) and placing some sensors after sleep. If pre-planned, a child life specialist may join the team to help with the hookup [1].

Strategies for a positive patient experience in the sleep lab are summarized in Table 14.2. One of the best strategies for younger children is distraction with play/games during a procedure [1, 25]. Parents should be encouraged to be distraction coaches for their children during the procedure as they know their children best. Age developmentally appropriate interventions can be implemented during the hook-up (Table 14.6) [32]. Younger children tend to have more distress during procedures and require more distraction/intervention, while older children can implement learned coping strategies [25].

Table 14.5 Child-friendly terminology of polysomnography equipment

PSG sensor	Child-friendly terminology	Child-friendly explanation
Sensor, electrode, and leads (e.g., ECG)	Stickers	Oval stickers the size of a quarter: for your chest, under your chin, and next to your eyes. The stickers have a small wet spot and a snap with a skinny string attached. This will show us to see your heartbeat, muscle tone, and eye movements while you sleep
Leg/limb movement sensors	Movement sticker	A rectangle sticker with a skinny string attached that shows how your legs move while you sleep
EEG electrodes	Tiny gold cups/hair jewelry	These are the size of a pencil eraser with a skinny string attached and they go on your head. They show what your brain is telling your body to do while you sleep
Pulse oximeter	Finger nightlight	This looks like a Band-Aid TM with a tiny red light on it. It goes on your toe or finger and shows how well you are breathing while you sleep (or how much oxygen is in your body for older kids)
Belts	Soft and stretchy bands	One is for your tummy, and one goes around your chest. This shows how you are breathing while you sleep
Snore sensor	Movie star microphone	A small sticker on your neck with a skinny string attached to show if you make any noises while you sleep
Thermistor	Plastic moustache	A small sticker under your nose and over your lip that shows if you are breathing through your nose or your mouth while you sleep
Cannula	Clear plastic moustache	A soft plastic tube that goes under your nose and shows how you breathe through your nose while you sleep
Video camera	Movie star night	You are the movie star tonight! Your doctor sees a movie of you while you sleep. All these things help your doctor know how you sleep and try to figure out how to help you to get a better night's sleep (so that you won't be as tired during the day/learn better in school, etc.)
Air hose/ tubing	Mini hairdryer	It blows cool air and makes a "shoo" sound when the air comes out

Adapted from Zaremba EK et al. Making polysomnography more "child friendly:" a family-centered care approach. Appendix A "Examples of child friendly terminology for PSG sensors" [1]
ECG electrocardiogram, *EEG* electroencephalogram

Safe Sleep Practices

Sleep laboratories must encourage and model safe sleep practices. Children <12 months should be accommodated in a crib with rails up. Sleep positioning should be supine for infants and laboratories should adapt safe sleep practices as outlined by the AAP guidelines [33]. In fact, modeling sleep positioning is helpful for future risk of SIDS and an opportunity for sleep labs to influence safe sleep for public safety [34, 35].

Bed sharing should be discouraged for infants and limited in older children for safety and quality, respectively. When possible, technologists should encourage the parent to distance themselves in a nearby parent bed to preserve sleep quality by minimizing parental movement and disruption. On the other hand, during the PSG, these children may have more difficulty with settling at night and parental presence at sleep onset may be needed. If bed sharing normally occurs at home, it may be difficult to change that long standing routine

Table 14.6 Interventions and coping strategies during a sleep study hookup and pre-sleep

Age	Intervention/distraction/coping strategies
Infants	Swaddling, holding, and rocking during hook-up; breastfeeding; oral sucrose if needed
Toddler	Bubbles, toys with sensory attractions (sound, light, or vibration) in those who enjoy them
Preschool	Reading books, telling stories, music, playing games, electronic apps, and toys
School-aged	Electronic apps, games or toys, interactive books such as seek-and-find books to promote relaxation
Adolescence	Movies/shows, electronic applications, games. Diversionary conversation, guided imagery, deep breathing, and relaxation

Adapted from Duda [32] (intervention portion)

on study night, so best be prepared for co-sleeping in order to reduce anxiety during the PSG procedure. Older children who share their bed at home with a parent may have more difficulty with sleep onset, less regular bedtimes, night-waking, and seeking parents at night [36]. PSG night may not be the night to change that long-standing behavior, so best to have a coping plan for sleeping arrangements for the child and family determined ahead of time. Often, just having the parent nearby in the same room as the child, but in the parent bed, may be sufficient.

The PSG Procedure, Scoring, and PSG Interpretation

Technologists and scorers should be familiar with the pediatric-specific scoring rules for PSG [37]. While the overall approach to sleep scoring is similar to that in adults, a few key differences are noted: sleep staging rules for infants and scoring rules for apneas and hypopneas. In addition, CO_2 measurement is "recommended" for pediatric PSG, while it is "optional" for adult [20]. Finally, the definition of hypoventilation differs in children compared with adults which impacts PSG scoring and interpretation [37].

After the PSG Procedure

Patient Experience

After the sleep study is completed, the team can offer praise and potential rewards as the sensors are removed from the child. Many children have experienced hurt when a band aid is removed, so it is important to eliminate that possibility by using gentle sting-free adhesive remover prior to pulling off tape or sticker-type sensors. Sleep laboratories may have a treasure box or other reward mechanism to help children and families feel satisfied with the completion of the study. Quality measures and feedback should be obtained for each study [1]. Familial satisfaction of the study can be measured by post-study questionnaires. In a telephone survey of families who underwent a PSG, the majority of families reported satisfaction with the PSG. Reasons for patient dissatisfaction included: children crying for a prolonged time, lights interfering with sleep, and pain from sensors or removal of tape [27]. Laboratories need to be prepared to minimize and manage these concerns.

Quality Measures

Sleep laboratories can assess quality using AASM guided processes and outcomes in pediatric OSA. Specifically, processes need to promote these important outcomes: improve detection of childhood OSA and reduce signs and symptoms of OSA [38]. While the AASM accreditation process does not require a specific pediatric accreditation process, there are some who advocate for one in order to maintain adequate quality of care, so this may change in the future [39]. Sleep laboratories should be ready to demonstrate quality metrics for pediatric patients.

Conclusion

PSG in the pediatric population is a need as well as an opportunity for labs to accommodate child-friendly approaches. Sleep laboratories attentive to pediatric operations are better positioned to attract referrals and meet the demands of pediatric sleep services. Some basic tools outlined in this chapter may help guide sleep centers in using the family-centered approach when engaging with children undergoing sleep studies. Implementation of procedures that follow guidelines, quality standards, and responsible care for the pediatric patient will ensure the optimal patient experience while delivering high-quality care.

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Technologies in the Pediatric Sleep Lab: Present and Future

15

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Abbreviations

BMI	Body mass index
CO2	Carbon di Oxide
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electrooculogram
ETCO2	End-tidal CO2
FFT	Fast Fourier transformation
HF	High frequency
HRV	Heart rate variability
HSAT	Home sleep apnea test
LF	Low frequency
OAHI	Obstructive apnea hypopnea index
OSA	Obstructive sleep apnea
PAT	Peripheral arterial tonometry
PSG	Overnight polysomnography
PTT	Pulse transit time
SDB	Sleep disordered breathing
SE	Sleep efficiency
SL	Sleep latency
SpO_2	Arterial pulse oxygen saturation
TCCO2	Transcutaneous CO_2
TST	Total sleep time
VLF	Very low frequency

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Introduction

Assessing sleep is important for the diagnosis of various sleep disorders. However, assessing sleep in children is challenging, especially in young ones and in infants. Various options consists of polysomnography (PSG) with or without CO_2 recording, spectral analysis of EEG, actigraphy, oximetry, pulse transit time, ECG analyses with heart rate variability (HRV), peripheral arterial tonometry (PAT), snoring sound analyses, and even several wearable activity trackers (like wrist watches) or smartphone applications. The following is a focused review of the various technologies with respect to time, development, and advantages/disadvantages of sleep assessments in children.

Polysomnography

Polysomnography (PSG) represents the gold standard for diagnosing sleep disorders in both adults and children and can be performed in children of all ages [1]. Two American Academy of Sleep Medicine (AASM) guidelines previously addressed the role of in-laboratory technician who attended PSG for the diagnosis of sleep disorders, respiratory and non-respiratory, in children [2, 3]. The standard overnight PSG in the pediatric population measures sleep parameters utilizing simultaneous recording of electroencephalogram (EEG), electrooculogram (EOG), chin and leg electromyogram (EMG), electrocardiogram (ECG), respiratory effort at the chest and abdomen, oro-nasal airflow (pressure transducer and/or thermistor), pulse oximetry, and capnometry (end-tidal or transcutaneous measurement).

The polysomnographic montage can be modified according to the patient's suspected disorder [4]. Although this technique provides detailed and highly accurate results, several disadvantages are also worthy of mention. It is necessary for the patient to stay overnight in the sleep laboratory, and a sleep technician is required to continuously attend to the study. Particularly in children, setup can be challenging, as the place-

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ment of numerous electrodes can be difficult in younger children or those with neurodevelopmental problems.

The sleep laboratory should be a non-threatening environment that comfortably accommodates the child and parent during the study. These requirements lead to slow, not scalable, inefficient, and expensive processes that may be of limited access to pediatric populations.

In recent years, there has been increased interest in the use of home sleep apnea tests (HSATs) in children, which can be performed in the home and typically include fewer sensors than PSG. However, because these devices measure fewer physiologic variables than PSG (e.g., absence of capnometry and inability to identify arousals), use of HSATs may lead to underestimation of the presence or severity of disease. Therefore, the absence of any of these measures must be carefully considered when evaluating the validity of HSATs in children.

Ambulatory Unattended Polysomnography

An alternative to in-lab PSG is the ambulatory home-unattended PSG (H-PSG). Use of type 2 devices (fully unattended PSG [5]) has been a subject of debate for years. It is expensive, complex and time-consuming but has the advantages of being a home-based complete sleep study allowing the diagnosis of not only SDB but also numerous other sleep disorders (such as periodic leg movements, circadian rhythm disorders, sleep bruxism, EEG abnormalities or insomnia). These devices are designed to perform similarly as in-laboratory technician attended PSGs, but in an unattended surrounding. Still the hook-up process must be performed by a trained sleep technician (either in the lab or at home), which limits the wider application of this technique. Furthermore, H-PSG also incurs some disadvantages when compared to PSG in the laboratory. H-PSG is not suitable when video recording (parasomnias, nocturnal epilepsy, and complex nocturnal behaviors) is needed, or when CO_2 measurements are required for suspected hypoventilation syndromes. Also, there are difficulties in performing daytime tests (MSLT, MWT) for evaluation of hypersomnolence disorders following H-PSG. There is also a slight discrepancy between the severities of OSA at home and in the sleep lab, such that H-PSG tends to moderately overestimate sleep apnea severity for mild to moderate OSA and to underestimate severity for more severe cases [6–8]. The H-PSG cost is likely to be less than in-lab PSG cost, notably when hospital facility costs are taken into account [8]. The costs are largely related to the necessity for specialized sleep technicians to visit patients' homes.

The ideal future for H-PSG would be to simplify technical aspects, allowing the patient or family member to setup the recording device at home independently and to couple it with remote monitoring in order to obtain optimum quality. A review article analyzing six prospective, randomized, crossover trials comparing H-PSG and in-lab PSG in adults concluded that this complex but comprehensive sleep assessment tool is reliable and accurate to diagnose OSA, in a comfortable way for the patients, where quality of sleep tends to be better. Failure rate of the recordings was low despite the absence of supervision [9]. Although H-PSG is frequently performed in adults, only few studies have been performed in children.

This type of study is potentially difficult in children since they tend to move frequently during sleep, resulting in artifacts, and may remove sensors during the night. In the Tucson Children's Assessment of Sleep Apnea study (TuCASA) which evaluated H-PSG in 157 children aged 5–12 years [10], Goodwin et al. reported excellent results overall (91% technically acceptable studies on the first night and 97% when an additional night was performed), but difficulty with obtaining airflow signals, with only approximately 50% of studies having artifact-free airflow signals for at least 6 hours. As part of the Caffeine for Apnea of Prematurity-Sleep trial (CAP-S), a large international follow-up study evaluating the feasibility of H-PSG in 201 school-aged children living in Canada and Australia [11], Marcus et al. also concluded that comprehensive, unattended, ambulatory PSG is feasible, technically adequate, and well tolerated in school-aged children when performed under research conditions. Artifact-free signals were obtained for ≥75% of recording time in more than 92% of subjects, with the exception of nasal pressure, which was satisfactory for ≥75% of recording time in only 67% of the subjects. However, some measure of airflow was present for ≥75% of recording time in 96% of subjects. Brockman et al. evaluated the feasibility of unattended polysomnography performed at home versus in the hospital in 101 children, aged newborn to 15 years [12]. Technically acceptable recordings were obtained in 93% of subjects; the likelihood of a study being technically adequate was not influenced by whether the study was performed in the hospital or at home.

Yet, the AASM task force on HSATs for the diagnosis of OSA in children [13] noted that there was insufficient data on type 2 portable devices to recommend these types of studies for children and that more research need to be done before a change of recommendations is justified.

Oximetry

Oximetry is a technique used for measuring the oxygen saturation (SpO_2) in the blood, commonly performed by pulse oximetry, analyzing the arterial oxygen saturation of the patient using a sensor usually placed on the finger measuring the absorption spectra of hemoglobin. Nocturnal oximetry has long been proposed as a screening tool for pediatric OSAS due to its reliability, simplicity, and suitability for children. In a large cross-sectional study of 349 children (6

mo to 18 y) referred to a pediatric sleep laboratory for possible OSAS, Brouillette et al. have demonstrated that oximetry has been successfully implemented as an abbreviated and low-cost testing modality for the diagnosis of OSAS in childhood [14]. A positive pulse oximetry result (at least three clusters of desaturation events, and at least three SpO_2 drops to less than 90%) increased the probability of a patient having OSA from 60% to 97%. A negative or inconclusive oximetry trend graph did not rule out OSA; indeed, referred children with negative pulse oximetry results had a 47% probability of having OSA on PSG [14]. In a subsequent study by Nixon et al. [15], the McGill oximetry scoring system was introduced to describe levels of severity of nocturnal hypoxemia, ranging from 1 (normal or inconclusive oximetry) to 4 (severely abnormal oximetry) based on numbers of clusters of desaturation events and SpO_2 drops to less than 90%. Later on, Pavone et al. [16] demonstrated in a prospective cohort study that the night to night agreement for abnormal oximetry and for McGill oximetry score was 97% and 89.9%, respectively. In a review article, evaluating 25 original studies, Kaditis et al. [17] summarized the utility of oximetry as a diagnostic tool for OSA in children. A positive pulse oximetry result (McGill oximetry score >1) is indicative of moderate-to-severe OSAS. Given the high positive predictive value (close to 100%), carying out a PSG does not appear to be required to refer the patient for adenotonsillectomy in cases of positive oximetry. An ODI4 >2 episodes/h combined with OSAS symptoms also exhibits high positive predictive value for AHI >1 episode/h. However, if the oximetry recording is negative or inconclusive, the clinical suspicion of OSAS should be assessed by nocturnal PSG. Thus, nocturnal oximetry emerges as a valuable, low-cost, and easy-to-use diagnostic modality to identify OSAS and facilitate treatment decisions among children with clear symptoms of SDB or when PSG is not available.

Another review article by Kaditis et al. [18], which summarized the conclusions of a European Respiratory Society Task Force on the diagnosis and management of obstructive sleep disordered breathing (SDB) in childhood aged 2–18 years, also concluded that when PSG is not fiscally or practically feasible, nocturnal oximetry should be used instead. Development of well-validated algorithms for the interpretation of nocturnal oximetry recordings could potentially improve further the value and usefulness of this approach as a diagnostic modality for OSAS diagnosis. Efforts in this direction using artificial intelligence tools have begun to emerge in the last several years [19–23].

Capnography

CO_2 monitoring during PSG is an important parameter for evaluating the adequacy of ventilation, and without using capnography such alterations can be readily missed. Traditionally, invasive procedures including arterial blood gases (ABG) were needed to assess the $PaCO_2$; however, advances in technology have enabled clinicians to obtain estimates of $PaCO_2$ noninvasively. The most commonly used noninvasive methods for assessing $PaCO_2$ include end-tidal CO_2 ($ETCO_2$) and transcutaneous CO_2 ($TCCO_2$) monitoring.

$ETCO_2$ devices sample exhaled air and provide continuous breath-by-breath analysis of CO_2. Inaccurate values can be seen with mouth breathing or with obstruction of the sampling line. In general, the $ETCO_2$ values tend to slightly underestimate the $PaCO_2$ (approximately 2–5 mmHg below the arterial $PaCO_2$ level). Transcutaneous methods warm the skin locally inducing hyperemia, and CO_2 then dissolves across the dermal structures and is measured by a skin electrode. As a result, $TCCO_2$ values do not change rapidly with each breath; however, they do provide overall trends with respect to $PaCO_2$ changes. Typically, $TCCO_2$ measurements are 4–5 mmHg higher than those obtained by ABG. Another consideration with $TCCO_2$ monitoring is the potential for skin lesions and/or burn from the warm electrode. In general, manufacturer recommendations are to reposition the skin electrode every 4 h to prevent thermal injury and poor signals.

In a review of the recent literature, Gerdung et al. [24] suggested that transcutaneous methods correlate strongly with $PaCO_2$ levels and can provide an accurate surrogate in replacement of ABGs. End-tidal methods provide timely information that can be used to assess hypoventilation; however, they display more variability, especially in patients with increased dead space and small tidal volumes. Given the benefits of CO_2 monitoring and the importance of assessing for the presence of hypercapnia, noninvasive continuous CO_2 monitoring should be considered for all patients undergoing polysomnography. In infants and children with upper airway obstruction, severe alveolar hypoventilation may occur during sleep without observable apnea or hypopnea. Measuring expired CO_2 can provide evidence for hypoventilation not detectable using oro-nasal airflow. Paruthi et al. [25] have demonstrated very good $EtCO_2$ waveforms as being available for 91% of children with suspected OSAS studied at accredited pediatric sleep laboratories, even in the presence of adenotonsillar hypertrophy. About 5% of children were observed to have alveolar hypoventilation in the absence of elevated AHI levels, providing evidence that CO_2 levels correlate poorly with other PSG indices. Such findings further emphasize the independent information that CO_2 provides on ventilation. The AASM Manual for Scoring of Sleep and Associated Events recommends monitoring for hypoventilation during diagnostic PSG in children [26]. Nasal exhaled $ETCO_2$ by capnography is the most commonly used surrogate for CO_2 measurement in children. $TCCO_2$ monitors might be valuable in patients in whom $ETCO_2$ is not accurate, such as infants or patients with parenchymal lung disease. A PSG pattern of obstructive hypoventilation, defined

as at least 25% of total sleep time with hypercapnia ($PaCO_2 > 50$ mmHg) in association with other clinical sleep-disordered breathing findings, is a commonly used diagnostic criterion for pediatric obstructive sleep apnea syndrome (OSAS) [27]. Thus, in infants and children sleep assessment, when respiratory disorder is an option, measuring CO_2 levels is essential.

EEG Spectral Analysis

The theoretical basis for spectral estimation is Fourier analysis, which is a mathematical method that decomposes a time-domain signal into a series of pure sine waves of different wavelengths. This is particularly useful in the analysis of EEG recordings, where the signal represents the combined activity of multiple networks of neurons throughout the brain that oscillate at different frequencies. Thus, the EEG can be mathematically decomposed into an infinite number of pure sinusoidal components, each of a different frequency, which when added together yield the original signal [28]. Just as a digitized signal is an approximation of its original analog signal, a fast Fourier transform (FFT) of that digitized signal is an approximation of these frequency components. EEG analysis with FFT is not free of technical problems, which can be minimized by choosing appropriate FFT parameters.

Conventional methods for assessing the disruption of sleep quality involve visual scoring of the EEG and an assessment of sleep architecture. Past studies have indicated that unlike adults, the sleep architecture of children with SDB seems to be relatively preserved, with only about 50% of apneic events terminating with a cortical arousal (as defined by adult criteria). However, it remains possible that analyses based on conventional criteria for adults are not sensitive enough for detecting sleep disturbance in children. Spectral analysis of the EEG is a technique that is readily available and has previously been used to examine sleep EEG in infants [29] and children [30, 31]. Spectral analysis may provide a more sensitive measure of sleep disruption at respiratory event termination in children with SDB than conventional sleep architecture or arousal indices. Yang et al. [32] demonstrated that when analyzed across a whole night of sleep, the results of visual scoring and EEG spectral analysis of sleep in children with SDB are not different from children without SDB and are well correlated with conventional measures of sleep architecture. In a later study, Yang et al. [33] also demonstrated that there were no significant changes in absolute EEG spectral power distribution in visually scored subcortical activations and non-arousals, despite clear reductions in delta and theta power during cortical arousals. These findings suggest that clinical visual scoring can accurately distinguish cortical arousals from subcortical activations and does not underestimate the number of cortical arousals that occur in children at respiratory event terminations. Thus, EEG power spectral analysis supports the findings from conventional measures that children with OSA do not show substantial differences in sleep quality across the night. However, in special cases, spectral analysis of the EEG may help in quantifying the depth of sleep. For example, the delta power band was very high in diabetic children demonstrating nocturnal hypoglycemia [34]. Thus, in some circumstances, quantifying the various frequency powers by EEG spectral analyses may help in better understanding the depth of sleep.

Actigraphy

Actigraphy is an objective, non-intrusive method for estimating sleep-wake patterns using activity-based monitoring. Sleep actigraphs are generally watch-shaped and worn on the non-dominant wrist for older children and on the ankle or calf for infants. The conventional actigraphy unit comprises an accelerometer-based motion sensor, a microprocessor and memory for data storage. Actigraphy can be a particularly valuable methodology for use among pediatric populations, where the common reliance on parental report alone may limit the range and accuracy of information about the child's sleep. Actigraphy devices are useful for assessing habitual sleep–wake cycles and sleep quality and maintenance, and within the clinical field, it is useful for identifying circadian disorders, insomnia, and hypersomnia and for documenting treatment response in children with sleep disorders. Despite the widespread use of actigraphy for sleep assessment, there is no standard in actigraphy sleep scoring rules. The most commonly used algorithms in pediatric actigraphy, as reviewed by Meltzer et al. [35], are the Sadeh algorithm [36] and the algorithm of Cole et al. [37]. Other main challenges with actigraphy usage, as discussed by Galland et al. [38], are the need for parental adherence to complete 24-h sleep–wake diaries over several consecutive days, the uncertainty regarding the placement of the device (wrist opposed to leg) depending on age or motor milestones, and the identification of day-time naps.

A recent AASM systematic review [39] supports the utility of actigraphy as a relatively low-cost, objective measure of sleep patterns and certain estimated sleep parameters in both children and adults, across a wide range of sleep disorders (particularly circadian dysrhythmia and insomnia), when conducted using validated algorithms with attention to sensitivity settings and standardized scoring procedures. The AASM clinical practice guideline [40] recommends that clinicians use actigraphy to estimate sleep parameters in adult and pediatric patients with insomnia disorder and circadian rhythm sleep-wake disorder. It is also suggested that clinicians use actigraphy to monitor total sleep time prior to test-

ing with the multiple sleep latency test in adult and pediatric patients with suspected central disorders of hypersomnolence. In healthy adults or children, as well as in those with insomnia and circadian disorders, the accuracy of actigraphs in detecting sleep vs wakefulness is considered very high. It obviously has the additional advantage of measuring several consecutive nights up to several weeks. However, due to movements at termination of SDB events and in patients with movement disorders, actigraphs may be insufficient and inaccurate. Some unique actigraphy algorithms were developed especially for SDB patients and are integrated in ambulatory devices which consist of actigraphy for detection of sleep apnea (detailed below).

Autonomic Signal Assessment

Although measurement of central nervous system (i.e., EEG) is considered superior and most common for sleep analyses in general, and sleep-disordered breathing in particular, in the recent two decades, extensive studies of the autonomic nervous system showed that both sleep and sleep-disordered breathing may be accurately and reliably assessed based on changes in autonomic signals. Although extensive data were collected in adults, some data are also available in children. Generally, during wakefulness there is a high sympathetic dominance, and as sleep deepens, the parasympathetic system becomes more dominant. During REM sleep, there is a unique pattern of activity of both sympathetic and parasympathetic systems. Since in each sleep stage there is a different autonomic activity, with different sympathetic/parasympathetic balance, assessing it may be the basis for sleep staging. As for SDB, since the termination of each SDB event is associated with abrupt increases in sympathetic activity, assessing changes in autonomic outputs may pave the way to diagnose SDB based on autonomic nervous system signals. In the following sections, we will review some methods to assess sleep and SDB based on autonomic signals in adults and in children. Such methods include heart rate variability analyses, peripheral arterial tone analyses, and pulse transit time analyses.

ECG Analyses: HRV

The heart rhythm is under the control of the autonomic nervous system predominantly by its efferent sympathetic and vagal parasympathetic activities affecting the sinus node, which are modulated by central brainstem (vasomotor and respiratory centers) and peripheral oscillators (respiratory modulation, thoracic pressure, and blood pressure modulation) [41]. Analysis of the heart rate variability (HRV) is a well-established technique for studying the modulatory effects of neural mechanisms on the sinus node, and two major components are seen: high frequency (HF, 0.15–0.40 Hz) and low frequency (LF, 0.04–0.15 Hz). The vagal activity is the major contributor to the HF component while the LF component is a relative marker of sympathetic modulation or a parameter including both vagal and sympathetic effects. More recently, the ratio between LF and HF powers has been suggested as a better marker of the sympathetic modulation, and the very low frequency (VLF, 0.003–0.04 Hz) has been measured, although the meaning of this component is still controversial. In general, VLF is considered as correlated with changes in parasympathetic activation. All of these markers (LF power, HF power, and LF to HF ratio) have been shown to change with both age and sleep stage [42]. Yet, at this time, it is still uncommon and not applicable to stage sleep and draw a hypnogram based solely on HRV data, although this may be developed in the future. However, assessing HRV may provide some indication regarding the general quantity and quality of sleep. For example, long sleep latency in children has been shown to be associated with lower HF (parasympathetic activity), while nocturnal awakenings, sleep latency, low sleep efficiency, and low sleep duration were related to higher LF/HF (sympathetic/parasympathetic balance) [43]. Thus, low sleep quality and/or short sleep duration is associated with changes in HRV (sympathetic over parasympathetic dominance). This has been shown in several studies in both healthy children and some specific patient groups such as children with autism spectrum disorder [44–47]. It should be mentioned that there are several other different methodologies to analyze and assess heart rate variability [48–54].

Since the major reason for referral for sleep studies is suspected SDB or OSA, many studies have investigated whether these are related to HRV [55–61]. In a study of 48 young adults (mean age 37 ± 11 years old, range 4–53), Gong et al. [57] have shown that the AHI was significantly associated with relative powers of very low frequency (VLF [%]) ($r = 0.641$, $P = 0.001$), and the ratio between low frequency and high frequency powers (LF/HF) ($r = 0.545$, $P = 0.049$), and inversely related to power of high frequency(HF[%]) ($r = -0.586$, $P = 0.002$). They concluded that HRV analysis is a powerful tool to screen for OSAHS [45]. Several other studies have also supported the accuracy of assessing HRV as a screening or even diagnostic tool for SDB, although the results were not always consistent [56, 59, 60]. Walter et al. [59] showed that HRV was altered in 80 children with SDB who were 7–12 years, and similarly Nisbet et al. reported the same results in 120 children with SDB [60]. Both reported that HF power was reduced in children with moderate to severe OSA. Thus, childhood OSA is indeed associated with HRV changes, but the precise or most sensitive and specific change is yet to be determined. Moreover, as an indication that the SDB affects the HRV, it has been shown in 18 chil-

dren with OSAS, aged 4.9 ± 2.4 years who were studied before and after adenotonsillectomy, that in all sleep stages the LF/HF ratio was significantly decreased (1.6 ± 2.7 to 0.6 ± 0.5 [light sleep]; 1.2 ± 1.6 to 0.5 ± 0.6 [deep sleep]; and 3.0 ± 5.4 to 1.4 ± 1.7 [REM sleep]) [61]. Thus, it appears that treatment of OSA in children reduces the sympathetic predominance seen prior to treatment. Currently, HRV changes are correlative to SDB and change back with treatment, but diagnosis of OSA cannot be made based on HRV analysis alone. Interestingly, some researchers found that analyzing the pulse rate variability (PRV) measured by pulse photoplethysmography is even more accurate than the HRV for the detection of sleep apnea [62]. They suggested that it is better to measure the peripheral pulse rather than the ECG. Indeed, measuring the peripheral blood flow by a novel technique based on autonomic signals was developed: The Peripheral Arterial Tonometry (PAT).

PAT

The PAT signal measures the finger's arterial pulsatile volume changes, by a unique plethysmography. These arterial tone changes are regulated by the alpha-adrenergic innervation of the smooth muscles of the finger's vasculature, and thus reflect sympathetic nervous system activities. Based on this signal, along with several additional signals, the WatchPAT device has been developed [63]. This ambulatory diagnostic device is based predominantly on four channels: PAT, pulse rate, oxygen saturation, and actigraphy, with additional optional channels such as snoring sound and body position. Based on analyses of these signals, it has been shown in adults to be accurate and reliable in detecting wakefulness vs sleep [64], sleep stages [65–68], arousals [69, 70], and respiratory indices for the diagnosis of sleep apnea [71–79]. It indirectly detects apnea/hypopnea events by identifying surges of sympathetic activation associated with the termination of respiratory events. This PAT information is further combined with heart rate and pulse oximetry data. The automatic algorithm of the system detects respiratory events and calculates the PAT respiratory disturbance index (PRDI). There are also some studies of this system in children, although substantially less than in adults [80, 81]. In a pioneer study of PAT in children, Tauman et al. [80] have shown that in 40 children aged 7.6 ± 2.6 years (range: 5.7–16.5 years), the PAT device identified pathologic arousals indexes (area under the curve 0.79, $P = 0.002$). Thirty-five percent of respiratory events (e.g., obstructive apnea or hypopnea) were associated with a visual electroencephalographic arousal, compared to 92% being associated with PAT attenuation events [80]. They concluded that in children the PAT need not be necessarily accurate in detecting arousals as in adults, but it detects autonomic arousals, the importance of which is yet to be explored. In a subsequent study from the same group on 10 healthy children, they showed that the sensitivity and specificity of the PAT in recognizing EEG arousals were 0.92 and 0.19, respectively, again indicating that EEG arousals are detected by PAT, but the latter also detects many additional arousals – autonomic (subcortical) arousals [82]. In a later study by Serra et al. [81], of the 28 children aged 5–12 years (mean 7.75 ± 1.69) with clinical symptoms of SDB, in whom pulse oximetry was negative, 60.7% (17 of 28) were positive. They concluded that PAT is superior to oximetry in detecting pediatric SDB. In a Chinese study of 50 children aged 3–11 years who were studied simultaneously with PSG and WatchPAT, the sensitivity and specificity of detecting AHI > 5/h were 0.952 and 0.858, respectively, with children older than 6 years showing better results than those younger than 6 years old [83]. In a very recent study of 36 children with suspected OSA, 10.2 ± 1.8 years old (range 8–15 years), PSG and WatchPAT were simultaneously recorded in the sleep lab [84]. Agreement between PSG and WP in detecting AHI was excellent (correlation of 0.89; $P < 0.001$). An AHI of 3.5 events/h and above provided the highest accuracy (76.9% sensitivity and 78.3% specificity). The authors concluded that data are still sparse, although in their study PAT had good agreement with PSG and may have a potential for ambulatory recordings in children. By similar methodology of simultaneous recording of PSG and WP in 38 adolescents (mean age 15.1 ± 1.4 years), Choi et al. [85] showed that the correlation between AHI measured by PSG and PAT was very high ($r = 0.945$, $P < 0.001$), and they concluded that the WP200 may be a clinically reliable tool for diagnosing OSA in adolescents [85]. Indeed, the FDA has recently approved the WatchPAT for usage as a diagnostic tool for OSA in adolescents older than 12 years old [86]. However, as reviewed here, the data are still relatively sparse, and definitely more studies are needed in this field. It seems that PAT can reasonably detect sleep stages and OSA in adolescents, but in children more data are required.

PTT

Another methodology assessing autonomic function which has been relatively widely studied is the Pulse Transit Time (PTT). PTT refers to the time a pulse wave takes to travel between two arterial sites, usually between the heart and the periphery. The speed at which this arterial pressure wave travels is directly proportional to BP. An increase in vascular tone and stiffness causes the PTT to shorten. Conversely, when vascular tone decreases, PTT increases. At this time, this measure is mostly used in research and less frequently clinically. It may serve as a surrogate noninvasive quantification of changes in arterial tone, BP, and BP variability. It is affected by both vascular tone and by the left ventricular pre-

ejection period. Since upper airway obstructive events in sleeping children frequently terminate without visible cortical EEG arousal, measuring autonomic arousals may be specifically valuable in children. The PTT may serve as noninvasive marker for subcortical arousals. Very commonly, respiratory arousals from sleep result in a drop in the PTT [87]. In an initial study, 24 symptomatic children and 10 normal controls underwent PSG including esophageal manometry and PTT measurements. The authors found that apnea, hypopnea, and respiratory effort-related arousal events terminated in a PTT arousal 91%, 83%, and 80% of the time, while in an EEG arousal only 55%, 51%, and 43% of the time (all $p < 0.05$), respectively. They concluded that in children PTT arousals are a more sensitive measure of obstructive events than visible EEG arousals [87]. Similar results were reported by several additional groups, indicating the superiority of PTT in children, specifically for detecting microarousals and respiratory-related autonomic arousals [88–90]. In a direct comparison between PAT and PTT in healthy children, O'Brien and Gozal reported that the sensitivity of PTT and PAT for recognizing arousals was 0.96 and 0.92, respectively, and the specificity 0.30 and 0.19, respectively [82]. Furthermore, one work has suggested that a model based on PTT may accurately detect central apneas in children [91]. Moreover, a combination of two autonomic methods such as PTT and HRV may substantially increase the sensitivity and specificity of detecting respiratory events based on autonomic signals [92, 93]. Some additional and more recent studies have shown that the correlation and agreement of detecting SDB based on PTT compared to PSG is reasonable and suggested that utilizing PTT may be used for a screening tool for OSA and SDB [94, 95]. As for the distinction between obstructive and central events, this latter study reported that PTT was highly sensitive (81%) but poorly specific (46%) in scoring 58 apneas as obstructive. PTT was less sensitive (46%) but highly specific (81%) to score 56 apneas as central [95]. The authors concluded that PTT may be used as an additional tool to respiratory inductance plethysmography to improve the scoring of apneas as obstructive or central in children. The high percentage of artifact is a limitation of PTT [95]. A recent meta-analysis which included all studies that used PTT as a diagnostic tool during sleep in infants, children, or adolescents found 21 articles which met inclusion criteria. PTT was used alongside polysomnography (PSG) in all 21 studies. Several of these supported the potential of PTT to detect central apneic events in both infants and children and obstructive events in children, with implications for use as a screening tool for OSA, albeit with some limitations [96]. One study showed significant negative correlations between PTT and systolic blood pressure. The authors concluded that PTT is simple to execute, cost-effective to run, and more tolerable than alternatives to measuring continuous BP in children, but its potential as a core clinical tool remains to be determined [96]. To summarize, the PTT has a very good correlation and can well detect SDB infants and children. It is currently used mostly for research, but in the future may be utilized for clinical purposes. Despite potentially good discrimination of autonomic signals between the various sleep stages, the single device which is in wide clinical usage based on this is the WatchPat. Potentially, for future challenge, a device which combines several autonomic data sources (i.e., PAT+PTT + HRV) may be a very powerful tool to detect sleep, sleep stages, and SDB in children.

Sound Analyses

Interest in breath sounds and the acoustic characteristics of snores began more than two decades ago [97]. Since then, there have been several reports attempting to shed light on respiratory problems based on analyses of acoustic signals recorded from various points on the chest wall and trachea. The pioneer study by Ben Israel and colleagues in 2012 [98] was the first time that analysis of snoring sounds alone has been shown to be accurate in quantifying the severity of SDB, expressed as the AHI. The authors studied 90 consecutive patients evaluated at the sleep lab for suspected OSA and simultaneously recorded their sleep by both regular PSG channels and by snoring sound investigation. The first 60 patients served as a training set in order to develop the algorithm for scoring apnea and hypopnea, while the remaining 30 patients were blindly analyzed by both methods to validate the algorithm for quantifying AHI. Results showed good agreement between both methods, as expressed by correlation analysis, Bland Altman analysis, and White Westbrook analysis. The major weakness of that study was that comparisons were based on whole night recordings rather than on single events analyses. Thus, it is possible that some events were overscored, and some were underscored with a reasonable overnight average, telling us less about event-by-event comparisons. However, the concept of detecting SDB events based solely on snoring signal recording from 1 meter above the patient's bed was an interesting and promising approach, with high potential for clinical applications. Since then quite many studies reported good sensitivity and specificity in detecting OSA and/or its severity in adults based on snoring sound analyses [99, 100]. Despite the ease and noninvasive nature of assessing snoring sounds, surprisingly the data in children are limited. In an early study of 29 children utilizing home audiotapes scored by seven observers, Lamm et al. [101] showed that the median sensitivity of the audiotape as a predictor of OSAS was 71% (range 43–86%) and the median specificity was 80% (range 67–80%) [101]. The presence of a struggle sound on the audiotape was the parameter most predictive of OSAS. There was a good level of

agreement among the seven audiotape observers, as demonstrated by a mean and range kappa statistic of 0.70 (0.50–0.93) for the 21 pairs of observers. Using a clinical score to predict OSAS, the sensitivity was 46% and the specificity was 83%. They conclude that findings on a home audiotape of children can be suggestive of OSAS but are not sufficiently specific to reliably distinguish primary snoring from OSAS [89]. In a recent combined study of predominantly adults (n = 113) and some children (n = 7), acoustic sound analyses have been shown to accurately classify patients into one of four groups (normal, mild, moderate, or severe OSA group). They reported an accuracy of 88.3% in the four-group classification and an accuracy of 92.5% in the binary classification (yes or no SDB). The authors suggested that experimental evaluation demonstrated that the models trained on the proposed acoustic biomarkers can be used to estimate the severity of SDB. They concluded that acoustic biomarkers may be useful to accurately predict the severity of SDB based on the patient's breathing sounds during sleep, without conducting attended full-night PSG. Their study implied that any device with a microphone, such as a smartphone, could be potentially utilized outside specialized facilities as a screening tool for detecting SDB, but again, they had only seven participants less than 18 years old [102]. Thus, we can conclude that acoustic snoring sound analyses may have a good potential for clinical application to detect SDB in children, but many more studies will be needed to translate this potential into real clinical life.

Wrist Consumer-Wearable Activity Trackers

Technological advancements, together with the increased awareness by the public on how important sleep is, led to the development of simple devices placed on the wrist that can potentially assess sleep in the patients' home on a nightly basis. These are typically consumer-wearable activity trackers, electronic devices used for monitoring fitness and other health-related metrics, based on movements and/or biosignals such as pulse. Commercial examples for such devices include Fitbit One, Beddit Pro, Fitbit Zip, Jawbone UP, Misfit Shine, Nike Fuelband, Striiv Smart Pedometer, and Withings Pulse [103, 104]. A recent meta-analysis reviewing 22 studies using such devices indicated higher validity of steps assessment but lower validity for sleep estimation. The evidence reviewed indicated high inter-device reliability for steps, distance, energy expenditure, and sleep for certain Fitbit models [105], but not for all models, and accuracy was not satisfactory. In a study of 40 healthy young adults (19 female) aged 18–30 years, studying the validity of five wearable devices – Basis Health Tracker, Misfit Shine, Fitbit Flex, Withings Pulse O_2, and a research-based actigraph, Actiwatch Spectrum, relative to PSG – the authors reported no difference and strong correlation of total sleep time as measured by the various devices compared to PSG [106]. However, sleep efficiency differed from PSG for Withings, Misfit, Fitbit, and Basis, while Actiwatch mean values did not differ from that of PSG. Light sleep time differed from PSG for all devices, while deep sleep time did not differ from PSG only for Basis [106]. Another study assessed the Fitbit Flex and actigraph (Actiwatch-2) during in-laboratory PSG in 21 patients with depression. They found that the Fitbit Flex demonstrated significant limitations in quantifying sleep and wake, relative to PSG [107]. It significantly overestimated sleep time and sleep-efficiency, while displaying poor ability to correctly identify wake epochs. In the sensitive setting, it significantly underestimated sleep time and efficiency relative to PSG. The authors concluded that it cannot be an adequate substitute for PSG in patients with depression [107]. Comparing Fitbit Flex device with polysomnography on an epoch by epoch basis, Kang et al. reported that agreement was high in good sleepers but significantly lower in insomnia patients [108]. Similar conclusions were reported by other studies of adults, reporting various levels of sensitivity, specificity, and agreement between these activity trackers and a validated method for recording sleep [109–111].

The data regarding these commercial devices are less extensively explored or validated in children. The few studies that were published reported conflicting results. For example, from one hand in a research of 63 children aged 3–17 years studied simultaneously by PSG in the lab, two different actigraphs, and Fitbit Ultra, it has been shown that compared to PSG, the Normal Fitbit Ultra mode demonstrated good sensitivity (0.86) and accuracy (0.84), but poor specificity (0.52); conversely, the Sensitive Fitbit Ultra mode demonstrated adequate specificity (0.79), but inadequate sensitivity (0.70) and accuracy (0.71). Compared to PSG, the Fitbit Ultra significantly overestimated TST (41 min) and SE (8%) in Normal mode and underestimated TST (105 min) and SE (21%) in Sensitive mode. Similar differences were found between Fitbit Ultra (both modes) and both brands of actigraphs tested [112]. The authors concluded that despite its low cost and ease of use for consumers, neither sleep-recording mode of the Fitbit Ultra accelerometer provided clinically comparable results to PSG. Thus, pediatric sleep researchers and clinicians should be cautious about substituting these devices for validated actigraphs, with a significant risk of either overestimating or underestimating outcome data including total sleep time and sleep efficiency [112]. On the other hand, in a different study, during an overnight laboratory sleep recording in 32 healthy adolescents, sleep and HR measures were compared between FitbitChargeHR™ and PSG. Epoch-by-epoch analysis showed that FitbitChargeHR™ had high overall accuracy (91%), high sensitivity (97%) in detecting sleep, and poor specificity

(42%) in detecting wake on a min-to-min basis. On average, FitbitChargeHR™ significantly but negligibly overestimated total sleep time by 8 min and sleep efficiency by 1.8% and underestimated wake after sleep onset by 5.6 min (statistically significant). The authors concluded that FitbitChargeHR™ showed good agreement with PSG and ECG in measuring sleep and HR during sleep, supporting its use in assessing sleep and cardiac function in healthy adolescents [113]. However, these accurate results were reported only for healthy adolescents and only in one comparative well-planned study. For children aged 3–18 years with SDB, a recent study reported again poor results. TST was significantly overestimated using the Fitbit Charge (by an average of 30 min), while wake time was underestimated (by 23 min). All measures showed a lack of concordance between the Fitbit Charge and PSG [114]. Thus, to conclude this section clearly, further studies are needed to assess the reliability of these commercial trackers in children and adolescents, both healthy and those with sleep disorders, and over prolonged periods of time. Currently the data do not support evidence to use these devices as a substitute for sleep recording, definitely not PSG PAT or approved recorders, and not even actigraphy. Perhaps with improved algorithm and better combination of movement and pulse rate recordings, the accuracy will improve, allowing the clinical usage of these devices.

Smart Phone Applications

The final section in this review on technologies as sleep recorders will focus on smartphone technologies. Several smartphone applications are available with attempts to improve sleep, lifestyle, to guide for relaxation, etc. Our scope in this section is to review only those applications that are intent on evaluating sleep or identifying sleep disorders. For example, in a study by Bhat et al., 20 volunteers with no previously diagnosed sleep disorders underwent in-laboratory PSG while simultaneously using a smartphone app (Azumio, Inc., Palo Alto, CA, USA) for iPhones [115]. There was no correlation between PSG and app-based sleep efficiency, light sleep percentage, deep sleep percentage, or sleep latency. The app significantly underestimated light sleep by 27.9%, significantly overestimated deep sleep by 11.1%, and significantly overestimated sleep latency by 15.6 min [115]. The app had high sensitivity but poor specificity in detecting sleep (89.9% and 50%, respectively). Conversely, Tal et al. [116] in their study on a smartphone application of "Earlysense" – a contact-free system placed below the mattress which senses heart rate and transmit the data to the smartphone – found, in a direct comparison to PSG on an epoch by epoch basis in 63 adult subjects, a linear correlation between TST measured by the sensor and TST determined by PSG, with a coefficient of 0.98 (R = 0.87) [116]. They concluded that the system showed good sleep staging capability with improved performance over accelerometer-based apps and collected additional physiological information on heart rate and respiratory rate [116].

A few studies evaluated smartphone applications in children as well. For example, the Phone Oximeter is a device integrating a pulse oximeter with a smartphone [117]. It has been studied on 143 children who were referred for a sleep lab evaluation compared to overnight standard pulse oximetry and PSG. The authors reported a good balance between sensitivity (88.4%) and specificity (83.6%) of this device in recognizing children with SDB. They suggested that it can help in screening children for SDB and be used for multiple night recordings, but not as a diagnostic tool [117]. The same group based on probably the same patients reported that they developed a model to detect epochs with SDB based on the smartphone-based pulse oximetry data together with analysis on the pulse rate variability driven from it [118]. The model provided a median accuracy of 74%, sensitivity of 75%, and specificity of 73%, based on an epoch by epoch comparison to PSG [118]. They added that the performance might decrease when analyzing children with a low number of SDB events. Similarly, studying 25 children aged 2–14 years, Patel et al. found that there was no correlation between total sleep time or sleep latency between the app and PSG. No combination of PSG sleep stages corresponded with app "stages" in a meaningful way [119]. However, substantially better results were reported by Toon et al. [120]. Studying 78 Children and adolescents with suspected SDB, simultaneously with Actiwatch, a commercial wrist-based device and a smartphone with a sleep application placed near their right shoulder, during their diagnostic PSG, the authors found no differences in mean TST, WASO, or SE between PSG and actigraphy or PSG and UP! [120]. They concluded that when compared to PSG, the smartphone application was analogous to Actiwatch2 and may have some clinical utility in children with SDB. So, it is hard to conclude at this time regarding these devices. It seems that with sensing pulse and perhaps snoring sounds and movements, with improved algorithms, there is a potential for these devices to be a reasonable surrogate of sleep and sleep quality for individuals (both children and adults). However, at this time, the data are really too sparse to draw conclusions. There are no data in infants or young children, and the data for others are specific either for healthy or only SDB participants. Much more research and development are needed to understand the role of these Apps, which currently are publicly used but whose accuracy is controversial. As for sleep disorders diagnoses, it seems that at this time the PSG is still the best and more reliable option, with some indications to clinically use actigraphy and autonomic-based devices (PAT).

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Upper Airway Imaging in Pediatric Obstructive Sleep Apnea

16

Monique A. L. J. Slaats and Stijn L. Verhulst

Abbreviations

2D	2-dimensional
3D	3-dimensional
AHI	Apnea hypopnea index
AN	Adenoidal-nasopharyngeal
ATE	Adenotonsillectomy
BMI	Body-mass index
CAD	Computer aided design
CBCT	Cone beam computed tomography
CFD	Computational fluid dynamics
CI	Confidence interval
CSA	Cross-sectional area
CT	Computed tomography
DS	Down syndrome
LR-OCT	Long-range optical coherence tomography
mCSA	Minimal cross-sectional area
MCW	Mandibular cortical width
MDCT	Multiple detector computed tomography MRI magnetic resonance imaging
mSv	Milisievert
oAHI	Obstructive apnea hypopnea index
OCT	Optical coherence tomography
OSA	Obstructive sleep apnea
PSG	Polysomnography
RDI	Respiratory disturbance index
SNA	Sella, nasion, and A-point
SNB	Sella, nasion, and B-point
T1	Longitudinal relaxation time
T2	Transverse relaxation time
TP	Tonsillar-pharyngeal
UA	Upper airway

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Introduction

Adenotonsillar hypertrophy is the most important predisposing factor in children with obstructive sleep apnea (OSA) [1–3]. The association between the subjective evaluation of tonsillar size and OSA severity as determined by polysomnography is weak. High-quality studies suggest no association [4–6]. Additionally, the pathogenesis of upper airway (UA) narrowing is more complex in children with risk factors such as obesity, craniofacial malformations, Down syndrome (DS), or neuromuscular disorders [7].

The first line treatment of pediatric OSA is adenotonsillectomy (ATE) [7, 8]. There are other non-surgical and surgical options for treatment that are used in residual OSA or complex OSA (children with risk factors) [7]. Treatment outcomes for ATE have been extensively studied and there is a high incidence of residual OSA after ATE, especially in children with risk factors such as obesity (up to 59%) and Down syndrome (up to 87%) [9–18]. Commonly described anatomical causes of persistent disease include mandibular deficiency, glossoptosis, macroglossia, soft palate enlargement, lymphoid hypertrophy surrounding the UA, and inferior displacement of the hyoid bone or abnormal neuromuscular control [3, 17, 19, 20].

Polysomnography gives the diagnosis of OSA but not the anatomical level of obstruction in the UA. In a time of personalized medicine, it seems crucial to couple the exact individual anatomical risk factor with the most appropriate treatment to avoid unnecessary risks and ineffective surgeries. Several studies investigated the role of UA imaging as noninvasive evaluation of UA obstruction. These techniques include lateral neck radiographs, cephalometry, computerized tomography (CT), cone beam CT, magnetic resonance imaging (MRI) and post-processing of these images using computational fluid dynamics (CFD) for functional respiratory imaging (FRI), long-range optical coherence tomography (LR-OCT), and drug induced sleep (sedation) endoscopy (DISE). Every technique has advantages and disadvantages, while an overview is presented in Table 16.1 [21].

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Table 16.1 Advantages and disadvantages of imaging techniques

	Advantages	Disadvantages
Lateral neck radiography	Fast procedure Widely accessible Low cost	Awake (Low) radiation 2D Limited differentiation of soft tissue
Cephalometry	No sedation Low cost	Awake (Low) radiation 2D Need for expertise Limited differentiation of soft tissue
(Cine) magnetic resonance imaging (MRI)	No radiation Sleep-like state 3D High resolution and high contrast visualizations of the UA Visualize multiple levels of obstruction	Sedation Not widely available Expensive
Computerized tomography (CT)	No sedation Widely accessible 3D	Radiation Limited differentiation of soft tissue Expensive
Cone beam CT	No sedation Low cost 3D	(Low) radiation Not widely accessible Limited differentiation of soft tissue
Functional imaging	No sedation (CT) 3D Differentiation of soft tissue (MRI) Sleep-like state (MRI)	Radiation (CT) Limited differentiation of soft tissue (CT images) Not widely available Expensive
Long-range optical coherence tomography	No sedation No radiation 3D Low cost	Not widely available Limited differentiation of soft tissue
Drug induced sleep (sedation) endoscopy	Fast procedure before surgery No radiation Sleep-like state Live video Visualize multiple levels of obstruction Supine position	Sedation Not widely available Cannot simultaneously view multiple levels of obstruction Need for expertise

This chapter reviews studies using imaging techniques that may further enhance our understanding about the mechanisms of UA obstruction leading to pediatric OSA and could assist in the selection of treatment.

Lateral Neck Radiography

Lateral neck radiography is relatively simple, is widely accessible, and has a low cost. However, the images are taken in an upright position in awake patients. One study in adults investigated the difference between supine and upright lateral cephalograms and observed no additional anatomical differences [22]. Another study in five adults with OSA measured the total volume and cross-sectional area (CSA) change in supine versus upright position by computerized tomography (CT). They concluded that the airway was significantly smaller when patients were in a supine position [23]. There are currently no such studies available in children. Furthermore, the airway is depicted in a two-dimensional (2D) view, resulting in a possible loss of information.

Another disadvantage is that this technique utilizes ionizing radiation. Effective dose is expressed in Sieverts which is a single dose parameter that reflects the risk of exposure in terms of whole-body exposure. An annual effective dose from natural background radiation is about 2.5–3 millisievert (mSv), the worldwide average natural dose is about 2.4 mSv per year. A lateral neck X-ray requires minimal radiation with an average of 0.2 millisievert (mSv) (reported variation in the literature ranges between 0.07 and 0.3 mSv) [24–26].

The obtained lateral neck radiography shows the vertebrae, the oral and nasal airways, the nasopharynx, part of the trachea, the epiglottis, the soft tissue in front of the vertebrae, and the adenoids and tonsils. Some ratios can be determined using different methods, the most frequently analyzed radiographic parameter in studies is the adenoidal-nasopharyngeal (AN) ratio (Fig. 16.1) [2, 3, 27–35]. However, a systematic review concluded that there are conflicting outcomes because of methodological problems that limit the applicability of these results to clinical decision-making [36]. A cohort study evaluated the ability of lateral radiography to assess adenoid hypertrophy in 72 children

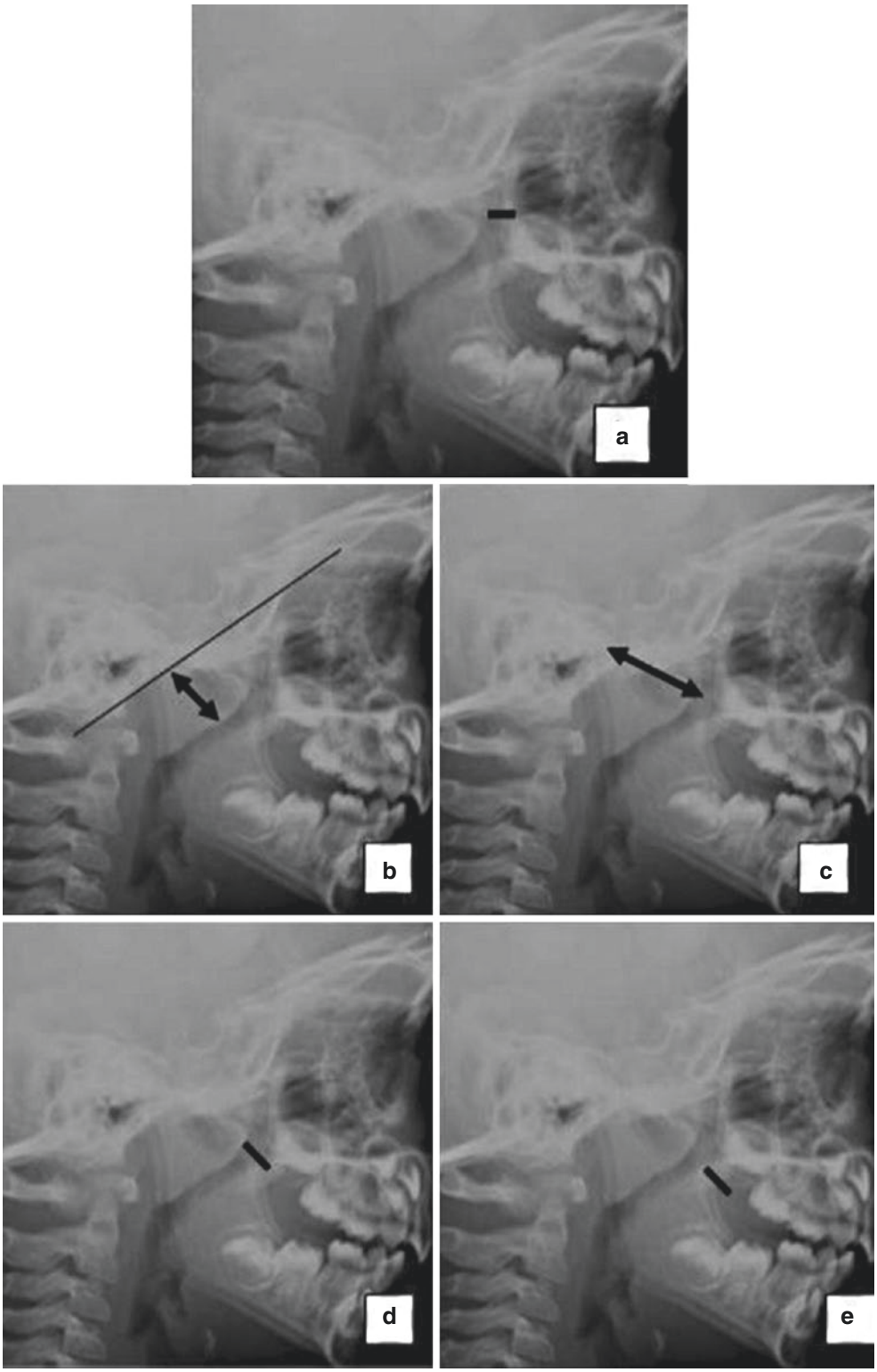

Fig. 16.1 (**a**–**e**) Lateral X-ray. (**a**) Hibbert's method: the distance from the anterior adenoid to the post-maxillary antrum. (**b**) The distance along a perpendicular line from the pharyngeal tubercle on the base of the skull to the adenoidal convexity (maximal adenoidal thickness). (**c**) Distance measured along a line from the posterior–superior edge of the hard palate to the spheno- occipital synchondrosis on the base of the skull. (**d**) Minimal width of the airway immediately behind the soft palate at (e). (**e**) Width of the supero-anterior soft palate 1 cm below the hard palate (half a centimeter in children younger than 3 years old). (From Waters et al. [37]. Reprinted with permission from John Wiley and Sons)

using four different methods [37]. Twenty-six children (36.1%) without OSA and only nine children (12.5%) with severe OSA were studied. The best correlations between OSA severity and radiography were found using the anterior airway measurement (the distance from the anterior adenoid to the post-maxillary antrum; method by Hibbert et al.) [33]. Using the definition of obstructive apnea/hypoapnea index (oAHI) >1 with adjustment for sex, age, body-mass index (BMI), the method of e (presented in Fig. 16.1) provided the largest receiver operating characteristic (ROC) area (0.775) for predicting OSA, with a sensitivity of 86.7% and a specificity of 55.6%.

Additionally, there are a few more studies that show correlations between lateral X-ray findings and OSA severity while one study failed to show a correlation [2, 3, 28, 29, 35]. Brooks et al. reported a correlation between obstructive apneas and AN ratio (according to the method described by Fujioka) in a study of 33 children. Children with OSA had a larger AN ratio (0.83 ± 0.3 vs. 0.69 ± 0.03; $p < 0.003$), resulting in reasonable, although suboptimal, positive and negative predictive values of 71% and 75%, respectively [28]. Li et al. investigated the value of tonsillar–pharyngeal (TP) ratio as a measure of tonsillar enlargement in 35 children (mean age of 6.2 (4–10) years old) with suspected OSA. There was a significant correlation between the TP ratio and the AHI ($r = 0.8$; $p < 0.001$) and oxygen desaturation index ($r = 0.51$; $p = 0.002$). However, there was no correlation between tonsil size and the TP ratio. The ROC curve analysis revealed that a TP ratio cut off of 0.5 was optimal for predicting severe OSA, with the area under the curve being 1.0. The corresponding sensitivity and specificity were 95.8% and 81.8%, respectively, while the positive and negative predictive values were 92.0% and 90.0%, respectively [3]. Xu et al. determined whether parents' observation, clinical examination, and lateral upper airway radio- graph were useful in diagnosing OSA in 50 children (OSA group; $n = 31$, mean age 7.8 ± 3.2 years old and primary snoring group; $n = 19$, mean age 8.1 ± 3.7 years old). There was a sensitivity of 81% and specificity of 58% for UA narrowing on lateral X-ray by AN ratio for predicting OSA. Secondly, combining UA narrowing with mouth breathing, nocturnal enuresis, observed apnea during sleep, intrusive naps, mouth breathing, enlarged tonsils, and radiologic features of narrowing increased the positive predictive value to 73% and the negative predictive value to 80% [2].

Currently, there are no studies that have investigated whether lateral neck radiography can predict the effect of treatment.

In summary, this technique has relatively good predictive values for the diagnosis of OSA. In view of the advantages associated with this technique, further studies in other and larger populations are warranted. Furthermore, the predictive value can be improved by incorporating certain clinical predictors such as obesity, mouth breathing, nocturnal enuresis, observed apnea during sleep, intrusive naps, and enlarged tonsils on clinical examination.

Cephalometry

Cephalometry involves a standardized lateral radiographic view of the head and neck with more calculations of markers, distances, and ratios (Fig. 16.2). Therefore, there is a need for an experienced radiologist. The method shows skeletal (including mandibular and hyoid position) and soft-tissue (tongue and soft palate) UA structures. The advantages and disadvantages are comparable to lateral neck X-ray. Due to several measurements, the position of the head is critical. The following angles are commonly described in cephalometric studies: maxillary protrusion is expressed by the sella, nasion, and A-point (SNA) angle, the mandibular protrusion is expressed by the sella, nasion, and B-point (SNB) and point A nasion to B (ANB) angle is the difference of the SNA and SNB angles. In sagittal direction, an increase of the ANB angle describes a skeletal Class II malocclusion and in the vertical direction it shows a mandibular clockward rotation [38–40].

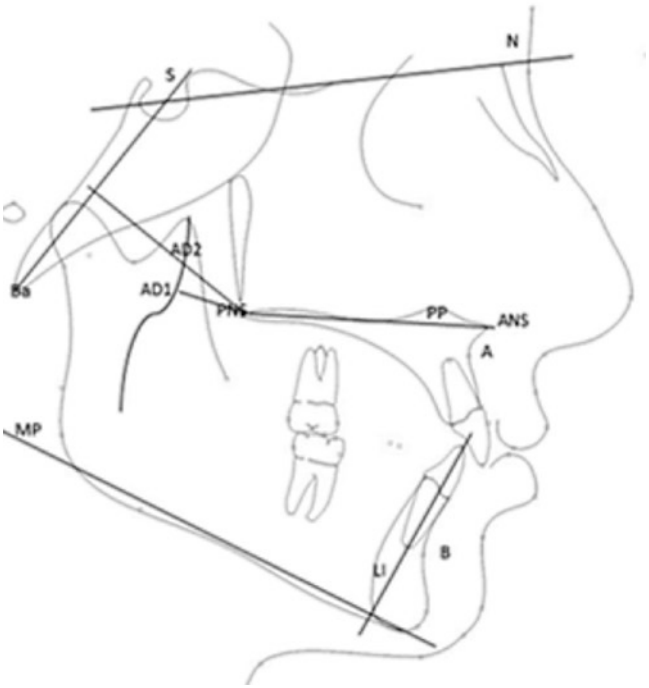

Fig. 16.2 Cephalometric references and landmarks used in the meta-analysis. S Sella, N nasion, Ba basion, ANS anterior nasal spine, PNS posterior nasal spine, PP palatal plane, A A-point, B B-point, MP mandibular plane (gonion-menton), PNS-AD1 distance from PNS to the nearest adenoid tissue measured along the line PNS- Ba, PNS-AD2 distance from PNS to the nearest adenoid tissue measured along the line perpendicular to S-Ba, LI, long axis of the mandibular incisor. (From Katyal et al. [48]. Copyright © 2013 American Association of Orthodontists. Published by Mosby, Inc. All rights reserved. Reprinted with permission from Elsevier)

Some case-control studies in adults investigated the usefulness of cephalometric measurements in OSA patients. A meta-analysis in adults has shown a strong correlation between OSA severity and mandibular plane hyperdivergence. However, this correlation was not strong enough to indicate that craniofacial morphology had a direct causal effect in the development of OSA in adults [41].

Several case series investigated the influence of skeletal abnormality in children and suggested that children with mouth breathing, adenotonsillar hypertrophy, or sleep-disordered breathing have a retropositioned mandible, nar-

row maxilla, increased lower anterior face height, increased mandibular plane angle, inferior position of the hyoid bone, and smaller airway space [42–46]. Several studies have also investigated whether cephalometry could predict the diagnosis of Obstructive Sleep Apnea Syndrome (OSAS). Two systematic reviews investigated the association between maxillomandibular discrepancy and OSA. They suggested that children with OSA have more skeletal Class II mandibular growth direction compared to normal children. However, an increased ANB angle of less than 2° in children with OSA and primary snoring, compared with the controls, might not be clinically significant. Evidence for a direct causal relationship between craniofacial structure and OSA could not be supported by these meta-analyses [47, 48].

Galeotti et al. analyzed the correlation between cephalometric variables and OSA severity in 62 children. They reported a correlation between increased oAHI and skeletal discrepancy expressed by ANB angle. Therefore, one could hypothesize that more severe OSA leads to an increased mouth-breathing pattern that in turn strongly affects skeletal growth with Class II skeletal malocclusion and hyperdivergent growth pattern in children [49]. Pirila-Parkkinen et al. investigated the capability of 2D lateral cephalography in recognizing pharyngeal obstruction compared to 3D MRI and clinical observation in 36 children with OSA. The study showed an association between the cephalometric nasopharyngeal and retropalatal airway measurements and MRI findings. However, retroglossal pharyngeal measurements by cephalography did not correlate with MRI variables. Palatal tonsils mainly are situated in the retroglossal region and because of their lateral position; enlarged tonsils can cause the transversal narrowing of the retroglossal airway, which is not detectable on the anteroposterior view of the cephalogram [50].

Similar as for the lateral neck radiography, there are currently no studies which used cephalometry to predict the effect of treatment in pediatric OSA.

In summary, it remains unclear if cephalometry can be a valid diagnostic tool and there are no studies using cephalometry to predict treatment outcome.

Magnetic Resonance Imaging (MRI)

MRI is another method to localize and diagnose the site of UA obstruction (Fig. 16.3). It is accurate, reproducible, and there is no need for radiation. Furthermore, it is possible to have moving images during sleep by cine MRI. However, MRI is expensive, and requires a long examination time, resulting in a higher probability of motion artifacts. That is why it often requires sedation that puts the patient in a state of mimicking physiological sleep as closely as possible, but this also makes it more invasive. Children with OSA are sensitive to the respiratory depressant effects of sedative and hypnotic drugs that affect the UA dynamics, including the possibility of increasing UA obstruction. Dexmedetomidine provides an acceptable level of sedation and less need for airway support during MRI studies [51–55].

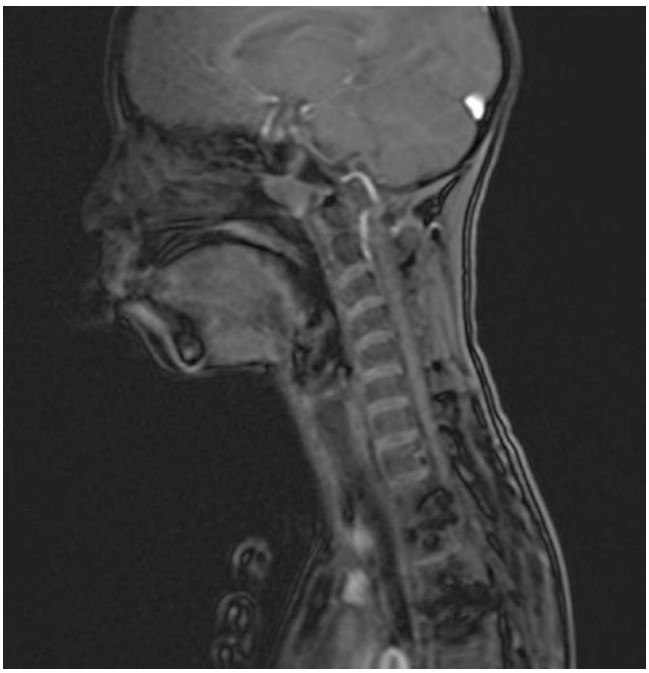

Fig. 16.3 UA imaging by MRI. Several studies have investigated the relationship between UA anatomy assessed by MRI and OSA severity

Normal-Weight Children

A case-control study investigated anatomical risk factors involved in the development of pediatric OSA in 40 normal-weight children (20 with OSA and 20 controls) by MRI. MRI performed in supine position, without sedation. Volumetric measurements were made from T1-weighted images and T2-weigthed images and were used to evaluate the lymphoid tissues. This study showed a significantly smaller UA volume (1.4 ± 0.7 cm^3 versus 1.6 ± 0.7 cm^3) and midsagittal nasopharyngeal airway (0.7 ± 0.2 cm^3 versus 1.2 ± 0.4 cm^3) in OSA patients. The axial cross-sectional area of the oropharyngeal airway was also smaller (0.5 ± 0.3 cm^3 versus 0.8 ± 0.5 cm^3). Thereby, children with OSA also had a significantly lager soft palate volume and midsagittal palate volume. Additionally, the adenoids and tonsils were considerably larger in the OSA group. Concerning skeletal structure, the study showed that the OSA group had a smaller mandibular volume and a lower vertical position of the hyoid bone [56]. Another study investigated the UA in sedated children with OSA by MRI. In a first study, they compared the UA structure in 18 young children with OSA (mean age

4.8 years) and 18 controls (mean age 4.9 years). They showed a correlation between increased tonsil and adenoid volume and AHI in sedated children [57]. Another study investigated 10 children with adenotonsillar hypertrophy and OSA and 10 controls. Children with OSA had a smaller UA volume, particularly during inspiration, whereas dilatation occurred during expiration. The OSA group had larger adenoid and tonsils in comparison with the control group. The volumes of both mandible and tongue were similar in both groups. The study concluded that the adenoid and tonsils in children with moderate OSA restrict the UA. Additionally, the study found that further UA restriction in OSA patients could be caused by enlargement of the soft palate [58].

Obese Children

Arens et al. investigated the body fat composition and UA structure in 44 obese children (22 with OSA and 20 controls). UA lymphoid hypertrophy, parapharyngeal fat pads, and abdominal visceral fat were significantly increased in obese children with OSA. In regression analysis, only lymphoid tissue correlated with OSA severity [20]. Another study evaluated the frequency of enlarged lingual tonsils in 71 obese children with sagittal fast spin-echo inversion recovery imaging. They concluded that obese children had a high frequency of enlargement of the lingual tonsils with a significantly higher prevalence in those who had previously undergone tonsillectomy. Enlarged lingual tonsils may thus play a role in the pathogenesis of persistent obstructive sleep apnea in obese children [59].

Nandalike et al. evaluated how ATE affects anatomical factors of airway obstruction in 27 obese children with OSA. All underwent polysomnography (PSG) and MRI during wakefulness before and after ATE. ATE was associated with a significant increase in soft palate volume, tongue size, and head and neck subcutaneous fat tissue. A complete resolution of OSA only occurred in 44% of cases and complete resolution was achieved in only 22% of children with severe OSA. Residual OSA was associated with substantial residual adenoid tissue, an increase in the volume of the soft palate and, to a lesser extent, the increased volume of the tongue [60].

Children with DS

Children with DS have certain anatomical factors that predispose for a higher risk of OSA: underdeveloped midface and mandibular hypoplasia, macroglossia, posterior-placed tongue, hypotonia, smaller upper airway, lymphoid hyperplasia, and obesity [51, 61–63].

Two studies used imaging in children with DS to investigate UA morphology. Uong et al. investigated the anatomical differences by MRI (size and shape of the upper airway in relation to surrounding tissue) between 11 children with DS without OSA and 14 controls without DS and OSA (mean age of 3 years old). Adenoid and tonsil volume were significantly smaller in the DS children. However, tongue, soft-palate, pterygoid, and parapharyngeal fat pads were similar. There was a smaller upper airway size in DS children, the authors suggested that this was caused by soft tissue crowding within a smaller mid- and lower face skeleton [63]. Another imaging study investigated the stiffness of the airway wall from MRI by a noninvasive method in 21 children with DS and OSA. Airway changes were evaluated by continuous positive airway pressure (CPAP). The localized airway and tissue elasticity were found to increase with increasing OSA severity. They concluded that elasticity-based patient phenotyping could potentially assist clinicians in decision making concerning the needed CPAP pressure [64].

Donnelly et al. concluded that persistent OSA in DS has multiple causes. The most common causes include macroglossia, glossoptosis, recurrent enlargement of the adenoids, and enlarged lingual tonsils [17].

Cine MRI

Cine MRI is a high-resolution imaging method that captures the dynamic movement of the UA in a sedated child. These dynamic images can show both the degree and the direction of airway collapse (anterior-posterior or circumferential). Thereby, it can sometimes show compensating of the tongue or jaw thrusting during the period of obstruction. It is performed for approximately 30 seconds at each level with a rate of imaging of about three images per second [65–69].

Donnelly et al. investigated 16 young patients with OSA and 16 without airway problems or airway diseases. These researchers showed several differences concerning dynamic airway motion [67]. OSA patients were much more likely to demonstrate intermittent collapses of the nasopharynx and exclusively demonstrated intermittent collapse of the hypopharynx. The mean change in diameter of the nasopharynx and hypopharynx, implicating a more compliant UA, was also significantly greater in the OSA group. Abbott et al. investigated 31 children (mean age of 11.3 years) with OSA and 21 control children (mean age of 3.5 years). They included OSA subjects with the following predispositions to obstruction: craniofacial anomalies, DS, persistent OSA, and pre-operative evaluation to complex airway surgery. All children underwent transverse phase gradient-echo cine MRI imaging of the hypopharynx with sedation. The airway

volumes were obtained by a k-means clustering algorithm and the airway wall motion was described. The study showed airway distention and airway collapse in children with OSA. Airway volume oscillated in both groups, but the amplitude was much larger in the OSA group. A clear limitation of this study is the fact that the mean age of the control group was much lower than the mean age of the OSA patients. A concern about the large difference in age is that UA size may increase by age. Interestingly, the size of UA volume in some of the youngest subjects with OSA had volumes as large as some of the oldest in the control group. In this study, airway volume did not correlate significantly with age in either the control group or the children with OSA [70].

In summary, MRI gives a better insight into UA anatomy because it provides a detailed assessment of the UA as the pharyngeal size and soft tissue anatomy (including adipose tissue). Several studies involving MRI have shown detailed correlations with OSA severity or the identification of critical anatomical sites. However, more research is needed for sensitivity or specificity for diagnosis and prediction of treatment outcome.

Computerized Tomography (CT)

CT is a fast, noninvasive technique to visualize the UA and is available in the majority of institutions (Fig. 16.4). CT images can be taken during wakefulness and sleep. A major disadvantage of CT is radiation. The radiation dose for a neck CT is approximately 3 mSv for adults [24, 71, 72]. Recently, cine CT or ultra-fast CT has been used more frequently and can obtain multiple images with a lower radiation dose. Fleck et al. evaluated the cine (dynamic 3D) CT technique for the UA in six children with OSA and compared the required radiation dose between these children. The radiation from a low-dose CT scan was between 0.08 and 0.27 mSv [73].

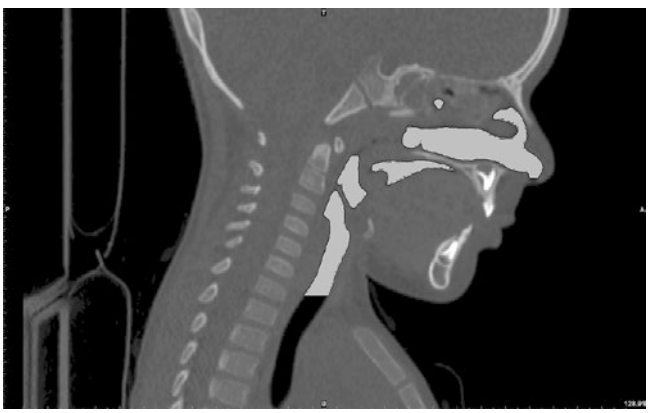

Fig. 16.4 CT image of the UA

The UA from nares to trachea can be reconstructed into three-dimensional (3D) models and subdivided into five zones for measuring volumes of different parts in the UA and CSA (Figs. 16.5 and 16.6).

Only three studies investigated the utility of CT in pediatric OSA. Van Holsbeke et al. investigated whether anatomical and functional properties of the airway were correlated with OSA severity in 33 children with OSA. The study concluded that children with OSA had a lower volume of UA zone 3, the overlap region of adenoids and tonsils, and a lower mean CSA of the UA. No correlation was found between the clinical scores of UA patency (Brodsky and Mallampati scoring system) and OSA severity indicating that imaging might be more powerful in the assessment of UA patency [74]. Slaats et al. further investigated whether functional respiratory imaging (FRI) by CT could provide more information about UA characteristics in 91 normal-weight children with OSA mainly to predict treatment outcome. They concluded, comparable with Van Holsbeke et al., which a smaller overlap region and a more concave shape of the UA correlated with more severe OSA. There was also no correlation with clinical examination and OSA severity. UA volumes could not predict treatment outcome in this study [75].

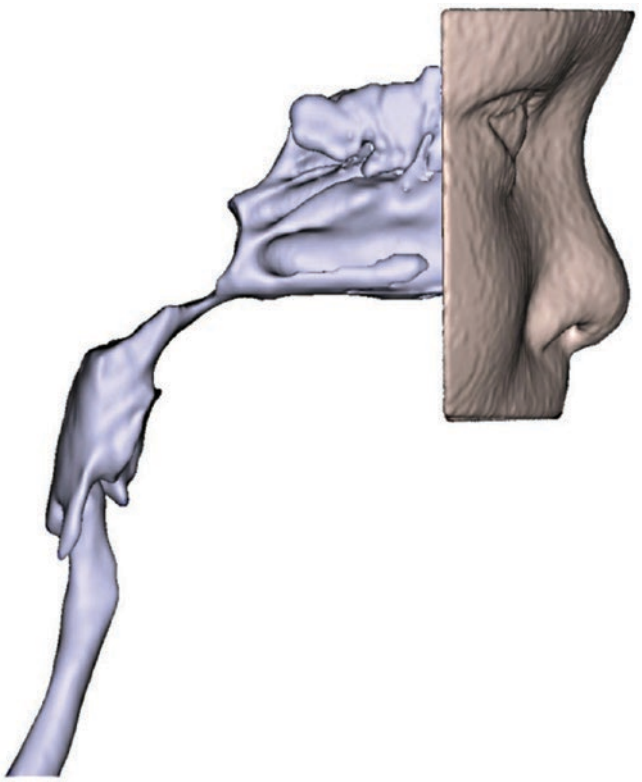

Fig. 16.5 Reconstructed into 3D model of the upper airway. (From Slaats et al. [75]. Reprinted with permission from John Wiley and Sons)

Another study about CT images and pediatric OSA was performed in children with DS. Slaats et al. characterized treatment outcome after ATE in 33 young children with DS and OSA by UA imaging (CT images). At baseline, children with more severe OSA had a smaller minimal passage through the upper airway. After treatment, persistent OSA was seen in 79% of the children; however, 79% had a decrease of >50% in oAHI after treatment. Children with less favorable response had a smaller volume of the zones below the tonsils, which is probably due to enlargement of the lingual tonsils, glossoptosis, or macroglossia that is not treated by ATE (Fig. 16.7). In conclusion, this study suggests that UA imaging could have an influence in treatment selection in children with DS and OSA. Exact cut-off values are needed to be confirmed by larger studies [76].

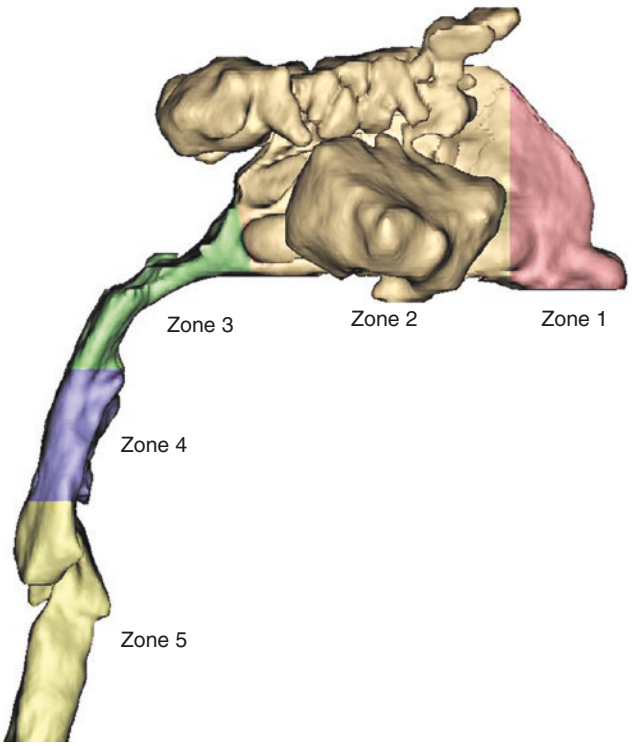

Fig. 16.6 3D model of the upper airway divided into five zones. Zone 1 = nostril to bottom of inferior turbinate; Zone 2 = bottom of inferior turbinate to choanae; Zone 3 = choanae to tip of uvula; Zone 4 = uvula to epiglottis; Zone 5 = epiglottis to the first vertebra. (From Slaats et al. [75]. Reprinted with permission from John Wiley and Sons)

In conclusion, CT also provides a detailed analysis of the anatomy. CT studies have shown detailed correlations with OSA severity or the identification of critical anatomical sites without sensitivity or specificity reported. One study indicates that UA imaging could have a role in treatment selection in children with DS and OSA. However, this was a very small study group and exact cut-off values are needed to be confirmed by larger studies. More research is needed in this group because DS is an important risk factor for OSA with a high incidence of residual OSA.

Cone Beam CT (CBCT)

Cone beam computed tomography (CBCT) is a low-dose radiation 3D imaging technique. A disadvantage is that it shows limited differentiation of soft tissue. CBCT is not available in all hospitals. However, it is widely available in dental and oral medicine. For example, it has been used for many maxillofacial applications such as for implant site imaging and treatment planning for craniofacial surgery and orthodontics [77].

The radiation dose is lower compared to normal CT and is more like that of low dose protocol CT. When used in maxillofacial imaging, CBCT produces an eight- to tenfold lower effective dose than a conventional CT examination using standard protocols [78–80].

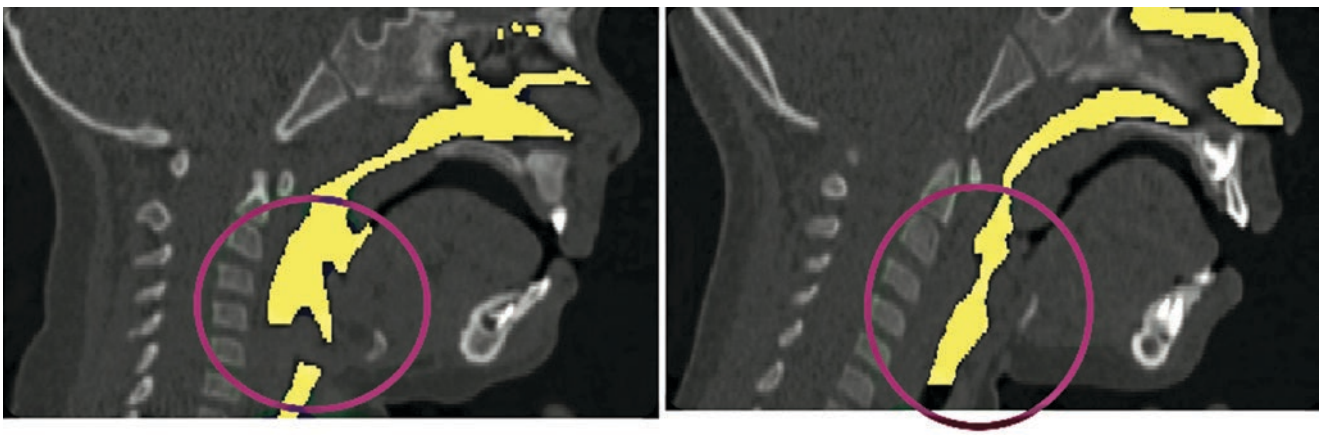

Fig. 16.7 Left: image of a child's UA with a decrease of more than 50% in oAHI after ATE Right: decrease of less than 50% in oAHI after ATE. (From Slaats et al. [76]. Copyright © 2018 American Academy of Sleep Medicine, reprinted with permission)

Some studies in adults have demonstrated that CBCT produces extremely accurate anatomical representations [81–83]. A review of the use of CBCT in adult patients with OSA concluded that there is a need for more research, but that the use of CBCT for both pre-operative planning and for postoperative evaluation of therapeutic interventions is likely to become increasingly important [84]. There are only a few studies in pediatric OSA. Eimar et al. investigated in 96 children diagnosed with or at risk of SDB, particularly OSA, whether these children had a reduced bone density estimated by mandibular cortical width (MCW) on CBCT images [85]. MCW demonstrates the highest sensitivity and specificity for detection of reduced bone density [86]. It represents the distance, in millimeters, between the lower borders of the mandible to the superior margin of the mandible cortex. MCW values were significantly lower in OSA children (MCW = 2.9 ± 0.6 mm) compared to control children (MCW = 3.5 ± 0.6 mm; $P = 0.002$). This finding may reflect alterations in bone homeostasis [85].

A case–control study verified the differences in the volume and areas of the UA between 27 children with persistent OSA after AT and a 20 sex-age matched healthy control group by CBCT. Children with OSA had a significant narrowing in the nasopharynx and in the lower portion of the UA. This result demonstrated that other factors than adenotonsillar hypertrophy, such as craniofacial abnormalities, could play a role in the pathogenesis of OSA [87]. Alsufyani et al. evaluated with a clinical pilot study the anatomical changes that occur in the UA before and after AT using CBCT in 12 children. Secondly, they evaluated whether changes in airway reflects in the quality of life [88]. Quality of life was tested by the OSA-18 questionnaire. Only UA constriction and patency correlated with changes in OSA-18. Airway patency gained by at least 150% and constriction relief by at least 15% showed marked improvement in OSA-18 by 40–55%. A limitation of this study was the method for diagnosis of OSA. This was based on history of nocturnal symptoms, physical examination, overnight pulse oximetry, and pediatric sleep questionnaire (PSQ-22) instead of the gold-standard polysomnography [7, 89]. Another limitation of this study was that the analysis did not include other OSA parameters such as saturation and a sleep study after treatment [89].

In conclusion, CBCT provides a detailed analysis of the anatomy by low dose protocol. Unfortunately, there are only a few studies in children that make it unclear if CBCT can be a diagnostic tool or predict treatment outcome.

Functional Respiratory Imaging (FRI)

FRI is a relatively new method that can simulate airflow dynamics and the resulting pressure distribution by anatomical narrowing by computational fluid dynamics (CFD). The 3D model (Fig. 16.6) is used for analysis of anatomical parameters, volume meshing (representation of interior volume), and CFD [74–76, 90]. Exact details about CFD are described in the article of Slaats et al. [75]. A few studies investigated the utility of CFD in children with OSA. Preliminary data showed that FRI could identify differences in the UA of children with residual OSA and correlates well with OSA severity than parameters obtained from physical examination [74].

Normal-Weight Children

One study compared CFD data in three children with OSA and three controls. The results suggested that pharyngeal airway shape in children with OSA significantly affects internal pressure distribution compared to nasal resistance [91]. A recent study investigated whether FRI by CT images could provide more information about UA characteristics in 91 normal-weight children with OSA without risk factors, mainly to predict treatment outcome. Imaging parameters correlated with OSA severity at baseline more than the tonsil score obtained by clinical assessment: a smaller overlap region of tonsils/adenoids, a higher resistance, and a more concave shape of the UA correlated with more severe OSA. Thereby, a less constricted airway, as characterized by both a higher conductance and a lower tonsil score, was associated with a less favorable response to (adeno)tonsillectomy. In conclusion, both UA conductance and the tonsil score predicted treatment response [75].

Obese Children

Mihaescu et al. evaluated computational simulation of pre- and post-AT by MRI in an obese child. A significant pressure drop was observed at the site of minimum CSA. There was an increase in airway CSA of the retropalatal pharynx. These findings indicate that ATE is associated with changes in flow characteristics [92]. A retrospective cohort study investigated whether CFD model endpoints correlated with treatment response of ATE in 10 obese children. MRI and CFD data before and after surgery were utilized to calculate the velocity and air pressure distribution. They reported more significant correlations between decreased OSA severity and CFD than with UA anatomical parameters [93].

Children with DS

Only one study investigated whether UA imaging combined with CFD could characterize treatment outcome in children with DS and OSA. They concluded that there was no extra value of CFD in prediction of treatment outcome. However,

this was a relatively small study and further studies including larger samples of patients before treatment are needed to validate a model to predict treatment outcome [76].

In conclusion, FRI is a relatively new promising method that may can help in treatment selection. There are only a few studies in children; most of the studies are small. A prospective cohort study concluded that FRI and clinical assessment predicted treatment outcome in children without risk factors. More research is needed to investigate the predictive value in children with DS and obese children because the percentage of residual OSA is higher in these populations.

(Long-Range) Optical Coherence Tomography

Optical coherence tomography (OCT) is another new noninvasive imaging modality to image the UA [94]. This is a diagnostic evaluation without radiation and sedation. This tool utilizes a broadband light source to produce high-resolution cross-sectional images of tissue components with a resolution of 10 μm. The UA can be scanned in approximately 20–40 seconds. The produced images are similar in resolution to those of conventional microscopy. Ridgway et al. investigated the utility of OCT in characterizing the microanatomy of the UA in 15 children in vivo. They concluded that this technique identifies the epithelium and lamina propria [95]. Long-range OCT (LR-OCT) puts the emphasis on a longer range capture of airway wall location by a rotary fiber optic for helical scan to quantify size and shape of hollow organs such as the UA to generate accurate 3D reconstructions (Fig. 16.8). CFD simulations can be performed on these models [96–98].

Two studies investigated the value of OCT in children with OSA. Lazarow et al. investigated the feasibility of LR-OCT to identify airway narrowing in children who underwent ATE. They demonstrated that CSAs were measurably larger in 46 children after ATE [97]. Another study presented the first, airflow simulations by CFD in pediatric airways. They assessed the effect of three realistic airway curvatures in eight children on predicted airway resistance by CFD (before and after ATE). The LR-OCT imaging was incorporated into airway endoscopy exams conducted as part of the standard care before and after surgery. The imaging selection was based on the best signal-to-noise ratio, the best contrast between air and tissues, and the least loss of structure. The airway surface was subjected to a bending algorithm implemented in the software to cure the vertical reconstruction. The algorithm was based on planar curves to sagittal CT and MRI imaged of three normal children. CSA values were obtained by using the area calculation function in Mimics™. Minimal CSA (mCSA) values were calculated by averaging the areas of five consecutive CSAs corresponding to a 1- or 2- mm thick slab of the OCT data of the smallest CSA value. Steady-state, inspiratory airflow simulations were conducted under laminar conditions, along with turbulent simulations by CFD. In this study, CFD findings corroborated that postoperative airway resistance was significantly less compared to pre-operative data. The individual resistances did not vary for different curvatures. This suggests that airway curvature may not be predictive of surgical effects on airway resistance [98].

In summary, this is a novel noninvasive technique to create 3D reconstructions of the UA using OCT images from pre- and postoperative cases. These 3D models provide insight into its structure and shape and can help identify regions of obstruction without radiation. It can be feasibly

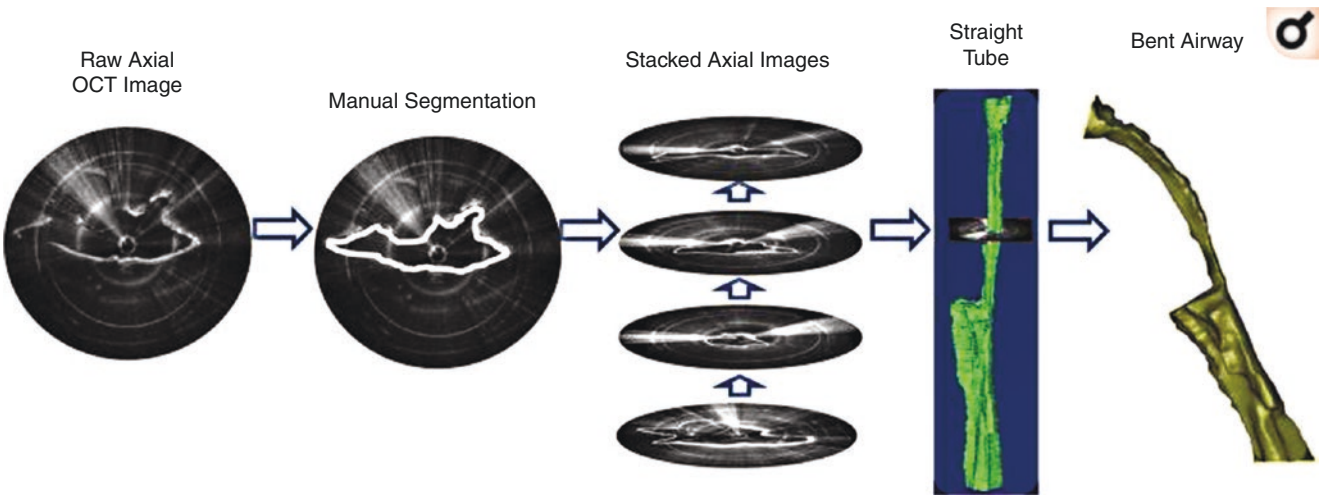

Fig. 16.8 Images converted to 3D model using Mimics software. (From Lazarow et al. [97]. Reprinted with permission from Elsevier)

obtained intraoperatively. Furthermore, more research needs to investigate the predictive value of these reconstructions for surgery selection and compare data in awake and sedated patients.

Drug-Induced Sleep (Sedation) Endoscopy (DISE)

DISE is another method to evaluate the level and degree of UA obstruction (Fig. 16.9). It allows UA visualization by flexible endoscopy or bronchoscope while the child is sedated. It is a promising technique in selecting the type of UA surgery because it provides live video of UA obstruction. There is no need for radiation; it is a simple, safe, and cost-effective technique [99]. However, its interpretation requires experience and the use of a standard protocol is recommended [99–111]. There are over 21 scoring methods described, of which six are in pediatric OSA. Only two studies reported a correlation between the scoring system and OSA severity [101, 102]. Another disadvantage is the utility of sedation during DISE as described earlier in MRI. A recent systematic review suggested that dexmedetomidine and ketamine do not lead to respiratory depression and are associated with less muscular relaxation, with a more sustained respiratory effort [53, 54]. Thereby, a disadvantage of DISE over cine MRI is that it is not possible to visualize multiple levels of obstruction at the same time. Besides, it is not possible to visualize the depth and thickness of abnormal tissues, such as enlarged lingual tonsils, what could be the cause of tongue base collapse [99].

The potential role for DISE prior to ATE and the effect on treatment outcome is not well defined and is subject of controversy. A review recommended not to systematically use DISE in otherwise healthy infants and children with OSA without prior UA surgery [105]. This recommendation contrasts with previous studies which have shown that DISE prior to ATE may change the surgical decision making, also in surgically naïve children [101, 104, 106–109].

In conclusion, pre-operative assessment combining DISE could have better outcomes than routine Ear Nose and Throat (ENT) examinations in pediatric OSA. Currently, there is no universally accepted standard score system, this will be necessary in order to provide a more consistent method. More research is needed in all groups of risk factors to determine the role for predicting treatment outcome.

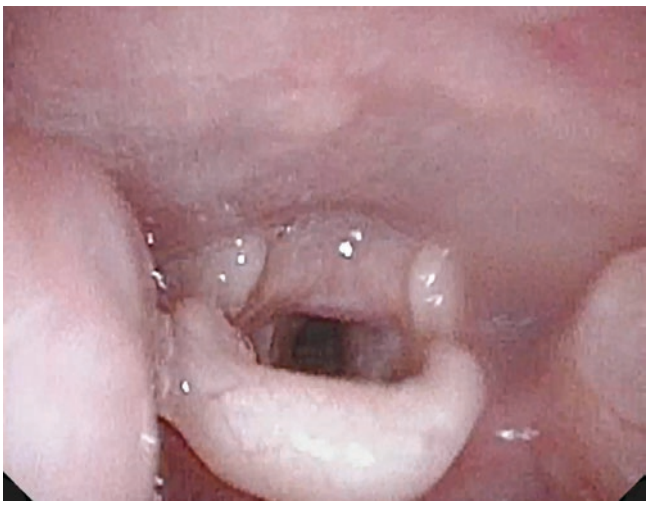

Fig. 16.9 An image during the endoscopy

Future Developments

Virtual surgery based on 3D constructions would be the next logical research opportunity in choosing an effective surgical strategy [112]. Children with DS or obese children should be prioritized because the percentage of residual OSA is much higher in these populations. A recent pilot study of Mylavarapu et al. investigated the use of virtual surgery and compared virtual surgery with actual surgery. Virtual surgeries were performed on 10 patients with moderate-to-severe OSA. Changes in oAHI and upper airway resistance, as calculated by computational fluid dynamics for pre- and postoperative modeling, matched well for 8 of 10 patients. Limitations of this study were that the authors did not describe the influence of age and did not compare the virtual surgery with surgical changes in anatomy by MRI after treatment [113, 114]. More research is needed to confirm the clinical usability of this technique in surgical planning and studies that investigate the prediction of treatment outcome. Additionally, there is need for more research using imaging or DISE in children with persistent OSA after treatment. The aforementioned use of virtual surgery modeling could also be expanded beyond ATE surgery.

Summary

Many (surgical) options exist for treatment of pediatric (persistent) OSA. In the present era of personalized medicine, progress has been made in identifying the exact cause of OSA in children.

There are limited data on the usefulness of the different imaging techniques as a diagnostic tool in pediatric OSA and predictive value for treatment outcome. Most of the studies had small sample sizes with different inclusion and exclusion criteria. These simple techniques can already assist in predicting the severity of OSA and are minimally invasive. Thereby, there is a suggestion that functional imaging or vir-

tual surgery could be of extra value in predicting treatment outcome. However, more research is needed to confirm the clinical utility of these techniques. Thereby, a comparison of the different imaging methods, including cost-effectiveness analysis, is warranted.

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Laboratory Tests in Pediatric Sleep Medicine

17

Leila Kheirandish-Gozal and David Gozal

Introduction

Sleep fulfills an essential and life-sustaining function. As such, it should not come as a surprise that when something is not well in the way we sleep, biological systems in many if not all of our organs will mount a response at the transcriptional and translational level, and as such lead to changes in the composition of body fluids in a predictable and consistent manner that can either serve as biomarkers of the disease or as biomarkers of the morbid consequences of the sleep disorder [1]. In addition, specific genetic risk factors may be associated with increased prevalence of a specific sleep disorder and may assist in determining whether a patient presenting with a constellation of symptoms and sign compatible with that disease is more likely to suffer from the disease or not.

In this chapter, we will review specific laboratory tests that may be useful when evaluating sleep conditions in children. Some of these tests are not necessarily implemented by all sleep practitioners, and as such the reader will have to use discretionary judgment regarding their utility in the clinical practice settings where they operate.

Pediatric Obstructive Sleep Apnea

Pediatric OSA is associated with an increased risk for a large number of comorbidities ranging from cognitive and behavioral deficits, endothelial dysfunction, and systemic hypertension, to metabolic perturbations, such as insulin resistance, dyslipidemias, as well as increased frequency of nocturnal enuresis, and excessive daytime sleepiness (EDS) [2–11]. Although the current definitive diagnostic tool for establishing the presence of OSA is based on the clinical presentation and more prominently on overnight polysomnography (PSG) [12], this labor intensive and costly test is only marginally predictive of any associated morbidities in patients with otherwise similar findings on the PSG. Indeed, although the prevalence of morbidities increases with the severity of OSA, there is still a very large proportion of children with even severe OSA who will not present any evidence of measurable morbidity. Exploration of ideal biomarker candidates that are reliably predictive of OSA-associated morbidities can be very useful and valuable in clinical decision making and in evaluating the response to treatment [13, 14]. Below is a short review of previously explored biomarkers aimed at the diagnosis of OSA or detection of OSA-associated morbidities. Some of these laboratory tests may also be helpful for other purposes rather than just sleep disorders, and such instances will be indicated when appropriate.

Diagnostic Tests

OSA-Associated Urinary Proteins

Proteomic approaches reveal that pediatric OSA is associated with specific and consistent alterations in urinary concentrations of specific protein clusters. Research shows Kallikrein-1, uromodulin, urocortin-3, and orosomucoid-1 have adequate accuracy to be used as an OSA diagnostic test in children when used in combination [15]. These assays have not been commercialized as of yet.

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High Sensitivity C-Reactive Protein (hs-CRP)

Hs-CRP has been shown to increase in children with OS, and the more severe the disorder, the more likely that hs-CRP will be higher [16–27]. However, there is substantial variability in the levels of hs-CRP that precludes its clinical use as a diagnostic biomarker, which by the way may be explained by genetic variance in both the CRP and interleukin-6 (IL-6) genes [28]. Nevertheless, because increased hs-CRP may reflect the presence of cognitive deficits, we routinely obtain hs-CRP levels in our clinical practice. As such, if any habitually snoring symptomatic patient has increased hs-CRP (>0.4 mg/dl), we are more likely to recommend treatment even when AHI is not very elevated in the PSG [29]. Similarly, use of hs-CRP before and after treatment may be helpful to guide the clinician as to whether adenotonsillectomy has been successful in normalizing the PSG or whether there is a likely risk for residual OSA to be present [30].

OSA-Associated Inflammatory Biomarkers/ Cardiovascular Biomarkers

As a low degree systemic inflammatory disease, pediatric OSA promotes the activation and circulation of pro-inflammatory cytokines, such as IL-6, interferon (IFN)-γ and tumor necrosis factor alpha (TNF-α). A large number of inflammatory markers have been investigated over the years, but their clinical use remains somewhat uncertain since most of the data relies on single centers, and well-designed multicenter trials are lacking [31–44]. Furthermore, there is also evidence that an important modulator such as vitamin D may be low in certain children with OSA [45].

In addition, altered plasma levels of adropin and B-natriuretic peptide may also provide an indicator of increased endothelial dysfunction, and therefore cardiovascular disease (CVD) risk in children with OSA [37, 46].

OSA-Associated Metabolic Biomarkers/ Metabolic Morbidity Biomarkers

With the global pandemic of obesity in children, OSA plays a significant role in increasing the risk of metabolic syndrome. As a pro-inflammatory and pro-thrombotic state, the major components of metabolic syndrome including insulin resistance, dyslipidemia, hypertension, and hyperglycemia increase the chance of developing cardiovascular disease and type 2 diabetes later in life, and as such detection of such increased risk may allow for earlier and timely intervention [8, 43, 47–52].

Accordingly, in all children undergoing PSG above the age of 4 years, and particularly in those who are overweight or obese (based on BMI z score), a fasting blood draw in the morning after the diagnostic polysomnogram, should be considered. Fasting levels of insulin and glucose, and a complete lipid panel profile including total cholesterol, triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels are not only correlated with the presence of metabolic dysfunction and worthy of attention and intervention (i.e., referral to obesity program, endocrinology, and/or nutritionist) [53–55], but may also be useful as a screening test in children with elevated BMI z scores irrespective of the sleep problem that prompted the referral.

Excessive Daytime Sleepiness in OSA

Evidence suggests that morning plasma TNF-α levels are increased in OSA, primarily due to sleep fragmentation and BMI, and are associated with increased excessive daytime sleepiness. However, there is substantial variability in morning plasma TNF-α levels, which is likely attributable to the presence or absence of the TNF-α-308G gene polymorphism [10, 11, 56–58].

Restless Leg Syndrome (RLS)/Periodic Leg Movement Disorder of Sleep (PLMDS)

Iron-Related Markers

In children with restless leg syndrome and periodic limb movement disorder of sleep, as well as children with restless sleep, serum ferritin levels should be closely monitored, and if so indicated, corrected by supplemental iron treatment. In children with PSG-diagnosed PLMDS and or with clinical diagnosis of RLS, ferritin levels of >50 μg/L, would be a required critical value to improve symptoms [59, 60]. Serum ferritin levels of <45 μg/L had been also linked to abnormal sleep movements, in children with ADHD [61–63], and in autism [64, 65]. More extensive evaluation of iron metabolism may be also indicated and include serum iron, total iron binding capacity, and hepcidin levels [66–69].

Narcolepsy/Idiopathic Hypersomnia/Primary Excessive Sleepiness

Orexin Levels in Cerebrospinal Fluid

Measurement of cerebrospinal (CSF) hypocretin-1/orexin is needed to establish unequivocally the presence of narcolepsy type 1. Hypocretin-1 levels <110 pg/ml have been shown to

have very high specificity (~99%) and sensitivity (88–94%) [70–72]. However, other conditions that also may present with REM sleep onset and EDS can exhibit reduced levels of hypocretin-1. Among these, Prader–Willi syndrome has been reported as potentially displaying low levels [73], but exclusion of this genetic condition should be relatively easy unless clinical features are also present.

Some studies have shown the presence of higher CSF histamine (HA) levels together with lower tele-methylhistamine (t-MeHA) levels leading to a significant decrease in the t-MeHA/HA ratios in pediatric patients with narcolepsy type 1 children [74]. Interestingly, some patients with atypical cataplexy may present evolving changes in both CSF hypocretin-1 and HA levels [75]. The value of measuring CSF hypocretin-1 levels in patients without cataplexy is doubtful [76].

Thyroid Panel

In the context of the snoring child, particularly if obesity is concurrently present, one may consider obtaining a thyroid panel to identify whether hypothyroidism may be contributing to sleep-disordered breathing, EDS, or other symptoms [77–79]. However, systematic evaluation of thyroid gland function in pediatric patients with breathing disorders during sleep is not usually recommended or necessary [80–82].

Thyroid evaluation is also usually not recommended in a setting of suspected narcolepsy. However, occasional reports are available of either low levels of thyroid hormone or favorable response and reductions in hypersomnolence in a patient with narcolepsy treated with thyroid hormone supplements [83, 84].

Human Leukocyte Antigen (HLA)-DQB1*06:02

Almost all narcoleptic patients are carriers of this HLA class II allele, while 30–50% of patients with hypersomnia but without cataplexy are carriers and 12–25% of all healthy individuals in carry this allele across different populations [85–90]. Accordingly, the presence of *HLA-DQB1*06:02* in children who also present symptoms of narcolepsy can be a supportive finding in the diagnosis of narcolepsy but is not pathognomonic.

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The Nocturnal Polysomnogram – Approaches to Recording, Scoring, and Interpretation in Infants and Children

18

Madeleine Grigg-Damberger and Steven Lopez

Abbreviations

AAO-HNS	American Academy of Otolaryngology–Head and Neck Surgery Society
AASM	American Academy of Sleep Medicine
AHI	Apnea-hypopnea index (mean number of apneas and hypopneas per hour of total sleep time)
AI	Apnea index (mean number of apneas per hour of total sleep time)
APA	American Pediatric Association
BMI	Body mass index
CA	Conceptional age
CAI	Central apnea index (mean number of central apneas per hour of total sleep time)
CMS	Centers for Medicaid and Medicare Services
CO_2	Carbon dioxide
CPT	Medical billing code
DPR	Dominant posterior rhythm of wakefulness
ECG	Electrocardiography, electrocardiogram
EEG	Electroencephalography, electroencephalogram
EMG	Electromyography, electromyogram
EOG	Electro-oculography, electro-oculogram
ERS	European Respiratory Society
$etCO_2$	end-tidal CO_2
GA	Gestational age
h	Hours
HI	Hypopnea index (mean number of hypopneas per hour of total sleep time)
HFF	High frequency filter
HVS	High voltage slow
KΩ	Kiloohms
LFF	Low frequency filter
LM	Leg movement(s)
LVI	Low voltage irregular
M	Mixed
NP	Nasal pressure transducer airflow sensor
NREM 1	Non-rapid eye movement sleep stage 1 sleep
NREM 2	Non-rapid eye movement sleep stage 2 sleep
NREM 3	Non-rapid eye movement sleep stage 3 sleep
NREM	Non-rapid eye movement sleep
nRWA index	Total number of stage REM sleep epochs with REM sleep without atonia on PSG/total number of REM sleep epochs in polysomnogram ×100
OAI	Obstructive apnea index (mean number of obstructive apneas per hour of total sleep time)
OSA	Obstructive sleep apnea
OSAS	Obstructive sleep apnea syndrome
PAOHI	Pediatric apnea-hypopnea index (mean number of pediatric obstructive apneas and hypopneas per hour of total sleep time)
PAP	Positive airway pressure
PLMD	Periodic limb movement disorder
PLMS	Periodic limb movements of sleep
PLMS	Periodic limb movements of sleep
PLMW	Periodic limb movement awake
PMA	Post-menstrual age
PSG	Polysomnogram
PVDF	Polyvinylidene fluoride film oronasal sensor
RBD	REM sleep behavior disorder

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REM	Rapid eye movement sleep
RERA	Respiratory event related arousal
RIP	Respiratory inductance plethysmography thoracoabdominal effort belts
RLS	Restless legs syndrome
RWA	REM sleep without atonia
s Seconds	
SDB	Sleep disordered breathing
SpO2	Pulse oxyhemoglobin saturation
Stage N	NREM sleep
Stage R	REM sleep
Stage T	Transitional sleep
Stage W	Wakefulness
TA	Trace alternant
$tcCO_2$	transcutaneous CO_2
TST	Total sleep time
UK	United Kingdom
US	United States
WASO	Wake after sleep onset
y	Years
μV	Microvolts

Polysomnography (also called a sleep study) simultaneously records multiple different biophysiological parameters continuously across a sleep period to characterize sleep and identify (and sometimes treat) sleep disorders. The resulting study is a polysomnogram (PSG). Because PSG records concurrently multiple physiological signals, it allows us to correlate specific changes or abnormalities of one physiological variable with specific conditions defined by another variable (e.g., sinus bradycardia occurring with an obstructive apnea, periodic limb movements (PLMs) during NREM 2 sleep, and a sleep terror from NREM 3 sleep). As a result, PSG is a far more powerful tool than individual independent measurements of each variable. This advantage is offset by difficulties related to optimal digital monitor display of disparate parameters and the challenges for reliably detecting a multitude of diagnostic patterns of value among all these variables.

Indications for Nocturnal Polysomnography in Children

In 2011, the American Academy of Sleep Medicine (AASM) published comprehensive evidence- and consensus-based guidelines for respiratory and, in 2012, non-respiratory indications for PSG and multiple sleep latency testing (MSLT) in children [1–4].

Summary of the AASM Indications for Level 1 PSG in Children and Adolescents [1, 2, 5, 6]

- Sleep-related breathing disorders (SRBD) such as obstructive sleep apnea (OSA), central sleep apnea (CSA), or sleep-related alveolar hypoventilation
- Preoperative assessment before upper airway surgeries for OSA
- Titration of positive airway pressure (PAP) to treat SRBD
- Confirm treatment efficacy of PAP, oral appliances, weight loss, or upper airway surgeries in SRBD
- With a multiple sleep latency test (MSLT) as part of the evaluation of narcolepsy, idiopathic hypersomnia, or other central hypersomnias
- Confirm REM sleep behavior disorder and/or REM sleep without atonia
- Evaluate episodic paroxysmal nocturnal events with expanded EEG and video-PSG which are (1) unusual or atypical because of age of onset, time of night, duration, or particular accompanying motor behaviors (e.g., stereotyped, repetitive, dystonic, or focal); (2) frequent (≥2–3 nights per week); and/or (3) potentially injurious, or disruptive to the patient or family
- Suspected sleep-related epilepsy when the initial clinical evaluation and standard EEG are inconclusive, to help distinguish from parasomnias
- Assess and treat SRBD in patients with neuromuscular disorders and symptoms of SRBD
- Confirm and treat congenital central alveolar hypoventilation syndrome including late onset types
- Assess for periodic limb movement disorder in children suspected to have restless legs syndrome, when additional supportive data (demonstration of periodic leg movements) are desired to help confirm the diagnosis

Other clinical practice guidelines for pediatric PSG have been published, and some of their recommendations require mention. In 2012, the American Academy of Pediatrics (AAP) published updated guidelines diagnosing and managing childhood obstructive sleep apnea (OSA) [7]. These recommend a PSG for all children who snore and have symptoms and/or signs suggestive of obstructive sleep disordered breathing (OSDB) before adenotonsillectomy because (1) history, physical exam, audio/visual recordings, and standardized questionnaires have poor sensitivity and specificity for distinguishing primary snoring from OSA syndrome (OSAS) [8] and (2) a preoperative PSG helps stratify OSA

severity and identify those at greater risk for perioperative complications and likely to need a postoperative PSG [2, 7].

In 2019, the American Academy of Otolaryngology–Head and Neck Surgery Society (AAO-HNS) published revised clinical practice guideline recommending which children should have a preoperative PSG before upper airway surgery for OSA: (1) those with complex medical conditions (including a body mass index (BMI) ≥95th percentile, Down syndrome, craniofacial abnormalities, neuromuscular disorders, sickle cell disease, and/or age < 3 years) or (2) children in whom need for surgery is questioned (e.g., discrepancy between tonsil size and severity of OSA symptoms reported or parents uncertain about the need for surgery) [9–11]. Overnight hospitalization after tonsillectomy is recommended in children younger than 3 years and/or those with severe OSA on PSG (i.e., an obstructive apnea-hypopnea index [AHI] > 10/h per hour and/or an oxygen desaturation nadir <80%). Despite these recommendations, preoperative PSG is performed at most in 35% of US children before adenotonsillectomy for suspected OSA [12, 13]. A 2013 survey of 542 pediatric otolaryngologists in the UK found <2% ordered preoperative PSGs [14].

As in adults, PSG is not the best first test for evaluating insomnia, restless legs syndrome (RLS), circadian rhythm sleep/wake disorders, typical uncomplicated parasomnias, epilepsy, depression, chronic lung disease, sleep bruxism, and/or behaviorally based sleep problems [5, 6]. However, if typical sleep terrors or sleepwalking events occur more than 2–3 times per week, a PSG is warranted to identify another sleep disorder triggering them (most often mild OSA, occasionally RLS or periodic limb movement disorder (PLMD)) [15, 16]. Below is a summary of red flags for atypical parasomnia in children which warrant consideration of comprehensive in-laboratory video-PSG.

Red Flags for Atypical Parasomnias in Children

- Atypical, stereotyped, or repetitive clinical features
- Begin or recur in adulthood
- Frequent (>2–3 times per week)
- Are potentially injurious (or have caused injury) to the patient or others
- Disrupt sleep-wake schedules of patients and family
- Complaints of excessive daytime sleepiness or insomnia
- Symptoms suggestive of sleep apnea or periodic limb movements
- Frequent dream enactment behavior later in the night
- Occur just after falling asleep or before awakening in morning

Classification of Sleep Studies

The AASM and the Centers for Medicaid and Medicare Services (CMS) in the USA classify sleep studies into four categories (levels 1–4, Table 18.1) based upon how many different physiological signals are simultaneously recorded and whether a sleep technologist was present throughout the study [17, 18]. A level 1 PSG (CPT code 95810) is performed attended in a sleep laboratory recording a minimum of seven channels including electroencephalogram (EEG), bilateral electro-oculogram (EOG), submental electromyogram (EMG), electrocardiogram (ECG), airflow, thoracic and abdominal respiratory effort, pulse oximetry (SpO_2), video, and sometimes carbon dioxide (CO_2) monitoring [5, 19]. A type 1 sleep PSG is considered the reference standard against which other diagnostic methods are evaluated [20]. Figure 18.1 shows a representative example of a level 1 pediatric PSG from our laboratory.

A level 2 study is level 1 PSG recorded unattended (i.e., without a sleep technologist present), in or out of the sleep laboratory. A level 3 study records a minimum of four cardiorespiratory channels including ventilation, oximetry, and ECG or heart rate. A level 4 study usually records only one to two cardiorespiratory signals (usually pulse oximetry, sometimes airflow). According to CMS, a level 3 or 4 study can be recorded in or out of the sleep laboratory, attended or unattended by a sleep technologist, but is usually recorded unattended at home. Most home sleep apnea tests (HSAT) are level 3 studies. A 2017 position paper by the AASM advised that home sleep apnea testing is not yet recommended to diagnose OSA in children nor covered by medical insurance in the USA [21].

Table 18.1 Classification of types of sleep studies

Study type	Parameters monitored
I	Minimum of 7 including EEG, EOG, chin EMG, airflow, respiratory effort, oxygen saturations, and ECG. Attended by a sleep technologist
II	Minimum of 7 including EEG, EOG, chin EMG, airflow, respiratory effort, oxygen saturations, and ECG. Unattended by a sleep technologist
III	Minimum of 4 channels including EKG or heart rate, oxygen saturations, two channels of respiratory effort or one respiratory effort channel and one airflow channel. Attended or unattended by a sleep technologist
IV	1–2 channels, one of which is airflow or include actigraphy, oxygen saturations, and peripheral arterial tone. Attended or unattended by a sleep technologist

Source: CMS Manual System. Pub 100-03 Medicare national coverage determinations, Transmittal 86, Centers for Medicare & Medicaid Services website: https://www.cms.gov.transmittals/downloads/R86NCS.pdf

EMG electromyogram, *EEG* electroencephalogram, *EOG* electrooculography, *HR* heart rate

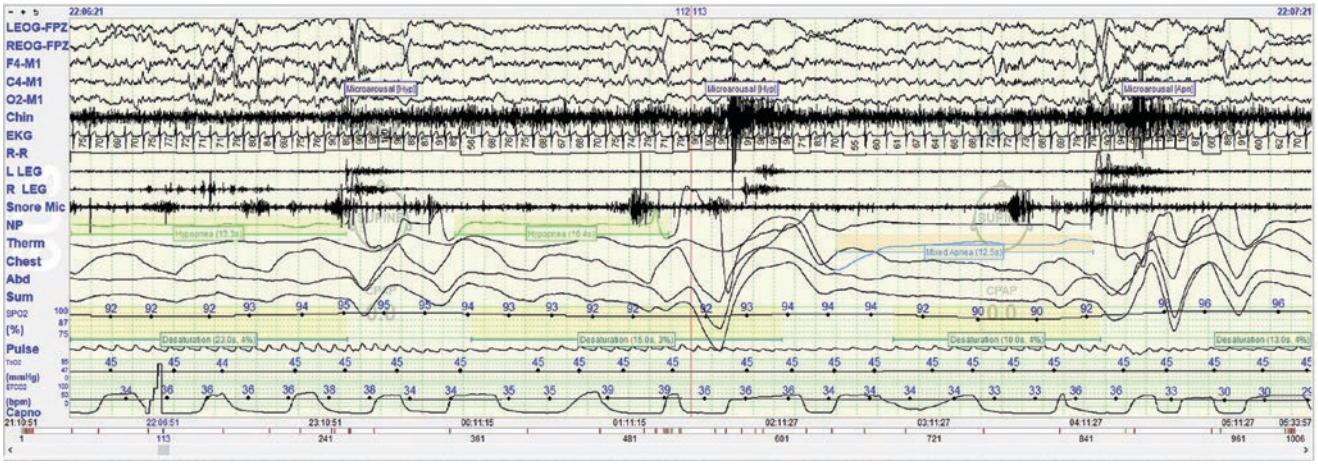


Fig. 18.1 A representative example of the montage used to record sleep in children from our sleep laboratory. Recorded in an 11-year-old in NREM 1 sleep, it shows two obstructive hypopneas and one mixed apnea which cause oxygen desaturations to 90–92% and arousals. The PSG montage listed on left records: electro-oculography (EOG) of the left and right eyes referenced to the midline frontopolar electrode (L-EOG-FPZ, R-EOG-FPZ); right frontal, central, and occipital electrodes referenced to the left mastoid (F4-M1, C4-M1, O2-M1); chin (submentalis electromyography [EMG]); EKG (modified lead II EKG); R-R: R-R interval; left and right anterior tibialis EMG (L Leg, R Leg); snore mic (snore microphone); NP (nasal pressure airflow); Therm (thermal sensor); Chest, Abd, and Sum (respiratory inductive plethysmography thoracic, abdominal, and sum sensors); SpO_2 (pulse oxyhemoglobin saturation); pulse (pulse oximetry waveform); $tcCO_2$ (transcutaneous carbon dioxide [tc-CO2]); et-CO_2 (end-tidal CO_2); Capno ($etCO_2$ capnograph)

Advantages, Disadvantages, and Contraindications for Pediatric Level 1 Polysomnography

A level 1 PSG allows comparison of multiple different biological signals simultaneously identifying correlations and interactions between them. A technologist is present throughout to identify, repair, replace, intervene, protect, and test treatment(s) if needed. The severity of sleep-disordered breathing (AHI, mean number of apneas and hypopneas per hour) can be derived from total sleep time (TST), not time in bed. AHI based on time in bed may be falsely low, underestimating OSA severity if too much of the night is spent awake.

Level 1 PSGs are expensive, time- and labor-intensive to record, score, and read. Patients can wait weeks or months to get a study because demand often outstrips availability, especially for infants and young children because many sleep laboratories are less comfortable recording them. Level 1 PSG typically recorded for one night of sleep in the artificial environment of the sleep laboratory provides a narrow view of how a child naturally sleeps. This results in so-called First Night Effect: more time supine, less REM and NREM 3 sleep, and more Wake after Sleep Onset (WASO) and NREM 1 sleep on the first night [22, 23].

There are no absolute contraindications to in-laboratory level 1 PSG if it is clinically indicated. However, a PSG is best recorded in those medically stable. Findings on a sleep study recorded in a sick child (even one near to discharge from the hospital) are unlikely to represent the baseline condition, and treatment recommended less likely to be implemented if the PSG findings are thought largely due to the illness. An in-hospital bedside level 1 PSG can be an expensive endeavor. In the sleep laboratory, one technologist can usually record two patients; in the hospital only one. Moreover, reimbursement for the technical component of the PSG lost in the bundled hospital diagnosis-related group (DRG) billing. If a sleep study is needed before discharge from the hospital, it usually should be the last test when the patient's condition has been stabilized.

Standards and Guidelines Used by Accredited Sleep Centers in the USA to Record and Score Nocturnal Pediatric Polysomnograms

Accredited sleep centers in the USA record, score, and interpret level 1 PSGs in infants, children, and adolescents using *the AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical* Specifications [24]. First published in 2007, the AASM Scoring Manual was designed to be revised and updated, available as a book or online (https://aasm.org/clinical-resources/scoring-manual). The AASM Scoring Manual was and is continuing the brave effort to standardize how PSG in the USA should be recorded, analyzed, and reported. Before it, we were never certain that a sleep study across city, state, country, or over sea was comparable.

We used the latest update (version 2.6, updated January 10, 2020) to write this chapter [24]. AASM sleep laboratory

accreditation guidelines that detail specifications for the sleep laboratory environment, medical and technical staff requirements, protocols, quality assurance, and necessary elements required for study reports are cited in the text when relevant (https://aasm.org/accreditation/).

Child-Friendly Polysomnography Techniques

From an adult's perspective, applying and recording a PSG is a noninvasive and harmless procedure, but it can be onerous, intrusive, and frightening for many children. Zaremba et al. (2005) recommend the use of child-friendly techniques for performing PSG in children [25]. Preparing the child and caregiver before the PSG (1) lessens anticipatory anxiety and procedural distress, (2) increases cooperation, (3) improves parental satisfaction, and (4) helps the child tolerate future medical procedures [25].

Preparing a Child for In-Laboratory Polysomnogram

The sleep clinician ordering a PSG in a child should describe the procedure using age-appropriate positive terms and explanations of why it is needed. We have patients and parents watch a video showing how a PSG is done and give a patient handbook detailing the process. We provide a tour of the sleep laboratory before scheduling the PSG. We discuss in advance what special equipment and care medically fragile and/or developmentally challenged children will require the night of the PSG (e.g., feeding tubes, suctioning devices, peritoneal dialysis, mechanical ventilator, tracheostomy caps), and which sleep technologist is best qualified to do the study. Children are invited to bring personal items to make the night more theirs (favorite toy, stuffed animal, pajamas, blanket, doll, action figure).

We order 1:1 staffing (1 technologist: 1 child and parent) for medically fragile, developmentally challenged, and/or children who have a history of difficulty tolerating "procedures." We identity these children by asking whether the child has had difficulty tolerating tests, surgeries, medical procedures, sitting still for haircuts, and/or has sensory sensitivities to noise, touch, smell, or textures. If it seems likely the child will have great difficulty cooperating for PSG (or has failed it before) and the PSG is needed, we recommend a referral to Child Life therapy [26].

We allow at least 1.5 hours before usual sleep onset in children younger than 6 (or those with special needs) to permit them to adapt to the laboratory and hook up and 2 hours if an expanded EEG montage is needed. A PSG recording should be at least 8 hours in duration and ideally collect 6–8 hours of sleeping data [20]. Longer sleep technologist shifts are needed when recording PSG in children because of their longer bedtimes and sleep needs: 14–17 hours for newborns (ages 0–3 months), 12–15 hours for infants (4–12 months), 11–14 hours for toddlers (1–2 years), 10–13 hours for preschoolers (3–5 years), 9–11 hours for schoolchildren (ages 6–13 years), and 8–10 hours for teenagers (www.sleepfoundation.org). Ideally, the timing of the PSG should mimic the child's bedtime as closely as possible [27].

A PSG is best not performed when the patient is acutely unwell or has that day received a vaccination [20]. Acute illness may exacerbate sleep-disordered breathing or other sleep problems. Unless the PSG is performed for a special purpose (suspected narcolepsy or parasomnia), patients should maintain their usual sleep habits prior to the study. Most often we recommend children to avoid caffeinated or energy drinks the day of the PSG. Medications the patient takes should be reviewed. Hypnotics, sedatives, and opioid-based analgesics can worsen/induce SDB and may alter sleep architecture and arousal thresholds [20]. Antidepressants, antipsychotics, benzodiazepines, and barbiturates can alter sleep architecture, arousal thresholds, sleep spindles, muscle tone, and/or leg movements. The clinician ordering the PSG needs to decide whether clonidine, caffeine, melatonin, nasal steroids, antihistamines, methylphenidate, and/or dexamphetamine should be continued the night of the study. In some cases, withdrawal of a chronic medication/substance may further disturb sleep. Sedation to obtain sleep in a pediatric PSG is best avoided.

Creating a Sleep Laboratory Welcoming to Children

Creating a child-friendly laboratory begins with sleep technologists who enjoy working with children and families. Other necessities include (1) age-appropriate and nonthreatening décor, (2) space for a parent to sleep, (3) access to a refrigerator and cooking appliances for infant formulas and foods, (4) age-appropriate cribs and beds with side rails, (5) padded sharp corners and covers for electrical outlets, (6) good insulation between study rooms when children cry, and (7) equipment, protocols, and staff training to handle pediatric emergencies [25, 28–30]. Ideally, the bedroom should resemble a child's room (except for microphone, video infrared camera, supplemental oxygen, PAP, and suctioning apparatus). Beds should have railings; cribs should be available for children younger than 2 years (unless they co-sleep). We prefer to perform the "hook-up" in a different room which separates the "technical experience" from the "sleep room."

Applying Polysomnographic Sensors in Children

A child with a developmental age younger than 6 years has limited ability to cooperate with the PSG setup and procedure. Children when stressed tend to regress. Younger children need short concrete explanations and should be told how long the setup will take. Sleep technologists need to exhibit patience and flexibility, be playful, exhibit positive attitude, and speak in a soft soothing voice during the "hook-up." We ask about tape, adhesive, and latex allergies; if reported, we use hypoallergenic materials (and enter the problem in the electronic medical record).

The skin of children (especially infants) is much thinner than adults requiring a gentler (less abrasive) approach to cleaning electrode and sensor sites. Some children (often those with neurodevelopmental and/or autism spectrum disorders) have sensory processing disorders. Distraction during the PSG may help. Avoid laying down or restraining a child when applying PSG sensors. Position a child who can sit comfortably in the caregiver's lap in a "position of comfort" (chest-to-chest hugging, sitting sideways or forward) because in such positions they tend to feel less vulnerable, are better able to maintain a sense of control, and cooperate.

Child-Friendly Polysomnographic Sensor Application Techniques

- Everyone needs to know their job in the PSG setup: the child needs to sit still as best they can, the parent helps the child to cooperate with the procedure, and the sleep technologist applies the sensors.
- Realize the parent knows the child best. Ask the parent: (a) What helped your child manage hard things in past? (b) What may help the child cooperate with the PSG hook-up? (c) What are your child's warning signs of impending meltdown and how to best handle it? (d) Anything more to share to make this a more positive experience?
- The sleep technologist uses child-friendly terminology for the PSG sensors and explanations for the setup and procedure [25]. Medical play can help the child cooperate [31–34].
- Encourage the child to touch the sensors and equipment.
- Demonstrate how and where a sensor is applied on their doll or stuffed animal before placing it on the child.
- Give the child choices (Do I put on the leg or chin sticky first? Which finger for your finger nightlight? Would like to hold the mirror and watch me put stickers on your chin?)
- Ask the child to blow bubbles up in the air while attaching the chin EMG or put the play electrode on the doll while you place one on the child.
- Praise the child every step of the way ("great job, way to go, awesome, give me five").
- Provide a distraction box (e.g., stickers, musical and light-up toys, books that pop up, look and find books, musical push buttons, and bubbles) to engage the child while you apply sensors [35].
- Extra time and time outs are often needed to apply electrodes for children who are emotionally labile, developmentally challenged, have sensory issues, or become frightened. However, sometimes the technologist needs to move fast and get it done.
- Nasal airflow sensors are particularly odious to children, and the technologist may need to wait till the child is deep asleep to apply them. Sometimes, the technologist cannot attach all sensors awake.

Final setup advice: (1) breaks can prolong a difficult setup and increase the likelihood of sweat artifact. Take a break after the setup and before lights out; (2) when the child decompensates, the best strategy is to move quickly (alert the parent of this plan); and (3) the technologist may not be able to "get them all on" in setup; technologist determines when is the best time to delay applying some sensors later. When a child is extremely intolerant of sensor placement, we may resort to plan B (technologist observation, respiratory belts, pulse oximeter, and video) and rarely plan C (technologist observation, pulse oximeter, and video).

Overnight Level 1 Pediatric Polysomnographic Recording Procedure

Once the PSG "hook-up" is complete, the sleep technologist escorts the child and caregiver to the study bedroom which has been made as inviting as it can be (save hospital-grade beds with rubberized pads beneath for enuresis, PAP machines, and oxygen delivery devices). The child and parent often voice concerns about "all the wires tying them down, preventing them from rolling in the bed, or visiting the bathroom," "being watched," or fear they won't sleep. We reassure them they are easily disconnected from the recording device and can roll around or leave the bed without dif-

Table 18.2 Pediatric level 1 polysomnogram biocalibration protocol

Check, observe, and, if needed, fix	Purpose
Check and document impedances for all the EEG, EOG, and EMG electrodes; fix if needed	Ensure impedances for EEG, EOG, and EMG derivations are ≤5 KΩ and relatively equal
Wake EEG recorded for 30 seconds with patient lying quietly with eyes closed	Identify dominant posterior rhythm for scoring wake and sleep onset
Look up, down, left, right, and blink without moving head	Identify presence and direction of horizontal and vertical eye movements; appreciate subtle eye blinking
Grit teeth or chew	Assess display of chin EMG
Snore or hum	Check snoring microphone channel
Breathe in and out	Check for sufficient sensitivity and proper polarity of airflow and respiratory effort channels
Hold breath for 10 seconds	Ability to record an apnea
Breathe only through nose for 10 seconds, then only through mouth for 10 seconds	Confirm Nasal pressure and oronasal thermal airflow sensors functioning properly, displaying sufficient signal amplitude and proper polarity
Take a deep breath and exhale slowly for 10 seconds (prolonged expiration)	Identify prolonged expiration seen with sleep-related expiratory groaning
Flex left foot/raise toes on left foot (×5) then flex right foot/raise toes on left foot (×5)	Optimal functioning of anterior tibialis leg EMG
Flex fingers on right hand (×5) and then left hand without bending at the two distal joints, then extend fingers on left and then right hand without moving the wrist if upper extremity EMG is recorded	Optimal functioning and display of flexor digitorum superficialis and extensor digitorum communis when recording upper limb EMG muscles for suspected REM behavior disorder

ficulty. We show them their bedroom is equipped with an infrared camera and audio system that allows the sleep technologist to see, hear, and communicate with them without entering the bedroom. After tucking them in, the sleep technologist returns to the recording control room.

Before starting the PSG, the sleep technologist performs a biocalibration (Table 18.2) to ensure that each of the signals is recorded properly. The parent can assist with commands if needed (e.g., passively closing the child's eyes saying "let's play peek-a-boo" to identify the dominant posterior rhythm for scoring wakefulness and sleep onset). Following this, the sleep technologist says "It's time to sleep" via intercom (and marks "Lights Out" noted on the digital PSG). The child is monitored from the control room via video and digital PSG data scrolling on a digital computer screen (typically displayed in 30- or 60-second time frames).

Across the recording, the sleep technologist (1) enters detailed observations onto the digital PSG recording, (2) detects and fixes malfunctioning sensors, (3) helps the patient to the bathroom, (4) intervenes if potentially injurious behaviors occur, (5) decides if and when to titrate PAP or add supplemental oxygen, and (6) repositions the patient to obtain sleep in a particular body position (often supine).

Technologists need to be on "heightened alert" for the tendency of children and infants rolling and becoming entangled with electrode and sensor cables, or suddenly sitting up in the bed screaming, crying, and/or bolting from it. Children too often repeatedly remove sensors across the recording requiring watchful observation and prompt remediation by the technologist. Good sound (kept on), infra-red video, and cameras with zoom-in capacity are needed to catch these (and score the studies).

The study continues until the final awakening and "Lights On." After the final awakening in the morning, the sensors are removed. Encouraging the child to help with sensor removal can help them feel more in control. The parent is asked to complete a post-sleep questionnaire inquiring how they felt the procedure went. The child and parent are offered a shower (most decline) and then discharged home (often with a celebratory toy, badge of honor for being a good patient, stickers, and/or crayons).

Which Biophysiologic Signals Are Recorded in Level 1 Polysomnography and Why

The recommended signals when recording a diagnostic level 1 pediatric PSG include EEG (frontal, central, occipital referenced to the contralateral mastoid), bilateral EOG, chin EMG, ECG, bilateral anterior tibialis leg EMG, SpO_2, snore microphone, nasal pressure (NP) and oronasal thermal sensor airflow, thoracic and abdominal respiratory effort, end-tidal and/or transcutaneous CO_2, body position, and digital video recording (Fig. 18.1).

Electroencephalography (EEG)

EEG is the best indicator of sleep and wakefulness (except in infants 0–2 months of age where regularity of respiration is a better biomarker of sleep/wake states). The AASM Scoring Manual recommends preferentially recording EEG from the right frontal, central, and occipital scalp regions referenced to the left mastoid (F4-M1, C4-M1, O2-M1). The left frontal, central, or occipital electrodes referenced to the right mastoid (F3-M2, C3-M2, O1-M2) are also placed to be used as backup if the F4, C4, or O2 malfunction. In children younger than 2 years of age, we prefer to simultaneously record and display F4-M1, C4-M1, O2-M1, F3-M2, C3-M2, O1-M2, C3-Cz, and Cz-C4 to detect asymmetric sleep spindles [36].

Recording frontal, central, and occipital EEG permits us to recognize the distinctive EEG markers of sleep/wake

states: (1) W is best identified by the presence of a dominant posterior rhythm (DPR) in the occipital EEG derivations which attenuates with eye opening or attenuation; (2) sleep spindles, vertex waves, and saw tooth waves are usually best seen in central EEG derivations; and (3) K-complexes and slow wave activity of N3 are often best seen in the frontal EEG channels. We score sleep/wake states displaying PSG epochs lasting 30 seconds (10 mm/sec).

EEG in PSG is recorded with the low frequency filter set at 0.3 Hz and high frequency filter at 35 Hz. We begin the recording with the sensitivity set at 7 μV/mm but often have to decrease the sensitivity to 10–15 μV/mm in children especially in N3 sleep where slow wave activity often measures 100–400 μV peak-to-peak. When epileptiform or ictal EEG activity is observed, high-frequency filter should be increased to 70 Hz. We sometimes record the so-called expanded EEG montages when we want to correlate sleep events, arousals, and awakening with interictal epileptiform discharges, nocturnal events, and seizure occurrence [37]. Figure 18.2 shows an expanded EEG montage recorded on a child with epilepsy from our laboratory.

Electro-Oculography (EOG)

Eye movements help us to identify sleep onset and REM sleep: slow eye movement is a reliable biomarker of drowsiness and N1 sleep and rapid eye movement is a biomarker of R sleep. EOG detects changes in electrical fields generated by the movement of the eyeballs because the eye has a horizontal dipole with a strong positive charge in the cornea and a minor negative charge at the retina.

Slow eye movements (SEMs) (1) are sinusoidal conjugate eye movements with an initial deflection that usually lasts >500 msec, (2) are typically first seen before dropout of the dominant posterior rhythm (so-called DPR), and (3) continue to occur during NREM 1 and usually disappear before sleep spindles and K-complexes of N2 sleep appear, and (4) their prevalence progressively decreases across NREM-REM sleep cycles of a night of sleep [24].

Rapid eye movements (REMs) (1) are sharply peaked eye movements with an initial deflection lasting <500 msec (usually <200 msec), frequency > 1 Hz, amplitude ≥20 μV, and duration 50–200 msec, (2) are more often conjugate, but can be asymmetric or dysconjugate, and (3) occur preferentially in REM sleep but are observed during wakefulness [38, 39].

The AASM Manual recommends EOG (and EEG) recordings be displayed using an LLF filter setting of 0.3 Hz, HFF 35 Hz, and initial sensitivity 7 μV/mm [24]. Using the same sensitivity for the EEG and EOG derivations allows us to view frontal EEG activity in the EOG derivations. The HFF 35 Hz is needed to the rapid upslope of REMs.

The AASM permits use of two different EOG montages. The recommended placement is the left EOG (E1) 1 cm *below*

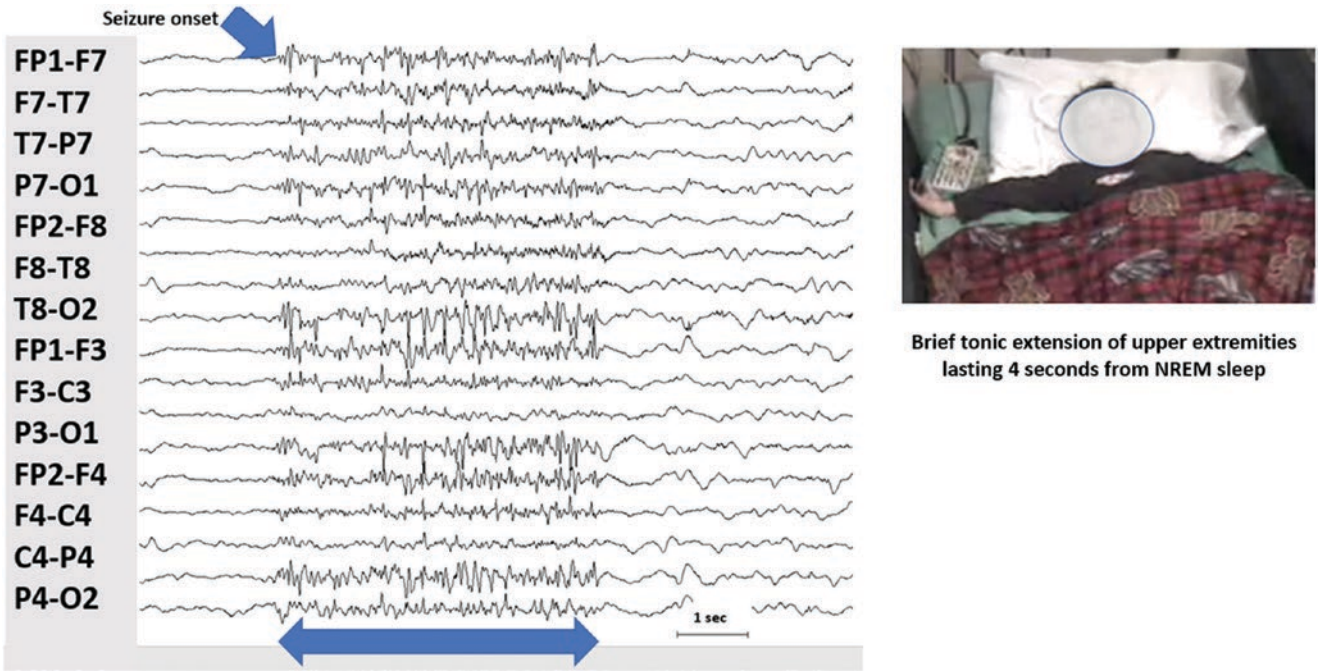


Fig. 18.2 A 10-second PSG epoch recorded in the sleep laboratory using expanded bipolar longitudinal EEG montage. Note the expanded EEG montage. An electrographic tonic seizure occurs; seizure onset marked by the arrow. It lasts for 4 seconds and is accompanied by a brief elevation and tonic extension of the upper extremities from NREM 1 sleep. The electrographic seizure is characterized by paroxysmal fast activity

and 1 cm lateral to the left outer canthus and the right EOG (E2) 1 cm *above* and 1 cm lateral to the right outer canthus and referencing both to the right mastoid electrode (M2). The recommended EOG montage is E1-M2, E2-M2 (i.e., both the left and right EOG are referenced to the right mastoid electrode). The left mastoid electrode (M1) is placed as a backup reference should M2 malfunction. Using the recommended EOG derivation: (1) conjugate eye movements produce out-of-phase movements; (2) EEG activity shows in-phase voltage deflections; (3) EEG and artifacts are easy to recognize; (4) the direction of eye movements cannot be determined; and (5) eye blinks are usually missed (Fig. 18.3).

We prefer the following acceptable EOG montage: E1 1 cm below and 1 cm lateral to the left outer canthus and E2 1 cm below and 1 cm lateral to the right outer canthus, both referenced to the midline frontopolar electrode (FPZ). The advantages of E1-FPZ and E2-FPZ are as follows: they better detect subtle eye blinks and the specific direction of eye movements (Fig. 18.4).

Mentalis Electromyography (Chin EMG)

Chin EMG is recorded during a PSG to assess axial skeletal muscle tone and activity. The chin EMG is particularly useful for identifying the loss of EMG activity during REM sleep (called REM sleep without atonia). It is also useful in identifying arousals, awakenings, swallowing, chewing, and bruxism during PSG.

The chin EMG tends to decrease at sleep onset, further diminishes with increasing depth of NREM sleep, and reaches its lowest level of activity in REM sleep. The onset, presence, and offset of REM sleep are identified when the chin EMG is absent or at its lowest amplitude in the recording. The AASM Scoring Manual requires a transient increase in chin EMG lasting ≥1 second, which is required to score an EEG arousal during REM sleep (but not in NREM) [24].

The AASM Scoring Manual recommends placing three electrodes to record chin EMG: chin Z (midline 1 cm above the inferior edge of the mandible); chin 1 (2 cm below the

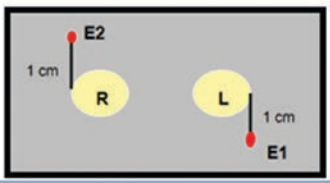
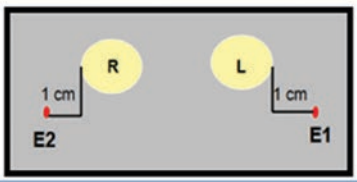
Recommended EOG Montage	Acceptable EOG Montage
E1-M2 E2-M2 	E1-FPz E2-FPz 
Conjugate eye movements produce out-of-phase, EEG activity in-phase voltage deflections.	Shows direction of eye movements: vertical in-phase in both EOG and horizontal out-of-phase.
Cannot determine direction of eye movements	Eye-blinking easily identified as in-phase EOG.
Will miss some low amplitude eye movements	Detect all eye movements
Easy to distinguish artifacts and EEG	Less easy to distinguish artifacts and EEG: coexisting EEG in-phase intermixed with vertical EOG

Fig. 18.3 Comparison of the recommended and acceptable electro-oculography (EOG) montages of the AASM Scoring Manual. The AASM permits use of two different EOG montages. The recommended EOG montage is E1-M2, E2-M2 (i.e., both the left and right EOG are referenced to the right mastoid electrode). The recommended EOG montage is E1-M2, E2-M2. The left mastoid electrode (M1) is placed as a backup reference should M2 malfunction

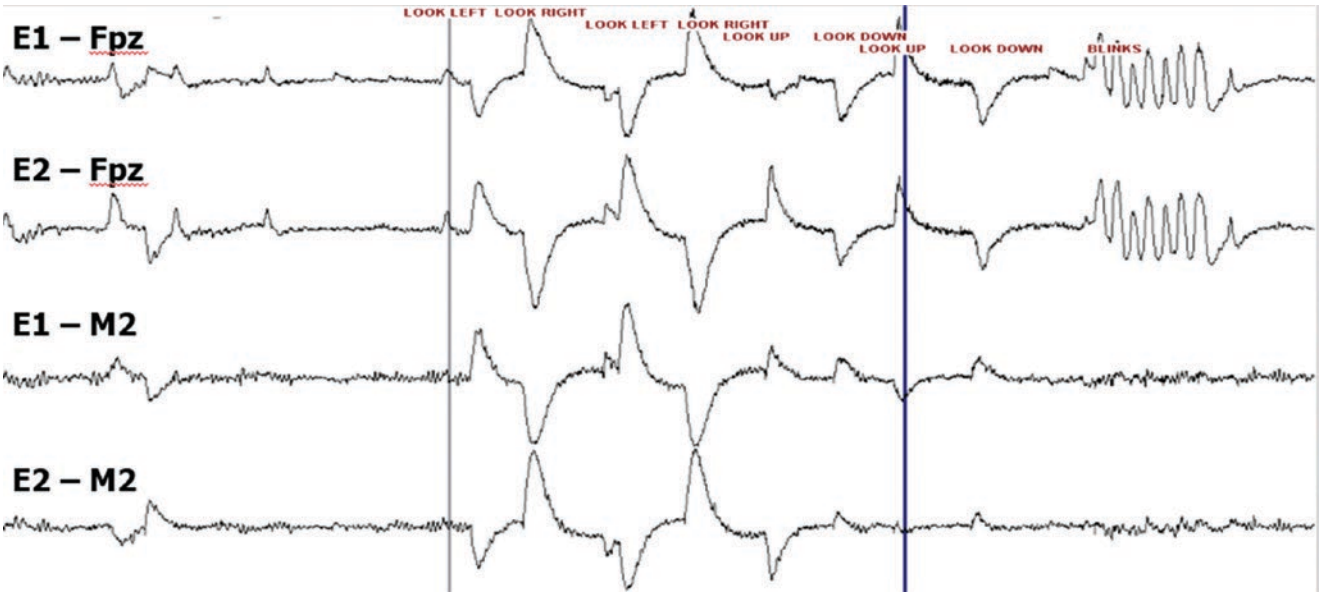


Fig. 18.4 This graphic illustrates the advantages of using AASM alternative electro-oculography (EOG) versus recommended EOG montage. The acceptable EOG montage places the left EOG (E1) 1 cm below and 1 cm lateral to the left outer canthus and the right EOG (E2) 1 cm below and 1 cm lateral to the right outer canthus. Both are referenced to the midline frontopolar electrode (FPZ). The advantages of E1-FPZ and E2-FPZ are that they better detect subtle eye blinks and the specific direction of eye movements

inferior edge of the mandible and 2 cm to the left of the midline); chin 2 (2 cm below the inferior edge of the mandible and 2 cm to the right of the midline). The chin EMG montage is Chin Z-Chin 1 or Chin Z-Chin 2. If the midline chin electrode malfunctions, the AASM Manual recommends replacing it because the inferior mandibular electrodes cannot be linked to each other. The frequency range of submentalis muscle activity is typically 20–200 Hz, so the LLF is set at 10 Hz and the HFF at 100 Hz, and the initial sensitivity is adjusted to 2–3 μV to provide an adequate baseline EMG level during wakefulness.

Multiple Biological Signals Recorded to Assess Breathing During Sleep

Multiple different respiratory sensors are used to record respiration during a level 1 PSG because most provide only qualitative data (and frequently malfunction). The AASM Scoring Manual specifies which sensor is preferentially recommended to identify a particular respiratory event. For example, the recommended sensor to identify apneas in a diagnostic study is the oronasal thermal sensor, the Airflow signal from positive airway pressure (PAP) device during PAP titration. If one recommended sensor becomes unreliable or unreadable, alternative sensors are recommended by the AASM Scoring Manual. Table 18.3 summarizes the recommended and alternative respiratory sensors during level 1 PSG for children.

Table 18.3 AASM recommended and alternative sensors to record respiration in level 1 pediatric polysomnograms

Respiratory event	Preferred sensor	Alternative sensors
Apnea	Oronasal thermal airflow sensor during *diagnostic* study PAP device flow signal during PAP titration	NP with or without square wave transformation of signal RIP sum or RIP flow (calibrated or uncalibrated) $etCO_2$
Hypopnea	NP with or without square wave transformation during diagnostic study PAP device flow signal during PAP titration	Oronasal thermal sensor RIP sum (calibrated or uncalibrated) RIP flow (calibrated or uncalibrated) Dual thoracoabdominal RIP belts (calibrated or uncalibrated)
Respiratory effort	RIP (calibrate or uncalibrated) Esophageal manometry	None
Blood oxygen	Pulse oximetry with maximal average time of ≤3 seconds at heart rate of 80 beats per minute	None
Hypoventilation	$etCO_2$, $tcCO_2$, or arterial pCO_2 during diagnostic study tcCO2 or arterial pCO2 during PAP titration	None
Snoring	Acoustic sensor (microphone), piezoelectric sensor, or NP transducer	None

Legend: *$etCO_2$* end tidal CO_2, *NP* nasal pressure, *PAP* positive airway pressure, *RIP* respiratory inductance plethysmography, *$tcCO_2$* transcutaneous CO_2

Thermal and Nasal Pressure Sensors Monitor Airflow

The AASM Scoring Manual recommends simultaneously recording airflow during a level 1 PSG using both a nasal pressure (NP) and oronasal thermal sensors because they provide complementary information and can serve as a backup sensor when the other malfunctions or becomes unreliable.

NP sensor measures airflow through the nose and is a nasal cannula connected to a pressure transducer which provides a signal proportional to the square of the airflow [40]. The NP is sensitive to even subtle changes in airflow and preferentially used to identify hypopneas and RERAs in infants, children, and adults.

The inspiratory portion of the NP waveform can display flattening which is surrogate of flow limitation. Flow limitation is regarded as a manifestation of upper airway resistance and may be the only sign of long periods of partial upper airway obstruction in children with obstructive SDB (Fig. 18.5). Three studies have found that the NP sensor is more sensitive than the thermal sensor for detecting hypopneas [41–43]. One such study found that 42% of hypopneas were detected only by the NP in 30 children, and 38% of obstructive events were detected by both the NP and thermal sensor such that the AHI was higher when using NP compared with the thermal sensor [41]. Another study compared the thermistor alone and thermistor with NP in 40 children and found that the NP-derived mean AHI was higher than that detected using the thermistor alone (7.0 vs. 5.9 per hour of sleep, respectively) [43].

Unfortunately, the NP is the sensor most likely to malfunction in a pediatric PSG and least liked by children [43]. Poor or intermittent loss of the NP signal can be observed due to the following reasons: (1) the child pulls it from the nose; (2) profuse nasal secretions; (3) mouth breathing; (4) positive airway pressure (PAP) and/or supplemental oxygen therapy simultaneously delivered via a split nasal cannula; and/or (5) tachypnea. Improper size and/or location of the nasal cannula can significantly alter the NP signal. Ill-fitting nasal cannula prongs which partially or completely obstruct one or both nares have been shown to lead to higher apnea and arousal indexes. Too large a nasal cannula in small nostrils often results in a small NP signal and too small a nasal cannula in large nostrils results in a large NP signal. The NP is recorded with the direct current (DC) or 0.03 Hz and the HFF set at 15 Hz. If the HFF is set at 100 Hz, snoring artifact is displayed.

Oronasal thermal airflow sensors are recommended as the preferred sensor to detect apneas. Thermal sensors detect changes in airflow signal through the mouth and nares because expired air is warmed to body temperature. The signal from oronasal thermal sensors is not proportional to flow and overestimates flow as flow rates decrease. Three different types of thermal sensors are approved by the AASM Scoring Manual: thermistors, thermocouples, and polyvinylidene fluoride

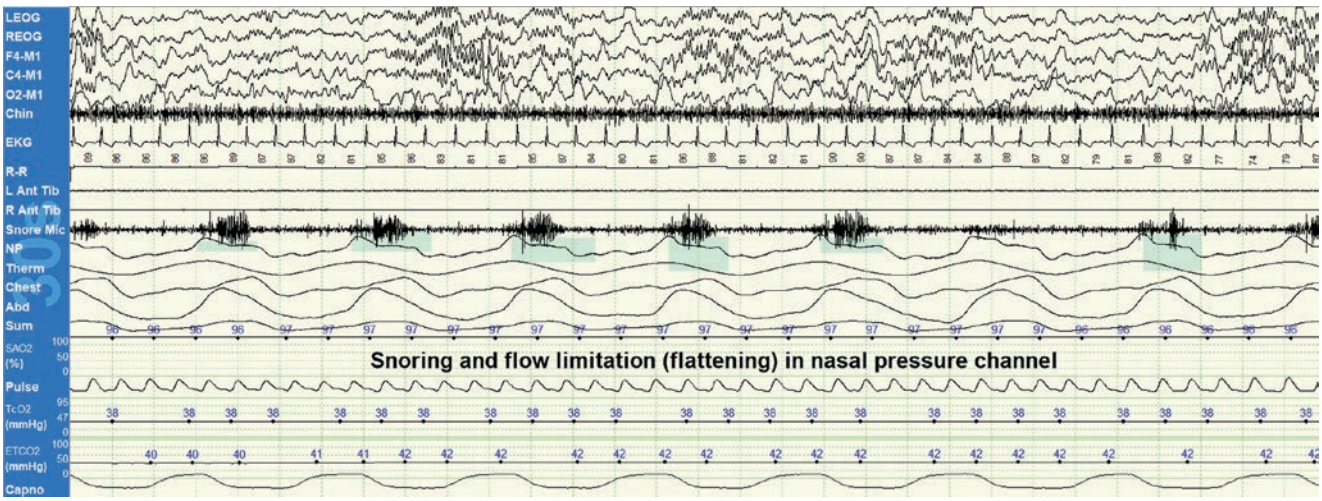


Fig. 18.5 A 30-second epoch recorded on level 1 overnight PSG showing continuous inspiratory snoring in snore microphone channel and flow limitation (flattening in the nasal pressure sensor). The inspiratory portion of the NP waveform can display flattening which is surrogate of flow limitation. Flow limitation is regarded as a manifestation of upper airway resistance and may be the only sign of long periods of partial upper airway obstruction in children with obstructive sleep disordered breathing. The PSG montage listed on the left is the alternative EOG montage with the left and right eye channels referenced to the midline frontopolar electrode (L-EOG-FPZ, R-EOG-FPZ); the right frontal, central, and occipital electrodes referenced to the left mastoid (F4-M1, C4-M1, O2-M1); Chin (submentalis electromyography [EMG]); EKG (modified lead II EKG); R-R: R-R interval; left and right anterior tibialis EMG (L Ant Tib, R Ant Tib); Snore Mic (snore microphone); NP (nasal pressure airflow); Therm (thermal sensor); Chest, Abd, and Sum (respiratory inductive plethysmography thoracic, abdominal, and sum sensors); SAO_2 (pulse oxyhemoglobin saturation); Pulse (pulse oximetry waveform); $tcCO_2$ (transcutaneous carbon dioxide [tc-CO2]); et-CO_2 (end-tidal CO_2); Capno ($etCO_2$ capnograph)

(PVDF) film. A thermocouple is made of dissimilar metals that generate a variable voltage in response to temperature fluctuations (cooler inspired air, warmer expired air). A thermistor is a variable resistor which responds to temperature changes producing a signal. The PVDF film oronasal sensor produces an airflow signal which is roughly proportional to the temperature difference between two sides of the film. The signal from thermal sensors is not proportional to flow and overestimates flow as flow rates decrease. PVDF film oronasal sensors can detect changes in both nasal pressure and oronasal air temperature such that they could allow us to record only one airflow sensor. However, PVDF oronasal sensors often do not detect flow limitation. The thermal sensor LFF is set at 0.01 Hz and HFF at 15 Hz.

Respiratory Effort Monitored Using Respiratory Inductance Plethysmography

We typically monitor thoracic and abdominal respiratory effort using dual belt (thoracic and abdominal) respiratory inductance plethysmography (RIP). An RIP belt consists of a sinusoid wire coil insulated in elastic [44]. Changes in the cross section of the wire are converted into a small signal that then is amplified in order to be displayed on the PSG trace. One band is worn around the chest at the level of the nipple and another around the abdomen near the umbilicus. Changes in thoracic and/or abdominal diameter, cross-sectional area, and circumference all are directly proportional to changes in lung volume such that with normal tidal breathing the amplitude of the RIP waveform correlates with lung volume [45]. Dual effort belts are recommended because (1) some patients have larger excursions in either the thorax or abdominal belts during the night, and this can vary with body position; (2) if one belt fails, we still have the other to read; and (3) dual belts are particularly useful for detecting paradoxical motion of the thorax and abdomen to identify obstructive breathing (Fig. 18.6) [40]. RIP belts tend to slip as children change position during sleep [44].

We also display RIPsum which sums the signals from the thoracic and abdominal effort (Fig. 18.6). During normal breathing, the ribcage expansion during inspiration follows the abdomen resulting in a slight asynchrony between the two breathing movements. When airway obstruction occurs, asynchrony of the ribcage and abdominal signals manifests as a phase shift between the thoracic and abdominal signals accompanied by a decrease in the amplitude of the RIPsum signal. Sometimes, paradoxical breathing is seen during an obstructive apnea. The chest normally moves inward during inhalation. If the chest moves outward during inspiration the thoracic and abdominal signals will then be out of phase (see Fig. 18.6 above). It is called paradoxical breathing, a sign of obstruction, and accompanied by flattening in the RIPsum signal. RIP belts even calibrated may not detect feeble respi-

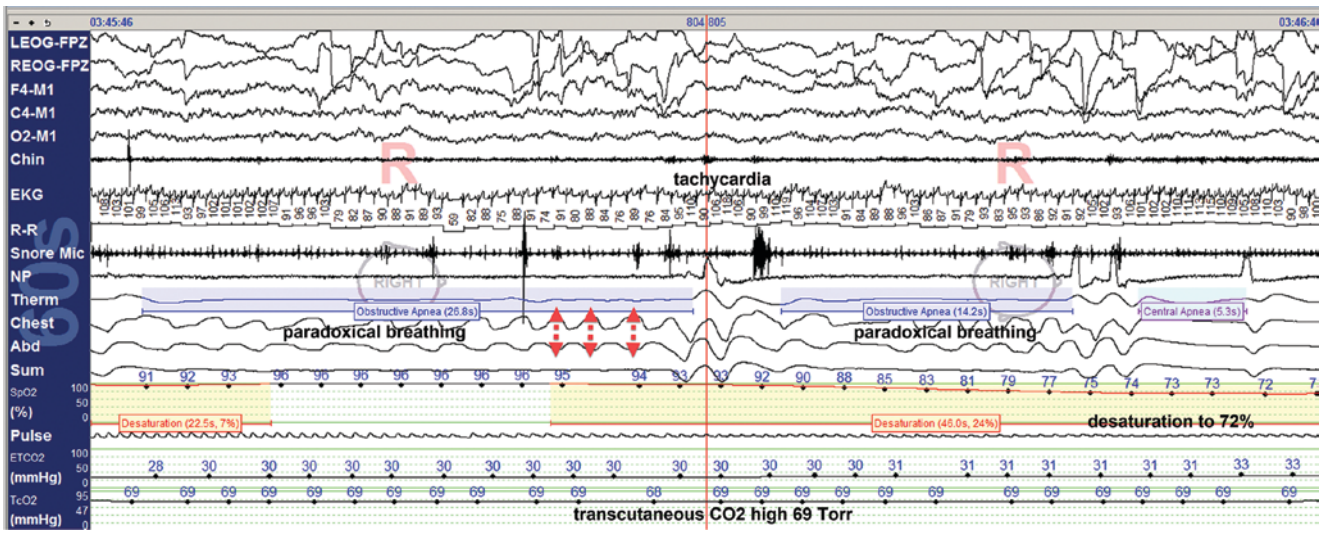


Fig. 18.6 A 60-second epoch of overnight PSG recorded on a 3-year-old with severe obstructive sleep apnea much worse in REM sleep. During REM sleep, long-lasting obstructive sleep apneas are observed (27 and 14 seconds, respectively). The first obstructive apnea causes an oxygen desaturation to 72% and relative tachycardia. Note the paradoxical breathing which confirms that the respiratory events are obstructive apneas. The sum channel of respiratory effort shows a decrease in amplitude reflecting the paradoxical breathing. The transcutaneous CO_2 was elevated (69 Torr) due to obstructive hypoventilation. The end-tidal CO_2 is falsely low at 30 Torr perhaps due to tachypnea (24 breaths per minute) and mouth breathing. The PSG montage listed on the left is the alternative EOG montage with the left and right eye channels referenced to the midline frontopolar electrode (L-EOG-FPZ, R-EOG-FPZ); right frontal, central, and occipital electrodes referenced to the left mastoid (F4-M1, C4-M1, O2-M1); Chin (submentalis electromyography [EMG]); EKG (modified lead II EKG); R-R: R-R interval; Snore Mic (snore microphone); NP (nasal pressure airflow); Therm (thermal sensor); Chest, Abd, and Sum (respiratory inductive plethysmography thoracic, abdominal, and sum sensors); SAO_2 (pulse oxyhemoglobin saturation); Pulse (pulse oximetry waveform); $tcCO_2$ (transcutaneous carbon dioxide [tc-CO_2]); et-CO_2 (end-tidal CO_2)

ratory efforts in some patients resulting in obstructive apneas misclassified as central apneas. PVDF film respiratory sensors are approved and often used to record respiratory effort in adults, but they are not yet approved by the AASM Scoring Manual for children. Griffiths et al. (2017) reported that scoring of respiratory events was not significantly different among 50 children (average age 7.8 years) using PVDF and RIP belts [46]. Outliers in AHI accounted for less than 5% of the data overall. Obstructive apneas were reliably identified using either PVDF or RIP, but there was a wider scatter of data when scoring obstructive hypopneas without particular bias for one or another sensor.

Pulse Oximetry

We monitor arterial oxygen saturation during level 1 PSG using pulse oximetry with short sampling times (≤3 seconds at heart rates ≤80 beats per minute) to avoid missing brief desaturation events and associated apneas and hypopneas in children. The reliability of the pulse oximetry tracing is improved by recording the pulse amplitude waveform which helps identify desaturations to poor probe function [27].

Causes of pulse oximeter artifact or malfunction in children are as follows: (1) movement, (2) poor perfusion in patient who is hypovolemic, hypotensive, or cold, (3) inadequate light transmission detected by device because of tissue edema, nail polish, dark or thick skin, or improper probe placement, (4) excessive ambient room light, and (5) venous pulsations misinterpreted as arterial. The AASM Scoring Manual specifies that the maximal pulse oximeter signal averaging time needs to be ≤3 seconds.

Carbon Dioxide Monitoring (Capnometry)

The AASM Manual requires capnometry when recording pediatric PSG using end-tidal carbon dioxide ($etCO_2$) and/or transcutaneous CO_2 ($tcCO_2$) in children ≤18 years of age. Sleep-related hypoventilation in children is defined the the PaCO2 is greated than 50 mm Hg for more than 25% of total sleep time (TST), measured by either endtidal, transcutaneous and/or arterial PCO2.

End-Tidal Carbon Dioxide Monitoring

The $etCO_2$ is not a flow signal, but rather it measures molecules of expired CO_2. It measures nasal cannula and provides breath-to-breath variability with respect to the $PaCO_2$ [47]. Normal $etCO_2$ values are 30–43 mm Hg (compared to normal $PaCO_2$: 35–45 mm Hg). The $etCO_2$ correlates poorly with the arterial blood gas in patients with acute respiratory illnesses, small lung volumes, obesity, or chronic lung disease. Apneas can be observed in the $etCO_2$ capnograph but usually lag 10 seconds or more behind the NP and thermal sensor (Fig. 18.5). It is crucial to obtain a plateau in $etCO_2$ capnograph waveform for the signal to be considered valid (as shown in Fig. 18.5). A sustained low $etCO_2$ with a good alveolar plateau warrants consideration of hyperventilation and a high $etCO_2$ with a good plateau warrants hypoventilation. A low $etCO_2$ without a good plateau can be seen with tachypnea. The $etCO_2$ signal can be inaccurate or unreliable in the presence of (1) mouth breathing, (2) profuse nasal secretions, (3) cannula against posterior aspect of nares, (4) only one cannula prong in nostril, (5) nasal obstruction, (6) kink or excessive moisture in $etCO_2$ tubing, (7) PAP or O_2 therapy also being delivered via the nasal cannula, (8) tachypnea, and/or (9) small lung volumes.

Transcutaneous Carbon Dioxide Monitoring

The tcCO2 sensor is usually placed on the trunk (right second intercostal space and mid-clavicular space), but if the child is obese on the right forearm or ear lobe. The sensor applied to the skin induces a local hypermetabolic state (hyperemia increases arterial blood supply to superficial vessels) which leads to increased CO_2 production detected in the pH of the sensor's electrolyte solution. Because of this, the $tcCO_2$ does not provide breath-to-breath changes in CO_2, rather trends in $PaCO_2$ over 2 minutes. As opposed to the $etCO_2$, the $tcCO_2$ measurements correspond well with ABG even in the medically ill and are typically 4–5 mm Hg higher than the ABG. The $tcCO_2$ membrane requires 10 minutes for stabilization when first applied, so values within the first minutes are unreliable. Most $tcCO_2$ device manufacturers recommend moving the skin electrode every 4 hours to prevent thermal injury, poor signal, or signal drift.

Clinical judgment is essential when assessing accuracy of $tcCO_2$ (and the $etCO_2$). The $tcCO_2$ should be calibrated with a reference gas according to manufacturer's recommendations and when accuracy of reading is doubtful. The $tcCO_2$ can be unreliable if the following are noted: (1) abnormally high values due to calibration problems of device, (2) abnormally low value due to poor fixation of electrode, (3) insufficient electrode temperature, (4) wide fluctuations of values caused by motion artifacts, or (5) perfusion problems such as skin diseases, edema, and/or hypovolemia. Use of the heated $tcCO_2$ electrode may cause the skin underlying it to blister (which we have rarely encountered).

Transcutaneous capnometers are much more expensive than $etCO_2$ (initial layout $20,000 for $tcCO_2$ vs. $6000 for $etCO_2$) [47]. The $tcCO_2$ membrane (which at best lasts for two patients) costs $13, skin adaptors to fix the sensor on the skin $3.50 per patient, and the calibration gas $70 (which allows for 100 measurements). Kirk et al (2006) recorded overnight diagnostic PSG in 609 children (mean age 8 ± 5 years) [48]. Interpretable $tcCO_2$ data are available for 62% ± 35% and 72% ± 25% of the total recording time from the $etCO_2$ and $tcCO_2$ channels, respectively. The maximum and mean CO_2 measures obtained from both devices are 0.1 ± 5.4 mm Hg and 0.6 ± 3.9 mm Hg, respectively.

Electrocardiography (ECG)

ECG is recorded in level 1 PSG using a modified lead II placement with a positive electrode on the left torso just beneath the last rib in the midclavicular line (and parallel to the left hip) and the negative electrode right just below the right clavicle (and parallel to the right shoulder). The ground electrode is placed below the left clavicle or on the left arm. Waveforms are surface positive. Heart rate, sinus bradycardia and tachycardia, wide and narrow complex tachycardia, asystole, atrial fibrillation, and atrial flutter can be identified using a single channel. However, a single channel cannot be used to identify cardiac ischemia or PQRST complex abnormalities. The ECG LLF is 0.3 Hz and HFF 70 Hz.

Other Biological Variables Recorded During Level 1 PSG

Leg surface EMG is recorded independently from the left and right anterior tibialis muscles to identify sleep-related movement disorders, movements, and arousals. Two surface EMG electrodes are placed along the long axis of each anterior tibialis 2–3 cm apart or 1/3 the length of the muscle, whichever is shorter [49]. Impedances should be less than ≤10 KΩ (less than ≤5 KΩ for research studies). The initial sensitivity is 5 μV/mm, the LFF set at 10 Hz, HFF at 100, Hz and digital sampling rates ≥200 Hz.

When REM sleep without atonia (RWA) or NREM arousal parasomnias are suspected, we typically also record surface EMG from flexor digitorum superficialis and extensor digitorum brevis muscles because REM behavior muscle activity often occurs preferentially in the upper extremities [50–52]. Loss of REM atonia is the hallmark polysomnographic feature of RBD, only occasionally encountered in pediatric PSG, most often than either narcolepsy type 1 or Tourette syndrome.

Surface EMG electrodes can be placed on the masseter muscles to confirm sleep bruxism and the paraspinal muscles to record rhythmic movement disorder. Expanded EEG montages are employed when sleep-related seizures are considered (Fig. 18.7). Time-locked infrared video monitoring with zoom camera features are encouraged. We use the video recording in pediatric PSG: (1) to identify artifact, movement, or parasomnia; (2) identify the abnormal breathing sounds: snore, snort, sigh, gasp, wheeze, or stridor; (3) patient out of bed and technologist or parent in room; (4) who really is snoring (patient or parent); (5) who or what caused the probe to malfunction; and (6) who or what caused the patient to arouse or wake.

Split Night or Full Night Positive Airway Pressure Titration Level 1 PSG

PAP therapy is a treatment for sleep disordered breathing (SDB) and can be titrated in the second half of a diagnostic PSG (so-called "split night PAP titration) or as a full night PAP titration. We usually do not perform a split night PSG on

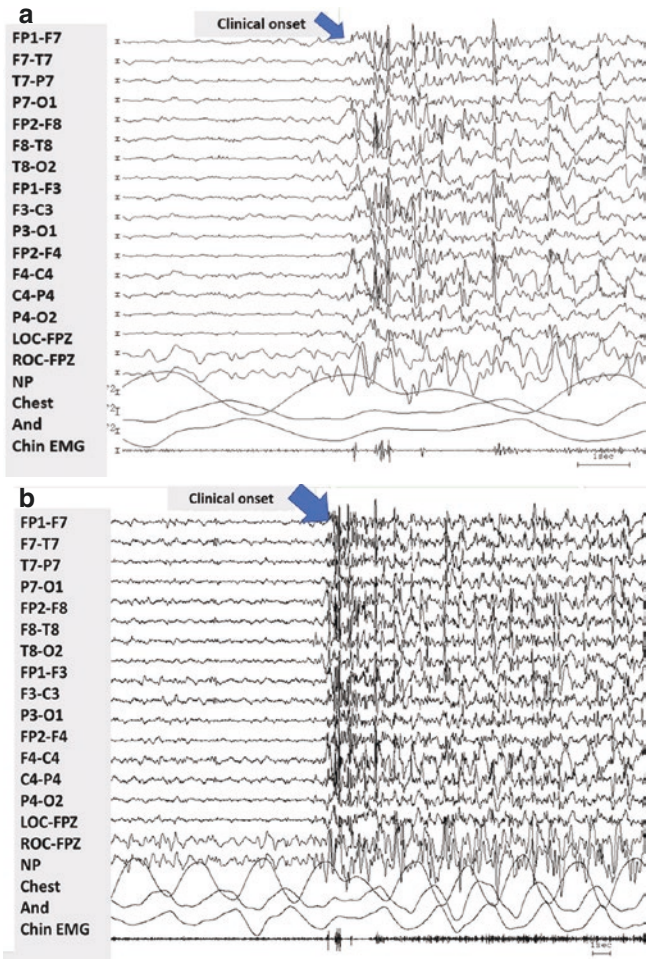


Fig. 18.7 A clinical-electrographic seizure from NREM 2 sleep in a 8-year-old recorded in an overnight polysomnogram. Both figures show the onset of the electrographic and clinical seizure (arrow) using an expanded EEG montage: (**a**) displayed for 10 seconds and (**b**) displayed for 30 seconds. The montage shows a bipolar anterior-posterior longitudinal montage. A few channels of PSG are shown: left and right EOG (LOC-FPz, ROC-FPZ); nasal pressure airflow (NP); respiratory effort (Chest, Abdomen), and Chin EMG

children with developmental ages younger than 8 years. PAP titration is best performed and accepted by children by first showing the child masks and pressurized air (called PAP desensitization), especially since many of these children have complex medical issues [48, 53, 54]. The AASM has published guidelines for titrating PAP therapy and performing split night PSGs in adults and children and reviewed elsewhere in this text [55]. When scoring respiratory events while titrating PAP, the recommended airflow sensor is from the PAP device.

Capped Tracheostomy and Mechanical Ventilation Overnight Level 1 PSG

We are sometimes asked to record a level 1 PSG while capping a child's tracheostomy when sleeping as one of the last steps before decannulation [56–58]. We perform capped tra-

cheostomy PSGs after the child tolerates the tracheostomy tube being capped the entire day awake. We start the capped trach PSG with the trach uncapped, recording the first NREM-REM cycle as a baseline. We then cap the trach for remaining portion of the study if tolerated.

The sleep technologist observes for respiratory distress, tachypnea, OAHI >10/h, hypoventilation ($etCO_2$ > 50 mm Hg >25% TST), and/or prolonged desaturation (more than expected than patient's baseline oxygen) [59]. Supplemental oxygen via nasal cannula is occasionally added (especially if patient typically sleeps with it). Sometimes, we are also asked to record PSG in the pediatric intensive care unit to (1) identify patient-ventilator asynchrony, (2) optimize ventilator settings during sleep, and/or (3) assess likelihood of discontinuing mechanical ventilation when sleeping [60, 61].

Successful vs. unsuccessful respiratory parameters in 210 decannulation attempts among 189 children showed the following: mean AHI 1.7/h vs. 12.8/h, REM AHI 5.1 vs. 20/h, and nadir SpO_2 89% vs. 82%, respectively [59]. Another study found the favorable PSG parameters for successful decannulation in 53 children and are as follows: AHI ≤ 10/h, OAHI ≤5/h, and absence of sleep-related hypoventilation [58].

Abbreviated 4-Hour Nap Level 1 PSG

A nap PSG is a level 1 PSG recorded in the sleep laboratory most often for 4 hours in the afternoon. REM sleep may be missed in the afternoon nap, and SDB in children may occur only or preferentially in REM sleep. Two studies found that nap PSG has a good positive predictive value (77–100%) but a poor negative predictive value (17–49%) for identifying OSA in children [62, 63]. A nap study may confirm a child has OSA but may underestimate the severity of the OSA which occurs at night, especially if REM sleep is not recorded [2, 3].

Kahlke et al. (2013) compared 4-h evening recordings to overnight PSG in 105 infants ≤24 months old [64]. All children had at least one REM period in the first 4 hours of sleep. Mean oxygen saturations and end-tidal CO_2 did not significantly differ between full-night and 4-h PSG. The 4-h PSG showed high sensitivity for total AHI (100% for 6 months and 93% for >6 months, respectively), obstructive AHI (98% and 91%, respectively), and central apnea index (100% and 72%, respectively). Agreement was lower for those with lower AHI. The authors argued that the high sensitivity between full-night and 4-h PSG supports the use of 4-h PSG in children 24 months and under, especially those 6 months of age.

Scoring of Level 1 Nocturnal Polysomnogram First Done by Sleep Technologists

Sleep technologists are usually the first to score the PSG. Sleep/wake states are first scored in 30-second epochs from Lights Out to Lights On using the AASM Scoring Manual rules for scoring sleep/wake states. Some also mark arousals and awakenings as they score sleep/wake states. Then the technologist identifies, tags, classifies, and marks the duration of respiratory events: apneas, hypopneas, respiratory event-related arousals [RERAs], oxygen desaturations, increased work of breathing, hypercapnia, hypoxemia, and hypoventilation. The effects of respiratory events (arousals, awakenings, changes in heart rate/rhythm) are then marked or tagged. Oxygen desaturations are often automatically marked by the digital PSG system, but they can be deleted if artifactual. Next, the technologist tags periodic limb movements during sleep (PLMs), flagging if they cause arousals or awakening. Sometimes, automatic scoring of leg movements is done and then edited by the technologist. Last, the technologist may mark (or the interpreter reviews comments entered during the recording) the following: paroxysmal motor behaviors, parasomnias, interictal epileptiform discharges (IEDs), REM sleep without atonia (RWA), and REM sleep dream enactment behaviors [65–69]. It more often takes a sleep technologist 1.5–3 hours to score a level 1 PSG depending on complexity and abnormalities present. Once scored, the digital PSG system program tabulates and collates summaries of the data and generates a visual summary of the PSG (called a hypnogram). The scored PSG then goes to the sleep specialist for review, revision, and interpretation. A sleep study report is typically accompanied by tables summarizing the data, a hypnogram (Fig. 18.8), and an interpretation of the findings.

Scoring Sleep/Wake States in Children 2 Months to 18 Years of Age

The AASM Scoring Manual provides rules for scoring sleep/wake states in level 1 PSG for infants 0–2 months of age and 2 months to 18 years. We will discuss the scoring rules for 2 months to 18 years first because sleep studies in infants 0–2 months are reserved for a select few. The AASM Scoring Manual recommends that 30-second epochs of sleep in a level 1 PSG in infants 2–5 months are usually best scored as NREM (N) or REM (R) sleep until the EEG markers of NREM 2 (sleep spindles, K-complexes) and NREM 3 (high-voltage slow-wave activity) develop. Table 18.4 summarizes when the typical EEG biomarkers of sleep and wakefulness are first observed in children and Table 18.5 shows how they change in appearance across infancy, childhood, and adolescence.

The Dominant Posterior Rhythm of Wakefulness Develops with Age

Wakefulness (W) is most easily recognized in a 30-second epoch of a level 1 PSG by a dominant posterior rhythm (DPR). The dominant reactive EEG rhythm is best seen over the occip-

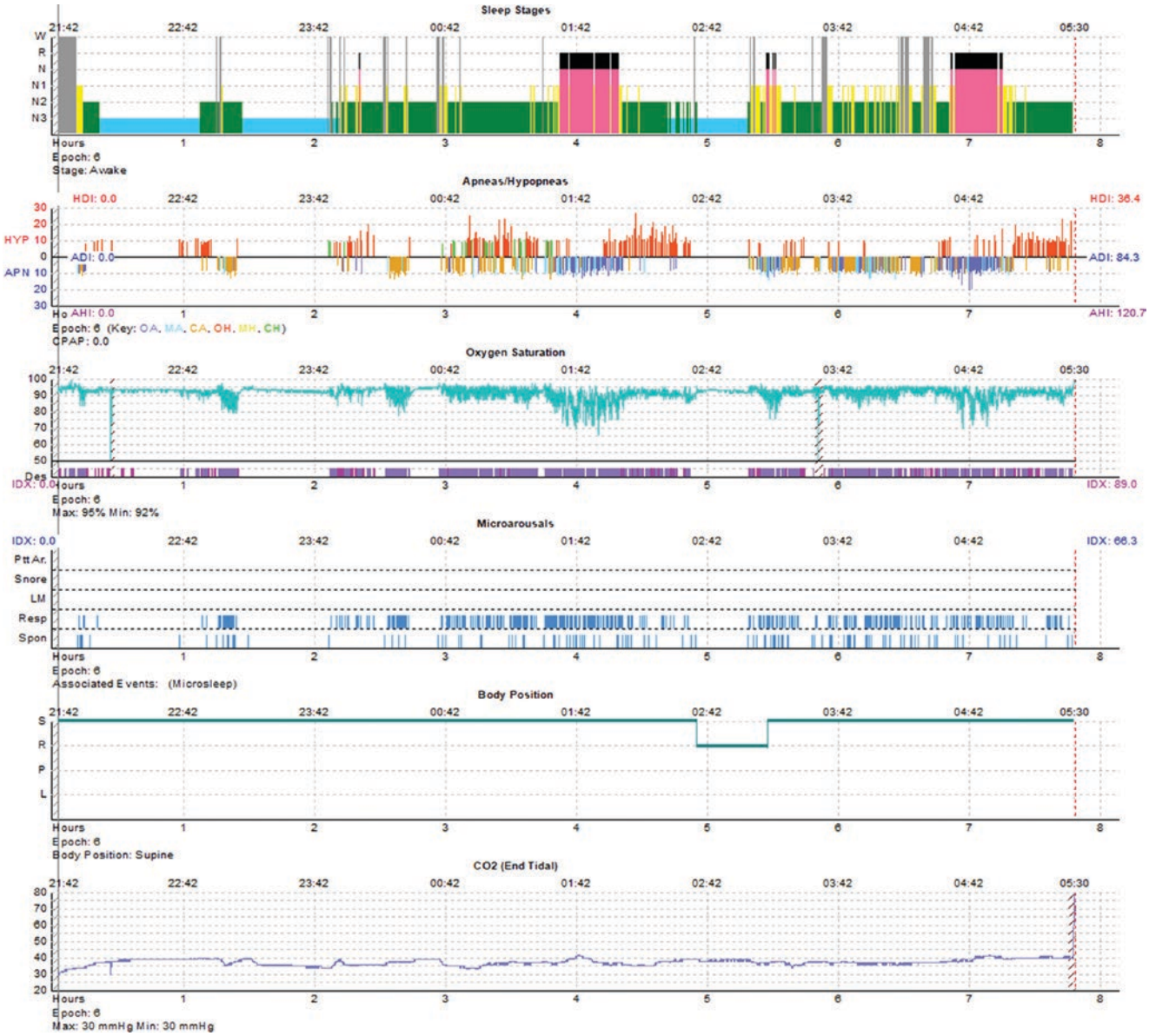


Fig. 18.8 Hypnogram of a 6-year-old with severe obstructive sleep apnea. The figure shows a hypnogram summarizing a polysomnogram recorded in a 6-year-old with severe obstructive sleep apnea. Channels displayed from top to bottom are sleep stages, apneas and hypopneas, oxygen saturation, microarousals, body position, and end-tidal carbon dioxide

Table 18.4 At what age do the different distinctive PSG features of sleep and wake first appear?

Distinctive PSG EEG feature	Developmental age when usually first seen
Sleep spindles	6 weeks to 3 months post-term; first appear maximal over midline *central* (CZ) and shift left to right (C3, C4)
Saw tooth waves of REM sleep	As early as age 7 weeks post-term and prominent over the frontal (F3, F4, FZ) and central (Cz, C3, C4) regions Typically 2–6 per second
Dominant posterior rhythm (DPR)	3.5–4.5 Hz by 3–4 months post-term; 5–6 Hz by 5–6 months; 7.5–9.5 Hz by 3 years; mean 9 Hz by 9 years, and 10 Hz by 15 years; maximal over occipital electrodes
K-complexes	First appear at age 3–6 months post-term and maximal over frontal regions
Slow wave activity (SWA) of NREM 3 sleep	2–5 months post-term and maximal over frontal regions
Hypnagogic hypersynchrony (HH)	3–6 months post-term
Vertex sharp waves (V-waves)	4–6 months post-term

Table 18.5 Summary of EEG features of sleep and wakefulness from infants to adolescents

	Infancy (2–12 months)	Early childhood (12–36 months)	Preschool (3–5 years)	School children (6–12 years)	Adolescents (13–20 years)
Dominant posterior rhythm (DPR)	DPR first seen 3–5 months; irregular 50–100 μV by 3–5 months; 5–6 Hz by 5–6 months; 7 Hz by 12 months DPR < 5 Hz by 1 y abnormal Reactivity of DPR to eye opening is first seen in 3–6 months	DPR 6–8 Hz rarely up to 9.5 Hz typically intermixed with slower activity Asymmetric mu (unreactive to eye opening) beginning at age 2 y over central (maybe mistaken for DPR)	Most children by age 3 have DPR of 8 Hz, amplitude increases from age 3 to 8 years, often 100 μV	DPR more often is 10 Hz by 10 years and intermixed with posterior slow waves of youth Mu activity over central region is most prominent in the second decade of life	Average DPR 10 Hz, range 9–11.5 (only 5% have >11.5 Hz); 5–10% of normal subjects have no DPR Gradual disappearance of intermixed slow activity in DPR which occupies 10–15% of DPR in adolescence Mature wake EEG observed by 16 y to as late as 30 y
Drowsiness and NREM 1	Hypnagogic hypersynchrony (4–6 Hz) First seen at age 6–8 months, maximum in frontocentral regions	Marked hypnagogic hypersynchrony continuous or in bursts	Hypnagogic hypersynchrony disappearing, rare in normal children after age 6 y	Gradual alpha dropout with increasing slow activity; rhythmic anterior theta (6–7 Hz) may be seen	Gradual alpha dropout with stretches of low voltage, mostly slow activity Rhythmic anterior theta seen but declines as approaching adulthood
Sleep spindles	If no sleep spindles, score all NREM sleep as NREM (N); once sleep spindles are present, score N1, N2, and N3; 12–14 Hz sleep spindles first seen at 44–46 w CA over midline central; sleep spindles often last for 8 up to 10–15 seconds, especially around 3–4 months	70% of sleep spindles are synchronous by 1 y; 100% by 2 y; sleep spindles often are sharply contoured, maximal over central and parietal regions 12–15 Hz	Symmetrical 12–15 Hz sleep spindles are maximal over midline central; independent 11–12 Hz frontal spindles may also be seen	Symmetrical 12-15 Hz sleep spindles maximal midline central often associated with K-complexes; frontally predominant 10-12 Hz spindles may also be seen	Sleep spindles now maximal in vertex, central, and parietal regions; frontal spindles disappear after age 13 y Sleep spindles often associated with K-complexes
Vertex waves and K-complexes	K-complexes first appear 5–6 months, maximal in frontal region Rare broad vertex waves, maximal in central and first seen in 6 months	Mature vertex waves by 16 months, maximal in central	K-complexes occur in rapid runs (3–9 in 1–3 seconds) at ages 3–9 years, predominantly surface-negative component	K-complexes maximal in frontal, vertex waves central	K-complexes maximal in frontal, vertex waves central
REM (R) sleep	4–5 Hz with bursts of saw tooth waves at 5 months	Slow activity (2–5 Hz) and at times desynchronization is seen	Prolonged runs or bursts of often notched 5–7 Hz theta activity	Less slow activity and more low-voltage desynchronized EEG	Mature REM sleep pattern of low-voltage desynchronized EEG, may see alpha activity often 1–2 Hz slower than DPR

ital region in relaxed wakefulness and eyes closed. The DPR is "reactive" because it tends to attenuate with eye opening or attention. The DPR is first seen in infants between ages 3-4 months post-term; the frequency then 3.5–4.5 Hz and maximal over the occipital EEG derivations. Spontaneous eye closure in an infant suggests drowsiness, so the DPR in an infant is best elicited using passive eye closure (saying "peak-a-boo"). We encourage the technologist to perform this maneuver during biocalibration before starting PSG recording.

By 12 months of age, the mean DPR is 6–7 Hz (range 6–8 Hz) and present in 70% of normal controls. By 3 years of age, the mean DPR in 82% of controls is 8 Hz (range 7.5–9.5), 9 Hz by 9 years in 65% of normal controls, and 10 Hz by 15 years. The mean DPR in adults is 10.2 ± 0.9 Hz and only 5% have a DPR >11.5 Hz. Ten percent or more of adults have no DPR (so-called "poor alpha generators"). The DPR averages 9.7 Hz in older adults. The DPR is normally ≥8.5 Hz in healthy oldest old. Figure 18.9a–d shows how the DPR changes with age in children.

The AASM Scoring Manual specifies that 30-second epochs of the PSG are scored as W if more than 50% of the 30-second epoch contains either or both of the following: (1) age-appropriate DPR over the occipital region; (2) other findings consistent with wakefulness: eye blinks; (3) rapid eye movements accompanied by normal or high chin muscle tone; (4) and/or reading eye movements.

The DPR in children and adolescents often contains intermixed slower EEG frequencies. Posterior slow waves of youth (PSW) are intermittent runs of bilateral (but more often asymmetric) 2.5–4.5 Hz slow waves superimposed, riding

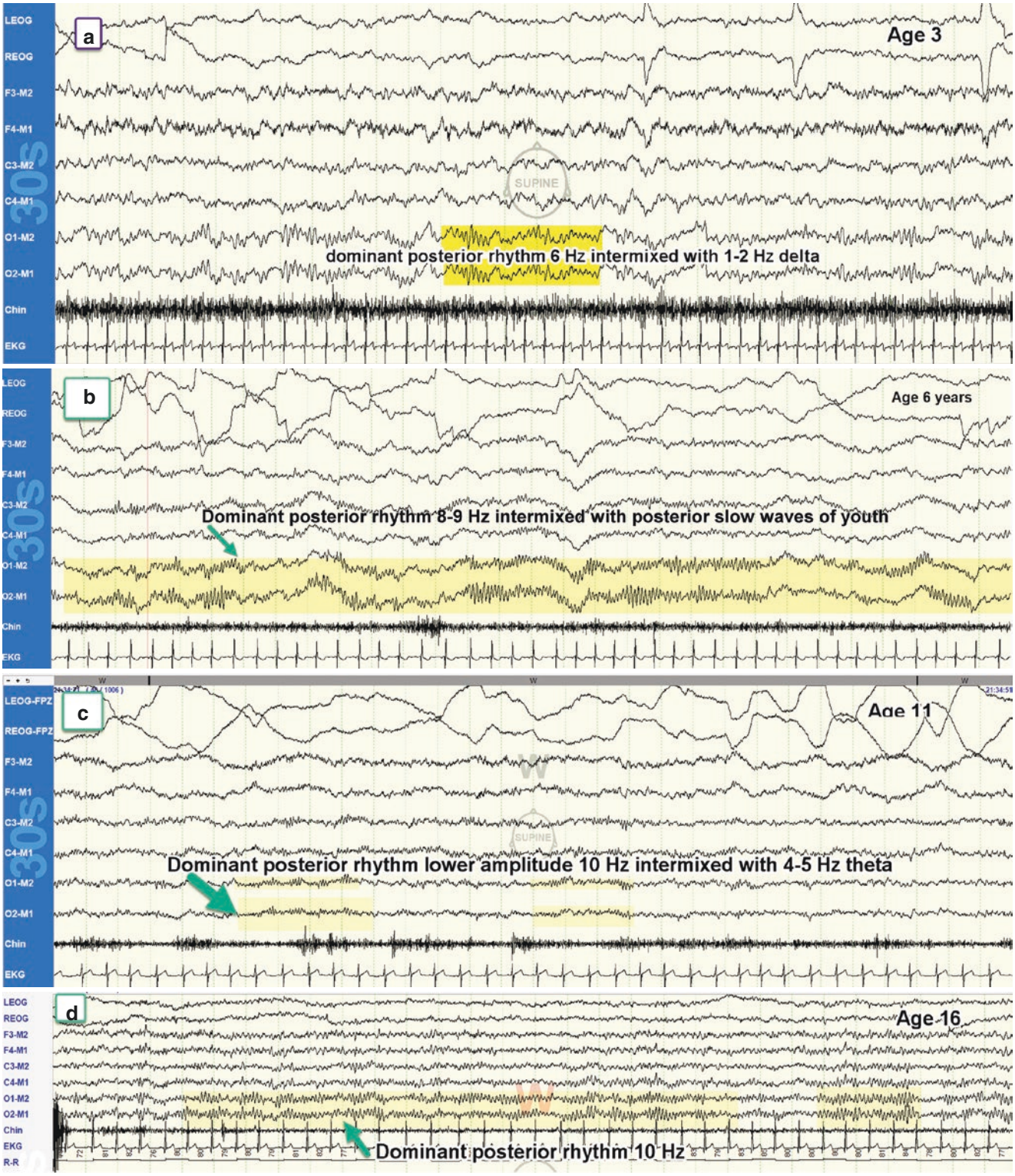


Fig. 18.9 How the dominant posterior rhythm (DPR) of relaxed wakefulness with eyes closed changes with age in children and adolescents. (**a**) A 30-second epoch of PSG recorded in wakefulness with eyes closed in a 3-year-old shows a dominant posterior rhythm (DPR) of 6 Hz over the occipital regions intermixed with medium amplitude 1–2 Hz delta activity bilaterally; (**b**) a 30-second epoch of PSG recorded in a 6-year-old which shows a DPR of 6 Hz intermixed with posterior slow waves (PSW) of youth; (**c**) a 30-second epoch of PSG recorded in an 11-year-old which shows 8–9 Hz intermixed with PSW; (**d**) dominant posterior rhythm in a 16-year-old shows a well-sustained 10 Hz alpha rhythm maximal in the occipital EEG derivations in this 30-second PSG recorded in wakefulness with eyes closed

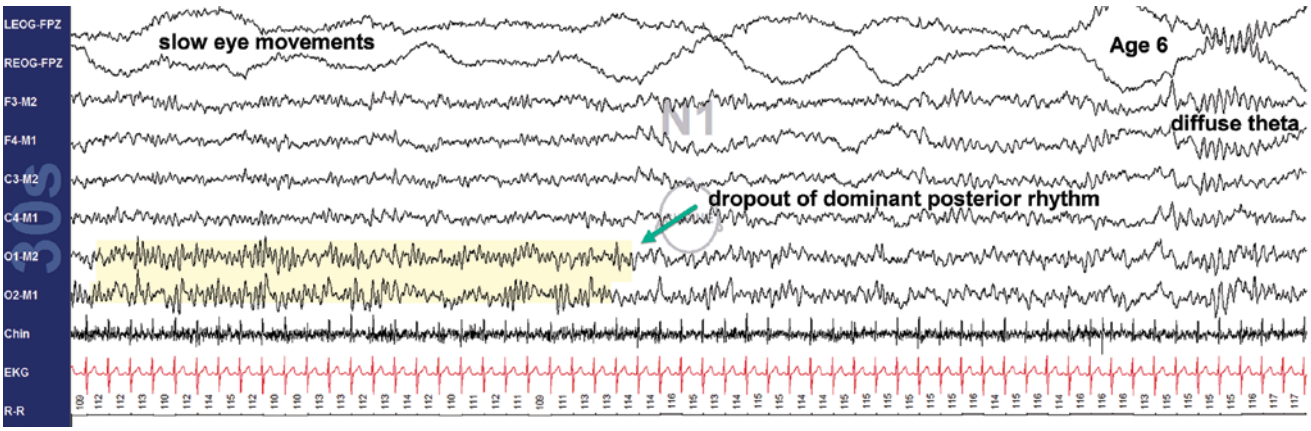


Fig. 18.10 Dropout of alpha rhythm with drowsiness at age 5. A 30-second epoch of PSG recorded in a 6-year-old shows slow eye movements in the eye movement channels (LEOG-FPZ, REOG-FPZ) which more often precede dropout of the dominant posterior rhythm (green arrow). The DPR contains appropriate amounts for age of intermixed slower EEG frequencies. Note diffused theta activity at the end of the epoch, one of the many EEG patterns of drowsiness/NREM 1 sleep in children

upon, or fused with the DPR (Fig. 18.9b, c). Intermixed slowing is "normal" when it is less than 120% the DPR amplitude, blocks with eye opening, and disappears with drowsiness. Posterior slow waves of youth (PSW) are 2.5–4.5 Hz slow waves which are superimposed, riding upon, or fused with the DPR. PSW tend to occur in intermittent runs, bilateral but often asymmetric (higher amplitude on one side or the other). PSW is uncommon in children younger than 2 years of age, maximal prevalence ages 8–14 years, and uncommon after age 21. Arrhythmic or rhythmic 2.5–4.5 Hz slowing intermixed with the DPR is common in children; the amount of intermixed slowing decreases, and its frequency increases with age, typically maximal between ages 5 and 7 years.

Drowsiness/Wake-Sleep Transition

In infants 6–8 months of age drowsiness in the EEG is characterized by the gradual appearance of diffuse high-amplitude (often 75–200 μV) 3–5 Hz activity. The amplitude of the EEG during drowsiness is typically of higher amplitude, more diffuse and 1–2 Hz slower than the waking EEG background activity. Diffuse runs or bursts of rhythmic or semi rhythmic bisynchronous (75–200 μV) 3–4 Hz activity maximal over the occipital regions and/or even higher amplitude (>200 μV) 4–6 Hz theta activity over the frontocentral or central regions characterize drowsiness in children of ages 8 months to 3 years. In children 3 years or older, drowsiness is characterized by 1–2 Hz slowing of the DPR and/or the DPR becomes diffusely distributed and then is gradually replaced by low-voltage mixed-frequency activity.

Scoring NREM 1 Sleep

In pediatric subjects who generate a DPR score, N1 is scored if the DPR is attenuated or replaced by low-amplitude mixed-frequency activity for >50% of the entire 30-second epoch (Fig. 18.10). In those who do not generate a DPR, N1 is scored beginning with the earliest of any of the following: (1) 4–7 Hz activity with slowing of background frequencies by ≥1–2 Hz from those of stage W, (2) slow eye movements, (3) vertex sharp waves, (4) rhythmic anterior theta activity, (5) hypnagogic hypersynchrony, and/or (6) diffuse or occipital predominant high-amplitude rhythmic 3–5 Hz activity.

NREM 1 definitions are worth understanding. Sleep onset is the start of the first 30-second epoch scored as any stage other than W. Vertex sharp waves (V waves) are sharply contoured waves which last <0.5 seconds maximal over central region distinguishable from background EEG activity and most often seen in N1 or N2 (Fig. 18.11). Hypnagogic hypersynchrony (Fig. 18.12) is a distinctive pattern of drowsiness and N1 in children is characterized by paroxysmal bursts (≤ 2 seconds) or runs (lasting >2 seconds) of diffuse high-amplitude sinusoidal 75–350 μV 3–4.5 Hz waves usually widely distributed but often maximal over central, frontal, or frontocentral regions. Hypnagogic hypersynchrony is seen in 30% of infants 3 months post-term, 95% ages 6–8 months, it becomes less prevalent after ages 4–5 years, only seen in 10% of healthy children age 11, and rarer after age 12. Rhythmic anterior theta activity is more often seen in adolescents when drowsiness is characterized by runs of rhythmic 5–7 activity maximal over frontal or frontocentral regions (Fig. 18.13).

Recognizing and Scoring NREM 2 Sleep in a Nocturnal Polysomnogram in Children

Rudimentary sleep spindles appear in infants as young as 43 weeks post-menstrual age (PMA) over the midline central regions (CZ). However, sleep spindles are most consistently present after 46 weeks PMA and still maximal over CZ. Sleep

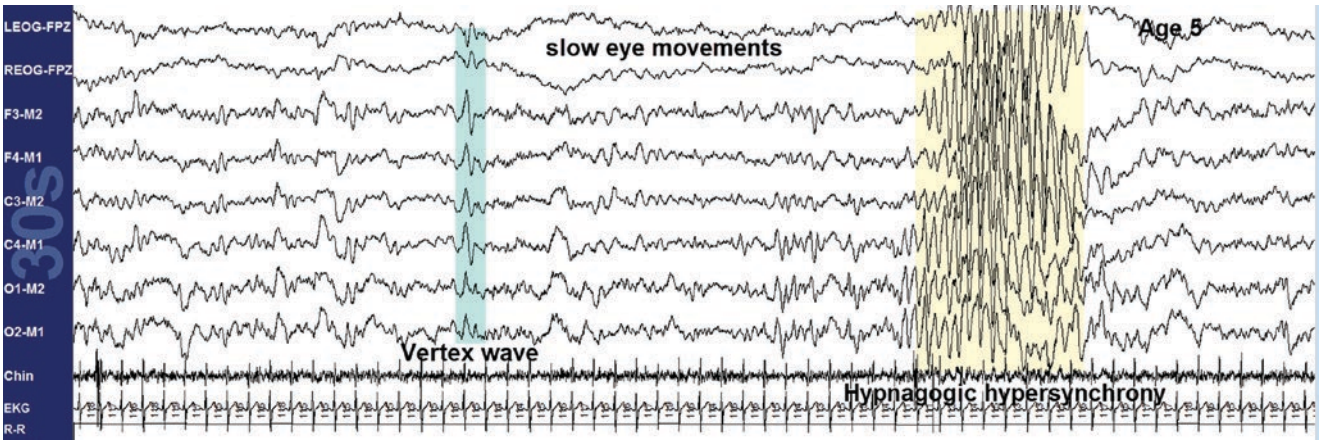


Fig. 18.11 Hypnagogic hypersynchrony and vertex activity at age 5. Vertex sharp waves (V waves) are sharply contoured waves which last less than 0.5 second maximal over the central region (C3-M2, C4-M1, CZ) and which are distinguishable from background EEG activity and most often seen in NREM 1 or NREM 2 sleep

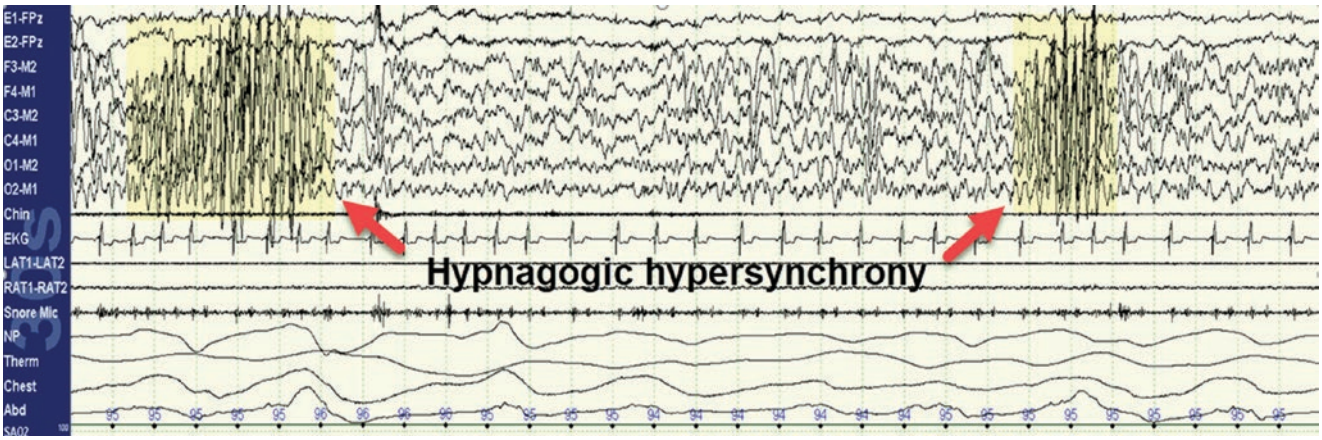


Fig. 18.12 A 30-second of PSG recorded in NREM 1 sleep in a 5-year-old, which shows a paroxysmal burst of hypnagogic hypersynchrony (yellow highlight), vertex wave (aqua highlight), and slow eye movements. Hypnagogic hypersynchrony is a distinctive pattern of drowsiness and NREM 1 in children and is characterized by paroxysmal bursts (<2 seconds) or runs (lasting >2 seconds) of diffuse high-amplitude sinusoidal 75–350 μV 3–4.5 Hz waves usually widely distributed but often maximal over central, frontal, or frontocentral regions. Hypnagogic hypersynchrony is seen in 30% of infants 3 months post-term, 95% ages 6–8 months, it becomes less prevalent after ages 4–5 years, only seen in 10% of healthy children age 11, and rarer after age 12

spindles are often asynchronous until 1–2 years of age (most often synchronous by 18 months, abnormal if asynchronous after 2 years of age). At 6 months of age only 50% of sleep spindles are synchronous (i.e., occurring simultaneously over the left and right central EEG derivations); 70% at 9 and 12 months. All sleep spindles should occur synchronously by 2 years of age. Between 3 and 4 months PMA, sleep spindles often last 5–8 seconds or longer (Fig. 18.14).

Sleep spindles first appear in NREM 2 sleep. Eighty percent of children <13 years of age have two independent scalp locations and frequency ranges for sleep spindles: 11–12.75 Hz over the frontal regions (Fig. 18.15) and 12.5–14.5 Hz over the centroparietal regions [70]. The peak frequency of centroparietal spindles gradually increases with age, whereas the frequency of frontal spindles abruptly increases in early adolescence. The EEG power of frontal spindles decreases significantly after age 13. K-complexes typically appear approximately 5–6 months post-term and are maximal over the frontal (F3-M1, F4-M2) and prefrontal regions. The surface negative component of K-complexes is of highest amplitude and most sharply contoured by ages 3–5 years. Vertex waves in children are often "spiky" in appearance and can occur in runs intermixed with K-complexes (Fig. 18.16).

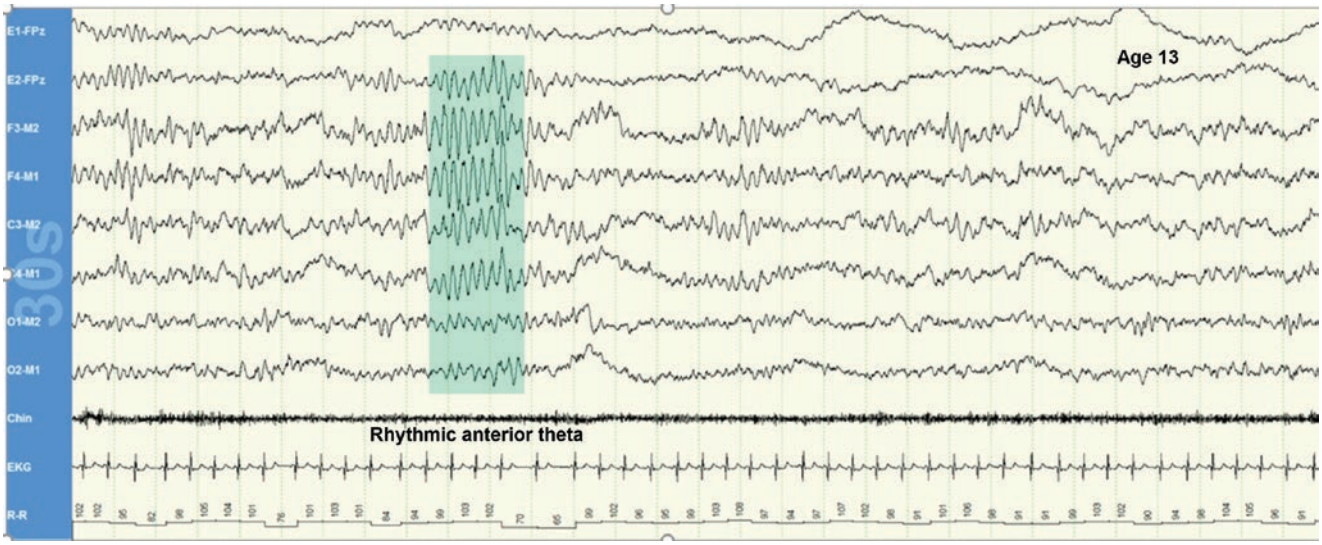


Fig. 18.13 A 30-second epoch of PSG recorded in NREM 1 in 13-year-old shows a single run of rhythmic anterior theta activity which is most often seen in adolescents when drowsiness is characterized by runs of rhythmic 5–7 activity maximal over frontal or frontocentral regions

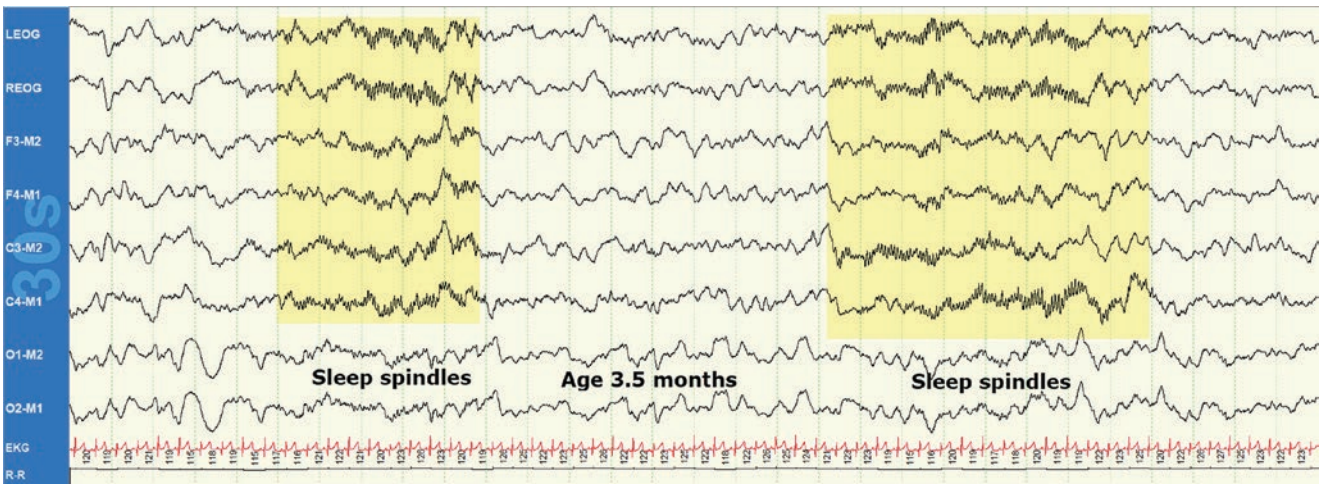


Fig. 18.14 A 30-second epoch of PSG recorded in a 3-month-old is typical for maturational age long-lasting sleep spindles. Between 3 and 4 months PMA, sleep spindles often last for 5–8 seconds or longer

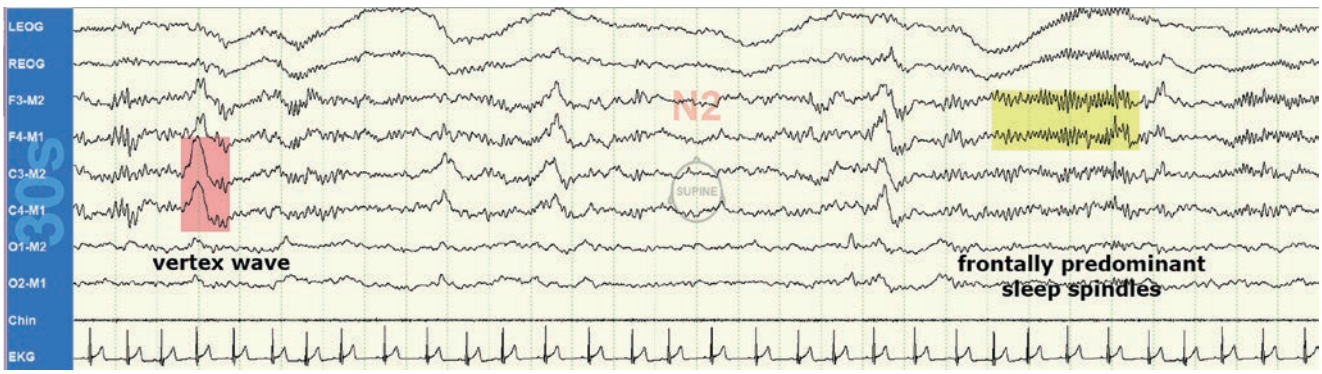


Fig. 18.15 A 30-second epoch of PSG recorded in a 6-year-old during NREM 2 sleep shows frontally predominant sleep spindles (yellow highlight) and vertex waves (salmon highlight)

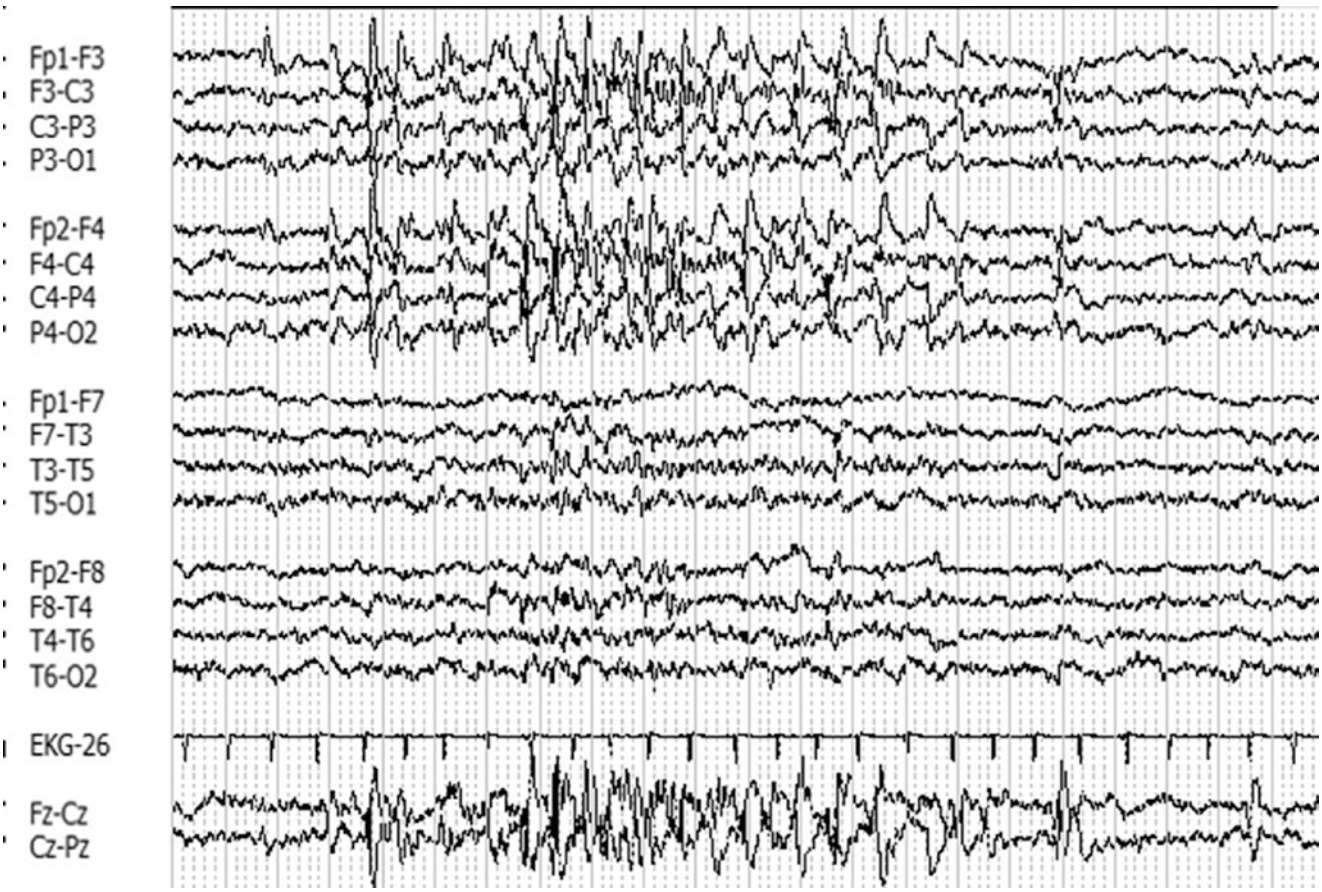


Fig. 18.16 Run of spiky-appearing K-complexes and vertex waves in an 8-year-old

Scoring NREM 3 Sleep in Children

NREM 3 (defined as ≥75 μV ≤ 2 Hz occupying >20% of a 30-second epoch) is usually present in infants of 5–6 months term. Infant sleep researchers report they could score NREM 3 as early as 2–4.5 months term, but most often 3–4.5 months post-term. The slow wave activity (SWA) in children (and adults) is often 100–400 μV and typically maximal over the frontal regions (although in many it is equally present over the frontal and central EEG derivations). Figure 18.17 shows representative samples of SWA in NREM 3 in children.

Scoring REM Sleep in Children

All of the brain neuronal wiring for REM sleep is present in healthy infants by 32 weeks GA [71]. Eighty percent of sleep time in premature infants is spent in REM sleep. Infants at term spend 50% time sleeping in REM sleep. Sleep onset in infants ≤3 months post-term is typically REM (R) sleep. The continuous low-voltage mixed-frequency EEG activity of stage R in infants and children resembles adults, although the dominant frequencies increase with age: (1) approximately 3 Hz activity at 7 weeks post-term; (2) 4–5 Hz with bursts of saw tooth waves at 5 months; (3) 4–6 Hz at 9 months; and (4) prolonged runs or bursts of often notched 5- to 7-Hz theta activity at 1–5 years of age. By ages 5–10 years, the EEG during REM sleep resembles that of adults and is characterized by low-voltage mixed-frequency activity with bursts of 4–6 per second saw tooth waves maximal over the central regions and most prevalent during phasic REM and maximal over midline central (Cz) electrode. Figure 18.18 shows how the EEG of REM sleep changes with age in children. The AASM Manual emphasizes that sleep spindles may be present during the first or second REM sleep periods but if all other behavioral markers of REM sleep are present (e,g., rapid eye movements, reduced chin EMG tone, low voltage mixed frequency EEG) should not prevent scoring the epoch as stage R.

Scoring Arousals in Children of Ages 2 Months to 18 Years

An arousal is scored in any stage of sleep when there is an abrupt change in EEG frequency in the alpha and theta or frequency higher than 16 Hz excluding spindles lasting at least 3 seconds and preceded by ≥10 seconds of sleep

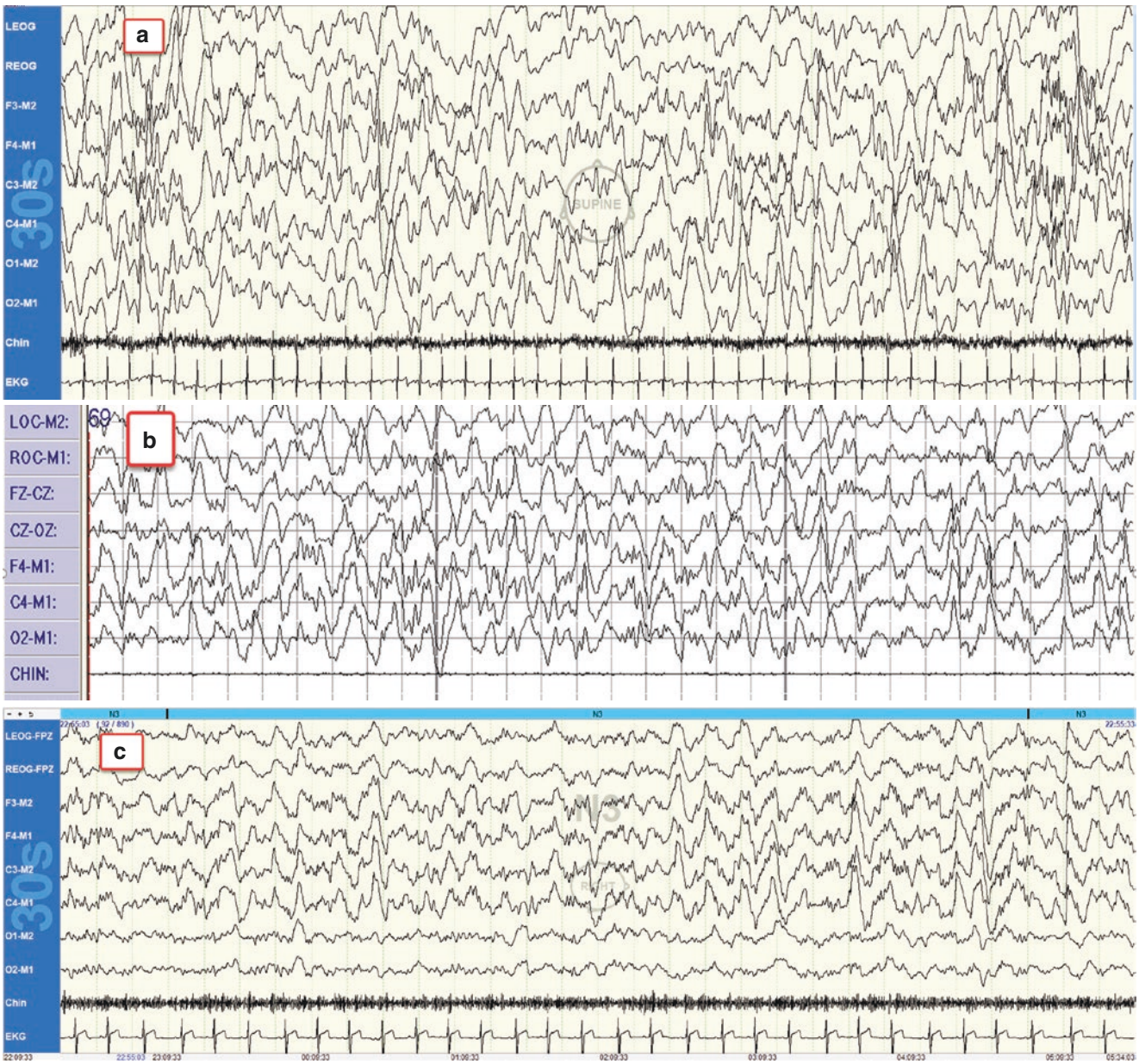


Fig. 18.17 Representative examples of NREM 3 at different ages: (**a**) age 3; (**b**) age 7; (**c**) age 16

(Fig. 18.19). For an arousal to be scored in stage REM, it must be accompanied by an increase in the chin EMG lasting ≥1 second.

Scoring Respiratory Events in Children of Ages 2 Months to 18 Years

After scoring sleep/wake states and arousals in a pediatric PSG, we then score apneas, hypopneas, and respiratory effort-related arousals (RERAs) using the AASM Scoring Manual. An apnea in a child is scored if there is a ≥ 90% drop in the peak airflow signal excursion for ≥2 breaths compared to the pre-event baseline using an oronasal thermal sensor (diagnostic study), PAP device flow (titration study), or an alternative sensor if oronasal sensor malfunctions (diagnostic study).

Apnea types (obstructive, central, mixed) are identified by respiratory effort. *Obstructive apnea* in a child is defined as a ≥ 90% decrease in inspiratory effort for ≥2 breaths throughout the entire period of absent oronasal airflow. *Central apnea in* a child is characterized by absent respiratory effort throughout the event and one of the following: (1) lasts ≥20 seconds; (2) lasts ≥2 breaths during baseline breathing and is associated with an arousal **or** a ≥ 3% arterial oxygen desaturation; or (3) lasts at least two breaths and accompanied by a fall in

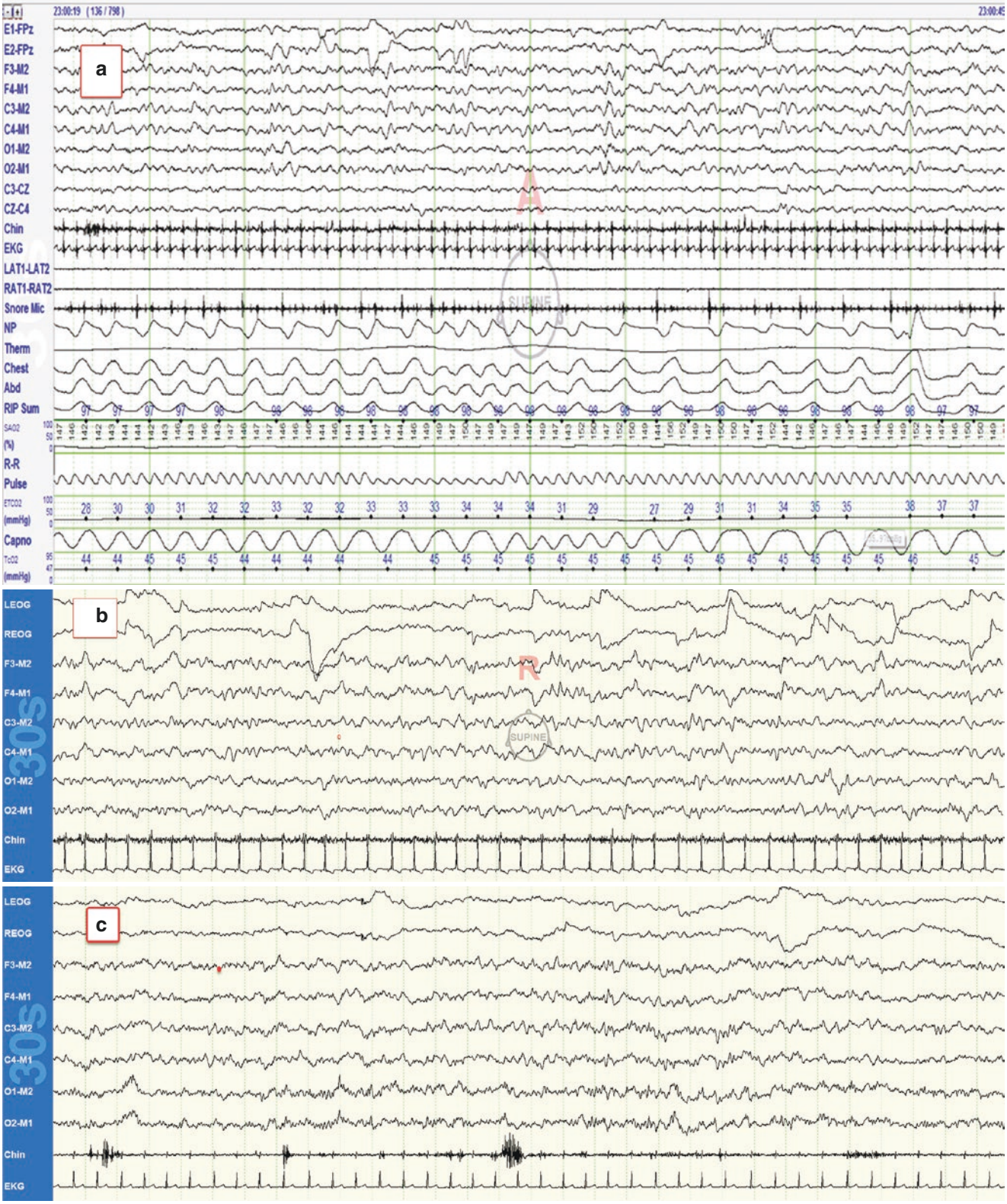


Fig. 18.18 Representative example of REM sleep at different ages: (**a**) full term infant; (**b**) age 7; (**c**) age 14

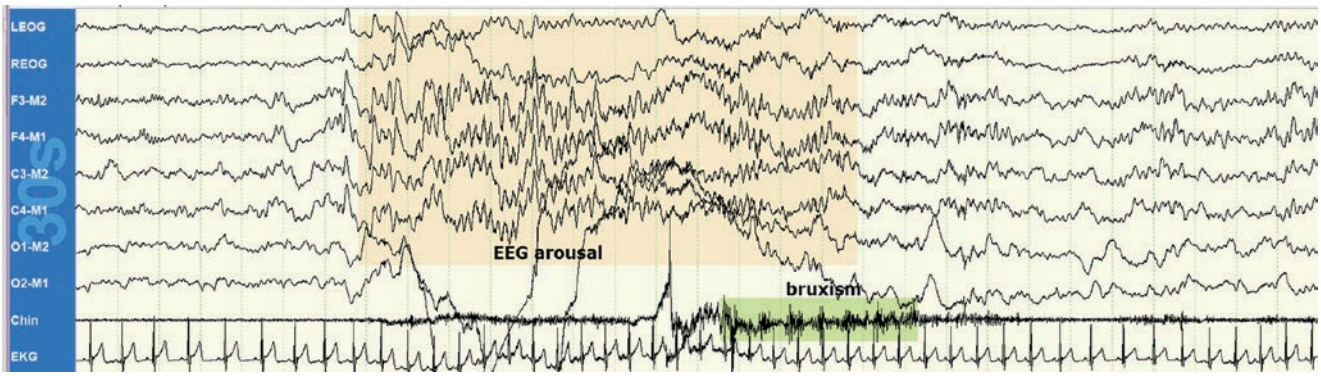


Fig. 18.19 Arousal from NREM sleep followed by bruxism

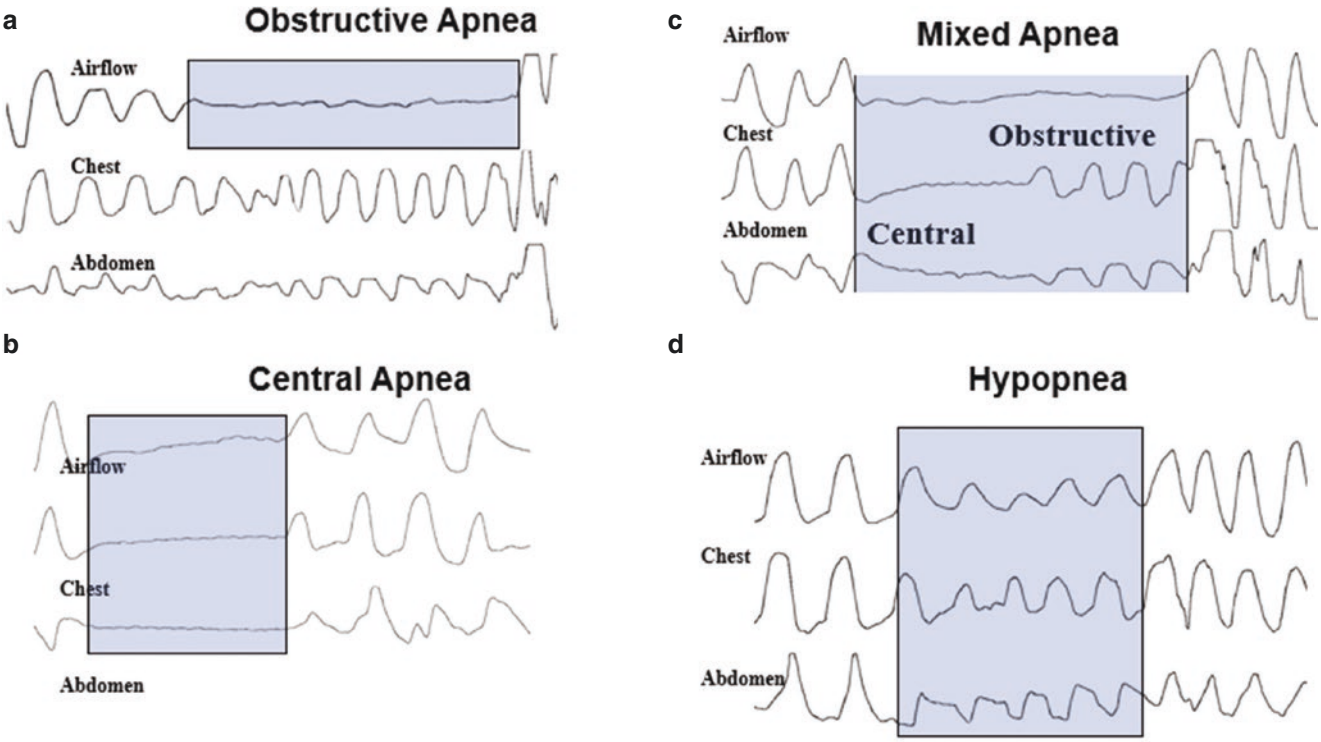


Fig. 18.20 Representative examples of obstructive, mixed, and central apneas and hypopneas

the heart rate to <50 beats per minute (bpm) for ≥5 seconds or < 60 bpm for 15 seconds in infants less than 1 year of age. *Mixed apnea is* associated with absent respiratory effort during a portion of the event and inspiratory effort during another portion in either order and lasts ≥2 breaths. If a portion of a respiratory event meets criteria for a hypopnea and another portion meets criteria for apnea, the entire event should be scored as an apnea. The specific duration of central and obstructive components of a mixed apnea are not specified (insufficient evidence to do so but it could be only one breath). Figure 18.20 shows representative examples of obstructive, central, and mixed apneas and hypopnea. Figure 18.21 shows an obstructive apnea in a child.

A *hypopnea* is scored in a pediatric level 1 PSG if the peak signal excursions decrease by ≥30% (but <90%) for ≥2 breaths of pre-event baseline using nasal pressure (diagnostic study), PAP device flow (titration study), or an alternative hypopnea sensor (diagnostic study), and they are accompanied by either ≥3% oxygen desaturation and/or an arousal (Fig. 18.22). Scoring hypopneas as central or obstructive in type is optional in children. Obstructive hypopneas are scored if they are accompanied by snoring, flow limitation, paradoxical breathing, and/or increasing respiratory effort to open the airway. Central hypopneas are scored by the absence of snoring, flow limitation, and paradoxical breathing. Distinguishing central from obstructive hypopneas is

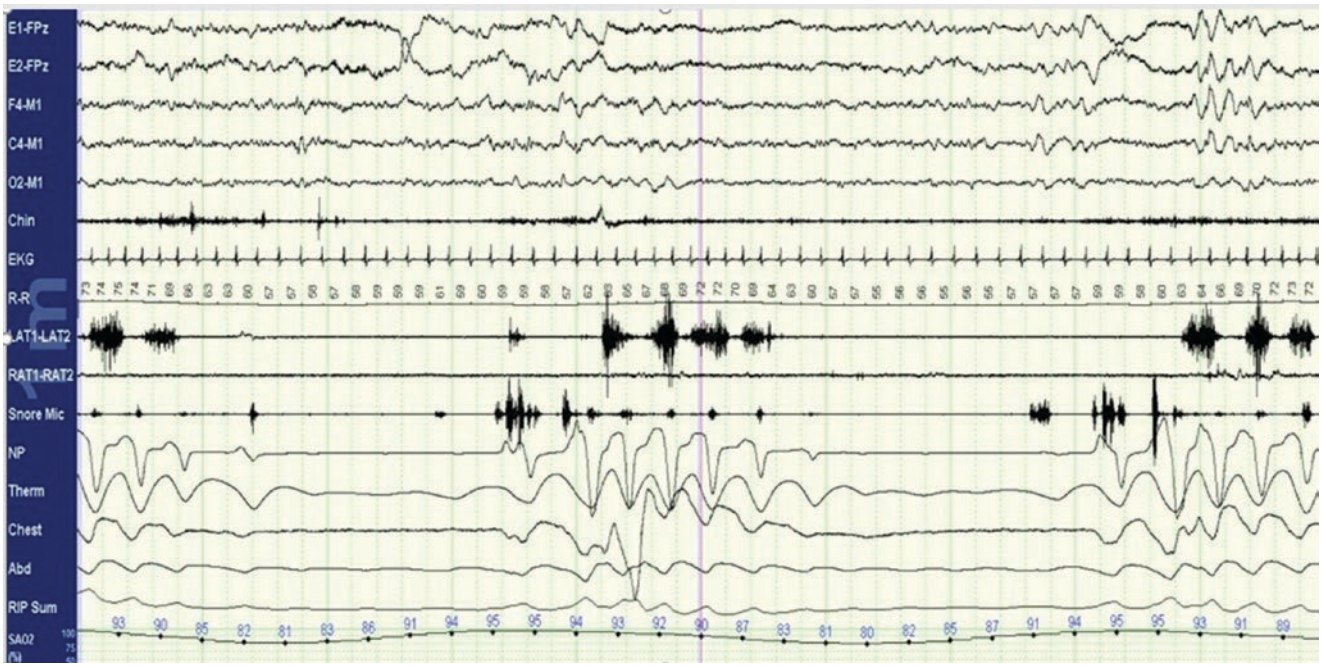


Fig. 18.21 A run of two obstructive apneas in a child

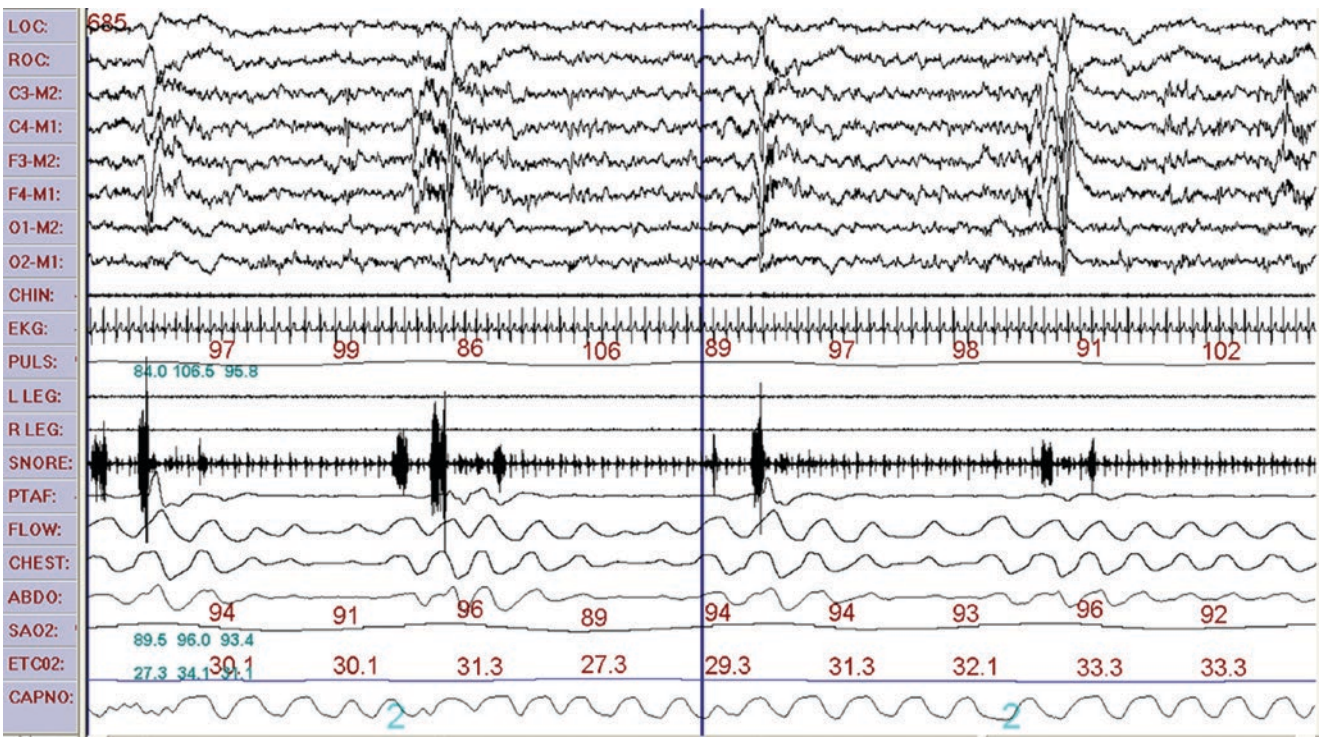


Fig. 18.22 Run of obstructive hypopneas in a child

particularly challenging in children; the AASM Scoring Manual does not require us to score them.

Respiratory effort-related arousal (RERA) is defined as a sequence of ≥2 breaths of increasing respiratory effort, flattening of inspiratory portion of the NP signal (diagnostic study) or PAP device flow (titration study) waveform (a decrease of <30%), snoring, and/or an increase in the end-tidal PCO_2, which cause an arousal or awakening. The decision to score RERAs in children is also optional and again we have given up trying especially in infants and younger children.

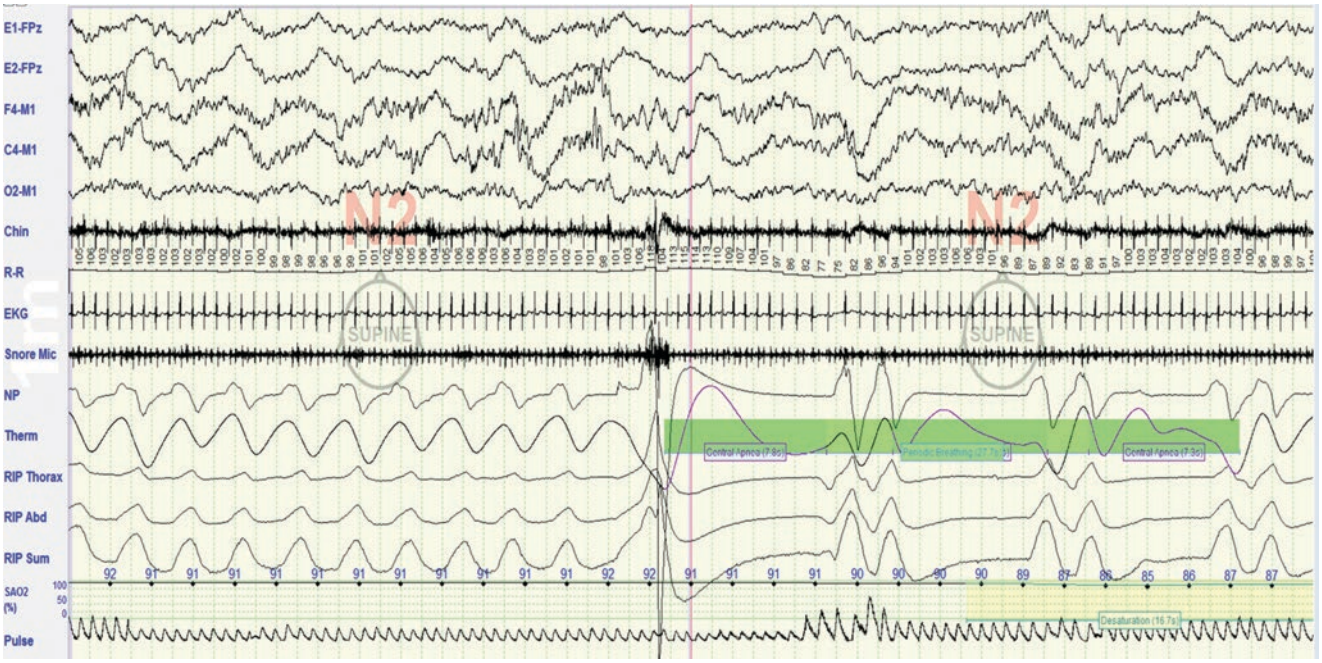


Fig. 18.23 Run of periodic breathing in a child following an arousal from NREM 2 sleep

Hypoventilation during sleep is scored in a pediatric PSG when >25% of the total sleep time as measured by either the arterial PCO_2 or surrogate is spent with a $PCO_2 > 50$ mm Hg. Respiratory events are scored as *periodic breathing* if there are ≥3 episodes of central apnea lasting >3 seconds separated by ≤20 seconds of normal breathing. Central apneas that occur within a run of periodic breathing should be scored as individual apneas as well. Figure 18.23 shows a brief run of periodic breathing in a child following arousal from NREM 2 sleep.

Event duration from nadir preceding the first breath is reduced to the beginning of the first breath that approximates the baseline breathing amplitude. Apnea duration is preferentially measured using the oronasal thermal sensor (diagnostic study) and the PAP device flow signal (PAP titration). Hypopnea duration in a diagnostic study measured using NP signal, the PAP device flow signal in a PAP titration. If recommended sensor fails and signal is inaccurate, use alternate sensor. If the baseline breathing amplitude cannot be easily determined (and when the underlying breathing variability is large), terminate a respiratory event (1) when there is a clear and sustained increase in breathing amplitude OR (2) when an event-associated oxygen re-saturation of ≥2% has occurred. If an apnea or hypopnea begins or ends during an epoch that is scored as sleep, it can be scored and included in calculating the apnea hypopnea index (AHI). However, if the apnea or hypopnea occurs entirely during an epoch scored as wake, it should not be scored or counted in the AHI. If these occurrences are a prominent feature of the PSG and/or interfere with sleep onset, their presence should be mentioned in the narrative summary of the study.

When observing respiratory events in a PSG, we further assess do these: (1) cause arousals and/or awakenings; (2) worse during REM sleep or when sleeping supine; (3) associated with oxygen desaturation; (4) are oxygen desaturations worse in REM sleep or when supine; and (5) affect on ECG (e,g., cause a sinus bradytachycardia response or sinus pause). We also identify and report other signs of pediatric obstructive sleep disordered breathing: (1) airway protective maneuvers (persistent mouth opening/breathing, neck hyperextension, avoiding sleeping supine) on video-PSG; (2) snoring, noisy breathing, stridor; (3) flow limitation in the NP sensor accompanied by snoring and hypercapnia (so-called obstructive hypoventilation); and (4) tachypnea and/or increased work of breathing.

Once respiratory event scoring is complete, the digital PSG program then tallies the number of apneas, hypopneas, and apnea types (obstructive, central, mixed) and calculates the mean number of apneas and hypopneas per hour of sleep (AHI), the mean number of pediatric obstructive apneas and hypopneas per hour of sleep (PAOHI), mean number of central apneas per hour of sleep (CAI), and the mean number of obstructive apneas per hour of sleep (OAI). For example, the PAOHI is the number of obstructive apneas and hypopneas × 60/total sleep time. Oximetry and arousal data are tallied providing mean SpO_2 and nadir SpO_2 in wakefulness, NREM, and REM sleep, ≥ 3% oxygen desaturation index (ODI), and percentage of $SpO_2 \leq 90\%$ (or 88% at our altitude). A total sleep time with $CO_2 > 50$ mm Hg (Torr) is reported.

Scoring Pediatric Periodic Limb Movements in Sleep

The AASM Scoring Manual currently recommends that periodic limb movements in sleep (PLMS) are scored from the tibialis anterior's EMG signal (Fig. 18.24). A leg movement (LM) is scored when the EMG amplitude increases by 8 μV over baseline for ≥0.5 seconds but ≤10 seconds. A PLM series is scored if ≥4 such movements occur in a row, provided each individual movement occurs within 5–90 seconds of its neighbor. LMs are scored as being associated with an arousal when the two occur simultaneously, overlap, or when the end of one occurs in <0.5 seconds of the beginning of the other, whichever comes first. PLMs are totaled and averaged over the total recorded sleep time to calculate the PLM index (PLMI) and the PLM arousal index (PLMAI).

In 2016, a joint task force of the International and European Restless Legs Syndrome Study Groups and World Association of Sleep Medicine revised and updated standards for recording and scoring leg movements in PSG [49]. These redefine the minimum inter-movement interval (IMI) between consecutive PLMS as ≥10 seconds (vs. ≥ 5 seconds). The authors justify changing the IMI from ≥10 to ≤90 from previous ≥5 to ≤90 seconds because (1) IMI of all LM have a bimodal low point at about 10 s and (2) using the 10–90 s range had minimal effect on the number of PLMS in patients with RLS, but greatly reduced the number of PLM in wakefulness. Another significant revision is as follows: arousals are scored as related to PLMS if they occur within ±10 seconds of a PLM (and those related to respiratory events scored).

Scoring REM Sleep Without Atonia

REM sleep behavior disorder (RBD) is characterized by increased muscle activity (REM sleep without atonia, RWA) associated with abnormal motor and vocal behaviors during REM sleep [72]. To best identify RWA and RBD behaviors, additional EMG electrodes and careful review of patient's motor behaviors and vocalizations are required, especially during phasic REM sleep.

The AASM Manual criteria for scoring RWA in a 30-second epoch of REM sleep are as follows: (1) excessive tonic (sustained) chin muscle activity ≥50% of the epoch in which the chin EMG amplitude higher than observed in NREM sleep epochs (Fig. 18.25) and (2) excessive phasic (transient) activity in which ≥5 of sequential 3-second mini-epochs contain bursts of transient muscle activity (0.1–0.5 seconds and ≥ 4 times higher amplitude of the background EMG activity) (Fig. 18.26). Phasic activity can be scored in the chin or limb EMG channels.

An elegant study by Frauscher et al. (2008) systematically evaluated which of the 13 skeletal muscles provided the highest rate of REM sleep phasic activity in 17 adults with RBD [51]. They scored 3-second epochs and found that the

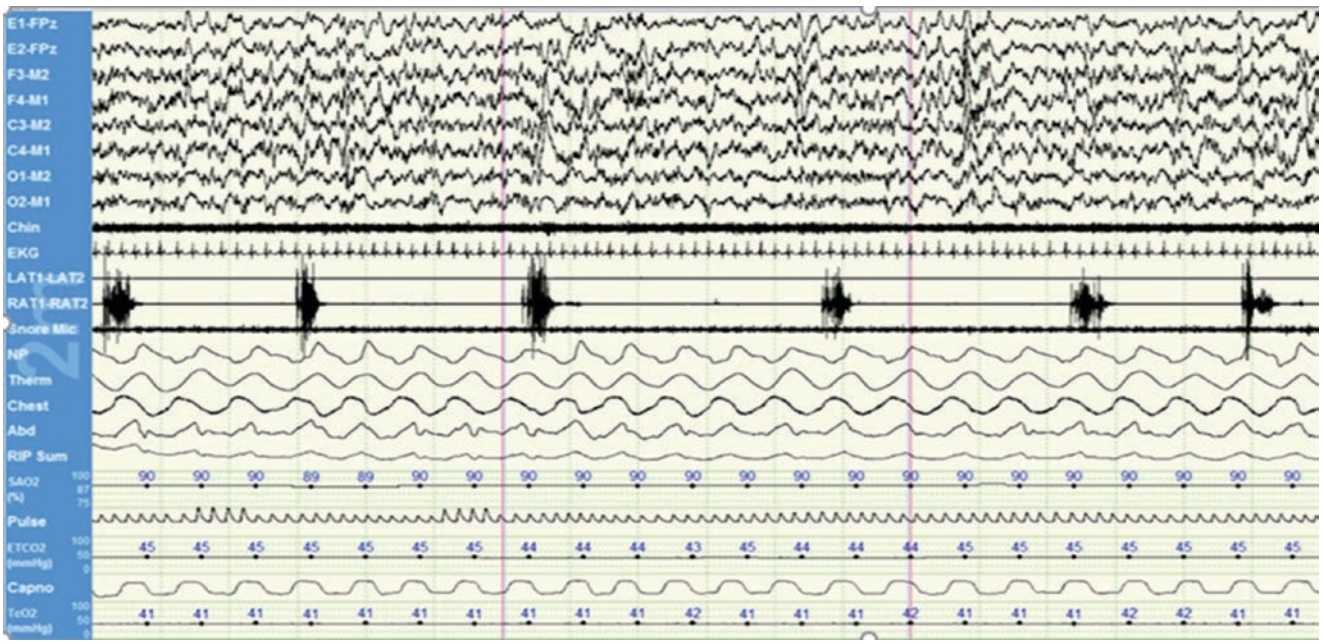


Fig. 18.24 A 180-second epoch from a PSG showing 6 periodic limb movements occurring during NREM 2 sleep which only involved the right anterior tibialis muscle. Note how periodically these recur and do not cause arousal. The study was recorded using our standard pediatric PSG montage

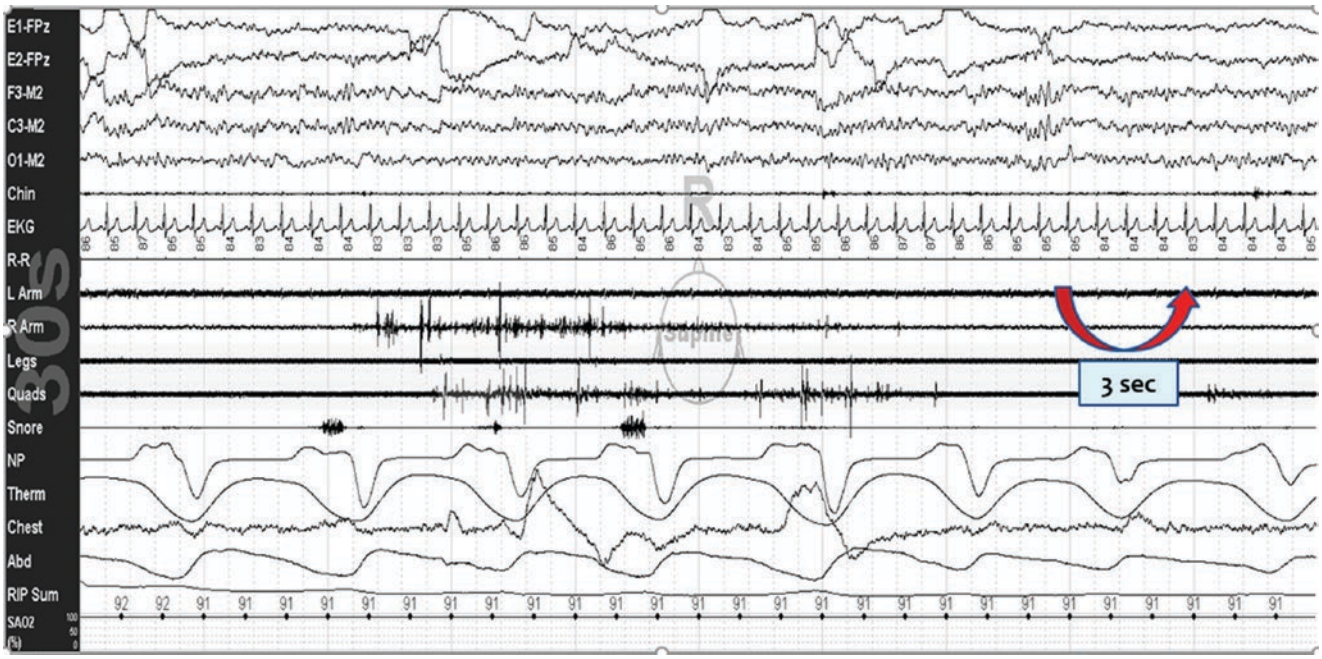


Fig. 18.25 A 30-second epoch of PSG which shows excessive tonic muscle activity in the mentalis (chin) EMG during REM sleep. Note the other PSG markers of REM sleep (rapid eye movements in E1-FPZ and E2-FPZ), low voltage mixed EEG frequencies in the EEG channels (F3, C3, O1 referenced to M2), and irregular respiration in the respiratory channels. The AASM scores excessive tonic activity in 30 second if >50% of the epoch contains excessive tonic EMG activity in the chin or limb EMG during REM sleep

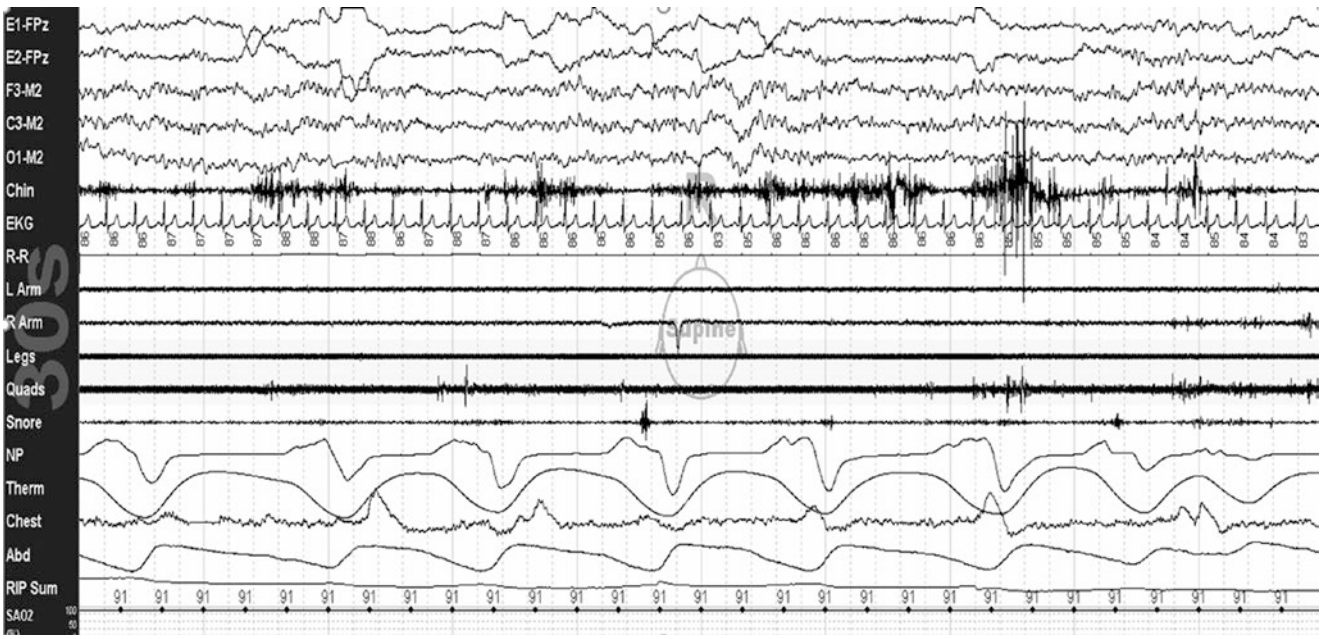


Fig. 18.26 A 30-second epoch of PSG which shows excessive transient (phasic) activity in the right flexor digitorum superficialis and quadricep muscles during REM sleep. The AASM scores a 30 sec of REM sleep as RWA if > 50% of sequential 3 second mini-epochs containing bursts of transient (phasic) muscle activity. Excessive transient muscle activity are defined as bursts of EMG activity which last 0.1–5.0 seconds and are at least 4 times as high in amplitude as the background EMG activity

mean percentages of phasic EMG were highest in the mentalis (42 ± 19%), flexor digitorum superficialis (FDS) (29 ± 13%), and extensor digitorum brevis (EDB) (23 ± 12%) muscles. The chin EMG only detected 55% of all the mini-epochs with phasic EMG activity; recording the mentalis, FDC, and EDB detected 82% of all mini-epochs containing phasic EMG activity. This led to the so-called SINBAR montage recording mentalis and bilateral FDS and EDB muscles to best identify RWA and RBD. A 2011 study showed that the SINBAR montage detected 94% of the motor and vocal manifestations occurring in 11 adults with RBD [52]. The authors reported that RBD dream enactment behaviors were most efficiently identified by reviewing epochs containing prominent phasic limb EMG activity. The mentalis did not show phasic EMG activity in 36% of the behavioral events seen in the video [52].

We calculate the nocturnal RWA (nRWA) index when observing RWA in a PSG: (total number of stage R sleep epochs with RWA (tonic and/or phasic) on the PSG/total stage R sleep epochs on the PSG) × 100 [73]. If not too difficult, the calculation can be repeated to derive subcategories of tonic nRWA and phasic nRWA indexes. If an epoch contains both phasic and tonic RWA, it can be scored as excessive phasic RWA. We find it best to review video-PSG during epochs of prominent excessive phasic REM sleep EMG activity to best identify RBD dream enactment behaviors. Last, we find it best not to score chin EMG associated with arousals from sleep, gross body movements induced by the technologist or co-sleeping parent, obstructive or central events, or bruxism when scoring RWA. Finally we asked, "how does one score REM sleep in patients in whom RWA is highly prevalent?" We find it best to use scoring rules first recommended by the Montplaisir group [74]: (1) sleep stages were scored using AASM criteria except permitting scoring REM, despite excessive chin EMG; (2) first rapid eye movement in EOG determines the onset of a REM sleep period; and (3) stop scoring a REM sleep period when: (a) rapid eye movements are no longer seen in three consecutive minutes; (b) an awakening occurs; or (c) K-complexes or sleep spindles are observed.

Scoring Sleep/Wake States in Infants 0–2 Months of Age

On July 1, 2015, the AASM published rules for scoring sleep in level 1 PSG for infants 0–2 months of age [71, 75, 76]. Sleep/wake should be scored in 30-sec epochs for Lights Out to Lights On as either wakefulness (W), REM (R), NREM (N), and transitional (T) sleep. Using the terms "active" for R sleep, "quiet" for N sleep, and "indeterminate" for T sleep is discouraged.

Crucial to Know the Infant's Gestational and Chronological Age

When scoring a PSG in infants 2 months post-term, it is crucial to know their gestational age (GA) and post-menstrual age (PMA) because the brain and the EEG continue to develop and mature at a similar rate independent of whether the infant is in utero or post-delivery [71]. The EEG in a PSG of a healthy low-risk premature born 32 weeks GA when 8 weeks old should resemble that of a normal 40 weeks GA infant born 2 days earlier.

GA is the time elapsed between the first day of the mother's last menstrual period and the day of delivery expressed in completed weeks [77]. PMA is the time elapsed in days, weeks, or months since birth. Two weeks are added to the PMA if the pregnancy was achieved using assisted reproductive technology. At birth, an infant is classified as premature (<37 weeks gestation), full-term (37 to 42 weeks), or post-term (born after 42 weeks). A neonate is a child during the first 28 days after birth; an infant is a child between 1 and 12 months of age [77].

Technical Considerations When Recording Level 1 PSG in Infants 0–2 Months Old

The EEG montages that permit adequate display of young infant EEG are F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, and O2-M1. However, additionally, recording C3-Cz and Cz-C4 can help detect early and asynchronous sleep spindles which may appear as early as 43 weeks PMA over CZ, using neonatal EKG electrodes made of hydrocolloids for EKG, chin EMG, and EOG (gentler for their thin skin). EEG is often of higher amplitude, so sensitivity is more often 10–15 μV/mm (but starts with routine 7 μV/mm). The EOG electrode distance from eyes may need to be reduced from 1 to 0.5 cm and chin EMG electrodes from 2 to 1 cm. Chin EMG sensitivity is best set at 2 μV/mm. The AASM Manual recommends that we use a modified lead II (right and left anterior chest walls) to record EKG, but sometimes we place electrodes on the right and left arms which permit simultaneous recording of EKG and arm movements. Figure 18.27 shows our routine infant PSG montage (and periodic breathing) in a term infant.

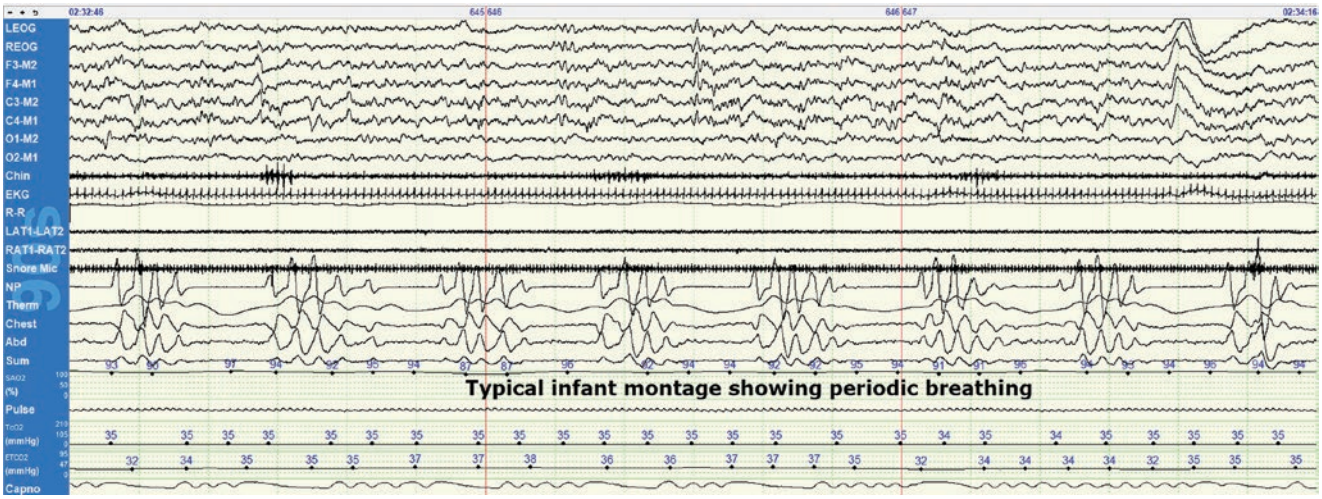


Fig. 18.27 Routine infant PSG montage. A 90-second epoch of PSG recorded on an infant using our standard infant PSG montage. We record left and right EOG, left and right frontal, central, and occipital EEG referenced to the contralateral mastoid (F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, O2-M1), chin EMG, EKG, R-R interval, left and right anterior tibialis muscles, nasal pressure (NP), thermal sensor (Therm), respiratory effort (Chest, Abd), pulse oxyhemoglobin saturation (SpO_2), pulse waveform (Pulse), transcutaneous CO_2 ($tcCO_2$), end-tidal CO_2 ($etCO_2$), and capnograph (Capno). Periodic breathing is observed

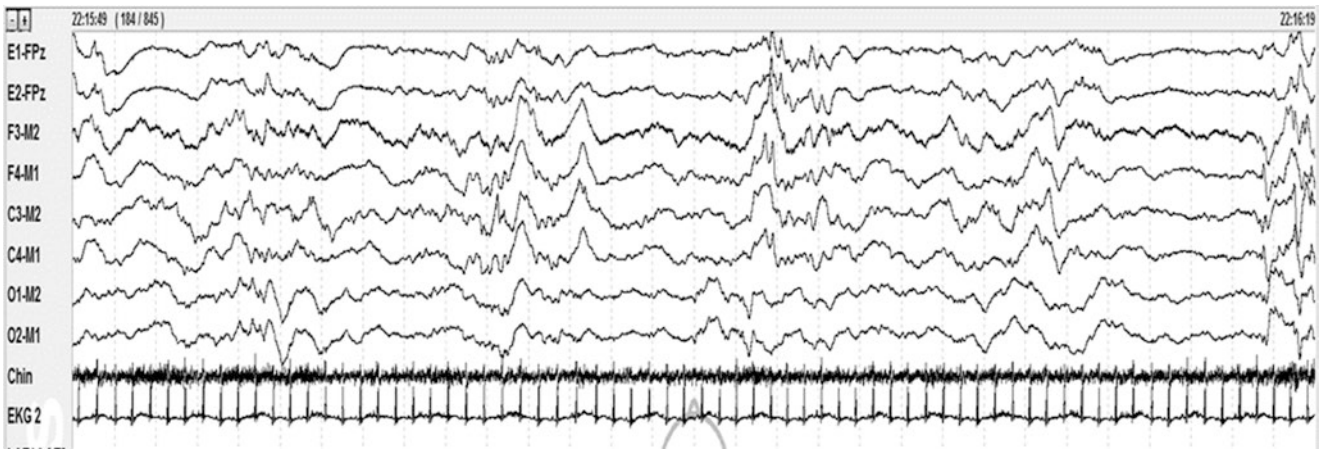


Fig. 18.28 A 30-second epoch of trace alternant NREM sleep recorded in a term infant

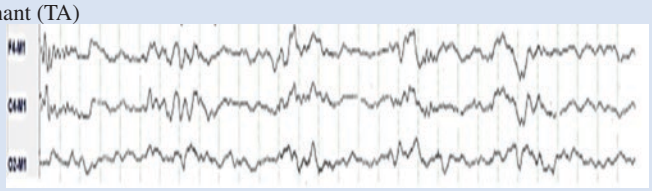
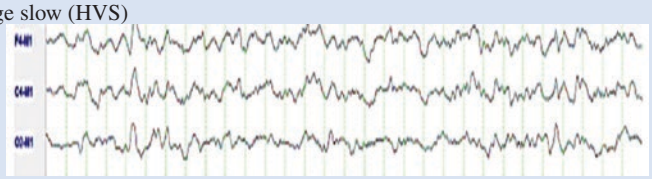
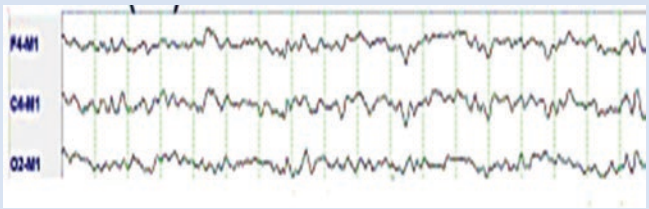
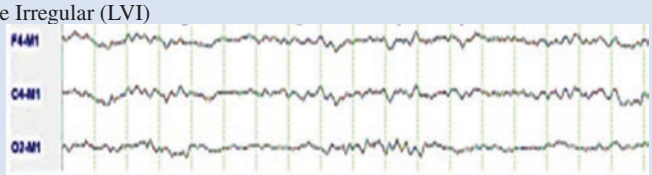
Scoring Sleep/Wake States in Infants 0–2 Months Old

We find it useful to pose five questions when scoring sleep in infants this young: (1) Are the eyes open? (2) Is respiration regular or irregular? (3) Are rapid eye movements present or absent? (4) Is the chin EMG tone present or absent? (5) Is EEG background continuous or trace alternant?

Why are these questions helpful? Sleep onset is more often REM sleep until 2–3 months post-term. Drowsiness in infants 0–2 months is best characterized by visual observation (supplemented by later video review). Wide open eyes are the most crucial determinant of stage W in infants of this age. Sustained eye closure is the best physiological marker of drowsiness in an infant of this age. Regularity (or irregularity) of respiration is the single most useful PSG characteristic for scoring sleep stages. REMs are most often seen in stage R (but can be seen in W).

Chin EMG atonia is the least reliable PSG measure of stage R, inappropriately present in 15% of REM epochs. Chin EMG is variable in stage N, generally lower than in W and higher than in R. Chin EMG tone preserved 80–85% of epochs of N sleep; its presence is useful whereas its absence is not. Stage N can still be scored with low EMG tone if at least four other criteria for stage N including regular respiration are met. The AASM Scoring Manual recommends scoring the EEG in infants 0–2 months simply as "continuous" or "discontinuous" to determine scoring W, N, R, or T because the only distinctive sleep EEG pattern is trace alternant (Fig. 18.28). The other EEG patterns, high voltage slow (HVS), low voltage (LVI), or mixed (M), are not specific for one sleep/wake state (Table 18.6).

Table 18.6 AASM scoring manual definitions of EEG patterns of sleep and wake in infants 0–2 months old

EEG pattern and sleep stages seen	AASM manual definition	Representative EEG sample and comments
Trace alternant (TA) NREM only	≥3 alternating runs of bilaterally symmetrical, synchronous, high-voltage (50–150 μV) bursts of 1–3 Hz delta activity lasting 5–6 seconds (range 3–8 seconds) alternating with periods of lower amplitude (25–50 μV) of 4–7 Hz theta activity (range 4–12 seconds)	Trace alternant (TA)  TA first appears at 37 weeks CA, prominent pattern at 40 weeks CA, disappears after 44 weeks CA; after 44 weeks CA, it is replaced by HVS. Interburst intervals (IBIs) last for 4–6 seconds at 35–36 weeks CA, 2–4 seconds at 37–44 weeks. Amplitude of IBIs increases with increasing CA. Permissible to look at preceding and following epochs to see TA pattern
High-voltage slow (HVS) NREM, rarely REM	Continuous, synchronous, symmetrical, predominantly high-voltage (100–150 μV) 1–3 Hz delta activity which often has an occipital or central predominance	High-voltage slow (HVS)  HVS precedes TA when 2 patterns present during same NREM period. HVS is the more mature EEG pattern of stage N sleep at term
Mixed (M) Wakefulness or REM, rarely NREM	Both high-voltage slow and low-voltage polyrhythmic components intermingled with little periodicity; lower amplitude than seen in HVS	Mixed (M)  Continuous, irregular, synchronous, symmetrical, low-amplitude (<50 μV) 5–7 Hz theta intermixed with occasional >100 μV 2–4 Hz slow waves; M typically seen in REM sleep after period of W
Low-voltage irregular (LVI) REM or wakefulness	Continuous, low–voltage, mixed-frequency activity with delta and predominantly theta activity	Low Voltage Irregular (LVI)  Continuous, irregular, centrally predominant 25–50 μV 4–7 Hz activity intermixed with occasional 1–3 Hz delta of similarly low amplitude LVI seen in REM sleep typically after a period of NREM sleep

AASM Rules for Scoring Sleep/Wake States in Infants 0–2 Months Old

The AASM Scoring Manual recommends scoring an infant 0–2 months of age PSG by assigning a stage to each 30-second epoch (W, T, R, or N). If two or more stages coexist, assign stage comprising greatest portion of epoch. Score sleep onset as the first epoch of sleep (often REM sleep until 2–3 months post-term). Sleep and wakefulness in infants 38 to 48 weeks CA are scored based on (1) behavioral observations, (2) regularity or irregularity of respiration, and (3) EEG, EOG, and chin EMG patterns.

Stage W is scored in an infant 0–2 months of age if a, b, or c presents majority of epoch: (a) eyes wide open (for majority of epoch), (b) vocalization (whimpering, crying) or actively feeding, or (c) all of the following are met: (i) eyes open intermittently, (ii) rapid or scanning eye movements observed, (iii) sustained chin EMG tone with bursts of muscle activity, (iv) irregular respiration, and (v) continuous patterns of LVI or M shown by EEG. An example of W in a 40-week PMA infant is shown in Fig. 18.29.

Transition to sleep is characterized by intermittent eye closure, absence of focused attention, and/or relative immobility and best recognized by the technologist at the bedside

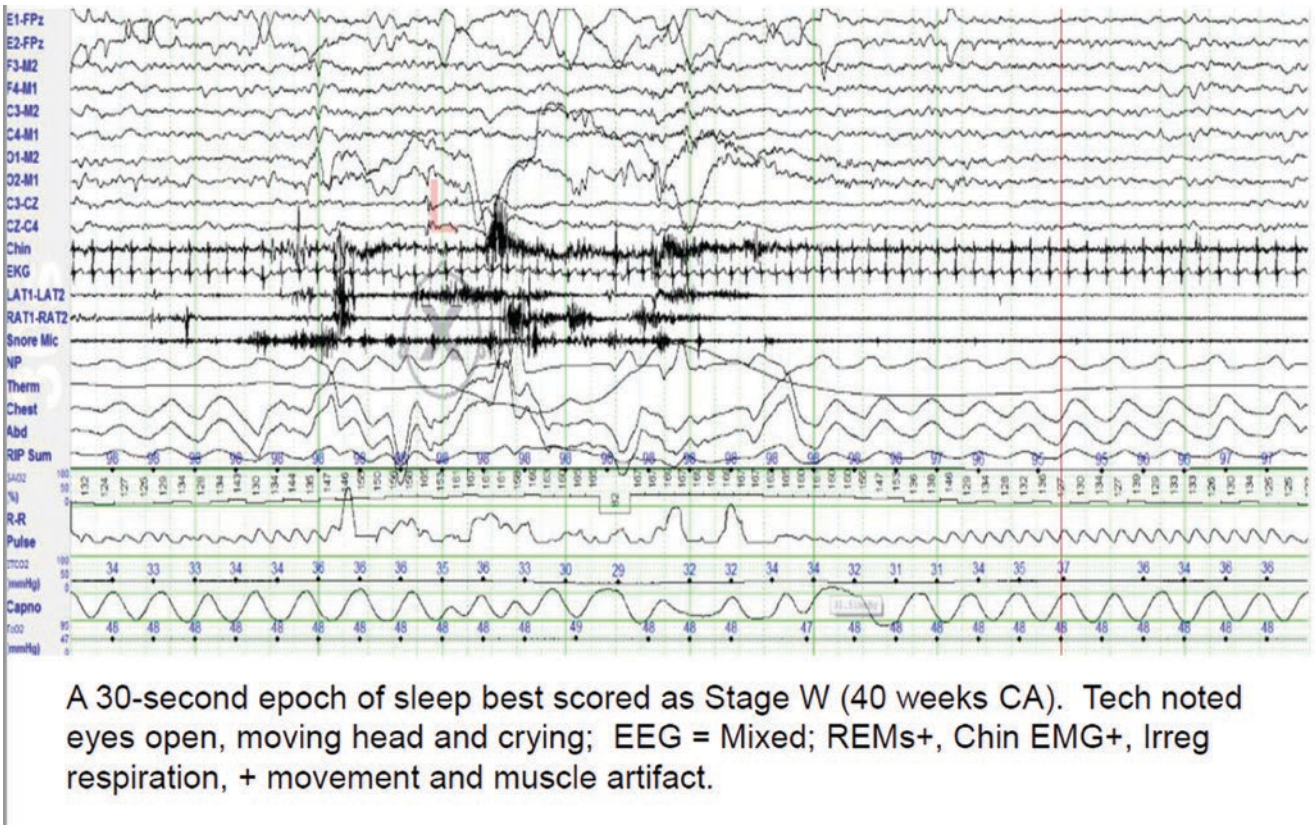


Fig. 18.29 A 30-second epoch of PSG recorded in term infant of 40-week PMA scored as stage wakefulness (W). The technologist noted that the infant's eyes are open, and he is moving and crying. EEG shows continuous mixed EEG frequencies. Rapid eye movements, irregular respiration, movement, and muscle artifact are observed

[71]. The AASM Manual advises that if the eyes are closed for ≥3 minutes, the infant is considered asleep (consensus vote). An increase in the amplitude of theta and delta activity, especially over the frontal EEG derivations, may be observed in the transition from W to T.

Sleep onset in infants of this age is most often REM sleep (often preceded by a few epochs best scored as stage T). R is scored in a 30-second epoch of PSG in an infant 0–2 months of age if ≤4 are present including irregular respiration and REMs: (1) low chin EMG (for the majority of the epoch); (2) eyes closed with at least one rapid eye movement (concurrent with low chin tone); (3) irregular respiration; (4) mouthing, sucking, twitches, or brief head movements; and (5) exhibition of a continuous pattern without sleep spindles by EEG. An example of R in a 44-week PMA infant is shown in Fig. 18.30. Because REMs may not be seen on every page, epochs following an epoch of definite R in the absence of REMs may be scored if the EEG is continuous without TA or sleep spindles and chin muscle tone low for the majority of the epoch, and if there is no intervening arousal.

Stage N is scored in a 30-second PSG epoch is ≥4 are present including regular respiration for the majority of the epoch: (1) eyes are closed with no eye movements; (2) chin EMG tone present; (3) regular respiration; and (4) EEG patterns of TA, HVS, or sleep spindles are present. An example of N in a 48-week PMA infant is shown in Fig. 18.31. Stage T is scored in a 30-second PSG epoch if it contains ≥2 discordant PSG state characteristics: 3 NREM +2 REM or 2 REM + 3 NREM state characteristics. T sleep most often occurs in transitions to sleep, especially W to REM sleep (less of R to N) and following arousals or awakenings. An example of T in a 44-week PMA infant is shown in Fig. 18.32.

Sleep Cycle Patterns in Infants 0–2 Months of Age

Normal healthy infants at term (38–42 weeks CA) spend 16–18 hours per day sleeping, 50% in REM sleep. Until approximately 44 weeks CA, sleep cycles repeat in a polyphasic pattern across the 24-hour day interrupted about every 3–4 hours by an awakening for feeding and care [78] (Table 18.7).

In normal healthy infants 38–42 weeks CA, sleep cycles typically last for a mean of 50–60 minutes (range 30–70 min-

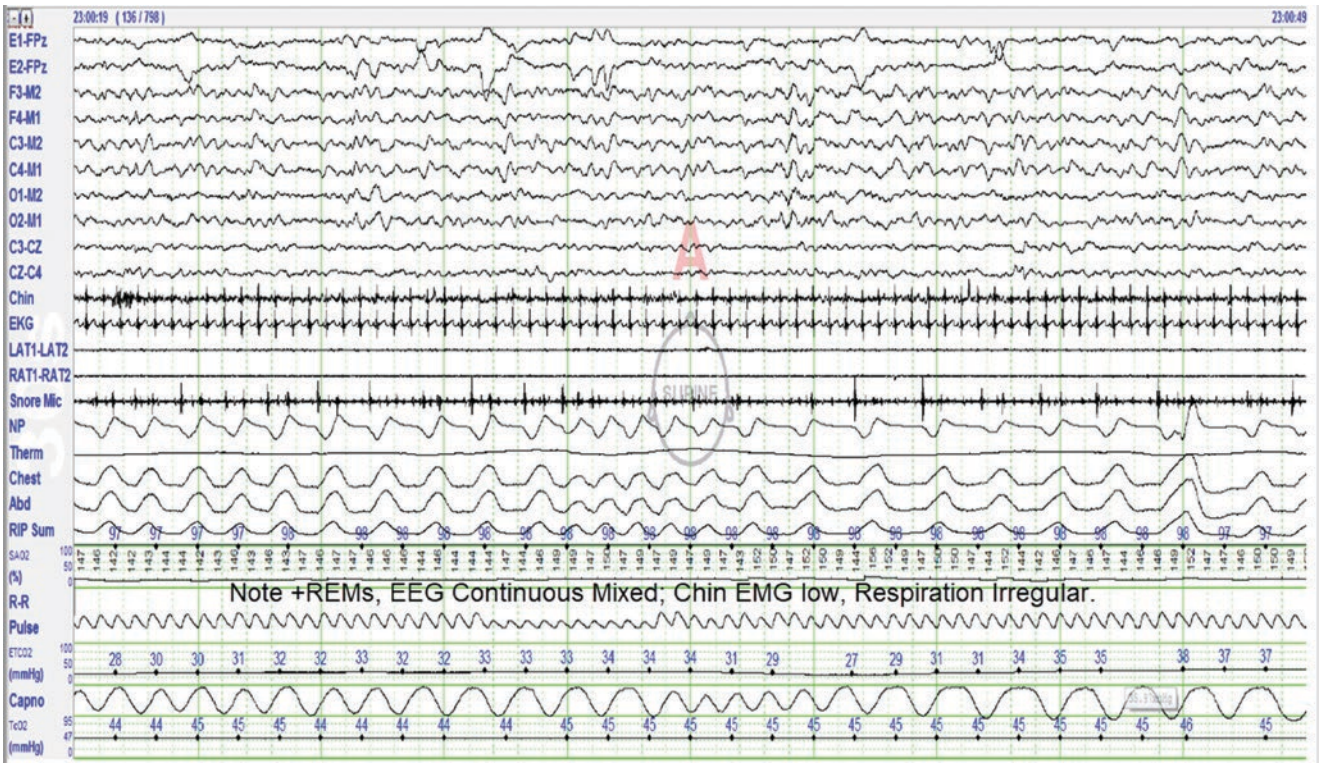


Fig. 18.30 A 30-second epoch of REM sleep recorded in a term infant 44 weeks PMA. During this epoch the classical features of REM sleep are seen: the EEG shows continuous, low-voltage mixed EEG activity; the chin EMG is low; and respiration is irregular

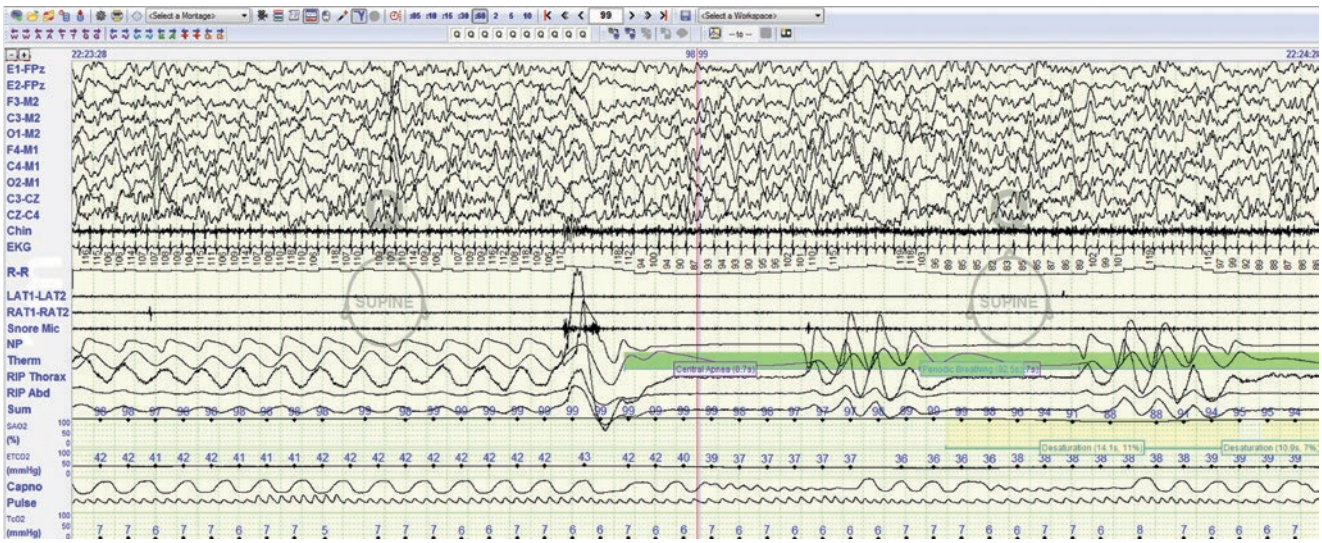


Fig. 18.31 A 60-second epoch recorded in an infant of 48-week PMA during NREM high-voltage slow-wave sleep. A run of periodic breathing is observed

utes) and 60 minutes at 43–48 weeks CA [79]. At 43–48 weeks CA, sleep cycles average 60 minutes, wake periods are primarily to feed, the first half of the night sleep is more restless, and artifact is more likely particularly in R sleep [79]. W usually accounts for only 8–10% of a 24-hour day in infants up to 8 weeks post-term [78].

Within a given R-N-R sleep cycle, R lasts for 10–45 (mean 25) minutes, N 20 minutes, and T 10 minutes [78, 80]. EEG pattern seen in the first R sleep of a sleep cycle after W is typically mixed and comprises 25–30% of the cycle. NREM sleep following a first period of R often begins with a brief period of HVS for 3–5% of the cycle and then a lon-

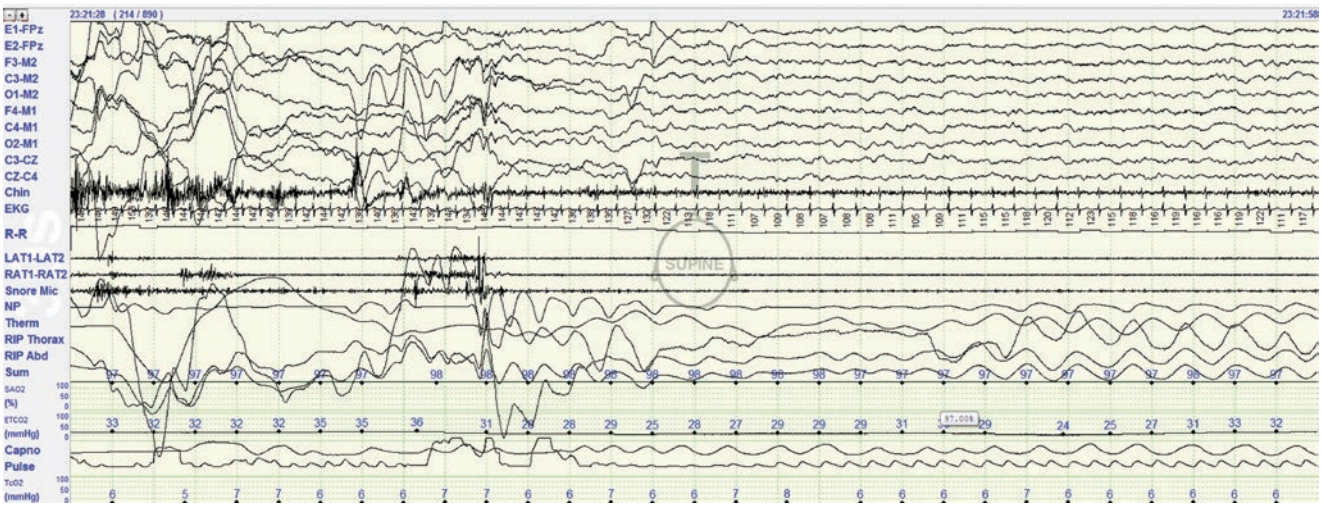


Fig. 18.32 A 30-second of PSG best scored as stage transitional (T) recorded in a term infant of 44-week PMA. Note rapid eye movements, irregular respiration, but preserved chin EMG and muscle and movement artifact

Table 18.7 Summary of PSG sleep/wake characteristics in infants 0–2 months old

State	Behavior	Respiration	EEG	EOG	Chin EMG
Wakefulness (W)	Calm or active with eyes open, crying, feeding	Irregular, rapid, and shallow	LVI or M	Eye blinks, conjugate 0.5–1 Hz vertical eye movements, conjugate irregular sharply peaked REMs, scanning lambda waves (sharply contoured 250–350 ms waveforms occipital regions) transient eye closure crying	Present, movement artifact
REM (R)	Eyes closed, REMs, sucking, grimacing, squirming, facial grimaces, fine limb muscle twitches, chin, body and limb tremors, intermittent stretching, large athetoid body movements	Irregular, some central apneas, or periodic breathing may be seen	LVI or M (rarely HVS)	Eyes closed with (and without) REMs	Low with or without transient motor activity
NREM (N)	Eyes closed, few or no movements, periodic sucking can occur	Regular	TA, HVS, M, or sleep spindles	Eyes closed with no eye movements	Present, could be lower than W

Legend: *LVI* Low-voltage intermixed, *M* Mixed, *HVS* High-voltage slow, *REMs* rapid eye movements, *TA* trace alternant, *W* Wakefulness

ger period of TA for 25%. The sleep cycle ends with another period of R but typically with LVI and for 25% of the cycle. Nearly 10–15% of epochs of sleep within the REM-NREM-REM ultradian sleep cycle are best scored as T sleep; these most often occur at sleep onset and stage shifts especially from REM to NREM and following arousals.

Scoring Respiratory Events in Level 1 PSG in Infants of Ages 0–2 Months Is Challenging

We face many challenges when scoring respiratory events in PSG in infants 0–2 months of age. Brief central apneas are common after sigh, arousal, body movement, sleep onset, sleep/wake transitions, and during phasic REM sleep. When central apneas occur related to these, they are considered physiologic (i.e., normal). Brief oxygen desaturations <90% are seen in most term infants during periodic breathing, REM sleep, and after normal physiologic respiratory pauses. One study found the lower limit of normal for brief oxygen desaturations to be <80%: day 1, 15/h; day 4, 41/h; day 39, 30/h. Moreover, only 48% of the desaturation events at day 1 were associated with apnea, gradually increasing to 94% at age 6 months, which is coincident with lung volume development.

Fairly accepted concepts when scoring sleep apnea in term infants younger than 2 months post-term are as follows: (1) longest apneas are usually mixed in type; (2) apneas lasting >10 s are typically mixed events; (3) obstructive and mixed apneas are rare such that an OAI >1/h or MAI >1/h TST are abnormal; and (4) brief central apneas lasting 3 to <10 s are common in term infants and more often physiologic if they follow a sigh and arousal, during REM sleep or periodic breathing; and (5) periodic breathing is common in infants less than 3 months post-term but typically <5% of

TST. Figure 18.33 shows mixed apnea in an infant of 42-week PMA and Fig. 18.34 shows an obstructive apnea in an infant of 44-week PMA with Pierre Robin sequence.

We are particularly concerned about the effects of hands-on care disrupting sleep and causing respiratory events in infant PSG. Levy et al. (2017) retrospectively analyzed the

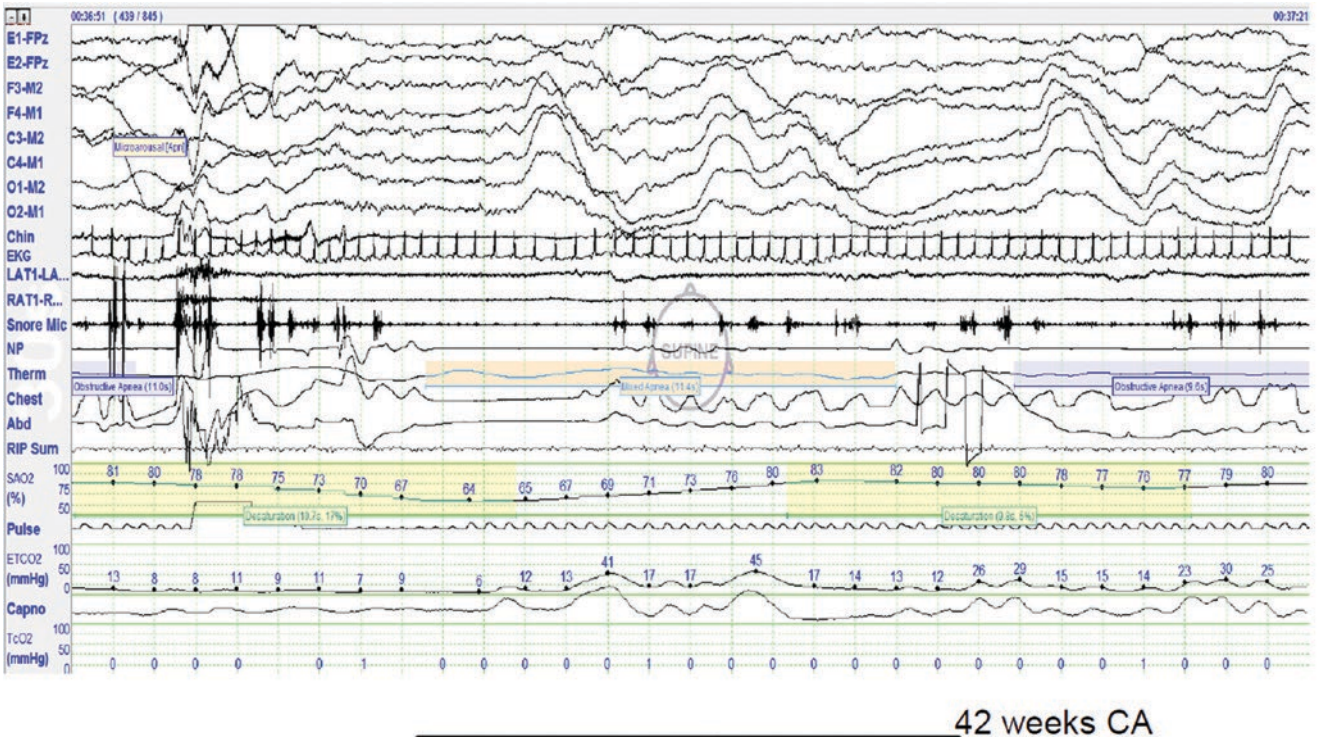


Fig. 18.33 A 60-second epoch of PSG recorded in a 42-week PMA infant showing mixed and obstructive apneas. Note how the mixed apnea lasts for 11 seconds and causes an oxygen desaturation to 76%

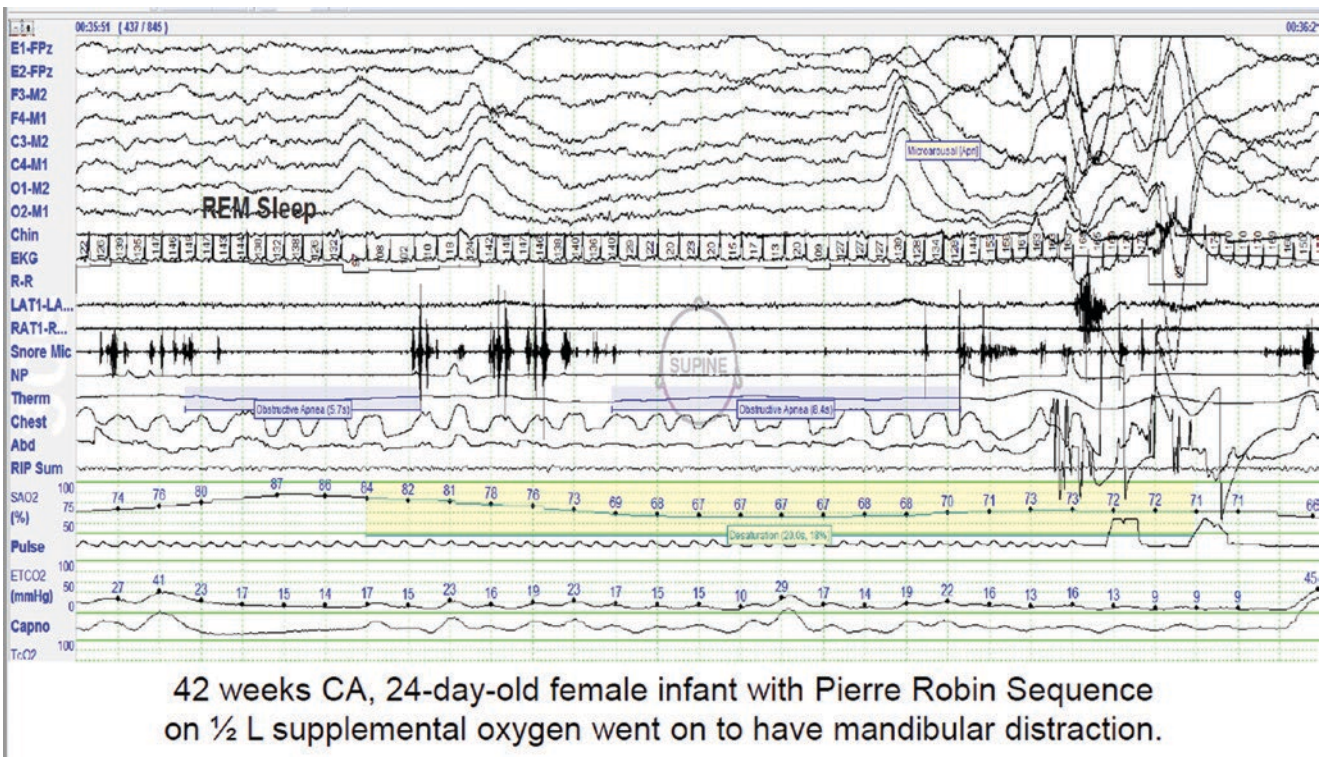


Fig. 18.34 Obstructive apneas in an infant of 42-week PMA with Pierre Robin sequence which last for 6–8 seconds but cause desaturations to 67%

effects of care and handling during 4-hour level 1 PSG in 25 medically stable infants (mean GA 39 ± 2 weeks) [81]. They found that neonates spent 27% (65 minutes) being handled (a third of it by sleep technologist) and only 50% had a complete sleep/wake cycle during the recording. The study showed that on average when the sleeping infants were touched or contacted: (1) 57% caused arousals; (2) 20% caused desaturations; (3) 16% caused apneas; (4) 8% caused hypopneas. Hypopneas were most likely to occur following contact with infants in REM sleep (28%).

Review and Interpretation of Nocturnal Pediatric Polysomnograms

Interpreting a level 1 pediatric PSG begins with reviewing why the sleep study is being performed [27]. Children studied in our laboratory almost always have a sleep medicine consultation before a PSG and we review the consult with attention to (1) sleep/wake complaints prompting the PSG; (2) child's typical bed, sleep, and wake times; (3) comorbidities; (4) medications; (5) presence and size of tonsils, prior adenotonsillectomy; and (6) results of previous polysomnography. The physician interpreting the PSG needs to know what medications and substances the patient normally takes and what were taken the night of the PSG, and then assess the impact of these on the study results.

Sixty percent of referrals to our pediatric sleep center are for snoring in children and most have or had large tonsils. Fifteen percent are referred for behavioral insomnias, 5% parasomnias, 5% circadian rhythm disorders, and 5% central hypersomnias including narcolepsies. In two-thirds of all consults, the parents and/or referring providers want to know if the child's other medical, neurological, emotional, learning, behavioral, and/or learning problems are caused or made worse by their sleep problems. We also need to know whether the parents really want the tonsils out, or "just checking."

Review Biocalibration, Hypnogram, and Technologist's Comments

Knowing why the PSG was ordered, we open the PSG already scored by the technologist on our computer desktop retrieved from our sleep center database. We display the first 30-seconds of biocalibration on the PSG, the hypnogram, the video window, the technologist's comments on two digital video monitors.

We find it useful to first review the technologist comments: (1) how the study went (needed television on to fall asleep, would not put away cell phone, mother snored louder than patient); (2) charting bihourly presence and volume of snoring, respiratory rate, heart rate, SpO_2, and CO_2; (3) malfunctioning probes and what electrodes were not placed till when (or never and why); (4) unusual events (confusional arousals, seizures, interictal epileptiform activity); (5) PAP titration details; and (6) caveats, conundrums, confounders, and a gestalt of how the study went in general.

Reviewing the biocalibration performed before starting the PSG recording is useful to: (1) identify the patient's DPR is awake when the child closes eyes awake; (2) observe how eye movements appear in the PSG when looking up, down, side to side; and (3) how activities such as snoring, mouth breathing, nasal breathing, apnea, prolonged expiration, leg and hand movements appear in this particular patient's PSG. Next we study the sleep architecture on the hypnogram asking does it show (1) appropriate NREM-REM sleep cycling for the child's age; (2) sufficient percentages of the different sleep stages for age and a first night effect; (3) rapid or delayed onset of sleep (typical by history or a first night effect); (4) early or delayed REM sleep onset; (5) paucity of NREM 3 and/or REM sleep (and impact of these on results); and (6) early termination of study (why).

We ask other questions prompted by review of the hypnogram: (1) How long did it take the patient to fall asleep after lights out? (2) Were Lights Out (and Lights Out) at times similar to bedtimes reported at home? (3) Was greater time spent in NREM 3 sleep than expected for age (diluting AHI and begging question of chronic sleep deprivation/restriction); (4) Was REM sleep delayed (if so, was it a medication effect, e.g., clonidine, or due to the effect of sleep disordered breathing); (5) Early onset of R sleep less than 15 minutes after sleep onset (could this patient have narcolepsy); and (6) What caused the arousals and awakenings?

We then scan the other signals displayed in the hypnogram (oxygen saturation, apneas/hypopneas, capnometry, continuous heart rate, and epochs of REM sleep without atonia) and note the relationships between them (e.g., lower oxygen desaturations and more apneas in supine and/or in REM supine). Studying the respiratory data, we ask the following: (1) Were most events hypopneas? (2) What types of apneas predominate (obstructive and/or central)? (3) Were runs of central apneas periodic breathing (can open the PSG at that point and look)? (4) Were apneas often prolonged (20 seconds or longer) suggesting impaired arousal mechanisms? (5) Are apneas and/or hypopneas positional (occurring twice as often more when sleeping supine or prone) than lateral? (6) Were there long runs of central apneas in NREM sleep (periodic breathing)? (7) Do apneas/hypopneas cause arousals and/or desaturations, fragment sleep, and frequent arousals/awakenings?

Now Review the Video-Polysomnogram

We find it useful to view the PSG in different epoch sizes when scoring particular types of events. For example, sleep/wake

states and arousals are best identified and scored using a 30-second epoch. Whereas, respiratory events (such as apneas, hypopneas, desaturations) best scored using epoch windows of 60, 90 or 120 seconds. Sometimes, 2 or 5 minutes epochs best display periodic breathing. PLMs are best scored using 90–120 second epochs. Last said, atypical EKG rhythms or EEG activity suspicious for epileptiform or ictal EEG activity are best scored displaying 10- or 15-second epochs of the PSG.

While reviewing, we may stop and verify the nature of arousals, awakenings, large body movements, seizure, confusional arousal, or RBD behaviors and snoring using audio video recording. We typically read PSGs using two computer monitors. We find it useful to display and run the time-locked audiovideo image on the second monitor when scanning the recording. This allows us to correlate the moving video as we scan the recording observing: (1) how often the patient changes position; (2) is the neck hyperextended; (3) mouth breathing; (4) is parent in the patient's bed crowding the patient; or (5) the parent is answering on their cell phone.

Once Reviewed and Revised, Generate a Report of the Polysomnogram

Having completed the review and editing of the PSG, we use the digital PSG program to generate a report which includes tables of data, hypnogram, and technologist's comments. Our laboratory tailors these for us.

Provide a Summary and Interpretation of the Polysomnogram

Most sleep studies are done for suspected SDB; for these we summarize (1) the presence/absence of sleep disordered breathing; (2) PAOHI, RDI, OAI, CAI, HI; (3) the presence and loudness of snoring; (4) whether SDB was intermittent, last part of night, positional, or predominant during REM sleep; (5) mean and nadir SpO_2 in W, N, and R sleep; (6) $\geq 3\%$ oxygen desaturation index (3%-ODI), and (7) time with $SpO_2 \leq 88\%$ (We live at 5000 feet above sea level). We comment upon sleep-related central or obstructive hypoventilation if present and whether the respiratory events caused arousals/awakenings (if so, how often and how long). Taking all these into account, we analyze and report the severity of the SDB.

When interpreting sleep disordered breathing in a child's PSG we recommend the following: (1) do separate CAI from POAHI; (2) don't overinterpret the clinical significance of short central pauses, especially if they are post-sigh, post-movement, or post-arousal; (3) verify extreme values (SpO_2 50% often artifact); and (4) do interpret all aspects of breathing during sleep: desaturations, respiratory rate, paradoxical breathing, phasic bursting of chin EMG, flow limitation, respiratory-related arousals. It is important not to "get stuck on the AHI" when interpreting a child's PSG. The AHI provides a measure of frequency of respiratory events but tells us nothing about other biomarkers of OSDB including OAI, $\geq 3\%$ODI, nadir SpO_2, TST spent with $SpO_2 \leq 90\%$ or 88%, mean respiratory rate in N3 and its relation to snoring, flow limitation in NP sensor, and CO_2 (obstructive hypoventilation). We further assess the presence or absence of snoring, noisy breathing, and inspiratory stridor. We note and describe flow limitation, its impact on gas exchange and sleep continuity, RERA patterns, phasic chin EMG bursts, and paradoxical breathing. When observing respiratory events, we check whether they mostly occur in transitions between wake/sleep states.

When the sleep study shows abnormalities other than sleep disordered breathing, we identify and summarize these. See below for a summary of abnormalities or significant findings often reported in sleep study reports. We report and discuss (1) alterations in sleep architecture (and their impact upon the other results and findings); (2) the presence and severity of PLMS (and how often they cause arousals and whether they are related to respiratory events); (3) whether parasomnias occur. We describe when, what, and how many occurred and whether they were triggered by environmental stimuli (co-sleeping parent), sleep disordered breathing, PLMS or spontaneous, and what stage of sleep they emerged from. Lastly, we provide recommendations based on the sleep history, physical examination, purpose of study. When providing all these, we use whatever normative PSG data we have (summarized in the last section of this chapter).

Abnormalities or Significant Findings Often Reported in Sleep Study Reports

- Sleep-related breathing disorders
- Short or delayed sleep onset latencies (some of which may represent first night effect)
- Short REM sleep latency (less than 15 minutes after sleep onset)
- Absent REM or NREM 3 sleep (some of which may be medication or first night effect)
- Frequent arousals (and their causes if apparent)
- Excessive position shifts, sleep stage shifts, limb movements, and excessive motor activity during NREM and/or REM sleep
- Excessive or exclusive amounts of transitional or indeterminate sleep
- Excessive loss of normal skeletal atonia during REM sleep (RSWA) and REM sleep behavior disorder events
- Abnormal EEG background or indeterminate sleep/wake states
- Excessive periodic limb movements, percentage that cause arousals/awakening, and periodicity of them
- Parasomnias, seizures, interictal epileptiform discharges, EEG variants, or PSG artifacts

Interpreting Pediatric Polysomnogram Cognizant Normative Data

In order to interpret a PSG, we need normative data based upon single overnight level 1 PSGs recorded in infants, children, and adolescents using AASM Scoring Manual rules.

First Night Effect in Children

Prospective studies evaluating FNE in children and their impact on PSG results suggest that (1) children and adolescents exhibit FNE comparable to adults; (2) children with and without OSA exhibit significant night-to-night-variability in sleep parameters, but not in respiratory parameters; (3) an adaptation night is necessary if a PSG is done to study sleep architecture but not when only the nocturnal respiratory pattern is investigated; and (4) one night of PSG is usually sufficient to confirm OSA, but not reliable for sleep architecture [7, 22, 23, 82–84].

Night-to-Night Variability in Pediatric Polysomnogram

A prospective study evaluated night-to-night variability of respiratory and sleep parameters in 30 snoring children (mean age 4.1 ± 2 years) recording two level 1 PSG 7–27 days apart (mean 14 ± 5 days) [84]. They found that the mean respiratory variables were not significantly different from night to night. The only significant sleep parameter difference was in N2 sleep. The PSG clinical diagnosis remained the same on both nights for all children, although the disease severity differed slightly in two patients. Of note, intrasubject respiratory parameters demonstrated considerable variability especially in those with severe OSA.

Normative Single Overnight Level 1 PSG Data for Pediatric Sleep Architecture and Arousals

Uliel et al. (2004) recorded a single night of in-laboratory PSG in 70 healthy normal children (8.0 ± 4.6 y, range 1–15 y) [85]. They found that TST was 6.5 ± 1.2 h and sleep efficiency (SE) 91 ± 7%. The percentage of sleep stages was as follows: N1 4.1 ± 4.1%, N2 48.9 ± 9.7%, N3 25.2 ± 9.1%, and R 17.4 ± 5.7%.

Three other studies in children of ages 1–15 years reported the following: N1 4–7.7%, N2 36–49%, N3 14–32%, and R 17–21% of TST [86–88]. More recently, Scholle et al. published three studies which provide normative data for qualitative sleep parameters [89], arousal events [90], and cardiorespiratory parameters [91] for a single night of level 1 PSG recorded in 209 healthy German children scoring them using the AASM Scoring Manual rules [89–91]. We still find it difficult to provide definitive pronouncements of abnormal sleep architecture on a single night of pediatric PSG because of first night effects.

Scholle et al. (2012) found that arousals lasting ≥3 seconds (10th to 90th percentile) in first night level 1 PSG averaged 7.7 (5–11) at 1.4 y to 6.1 (3–9) at 16.9 years [90]. Spontaneous arousals/h of sleep are as follows: 1.6 (0.4–4) at 1.4 y vs. 2.6 (1–5)/h TST at 16.9 y. Respiratory arousals/h of sleep are as follows: 0.2 (0–1)/h at 1.4 y vs. 0.0 (0.0–0.3)/h at 16.9 y. So, spontaneous arousals >12/h and respiratory arousals >1/h are probably abnormal in an overnight pediatric PSG.

Normative Single Overnight Level 1 PSG Sleep-Related Respiratory Data

Uliel et al. (2004) found normal values for the following: OAI 1/h, CAI 0.9/h, nadir SpO_2 89%, baseline sleep SpO_2 92%, and $PetCO_2$ > 45 mm Hg < 10% of TST [85]. Wang et al. (2016) recorded overnight PSG in 99 children (ages 3–14 years) and found that the average AHI was 1 ± 1 vs. 0.5 ± 0.6 between the two age groups [92]. Average CAI was 0.7 ± 0.8/h in the younger children vs. 0.3 ± 0.4/h in the older. The mean nadir SpO_2 was lower in the younger children because of central apneas causing the lowest desaturation.

Scholle et al. (2011) found that the 90th percentile for the AHI was 3.2/h TST for the second year of life, ≤ 2.5/h for ages >2 and ≤ 6 years, and ≤ 2.1/h for ages >6 and < 18 years [91]. In normal children, central apneas were observed but no obstructive or mixed apneas. Arousals or desaturations induced by central apneas were rare (occasional in younger children). Central apneas when observed were more common in REM than NREM sleep. Apneas after gross body movements decreased with increasing age. Periodic breathing decreased with age and absent in adolescents. Mean heart rates were lower in sleep and lowest in NREM sleep.

In 2016, the European Respiratory Society (ERS) published an evidence-based systematic review on the diagnosis and management of OSAS in children 2–18 years [93]. In children without SDB symptoms or morbidity, or abnormalities predisposing to SDB, the 90th percentile for the AHI (using AASM 2007 scoring rules) is 3.2/h TST for the second year of life, ≤ 2.5/h for ages >2 and ≤ 6 years, and ≤ 2.1/h for ages >6 and < 18 years [93]. It is important to emphasize that the upper centiles of the frequency of respiratory events (apneas, hypopneas, and desaturation events) in asymptomatic children and the lower centiles in children with SDB overlap [93]. Given

this, PSG parameters in children need to be interpreted considering the sleep/wake complaints, SDB-related morbidities, and expected response to treatment interventions.

Central apneas in children are associated with fluctuations in heart rate and blood pressure, and central apneas following movement or sigh are more common in children with OSAS. A case–control study evaluated central apnea on PSG in 53 children ages 7–12 years referred for suspected SDB and 21 age-matched healthy controls [94]. They found that: (1) central apneas following movement or sigh were more frequent in children with OSA; and (2) central apneas following movement or sigh were associated with significantly larger rises in mean arterial pressure and heart rate than spontaneous central apneas. One study showed CAI decreased in children with OSAS following adenotonsillectomy [95]. Mild central sleep apnea is common in children with OSA. One study found 15% of 101 children with OSAS who underwent adenotonsillectomy had central apnea, defining central apnea as a CAI >1/h. The mean preoperative CAI in these children was 3.9 ± 2.9 per hour of sleep; the mean post-operative CAI 1.9 ± 4.8.

Cutoff Values for Diagnosing OSA on PSG in Children of Ages 1–23 Months

In 2017, the European Respiratory Society (ERS) published a seminal statement summarizing the evidence and current practice on the diagnosis and management of obstructive SDB in children 1–23 months old [96]. A systematic review of 10 studies by Ng et al. (2013) found that the 90th percentile for obstructive or mixed apneas in healthy asymptomatic children of ages 1–23 months was <1/h TST and hypopneas were uncommon [97]. The 90th percentile for 3%-ODI in 37 healthy infants was 2.2/h of sleep (1.1–1.9 years old) [98]. AHI severity was defined as follows: mild OSA 1–4/h, moderate >5–10/h, and severe >10/h of TST [96].

Healthy infants living at high altitudes have more obstructive events and oxyhemoglobin desaturations than infants at sea level, but these findings improve with older age [96]. For healthy infants living at >2500 meters above sea level, the 95th percentile for OAHI was 28/h of TST at age < 45 days decreasing to 1.8/h at 10–18 months in 122 infants [98]. Moreover, the 95th percentile for 3%-ODI during REM sleep ranges from 170/h at age < 45 days to 68/h at age 10–18 months [99].

Excessive Periodic Limb Movements

How many PLMS are too many in a pediatric PSG? Two of three studies found that total LM and PLMS are higher in younger than older children and decrease with increasing age. Significant night-to-night variability in PLMS has been observed in children and one night may not be enough to measure PLMS in children: two or more nights may be needed for clinical and research purposes.

Studies have shown that the children can have shorter and more variable intervals, often <10 s. The number of short intervals between LM is higher in younger children and tends to decrease with age. The generator for periodicity in children may cause shorter IMI than in adults. Given this, the minimum IMI of 10 seconds may not be appropriate for children.

A retrospective study by Marcus et al. (2014) supporting the clinical PLMI cutoff of >5/h confirmed that among the 195 healthy, non-snoring children aged 5–17 years recruited from the community, the median PLMI was 0/h (range 0–36/h): 8% had a PLMI >5/h and only 1.5% >15/h [100]. Children with a PLMI >5/h had a higher arousal index than those with a lower PLMI (12 [9–15] vs 8 [6–10]/h, respectively).

Five or more spontaneous stereotypical periodic limb movements of sleep (PLMS) are defined as indicative of probable or possible periodic limb movement disorder (PLMD) and restless legs syndrome (RLS) in children of ages 2–12 years. A prevalence rate of 5–25% is reported for ≥5 PLMS/h TST in children on overnight level 1 PSG. A 2015 prospective study of PLMS in a single overnight level 1 PSG in 52 healthy children of ages 1–18 years found that PLMS ≥5/h TST (more often 10/h) was common in healthy children younger than 10 years of age [101]. The PLMS index decreased significantly from 9.6/h TST (2.0–10.9) in group 1 to 1.5/h TST (0.0–4.7) in group 6. Arousals were associated with 35% of total LMS and PLMS without age dependence. Inter-movement intervals (IMI) showed decreasing incidence of shorter intervals with age: the periodicity index (PI) decreased from 0.2 (0.1–0.3) in group 1 to 0.1 (0.0–0.2) in group 6 reflecting the low real periodicity of leg movements in healthy children and adolescents.

REM Sleep Without Atonia and REM Sleep Behavior Disorder

How many epochs of REM sleep need to contain RWA to be abnormal (and support a diagnosis of RBD)? Frauscher et al. (2012) found that the 3-sec mini-epoch cutoff for a diagnosis of RBD in adults was 18% for "any" EMG activity in the mentalis muscle and the combination of "any" EMG activity in the mentalis muscle, with both phasic flexor digitorum superficialis muscles yielding a cutoff of 32% for patients with either idiopathic RBD or RBD associated with Parkinson's disease [50].

How much REM sleep without atonia is abnormal in a pediatric PSG? Bin-Hasan et al. studied how much RWA was observed in overnight level 1 video-PSG done in 41 children

(11 with NT1, 6 NT2, 12 idiopathic hypersomnia, 11 subjective hypersomnia) [73]. The median nRWA index in those with NT1 was 30 times greater than those with idiopathic hypersomnia (9.2% [1.5, 24.1] vs. 0.3% [0, 8.2]) and 15 times greater than those with subjective hypersomnia (0.6% [0, 4.5]). The median nRWA index in those with NT1 did not differ from those with NT2 (3.9% [0, 30.3]).

Bin-Hasan et al. found a nRWA index ≥1% in children/adolescents provided a robust sensitivity of 88% for pediatric narcolepsy (100% for the NT1 subtype) but had a poor sensitivity of 61%. The modest specificity of the ≥1% nRWA index is due to the high prevalence of nRWA among children in general. Eighty percent of all children/adolescents had at least one epoch of REM sleep-containing RWA [73, 102]. An nRWA index cutoff of ≥8% provides excellent specificity (96%) for the diagnosis of pediatric narcolepsy but has poor sensitivity (53%). Patients with NT2 had more intermediate levels of RWA and RBD; we do not know whether the nRWA index in NT2 predicts the later development of cataplexy.

Among the children with NT1, median nocturnal REM sleep activity was more frequent than median nocturnal REM sleep phasic activity (6.4% [0.6, 19.4] versus 1.6% [0, 9.3]). Eighty percent of patients with NT1 and 50% with NT2 had RWA in daytime REM sleep periods captured on the MSLT. The median daytime RWA indexes were 7.1% [0, 60.7] in those with NT1 and 1.1% [0, 21.7] in NT2. Only two patients with NT1 and two with NT2 have vocalization and/or complex motor movements consistent with RBD on their PSG. RBD behaviors were not seen in children with idiopathic or subjective hypersomnia.

Recognizing REM Sleep Behavior Episodes in Video-Polysomnography

RWA and RBD are most often seen in children or adolescents with narcolepsy type 1 [73]. A 2017 case–control study compared motor events during REM sleep using video-PSG in 40 children (mean age 12 ± 3 years) with narcolepsy type 1 (NT1) and 22 age- and sex-matched controls [102]. Elementary (brief non-purposeful) movements from either NREM or REM sleep were seen in NT1 and controls.

Complex RBD behaviors were only seen in children with NT1 (13 of the 40). RBD episodes in 7 were brief (up to 2 minutes) when they would gesture energetically or raise head and arms trying to grab or throw something. In the other 6, RBD episodes were longer characterized as slow, calm, repetitive gesturing (searching for or handling imaginary objects). Complex RBD behaviors (1) tended to be brief (seconds to minutes) and (2) involved the limbs (arms more than legs) and the face; (3) vocalizations ranged from talking quietly, mumbling, crying, laughing, to rarely yelling; (4) frequent brief eye opening was observed during RBD episodes in six; (5) violent RBD behavior was noted in only one child; (6) EEG during RBD episodes often shows bursts of alpha and theta activity; (7) RBD behaviors tended to recur in a stereotyped fashion for several times during the night, up to be almost continuous, and often grossly stereotyped for the individual; (8) RBD behaviors were also observed on next day MSLT in 7/40.

Summary

Special considerations are needed when recording, scoring, and interpreting level 1 PSG in infants, children, and adolescents. Sleep studies need to be scored and interpreted cognizant of the effects of age and development. Interpretation requires knowledge of normative data tempered by gaps in evidence.

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Multiple Sleep Latency Test

19

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Multiple Sleep Latencies in Adults

Introduction: Excessive Daytime Sleepiness (EDS) and Repercussions

Excessive daytime sleepiness (EDS), a prominent public health issue, is defined by the difficulty in maintaining alertness which occurs in an inappropriate situation [1]. Typical manifestation will be sleep attacks or onset of irresistible sleep episodes. EDS is associated with decreased quality of life [2, 3], impaired cognition [4], cardiovascular and cerebrovascular episodes [5], and increased risk for accidents [6]. The prevalence of the condition is approximately 5% in the general population, ranging from 0.3% to 16.3% [7].

Subjective Diagnostic Methods

EDS diagnosis is based on clinical characteristics and instrumental tools such as standardized questionnaires and sleepiness scales that are used to evaluate patients' sleepiness. One of the first scales designed and validated for measurement of sleepiness was the Stanford Sleepiness Scale (SSS) [8]. This scale, constructed as a seven-point rating scale of equal-appearing intervals, from wide awake to devastatingly sleepy, was designed and validated using sleep deprivation. Another approach to measuring sleepiness is exemplified by the Epworth Sleepiness Scale (ESS), one of the most common tools used to subjectively assess daytime sleepiness [9]. This scale is commonly used by sleep specialists to evaluate consequences of sleep deprivation on behaviors. The scale consists in eight self-administered questions that aim to evaluate the probability that subjects will fall asleep in various real-life situations. Scores range from 0 to 24, a score of 10 or higher suggesting daytime sleepiness. Due to its subjective nature, the latter scale has some issues related to the ambiguity of the terms used and the possible impact of psychological factors (anxiety, depression) on patient answers, which are not taken into account [10, 11].

Objective Diagnostic Methods

The most commonly used technique for objective evaluation of daytime sleepiness is the multiple sleep latency test (MSLT). This method measured the average elapsed time through assessing how quickly a participant falls asleep when asked to fall asleep under standardized laboratory conditions. The MSLT is recognized as the gold standard for diagnosis and evaluation of central hypersomnia, especially narcolepsy.

MSLT was developed by Mary A. Carskadon and William C. Dement in the Stanford University laboratory of Dr. Dement, during the early 1970s [12]. It consists of four or five consecutive 20-minute nap times carried out at 2-hour intervals. MSLT is recommended to be performed following an overnight polysomnography (PSG), to exclude daytime sleepiness resulting from other causes such as sleep deprivation or sleep fragmentation (sleep apnea, periodic leg movements, etc.). The conventional recording MSLT techniques include central (C3-A2, C4-A1) and occipital (O1-A2, O2-A1) electroencephalogram (EEG) derivations, left and right eye electrooculograms (EOGs), mental or submental electromyogram (EMG), and electrocardiogram (EKG). The first nap starts 1.5–3 hours after PSG has ended.

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Sleep onset for clinical MSLT is determined by the time lights are turned off to the time the participant enters any stage of sleep, including sleep stage 1 NREM. In some conditions when the occurrence of REM sleep is not at issue, sleep onset could be defined as the occurrence of three consecutive epochs of Stage 1 sleep or the first epoch of another sleep stage to avoid the inadvertent "early awakening" of a subject [12].

Sleep onset is defined as the first epoch of greater than 15 seconds of cumulative sleep in a 30-second epoch. During each nap, after onset of the first sleep period, the test will last for 15 minutes to assess whether rapid eye movement (REM) sleep has occurred. Sleep latency is considered from the time the lights are turned off to the onset of the first sleep period. This latency is then averaged over all naps to obtain mean sleep latency. The REM sleep latency is defined as the time from the first sleep onset to the first period of REM sleep, regardless of the intermediate stage of sleep or wakefulness. According to the guidelines, each nap should be terminated 15 minutes after the onset of sleep whether REM or any stage of sleep occurred. If there is no sleep after 20 minutes, the test is terminated.

In the initial MSLT guidelines published in 1986 by Carskadon [12], it was proposed that a short sleep latency (less than 5 minutes) indicated a pathological level of daytime sleepiness. This level was associated with impaired performance in patients and in sleep-deprived normal controls. The association of short sleep latency and of at least two sleep onset REM periods (SOREMPs) in a series of five sleep latency tests across a day is recommended for the diagnosis of narcolepsy. Then the guidelines were updated in 2005 [13, 14]. The mean sleep latency is now less than 8 minutes [13]. A study in a large number of patients confirmed that an 8-minute threshold for sleep latency on MSLT allowed evaluation of central hypersomnia [15]. However, the different definitions of sleep onset at MSLT could help to differentiate idiopathic hypersomnia (IH) from narcolepsy. Indeed, sleep latency could be assessed either by the latency of any stage of sleep, including sleep stage 1 NREM (SL) either by the occurrence of three sleep Stage 1 NREM epochs or any other sleep stage epoch, (sustained SL [SusSL]).

Idiopathic hypersomnia patients showed significantly longer SusSL than SL (7.7 ± 2.5 versus 5.6 ± 1.3 minutes, respectively) compared to narcoleptic patients without cataplexy (5.8 ± 2.5 versus 5.3 ± 2.2 minutes) and with cataplexy (4.1 ± 3 versus 3.9 ± 3 minutes).

Normative MSLT Data

Since the 1960s, MSLT assesses SOREMPs during naps, and SOREMPs have been recognized as a neurophysiological marker for narcolepsy [16]. Obtaining normative MSLT data and reliability scoring data for SOREMPs on MSLT was important. A study in 139 young healthy volunteers found that about 17% of volunteers presented with ≥2 SOREMPs without complaining of sleep or psychiatric problems [17]. This finding led to a great controversy. Studies in healthy volunteers aged 20–69 years old without any sleep problems or from the general population revealed that 3% and 3.9% of participants, respectively, had at least 2 SOREMPs [18, 19]. More recently, Mignot et al., in a study evaluating the frequency and correlates of SOREMPs during MSLTs in a randomly selected sample of adults, reported that multiple SOREMPs were more often observed in males (13.1%) than in females (5.6%). About 5.9% males and 1.1% females met the diagnostic criteria for narcolepsy with a mean sleep latency ≤8 minutes and ≥2 SOREMPs. In addition, males with multiple SOREMPs had shorter REM latency during nocturnal polysomnography (NPSG) and were more sleepier on the MSLT than those with no SOREMPs [20]. In conclusion, these studies showed the presence of ≥2 SOREMPs in general population without sleep disorders or EDS. Although SOREMPs can also be observed in the general population [20, 21], MSLT remains the gold standard method to diagnose narcolepsy and idiopathic hypersomnia (IH).

Factors Influencing MSLT

A variety of variables can affect MSLT results. External factors must be controlled and minimized to gain interpretable diagnostic data. To ensure accurate interpretation of data and MSLT outcomes for diagnosis of central hypersomnia, these factors should be considered, as recommended by the American Academy of Sleep Medicine (AASM) in 1992 [22] and in 2005 [23].

Age

Evidence shows that age plays an important role in MSLT results. Mary Carskadon showed that one-third of young adults, two-thirds of older adults, and nearly 90% of the elderly population had a sleep latency shorter than 5 minutes in at least one test. This study disclosed that adults were significantly more somnolent than adolescents and that elderly volunteers were more somnolent than the younger groups [24]. Dauvilliers et al. also evaluated the effect of age on MSLT results in a large population of narcoleptic patients and found that, with age, the number of SOREMPs decreased and the mean sleep latency increased [25]. This study demonstrated that the influence of age on MSLT results should be taken into account when diagnosing narcolepsy as the current criteria may be too stringent for elderly patients.

Sleep Deprivation

Sleep deprivation prior to the test is the most challenging external factor that influences the sleep latency recording using MSLT. Mary Carskadon conducted MSLT in healthy

subjects involved in sleep deprivation experiments and found significant correlations between the degree of deprivation and sleep latency [26–28]. Other studies showed that increased SOREMPs in relation to sleep deprivation were recorded using MSLT [29, 30]. More precisely, less than 6 hours of nocturnal sleep time on the night prior to MSLT can reduce the sleep latency and increase the number of SOREMPs recorded, which can in turn influence the diagnosis of narcolepsy [31]. This is why PSG is recommended prior to MSLT in order to gain an objective evaluation and diagnosis of central hypersomnia. It is also recommended to obtain sleep logs for 1 week prior to MSLT performance to assess sleep-wake schedules.

Stimulants or Drugs, Exercise, Meals

It is reported that drinking alcohol before MSLT has a tendency to reduce sleep latency and REM sleep latency [32]. Conversely, smoking before a test may induce a delayed sleep latency [33]. Dzodzomenyo et al. found that among 383 patients under 21 years of age undergoing MSLT, 10% tested positive for drugs, particularly for tetrahydrocannabinol (THC) cannabinoids. No child under 13 years old was urine drug test (+) for THC [34]. Six percent of patients with MSLT findings consistent with narcolepsy were drug screen (+) for THC; 71% of patients with drug screen (+) for THC had multiple sleep onset REM periods (SOREMS). These findings highlight the importance of urine drug screening in interpreting MSLT findings, particularly for children ≥13 years of age. Amphetamines or stimulants, which can be prescribed for the treatment of narcolepsy [35], can also increase wakefulness and sleep latency [36]. Consequently, AASM recommends that drug screening be performed on the morning of MSLT [23]. Smoking has to be stopped at least 30 minutes prior to each nap opportunity. Vigorous physical activity should be avoided during the day and any stimulating activities by the patient should end at least 15 minutes prior to each nap opportunity. The patient should abstain from any caffeinated beverages and avoid unusual exposures to bright sunlight. A light breakfast is recommended at least 1 hour prior to the first trial, and a light lunch is recommended immediately after the termination of the second noon trial.

Treatments

Stimulants, stimulant-like medication, and REM suppressing medication, such as antidepressants, can influence MSLT results and should ideally be stopped 2 weeks before MSLT. Antidepressants such as venlafaxine, fluoxetine, or tricyclic antidepressants effective in treating cataplexy have a minor effect on sleepiness but can suppress SOREMPs [37].

Although MSLT is the gold standard to evaluate daytime sleepiness, it is not recommended to evaluate treatment-related changes on patients with hypersomnia. MSLT is less sensible than the Maintenance of Wakefulness test in this context. Indeed, a survey comparing the relative efficacy of different pharmacological treatments (pemoline, modafinil, dextroamphetamine, and methylphenidate) concluded that it is difficult to know whether any changes in sleep latency measured by the MSLT is related to the therapeutic effect [38]. Interestingly, beneficial effects of sodium oxybate (SO) on sleep architecture have been carefully reported in narcoleptic patients, with a significant increase in slow wave sleep and a decrease in the amount of sleep stage 1 and of awakenings [39] but also displayed an improvement on mean sleep latency in these patients [40].

Fourth or Fifth Nap

A fifth nap can be recommended in MSLT studies, particularly if patients have only one SOREMP during the previous four naps. Muza et al. reported that in 16% of cases a diagnosis of narcolepsy was given directly due to the inclusion of the fifth nap on the MSLT. However, they also found that the mean sleep latency increased due to fifth nap inclusion in 53% of cases (16 patients did not sleep in the fifth nap) [41]. As the fifth nap is performed at 5 pm, patients are less likely to sleep as they are expecting to go home. Tashiro et al., studying the effect of hospital discharge after MSLT, showed that the median sleep latency was not significantly different between the two groups. The sleep latency was 12.6 minutes in the group discharged immediately after the MSLT, and 10.9 minutes in the group discharged after an additional night [42]. However, in the subgroup of patients with pathological MSLT, there was a trend towards prolonged sleep latency in the last run in patients discharged immediately after the test (5.6 ± 3.1 minutes vs 6.7 ± 3.4 minutes).

Conditions During the Test

Standardization of test conditions is critical for obtaining valid results. Sleep rooms should be dark and quiet during testing. Room temperature should be set based on the patient's comfort level. Sleep technologists performing MSLTs should be experienced in conducting the test. At the start of each test, they conduct the biocalibration, give the instructions to the patients, that is, "Please lie quietly, assume a comfortable position, keep your eyes closed and try to fall asleep", turn off the light, and carefully follow the test procedure.

Pathologies Influencing MSLT

Central Hypersomnias

Narcolepsy

Narcolepsy is a rare, chronic disorder that affects the regulation of the sleep wake cycle. The main manifestations of narcolepsy include excessive daytime sleepiness, cataplexy,

sleep paralysis, hypnagogic hallucinations, and disturbed nocturnal sleep. However, all these symptoms are only present together in about 15% of patients [43]. Cataplexy is absent in 20–40% of narcoleptic patients [44]. Narcolepsy is thus classified into narcolepsy type 1 (narcolepsy with cataplexy) and narcolepsy type 2 (narcolepsy without cataplexy) [14]. Narcolepsy type 1 is caused by a deficiency in hypocretin-1 (also called orexin) peptides released from the dorsolateral hypothalamic neurons, probably through autoimmune destruction of hypocretin cells. Low levels of hypocretin in the cerebrospinal fluid (CSF) are a specific marker of narcolepsy type 1. Nevertheless, measurement of hypocretin is not recommended as a routine criterion. MSLT is still the recommended method for the diagnosis of narcolepsy [14].

According to the International Classification of Sleep Disorders 3 (ICSD-3), the MSLT criteria for narcolepsy include a mean sleep latency less than 8 minutes and at least 2 SOREMPs during MSLT or NPSG [45]. MSLT has a good sensitivity, specificity, and reliability for the diagnosis of narcolepsy [46]. Due to the absence of cataplexy or a specific biological marker, the diagnosis of narcolepsy type 2 remains challenging [47].

It is important to note that the occurrence of SOREM in the preceding NPSG can be counted together with the SOREMPs in the MSLT [41]. Indeed, short REM latency (less than 15 minutes) during NPSG is a specific, but not sensible, marker of narcolepsy [48–51]. Short REM latency during NPSG predicts occurrence of SOREMPs during MSLT [20] and short sleep latencies during MSLT is strongly related to the occurrence of SOREM during NPSG [17, 52].

Idiopathic Hypersomnia

Idiopathic hypersomnia (IH) is a rare disease. No epidemiologic studies have been reported in the literature and its pathophysiology remains a mystery to this date. The age of onset for IH is usually under 30 years with symptoms present during childhood [53]. There are no specific clinical characteristics or biomarkers available for IH diagnosis [54]. According to ICSD-2, there are two IH phenotypes: IH associated with long sleep time (cases with a night sleep longer than 10 hours) and IH without long sleep time (cases with a night sleep of 6–10 hours) [14]. According to ICSD-3, IH diagnosis is made when a mean sleep latency less than 8 minutes on MSLT and less than 2 SOREMPs are recorded [45]. However, a study found that, after 4 years, only 50% of IH patients could still be considered IH on MSLT, displaying poor reproducibility of PSG-MSLT in IH [55]. The MSLT study must be carried out when other factors, such as sleep deprivation, have been excluded. Additional supportive features for IH are sleep drunkenness, long (> 1 hour) unrefreshing naps, and high sleep efficiency (≥90%) on the PSG. The diagnosis of IH is based on differential diagnosis as there are no specific biomarkers. Thus, further investigations concerning IH are warranted.

Secondary Excessive Daytime Sleepiness

Primary Insomnia

Early studies evaluated differences recorded by MSLT between patients with insomnia and controls but no differences were found, likely due to the small sample sizes observed and the non-standardized definition of sleep onset [56, 57]. However, several studies reported that mean sleep latency calculated by MSLT in insomniacs is longer than in controls (14.7 minutes in insomniacs vs 12.3 minutes in controls) [58–60]. Long sleep latency in insomnia could be due to the "hyperarousability" characteristic of this pathology.

Sleep-Related Breathing Disorders

A study in volunteers who did not complain of sleep disorders or other psychiatric diseases reported that more than two SOREMPs occurred due to the presence of sleep apnea [30]. Sleep-related breathing disorders are another important cause of EDS. MSLT has been used to investigate residual sleepiness in obstructive sleep apnea (OSA) patients [61]. In 1982, Walsh et al. found that 28% of patients with sleep apnea syndrome had two or more SOREMPs [62]. Further studies demonstrated that 4.7% of individuals with sleep-related breathing disorders had at least two SOREMPs, especially those with the lowest oxygen saturation levels [49, 52]. A similar result was found in the Mignot et al. study from a large population [20]. Fong et al. further suggested that mean sleep latency was related to the severity of OSA [63].

Sleep Fragmentation/Periodic Leg Movements

MSLT has been used to evaluate the effects of sleep fragmentation on daytime sleepiness. Sleep fragmentation was performed in 36 subjects whose sleep was disrupted for two consecutive nights, and daytime sleepiness was evaluated during the following day. Results showed that sleep fragmentation reduced daytime alertness [64] and decreased sleep latency on MSLT [65]. For example, periodic leg movements can induce sleep fragmentation.

Periodic leg movements (PLMs) are regarded as rhythmical extension of the big toe and dorsiflexion of the ankle with occasional flexion of the knee and hip [66, 67]. PLMs were first observed in the restless legs syndrome (RLS) [67], and then they were found in other sleep disorders. Dauvilliers et al. [68] assessed the impact of PLMs on daytime function in patients with narcolepsy. Patients with an elevated index of PLMs had a lower REM efficiency and a shorter MSLT latency. PLMs could also be related to daytime somnolence in adult patients with narcolepsy.

Other Neurological Disorders

An MSLT study conducted in patients with dementia with Lewy bodies (DLB) and Alzheimer's disease (AD) disclosed that daytime sleepiness occurs more often in patients with dementia with Lewy bodies than in patients with Alzheimer's disease [69]. Further studies, however, need to be conducted to confirm these findings.

Attention-deficit/hyperactivity disorder (ADHD) is more common in children, but can persist in adulthood [70]. The prominent characteristics of ADHD include symptoms of inattention, hyperactivity, and impulsivity that begin in the early childhood. However, Sobanski et al. did not find differences in MSLT between adults with ADHD compared to controls [71]. MSLT might not be the appropriate method for evaluation of daytime sleepiness in adult ADHD patients and more suitable methods need to be further studied.

Reliability

Test-retest reliability of MSLT is high in narcolepsy when two testing protocols are performed within 3 weeks [72]. However, inter-test intervals are generally longer than 3 weeks in clinical practice, and few studies measured the stability of MSLT under these real-life conditions. However, a longitudinal follow-up study demonstrated that MSLT had good test-retest validity in narcolepsy type 1 patients [73]. However, the test-retest validity of MSLT is highly dependent on the studied population. It is reported that retest reliability in healthy subjects can reach 0.97 over 4–14 months [74]. Trotti et al. evaluated the test-retest reliability of MSLT in patients with narcolepsy without cataplexy and idiopathic hypersomnia and found poor test-retest stability in these patients [75]. However, some limitations such as patients' selection bias and long duration between the tests (with an average of 4 years and maximum of 17 years) might explain this result. Moreover, retest reliability was relatively low for other pathological conditions such as Parkinson's disease (0.53–0.73), even when performed on consecutive days [76], or insomnia (0.44) evaluated over 8 months [60].

Indications of MSLT

MSLT preceded by NPSG is the recommended method to objectively evaluate daytime sleepiness in central hypersomnia. MSLT is indicated as part of the evaluation of patients with suspected narcolepsy to confirm the diagnosis and may be helpful in evaluating patients with suspected idiopathic hypersomnia. However, it is not recommended for recurrent hypersomnia (Kleine–Levin syndrome), the other sleep disorders, or neurological pathologies. When performed, this test must be conducted in standardized conditions and the results should be integrated in a complete evaluative picture including clinical history, other objective test results, and medical information.

MSLT in Children

Introduction

An increasing number of children are suffering from excessive daytime sleepiness, mainly due to sleep curtailment. In a study evaluating somnolence in a single school district in the United States, Pagel et al. reported that 45% of teenagers complained of daytime sleepiness and 16% of them fell asleep in class [77]. The prevalence of EDS in school-aged children reported by teachers or parents was 15% [78]. Recently, Kolla et al. reported that in a large population of adolescents aged 13–18 years ($n = 6483$), 41.5% of US adolescents fell asleep during the daytime, and 11.7% met the criteria for hypersomnolence [79]. EDS in children is often ignored but it has significant adverse effects on learning, mood, and behavior [80, 81].

Subjective Diagnostic Methods

The Pediatric Daytime Sleepiness Scale (PDSS) is the usual recommended questionnaire for the subjective measurement of EDS in children and adolescent [82]. However, despite its initial development in adults, the ESS is commonly used in pediatric population [83, 84]. However, this questionnaire was not fit for young children and different modified versions of the ESS have been developed with a wide age-range [85, 86]. In order to overcome some difficulties and limitations posed by these modified versions, Johns et al. developed a new standardized version of the ESS, namely Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) [87]. In this version, the reference to alcohol is omitted from item 7 and replaced by "sitting quietly by yourself after lunch," and "a classroom at school" replaces public place in item 3. Item 8, "in a car, while stopped for a few minutes in the traffic" is replaced by "sitting and eating a meal." The ESS-CHAD has been shown to be valid and reliable in measuring daytime sleepiness among adolescents between 12 and 18 years of age [88]. However, the validation of ESS-CHAD needs to be further investigated in children under the age of 12 and in clinical conditions.

Objective Diagnostic Methods

MSLT is technically feasible and has been recognized as a valid objective tool for the evaluation of daytime sleepiness in children of 5 years and older [89, 90]. However, there are currently no widely accepted MSLT norms for children, especially in preschool children for whom daytime napping is to be expected. In small groups of children, normative data for the MSLT have been reported to be 17.5 ± 3.5 minutes (n = 46, age 9.2 ± 1.5 years) [91] and 17.1 ± 2.4 minutes (n = 25, age 8.7 ± 1.1 years) [92]. The same protocol for the MSLT testing is recommended in children, with at least 6 hours of sleep during prior NPSG, even if children generally have higher sleep needs than adults.

Factors Influencing MSLT

Age-Puberty

According to Carskadon's study, normal preadolescent children are less likely to fall asleep during MSLT, suggesting that using adult-based criteria could lead to an underestimation of mild degrees of sleepiness in children [93–96]. In order to overcome this concern, 20-minute nap opportunities have been increased to 30 minutes in some studies. Thus, using 30-minute duration tests, Randazzo et al. showed that children between 10 and 14 years old had long mean sleep latencies (up to 23.5 minutes) if they were not sleep deprived [97]. However, more research is needed to confirm the value of longer nap opportunities.

Puberty is also a specific factor influencing daytime sleepiness. Mary Carskadon followed adolescents across their puberty, evaluating them with Tanner scale (from pre pubertal children [Tanner 1] to mature pubertal adolescent [Tanner 5]). She showed that MSLT scores displayed a tendency towards decreased diurnal alertness in the more mature adolescents, especially early in the afternoon [93, 94, 98]. Indeed, these studies showed a midday increase in daytime sleepiness in Tanner stage 3 and 4 adolescents, an effect not seen in Tanner 1 and 2 children [93, 94, 98].

This evidence suggests that older adolescents may have increased sleepiness midday, but further data are needed, particularly regarding the impact of early school start times and sleeping in on weekends on the results of the MSLT. Indeed, morning awakening time also plays a pivotal role on the MSLT interpretation. Carskadon et al. [99] evaluated teenager's responses to an earlier school start time in terms of daytime sleepiness in normative adolescents without narcoleptic symptoms. In this study, the students in tenth grade with early school start time of 07:20 have a mean MSLT of 8.5 minutes. However, mean sleep latency in the ninth graders with school start time of 08:25 was 11.4 minutes. The sleep latency was particularly short for the first nap at 08:30 (5.1 vs. 10.9 minutes). Meanwhile, it is noted that the rate of REM sleep occurrence in ninth grade (12.5%) was lower than in tenth grade (48% had at least one REM episode, and 16% had two REM sleep episodes).

Sleep Restriction/Deprivation

Sleep deprivation is also another prominent factor that influences daytime sleepiness in children. A sleep restriction (SR) study conducted in 10- to14-year-old children showed that when children were under SR (5 hours of sleep), they had shorter sleep latencies measured by MSLT (14.4 minutes) than when in non-sleep-restricted conditions (11 hours of sleep) (23.5 minutes) [97].

Stimulants or Treatments

Stimulants could also influence MSLT results in children. For example, in the United States, most children ingest caffeine in a daily manner, through caffeinated beverages for instance [100, 101]. Intake of caffeine increases sleep latency (by approximately 4 minutes) during MSLT in adult subjects [102]. Caffeine in the evening increases sleep latency, decreases sleep efficiency, and sleep duration [103, 104] and alters alpha EEG activity during daytime [105] in children and adolescents. A large sample study conducted on EDS reported that urine and serum drug testing in children revealed caffeine-positive samples in 32% of cases [106]. However, there were no differences in MSLT results between children with positive or negative caffeine screening, except for a narcoleptic child who had a false negative MSLT when he was screened positive for caffeine. If caffeine screening before MSLT does not seem mandatory, sleep physicians should at least document the caffeine intake history during clinic visits for sleep complaints and EDS.

As for treatments, evidence of the MSLT to assess response to treatment for narcoleptic children is seldom. Ivanenko et al. [107] determined the effects of modafinil on EDS in narcolepsy or IH children. Results showed that modafinil prolonged mean sleep latency (from 6.6 ± 3.7 minutes to 10.2 ± 4.8 minutes) compared to baseline. Huang et al. [108] found that modafinil and SO treatments all improved mean latency of MSLT (3.0 ± 4.5 minutes to 5.35 ± 5.6 minutes and 2.8 ± 3.1 minutes to 4.6 ± 3.7 minutes respectively) compared to baseline in adolescents with narcolepsy, although MSL remained <6 minutes and the number of SOREMPs at MSLT changed little. Moreover, Yeh et al. showed that ESS scores were considerably more sensitive than MSLT scores in documenting efficacy of modafinil in narcoleptic children, MSLT scores remaining in the pathologically sleepy range [109].

Pathologies Influencing MSLT

Central Hypersomnia

Narcolepsy

Previous studies demonstrated that disease onset for nearly half of narcoleptic patients occurred prior to the age of 18 years old [110]. Clinical manifestations, such as excessive daytime sleepiness and cataplexy, are often more severe in children than in adults [110]. The delay between disease onset and diagnosis of narcolepsy can be more than 10 years [111]. In addition, weight gain being a prominent co-characteristic of childhood narcolepsy [37, 112, 113], 82–86% of narcoleptic children gained at least 4 kg within 6 months of disease onset [37]. Obesity affects more than 50% of narcoleptic children, and is more prominent when disease onset occurs at early age (≤10 years old) [114]. Poli et al. reported that narcolepsy with cataplexy occurring during pre-pubertal age is frequently associated with precocious puberty and overweight/obesity [115].

MSLT was recognized as an adequate tool to diagnose narcolepsy in children [89]. In a study including 44 pre-pubertal narcoleptic children, Guilleminault et al. demonstrated that the mean sleep latency was below 5 minutes (mean ± SD of 1.5 minutes ± 39 seconds) and that the rate of SOREMP occurrence is very frequent in all children [116]. However, Aran et al. found that 15% of pre-pubertal narcoleptic children did not present both MSLT criteria for narcolepsy diagnosis [37]. In a latter study on a large group of children with narcolepsy type 1 (n = 361), Han et al. [117] found that most of the narcoleptic children (93%) had the MSLT criteria of narcolepsy (<8 minutes and ≥2 SOREM). In this study, prepubertal children had lower number of SOREMPs (2.1 ± 0.1) than mature pubertal adolescents (3.8 ± 0.7). These differences were most likely related to age of MSLT test rather than age of disease onset.

Our team conducted a large cohort study from four different reference centers for narcolepsy in France (Narcobank study). This work included 117 narcoleptic children, with a mean age of 11.6 ± 3.1 years, 43.7% of whom were less than 10 years old at diagnosis, 81% of whom presented with cataplexy and 91% with DQB10602. We found that 18.4% of children had a mean sleep latency on MSLT longer than 8 minutes. All these children had either the presence of clear-cut cataplexy (n = 12) or more than two SOREMPs (n = 7). There were no significant differences for the age of disease onset, the age at which PSG was performed or the diagnosis delay, between the narcoleptic children with longer sleep latencies and the others. No significant correlation was found between sleep onset latency on MSLT and sleep efficiency, apnea–hypopnea index, or respiratory-related arousals. However, there was a significant difference between children who did 4 or 5 nap tests. A higher proportion of children who underwent 5 tests had latencies longer than 8 minutes (30.9%) compared to children who only did four naps (4.2%) [114].

Following this initial work, we conducted a single-center study in Lyon on the fifth nap in 43 children with idiopathic narcolepsy (17 boys) of mean age 12 years old (5–18 years) (unpublished data). When comparing the results obtained with either 4 or 5 tests, we found no difference in the diagnosis of narcolepsy. All narcoleptic patients had >2 SOREMPs at 4 or 5 tests with no significant differences on sleep latency (4.3 ± 3 minutes for the 4-test group vs 3.6 ± 3 minutes in the 5-test group). However, in our protocol, the children do not go home immediately after the fifth nap.

When recently reviewing our database which now includes 101 idiopathic narcoleptic children (Table 19.1), only 7 children (6.9%) did not meet the criteria for narcolepsy using MSLT. All these children had cataplexy and were HLA positive, and only two children had CSF hypocretin measurement (178 ng/L and 5 ng/L). Four children with a median age of 10.2 (8.5–11.8) years, 3 of whom were boys, had sleep latencies ≥8 minutes (median 9 (8–10) minutes) but had at least 2 SOREMPs on MSLT. These 4 children had undergone 4 tests except one who did not sleep during the fifth test and had a mean latency of 10 minutes. The three other children who did not meet the criteria for narcolepsy [median age 13.7 (16.6–16.8) years, two

Table 19.1 Characteristics of idiopathic narcoleptic children from the Reference Center in Lyon

n	101
Male, %	57.4
Obesity, %	23.4
Overweight, %	41.6
Cataplexy, %	94
Hypnagogic hallucinations, %	41
Sleep paralysis, %	20.4
Age at diagnosis, years	12.6 (5.3–17.6)
<11 years, %	39
Age at disease onset, years	9.7 (4.2–15.8)
Time between onset and diagnosis, years	1.6 (0.2–11.3)
Body mass index (BMI), kg/m^2	22.5 (15.4–36.2)
BMI-Z score	2.69 (−1.76–9.04)
Epworth sleepiness scale	17 (9–25)
Epworth >10	94.7
HLA DQB1*0602 (n = 95), %	100
CSF Hypocretin-1 (n = 45)	25 (0–178)
Multiple sleep latency tests *median (range)*	
Number of tests	4 (4–5)
Mean sleep latency	2.75 (0–10)
Mean sleep latency <8 minutes, %	96
Sleep onset in REM periods, n	4 (1–5)
Sleep onset in REM periods, %	97
Number of patients with the 2 criteria, %	93
Sleep onset in night polysomnography (n = 91)	9 (0–225)
Sleep onset in night polysomnography, %	51.6

girls] had short sleep latencies [median 4 (1.25–4) minutes] but presented with only one SOREMP on MSLT. However, one of those children had SOREM in PSG and the other two had a REM latency under 60 minutes (56 and 58 minutes). Recently, Pizza et al. reviewed the MSLT characteristics of 357 suspected narcolepsy aged below 18 years, including 228 children with available CSF hcr-1 assay and proposed that a mean sleep latency ≤8.2 minutes or at least two SOREMPs at the MSLT are valid and reliable markers for the diagnosis of pediatric NT1 diagnosis [118]. Age or sex did not significantly influence these results. However, there were relatively rare young children (<6 years of age) in this study and further studies are needed to confirm these results in very young children.

Idiopathic Hypersomnia

There were very few studies concerning IH in children. Children with long night sleep time (>10 hours) and a normal MSLT were involved in IH group in some studies. Han et al. [117] conducted MSLT in 417 children less than 18 years old. IH children involved had a long sleep latency (12.3 ± 0.45) more than 8 minutes compared to narcolepsy with (3.4 ± 0.15) or without cataplexy (2.7 ± 0.67). The number of SOREMP (1.2 ± 0.18) of MSLT met the criteria of less than two SOREMP in these children.

Secondary Excessive Daytime Sleepiness

Obstructive Sleep Apnea

Obstructive sleep apnea is also one of the most important causes of EDS in children. Gozal et al. [119] evaluated the incidence of EDS using MSLT in 54 children (6.7 ± 0.3 years) with OSA, 14 children (7.3 ± 0.8 years) with primary snoring and 24 controls (6.1 ± 0.2 years), children with OSA showed shorter sleep latency compared to other two groups. In addition to evaluate the effect of obesity, Gozal et al. [120] underwent MSLT between 50 nonobese snoring children (6–9 years) and 50 age-, gender-matched obese children (BMI-Z score >1.67) with the presence of OSA of similar severity, mean sleep latency was significantly shorter in obese children (12.9 ± 0.9 minutes) than in nonobese children (17.9 ± 0.7 minutes) at any given level of obstructive sleep apnea severity. Chervin et al. [121] performed MSLT following PSG in 103 children (5–12 years) with suspected sleep-disordered breathing (SDB), and then 77 children were scheduled for clinically indicated adenotonsillectomy (AT). The results showed that the AT in OSA children could improve mean sleep latencies on the Multiple Sleep Latency Tests. In a study performed by Gozal et al. [122], EDS in pediatric OSA measured by MSLT is closely associated with increased inflammatory factors such as TNF-α levels. Moreover, surgical treatment of OSA results in reductions in TNF-α levels along with prolonged sleep latency.

Periodic Leg Movements

There are few available data on PLMs and sleepiness among children. Chervin et al. [123] assessed the frequency and clinical effect of PLMs with or without arousals in children before and after AT. There is no substantial impact of PLMs on MSLT. The impact of PLMs on EDS keeps poorly understood in children and need to be investigated.

Other Sleep Pathologies

Attention-Deficit/Hyperactivity Disorder

ADHD is one of the most common neurobehavioral disorders in childhood and the prevalence in school children is 3–5% [124]. Contrary to what Prihodova et al. showed [92], Lecendreux et al. found that children with ADHD, aged between 5 and 10 years old, were more sleepy during the day, as shown by the MSLT, and had longer reaction times compared to control children. In this study, the differences were not due to alterations in the quality of nocturnal sleep [125]. These results were confirmed by Golan et al. [126]. Children with ADHD children were significantly sleepier during the day than those in the control group (mean MSLT score of 21.9 ± 5.5 minutes versus 27.9 ± 2.0 minutes). However, nearly 50% of children with ADHD in the latter study suffered from sleep problems [127]. Thus, children with ADHD seem to suffer from daytime sleepiness and MSLT could be regarded as a method to measure it objectively. It is however important to consider that children with ADHD could also present with primary sleep disorders, especially sleep-related breathing disorders and periodic limb movement disorder.

Indications of MSLT

MSLT, preceded by NPSG, is indicated as part of the evaluation for suspected narcolepsy in children. MSLT is optional in children suspected of having hypersomnia from causes other than narcolepsy to assess excessive sleepiness and to aid in differentiation from narcolepsy [89]. MSLT has been standardized into a form that reliably measures sleepiness in various conditions in adults. It is recommended to follow this standardized procedure in children.

Conclusions

MSLT is the recommended method to evaluate objectively daytime sleepiness in adults and in children. The results have to be interpreted when integrated with the clinical evaluation with consideration of age, pubertal stage, regularity of the sleep patterns, caffeine consumption, and

urine drug screening for the adolescents. MSLT has a good sensitivity for diagnosis narcolepsy in children aged 5 years and older. However, normative data on large control population, especially in preschool children, are still lacking.

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Actigraphy

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Hawley E. Montgomery-Downs and Liat Tikotzky

Over the past 20 years, the use of actigraphy to estimate sleep-wake patterns in pediatric populations has increased markedly [1, 2]. Though the features of currently available actigraphy systems vary widely, they generally include a small, nonintrusive wristwatch-like device with a sensor that collects the wearer's movement magnitude and velocity, a port for downloading these data, and proprietary software and algorithms to analyze them. The sensor is typically worn around the nondominant wrist (by adolescents and older children) or an ankle (by infants and toddlers). When downloaded in the laboratory or clinic, the stored output is analyzed using specific (i.e., age-appropriate) software algorithms, wearer input (e.g., behavioral diary), and technician expertise in order to identify periods when the wearer was asleep or awake—based on the absence or presence, respectively, of body movements. A visual summary of the cumulative data, referred to as an "actigram," provides a qualitative overview and insight into wearer patterns, while software can be used to calculate detailed quantitative data.

Polysomnography (PSG) is the undisputed "gold standard" for identifying sleep, including among pediatric populations. PSG provides detailed information about the sleep stages and other physiologic (e.g., cardiorespiratory) measures essential for diagnosing most sleep disorders. However, this predominantly laboratory-based assessment (home-based PSG is rarely appropriate in pediatrics) is expensive, time-consuming, and intrusive. PSG also requires that the individual sleep in an unusual environment interferes with the sleep under assessment, causing a "first night effect" [3]. Thus, despite being the gold standard, PSG cannot provide information about normal sleep patterns or changes over time, especially among pediatric populations.

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For these reasons, actigraphy is often used as a separate, and sometimes complimentary, tool for both clinicians and researchers who wish to collect ambulatory assessment of sleep and sleep patterns, including over the relative long term (i.e., including continuous recordings for weeks) in the natural sleeping environment. Our purpose with this chapter is to provide an overview of: the validity and uses of actigraphy as a sleep assessment tool in pediatric sleep medicine and research; factors to consider when using actigraphy for clinical or research purposes; and issues specific to using actigraphy in clinical populations. Note that we focus herein on United States Food and Drug Association-approved medical devices; a section at the end of this chapter addresses invalid devices currently marketed to consumers for sleep self-monitoring which are also used by some clinicians and investigators.

Current Professional Recommendations for Clinical Use

In 2018, the American Academy of Sleep Medicine (AASM) issued its updated Standards of Practice for using actigraphy for the assessment of sleep and sleep disorders [4]. Their recommendations were based on a comprehensive review of all high-quality, published studies using, and assessing the use of, actigraphy. In general, actigraphic devices have been found useful for assessing differences between normative and clinical populations on sleep quality and maintenance, insomnia, and circadian rhythm disorders [5–8]. Specifically, the committee conditionally suggested, "*that clinicians use actigraphy in the assessment of pediatric patients with insomnia disorder [or] circadian rhythm sleep-wake disorder [and] to monitor total sleep time prior to testing with the Multiple Sleep Latency Test [in pediatric patients] with suspected central disorders of hypersomnolence.*" The committee also issued a strong recommendation, "*that clinicians* not *use actigraphy in place of electromyography for the diagnosis of periodic limb movement disorder [in pediatric patients].*" *(p. 1231).*

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These updated recommendations are expected to influence reimbursement for clinical use, at least in the United States. Currently, a Current Procedural Terminology (CPT) Category code is used for actigraphy. Under Medicare, CPT code 95803 is a stand-alone CPT code defined as, "Actigraphy, testing, recording, analysis, interpretation and report (minimum 72-hours to 14 consecutive days of recording, requires the patient to wear a home monitor for 24-hours a day for 3 to 14 days)." [9]. Despite this, there are currently no standard or set fees in pediatrics and most clinics are not compensated for actigraphy studies.

Validity of Actigraphy for Estimating Pediatric Sleep

It is important to briefly review how we test the veracity of any device in the field of sleep research. This is important in part because many studies still use inappropriate statistical techniques; thus, understanding the best practices in validity assessment will help the user identify which results are valuable. Specifically, use of the Pearson correlation is inappropriate because the r test statistic tells us about association (increase in X relative to Y) rather than agreement or concordance (whether X and Y change at the same rate along the same scale). Indeed, a perfect Pearson correlation can be found between two instruments with widely divergent measurement scales, as shown in Fig. 20.1.

Note that the correlation coefficient for the hypothetical data in this figure is nearly perfect, despite the fact that the respective axis values are widely divergent. A number of actigraphy assessments have relied on inappropriate statistical techniques (for review see [2, 10]). Further, the comparison of means relies on measurement error that would bolster the investigator's ability to "fail to reject the null hypothesis," and hence find a lack of difference between measures.

In contrast, an appropriate method to assess instrument validity is calculation of sensitivity and specificity, along with graphic representation using the Bland–Altman concordance technique [11, 12]. By convention within the sleep field, sensitivity is the proportion of PSG-recorded 30-second epochs of sleep that are accurately classified by the test instrument, while specificity is the proportion of epochs accurately classified as wake. We cannot overemphasize the importance of considering both sensitivity and specificity. Like a broken clock that tells the correct time twice daily, a sleep monitoring device that always reports that its wearer is sleeping will always be correct whenever the wearer is actually sleeping (100% sensitive), but that device will be never correct when the wearer is awake (0% specific). A scenario like this may seem as hypothetical as the data in our figure—but in fact some studies show specificity worse than what would be expected by chance.

The Bland–Altman concordance technique is not a test statistic, but rather a graphic comparison between two methods of measurement created by plotting the difference between the test device and gold standard against the gold standard, as shown in Fig. 20.2.

A highly valid test device will result in the differences between the two gathering along the 0-difference line in the horizontal center of the figure, demonstrating that the test device output is the same as the gold standard, and that it is consistently the same across the entire range of possible outputs. In this way, the near-perfect correlation in Fig. 20.1 is revealed as actually having highly different outputs between the two measures and shows that these discrepancies change based on the gold standard value (i.e., agreement is better at higher gold standard values).

To demonstrate these principles, we highlight several classic studies that have used appropriate analytic approaches to assess the validity of actigraphy for use in pediatric populations:

- Example 1: Insana and colleagues [13] examined validity of one brand of actigraphy in 14-month-old infants. While a statistically significant correlation was found between PSG- and actigraphy-recorded total sleep time, a Bland–Altman concordance analysis demonstrated that, compared to PSG, the default wake threshold value produced an actigraphy underestimation of total sleep time of more than 1 hour among 55% of infants. The range of differences between PSG and actigraphy for total sleep time was 6–276 minutes. Sensitivity of actigraphy in these infants was 92.4% for total sleep time, with specificity of actigraphy for identifying wake was 58.9%. The overall accuracy of actigraphy for identifying both sleep and wake was 89.6%.
- Example 2: Sitnick and colleagues [14] used videosomnography to examine the validity of actigraphy in a population of preschoolers with and without developmental disorders. Similar to the Insana study, this study found actigraphy to underestimate sleep time and overestimate wake after sleep onset. More concerning, the authors report instances when the child was clearly awake and moving, yet the actigraph reported that the child was asleep. Although placement of the device (ankle versus wrist) and sensitivity thresholds may have contributed to these findings, the results provided an important cautionary tale.
- Example 3: In a study of kindergarten-age children in Switzerland, Werner and colleagues [15] compared actigraphy to parent-report surveys and sleep diaries, common methods in clinical and research settings. Using the Bland–Altman concordance technique, the authors found satisfactory agreement between diary and actigraphic-reported sleep start, sleep end, and sleep period; however, the agreement for actual sleep time and wake after sleep onset was poor.

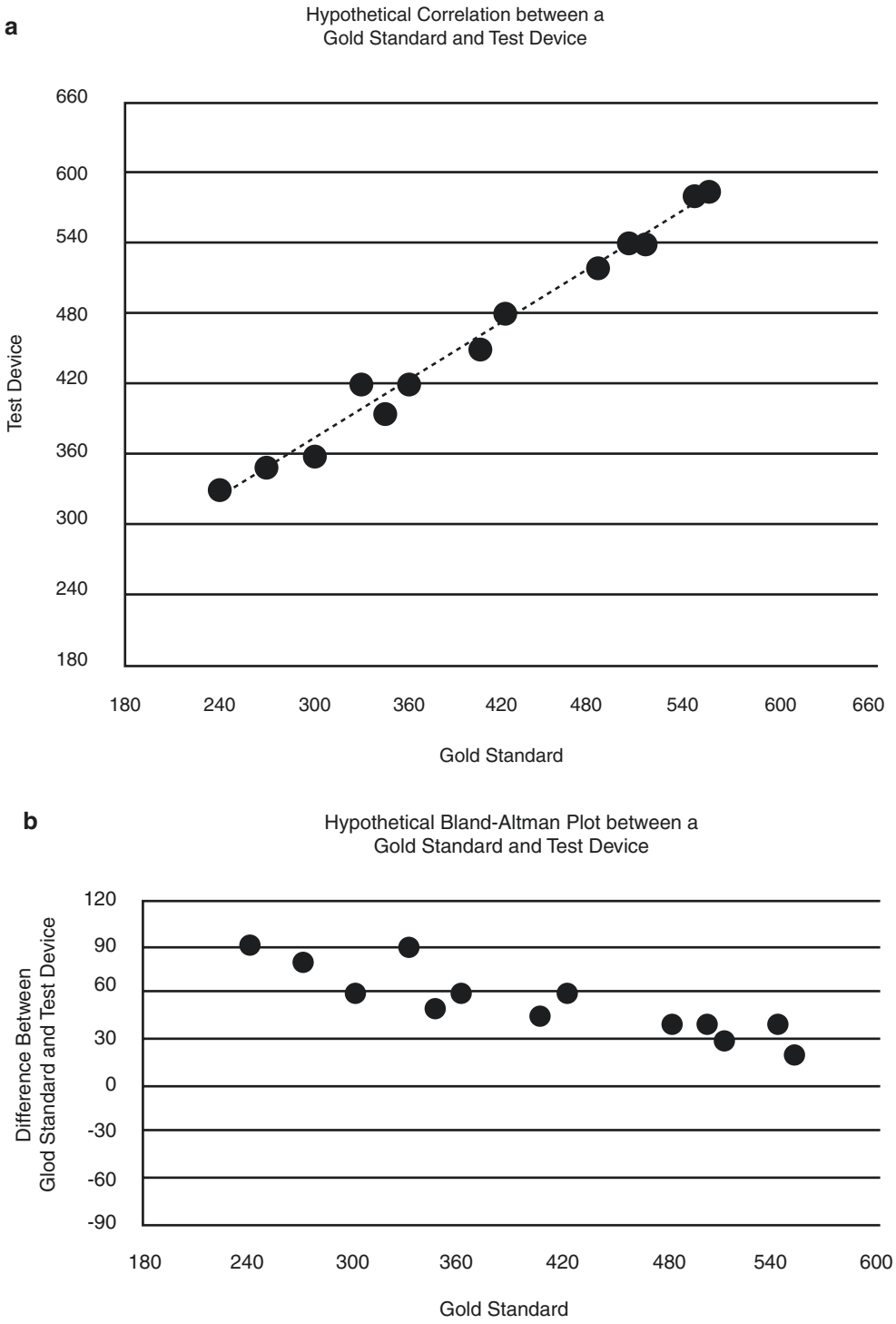

Fig. 20.1 Use of mock data to illustrate (**a**) inappropriate and (**b**) appropriate validation analyses. (**a**) Inappropriate validation analysis: simulated scatterplot with regression line for total sleep time (minutes) between simultaneously assessed fictitious gold standard method (*X* axis) and test device (*Y* axis). Actual Pearson correlation coefficient for these mock data: $r = 0.993$. (**b**) Appropriate validation analysis: Using the same simulated data plotted above, this Bland-Altman plot shows total sleep time (minutes) for the fictitious gold standard method (*X* axis) plotted against the difference between the gold standard and test device (*Y* axis). Actual difference and variance between methods: Mean = 54.23 minutes; standard deviation ±22.0 minutes

- Example 4: In their study of children of ages 3–18 years, Meltzer and colleagues [16] found developmental differences in the sensitivity and specificity of actigraphy. Namely, sensitivity was best in adolescents (0.92–0.97). Although still acceptable, sensitivity was worst in preschoolers (0.85–0.91). Similarly, specificity was best in preschoolers (0.75–0.80) and the worst in adolescents (0.54–0.58). Unlike previous studies, Meltzer and colleagues compared two different brands of actigraphs with concurrent PSG. These head-to-head comparisons found an average difference of 25 minutes between brands in total sleep time using the Bland–Altman technique.
- Example 5: Most recently, Tikotzky and Volkovich used extensive longitudinal data on nocturnal awakenings collected from families of healthy infants during postpartum months 3–18. Their report revealed how infant actigra-

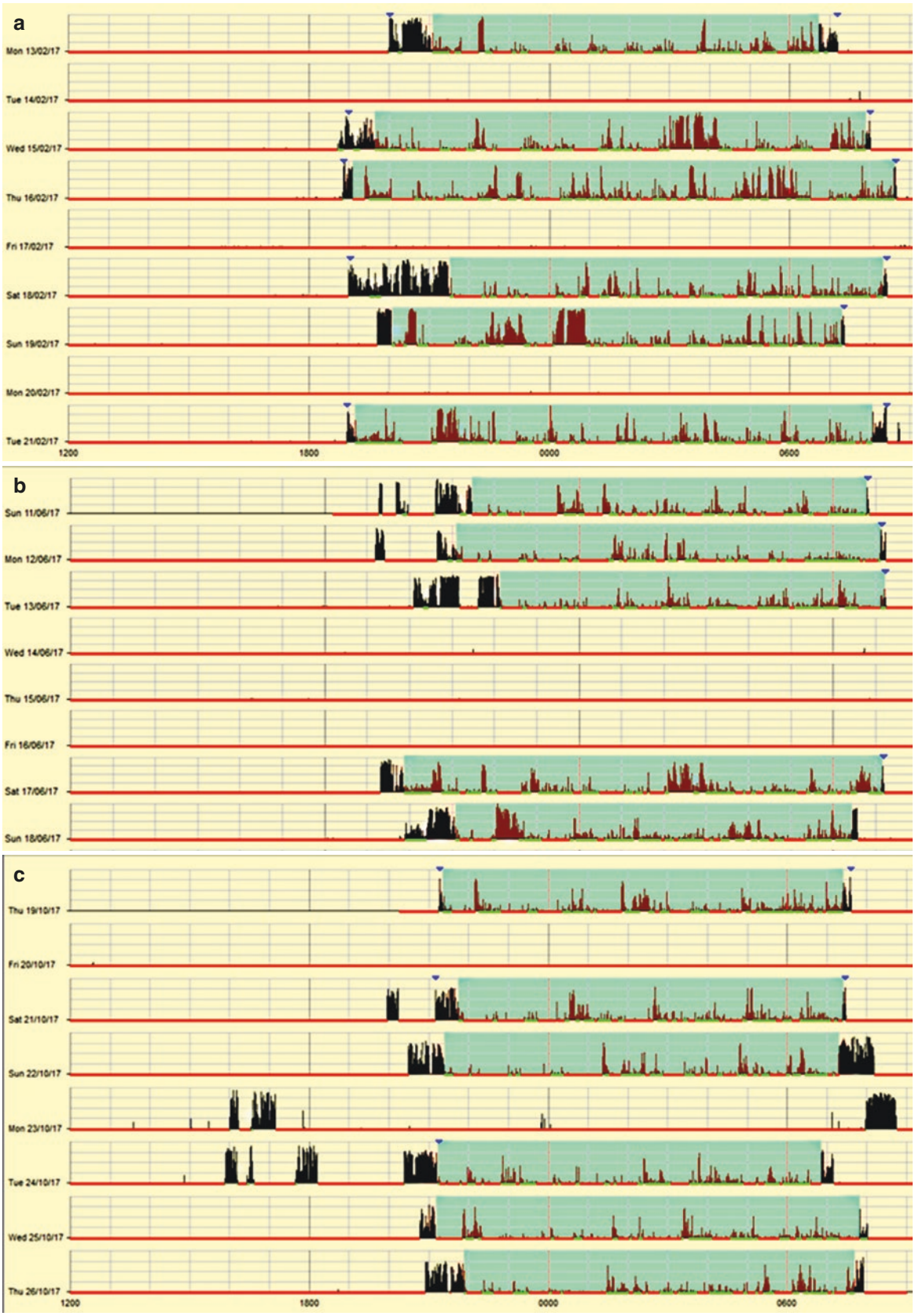

Fig. 20.2 Infant X at (**a**) 4, (**b**) 8, and (**c**) 12 months of age, demonstrating patterns of increasingly consolidated nocturnal sleep over time. (**a**) Age 4 months, with average 90% sleep efficiency, 73 minutes of wake after sleep onset, and 4.4 long (>5 minutes) awakenings. (**b**) Age 8 months, with average 92% sleep efficiency, 48 minutes of wake after sleep onset, and 3.6 long (>5 minutes) awakenings. (**c**) Age 12 months, with average 96.5% sleep efficiency, 21 minutes of wake after sleep onset, and 1.8 long (>5 minutes) awakenings

phy, sleep diaries, and the Brief Infant Sleep Questionnaire converge: the three assessment methods were significantly correlated, and each clearly demonstrated that infant sleep consolidated over time. However, using Krippendorff's α and the Bland–Altman technique absolute agreement between these methods regarding infant awakenings was poor, and worsened over time [17].

A complete dissection of the factors contributing to the varying performance of these devices is beyond the scope of this chapter. However, it is critical to note that selection of an appropriate device and/or settings can be challenging for the clinician or researcher due to the lack of standardization across brands. Several companies market these devices, yet each brand—and even models within the same brand—differ in their recording and analysis specifications, memory capacities, and capabilities. This continues to be a rapidly growing technology; those considering investing in actigraphy should consult the manufacturer's representatives, current users, and peer-reviewed literature (i.e., articles using appropriate statistical and analytical methods) to determine which system has been validated for their population of intended use.

Clinical and Research Considerations

When Not to Use Actigraphy

While actigraphy can be a complementary assessment tool with an important place in the pediatric sleep medicine clinic, it is not a substitute for PSG, which remains the clinical standard for the diagnosis of sleep disordered breathing, periodic limb movement disorder (PLMD), and narcolepsy. Several studies of actigraphy in children with these disorders verify that actigraphy should not be the primary diagnostic tool. A good example is pediatric PLMD.

PLMD is a frequently misdiagnosed sleep disorder that causes sleep fragmentation and consequent neurobehavioral dysfunction [18]. Accurate, simple methods for the home diagnosis of pediatric PLMD would be a major advance for the field. At one time, software was marketed that enabled actigraphs to be worn around the balls of the feet to identify periodic limb movements. While there was some evidence for reasonable sensitivity and specificity among adults [19], a validation assessment with children [20] showed poor agreement that would lead to serious misdiagnosis. This example underscores the importance of thorough, age-specific validation.

When to Use Actigraphy

In addition to the AASM practice parameter recommendations described above, there are many appropriate clinical applications for actigraphy in pediatric sleep medicine and research. Actigraphy can be a highly valuable stand-alone or complementary assessment tool when used in conjunction with sleep diaries and by a trained clinician using visual inspection. Applications that have answered important clinical and basic questions include use for clinical complaints of excessive daytime sleepiness, prolonged sleep onset latency, multiple and/or prolonged night waking, and restless sleep. For each of these, actigraphy can provide additional information above and beyond a subjective history, as well as when the results of PSG are negative. In addition, actigraphy can provide useful information about sleep patterns and durations for the 7–10 days prior to a PSG with MSLT (i.e., to verify that excessive sleepiness is not due to sleep deprivation or a delayed sleep phase). Differential diagnoses that may be seen with actigraphy include poor sleep hygiene, irregular sleep patterns, insufficient sleep, and poor sleep quality or low sleep efficiency.

Infant sleep research is another area highly appropriate for use of actigraphy. Actigraphy pioneer Dr. Avi Sadeh developed the first algorithm for validly identifying sleep and wake in healthy infants [21]. His cumulative work has included breakthrough insights into the development of sleep consolidation during infancy [22] and childhood [23]. His research also demonstrated that actigraphy can be used to distinguish between sleep-disturbed and "control" infants [21, 24], and to assess the efficacy of behavioral sleep interventions. In one study [25], he examined two behavioral sleep interventions, using both actigraphy and sleep diaries, to demonstrate that whereas parents reported a significant decrease in the number of infant night-wakings following the intervention, actigraphy indicated only a small decrease. These findings suggested that the interventions helped infants acquire self-soothing capacities, which they learned to implement after naturally awakening during the night. Thus, as actigraphy showed, night-wakings do not disappear following sleep interventions, but parents probably become less aware of them as a result of the infant's growing ability to resume sleep independently. Dr. Sadeh's work highlighted the importance of assessing sleep by multiple methods in order to achieve a comprehensive and deeper understanding of children's sleep, given the fact that different assessment methods may yield different results.

Actigraphy can be particularly suitable for the assessment of sleep in longitudinal studies. Whereas PSG would probably not be applicable for recurrent assessment, actigraphy provides a convenient, relatively inexpensive, and nonintrusive objective method to follow sleep development along multiple assessment points. The development of sleep consolidation during infancy as captured by actigraphy can be clearly seen in Figs. 20.2, 20.3 and 20.4. Unlike the increase in sleep consolidation presented in these figures, Fig. 20.5 shows an infant with consistent long awakenings throughout the first year.

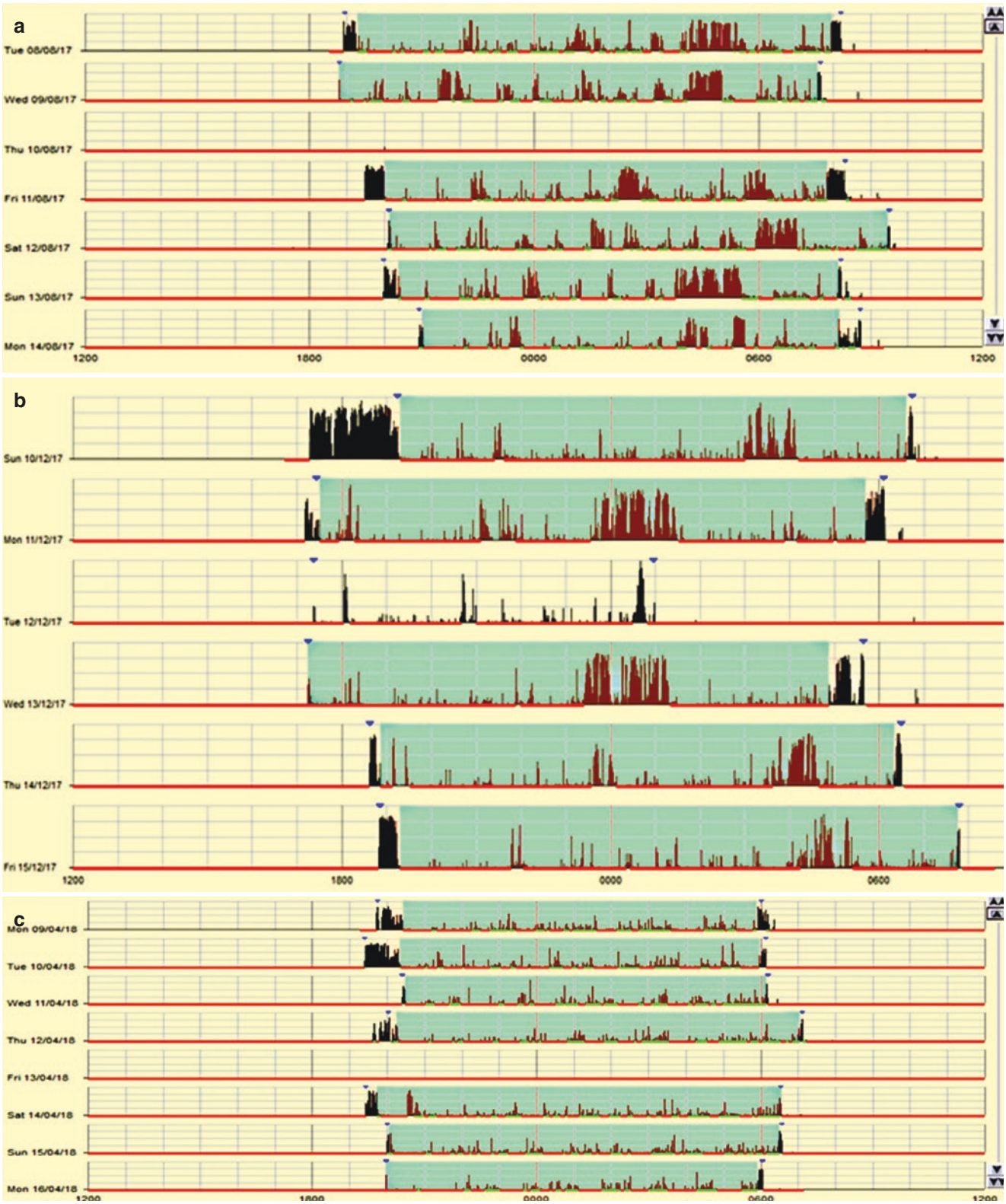

Fig. 20.3 Infant Y at (**a**) 4, (**b**) 8, and (**c**) 12 months of age, demonstrating patterns of increasingly consolidated nocturnal sleep over time. (**a**) Age 4 months, with average 83% sleep efficiency, 125 minutes of wake after sleep onset, and 5.3 long (>5 minutes) awakenings. (**b**) Age 8 months, with average 83% sleep efficiency, 121 minutes of wake after sleep onset, and 3 long (>5 minutes) awakenings. (**c**) Age 12 months, with average 98% sleep efficiency, 8 minutes of wake after sleep onset, and 0.9 long (>5 minutes) awakenings night-wakings

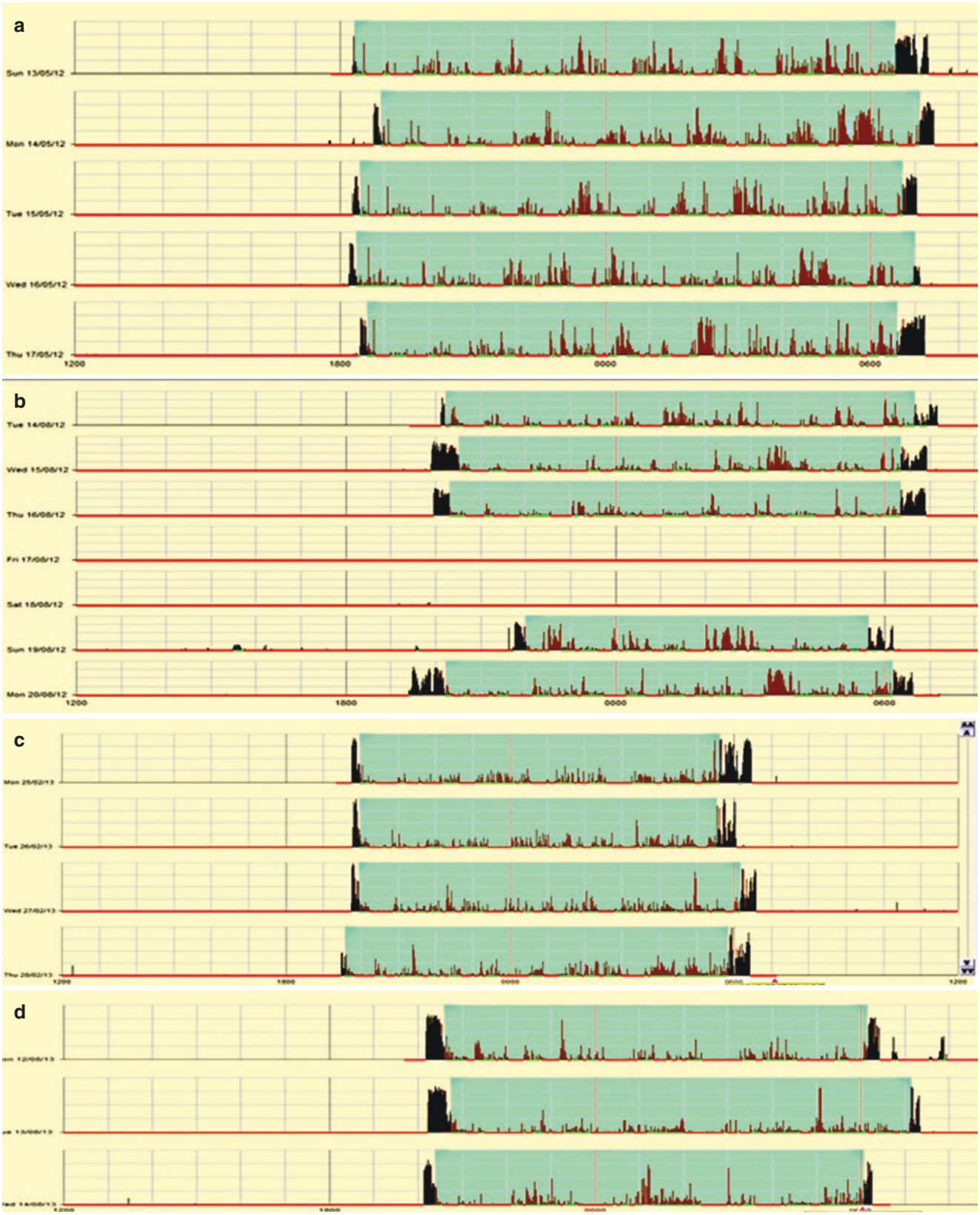

Fig. 20.4 Infant Z at (**a**) 3, (**b**) 6, (**c**) 12, and (**d**) 18 months of age, demonstrating patterns of increasingly consolidated nocturnal sleep over time. (**a**) Age 3 months, with average 92% sleep efficiency, 60 minutes of wake after sleep onset, and 3.8 long (>5 minutes) awakenings. (**b**) Age 6 months, with average 93% sleep efficiency, 37 minutes of wake after sleep onset, and 1.8 long (>5 minutes) awakenings. (**c**) Age 12 months, with average 99.5% sleep efficiency, 2.5 minutes of wake after sleep onset, and 0 long (>5 minutes) awakenings. (**d**) Age 18 months, with average 99% sleep efficiency, 8 minutes of wake after sleep onset, and 0.3 long (>5 minutes) awakenings

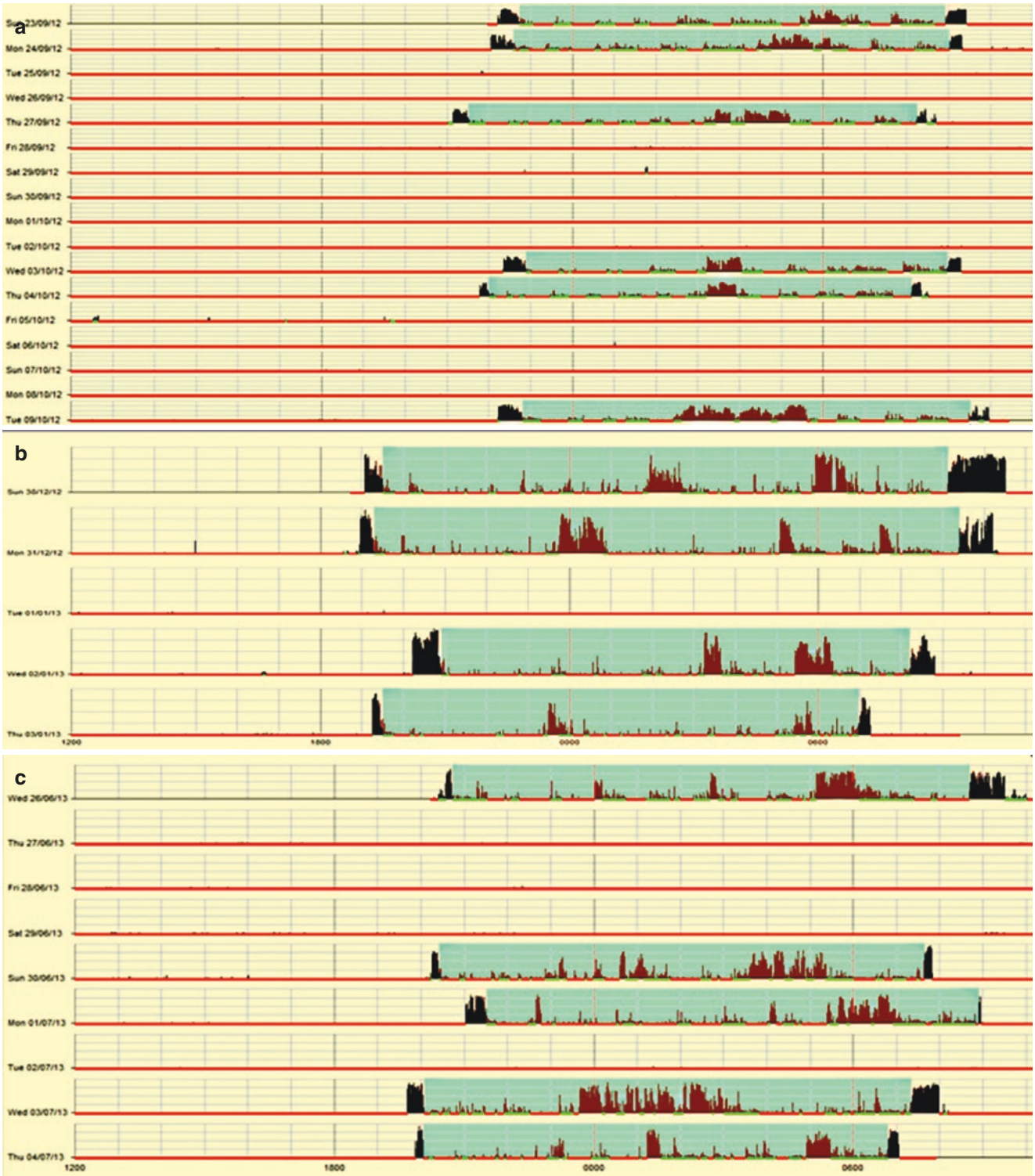

Fig. 20.5 Infant Q at (**a**) 3, (**b**) 6, and (**c**) 12 months of age, demonstrating persistent long nocturnal awakenings. (**a**) Age 3 months, with average 86% sleep efficiency, 90 minutes of wake after sleep onset, and 2.7 long (>5 minutes) awakenings. (**b**) Age 6 months, with average 90% sleep efficiency, 76 minutes of wake after sleep onset, and 2.3 long (>5 minutes) awakenings. (**c**) Age 12 months, with average 86% sleep efficiency, 96 minutes of wake after sleep onset, and 4.6 long (>5 minutes) awakenings

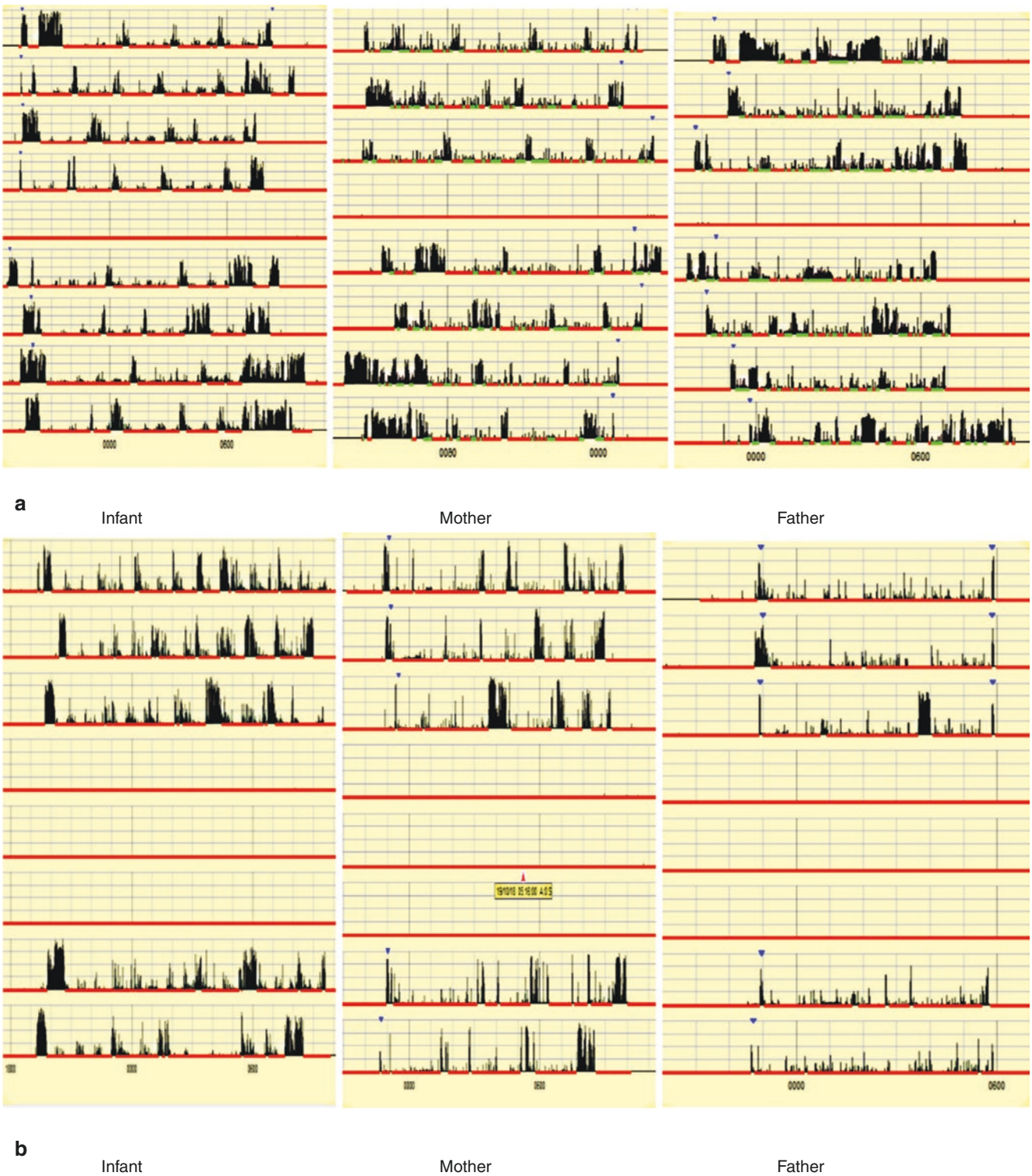

Fig. 20.6 Concurrent sleep patterns for each member (infant, mother, and father, respectively) of two families at 4 months postpartum. (**a**) Family 1 shows typical infant sleep and marked sleep disturbances in both parents. (**b**) Family 2 shows marked synchrony between the infant and mother, while the father's sleep is relatively undisturbed

Actigraphy can also be used in clinical and research settings to assess differences and similarities in sleep between family members. Figure 20.6 demonstrates synchronous assessments of sleep in two families (i.e., infant, mother, and father).

Pediatric Actigraphy Considerations and Challenges

There are a number of specific considerations when using actigraphy in pediatric populations.

Device Placement

Most validation studies have assessed nondominant wrist placement. However, in younger children (i.e., infants and toddlers), it is more appropriate to place the device around the ankle. It has also been suggested that in some special populations (e.g., children with autism), the actigraphy may be placed in the pocket or shoulder of a tight-fitting shirt [26], though further validation is needed for this placement.

Artifact

In order to reduce artifact from extraneous movement, it is essential that concurrent diaries be kept, to allow user-identification of likely sleep periods versus when the actigraph may have been removed for bathing, swimming, etc. In addition, sleep diaries provide information about periods when the child appears awake even though they were sleeping (e.g., napping in a swing or moving car), or when the child was awake but may appear asleep (e.g., resting in front of the television). While sleep diaries provide adjunct for artifact reduction, they are also limited insofar as the reporter (i.e., usually parents) may be sleep deprived (known to impact episodic memory) and/or be unaware of when their child fell asleep at bedtime or when they are awake at night.

Recording Time

Recording duration for most purposes needs to be at least 7 days [27], and five usable nights are required for recording reliability. Collecting seven nights of data also allows inclusion of both weekdays and weekends, which often differ in children and adolescents. Extended recording also accommodates potential data loss from illness, protocol nonadherence (e.g., forgetting to wear the device or complete the sleep diary), or technical failure of the device.

Care and Return of the Device

Because actigraphs are relatively expensive, it is important to communicate with both the parent and child about proper care of the device. For example, although some brands of actigraphs are water-resistant or waterproof, others must be removed for bathing. The clinician or investigator should also consider whether to ask that the device be removed and left at home if there is a chance that it could be lost or damaged (e.g., while playing contact sports). Some sleep laboratories ask the parent to sign a contract indicating that if the equipment is lost, they will be responsible for its replacement (we know of cases in which homeowners' insurance has covered this expense). Although patients or participants may be provided with a prepaid mailing envelope to return the device, we encourage an in-person meeting to collect the device; this allows the clinician or investigator to go over the actigram in person and ask about potential artifacts.

Reference Values

A recent publication has improved actigraphy interpretation by providing comprehensive reference values for pediatric actigraphy, based on a very large sample of healthy school-age children and adolescents of ages 6–17 years [28]. Similar reference values will eventually be valuable for infants and younger children, as well as clinical populations. Until then, it is important to interpret results in the proper context, by comparison to other studies in which similar devices and technical specifications were used.

Publishing and Reporting

When publishing actigraphy research results and developing clinical report templates, it is imperative we include a description of how the data were obtained. This checklist can be used as a reporting guide for essential parameters [1].

Checklist of essential parameters for reporting use of actigraphy

Device/System information
Device name, specific model, manufacturer
Device placement (e.g., nondominant/dominant wrist, left/right ankle)
Epoch length, mode, algorithm, wake sensitivity threshold
The type and version of software used
Sensitivity and specificity, rationales for use of all of the above
Sleep diary
Type of sleep diary used (e.g., paper, electronic, telephone call)
Who completed sleep diary (i.e., parent, child)
Frequency of diary completion (e.g., at bedtime only, morning and evening)
Use of event marker
Data collection and processing (including missing data)
Number of nights of data collection
Number of weekday and weekend nights (if relevant)
Methods used to identify and handle artifact
Data lost to:
Technical failure
Participant nonadherence (e.g., not wearing device/completing diary)
Artifact
Data variables
Define each variable, including those autocalculated using software
Define all scoring rules, using common/standardized terms

Adapted from [1]

Consumer-Marketed Wearable Trackers

The first nonmedical sleep tracking device—marketed directly to consumers—became available online in 2010. In 2011, it was demonstrated that this device did not provide valid sleep information compared to either PSG or actigraphy (i.e., had high sensitivity but quite poor specificity) [29]. The market for these devices has continued to escalate, despite repeated independent testing showing their poor

validity. The direction of inaccuracy in performance of these devices is that that they fail to detect period of wake, and thus over-represent the quality and quantity of sleep (a potentially dangerous "false negative" self-test). In its 2018 position statement on consumer-based sleep technology (CST), the American Academy of Sleep Medicine asserted,

> Given the lack of validation and United States Food and Drug Administration (FDA) clearance, CSTs cannot be utilized for the diagnosis and/or treatment of sleep disorders at this time. However, CSTs may be utilized to enhance the patient-clinician interaction when presented in the context of an appropriate clinical evaluation. The ubiquitous nature of CSTs may further sleep research and practice. However, future validation, access to raw data and algorithms, and FDA oversight are needed [30, p. 877].

In the meantime, it is clear that these devices are inadequate for monitoring sleep for clinical or research purposes and their use by parents for young children or by adolescents should not be endorsed or encouraged.

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Defining Normal in Pediatric Sleep: Some Thoughts and Things to Think About

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David Gozal and Leila Kheirandish-Gozal

Sleep disorders in general and, more specifically, sleep disordered breathing are highly prevalent conditions in children of all ages. Although the diagnosis of such conditions may seem relatively straightforward in most cases, there are many occurrences whereby symptomatic children undergo diagnostic studies and the results of such tests are interpreted as "normal." We cannot stop but wonder what does "normal" mean in pediatric sleep medicine? The definition of a normal sleep study is not a trivial process, and requires a methodical delineation of representative normative data, clinical and prognostic implications of the demarcation between "normal" and "abnormal," and ultimately demonstration of the effectiveness and reliability of such approaches. Unfortunately, despite major progress in our understanding of many sleep disorders in children, clinically solid and robust normative reference sleep test measures (e.g., polysomnography, polygraphy, actigraphy) are lacking, and more importantly there is no real consensus on any of these important aspects. As such, substantial divergence of opinions among sleep specialists emerge regarding the criteria they use to establish the need or lack thereof of any therapeutic intervention to address the symptoms that prompted the clinical referral to their practices. Such paucity of well-validated data, however, is an opportunity to explore more refined options that ultimately allow for improved personalization and precision in the decision of normal vs. abnormal vs. treatable. For example, incorporation of symptom scores, test results, and critical biomarkers into validated algorithms would yield improved rational for clinical decisions and ultimately better outcomes. There is no doubt that evidence-based approaches to the evaluation of community or clinical referral pediatric populations need to be predicated on scientifically pragmatic and reliable diagnostic approaches that constantly refine the concept of "normal."

The increasing awareness by the medical community and by the public on the importance of sleep along with major advances of sleep medicine over the last several decades, which hopefully have been thoroughly covered in the other chapters of this book, have prompted a high demand for pediatric sleep medicine consultations all around the world. Indeed, the relatively high prevalence of conditions such as obstructive sleep apnea (OSA), periodic leg movement disorder of sleep (PLMDS), or insomnia in the pediatric age range has prompted dynamic and sustained increases in our understanding of their pathophysiology and morbidity. Unfortunately, the herd approach whereby one diagnostic test or one treatment fits all does not work!!!

In the last several years, we have come to realize and so have the parents of our patients that they need a very personalized and precise approach to their sleep problems, and that such precision requires much better definition of what constitutes "normal." For example, emerging data in adults have recently shown that it is not only sleep duration or sleep quality or continuity that determines the presence of end-organ morbidities. In fact, sleep irregularity, that is, how much variability in bedtime and wake-up times is present despite globally the same duration of sleep can lead to markedly divergent risk [1–4]. Irregular sleep schedules have also been associated with higher body mass index, and cardiovascular and metabolic risk in community children [5]. Similarly, when evaluating a large proportion of sleep disorders such as OSA or PLMDS, exclusive reliance on clinical history and physical examination will lead to notorious imprecision in our ability to predict who among symptomatic patients are indeed affected as demonstrated by a sleep study and who are those that notwithstanding the symptoms exhibit a sleep study overnight polysomnogram (PSG) which according to current criteria would be defined as being within normal lim-

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its. In the past, there were those who proposed that every child who is symptomatic, for example, habitually snores during sleep, should be treated without the need for any diagnostic confirmatory test such as a PSG. There are others who have suggested that in the presence of characteristic symptoms and potentially some supportive physical findings, simplified testing procedures could be used such as home-based polygraphy or overnight oximetry [6–23]. We have been among those advocating for such approach, since it has the potential of markedly expanding the availability of testing, and if scalable operations that can become automatic and therefore do not require the onerous and time consuming labor of scoring and interpretation [16, 24–34], then marked reductions in costs can be gained while reserving the pediatric sleep laboratories to those cases in which the diagnosis remains unclear or the clinical presentation is complex and nebulous and therefore more sophisticated diagnostic systems are necessary.

There are those who say that you will know it when you see it to the a priori simple question of whether this child has OSA or PLMDS? Not so fast…! Let's present a scenario where a 4-year-old presents to your sleep clinic referred by their primary care physician because parents have complained that the otherwise healthy child except for seasonal allergic rhinitis, snores almost every night, has frequent scary nightmares, and is often grumpy in the morning. We could adopt a frequently applied answer to the question: how do you know that this symptomatic child before you in clinic does not need any treatment because his PSG is normal? Indeed, if the apnea-hypopnea index (AHI) of this child is less than one per hour total sleep time (TST), we will tell the parents that the PSG is normal, and this is the end of the visit. However, the child came to be evaluated because of significant symptoms, and the fact that the sleep study is normal does not necessarily indicate that this child is healthy and does not suffer from a sleep disorder.

What cutoff values of AHI, oxyhemoglobin desaturation index (ODI) 3%, periodic leg movement index (PLMI), etc., should we then adopt as demarcating normal from pathological? Should we use statistical classifiers? In such instance, should we adopt 2, 3, 5 standard deviations beyond the mean of the sleep measure as obtained from a representative cohort of healthy community children spanning over the whole pediatric age range to determine that that measure is pathological and requires treatment? How would such set of rules affect the decision algorithm and how many symptomatic children would be excluded from the "abnormal" ergo has "disease" category? These are difficult issues because there is very little correlation between the phenotypic expression and severity of the sleep disorder (i.e., the reported or measurable severity of symptoms, signs, and disease-associated morbidities) and the actual polysomnographic measures by which we currently define that the test is "abnormal."

For example, let's take excessive daytime sleepiness (EDS) in children with habitual snoring who underwent PSG evaluation. It is clear that a proportion of children with OSA manifest loosely defined EDS and that as the severity of OSA increases (as defined by ether increasing AHI, increasing severity of hypoxemia, or enhanced sleep fragmentation), the probability of exhibiting EDS is also increased [35–39]. However, symptoms and physical findings do not assist with the decision of whether OSA is present or not [40]. Furthermore, if you ask the parents of snoring children, the prevalence of EDS using a sleepiness questionnaire such as the modified Epworth score is relatively low ranging between 8 and 15% [41–54], even though when EDS is present, it is more likely that OSA is also present, that is, EDS adds specificity at the expense of sensitivity [55, 56]. Moreover, if EDS is evaluated more objectively using the Multiple Sleep Latency Test (MSLT), then only a small proportion of children will exhibit mean sleep latencies <10 min and such proportion is augmented as the severity of sleep-disordered breathing is increased [35], or more particularly when children are obese [57]. In light of the marked variability in the expression of EDS among snoring children or even among those fulfilling criteria for moderate to severe OSA, and the fact that EDS as defined by MSLT results could be definitely present even in children with snoring but otherwise statistically normal PSGs, we attempted to identify other PSG-derived measures that may predict increased sleep propensity in habitually snoring children. One of such efforts involved looking at respiratory-related arousals relative to spontaneous arousals, and indeed, evidence of dynamic regulation of arousals emerged whereby spontaneous arousals were likely to progressively decline when increased frequency of respiratory arousals took place up to a certain limit at which time it would seem that the compensatory capacity to accommodate sleep fragmentation induced by sleep-disordered breathing was exceeded and therefore it would be reasonable to assume that sleepiness would be more likely to emerge [58]. Interestingly, the cut-off AHI at which this phenomenon of "compensatory decompensation" seemed to become manifest was between five and seven events per hour TST, and this figure will recur in our subsequent discussion below. The corollary to this observation was that there should be some biological measures that could more objectively serve as accurate reporters of EDS, and circulating levels of tumor necrosis factor α (TNF) were proposed with variable success, likely related to genotypic variance [59–63]. Therefore, we will be confronted with a clear conundrum: Assuming proper sleep hygiene and sleep duration by these two families, a snoring child with a AHI <1/hour TST and significant sleepiness (falling asleep at school and at home) and a snoring child with a AHI >5 hour TST without any evidence of EDS. All of us would treat the latter but would feel very

ambivalent about treating the former. It is through examples like this that we come to the realization that: (i) the large variability of the phenotypic expression of a sleep disorder in children; (ii) the relatively limited value of current PSG-derived measures to guide treatment decision or to predict morbidity.

The problems raised by the inaccuracy of PSG-derived measures and cut-offs to demarcate disease (i.e., morbidity) are not only limited to EDS, but also affect many other putative consequences of sleep disorders. Indeed, even though we reported that there was a positive and significant association between the probability of cognitive deficits and the standard PSG measures (AHI, nadir SpO_2, respiratory arousal index) [64], the frequency of weekly snoring (nights per week) emerged as a stronger predictor of a composite cognitive measure than the AHI [65]. Of note, the AHI cut-off at which the probability of cognitive deficits increases is also situated around five to seven per hour TST, and that the negative findings related to the absence of significant improvements in cognitive function in the only randomized trial to date, the children adenotonsillectomy trial (CHAT) study can be simply explained by the absence of sufficient power to identify such improvements when the majority of the children who participated in the trial had a priori and unsurprisingly normal cognitive function [66]. Indeed, such cognitive batteries are designed to detect and diagnose children with substantial losses (i.e., developmental delay) and with standard deviations that are 10–15% of the whole scoring range it is not surprising that small improvements may not be detectable. We will also remark that cognitive assessments are not a routine part of any of the clinical evaluations we perform in the Pediatric Sleep Clinic, and that the only information we gather is how the patient is overall doing academically if they are of school age.

To search for solutions, let us therefore enumerate the list of issues and problems that the field of pediatric sleep medicine will have to resolve in the upcoming years:

- How do we define a "normal' PSG? [67–74]
- Does PSG contain embedded prognostic and morbidity-related information (biomarkers) that can be extracted using artificial intelligence and deep learning approaches? [75–78]
- Identifying simplified and optimized diagnostic approaches that are scalable and reliable [24–32, 79, 80].
- Delineating additional clinical features that enable patient diagnostic and therapeutic decisions [81, 82].
- Identifying potential biomarkers that promote a better understanding of the phenotype and the response to therapy [83–89].
- How do we enable precision medicine in pediatric sleep medicine? [90]

As mentioned in the introductory lines, the field of pediatric sleep has achieved remarkable growth and expansion in both scientific content and clinical know how. However, the empirical trajectory that has brought us this far is proving insufficient as far as addressing important discrepancies between the findings in our very expensive diagnostic workhorse (i.e., PSG) and clinical decision making. As we continue evaluating children with sleep-related issues in our clinics, we need to be reminded of the list of issues that remain unresolved and keep a healthy and skeptic approach when confronted with discrepancies between the symptoms and the findings of the diagnostic tests we have used. In the words of the famous and erudite physician Maimonides (AD 1137–1204):

The more accomplished one is in that science, the more precise his investigations are, the more doubts and difficult questions arise in him. He will go into additional investigations and will hesitate in some of his answers [91].

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Part V

Pharmacotherapy of Sleep Disorders in Children

Stimulants

22

Stéphanie Bioulac and Patricia Franco

Introduction

Central nervous system stimulants and sympathomimetic amines are commonly named *Stimulants*, drugs structurally similar to endogenous catecholamines (i.e., dopamine and noradrenaline). Stimulants, especially amphetamine, are one of the oldest substances available in United States. In 1887, amphetamine was first synthesized and found in the 1920s to be a potential alternative to ephedrine which had been used for the treatment of asthma [1]. Amphetamine is also one of the oldest psychotropic substances used in psychiatry. Indeed, few years later, in 1937, Bradley described for the first time the decrease of impulsive and aggressive behaviors in attention deficit hyperactivity children with the use of amphetamine (Benzedrine) [2].

Stimulants currently used in sleep medicine are amphetamine like compounds (amphetamine, methamphetamine, methylphenidate, pemoline), mazindol, modafinil-armodafinil, some antidepressants with stimulants properties (i.e., bupropion), and caffeine. In child and adolescent sleep clinic, modafinil and amphetamines (and amphetamines-like compounds) are commonly used and described in this chapter.

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Amphetamines and Amphetamine-Like Compounds

Pharmacological Effects

Chemical Entities

Amphetamine belongs to the class of drugs called the ß-phenylethylamines, chemical structure close to endogenous catecholamines.

Phenylisopropylamine is constituted by three structural components: an aromatic nucleus, a terminal amine, and an isopropyl side chain. This scaffold constitutes the template for various other psychoactive molecules. Methamphetamine is characterized by an additional methyl group attached to the amine.

Amphetamine-like compounds, such as methylphenidate and pemoline, are structurally similar to amphetamines; all compounds include a benzene core with an ethylamine group side chain. Pemoline has been withdrawn from the market in several countries because of liver toxicity.

Pharmacological effects of most amphetamine derivatives are isomer specific. These various effects occur at the pharmacokinetic level (absorption, brain penetration, metabolism, elimination). For example, D-amphetamine is a far more powerful stimulant (more wakefulness) than L-amphetamine. Dextro-amphetamine is available in 5 mg tablets as Dexedrine and Attentin.

The most common commercial form of methylphenidate is a racemic mixture of a D- and L- enantiomer. Methylphenidate is available in immediate as Ritalin and sustained-release formulations marketed under the prescription names of Concerta, Quazym, Medikinet, Ritalin LP. The US Food and Drug Administration (FDA) and other European Health Administrations, like in France, have classified amphetamines and amphetamine-like compounds as schedule II controlled substances, meaning that they are available only by physician prescription because, although they have therapeutic value, they have a high potential for abuse and psychological or physical dependence.

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Pharmacokinetics

Amphetamine is a lipid soluble substance that is well absorbed by the gastrointestinal tract. Peak levels are attained about 2 hours after oral administration with quick tissue distribution and brain penetration. Protein binding is variable with an average volume of distribution of 5 l/kg. The average half-life is 10.25 hours. Hepatic catabolism and renal excretion are implicated in the inactivation of amphetamine. Urinary excretion is influenced by urinary pH [3].

In the same line, methylphenidate is quickly absorbed after oral administration. Nevertheless, it has low protein binding and is short-acting (in its immediate release form) with an effect about 4 hours and half-life of 3 hours [3]. The duration of action is approximately of 8 hours for the sustained-release formulations.

Mechanisms of Action

The primary central nervous system effects of amphetamine and methylphenidate within the brain include increased catecholamine availability in striatal and cortical regions.

Amphetamine has been characterized as a dopamine releaser; three major mechanisms are usually described. First, it is a substrate for the dopamine transporter that competitively inhibits dopamine uptake. Second, it facilitates the movement of dopamine out of vesicles and into the cytoplasm. And then it promotes dopamine transporter-mediated reverse-transport of dopamine into the synaptic cleft [4].

Pharmacodynamics

Amphetamine is taken into presynaptic nerve terminals by the association with one chloride ion and two sodium ions. This complex—amphetamine with the ions—is actively transported by monoamine reuptake transporters. Amphetamine acts competitively with the endogenous monoamines. Thus, the greater the number of amphetamines the more internalized amphetamine will be found [5]. Once inside the presynaptic terminal, amphetamine displaces other monoamines to be stored by VMAT2 (vesicular monoamine transporter 2) [6].

This mechanism of action is complemented by the inhibition of the reuptake of monoamine oxidase [5]. This activity is not done as an inhibitor per se but more as a competitive substrate. Thus, amphetamine is recognized to be a weak dopamine reuptake inhibitor, moderate noradrenaline reuptake inhibitor, and very weak serotonin reuptake inhibitor. Another mechanism of action of amphetamine is the inhibition of the mitochondrial-bound enzyme monoamine oxidase which is the catalytic enzyme in charge of degrading all the excess of neurotransmitters [5].

Indications

The major indications of methylphenidate and amphetamines are narcolepsy, idiopathic hypersomnia, and attention deficit hyperactivity disorder (ADHD).

The recent network meta-analysis from Cortese (2018) [7], exhibited that methylphenidate (in children and adolescents) as the preferred first pharmacological choice for short-term pharmacological treatment of ADHD, even though amphetamines were marginally superior to methylphenidate. With respect to tolerability, in children, amphetamines were less well tolerated than placebo and significantly increased diastolic blood pressure in children and adolescents. In these populations, methylphenidate was the only drug with better acceptability than placebo. These results are in accord with NICE (National Institut for Health and Care Excellence) guidelines, in which methylphenidate is recommended as the first choice in children and adolescents [8]. This guideline covers recognising, diagnosing and managing ADHD in children, young people and adults. It aims to improve recognition and diagnosis, as well as the quality of care and support for people with ADHD.

Side Effects

Stimulants are generally well tolerated.

Sympathomimetic properties of stimulant medications induce cardiovascular effects. Patients may experience increases in heart rate and blood pressure (increasing both systolic and diastolic blood pressure). The average increase in systolic blood pressure is 3–4 mmHg, average increase in diastolic blood pressure of 1–2 mmHg, and average increase in heart rate is three to four beats per minute [9].

The most common acute adverse reactions to stimulants include mild gastrointestinal disturbance, loss of appetite, dryness of the mouth, insomnia, palpitations, cardiac arrhythmias, and headache. Other adverse effects include agitation, irritability, confusion, dysphoria, and mild depression of the mood. Flushing, pallor, excessive sweating, and muscular pains are other side effects described. Sleepiness or listlessness can occur also when the effects wear off.

Some side effects occur during long-term treatment in narcolepsy patients as irritability, headache, bad temper, and profuse sweating. Less common side effects are loss of appetite, nausea, gastric pain, insomnia, irritability, hallucinations, palpitation, muscle jerking, chorea, and tremor.

Effects on growth are usually reported but there is wide variability with some children unaffected [10], and others reporting moderate growth suppression [11]. About one-third of children and adolescents report decrease in appetite. In most subjects, this effect is transient or clinically insignificant. In fact, these effects appear to attenuate over time and

terminal adult height is not necessarily reduced [12]. The recent study from McCarthy (2018) showed that methylphenidate use in boys with ADHD is associated with low body mass index [13]. However, this effect was only observed in certain groups and this work was unable to confirm that methylphenidate use is associated with reduced height (≤3rd percentile).

Drug Abuse and Misuse

Along with increases in prescribing frequency, the potential for abuse has increased. The mechanisms underlying abuse of stimulants are complex but have been shown to involve dopaminergic systems of ventral tegmental area. Modifications in adrenergic and serotoninergic systems may also be important [3]. Intranasal abuse produces effects rapidly that are similar to the effects of cocaine. If reinforcement appears in the early stages of drug use, tolerance is common during long-term administration. The clinical description of stimulant abuse produces various kinds of psychiatric symptoms. Appetite suppression is also frequently described. Interestingly, stimulant abuse in narcoleptic patients is very rare [3]. Prevention of methylphenidate abuse needs to be a shared responsibility between the practitioner, the parents, and the patient. All participants in therapy need to be educated about the abuse potential of methylphenidate [14].

Contraindications

Stimulants are contraindicated if patients have a history of glaucoma. Amphetamines are not absolutely contraindicated, but they should be avoided in patients with hyperthyroidism, symptomatic cardiovascular disease, and moderate to severe hypertension. In ADHD children with seizure disorder, stimulants are not contraindicated, but stimulants may lower seizure threshold [9].

Patients should not take stimulants if also taking monoamine oxidase inhibitors within 14 days. Caution is advised for methylphenidate with following medications: anticonvulsants, tricyclic antidepressants, and anticoagulants.

Management

Dosage

The usual chronic oral dose of dextroamphetamine is 5 mg two to three times daily, sometimes, larger dose is used in the range of 10–20 mg. Dextroamphetamine is not usually used in children.

In adults, the usual dosage of methylphenidate is 10 mg two to four times per day. Because of individual differences, some patients require 40–60 mg per day while others require only 10–15 mg per day. In children, the initial dosage is 0.3 mg/kg, the maximal dosage recommended is 1 mg/kg or 60 mg/day.

Initiation

Children and adolescents should be evaluated for cardiac disease risk factors prior to initiation of stimulant therapy. Complete medical history, family history, and physical examination should be realized. Current guidelines recommend that a medical practitioner performs an electrocardiogram. In some circumstances, it is possible to refer to a cardiology specialist.

Monitoring

No laboratory testing is indicated. Clinical monitoring includes neurological examination, blood pressure, heart rate, sleep, appetite, behavior, and mental modifications. Finally, it is important to record growth parameters (height, weight, body mass index).

Medication is adjusted on a weekly basis and initial monthly follow-up is recommended. For the first year, medical follow-up can be realized every 3 months, then every 6 months in children with long-term stability [9].

Habitually, stimulants improve ADHD children, but sometimes a patient may respond better to one stimulant over another. Even if stimulants are approximately equivalent in efficacy and side effects, various children and adolescents respond better to one over another. In this case, if one stimulant is not efficacious at the highest posology, the practitioner should try another stimulant medication. Sometimes, the practitioner has to try different stimulant medications to find the better molecule considering the balance of efficacy versus tolerance.

Tables 22.1 and 22.2 summarize medications of methylphenidate and amphetamine.

Modafinil

Modafinil is a stimulant drug marketed as a "wakefulness promoting agent," is a "young" substance developed in France in the 1970s, available in Europe since 1986. In 1988, this molecule was first approved for the treatment of narcolepsy.

Modafinil is a primary metabolite of adrafinil. It lacks adrafinil's terminal amide hydroxy group and is better tolerated. Its advantage is once-daily dosing. Modafinil has not been approved by US Food and Drug Administration or European Medicines Agency for use in children <17 years. Although this decision was based on the absence of safety data from well-conducted trials in children, an international group of pediatric sleep specialists, based on clinical experi-

Table 22.1 Immediate release and extended release methylphenidate medications

Drug	Formulation tablet (mg)	Duration (hours)
Immediate release methylphenidate		
Ritalin® *Methylphenidate*	5-10-20 Doses typically divided 2–3/day	2–4
Methylin® *Methylphenidate*	5-10-20 Chewable: 2.5-5-10 Solution: 5–10 mg/ml	
Focalin® *Dexmethylphennidate*	2.5-5-10	3–5
Extended release methylphenidate		
Methylin®ER *Methylphenidate*	10-20	4–6
Metadate®ER *Methylphenidate*	10-20	7–8
Metadate®CD *Methylphenidate*	Capsules 10-20-30-40-60 Can be sprinkled	6–8
Ritalin SR® *Methylphenidate*	20	6–8
Ritalin LA® *Methylphenidate*	Capsule 10-20-30-40 Can be sprinkled	6–8
Quillivant®XR *Methylphenidate*	20-30-40 Suspension 25mg/ml	9–12
Quillichew®ER *Methylphenidate*	20-30-40	8
Concerta® *Methylphenidate*	Capsule 18-27-36-54 Cannot crush or cut	9–12
Daytrana® *Methylphenidate*	Patch 10-15-20-30 Apply to hip 2 hours before effect needed, remove 9 hours after application/can remove 9 hours for shorter duration of effect	12
Focalin®XR *Dexmethylphenidate*	Capsule 5-10-15-20-30	9–12

Table 22.2 Immediate release and extended release amphetamine medications

Drug	Formulation tablet (mg)	Duration(hours)
Immediate release amphetamine		
Adderall® *Amphetamine*	5-7.5-10-12.5-15-20-30	4–6
Eveoko® *D- and I-amphetamine*	5-10	
Dexedrine® Dextrostat® *Dextroamphetamine*	5-10	4–5
Attentin® *Dextroamphetamine*	5	
Procentra® *Dextroamphetamine*	Solution: 5 mg/ml	
Zenzedi *Dextroamphetamine*	2.5-5-7.5-10-15-20	
Extended release amphetamine		
Adderall XR® *Amphetamine and dextroamphetamine*	5-10-15-20-25-30 Can be sprinkled	8–12
Adzenys® *Amphetamine*	Oral disintegrated tablet 3.1-6.3-9.4-12.5-15.7-18.8	8–12
Dexedrine SR® *Amphetamine*	5-10-15	8–10
Dyanavel XR *Amphetamine*	Suspension:2.5 mg/ml	8–12
Vyvanse® *Lisdextroamphetamine*	20-30-40-50-60-70	8–12

ence with over two decades of experience using modafinil, suggested that modafinil can be used safely in children and adolescents with good efficiency and few side effects [15].

Pharmacological Effects

Pharmacokinetics

Modafinil is quickly absorbed but slowly cleared. This substance is around 60% bound to plasma protein and its volume distribution is around 0.8 L/kg. Cytochromes P-450 3A4/5 and P-450 2C19 are involved in this metabolism. Its half-life is 9–14 hours.

Mechanism of Action

The exact mechanism of action of modafinil is uncertain. One hypothesis is that modafinil acts by a synergistic combination of mechanisms, including direct inhibition of dopamine reuptake, indirect inhibition of noradrenalin reuptake in the ventrolateral preoptic, and orexin activation. It involves dopaminergic rather than non-dopaminergic effects. It is a stimulant agent that enhances the activity of wake-promoting neurons by increasing the extracellular concentration of dopamine, a rise being caused by blockade of the dopamine transporter [16]. Modafinil has also partial alpha 1B-adrenergic agonist effects by directly stimulating the receptors [3]. Modafinil could also activate glutamatergic circuits while inhibiting gamma- aminobutyric acid (GABA).

Indications

Modafinil has been specifically developed for the treatment of narcolepsy [17]. The positive effects of modafinil on sleepiness have been also reported in a retrospective study on a small series of narcoleptic children [18]. This molecule is also effective for ADHD, fatigue in multiple sclerosis, and Excessive Daytime Sleepiness (EDS) in myotonic dystrophy or Prader–Willi syndrome. It could be used in Klein–Levin syndrome.

Several factors make modafinil an attractive alternative to amphetamine medication. First, modafinil has no or minimal adverse impact on blood pressure. Secondly, dependence is limited with this substance. Third, modafinil has minimal impact on the neuroendocrine system (cortisol, melatonin,

and growth hormone levels). Fourth, the pharmacological profile of modafinil differs from stimulants. Patients usually feel less irritable or agitated with modafinil. Patients do not experience severe rebound sleepiness after modafinil is eliminated. These kinds of behaviors are described with amphetamine or methylphenidate.

Because of the safety profile and the low abuse potential, modafinil is the first-line treatment of EDS in narcolepsy.

Side Effects

Modafinil is usually well tolerated. Most described side effects are nausea and headache. Irritability and rhinitis are also described. Extremely rare, but important to know, risk of serious skin rashes and Stevens–Jonson Syndrome. Because of its hepatic and renal elimination, modafinil must be used at lower posology in hepatic or renal insufficiency. Modafinil has a number of potential drug interactions. One of the most important interactions is with ethynyl estradiol. That is why it is recommended not to use modafinil with low-estrogen contraception and to choose another method of contraception.

Modafinil is thought to have less potential for abuse than other stimulants due to the absence of any significant euphoric or pleasurable effects.

Management

The recommended starting daily dose is 100 mg in the morning. Another dose can be added around noon to extend the alerting effects. According to physician assessment, doses can be increased up to 400 mg (maximum 600 mg). The same dosage is used in children.

Physicians prescribing modafinil for an extended time should periodically re-evaluate the long-term use on an individual patient basis.

Contraindications

Stimulants are contraindicated in patients with uncontrolled moderate to severe hypertension and in patients with cardiac arrhythmias.

Mazindol

Mazindol is a sympathomimetic amine, which is similar to an amphetamine. It inhibits uptake of catecholamines and blocks the binding of cocaine to the dopamine uptake transporter. It is effective on EDS and cataplexy. It has few effects on mood and on cardiovascular system, but it is problematic and often causes side effects such as anorexia, nausea, constipation, urinary retention, and nervousness. Less common side effects are vomiting, tremor, and angioneurotic edema. Effective dose is around 2–8 mg daily. In a retrospective study on 139 patients aged 36 ± 15 years (range: 9–74) suffering from narcolepsy (n = 94, 66% 41 with cataplexy), idiopathic (n = 37) and symptomatic hypersomnia (n = 8) refractory to modafinil, methylphenidate, and sodium oxybate, we reported a long-term, favorable benefit/risk ratio in 60% of the patients, including a clear benefit on cataplexy [19]. Although, in this study, eight of our narcoleptic children were treated with mazindol, two of them had cardiac side effects (resistant ventricular extrasystoles, which did not disappear after stopping mazindol, and aortic valvular heart disease) [19, 20]. This treatment is actually not allowed for children in France.

Other Waking Promoting Agents

Pitolisant

Pitolisant is a medication for the treatment of EDS in narcolepsy, with a novel mechanism of action [21]. Pitolisant is a potent, selective histamine 3 (H_3)-receptor antagonist/inverse agonist that increases histamine synthesis, release, and transmission in the brain. We recently documented an impairment in histamine neurotransmission in children with narcolepsy type 1 (narcolepsy with cataplexy), supporting the therapeutic potential of histaminergic medications [22].

Pharmacological Effects

Pharmacokinetics

Although the pharmacokinetics of pitolisant has been characterized in adults [23], the pharmacokinetic profile has not yet been established in children. In adults, pitolisant is absorbed rapidly after oral administration, with a time to maximum plasma concentration (t_{max}) of approximately 3 hours and a plasma half-life of 10–12 hours. Pitolisant is metabolized via cytochrome P450 (primarily enzymes CYP3A4 and CYP2D6) into several inactive metabolites. The pharmacokinetics of a therapeutic agent may differ between children and adults because of differences in anatomical and physiological characteristics that affect drug disposition [24]. Although treatments approved for adults with narcolepsy (e.g., modafinil/armodafinil for EDS) are used off-label in children and adolescents, clinical trials on the safety, efficacy, and dosing of these agents have not been conducted in pediatric patients. Recently the pharmacokinetic profile and tolerability of pitolisant have been evaluated in children and adolescents with narcolepsy (article in preparation).

Mechanism of Actions

The widespread projection of histamine (HA) neurons constitute a major wake-promoting system (reviewed in [25]). Located in the tuberomammillary nucleus and adjacent areas of the posterior hypothalamus, they exhibit the most wake-selective discharge pattern so far identified in the brain. HA modulates the neuronal activity of target structures through H1, H2, H3, and perhaps H4-receptors. Activation of postsynaptic H1-receptors elicits cell depolarization and tonic neuronal discharge, leading to general brain arousal, while activation of postsynaptic H2-receptors increases neuronal excitability and discharge rate and therefore could promote cortical arousal [26]. Finally, H3-receptors on both HA and non-HA neurons play a role as auto- and hetero-receptors [21] and are involved in sleep-wake control through negative feedback on HA neurons [27]. Drugs causing acute enhancement of transmission, such as H3-receptor inverse agonists, promote waking [28].

Indications

Pitolisant is approved by the European Medicines Agency for the treatment of narcolepsy with or without cataplexy in adults. Pitolisant showed to decrease narcolepsy episodes in hypocretin-knockout mice [28], in adolescent narcoleptic patients with resistant EDS [27] and decreased EDS and cataplectic attacks in double-blind, randomized, parallel-group controlled trial in adult narcoleptic patients treated by pitolisant versus modiodal [29, 30]. At doses up to 40 mg, pitolisant was efficacious on EDS compared with placebo, and well tolerated compared with modafinil and significantly decreased the number of cataplectic attacks. A double-blind placebo randomized control study is already on going in narcoleptic children. In our previous study in adolescent narcoleptic children resistant to other psychostimulants, pitolisant has shown good efficiency on sleepiness with few side effects [27].

Side Effects

The most frequent adverse events in the pitolisant group were insomnia (8.4%), headache (7.7%), irritability (1.86%), anxiety (2.1%), and nausea (4.8%), most being mild or moderate except one case of severe nausea or digestive discomfort. There were 28% of treatment related adverse events and only 2% of severe events in the two large studies [29, 30]. With regards to drug abuse potential, no patient on pitolisant had Diagnostic and Statistical Manual of Mental Disorders (DSM-5)-defined withdrawal syndrome during the withdrawal phase. No effects on blood chemistry tests or hematological or cardiovascular parameters.

Management

Pitolisant (Wakix 4.5 mg or 18 mg), patients take 4.5 mg in the morning during breakfast, before 12 hours in the first week, and increase to 9 mg in the second week, increasing progressively step by step every week until the maximal dosage at 36 mg is reached.

Contraindications

Severe hepatic impairment and hypersensitivity to pitolisant or any component of the formulation are contraindications. Precocious use if psychiatric troubles (depression, anxiety), renal or hepatic insufficiency, gastro-intestinal affections, cardiac troubles (QT), epilepsy, weight problem (anorexia or obesity) gestation, breastfeeding, enzymatic inductors (CYP3A4, CYP2D6; CYP3A4, CYP2B6, OCT1). Moreover, pitolisant may reduce effectiveness of hormonal contraception owing to it being a weak CYP3A4 inducer. Advise patients using hormonal contraception to use an alternative nonhormonal contraceptive method during treatment and for at least 21 days after discontinuing treatment.

Sodium Oxybate

Indications

It is a gamma- aminobutyric acid-B (GABA-B) receptor agonist and a gamma hydroxybutyrate (GHB) receptor agonist.

This medication improves both EDS and cataplexy. Both the American Academy of Sleep Medicine and the European Federation of Neurological Societies recognize sodium oxybate as a standard of care for the treatment of narcolepsy in adults, and its efficacy in reducing EDS and cataplexy has been shown in multiple randomized placebo-controlled trials [31, 32]. The use of sodium oxybate for the treatment of narcolepsy in children and adolescents has been described in several published case series [33, 34] and recently in a randomized placebo-controlled study in pediatric patients with narcolepsy [35]. In this multisite study and open-label investigation done at 30 sites in five countries (the United States, Finland, France, Italy, and the Netherlands), 100 type 1 narcoleptic patients aged 7–16 years who were randomly assigned to receive placebo and who were withdrawn from sodium oxybate had increased weekly cataplexy attacks when compared with those randomly assigned to continue treatment with sodium oxybate. On the other hand, the sleepiness score decreased when treated with sodium oxybate compared to placebo.

Side Effects

Common side effects are nausea, headaches, high blood pressure, dizziness, sleep walking, and confusion upon awakening. Other side effects are habitually less frequent—insomnia, suicidal ideation, dissociative feelings, tremor, and constipation. Commonly reported (>5%) adverse events in children were enuresis (21%), nausea (22%), vomiting (21%), headache (18%), decreased weight (15%), decreased

appetite (11%), nasopharyngitis (10%), and dizziness (7%). Two serious adverse events related to treatment (one event of severe acute psychosis and one event of moderate suicidal ideation) were reported and no deaths. Sodium oxybate seems the only stimulant treatment to induce weight loss after 1 year of follow-up in narcoleptic children [36].

The risk of misuse exists because of its ability to induce euphoria and craving in users. Careful monitoring of patients for dependence and abuse is necessary.

Management

The half-life is about 30 min and the duration of effects is about 3 hours. A second dose is taken 2.5–4 hours after the first dose for the maximal effectiveness.

Initial dose is 4.5 mg divided in two doses of 2.25 (one at bedtime, the other 2.5–4 hours after night). Effective dose is around 6–9 g per night (increase 1.5 g/week) in adults.

In children, the sodium oxybate initiation dose, titration, and maximum dose were based on patient's weight (for children <30 kg, initiation 2 g/night, increase of 1 g/night every week if necessary, with a maximal dose at 6 g/night; for children between 30 and 45 kg, initiation 2 g/night, increase of 1 g/night every week, with a maximum dose at 7.5 g/night).

Solriamfetol

Finally, another molecule was approved by the Food and Drug Administration for the treatment of EDS in adult narcolepsy patients, Solriamfetol (JZP-110). It is a new high-potency wake-promoting agent, a selective dopamine and norepinephrine-reuptake inhibitor without promoting the release of monoamines. An international, double-blind, randomized, placebo-controlled trial recently showed its efficacy on both objective and subjective sleepiness, and its safety in narcolepsy with and without cataplexy [37]. Solriamfetol was well tolerated with very common adverse reactions such as headache, nausea, decreased appetite, insomnia, and anxiety [38]. To date, no trials have been conducted to assess the efficacy of this agent in a population of children.

Conclusion

Stimulants have been used in the treatment of narcolepsy and other conditions of sleepiness since last century. Modafinil is the first-line treatment in narcolepsy because of its favorable side-effect profile. One other indication of amphetamine and amphetamine like-stimulants is ADHD.

However, in most countries in the world, all available treatments for narcolepsy are delivered off-label in the pediatric population [15, 39, 40]. In the United States, medications approved by the US Food and Drug Administration (FDA) for use in pediatric patients with narcolepsy include methylphenidate and amphetamines for EDS and sodium oxybate for EDS and cataplexy. However, few studies have been done to demonstrate efficacy in randomized placebo-controlled studies in pediatric patients with narcolepsy [35] or to evaluate the pharmacokinetic profile and tolerability of these treatments.

The pharmacological treatment is a part of the therapeutic approach of EDS. It is important to consider a global management following various points such as education (psychoeducation about disorder, about pharmacological treatment side effects, risks, etc.), dosing, and follow-up. It is important also to emphasize sleep hygiene. Moreover, most of these disorders are chronic disorders, a regular reassessment is needed.

Novel classes of stimulants are being developed implicating other histamine antagonists, thyrotropin-releasing hormone. Another possible avenue of treatment comprises hypocretin-based therapies.

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Somnogenic Agents in Children

23

Rafael Pelayo and Kin M. Yuen

Introduction

Wouldn't it be nice to able to have our children fall asleep when it was convenient for us? He or she "won't sleep" is a common complaint any clinician working with children will hear many times. As a clinician what goes through your mind when you hear these complaints? Do you look forward to working with patients with these complaints? There are many reasons an infant, or child, may be considered sleepless. By extension how often has a clinician heard an adolescent or adult patient complain that they "can't turn off" their brains? These are interrelated situations because sleeping is often perceived as an inconvenience by the general public.

Substances that promote sleep are among the oldest category of medications known. In antiquity, opium poppies and alcohol were known to promote sleep. The Greek god of sleep was Hypnos, from which the term hypnotics is derived. Hypnos's mother is Nyx, the goddess of night, and his brother is Thantos the god of death.

Considering that sleep and death were twin brothers in Greek mythology perhaps an innate fear of the dark while trying to sleep may seem an understandable response in children. It must also be kept in mind that for young children, the only time they may be predictably and routinely separated from their parents is when they are sleeping alone. Sleeping has a learned component. We teach our children when and where they will sleep. Children can learn to associate the darkness with being left alone.

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The Roman equivalent god to Hypnos is Somnus, from which the term somnogenic agents originate. Somnogenic agents and hypnotic medications are substances that promote sleep. These substances have that hypothetical potential to make the timing of sleep more convenient and predictable, but the pros and cons of their uses must be weighed carefully on a case-by-case basis. This is particularly important to keep in mind, since medications to promote sleep in adults usually do not have a pediatric indication. When these substances are used in a child, it is often done in an "off label" situation.

Medical History

There are times when recommending a substance to promote sleep in a child may be helpful. However, before there is any discussion about what medication should be used to help a child sleep, we must first fully understand why that child is not sleeping at the desired time in the first place. The key concept is timing. You cannot stop a child from eventually sleeping. They have such powerful homeostatic drives to sleep that children will fall asleep in situations that an adult would have great difficulty sleeping. You could hypothetically have a sleepy infant sleep on the ground in a highway emergency lane, but an adult would have great difficulty falling asleep in such a dangerous location. Therefore, when parents ask about obtaining a medication to help a child fall asleep, the issue is not usually about sleep per se, but about the timing of sleep.

This chapter will provide a clinical framework to understand what leads to sleeplessness in order to reach a diagnosis and treatment plan for children of all ages. Once a diagnosis is reached, then the family can understand and follow a rational approach to treatment. The temptation to jump to treatment before understanding the root cause of the sleep problem must be avoided if long term success is the goal.

At the immediate start of the clinical encounter parents may ask, "what can you give my child" or say their child

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"will not sleep" unless something is prescribed. If the patient is an adolescent, it must be determined if the adolescent thinks help is needed or is being forced to come for a clinical visit by their parent. Taking a large step back and getting a more comprehensive history is necessary before discussing any medication options.

How large a step back? The clinician should keep in mind that most sleep disorders have a familial component. For example, obstructive sleep apnea runs in families, as do parasomnias such as sleepwalking. So before asking too many details about how the child is sleeping, first ask about how the parents themselves are sleeping. It is especially important to learn about how they slept *before* they were parents. One of the adults may have had a prior history of insomnia that has sensitized him or her to the normal awakenings of an infant. For example, a parent of a 3-month-old infant may complain the baby wakes up twice a night. Upon questioning, they tell you the child falls asleep fairly quickly after eating. An infant with only two brief awakenings to feed would not ordinarily be considered pathological in this age group. However, the parent may say, "the problem is I can't fall asleep afterwards." In that situation, who has the sleep disorder, the parent, the infant, or both? It is not uncommon for people who have trouble sleeping to sometimes blame themselves. A parent may secretly harbor fears that the child may have inherited their sleep problems or worse yet, a parent may blame the other parent's side of the family!

Another common scenario may be a parent who has subacute obstructive sleep apnea (OSA). In other words, the parent has symptoms of OSA that have not been recognized nor treated. Now when that person becomes a new parent, the typical household interruptions of a newborn's sleep may be particularly burdensome. Clearly the parents' prior sleep history may be very important to help these families.

A clinician must also take a moment to understand the composition of the household. You need to know if there are grandparents, children, and other family members in the home. You need to know the sleeping arrangements of these family members. Did a parent give up a bedroom for a visiting family member, or was somebody displaced to a couch? Have in-laws come for an extended visit to help with the newborn, and what happens if and when they leave. This is why the symptoms of the patient, in this case the child, must be interpreted in light of how they impact the entire family. A comprehensive approach may require that other family members also be evaluated and treated for sleep disorders.

For new parents, the closest opportunity they may have to getting back to their lifestyles before they were parents is when their child is sleeping. Due to this, an unnecessarily large amount of pressure may be placed on the family, or on a particular parent, "to get" the child to sleep. This can create tension in the household. If there is difficulty with a child not sleeping, the usual bedtime routines may be viewed as a chore by the parents. They may begrudgingly take turns to help the sleepless child settle in for the night. It may be worthwhile to gently remind frustrated parents that they do not have to "get" their children to breathe or get hungry. Perhaps the strategies they are using, to try to get a child to sleep, may be the wrong approach and may even be causing a paradoxical arousal in the child. Preparing for bedtime may be the most stressful time for the family.

The clinician working with sleep disorders in children will encounter a wide range of family situations and compositions. Within every family unit, sleep disturbance of the younger members tends to affect every other member of that unit. Commonly, one partner of a dual-income household may temporarily put his or her career on hold when they become new parents. This puts pressure on the parent who continues to work to retain their employment and perhaps think they should not let their new role as a parent interfere with the work or career. The parent who "gets to stay home," may feel the additional pressure of not only being the primary care giver to the child but also to ensure that the sleep of the parent who works outside of the home is not disturbed. When the child sleeps well, the rest of the family may be in harmony. That family will not be making an appointment to talk to you about sleep. However, if the sleepless child is disrupting the sleep of the other family members, there may be resentment between the parent that "gets to stay home" and the parent that "gets to go to work."

Allergies may be an overlooked reason for sleeplessness and may also be an exacerbating factor. A clinician must ask if the child sleeps with any pets that the child may be allergic to. Unless directly asked, the family may not volunteer this information.

Sometimes two parents will come in with an infant or young child. It is not until they are directly asked will you learn that the couple is now separated or divorced. The sleep history in one household may be completely different from the other. Certainly, the presence of environmental allergens must be considered in both homes. Given the dynamic, complex, and nuanced situations that can occur in families it is not surprising that a clinician can find working with a sleepless child and their families to be very challenging. As the healthcare provider tries to unravel all this history from the parents in the limited time allotted for the clinic visit, so often the infant is sleeping peacefully in their arms or the young sweet child is playing quietly. It is hard to reconcile what is in front of you with the nighttime havoc being described.

There is a whole other layer of complexity when we consider the sleepless adolescents. Some parents may consider caring for adolescents to be the biggest challenge of parenting. Adolescents have a wider range of societal, psychological, and biological factors that can disturb their sleep. As

mentioned earlier, many households end the day with arguments about going to sleep and start the day with arguments about getting up in time for school. The adverse consequences of sleeplessness in an adolescent may be far worse than in a younger child, when you consider among, other things, the greater academic demands, the potential presence of suicidal ideations and the increased risks for automobile accidents.

Unquestionably, lack of sleep affects mood. The clinician must be prepared to work with parents who may be irritable or angry due to lack of sleep in themselves. They may also feel guilty that their child is not sleeping. Parents may be short tempered or frustrated with each other due to lack of sleep. The frustration or anger can also be directed at the healthcare provider. With adolescents, the day may begin with an argument about getting up in the morning, a stressful effort to get to school on time, and the day end with another argument about bedtime. Parents attempt to correct an adolescent's behavior may lead to resentment among family members that further exacerbates the sleeplessness. If the parent cannot trust their child to wake up in time, the parent who takes on the responsibility of getting the household started in the morning may develop their own sleep problems.

The complaint of sleeplessness for infants and young children should be distinguished from the diagnosis of insomnia. For example, a child with leg discomfort due to restless leg syndrome maybe sleepless but would be more appropriately diagnosed with a sleep-related movement disorder rather than with insomnia. However, the child's complaints may induce insomnia in the parents. Another example is, if a child has trouble sleeping due to an acute illness, such as an ear infection, the symptom of insomnia could be transiently present. Insomnia in general, refers to difficulty falling asleep and/or staying asleep to the point that it bothers a person the next day. Insomnia is a symptom that can become a diagnosis. It may be comorbid with other conditions. When this occurs the term "secondary insomnia" is discouraged, since it is misleading to think that resolving one medical problem will automatically correct the insomnia symptoms. Insomnia among children, is reported by parents when there is bedtime resistance, frequent awakenings, difficulty sleeping without a parent's intervention, or the child will not sleep alone, and interrupts the parents' sleep. Persistent insomnia over time can evolve into an insomnia disorder. The third edition of the International Classification of Sleep Disorders (ICSD-3) simplified and consolidated the previously described insomnia subtypes in children into the same diagnosis used in adults, chronic insomnia disorder [1]. This disorder requires that the presence of symptoms occur at least three times per week and be present for at least 3 months. In the ICSD-3 the daytime symptoms of chronic insomnia disorder in children includes fatigue, impaired attention or concentration, impaired social, family or academic performance, irritability, daytime sleepiness, and behavioral problems such as hyperactivity, impulsivity, and aggression. The diagnosis requires that the symptoms be present despite adequate time and circumstance to sleep.

When evaluating and treating a sleepless child, it is important to understand that sleep is a biological process, which has a learned component. It is analogous to eating. The need for food is biological, but what you eat is learned over time and may change. A child who has had negative experiences sleeping may become an adult with lifelong sleep problems, who then passes on these problems to their own future children. Yet the reality is that most sleepless children are readily treatable and often have a good prognosis.

In older toddlers and young school age children, problems with sleep may be related to bedtime refusal or limit-setting problems. Limit setting is characterized by stalling or negotiating behavior due to the parent not enforcing consistent rules at bedtime. These children may also have a history of daytime tantrums. These children will more often have difficulty falling asleep as opposed to trouble staying asleep. This pattern of behavior needs to be distinguished from children who have bedtimes that are too early. These bedtimes may have been chosen for the parents' convenience when a child is not yet physiologically sleepy. As will be discussed below in adolescents, there are circadian rhythm principles that need to be considered. Just like adults, children will have times of heightened alertness in the evening. This is usually a couple of hours before their usual falling asleep time. Trying to force a child to sleep during this window of time is an unnecessary uphill battle. A behavioral approach that may help will delay bedtime to a more appropriate time when the homeostatic drive for sleep and circadian time for sleep are more aligned.

All children may benefit from a predictable soothing bedtime routine and sleep environment, especially if they are sleeping alone. The bedtime routine must provide a feeling of serenity. We want children to learn that, when they are in bed at night, they are safe, comfortable, and loved. In this chapter, we will review the medication options that can be a part of the comprehensive therapeutic plan.

Over-the-Counter Substances Used for Sleep

If a parent is considering or willing to use a substance to help a child sleep, they are likely to first try a readily available over-the-counter medication rather than seeing a physician to obtain a prescription medication. Since these medications are available without a prescription, the parents may assume they are safer than "stronger" prescription option. This may

be an ill-informed assumption. For otherwise healthy infants, one of the first medications they are exposed to is over-the-counter *acetaminophen* [2]. They may receive acetaminophen for fever associated with immunizations or viral illness. During these times, the infant may appear to sleep better than usual to some parents. This may explain why some parents may subsequently give an infant acetaminophen for sleeping difficulties. Parents may not use the accompanying syringes to measure appropriate dosages, but instead use approximations with measuring cups. This practice can increase the risk of inaccurate dosages given to the infant or child. Since acetaminophen is available in a wide range of products marketed for children, parents may be unaware of the potential hepatoxicity if taken in excessive quantities.

Alcohol is also readily available, which allows it to be given by some parents to their infants in a putative attempt to help them sleep. Unless asked, parents may not volunteer that they have given alcohol to their infants or young children. For example, although very ill-advised in some parents may give an infant small amount of alcohol for teething pain *and not volunteer this information unless directly asked*. An infant may also be exposed to alcohol through breastmilk [3, 4].

Children of all ages, including infants, may have also been given *antihistamines*. Antihistamines are available over the counter and are marketed to treat symptoms of insomnia in adults. Antihistamines (diphenhydramine and hydroxyzine in particular) have the distinction of being the single most prescribed or obtained over-the-counter agents for insomnia [5]. One of the more frequently used antihistamines is *diphenhydramine*. Randomized controlled study evidence is lacking in support of using diphenhydramine for insomnia in children. One randomized trial in infants originally designed to last 2 weeks was stopped early due to lack of efficacy [6]. Adverse effects of antihistamines are predominately anticholinergic including: fever, mydriasis, blurred vision, dry mouth, constipation, urinary retention, constipation, tachycardia, dystonia, and confusion. Diphenhydramine poisoning can include catatonic stupor, anxiety and visual hallucinations with rare presentations having respiratory insufficiency, rhabdomyolysis, cardiac rhythm disturbances, and seizures. Fatal diphenhydramine toxicity has been reported in a case series of 5 infants 6–12 weeks old [7].

Since acetaminophen, alcohol, and antihistamines are all available over-the-counter in liquid form, often they are used to sedate an infant. Parents may not volunteer that they have already tried these substances before seeing a clinician. The clinicians should specifically ask about this when taking a history. Parents and clinicians must understand that sedation is not the same as normal sleep.

Perhaps one of the most popular over-the-counter substances given to help children and adolescents sleep is *melatonin*. Although melatonin is an over-the-counter product in the USA, it is under tighter control in some other countries. Also, melatonin agonists that do require a prescription have been developed and are available in the USA. A discussion of melatonin and melatonin agonists will serve as a transition from over-the-counter to prescription medications in this review chapter.

Melatonin and Agonists

Melatonin is frequently used for delayed sleep phase syndrome and jet lag, as it may have a phase-setting effect on the body [8, 9]. In adults taking melatonin, small amounts prior to bedtime is thought to be effective in raising the plasma melatonin to normal levels. The dosage that may be effective in children is unclear [10]. An analysis of over-the-counter melatonin in Canada raised strong concerns about the quality of the product [11]. Erland and colleagues analyzed melatonin by ultraperformance liquid chromatography in 30 commercial supplements. Melatonin content was found to range from −83% to +478% of the labelled content including within the same brand. Serotonin was found in 26% of the samples. Melatonin content did not meet label within a 10% margin of the label claim in more than 71% of supplements. An accompanying commentary to this article called for greater regulation of the sale of melatonin [12]. This lack of regulation may cause the quality of over-the-counter melatonin to be highly variable.

Melatonin has been used in children with sleeplessness due to circadian factors such as sleep phase delay disorder, blindness, and midline brain defects such as agenesis of corpus collosum as this may affect the pineal gland. Children with poor sleep associated with neurological syndromes have also had some positive outcomes including increased total sleep time and shorter sleep latency [9, 13–16]. A randomized trial of melatonin compared with bright light treatment against controls was done with 84 children (average age was 10 years old) [17]. The authors found that both melatonin and bright light treatment were able to shorten sleep latency, but the effect was stronger with melatonin. In clinical practice both of these treatment options can be combined depending on the clinical situation.

Ramelteon, a melatonin receptor agonist, has been approved for use in patients 18 years and older with sleep onset insomnia [18–20]. It has been reported to help the sleep of people with autistic spectrum disorder [19, 21]. It may be considered in adolescents with sleep phase delay syndrome. However, no clinical trials are available for patients younger than 18 years old. There was at least one report of it being used for the treatment of night terrors and sleepwalking in children [22].

Tasimelteon is a melatonin receptor agonist that was released by the FDA for the treatment of non-24-hour sleep

wake disorder in 2014 in adults. It has an affinity for human melatonin receptors MT1 and MT2, with a higher affinity for the latter. The clinical trials were done in blind adults with a circadian disorder [23, 24]. Safety and efficacy have not been established in pediatric patients. There is a hypothetical possibility that this medication may be useful to help entrain the sleep of children with significant circadian disruption to a more predictable schedule. However, to date there are no pediatric studies available.

Hypnotics

There is a paucity of clinical guidelines for the treatment of chronic insomnia in children. The American Academy of Sleep Medicine published a clinical practice guideline and systematic review of the evidence supporting various hypnotics in the treatment of chronic insomnia in adults [25]. This review found that the quality of the evidence supporting the use of any hypnotics was weak, since many of the clinical trials are sponsored by pharmaceutical companies and there are few head-to-head trials between various agents. Because many agents used commonly off label for the treatment of chronic insomnia in adults were not supported by clinical evidence, the American Academy of Sleep Medicine recommended against their use in children. These included antipsychotics such as quetiapine and antidepressants such as trazadone. In addition, the academy recommended that tiagabine, diphenhydramine, melatonin, tryptophan, and valerian not be used in the treatment of chronic insomnia in adults [25]. Insomnia has been shown to have a reliable response to placebo [26]. Given the lack of good evidence for so many medications used to treat insomnia in adults, it is important that a behavioral approach be the initial therapeutic approach in young children and adolescents.

Sleepless behavior in a child or adolescent may disrupt the pattern of sleep of the household. Often behavioral therapy is sufficient treatment for this insomnia pattern. However, in the situation of an extremely anxious or a special-needs child, adjunctive pharmacotherapy may be requested by the parents. Before making any pharmacological recommendations, the clinician should keep in mind that this is an age group with possible undiagnosed allergies, gastroesophageal reflux, obstructive sleep apnea, or restless leg syndrome. The medications that physicians are likely to recommend in this group are also the antihistamines since they are available in liquid form. Other medications used in this age group are benzodiazepines, such as clonazepam, which is available in a sublingual form. Melatonin is also often tried by parents and clinicians in this age group [27]. Some clinicians, in particular child psychiatrists, will recommend clonidine, an alpha2 receptor agonist, in this population. The use of a wide range of sedating medications in clinical use in these children includes trazadone, atypical antipsychotics, anticonvulsants, and short-acting hypnotics [28]. If the insomnia persists as the child grows older, a litany of agents may have been unsuccessfully tried.

A commonly described phenomenon is of children receiving sedating medication or hypnotic and becoming agitated instead of sleepy. This was described as a "paradoxical reaction" and typically no further explanation would be offered to the bewildered parents other than this happens sometimes. However, patients and their families deserve a better explanation. Why would a sedating medication have such a profoundly opposite effect? In retrospect, these paradoxical reactions may be due to inadequate dosing, not taking into account the circadian principles of sleep tendencies, or the child's state of mind at the time. In the absence of clear pharmacological guidelines, the natural inclination is to give the lowest possible dose of a medication to a child. However, when treating a child, especially one with a neurological or psychiatric condition, if the dose of medication is underestimated or administered at a time of heightened circadian alertness, the medication may disinhibit the child or create a dissociative state. The child may not have understood they were expected to go to sleep and may have had heightened arousal due to the novel and or perceived scary environment. The emergence of hypnagogic hallucinations may frighten the child or be misinterpreted as a delirium or psychotic reaction. Prior food intake may also interfere with absorption of the medication, or the child's usual medications may have induced hepatic enzymes or have other interactions further complicating the hypnotic administration consideration [29].

Owens et al. published a national survey for pharmacotherapy for insomnia among child psychiatrists in 2010 [28]. The ages of the children/adolescents were reported as 6–10 years, 10–20 years, and > 20 years. A surprising wide range of medications were being prescribed and recommended with little evidence-based data to support it. The authors concluded that insomnia is a significant clinical problem in children treated by child psychiatrists for a variety of behavioral, neurodevelopmental, and psychiatric conditions. In addition, there was a worrisome highly variable clinical approach to insomnia children.

Benzodiazepines

Benzodiazepines and benzodiazepine receptor agonist can be considered as therapeutic options to improve sleep [2]. Benzodiazepines are hypnotics that act as a GABA receptor agonist. The benzodiazepine most used in children for sleep is clonazepam; it is available in low-dose sublingual wafers that allow for easier administration. Clonazepam has been used for arousal parasomnias such as sleepwalking and sleep

terrors in children. Clonazepam may allow the child to sleep throughout the night and is thought to decrease the arousal threshold. This drug may be beneficial if this behavior is frequent and disturbing to the patient or family. A dose of clonazepam at 0.25–0.5 mg may be used. Benzodiazepines may lead to muscle relaxation and, therefore, caution is advised in children with obstructive sleep apnea, as it may exacerbate the condition.

Nonbenzodiazepine Hypnotics

Selective benzodiazepine receptor agonist including zolpidem, eszopiclone, and zaleplon are thought to offer some advantages compared with nonselective benzodiazepines. These selective benzodiazepine receptor agonists at low dosages are thought to preserve the overall sleep architecture and to have less rebound insomnia after discontinuation, when compared with nonselective benzodiazepines. These medications only have FDA approval for use in patients older than 18 years old and, therefore, the use of these medications in children is considered "off-label". There are reports of zolpidem abuse among adolescents. Randomized control trials for zolpidem and eszopiclone have had mixed results. Zolpidem was used in children aged 6–11 with attention-deficit/hyperactivity disorder and in teens aged 12–17 with chronic insomnia for 4 weeks against placebo in a randomized trial. At 0.25 mg/kg per day up to maximum of 10 mg. sleep onset latency was not significantly different from placebo [30]. This trial did report that some children had hallucinations. This would indicate that possibly the timing of the medication given was too early. The lack of improved objective sleep parameters that the dose of hypnotic used may have been too low. Eszopiclone was used in children and teens with ADHD from 6 to 17 years and showed no benefit over placebo in 2014 randomized trial. Significant number reported side effects of dizziness and headache [31]. In this trial, the maximum dose offered was 3 mg, which is also the maximum recommended for adults. It is possible that children and adolescents may have a different degree of hepatic metabolism and a higher dose would have possibly been more effective. The need for more clinical trials specifically designed for children is clear.

Conclusion

The quality of the evidence supporting the use of hypnotics in the treatment of chronic insomnia in adults is weak, and sadly it is even weaker in children. Providers have limited exposure during medical school and residency training to education regarding sleep disorders in general and specifically in the pharmacological management of insomnia in children and adolescents. Given the ubiquity of sleep complaints among people of all ages, training in sleep medicine should be a part of a comprehensive medical education.

A wide range of somnogenic agents are commonly recommended and prescribed for children and adolescents; therefore, there is a need for more research on these agents. Pharmacological guidelines need to be developed specifically for children rather than merely blindly applying adult guidelines with the assumption that dosages simply need to be lowered. Ideally, these guidelines should be FDA approved for the specific pediatric age range. Development of easy-to-swallow, chewable, or liquid forms of these medications are needed. Integration of behavioral approaches and education of the parents about sleep health is essential when considering the use of these agents.

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Drugs which affect Sleep

24

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Abbreviations

ADHD	Attention deficit hyperactivity disorder
AHI	Apnea–hypopnea index
CNSS	Central nervous system stimulant
CRSWD	Circadian rhythm sleep–wake disorder
FDA	Food and Drug Administration
NREM	Non-rapid eye movement
OSA	Obstructive sleep apnea
PLMD	Periodic limb movement disorder
REM	Rapid eye movement
RLS	Restless legs syndrome
SM	Smith–Magenis syndrome
SSRI	Selective serotonin reuptake inhibitors
SWD	Sleep–wake disorder

Introduction

Sleep medicine in pediatrics has been widely involved for the assessment of sleep disturbances such as insomnia or somnolence, or other more severe sleep–wake disorders (SWD) like narcolepsy [1]. However, it should be noticed that the Food and Drug Administration (FDA) does not provide a guide on how physicians should treat (with the most fruitful potential medical transcription) those SWDs, which are peculiar to children [2–4]. Nevertheless, wide research has been done in order to have safe and potential drugs/and or therapies for young people under 18 years old, who experience an SWD [5].

While the prevalence of SWDs in the non-adult population is 10–28% [6–8], engendering cognitive, emotional, and behavioral issues [9], the comorbidities of SWDs with other disorders/diseases provide a wider understanding of how pharmacotherapy affects sleep. For instance, prazosin, which is approved by the FDA as a treatment for hypertension, has shown promising results for ameliorating PTSD symptomatology and nightmares, although no particular FDA approval for prazosin exists for sleep disturbance in children and adolescents [10]. Another example is the use of melatonin, which is a safe treatment for insomnia in children with autism, with very few mild side effects, mostly daytime somnolence [11].

Moreover, theophylline, which is employed for asthma in children, seems to have a protective effect toward apnea and arterial oxygen saturation, while it does not have any effect on sleep quality [12, 13]. In more complicated respiratory diseases, such as cystic fibrosis, children have reported sleep disturbances [14]. When it is about lung transplantation, the immunosuppressive drugs taken in order to prevent rejection by the immune system, lead to insomnia [15]. Further regarding transplantation, lung or heart transplants were correlated with sleep apnea [16, 17] and poor quality of sleep [18], while hand transplants may create sleep issues, due to the use of immunosuppressive drugs [19].

Until now there has been limited literature review at the heart of sleep research to garner the drug effect on child or adolescent sleep in a more extensive view. Thus, the purpose of this study is to discuss this topic in a combined way, not only for SWDs, but also how drugs used in common pediatrics may affect sleep.

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Analysis

It is crucial to understand how many hours children should sleep during the newborn to adolescent stages, orienting the normal range of sleep duration. In a more detailed manner, newborns tend to sleep 12–18 hours per day, while infants and toddlers sleep 14–15 and 12–14 hours, respectively. Sleep hours tend to decrease in preschoolers (11–13), school age (10–11), and adolescents (8–9.25) [1]. However, the age stages can be interrupted by sleep disturbances, reducing or increasing the sleep duration.

Sleep–Wake Disorders and Their Pharmacotherapy: An Ambiguous Perspective

The lack of approved view of the FDA toward pharmacotherapy in sleep disorders in children is correlated with the lack of efficient and limited clinical trials. Nevertheless, there is a drug in the pediatric population (aged 7–17), which has been approved by the FDA such as sodium oxybate for narcolepsy. However, for other drugs, the FDA has saturated this praxis with dysfunction [20]. For this reason, stressing the drugs for sleep–wake disorders is cardinal to be established by research results (see Table 24.1).

Insomnia

Insomnia is characterized by a sense of sleeplessness with symptoms of lethargy or non-restfulness. Nine different types of drugs were found for the treatment of insomnia for individuals who are under 18 years old. Starting with sleep-promoting hormone melatonin, which has mostly been employed for treatment for children's insomnia. More specifically, based on meta-analysis, melatonin decreased the sleep onset latency [21]; there are side effects such as somnolence and nightmares in children [22]. The range of melatonin doses varies from 0.05 to 5 mg/kg, and it is recommended that melatonin should be consumed 1–2 hours before bedtime.

Moreover, other types of drug can ameliorate insomnia symptoms based on research evidence. Antihistaminergic drugs such as diphenhydramine (0.5–20 mg/kg) and hydroxyzine (1 mg) aim to reduce H1 histamine levels. Insomnia tends to be associated with high levels of histamines, because histamines promote arousal in the sleep–wake cycle during wakefulness. These drugs should be used 30 minutes before bedtime. Adverse effects such as sedation were observed [2].

Furthermore, though alpha-adrenergic receptor agonists (clonidine and guanfacine) enhance sleep, their mechanism on sleep is still unknown. But clonidine evokes REM suppression, and REM rebounds when clonidine is discontinuous. Recommended doses for clonidine ranged from 0.025 to 0.1 mg and for the dosing range of guanfacine waves 0.05–4 mg. These drugs are taken twice per day, namely at morning and evening [2, 4, 23].

Also, benzodiazepines hypnotics are prescribed more in adults than in children. The soporific effects of clonazepam have been used for insomnia treatment in children. It reduces arousals, and it is prescribed at doses between 0.25 and 0.5 mg, at bedtime [4]. Similarly, non-benzodiazepine receptor agonists may alleviate insomnia symptoms. Specifically, zolpidem (0.125–0.50 mg/kg at bedtime) is beneficial on treating sleep onset insomnia, and rarely for sleep-maintenance insomnia [24].

Regarding the antidepressants (trazodone, 5-HT2 receptor antagonist, 50 mg at bedtime), and tricyclic antidepressants like imipramine (0.05 mg/kg at bedtime) and amitriptyline (0.05 mg/kg at bedtime), though of vast use in the adult population for insomnia treatment, children are much less recommended, due mostly to the anticholinergic side effects [2, 25]. Therefore, a serotonin and melatonin precursor, namely $_{L}$-5-hydroxytryptophan (1–2 mg, at bedtime), is considered a safer therapeutic choice for insomnia, as well as the hypnotic agent, chloral hydrate (25–50 mg/kg or 1 g maximum; 15–30 minutes before bedtime) [2].

The most recent drug in research for insomnia in children is suvorexant, which is a hypocretin/orexin receptor antagonist [26]. Regarding non-adults, a single study from Japan was identified, which advocated that suvorexant (20 mg, 30 minutes before bedtime) reduced insomnia symptoms and improved overall sleep quality in adolescents suffering from insomnia. A total of 56.7% of the participants continued this drug, whereas the therapy was mostly abandoned due to unpleasant dreams (e.g., nightmares, which are reported anyway as known side effects). Nightmares are quite common in children/adolescents (their prevalence in adolescents in Japan is 35.2%), thus the prescription of this drug should be made carefully [26].

Parasomnia

Parasomnia (involuntary body movements involved during sleep) is mainly classified in two categories (according to the sleep stage they occur), namely NREM (non-rapid eye movement)-related parasomnias and REM-related parasomnias. These disorders are commonly treated by benzodiazepines (clonazepam, 0.125–2 mg, at bedtime), antidepressants (trazodone 25–50 mg, at bedtime), serotoninergic antide-

Table 24.1 Drugs for sleep–wake disorders in pediatric population

Sleep–wake disorders	Drug classes	Drugs and their doses	Timing of medication
Insomnia	Melatonin	0.05–5 mg/kg	1–2 hours before bedtime
	Antihistaminergics	Diphenhydramine (0.5–20 mg/kg) and hydroxyzine (1 mg)	30 minutes before bedtime
	Alpha-adrenergic receptor agonists	Clonidine (0.025–0.1 mg) and guanfacine (0.05–4 mg)	Twice daily dosing (morning and evening)
	Benzodiazepines hypnotics	Clonazepam (0.25–0.5 mg)	Bedtime
	Nonbenzodiazepine receptor agonists	Zolpidem (5 mg or 0.25 mg/kg)	Bedtime
	Antidepressants	Trazodone (50 mg), imipramine (0.05 mg/kg) and amitriptyline (5–50 mg)	Bedtime
	$_{L}$-5-Hydroxytryptophan	1–2 mg	Bedtime
	Chloral hydrate	25–50 mg/kg or 1 g maximum	15 to 30 minutes before bedtime
	Hypocretin/orexin receptor antagonists	Suvorexant (20 mg)	30 minutes before bedtime
Parasomnia	Benzodiazepines	Clonazepam (0.125–2 mg)	Bedtime
	Antidepressants	Trazodone (25–50 mg), paroxetine (20 mg) and imipramine (0.25–0.5 mg)	Bedtime
	$_{L}$-5-Hydroxytryptophan	2 mg/kg	Bedtime
	Melatonin	3–12 mg	30 minutes before bedtime or at bedtime
	Alpha-agonist hypotensive agents	Prazosin (1–15 mg)	Bedtime
	Antipsychotics (for nightmare disorder)	Risperidone (no data for children)	–
	Calcium entry blockers (for explode head syndrome)	Flunarizine (no data for children)	–
	Anticholinergics (for sleep enuresis)	Oxybutynin (0.1–0.3 mg/kg) and propiverine (0.8–1 mg/kg)	Bedtime
	Antidiuretics (for sleep enuresis)	Desmopressin (0.1–0.4 mg)	1 to 2 hours before water intake
Hypersomnolence	Central nervous system stimulants	Dextroamphetamine (5–30 mg) and methylphenidate (10–40 mg)	Twice daily dosing (morning and evening)
	Wake promoting agents	Modafinil (50–400 mg) and armodafinil (50–400 mg)	Twice daily dosing (morning and evening)
Cataplexy	Antidepressants	Imipramine (10–100 mg), clomipramine (10–150 mg), fluoxetine (10–30 mg), protriptyline (2.5–5 mg) and venlafaxine (37.5–75 mg)	Once a day
	Immunoglobulin therapy	Immunoglobulin G (400 mg-1 g/kg)	For 2 (1 g/kg) or 5 (400 mg) days per week
	Sodium oxybate	2–8 g	Twice daily dosing (bedtime and 2.5 to 3 hours later)
Circadian rhythm sleep–wake disorders	Melatonin	1–3 mg	Morning
	β1-adrenergic antagonists	Acebutolol (10 mg/kg or 200 mg)	Morning
	Vitamin B12	1.5 mg	Once a day
Sleep apnea	Antibiotics	Azithromycin (12 mg/kg)	Days of the month: 1–5, 11–15 and 21–25
	Leukotriene receptor antagonists	Montelukast (4–5 mg)	Once a day
	Corticosteroids	Fluticasone (50 μg)	Once a day
Sleep-related movement disorders	Iron supplementation	Ferrous sulfate (3–6 mg/kg)	Twice daily dosing
	Benzodiazepines	Clonazepam (0.25–0.50 mg) and temazepam (7.5–22.5 mg)	1 to 2 hours before bedtime
	Anticonvulsant	Gabapentin (100–900 mg)	30 minutes to 1 hour before bedtime
	Alpha-2 adrenergic agonists	Clonidine (0.05–0.4 mg)	30 minutes before bedtime
	Dopamine agonists	$_{L}$-dopa (250–600 mg), pramipexole (0.125–0.250) and ropinirole (0.125–0.250 mg)	For $_{L}$-dopa 4 doses (breakfast, lunch, afternoon, and evening) and in the evening or 2 or 3 hours prior to the start of RLS symptoms for pramipexole and ropinirole

pressants (paroxetine, 20 mg, at bedtime) and tricyclic antidepressants (imipramine, 0.25–0.5 mg, at bedtime), although solid evidence from randomized controlled trials, etc. is missing in pediatric sleep medicine [27–30]. Besides these classical treatments, there are anecdotally referred other remedies in pediatric sleep medicine; an open pharmacological therapy trial was conducted by Bruni et al. [31], where $_{L}$-5-hydroxytryptophan (2 mg/kg at bedtime) showed beneficial effects for the reduction of sleep terrors (a cardinal NREM parasomnia); the latter finding was attributed to the fact that $_{L}$-5 hydroxytryptophan tends to ameliorate the abnormal serotoninergic system dysfunction, connected with parasomnia disorders.

Furthermore, melatonin (3–12 mg at bedtime or 30 minutes before bedtime) was used for the treatment of NREM parasomnias (sleepwalking and sleep terrors) in a case study [32]. In particular, a 12-year-old male with Asperger's syndrome consumed 5 mg melatonin, 30 minutes before bedtime. During the treatment process, sleepwalking and sleep terrors vanished, and there was no recurrence of them for over 6 months. Melatonin has also been used in REM parasomnias (in REM sleep behavior disorder—RBD, which is a cardinal REM parasomnia characterized by dream-enactment motor behavior); melatonin in RBD seems to repair the normal REM-related muscle atonia, which is abolished in RBD, although this effect is modest and certainly needs more investigation [33].

Other drugs used in parasomnias with no sufficient data in pediatric sleep medicine, include clonidine, a α2 adrenergic agonist (which has been used for sleep paralysis, another known REM parasomnia), atypical antipsychotic drugs (e.g., risperidone, used for nightmare disorder, a REM parasomnia) and calcium entry blockers (flunarizine; tested for exploding head syndrome in adult population, which is a rare parasomnia) [30]. In a recent study with follow-up findings, prazosin (a sympatholytic drug, 1–15 mg at bedtime) reduced the severity of nightmares in children with PTSD-associated nightmares [34].

In sleep enuresis (another frequent parasomnia in pediatric sleep medicine), drugs such as anticholinergics, antidiuretic peptides, and antidepressants are mostly used [34]. For example, desmopressin (an antidiuretic drug, 0.1–0.4 mg 1–2 hours before water intake) can reduce bedwetting in 70% of the pediatric population, improving the quality of life of children [35]. Beneficial results were found with some other drugs: Imipramine, which is a tricyclic antidepressant, tends to reinforce the bladder by holding larger amounts of urine before a urinary urge; moreover, anticholinergics agents (oxybutynin, 0.1–0.3 mg/kg at bedtime; propiverine, 0.8–1 mg/kg at bedtime) improve the function of bladder capacity via increasing threshold volume, and by decreasing involuntary detrusor contractions [36].

Central Disorders of Hypersomnolence

This sleep disorder entity includes four main disorders: narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia, and Kleine–Levin syndrome. The most common finding in these disorders is hypersomnolence (a condition of abnormal prolonged sleep), while in narcolepsy there may be also cataplexy, which is the sudden partial or total loss of muscle tone triggered by strong emotions and driven by a deficit of orexin [37].

For the drug treatment of hypersomnolence, central nervous system stimulants (CNSS) and wake promoting agents are first line therapy. In practice, dextroamphetamine (a CNSS drug, 5–30 mg, with a twice daily dose regimen) has a more efficient effect on the increasing of alertness (four times) than methylphenidate (10–40 mg, with a twice daily dose regimen), while methylphenidate tends to alleviate somnolence in children [38]. CNSS drugs release dopamine and norepinephrine via presynaptic terminals or inhibited reuptakes. Also, wake promoting agents like Modafinil (50–400 mg with a twice daily dose regimen) and armodafinil (50–400 mg, again with a twice daily dose regimen) enhance the cortical arousal and increase histamine levels, as a result of which somnolence gets reduced [38]. Modafinil improves somnolence as shown by both subjective and objective measurements [39].

Moreover, antidepressants, immunoglobulin therapy and sodium oxybate have shown promising results for cataplexy [38]. The anticholinergic effects of tricyclic antidepressants (imipramine, 10–100 mg; clomipramine, 10–150 mg) modestly decreased cataplexy attacks [40]. Other types of antidepressants such as selective serotonin reuptake inhibitors (fluoxetine, 10–30 mg) and serotonin-norepinephrine reuptake inhibitors (venlafaxine, 37.5–75 mg) are also used for cataplexy in narcolepsy [41]. Finally, sodium oxybate (2–8 g), which is a gamma-aminobutyric acid (GABA) receptor agonist, which is the only FDA drug approved for pediatric narcolepsy with cataplexy, improves both daytime sleepiness and cataplexy [42]. Moreover, sodium oxybate may influence other REM phenomena in the context of narcolepsy (i.e., sleep paralysis); nevertheless, its mechanism of action remains equivocal. Sodium oxybate is administrated by twice-daily dosing with the first dose administered at bedtime and the second dose 2.5–3 hours later [42].

Finally, in a small sample of narcolepsy type 1 patients (four patients, two children), Dauvilliers et al. [43] used immunoglobulin G therapy (400 mg-1 g/kg), with a beneficial effect on both daytime sleepiness and cataplexy after a 7-month follow-up. On the other hand, the immunoglobulin G therapy gave beneficial evidence only on severe type narcoleptic children. The immunoglobulin G therapy is taken for 2 or 5 days per week, with doses of 1 g/kg and 400 mg, respectively [43].

Circadian Rhythm Sleep–Wake Disorders

Circadian rhythm sleep–wake disorders (CRSWD) are characterized by abnormalities in sleep architecture, affecting the timing of sleep and waking across the day. Melatonin (1–3 mg, taken in the morning) is the most used therapy for CRSWD. Melatonin has sleep-inducing and chronobiotic effects, with a beneficial effect on sleep onset latency reduction [44]. In a randomized double-blind placebo-controlled trial in pediatric population (3–12 years), Gringras et al. [45] found that though melatonin therapy reduced sleep onset latency, there was a non-statistically significant result on sleep efficacy; the authors stressed the importance of melatonin as a chronobiotic mechanism (phase-shift of the sleep–wake rhythm).

Nevertheless, in pediatric sleep medicine several issues regarding melatonin , that is, the required dosages, the type of melatonin to be used (e.g., immediate release versus extended release), its prolonged effect etc., remain to be clarified [44]. Melatonin is implicated in CRSWD also indirectly; β1-adrenergic antagonists (i.e., acebutolol, 10 mg/kg or 200 mg, taken in the morning) decreases melatonin production during the day via the noradrenaline stimulating pathway. Thus, acebutolol in children (aged 3–17) with Smith–Magenis syndrome (SMs), which is a developmental syndrome that includes sleep disturbances, that is, CRSWD due to high diurnal levels of melatonin, improved their sleep/wake profile by reducing naps, fatigue, sleepiness, and consequent attention issues during the day [46]. Ramelteon and Tasimelteon have been considered as possible treatments in SMs, but no large well-controlled pharmaceutical trials have been reported to date [47]. Finally, Vitamin B12 (1.5 mg) has been administered in a 15-year-old blind girl suffering from a free-running sleep–wake rhythm, with beneficial effects [48].

Sleep-Related Breathing Disorders

Sleep Apnea

Obstructive sleep apnea (OSA) is one of the most common sleep-related breathing disorders in children. The main therapeutic approach in pediatric OSA is based on surgery, because adenotonsillar hypertrophy is a common cause of OSA. However, a surgical approach may add risks during the operation and postsurgery period and proper criteria for this kind of surgery for OSA are still lacking today [2].

Drug therapy in OSA and especially in pediatric OSA has been scarcely investigated. Montelukast, which is a leukotriene receptor antagonist and a common drug for asthma treatment, and corticosteroids have been mostly used. In a randomized control trial with 6 weeks' corticosteroid treatment (fluticasone, 50 μg), OSA severity was reduced modestly; thus, apnea–hypopnea index (AHI) after steroid treatment was decreased from 11/h to 5/h [49]. Similarly, AHI reduction (AHI was decreased by >50%) in a sample of 23 children was achieved using montelukast (4 or 5 mg) in a treatment period of 12 weeks [50]. In a systematic literature review and meta-analysis, Liming et al. [51] have observed that montelukast and corticosteroids provide beneficial outcomes only for children with mild OSA and for short-term management only.

Another drug category that has been tested for OSA in pediatric sleep medicine is antibiotics. Don and colleagues [52] showed that azithromycin (a common macrolide), when given at 12 mg/kg and for the first 5 days of the month (the dose was repeated on days 11–15 and 21–25), ameliorated OSA when compared with placebo, by reducing adenoid and tonsil sizes; actually, azithromycin led to the relief of OSA symptoms, but surgery remained still the treatment of choice [52]. Azithromycin is also useful for the reduction of elevated levels of C-reactive protein [53], which not only is a potential biomarker of OSA, but also increases after adenotonsillectomy [54].

Sleep-Related Movement Disorders

The most common sleep-related movement disorders in the pediatric population are restless legs syndrome (RLS) and Periodic Limb Movement Disorder (PLMD). RLS, which is a common neurologic sleep disorder (2–4% in children), is described as an urge to move the legs, usually accompanied by uncomfortable or unpleasant sensations. The symptoms begin or worsen during rest or inactivity, are relieved by movement, and occur exclusively or predominantly in the evening or night [55]. There is a recent update on the pediatric diagnostic criteria [56, 57], while diagnosis of RLS is done on a clinical basis. PLMD is characterized by clinical sleep disturbance and by repetitive limb jerking during sleep (known as periodic limb movements of sleep) that is not better explained by another condition, medication use, or substance use [55]. Diagnosis of PLMD is done by specific polysomnographic criteria. PLMD is closely related to RLS existence, especially in the pediatric population, while both diseases are related to iron deficiency and have a genetic predisposition [57].

There is no FDA guidance for PLMD and RLS in children. Regardless of that, iron supplements mostly and dopamine agonists have been used as treatments of choice [58]. Iron supplementation in pediatric population (ferrous sulfate 3–6 mg/kg, dividing in two doses) with RLS and PLMD, showed a significant and long-term improvement after 2 years [59]. Moreover, iron supplement does not seem to have severe adverse effects on children with PLMD [60]. However, Reynold [58] has stressed that 27% of children with concomitant autism spectrum disorder and RLS developed gastrointestinal symptoms following iron treatment and the range of this side effect was 5–60% in treatment processing.

Benzodiazepines like clonazepam have been used in children with RLS, even though this was in younger children,

aged from 8 months to 2 years old. The recommended dose ranges from 0.25 to 0.5 mg, daily, and should be taken 1–2 hours before bedtime [61]. Also, research has bolstered the efficacy of clonazepam on the amelioration of anxiety issues, which may be comorbidities to RLS or PLMD; besides clonazepam, temazepam (7.5–22.5 mg depending on the age of the patient) has been used as well [62, 63].

Alpha-2-delta calcium channel ligands, such as pregabalin and gabapentin, which are mostly used in the treatment of RLS in adults, should be used with caution when about pediatric RLS/PLM, although they have already shown a good safety profile when used for pediatric epilepsy [64]. Gabapentin improves states of RLS or PLMD in children 6 years old and above. Gabapentin dosage increases along the age increase; more specifically, children between 6 and 12 years should get 100 mg/day, and if the symptoms are not alleviated, the regimen should be increased up to a maximum of 600 mg/day. For children between 12 and 18 years old, dosage ranges between 100 and 900 mg/day. Gabapentin should be taken 30 minutes to 1 hour before bedtime [61].

Alpha-2 adrenergic agonists (e.g., clonidine) are also an alternative for the treatment of RLS; however, their short-lasting action makes these drugs not suitable for sleep maintenance disturbances due to RLS. Side effects like nightmares or vivid dreams have been reported in 5% of children taken clonidine. Suggested dose is 0.05–0.4 mg, 30 minutes before bedtime [65].

Finally, the most widely used drugs for adult RLS/PLM, dopamine agonists and $_{L}$-Dopa, are certainly less indicated for pediatric RLS/PLM due to considerable side effects (i.e., sleepiness, hallucinations, nausea, obsessive and/or compulsive symptomatology). Dopamine agonists (pramipexole and ropinirole) have provided essential efficacy against moderate-to-severe RLS or PLMD. However, in adults, these drugs are associated with potential side effects of augmentation. Pramipexole and ropinirole should be consumed in the evening or 2 or 3 hours prior to RLS symptomatology onset and their doses range from 0.125 to 0.250 daily, according to RLS or PLMD severity [61]. $_{L}$-dopa (250–600 mg, in 4 doses (breakfast, lunch, afternoon, and evening)) has been used successfully in a double-blind study for the reduction of RLS and PLMD symptomatology [66].

What Pediatric Somnologists Should Take into Consideration When Drugs Used in Common Pediatric Practice Impact Sleep

Several medical therapies have adverse effects on sleep [67, 68]. Thus, we provide some examples of drugs that affect in pediatric population. Common pediatric drugs are mentioned in the World Health Organization (WHO) 2017 List (Table 24.2) [69].

Table 24.2 Medical specialties and the impact of drugs on sleep

Medical specialties	Drug categories or vaccines	Sleep side effects
Internal medicine	Corticosteroid drugs	Somnolence, insomnia, longer sleep, daytime naps and less awakening
	Beta-blocker drugs	Insomnia, nightmares, and restless sleep
	Immunosuppressive drugs	Insomnia, snoring, somnolence, restless legs syndrome and periodic limb movement disorder
	Phosphodiesterase-5 inhibitor	Insomnia
	Methylxanthine drugs	Improved sleep apnea
	First-generation antihistamines	Drowsiness
	Anesthetics	Midazolam: bed-wetting, night terrors and prolonged sleep Meperidine and hydroxyzine: prolonged sleep Ketamine: reduced REM sleep
Neurology and psychiatry	Antiepileptic drugs	Increased sleep tendency, somnolence, and insomnia
	Stimulants for attention deficit/hyperactivity disorder	Decreased sleep time, quality and efficiency, increased sleep tendency
	Antidepressants	Selective serotonin reuptake inhibitors: increased levels of arousals, REM density and stage 1 sleep. Tricyclics: increased stage 2 sleep, sleep architecture disruptions, decreased slow wave sleep, REM sleep suppression and sleep fragmentation
	Antipsychotic	Risperidone: somnolence and insomnia Haloperidol: improved total sleep time
	Non-benzodiazepine hypnotic	Zolpidem: increased the number of awakenings, sleep slow wave and rapid eye movement
Vaccines	Human papilloma virus vaccine	Insomnia and other unspecific sleep disturbances
	ASO-3 adjuvanted swine flu vaccine	Narcolepsy
	Diphtheria-tetanus-pertussis vaccine, H influenza type b vaccine, pneumococcal conjugate vaccine, inactivated poliovirus vaccine, and hepatitis B vaccine	Increased sleep durations

Internal Medicine

Dexamethasone, a common drug for allergies, immunological diseases, or tumors, affects sleep by modifying the level of alertness. Garbutt et al. [70] reported that 40% of children receiving dexamethasone for croup, complained about sleep disturbances. Rosen et al. [71] reported that children receiving dexamethasone for leukemia slept longer than usual during the first 5 days of therapy, with more daytime naps and less awakenings. Furthermore, in a recent review regarding steroids in pediatric population, 4.3% of children receiving corticosteroids reported sleep disturbances [72]. Other immunosuppressive drugs, like tacrolimus, cellcept, and prednisone have also sleep side effects such as insomnia, snoring, somnolence, RLS, and PLMD [73–75].

Beta-blockers have been widely used in children for the management of arrhythmias, hypertension, and benign tumors. Bernabeu-Wittel et al. [76] reported that among children receiving beta-blockers and more specifically propranolol, insomnia, and nightmares were the most common side effects. In a recent systematic review 3.7% of 1175 children with infant hemangioma treated with propranolol suffered from nightmares, with consequences on memory and learning [77]. De Graaf et al. [78] also reported that restless sleep appeared in 29% of children with hemangioma undergoing beta-blocker therapy. Moreover, 24% of pediatric population reported insomnia after treatment with phosphodiesterase-5 inhibitor, sildenafil, for pulmonary hypertension. However, in this study, it was not clear if insomnia was a clear side effect of sildenafil or consequence of the combination therapy of sildenafil with bosentan or ambrisentan (endothelin receptor antagonists) [79].

Methylxanthine or theophylline for asthma therapy, decreased apnea and oxyhemoglobin desaturation during sleep probably because of its bronchodilator effect, reduction of airways inflammation and normalization of pulmonary arterial pressure [12, 13, 80]. On the contrary, antihistamines, for the treatment of allergic rhinitis, wheezing, and other pulmonary diseases or infections, were not associated with improvement of apnea in infants when compared with placebo. Moreover, drowsiness was observed in children with allergic rhinitis treated with first-generation antihistamines due to their prominent CNS action [81].

Surgery and Anesthesia

Drugs used in anesthesia may change sleep structure in the postoperative period. Ritwik et al. investigated the side effects of the combination of meperidine and hydroxyzine versus midazolam in dental care. They observed that, in the first 8 to 24 hours, all children in the combined drug group had experienced prolonged sleep compared with the children in the midazolam group (66.7%) [82]. Furthermore, regarding midazolam, McGraw and Kendrick noticed that in the first postoperative week, children who got midazolam experienced bed-wetting and night terrors [83].

In randomized crossover studies in a pediatric intensive care unit, in children under zolpidem (a non-benzodiazepine hypnotic) or haloperidol (a typical first-generation antipsychotic agent) (due to severe burns), Zolpidem tended to increase the number of awakenings, whereas haloperidol did not have any significant effect on awakenings. There was a significant improvement with haloperidol in terms of total sleep time, which increased by 23% compared with the control group. Zolpidem on the other hand, increased slow wave sleep and REM sleep. In the same study population, administration of ketamine was related with low percentages of REM sleep, while there was no impact on slow wave sleep, frequency of awakenings, total sleep time and on percentages of stages 1 and 2 [84]. Similarly, in another postoperative study, sevoflurane, and halothane (another two common anesthetics) did not affect sleep at all [85].

Neurology and Psychiatry

Children with epilepsy under treatment have complaints about sleep disturbances. In 1992, Palm et al. [86] assessed sleepiness in pre-adolescents under antiepileptic drugs (valproate and carbamazepine) while and after drug withdrawal. It was shown that children who were receiving treatment experienced more sleep tendency and sleepiness than when off treatment. In another study, parents of epileptic children under antiepileptic drugs reported several sleep disorders such as sleep apnea, parasomnia, and daytime somnolence; the latter symptom, though very common in this study (75.8% of the children suffered from daytime sleepiness), seemed to be attributed to sleep apnea and to parasomnia rather than to antiepileptic drugs [87]. To be mentioned that potential side effects of antiepileptic drugs on sleep (i.e., insomnia, restless legs syndrome, parasomnia) have been mostly studied in adults, while data on children are quite scarce [88].

It is important to mention the effect of stimulants drugs on children with attention deficit hyperactivity disorder (ADHD), which are among the drugs of choice for this disorder; it has been shown by employing objective measurements, that stimulants decrease the sleep quality in these children [89]. Stimulants tend to increase alertness by reducing total sleep time, sleep efficiency in children with ADHD [90]. On the other hand, there has been data in favor of possible amelioration of sleep issues (e.g., insomnia or bedtime resistance) of children with ADHD following ther-

apy with stimulants [91]. Given the debatable data regarding the effect of stimulants on sleep of children with ADHD, Kidwell and her colleagues [92] conducted a meta-analysis; thus, it was shown that stimulants increased sleep latency and consequently decreased total sleep time and sleep efficiency, suggesting a negative effect on sleep in children with ADHD.

Antidepressants when used for depression seem to disturb both sleep quality and quantity in children and adolescents with major depression. Fluoxetine, which is a quite common SSRI drug, increases the number of arousals, stage 1 sleep, and REM density [93]. Tricyclic antidepressants such as imipramine cause sleep architecture disruptions and sleep fragmentation, decreased slow wave sleep, REM sleep suppression, and increased stage 2 sleep [94].

Antipsychotic drugs such as risperidone, commonly used in case of autism, may have adverse events such as somnolence. Kent et al. reported that daytime somnolence in autistic children following antipsychotic therapy with risperidone, was dose-related; the prevalence of somnolence was lower (3%) in children with low-dose risperidone, while it was quite high (55%) when about high dose [95]. In another study on children with developmental disorders under risperidone, somnolence was mostly prevalent (72.5%), but insomnia occurred as well (15.4%) [96].

Vaccines

Vaccination for human papilloma virus (HPV) was associated with insomnia in 3 out of 18 girls after the first dose; insomnia was alleviated after the second and third dose [97]. However, another study revealed a prevalence of 47.2% of any sleep complaint among girls vaccinated for HPV [98]. Increased risk of narcolepsy (4.7 to 14 times) was observed following vaccination with a monovalent 2009 H1N1 influenza vaccine, which was used in several European countries during the H1N1 influenza pandemic [99]. In China, a threefold increased risk of narcolepsy was observed during postepidemic H1N1 vaccination in 5.6% of the population [100]. It seems that Pandemrix may trigger the gene HLA DQB0602, which generates disturbance of the orexin system, and the vaccinated children were positive for this gene [99].

Finally, Franck and colleagues [101] used prophylactic acetaminophen in infants after several vaccinations (diphtheria-tetanus-pertussis vaccine, H influenza type b vaccine, pneumococcal conjugate vaccine, inactivated poliovirus vaccine, and hepatitis B vaccine) and observed shorter sleep duration in this population when comparing with non-receiving acetaminophen infants.

Discussion

The aim of this chapter was to investigate the effect of drugs on pediatric sleep medicine. Disturbed, “not normal”, sleep in children is associated with developmental and cognitive deficits and reduced learning or social skills and is a matter of special attention. However, this assessment is complicated as guidelines and official approvals regarding pharmacotherapy lack, mainly because of the absence of randomized, controlled trials. In addition, sleep disorders’ symptoms in children vary from adults’ and/or between different ages and special training in pediatric sleep medicine is still overall insufficient. Finally, several pediatric drugs in “daytime”, clinic practice affect sleep.

For the treatment of insomnia in children, several drugs such as melatonin, antihistaminic drugs, a-agonists, benzodiazepines and nonbenzodiazepine receptor agonists, antidepressants, $_{L}$-5-hydroxytryptophan, hypocretin/orexin receptor antagonists, and chloral hydrate have been proposed, in addition to behavioral therapies and sleep hygiene [2, 28]. However, the limited amount of available data in the literature and the lack of specific guidelines lead to caution in the selection of drug therapy and suggest that non-pharmacological treatments should be engaged first [2–4].

For parasomnias, again non-pharmacological assessments (i.e., avoiding parasomnia triggering factors, or adopting safety measures) are mostly suggested; if conservative measures are not adequate and drugs should be given, slow wave sleep suppressants such as benzodiazepines or tricyclic antidepressants, given for a short period and followed by slow tapering, are the most appropriate [2].

Regarding excessive daytime sleepiness (EDS) and hypersomnolence of central origin, there is only one drug with FDA approval; sodium oxybate is the only drug, which has received indication for the treatment of both EDS and cataplexy in the context of narcolepsy type 1 (narcolepsy with cataplexy) [50]. Besides that, several other drugs – not FDA approved – are used for the treatment of either hypersomnolence or cataplexy; thus, stimulants and wake-promoting agents have been used for the treatment of EDS, in hypersomnolence of central origin (i.e., amphetamines and modafinil), whereas norepinephrine reuptake inhibitors, histamine H3 receptor antagonists, could be an alternative therapy, while tricyclic antidepressants, SSRIs, and SNRIs have also been used for cataplexy treatment [42]. Finally, sleep hygiene rules, frequent and prescheduled naps against EDS, and education about the triggers and the nature of the episodes of cataplexy are extremely useful in the therapeutic approach.

Concerning pediatric RLS/PLM, again no FDA indications exist. For mild cases non-pharmacologic measures (sleep hygiene, physical exercise, and trigger control) are mostly indicated, while drugs are proposed only for chronic,

moderate to severe cases [61]. For children with iron deficiency and RLS or PLMD, oral iron supplementation is suggested [59, 60]. Limited data exist about benzodiazepines as an alternative therapy, whereas dopaminergic agents or alpha-2-delta calcium channel ligands should be used with caution in pediatric populations [61].

Surgery is the therapy of choice for OSAS in children, whereas nasal continuous positive airway pressure can be an alternative therapy for children not eligible for surgery or in case of residual disease. Nocturnal supplemental oxygen therapy can be suggested only as a temporary until definitive therapy [102]. For mild OSA when surgery (adenotonsillectomy) in not indicated or mild postoperative residual OSA, intranasal corticosteroids, leukotriene modifiers, and their combination could be a treatment of choice [51]. The minimum duration of therapy for sustained benefit is not known. Antibiotics may not fully provide persistent relief of apneas or prevent surgical therapy [52].

Also, several common pediatric medical therapies can affect independently sleep quality or quantity. Children receiving corticosteroids or other immunosuppressive drugs complain about sleep disturbances, such as insomnia, snoring, somnolence, RLS, and PLMD. Beta-blockers and especially propranolol and phosphodiesterase-5 inhibitor, sildenafil, can cause insomnia and nightmares. Methylxanthine or theophylline reduce apneas and oxyhemoglobin desaturation during sleep. On the contrary, treatment with first-generation antihistamines is associated with drowsiness in children. As far as the drugs used in common neurological/neurodevelopmental/psychiatric disorders (i.e., epilepsy, autism, ADHD, depression) is concerned, the overall impression is that the indicated drugs for these diseases may alter sleep/wake cycle by disturbing sleep's quantity and quality and by producing and/or increasing daytime sleepiness**.** Finally**,** vaccination is sometimes implicated in sleep disorders in children, with increased risk of narcolepsy reported during postepidemic H1N1 vaccination.

In summary, though pediatric sleep medicine is an important part of sleep medicine and of pediatrics as well, robust evidence and guidelines regarding its pharmacologic treatment are still lacking. Furthermore, several drugs used in common pediatric practice may affect sleep (its quality and quantity) and wakefulness as well. Therefore, more attention (i.e., more studies, more evidence and/or guidelines) should be paid in order to improve sleep and consequently overall well-being of the children.

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Part VI

Acute and Chronic Ventilatory Support in Children

Non-invasive Respiratory Support in Children with Sleep Disordered Breathing

25

Hui-leng Tan

Introduction

The past few decades have seen an exponential increase in the number of children on home respiratory support, in particular non-invasive continuous positive airway pressure (CPAP) and bilevel positive pressure ventilation (BiPPV) [1, 2]. The reasons for this increase are manifold: there has been improved medical management both driving and being driven by progress in medical technology; improved survival in conditions such as bronchopulmonary dysplasia and various inborn errors of metabolism; widening appreciation and better recognition and diagnosis of certain conditions such as obstructive sleep apnea (OSA); and possibly most significantly, there has been a profound alteration in attitude toward the role of home ventilation leading to its use in a far wider range of conditions. For example, a few decades ago, home BiPPV was rarely used in patients with neuromuscular diseases (NMD) but studies of its use in Duchenne muscular atrophy and spinal muscular atrophy (SMA) have shown convincing improvement in outcomes meaning BiPPV has now increasingly become standard of care.

This chapter will focus on respiratory support in the treatment of children with sleep disordered breathing (SDB); due to their prevalence, the emphasis will be on the treatment of OSA and sleep disordered breathing seen in NMD. Initially this chapter will start with the examination of the role of CPAP and BiPPV, including the newer hybrid modes of ventilation, before moving on to high-flow nasal cannula therapy (HFNC), which is starting to expand its role outside the hospital setting to that at home, and concluding with the use of supplemental oxygen in the context of its role in managing central sleep apnea.

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Continuous Positive Airway Pressure

The most common indication for home CPAP is obstructive sleep apnea, with some children needing it for airway malacia. The constant airway pressure delivered maintains airway patency throughout the respiratory cycle, improving functional residual capacity (FRC) and thus decreasing the work of breathing. For the treatment of pediatric OSA, the American Academy of Pediatrics recommends institution of positive airway pressure (PAP) therapy if either adenotonsillectomy is not performed or if there is residual OSA postoperatively [3]. Similarly, European Respiratory Society (ERS) guidelines also recommend PAP therapy as part of the stepwise approach to the treatment of OSA [3]. Patients requiring CPAP therefore tend to be children who are at higher risk of having residual OSA post adenotonsillectomy such as those who are obese or have other medical comorbidities resulting in increased upper airways collapsibility or structural obstruction, e.g., trisomy 21 and craniofacial syndromes.

The PAP Titration Task Force of the American Academy of Sleep Medicine (AASM) has recommended that CPAP pressures should start at a minimum of 4 cmH_2O and be increased until obstructive respiratory events (apneas, hypopneas, respiratory effort-related arousals, and snoring) are eliminated or the recommended maximum CPAP is reached [4]. This is suggested to be 15 cmH_2O in patients younger than 12 years, and 20 cmH_2O in patients older than 12 years. If patients do not tolerate the high pressures or if the maximum pressures have been reached without resolution of the obstructive events seen, BiPPV can be trialed.

CPAP is undoubtedly efficacious when administered correctly. Figure 25.1 shows an example of a child who had severe OSA with an AHI of 37/hTST, oxygen desaturations, and rises in CO_2. With CPAP of 8 cmH_2O, the AHI was reduced to 1.8/hTST with concomitant normalization of his gas exchange. A prospective multicenter study of 29 children randomly assigned to 6 months of CPAP ventilation or BiPPV showed that both were very effective [5]. However,

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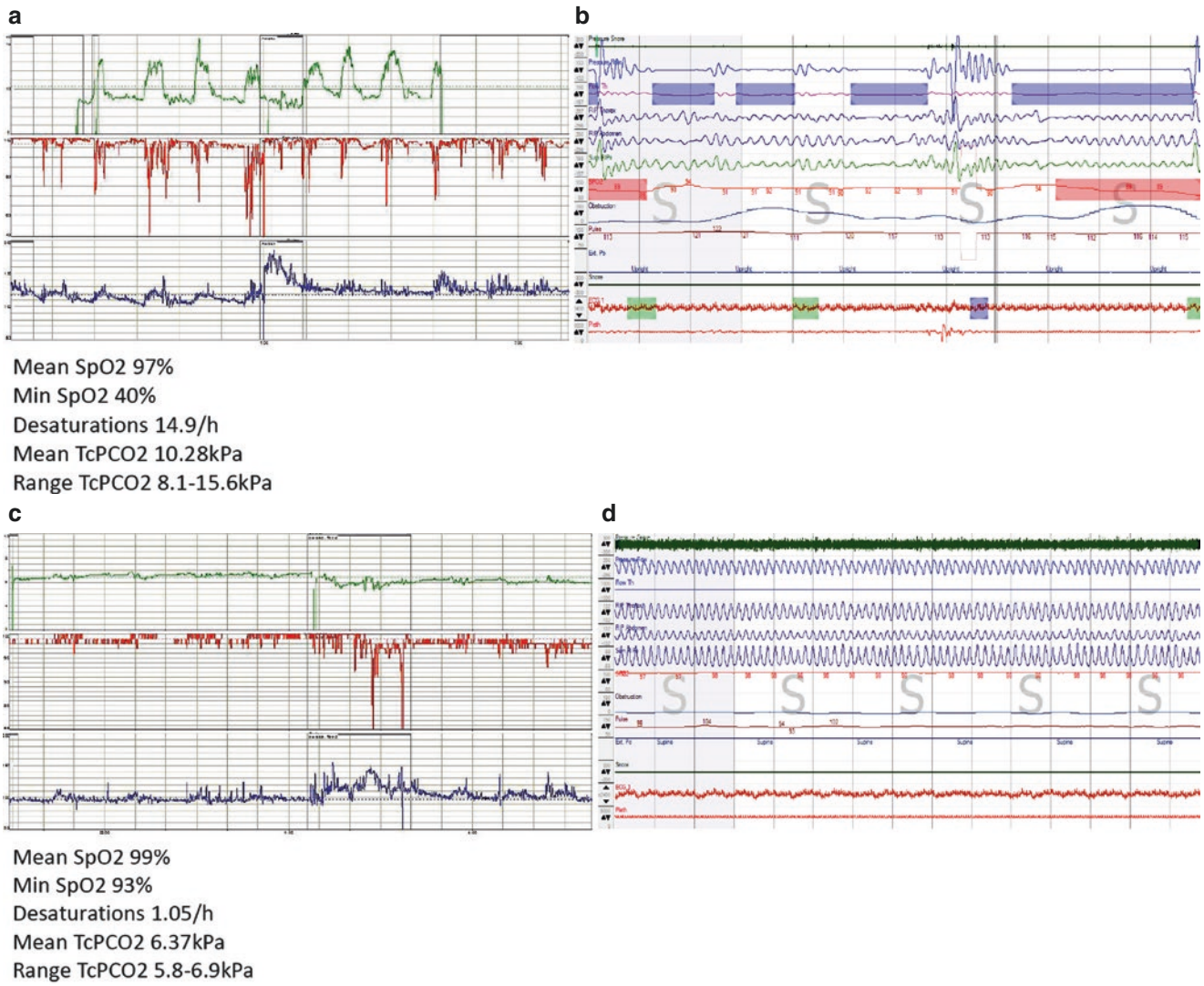

Fig. 25.1 (**a**) O_2CO_2 traces from a child with severe OSA (AHI of 37/hTST) showing oxygen desaturations and rises in CO_2. (Green trace, $TcPCO_2$; Red trace, SpO2; Blue trace, heart rate). (**b**) Example of obstructive events seen before treatment in the same patient. (**c**) O_2CO_2 traces from the same child on CPAP of 8 cmH_2O (AHI now 1.8/hTST), oxygen desaturations have resolved, and there are no longer rises in CO_2. (**d**) Resolution of obstructive events on CPAP 8 cmH_2O

what it also highlighted was the issue of adherence. A third of the subjects had dropped out before 6 months and the mean nightly use even in the adherent children was 5.3 ± 2.5 hours, which the authors considered suboptimal considering the average length of sleep of children. Nevertheless, what clinicians should feel encouraged by is that, as demonstrated by Marcus et al., even when adherence is suboptimal (mean use of just 170 ± 145 min/night), a significant improvement after 3 months of PAP therapy was still seen [6] in several neurobehavioral domains, such as attention deficits, Epworth sleepiness scale score, internalizing and total behavior symptom scores, and quality of life questionnaires. Similarly, in adolescents, even modest levels of CPAP adherence (of average 57% of sleep time during which CPAP was used) resulted in improved attention and academic functioning compared with a similar group of non-adherent adolescents [7].

Moreover, while challenging, good adherence is still possible, with Ramirez et al. reporting a mean PAP usage of 8 h 17 min ± 2 h 30 min per night [8]. This excellent adherence probably reflects the intensive resources invested, with the PAP therapy initiated by experienced staff in a designated pediatric inpatient unit, with frequent follow-up in the form of home visits, and inpatient sleep studies. Certainly, the AASM taskforce recommends that all potential CPAP titration patients should receive adequate education, hands-on demonstration, careful mask fitting, and acclimatization prior to titration [4]. This appears to be best delivered in the context of a multidisciplinary team approach. When the Children's Hospital of Philadelphia restructured their CPAP

program and hired a dedicated behavioral psychologist/program coordinator and respiratory therapist to provide more comprehensive treatment for patients and their families, they achieved significantly higher follow-up and attendance for CPAP titration rates [9].

Qualitative research has highlighted the importance of health education and family involvement in developing strategies that facilitate CPAP use specific to individual families [10]. Caregiver-reported self-efficacy, i.e., the belief that they have the ability to successfully administer CPAP, has also recently been identified as an important predictor of short-term CPAP adherence [11], once again emphasizing the importance of patient education and support.

The other key area in attempting to improve adherence is to improve comfort and thus patient tolerability of CPAP. Some examples of these strategies include starting at lower pressures when the CPAP is initially put on and slowly increasing to the target pressure over a set period of time (ramp), expiratory pressure relief, adding humidification to the circuit, and trying different masks to identify the most comfortable one with the best fit. While previously, finding an appropriate-sized mask that fit the child well could be challenging, especially for infants/young children or those with craniofacial syndromes, the range of commercial masks now available for pediatric patients has significantly increased in the past few years, giving clinicians more choice. The advent of 3D printing may also mean that customized masks could be more affordable in the future. Nasal pillows can also be a good alternative and have been shown in adults to be equally effective in delivering CPAP therapy as nasal mask interfaces [12]. However, due to their size, they are mainly used for older pediatric patients with larger nostrils. Overbergh et al. have trialed using the Optiflow™ Nasal Cannula (originally designed for the delivery of HFNC) as an alternative interface by connecting it to a regular CPAP device and showed a significant decrease in obstructive AHI (OAHI) and total AHI [13]. However, BiPPV cannot be administered via this interface because the leak from the interface meant triggering was insufficiently sensitive and resulted in patient ventilatory asynchrony.

After initiation on PAP therapy, regular long-term monitoring and follow-up is crucial. Pressure requirements change with the growth and development of the child and children will outgrow their mask interface. Side effects such as skin erythema or breakdown leading to pressure sores over the nasal bridge and flattening of the midface need to be carefully monitored for, as does adherence. A large telemonitoring trial in adults has shown that the use of CPAP telemonitoring with automated feedback messaging improved 90-day adherence in patients with OSA [14] and it thus may be a useful aid in children.

Bilevel Positive Pressure Ventilation

The main indication for home BiPPV is in the treatment of chronic respiratory failure. Normally, the central drive appropriately recruits the respiratory muscles to support the respiratory load. This equilibrium can be disrupted if there is a functional decrease in respiratory muscle capacity (e.g., NMD), increase in respiratory load (e.g., interstitial lung disease, obesity hypoventilation syndrome [OHS]), or abnormal central respiratory drive (e.g., congenital central hypoventilation syndrome [CCHS]).

Conditions That Can Potentially Result in Chronic Respiratory Failure Where Home BiPPV May Be Used

- *Functional decrease in respiratory muscle capacity*
  - Neuromuscular diseases:
    - Duchenne muscular dystrophy
    - Spinal muscular atrophy
    - Congenital myasthenia syndrome
    - Congenital myopathy
    - Congenital muscular dystrophies including rigid spine syndrome
    - Chest wall deformity
    - Scoliosis
- *Increase in respiratory load*
  - Obesity hypoventilation syndrome
  - Chronic lung disease of prematurity
  - Interstitial lung disease
  - Cystic fibrosis
  - Bronchiolitis obliterans
- *Central alveolar hypoventilation syndromes*
  - Congenital central hypoventilation syndrome
  - ROHHAD—rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation
  - Apnea of prematurity
  - Neurometabolic syndromes
  - Arnold-Chiari malformation
  - Acquired:
    - Brain tumors
    - Encephalitis
    - Cerebral infarction
    - Following head trauma/brain surgery

Neuromuscular Diseases

One of the most common medical conditions BiPPV is used for is NMD. It is now almost difficult to conceive that in the not too distant past, BiPPV was only started in NMD patients

when there was daytime hypercapnia. There has since been a shift toward a more proactive interventional approach. A randomized controlled trial of NMD patients with nocturnal hypoventilation who had not yet developed daytime hypercapnia was performed where patients were either started on non-invasive ventilation (NIV) or monitored (control group) [15]. In the control group, 70% and 90% required NIV within a year and within 2 years, respectively, and several were acutely admitted for ventilatory decompensation. The NIV group had significantly improved health-related quality of life scores. This led to a reappraisal of the timing of intervention and most clinicians now start NIV once nocturnal hypoventilation develops, particularly as this allows initiation in a planned, controlled manner. Often, because the symptoms of nocturnal hypoventilation can be subtle and develop slowly over time, patients may not necessarily volunteer they have developed symptoms, but only admit to them on direct questioning. Some may not even realize they are suffering from symptoms such as tiredness or attribute it to their underlying neuromuscular condition, and a recurrent theme in our practice is patients feeling after the institution of BiPPV that they now have more energy and better concentration at school. Other potential benefits of BiPPV include a reduction in respiratory exacerbations and the prevention of chest wall deformity in the younger children [16]. Furthermore, it is often useful to familiarize patients to BiPPV prior to elective surgery such as scoliosis surgery, so that it can be used in the peri-operative period [17].

The British Thoracic Society guidelines recommend that assessment for sleep disordered breathing should be carried out at least annually in children who have become non-ambulant because of progressive muscle weakness, who have never attained the ability to walk, or who have a vital capacity of <60% predicted [18]. Any patient with clinical signs of diaphragmatic weakness or symptoms of sleep disordered breathing should also be assessed. It must be remembered that children with rigid spine syndrome may have nocturnal hypoventilation despite near-normal vital capacity. In fact, it is crucial to appreciate the natural history of the individual neuromuscular diseases as some conditions such as spinal muscular atrophy (SMA) type 1, SMA with respiratory distress, and X-linked myotubular myopathy result in early ventilatory failure; conditions such as Duchenne muscular dystrophy and congenital muscular dystrophy have a slower, more progressive course; while in conditions such as facioscapulohumeral muscular dystrophy, ventilatory failure is rare. An understanding of genotype–phenotype interactions is also important for personalized care. A good example is patients with congenital myasthenic syndromes who often use BiPPV when they are tired. Those with *COLQ* mutations tend to have a progressive decline in their respiratory course and often need BiPPV for nocturnal hypoventilation [19]. In contrast, patients with *RAPSN*, *CHRNE*, and *CHAT* mutations are more prone to sudden apneas/crises. Their parents/carers need to be taught cardiopulmonary resuscitation including bag/mask ventilation, and BiPPV is often needed as part of management of these crises.

Further recent guidelines on the pulmonary care of SMA patients recommend that in infants and non-sitters, BiPPV should be started in all symptomatic patients with some experts recommending it before documented respiratory failure to prevent chest wall deformity and palliate dyspnea [20]. CPAP should not be used to treat chronic respiratory failure, but on rare occasions may be temporarily used to help maintain functional residual capacity in those who are unable to synchronize with the ventilator in BiPPV mode. Similarly, in those able to sit, BiPPV should be used in all symptomatic patients, with some experts recommending it during acute respiratory illnesses to facilitate discharge.

The use of BiPPV in neuromuscular diseases such as Duchenne muscular dystrophy has significantly improved survival [21]. Outcomes of children on BiPPV for other causes of sleep disordered breathing are largely dependent on the prognosis of the underlying condition. Chatwin et al. reviewed the children on long-term BiPPV over a period of 18 years [22]. Follow-up data were available for 449 children: 40% transitioned to adult care, 24% died, 1% proceeded to tracheostomy ventilation, and 9% discontinued ventilatory support. The majority of patients who discontinued did so because of improvement in their underlying condition and thus resolution of their sleep disordered breathing. These included children with chronic lung disease of prematurity and airway malacia; one cystic fibrosis (CF) patient had a lung transplant; and one child with atypical nemaline rod myopathy required respiratory support until 5 years of age, when the nocturnal hypoventilation improved and resolved. A systematic review of long-term non-invasive CPAP and BiPPV in infants showed improvements in respiratory parameters for infants with airway conditions and decreased hospitalizations and prolonged survival for children on BiPPV for NMD (mainly SMA 1) [23].

Congenital Central Hypoventilation Syndrome

Congenital central hypoventilation syndrome (CCHS) is a rare disorder typically due to a mutation in the *PHOX2B* gene. It is characterized by alveolar hypoventilation due to ventilatory insensitivity to hypercapnia and hypoxemia particularly during sleep as well as autonomic dysregulation [24]. Patients need to be on lifelong ventilation (or phrenic nerve stimulation) overnight. Most children with CCHS are ventilated via tracheostomy in the first few years of life to ensure effective oxygenation and ventilation, and therefore optimal neurocognitive outcome. When they are a bit older, children with the milder phenotypes who only require venti-

lation when asleep may be changed over to non-invasive BiPPV. A few centers opting to avoid tracheostomy have started non-invasive ventilation at time of diagnosis and have reported good outcomes [25]. It is crucial to remember that these children do not display the normal physiological responses to hypoxia and hypercapnia. Home oxygen saturation monitoring is necessary with some centers also providing home carbon dioxide monitoring. The American Thoracic Society recommends aiming for an end-tidal carbon dioxide tension between 30 mmHg and 50 mmHg, ideally between 35 and 40 mmHg, and $SpO_2 \geq 95\%$ [24].

Hybrid Modes

Hybrid modes of ventilation have been developed in an attempt to combine the advantages of pressure-targeted and volume-targeted modes of ventilation. These volume-assured pressure support (VAPS) modes use intelligent algorithms to adjust the pressure support delivered to ensure a stable respiratory target. The two main versions available commercially for home non-invasive ventilation are average volume-assured pressure support (AVAPS) developed by Phillips Respironics and intelligent volume-assured pressure support (iVAPS) developed by Resmed. These were originally designed for the adult market, in particular for patients with obesity hypoventilation, COPD, and neuromuscular disease [26].

AVAPS adjusts the pressure support delivered by varying inspiratory positive airway pressure (IPAP) between the IPAPmin and IPAPmax to guarantee the average tidal volume (TV) set. For example, if patient effort decreases, AVAPS increases the pressure support to maintain TV, but will not increase above IPAPmax and if patient effort increases, AVAPS decreases the pressure support to maintain TV, but will not decrease it below IPAPmin. It can be used in spontaneous (S), spontaneous timed (ST), pressure control (PC), and timed (T) modes and is for patients with a minimum tidal volume of 150 mL. Figure 25.2 shows an example

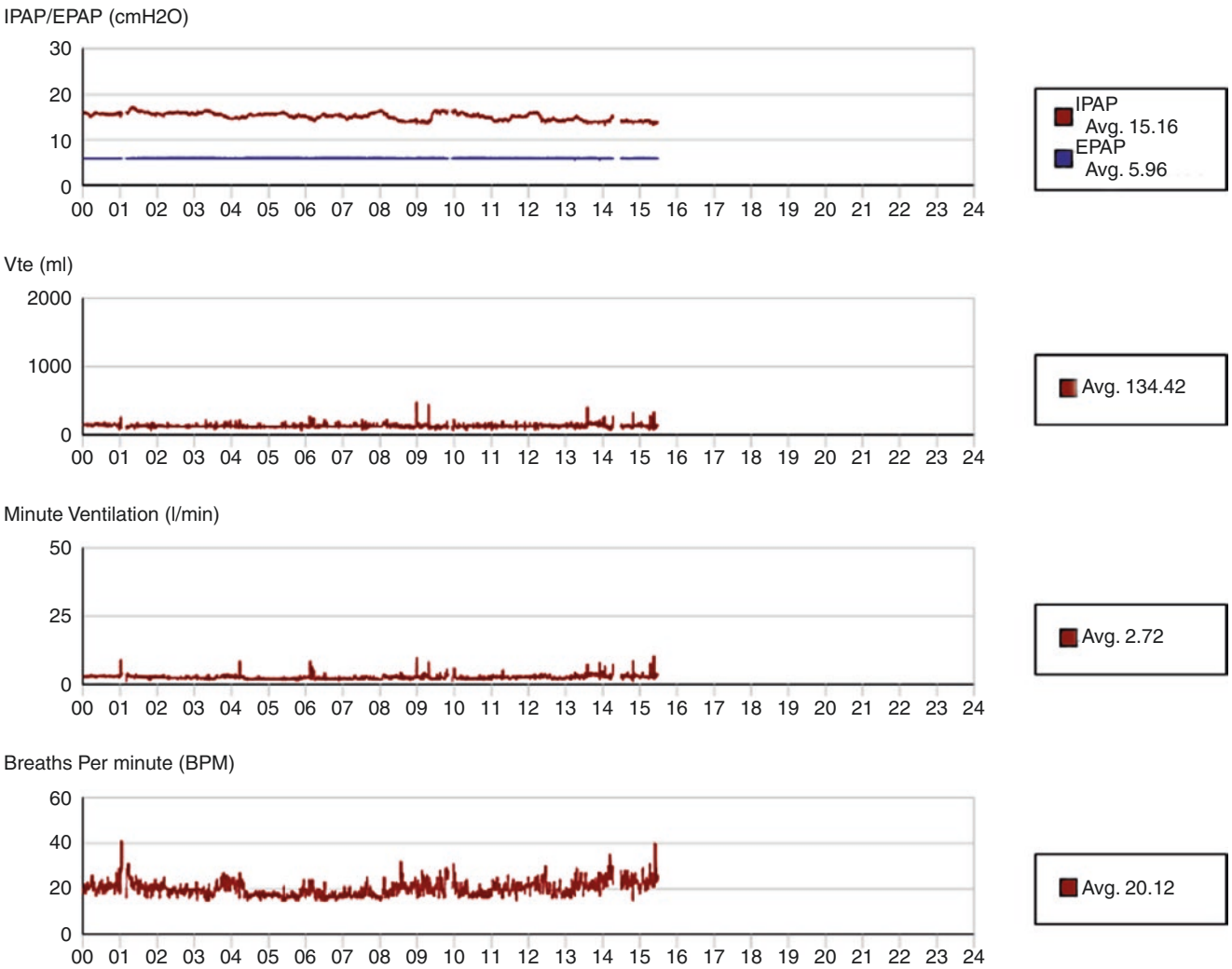

Fig. 25.2 Example of ventilator download data from a child with NMD on AVAPS showing the variation in IPAP over the course of the night

of the ventilator download data from a child on AVAPS showing the variation in IPAP over the course of the night.

In contrast, the iVAPS algorithm targets alveolar ventilation, adjusting the pressure support and providing an intelligent backup rate (iBR). The iBR technology learns the patients' breathing pattern, using this information to determine whether it delivers a backup breath if there is a pause in breathing. It therefore adapts to the patients' breathing effort while still maintaining target alveolar ventilation. It is intended for patients with a weight greater than 30 kg.

In pediatrics, these hybrid modes have been principally used in patients with neuromuscular disease, obesity hypoventilation, and congenital central hypoventilation syndrome.

Neuromuscular Disease

Patients with neuromuscular disorders can have varying pressure requirements in different stages of sleep. Using hybrid VAPS modes may confer the potential advantages whereby: (a) patients can be managed with lower pressures for most of the night but with increased pressures when required, potentially improving comfort and compliance; (b) as the disease progresses and the patient's ventilatory requirements change, VAPS modes should change accordingly; and (c) there is increased safety by guaranteeing an average tidal volume. There is therefore increasing use of this form of ventilation for NMD patients [8].

The literature supporting this switch is still emerging. A case report from Australia described the use of AVAPS in a 3-year-old girl with multiminicore myopathy [27]. Initially, she was ventilated in ST mode but despite pressures of 20/6 cmH_2O with good synchronization, there were still significant desaturations and carbon dioxide (CO_2) retention to a maximum $TcCO_2$ of 92 mmHg. It was noted that she had significant differences in ventilatory requirements in different sleep stages. She was therefore trialed on AVAPS with expiratory positive airway pressure (EPAP) 4 cmH_2O, IPAPmin 11 cmH_2O, IPAPmax 17 cmH_2O, and target TV of 80 mL (which is below that recommended by the manufacturers). This allowed her to be on lower pressure settings for periods of the night, with the higher pressures only when required and resulted in improved oxygen saturation and CO_2 profiles.

Kelly et al. performed a randomized cross-over trial of iVAPS and standard pressure support (PS) BiPPV [28]. They recruited patients referred to a ventilation clinic with newly diagnosed nocturnal hypoventilation naïve to BiPPV. Of the 18 patients who completed the protocol, 7 had neuromuscular weakness, 8 obesity hypoventilation, 2 COPD, and 1 scoliosis. iVAPS delivered a lower median PS compared with standard PS ventilation (8.3 [5.6–10.4] vs 10.0 [9.0–11.4] cmH_2O; $p = 0.001$) with no difference in the ventilatory outcome (mean SpO_2, CO_2, oxygen desaturation index) and sleep quality. This may not only minimize any deleterious effects of high pressure such as barotrauma, increased leaks, and gastric distension, but also increase ventilator adherence by optimizing patient comfort. The mean night-time use for iVAPS mode was greater than for standard PS mode by over an hour (5:40 [4:42–6:49] vs 4:20 [2:27–6:17] hh:mm/night; $p = 0.004$). These findings are particularly significant because if automation of ventilation settings by iVAPS is potentially as effective as PS ventilation initiated by a skilled health-care professional in controlling nocturnal hypoventilation, with better overnight adherence, iVAPS ventilation may reduce the clinician experience required for initiating domiciliary NIV, thus increasing its availability.

Obesity Hypoventilation

Respiratory mechanics can change significantly in obesity hypoventilation syndrome (OHS) patients when they change position, e.g., from lying supine to lateral, with corresponding changes in ventilatory requirements. Conceptually, hybrid VAPS modes may therefore be a more effective strategy for ventilation. A randomized cross-over trial of ten adult patients with OHS showed that AVAPS resulted in a greater reduction in nocturnal transcutaneous CO_2 compared with PS ventilation [29]. A subsequent study of 12 OHS patients had similar results with regard to improved CO_2, but this seemed to be at the expense of a slight decrease in sleep quality [30]. On AVAPS, the total sleep time and stage 2 sleep were less, while wake after sleep onset and awakenings >20s increased. Subjectively, with AVAPS, patients described a lighter sleep, of lesser quality, and more frequent awakenings; they also felt the ventilation was less comfortable. However, these were patients who were already on PS BiPPV for a median of 30 months and often when patients get used to a ventilator, they can find a change uncomfortable. Clearly, both studies were limited by the small numbers of patients recruited. Murphy et al. then performed a single-blind randomized controlled trial of 50 patients, which showed that AVAPS is as effective as standard PS ventilation [31]. Both groups demonstrated similar improvements in nocturnal ventilatory control, daytime gas exchange, daytime symptoms, daytime physical activity, and health-related quality of life. The level of sleep disruption was similar in both modes. The largest multicenter randomized controlled study published comparing VAPS, CPAP, and lifestyle modification (control group) showed that VAPS and CPAP were more effective than lifestyle modification in improving PSG parameters and clinical symptoms [32]. However, VAPS resulted in better respiratory functional improvements; e.g., some health-related quality of life assessments, spirometry,

and 6-minute walk distance improved more with VAPS than CPAP. Whether these gains translate into long-term benefits will be of much interest.

There has also been a case report of an 8-year-old boy with severe obesity hypoventilation who was successfully treated with AVAPS [33]. Initially, CPAP was tried but on his titration PSG, a CPAP pressure of 19 cmH_2O only resulted in partial reduction in his AHI and he would not tolerate higher CPAP pressures. A tracheostomy was even considered, but, fortunately, a trial of AVAPS was tolerated and resulted in significant improvement in the AHI, with improved oxygenation, ventilation, and sleep quality. Follow-up showed symptomatic improvement and good adherence to the therapy. It would have been interesting to see whether he responded as well to standard PS BiPPV.

Congenital Central Hypoventilation Syndrome

In CCHS, minute ventilation can vary significantly over the course of the night due to differences in the control of breathing during REM and NREM sleep with the alveolar hypoventilation being worse during NREM sleep. Given the rare nature of the disease, supporting evidence is again just from individual case reports and case series. There was a case report of a 16-year-old girl with CCHS who was successfully transitioned to AVAPS after previously being tracheostomy ventilated [34]. A retrospective chart review of eight CCHS patients who underwent both a PSG on standard ST mode and a consecutive follow-up study with the iVAPS mode showed iVAPS was associated with a reduction in the maximum TcCO2 during NREM sleep (43.0 [40.0–46.0] mmHg vs 46.5 [45.0–48.0] mmHg for ST mode; $p < 0.05$) [35]. They also reported a trend toward improvement in the sleep efficiency in iVAPS mode compared with ST mode, 90.1 versus 86.1% ($p = 0.06$). Anecdotally, we have had a small number of patients who had less variability in their CO_2 overnight in different stages of sleep and fewer arousals/awakenings when they were changed from standard PS ventilation to iVAPS.

As can be seen from the abovementioned summaries of published data, published pediatric data are still scarce, with much of the data extrapolated from adult studies. While similarly based on the principle of volume-assured pressure support, algorithms for the different hybrid modes of ventilation do differ, so settings are not directly interchangeable, and clinicians would benefit from an understanding of their ventilatory subtleties. Currently, theoretical advantages to this mode of ventilation can be made and anecdotally certain patients have responded well. However, future research is clearly needed, in particular in the form of randomized controlled trials to fully evaluate this potentially very exciting area of advance in pediatric ventilation.

High-Flow Nasal Cannula Therapy

High-flow nasal cannula therapy (HFNC) tends to be better tolerated than CPAP and has therefore been proposed as an alternative treatment strategy for children with OSA who do not tolerate CPAP. As its name suggests, HFNC delivers high-flow heated humidified oxygen or air via open nasal cannula. As the flow rate delivered is greater than the patient's normal inspiratory flow rate, its postulated mechanisms of action include the reduction in negative pressure generated during inspiration minimizing upper airway collapsibility, washing out of upper airway dead space, the generation of some positive airway pressure, and, finally, the activation of protective airway reflexes via nasopharyngeal mechanoreceptor or thermoreceptor stimulation [36, 37]. It is commonly used in the acute pediatric setting, as a form of respiratory support for bronchiolitis and on neonatal units for the treatment of respiratory distress syndrome (RDS) [38–40]. As post-extubation support for RDS, it appears to have similar efficacy to CPAP and nasal intermittent positive pressure ventilation in terms of preventing treatment failure, death, and chronic lung disease [40, 41]. However, two recent randomized controlled trials found HFNC to be inferior to nasal CPAP as primary support in RDS [42, 43].

One of the initial studies describing its potential use in the treatment of pediatric OSA compared HFNC with CPAP in 12 patients. There was a reduction in the degree of inspiratory flow limitation seen and the AHI was comparable to that of CPAP in the majority of the children [44]. A subsequent case series described HFNC use in both the hospital and home setting of five complex children with OSA (aged 2 months to 15 years) who were unable to tolerate CPAP. While HFNC did not result in complete resolution of the OSA, there was a significant improvement in their AHI, oxygen saturations, and symptoms [45]. Four of the five cases had severe OSA (AHI ≥ 15/h), and all improved to mild–moderate severity (AHI < 10/h) on HFNC and tracheostomy was even avoided in one case. There was also reduced CO_2 retention. A further case series by Hawkins et al. studied ten school-aged children intolerant of CPAP and also showed a reduction in the median OAHI from 11.1/hTST (IQR, 8.7–18.8/hTST) to 2.1/hTST (IQR, 1.7–2.2/hTST; $p = 0.002$), increased mean SpO2, higher SpO2 nadir, decreased SpO2 desaturation index, and reduced heart rate [36]. The authors also proposed a method of titrating HFNC, starting with an initial flow rate of 5 L/min for pediatric-sized cannula and 15 L/min for adult-sized cannula and increasing the flow in 5 or 15 L/min increments, respectively, until no more obstructive events were seen or the maximum recommended flow was reached (namely 20 L/min for pediatric cannula, 50 L/min for adult-sized cannula). Oxygen was added if hypoxia or desaturations persisted despite maximal flow of room air.

While the efficacy of HFNC as treatment for OSA may not be that of CPAP, an additional advantage to its tolerability may be the avoidance of midface hypoplasia that can result from pressure of the CPAP mask on growing facial structures, particularly in younger children [46]. However, HFNC also has its disadvantages: trauma to the nose has been described in preterm infants on HFNC [47]; the airway pressure generated is not regulated and there is no mechanism in place to prevent sudden increases in pressure. This in theory may result in air leak such as pneumothorax or pneumomediastinum and cases have been described when this has occurred in the context of HFNC being used for the treatment for bronchiolitis, post-elective gastrostomy surgery, and post-extubation after subdural hematoma [48]. Currently, it is not possible to objectively monitor adherence on these devices. It can also be difficult to get funding for home HFNC devices from insurance companies. Finally, of course there are also children who do not tolerate HFNC.

Supplementary Oxygen

Aside from the most common indication of improving oxygenation, supplementary oxygen also has a role in the treatment of central sleep disordered breathing. An elevated central apnea index (CAI) can be due to depressed ventilatory drive, or ventilatory control instability as reflected by raised loop gain. Loop gain describes the innate stability of any negative feedback system, and, in the case of ventilation, reflects the size of the corrective ventilatory response relative to the size of the ventilatory disturbance eliciting the correction. With a high loop gain, a small increase in breathing is more likely to cause a large corrective overshoot, resulting in an apnea. An elevated CAI in otherwise healthy children has been shown to be associated with a raised loop gain compared with controls [49].

Clearly, if the central apneas are due to depressed ventilatory drive, ventilatory support (usually in the form of BiPPV) and treatment of the underlying condition, e.g., neurosurgical intervention for Arnold-Chiari malformation, is required. However, if the predominant cause is secondary to increase in loop gain, oxygen can improve the apneas by reducing chemosensitivity, thus reducing loop gain [50]. In term infants, it has been shown that when newborn (4 days or less), their respiratory response to a sigh was highly stable but sluggish: when aged 4 days to 3–4 months, respiration was potentially more unstable (a small reduction in the damping factor caused prolonged oscillation) while, from 3 to 4 months onward, a more stable, mature response with rapid recovery had developed [51].

Premature infants often have periodic breathing and central apneas, this being attributed to immaturity of their respiratory control with hypoxia being a trigger [52, 53]. When increasing amounts of oxygen (up to 40%) were administered for 10 min in quiet sleep to preterm infants with periodic breathing and central apneas, the number of apneas and periodicity decreased through a decrease in the breath-to-breath variability of minute ventilation [54]. Administration of 0.25 L/min via nasal cannula overnight has subsequently been shown to be associated with an increase in the overall duration and percentage of total sleep time spent in quiet sleep with corresponding decrease in active sleep [55]. Improvement in respiratory stability was also observed with decrease in the number of apneas, amount of periodic breathing, and bradycardia.

Some Prader–Willi patients have central sleep disordered breathing (SDB) resulting in frequent desaturations. Abnormalities in the response to hypoxia and hypercarbia are well recognized in Prader–Willi syndrome due to absent peripheral chemosensitivity [56–58]. Urquhart et al. proposed that a potential mechanism for the central SDB seen in these patients is that a stimulus such as hypoxia or arousal causes a transient increase in ventilatory drive. Due to their blunted response to carbon dioxide, instead of the increased ventilation ceasing once the resultant reduction in $PaCO_2$ is detected by chemoreceptors, the mechanism overshoots and results in a fall in $PaCO_2$ to below the eucapneic level and the crossing of the "apnea threshold" [59, 60]. The subsequent resulting central apnea may in turn result in desaturation or be terminated by an arousal, both of which may further perpetuate this cycle. Supplemental oxygen has been shown to be efficacious in stabilizing the breathing pattern and treating the central SDB in Prader–Willi patients [60, 61].

Recently, sodium leak channel non-selective protein (NALCN) dysfunction has also been reported to be a cause of central sleep disordered breathing, and supplemental nasal cannula oxygen of 0.5–1 L/min significantly stabilized the respiratory breathing pattern and normalized oxygenation [62].

Conclusion

It is clear that respiratory support in the treatment of pediatric sleep disordered breathing is significantly impacting on the outcomes of an increasingly wide range of patients. While the direct impact on the pediatric setting is obvious, this also has implications for the planning of transition and adult care facilities given that increasing numbers of children on respiratory support are surviving into adulthood. CPAP and BiPPV currently remain the mainstays of non-invasive respiratory support but in the quest for personalized medicine, new modes of ventilation, more intelligent ventilators, and novel forms of assistive technology are being developed. There are still major challenges to be overcome, in particular issues with adherence and the training of community teams

and staff in local hospitals who will be faced with increasing numbers of children on these forms of respiratory support when they are admitted for incidental illnesses. Overall, however, the real progress being achieved makes this an exciting era in this field for both health care professionals and, more importantly, their patients.

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Part VII

Disorders of Sleep

Pediatric Insomnia: Etiology, Impact, Assessment, and Treatment

26

Lisa Medalie, Thuan Dang, and Christina L. Casnar

Introduction

The field of pediatric behavioral sleep medicine and related research is developing but is still in its infancy. Behavioral sleep medicine pertains to the role that psychologists play in assessing and treating sleep problems including, but not limited to, clinical interview, assessment, and behavioral treatment. Insomnia is perhaps the most common disorder managed in the field of behavioral sleep medicine. In order to evaluate and manage insomnia, specialists first need pediatricians to refer such patients to their clinic. Unfortunately, insomnia, along with other sleep disorders in children, is commonly underdiagnosed. In a study conducted at the Children's Hospital of Philadelphia, only 3.7% of 150,000 children were diagnosed with sleep difficulties by their primary care practitioners [1]. This is significantly lower than the prevalence rates reported in epidemiology studies. It is unclear whether pediatricians are not asking because they are not typically trained to ask about sleep or due to scarcity of pediatric sleep specialists for patients to see for follow-up.

It is recognized that adequate sleep is an essential component of wellness contributing to the optimization of growth and intellectual and emotional development of a child. Sleep architecture and sleep duration undergo significant changes as a child transitions from the early stages of infancy, progressing through childhood, and then transitioning to adolescence before adulthood. These changes frequently conflict with established schedules of families and schools. The physical and emotional demands of a baby can encourage parent involvement with sleep. While these interactions may initially help get the dyad through the night, the underlying message that parents will help with sleep ultimately disturbs sleep for both the child and parent. This sub-optimal pattern has potential to develop into a chronic problem and diagnostic criteria for insomnia need to be defined. Identifying triggers and perpetuating factors are the foundation of understanding insomnia. This step allows providers and parents to proceed with the necessary behavioral interventions.

The focus of this chapter is to provide an overview of the current literature and viewpoint on pediatric insomnia. The authors will start by explaining what we mean when we use the term "pediatric insomnia." Insomnia refers to having difficulty falling asleep, staying asleep, or waking up early with difficulty falling back asleep. As a result, insomnia sufferers may get too little sleep and experience related distress and dysfunction. In many children, insomnia will manifest as hyperactivity, problems with attention or concentration, mood or academic problems, or fatigue. Insomnia can be characterized as acute or chronic. According to the latest iteration of the International Classification of Sleep Disorders (ICSD-3), diagnostic criteria for chronic insomnia require that the problem occurs at least three times per week, and the sleep disturbance and associated daytime symptoms have been present for at least 3 months [2]. This diagnosis can be made based on self-report or parent report of difficulties with falling asleep or returning to sleep. It should be noted that these reported sleep/wake complaints cannot be explained by inadequate opportunity (i.e., enough time allotted for sleep) or inadequate circumstances (i.e., the environment is safe, comfortable, dark, quiet) for sleep.

In the previous edition of the International Classification of Sleep Disorders (ICSD-2), the term "Behavioral Insomnia of Childhood, Sleep Onset Association Type" described children who learned to fall asleep through established behavioral patterns associated with external conditions. This type of problem is most common in infants and toddlers. One example of this are children who fall asleep being rocked by

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a caretaker and then struggle to return to sleep without the repeated rocking motion. Children who struggled to follow bedtime rules and demonstrated protests or tantrums at bedtime were diagnosed with "Behavioral Insomnia of Childhood, Limit Setting Type." This type of insomnia is most common in pre-school and school aged children. For children who exhibited features of both conditions, "Behavioral Insomnia of Childhood, Combine Type" was the most appropriate diagnosis [3].

While Behavioral Insomnia of Childhood diagnoses were often used to describe sleep challenges in younger children, older children and teenagers often exhibited symptoms more closely resembling adult challenges. According to the International Classification of Sleep Disorders, 2nd Edition, Psychophysiological Insomnia was used to describe patients who experienced a cycle where sleep struggles resulted in a state of physiological, cognitive, and emotional arousal which would then lead to more insomnia [3]. These children and teens are affected by dysfunctional beliefs such as thinking "I will never be able to fall asleep." When assessing for pediatric insomnia, studies have demonstrated that when large groups of providers have diagnosed the same patients, poor diagnostic consistency emerged [4] which prompted the need for consensus documents [5].

In 2014, ICSD-3 was released, changing the approach to diagnosing insomnia. The current classification manual uses "Insomnia Disorder" to describe difficulties falling asleep or returning to sleep in children and adults. The specification "acute insomnia" is utilized for those who present with symptoms less than 3 months and report symptom resolution when triggering stressors are self-limited. The term "chronic insomnia" is utilized for those who report symptoms for at least 3 months. With the revised criteria introduced in ICSD-3, Behavioral Insomnia of Childhood and Psychophysiological Insomnia diagnoses are no longer listed in the manual; however, many providers still utilize the former approaches to explain or describe insomnia and conceptualize cases. This allows the providers to illustrate the struggle faced by patients and their family and helps explain the rationale for behavioral treatment strategies.

Prevalence

Pediatric insomnia is very common with an estimated prevalence of 25–40% in children of ages 4–10 years old. Archbold and colleagues found that insomnia is the most common reported sleep difficulty in pediatric sleep clinics with 41.4% reporting at least one symptom of insomnia in a sample of 1038 children [6]. Owens and colleagues [7] found that insomnia was reported in almost one-third of patients referred for evaluation to a psychiatrist. Bedtime resistance is problematic in 15% of these children with almost 11% associated with psychophysiologic insomnia [8]. In specific age groups, insomnia is estimated to be as high as 36% in pre-school children aged 3–5 years and 20% in school children aged 5–10 years [9]. The prevalence of insomnia in adolescents is estimated to be 11% [10], although estimates as high as 24% have been demonstrated in specific cohorts [11].

Despite the estimated epidemiological prevalence, pediatric insomnia continues to remain an underdiagnosed condition in primary care settings pointing to the need for additional education and support of primary care providers in the diagnosis and treatment of pediatric sleep disorders [12]. Interestingly, there is no difference in gender prior to puberty [13], but the prevalence of insomnia symptoms is highest in girls aged 11–12 years (~30%) [14]. While the prevalence data shows a range, most feel comfortable with summarizing that roughly 20–30% of children struggle with insomnia.

Etiology

There are intrinsic and extrinsic factors that are associated with an increased risk of insomnia in children. Instrinsic factors are risk factors for developing insomnia that are described as inborn features [15]. For example, if a baby is born with a colicky temperament, it can increase intrinsic vulnerability for sleep troubles during the early months and later on in life [16]. Many medical conditions such as atopic dermatitis, gastroesophageal reflux, milk allergies, restless legs, or sleep apnea have been known to interfere with sleep continuity and disrupt sleep architecture. Impacts on the rhythmicity and timing of melatonin secretion patterns as a result of inborn delayed or advanced circadian clock can result in misalignment favoring the occurrence of insomnia. Neurobehavioral conditions that result in developmental delay and psychiatric co-morbidities (e.g., autism, attention deficit hyperactivity disorder, generalized anxiety disorder) can foster dysfunctional or delayed learning of self-soothing. This may result in trouble with sleep onset or sleep maintenance.

In contrast, "extrinsic factors" are defined as environmental aspects or caregiver pattern responses that can promote the occurrence and perpetuation of insomnia in children. An example of such factors is evident in the presence of medical or psychiatric disorders in a caregiver. This can transfer from caregiver to child as behavioral cues that increase the risk of sleep problems. As a result, a caregiver's response to their child during the night is impacted by their own struggles. For example, a mother who is overly anxious may constantly check on her baby frequently at night disrupting her and the baby's sleep and altering the baby's ability to develop self-soothing techniques. The child may become dependent on the mother's presence to initiate or maintain sleep.

Inconsistent parenting styles between caregivers can result in intermittent reinforcement of sleep behaviors and can result in difficulty with developing consistent sleep onset maintenance patterns for children. Various and changing living conditions such as shared or distracting bedroom environments can increase the risk of insomnia in children [17].

Impact

The functional impacts of pediatric sleep disorders on children and families are immense [18, 19]. Children with insomnia have increased rates of psychiatric disorders and symptoms (e.g., anxiety and depression) and are more prone to irritability [20]. They also have secondary attention problems and hyperactivity that can sometimes result in a misdiagnosis of attention deficit hyperactivity disorders (ADHD) [21]. Pediatric sleep problems have been shown to affect academic performance [22]. Children with insomnia report lower quality of life and have higher risks for poor health outcomes [9]. Families also frequently report secondary functional impacts as a result of their child's sleep problems. For example, many caregivers report high levels of distress, worsening of psychological and medical health, and disruptions in their own sleep [23]. Given the scope of these functional impacts on child and family, the accurate diagnosis and implementation of effective interventions are of upmost importance.

Assessment

Identification and accurate diagnosis of pediatric sleep problems are necessary in order to inform treatment planning and recommendations. Misdiagnosis may lead to delayed recovery, increased child and family stress, or, in some cases, a worsening of sleep problems (e.g., stimulant use for attentional problems). It is important to remember that pediatric insomnia often presents differently than in older adolescents and adults with insomnia (e.g., hyperactivity as opposed to lethargy). Therefore, it is important to approach the assessment of pediatric insomnia in a structured and thoughtful manner. Several tools are available to help in the assessment of childhood sleep disorders (e.g., see Owens & Moore [24]). Most clinicians and researchers agree that there are several important steps necessary to ensure accurate assessment, which include conducting a thorough clinical interview, collecting sleep diaries, assessing psychiatric factors or comorbidities, and utilizing objects measures for collecting additional sleep data.

Assessment and diagnosis of pediatric insomnia start with a comprehensive clinical interview with a focus on sleep, as well as developmental, medical, and psychiatric histories [25]. Generally, when assessing for pediatric insomnia, the clinician should evaluate bedtime routines, sleep environment, sleep/wake schedule, difficulties initiating or maintaining sleep, abnormal movements/behaviors during sleep, and daytime impact (e.g., sleepiness, irritability, hyperactivity, and inattention). The interview should also include details about duration, frequency, and variability of sleep difficulties. Descriptions of interventions, including medications, and strategies attempted in the past will be helpful in informing treatment planning.

Completion of sleep diaries is also a valuable tool for aiding in the diagnosis and management of pediatric insomnia. These diaries can be completed 2 weeks prior to or after the initial evaluation and should include parents' estimate on their child's bedtime, time of sleep onset, awakenings, rise time, naps, perceived quality of sleep, and daytime alertness/sleepiness. From this information, the clinician can total the child's weekly sleep onset latency, wake after sleep onset, time in bed, total sleep time, and sleep efficiency. This data will inform targets for intervention and provide families with concrete data to track progress throughout treatment.

Subjective measures are also frequently used to assess sleep problems and concurrent psychiatric symptoms, given the high frequency of psychiatric comorbidities in pediatric insomnia [26]. Commonly used measures described in the literature include Behavior Assessment System for Children (BASC), Pediatric Symptom Checklist (PSC), Clinical Attention Problem Scale (CAPS), Children's Sleep Habits Questionnaire, and Pediatric Insomnia Sleep Index [27–29]. Subjective measures are helpful in that they can provide information about psychological factors that may be contributing to or a result of sleep problems and thus better inform treatment approach or help predict possible treatment barriers.

The use of objective tools to monitor sleep patterns is now much more common given advances in technology. A frequently used tool to assess for pediatric insomnia is the use of actigraphy. Actigraphy involves wearing a wristwatch-like device to monitor movement (via accelerometers) throughout the day and night [30–33]. These devices are typically worn for approximately 2 weeks, after which data can be downloaded and processed through validated algorithms to generate a summary of sleep and wake patterns. Similar to sleep diaries, actigraphy data can be presented visually to families to characterize sleep patterns and track response to intervention. One study comparing actigraphy to sleep diaries found that while sleep diaries are helpful in providing descriptions of symptoms of insomnia, actigraphy was more accurate in estimating sleep onset latency and total sleep time when compared to parent report [33]. Actigraphy is often preferred over more invasive objective tools (e.g., polysomnography) because it has greater external validity due to

its ability to capture multiple days of data in the natural home environment.

Typically, the use of overnight polysomnography (PSG) is not indicated for the assessment of pediatric insomnia; however, it is useful in other pediatric sleep disorders such as sleep-related breathing disorders, periodic limb movement disorder, and narcolepsy [34]. PSG typically involves a full night video recording of several physiological markers, including electroencephalography (EEG), eye and limb movements, respiratory function, and electrocardiogram (EKG), that is conducted in a sleep laboratory. Polysomnography can also be expanded to include an extensive EEG when there is suspected sleep-related epilepsy or atypical or potentially dangerous parasomnias. It can also be expanded to include a multiple sleep latency test (MSLT) when there is a suspicion of narcolepsy [35]. If a clinician has any concerns about the possibility of any of the sleep disorders described above, PSG is then warranted.

Treatment

The first-line intervention recommended for pediatric insomnia is behavioral treatment, such as Cognitive Behavioral Treatment for Insomnia (CBT-I) [36, 37]. CBT-I is an evidence-based intervention that utilizes several well-established behavioral techniques to improve sleep onset latency and sleep efficiency [38–46]. Techniques utilized for young and school-aged children include establishing consistent bedtime routines, standard or gradual extinction, and positive reinforcement [47]. Older children and adolescents often benefit from behavioral techniques that are similar to techniques used in adults, such as good sleep hygiene, stimulus control, sleep restriction, relaxation strategies, and cognitive-behavioral strategies to reduce anxiety [48].

For young and school-aged children, establishing a consistent bedtime routine is important for many sleep disorders, especially pediatric insomnia related to bedtime resistance and/or prolonged sleep onset. It is recommended that bedtimes be set to ensure a developmentally appropriate amount of sleep and coincide with the child's natural sleep onset time. The bedtime routine should be initiated approximately 20 to 45 minutes before the established bedtime. During this time, several soothing activities, such as taking a bath and reading a book, should be completed in the same way each night. This technique will help create sleep associations that will help prepare the child for sleep [49].

Standard or gradual extinction protocols are often helpful for children having difficulties initiating sleep independently, without the presence or assistance of their caregiver (e.g., sleep onset association insomnia). Standard extinction involves putting a child to sleep, leaving the room, and not returning until a predetermined time in the morning. During this time, caregivers must ignore all crying, protests, and tantrums. While this approach has been found to be highly successful, it is often very difficult for families to implement successfully. Gradual extinction involves weaning the child from dependence by slowly removing the presence of caregivers over time (e.g., moving further from the child each night, progressively waiting longer periods of time between checking on child). Gradual extinction has also been shown to be highly effective and more tolerable for families to implement.

Positive reinforcement strategies, such as behavior charts, are often helpful for many children. These techniques including using positive reinforcement (e.g., sticker chart and reward schedule) after the completion of a targeted goal (e.g., sleeping in own bed and only leaving bedroom once a night). Gradually, more challenging goals should be developed and implemented to help shape the child's sleep behaviors. In addition to positive reinforcement schedules, families may need to utilize other behavior techniques, such as active ignoring of undesired behaviors (e.g., crying, tantrums, etc.), to help reduce the frequency of negative sleep behaviors [50].

As noted above, older children and adolescents benefit from similar techniques to those used in treating adults with insomnia. Education about the principles of good sleep hygiene, including keeping a regular sleep-wake cycle and avoiding electronic devices before bed, is usually the first step in addressing sleep difficulties in this age group. This step alone can often improve child and adolescent sleep and is often fairly easy for families to implement. Stimulus control (e.g., only using the bed for sleep, leave the bed when can't sleep, and read a book in chair instead) and sleep restriction (e.g., limiting the time in bed to the actual sleep time) are also useful strategies to better improve sleep associations and sleep behaviors. Teaching relaxation techniques (e.g., deep breathing, progressive muscle relaxation, and guided visualization) and cognitive-behavioral strategies (e.g., worry-time and cognitive restructuring) can also help reduce bedtime stress, as well as sleep-related and non-sleep-related anxieties [22, 51–53].

Currently, there are no pharmacological interventions approved by the US Food and Drug Administration (FDA) for the treatment of pediatric insomnia; however, melatonin is commonly used in the treatment of both adult and pediatric sleep difficulties [54–58]. Melatonin is a natural occurring hormone that helps regulate sleep-wake cycles. The use of synthetic melatonin has been shown to be effective in combination with behavioral interventions, especially for children with other medical, psychiatric, and/or neurodevelopmental disorders, as these children often experience more severe and/or chronic sleep problems than typically developing children [59–61].

Future Directions

As outlined in this chapter, pediatric insomnia is a highly occurring condition that impacts a child's attention and academic, emotional, and behavioral functioning. Pediatric insomnia also has familial impact, as many caregivers of children with insomnia report significant levels of distress and the disruption of their own sleep cycles. Given the significance of these difficulties for both the child and family, more research is needed to address gaps in the current understanding and treatment of pediatric insomnia.

Many children with sleep problems present to clinic at the behest of their caregiver and have little motivation for change. Additionally, many parents are suffering from their own sleep difficulties and have limited capabilities to successfully track and implement the often-difficult techniques and strategies recommended in the treatment of pediatric insomnia (e.g., daily sleep diaries, standard/gradual extinction, and removing electronics from the bedroom at bedtime). Currently, there is limited research examining family barriers to treatment. Future research in this area would be beneficial in that it may help speed the treatment process, reduce the number of clinic visits necessary, and increase overall family satisfaction. Research investigating the effectiveness of internet-based treatments and telehealth for pediatric sleep disorders may also help reduce family burden and help ensure the assessment of evidence-based interventions for families with difficulties accessing quality care.

Finally, while no medication has been approved by the FDA for the treatment of pediatric insomnia, a recent study found that as many as 81% of pediatric psychiatry visits related to sleep problems resulted in the prescription of an off-label medication [46]. This is particularly alarming, given the strong evidence for the efficacy of interventions such as CBT-I in treating pediatric insomnia. Behavioral interventions present very low risk to children; however, many medications prescribed for the treatment of sleep problems carry high medical and/or psychiatric risks. Research assessing the use of medication in pediatric insomnia and long-term outcomes is necessary to better understand the risks (e.g., negative side effects) and benefits in the use of medication in pediatric sleep disorders.

Summary

Insomnia is a highly prevalent problem in the pediatric population. Intrinsic and extrinsic contributions must be fully investigated to best understand the unique presentation of each patient. There have been significant advances in the assessment of pediatric insomnia, as well as other childhood sleep disorders, with the use of subjective and objective measurement tools. Behavioral interventions designed for young children through adolescents have demonstrated great efficacy and effectiveness in treating pediatric insomnia. However, future research is still needed to help better understand the family barriers to treatment, explore the use of technology to further expand intervention scope, and investigate the long-term risks and benefits of pharmacological interventions in pediatric insomnia.

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27 Apnea of Infancy, Apparent Life-Threatening Events, and Sudden Unexplained Death in Infancy

Dawn E. Elder and Barbara C. Galland

Apnea of Infancy

Definition

The American Academy of Pediatrics defines apnea of infancy as "an unexplained episode of cessation of breathing for 20 seconds or longer, or a shorter respiratory pause associated with bradycardia, cyanosis, pallor, and/or marked hypotonia" [1]. There is no qualification included regarding the degree of bradycardia or cyanosis to be concerned about. Also, there is no evidence to be found in the literature for the 20-second length definition [2]. For infants in the first year of life, the American Academy of Sleep Medicine guidelines recommend that all types of apnea be defined using a two missed breath definition, but for central apnea, an arousal or defined change in oxygen saturation and heart rate are also required to formally score and count the apnea [3].

Physiology of Breathing in Early Infancy

An understanding of normal breathing patterns in newborn term infants is important before considering the pathophysiology. In the first few months of life, two main sleep states are recognized in infants: active sleep (AS), the equivalent of rapid eye movement (REM) sleep, and quiet sleep (QS), the equivalent of non-REM sleep [4]. As with older children and adults, breathing tends to be regular in QS and more irregular in AS. Apneic pauses are more common in REM than non-REM sleep. Sometimes this irregularity can be noticed by infant caregivers and cause concern. The presence of sighs may also be noted. Sighs are more frequent in the newborn than the adult and can be followed by a respiratory pause which may occur immediately after the sigh or after one to three normal breaths [5].

Another normal physiological breathing pattern that may be noted by caregivers is periodic breathing. Periodic breathing (PB) is characterized by brief pauses in breathing, alternating with periods of regular respiration also of short duration, and is defined as ≥3 cycles of respiratory pauses ≥3 seconds in length with the duration of regular respiration between each respiratory pause being ≤20 seconds [3]. Periodic breathing is seen more frequently in preterm than term infants, and the periodic cycle duration decreases from birth to 6 months of age in both groups [6]. Variation in oxygen desaturation occurs with the respiratory pauses of PB and can be more marked in hypoxic infants [6, 7].

Arousal from sleep is an important contributor to the maintenance of continuous respiration. Term and preterm infants frequently encounter situations where the airway is compromised either internally by secretions or airway collapse or externally by obstruction of the nose or mouth. In these situations, arousal enables the infant to clear the airway and recommence regular respiration [8]. Thresholds to arousal from sleep are greater in QS than AS throughout early life in healthy term infants [9].

Pathophysiology

The prevalence of habitual snoring (snoring ≥3 nights/week) in infants varies across studies and is estimated to be 3.0–6.6% [10–13] in the first year of life, with some studies reporting it as high as 9–14.5% [14, 15]. The variation may be explained by the heterogeneity of the studies, variation in the definition of habitual snoring, presence of colds, and protective effects of breastfeeding [13]. Data from a large (n = 12,477) epidemiological study, the Avon Longitudinal Study of Parents and Children (ALSPAC), indicate that 19% of parents note habitual apneas in their children at 6 months of age [14]. It could not be determined whether those were central or obstructive events,

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but rates for habitual mouth breathing and snoring were similar, suggesting that this likely represented a degree of sleep-disordered breathing. These symptoms appeared to resolve to some degree by 18 months of age and increased in prevalence again after the age of 2. Cluster analysis of these data indicated that in the total group followed to 81 months of age (6.75 years), 50% remained asymptomatic throughout this time period, and the "late snore and mouth breathing" cluster (20%) remained asymptomatic until 4 years of age [16]. The "early snores" (10%) and "early apnea" clusters (10%) had peak symptoms at 6 and 18 months of age, respectively. The remaining "all SDB after infancy" cluster (10%) had peak symptoms from 30–42 months that remained elevated.

Respiration can be interrupted in a number of ways in infancy through the disturbance of physiological processes. Congenital anomalies [17] or upper body positions can result in, or predispose to, upper airway obstruction, e.g., an immature infant with head unsupported in a car seat [18]. In healthy newborn infants, passive neck flexion can diminish airflow or functionally occlude the upper airway for periods ranging from 3 to 18 seconds [19]. Infants are also vulnerable to external obstruction of the airway, and factors that affect arousal may affect an infant's ability to respond to an external obstruction. Exposure to maternal smoking is associated with decreased arousability to hypoxia in QS in infants at 5–6 months of age despite an intact ventilatory response [20]. Obstructive apnea is also more frequently found in cigarette-exposed healthy infants than in controls [21]. Brief obstructive events have also been reported as being more frequent in overweight infants compared with controls [22]. Infants with significant viral and bacterial illness can present with apnea. This classically can occur with the initial presentation of an infant with bronchiolitis and is most usual in infants less than 3 months of age [23].

McNamara and Sullivan described polysomnography data for 11 infants with symptomatic apnea who were studied at monthly intervals to 6 months and then at 9 and 12 months of age [24]. Infants were included in the study if they had either at least 30 apneic events per hour or 5 obstructive events per hour. All pauses of at least two respiratory cycle lengths were included. The apnea index (number of events per hour) decreased over time in both REM and NREM sleep. Apnea was most common at 2 months of age, and associated decreases in oxygen saturation were also more common at this age. Both obstructive and central apnea showed resolution in the first year of life.

Diagnostic Approaches: History and Examination

Infants may present with an initial severe apneic event. If that is the case, then a careful history needs to be taken about the event itself. The history should particularly address whether the infant airway may have been obstructed by an external barrier such as if the infant were in an unsafe sleeping situation. An acute presentation with apnea may be the first sign of sepsis, so other symptoms of sepsis or viral infection should be considered. For other infants, the concerns may relate to a number of issues about the infant's breathing that the caregivers have been concerned about over time. Enquiry should be made about snoring and sweating and frequent wakening. Preterm infants have an increased risk of obstructive sleep apnea (OSA), so a perinatal history should be obtained. History should be followed by a complete examination including a neurological examination assessing tone and development. A priority should be to consider whether the infant is acutely unwell. As with the older child, the examination should consider face shape, the nasal airway, and the oral airway. In the newborn or younger infant, congenital anomalies should be ruled out.

Differential Diagnoses: Causes

Congenital anomalies apparent in the newborn period are usually associated with obstructive rather than central apnea. These can include syndromes associated with face shape such as Treacher Collins and Goldenhar syndromes and syndromes associated with large tongue size such as Beckwith-Wiedemann and Down syndromes. Laryngomalacia can also present in the newborn and may be associated with obstruction demonstrable on polysomnography. Pierre Robin syndrome includes micrognathia and a cleft palate, but micrognathia may also occur in isolation and be associated with increased respiratory effort and failure to thrive in infants sleeping supine. Infants with syndromes associated with hypotonia, such as Prader-Willi syndrome, may also present because of caregiver concern about their breathing. Failure to extubate an otherwise healthy term infant who presents with severe apnea may be an indication of congenital hypoventilation syndrome. This disorder is discussed in Chap. 53. In the first few months of life, a new presentation of apnea may be associated with both viral infections, including bronchiolitis, and bacterial infections which are either systemic or affecting the central nervous system.

As the first year of life continues, infants may present with sleep-disordered breathing in a manner similar to older children with snoring, sweating, and waking at night. In a report of a single-center 7-year experience in the management of OSA in 97 infants, snoring was an indication for referral in 53% and concern about nocturnal desaturations, an indication in 24% [25]. Other reasons included previous abnormal pneumogram, suspected apparent life-threatening event, screening for sleep-disordered breathing, hypoventilation, diaphragmatic flutter, failed car seat testing, suspected apnea of prematurity, and as a routine test before growth hormone treatment. Of these infants 41% had mild OSA, 20%

had moderate OSA, and 39% had severe OSA based on the usual definitions for apnea hypopnea index (AHI) of 1–5/hr, 5–10/hr, and >10/hr, respectively. Risk factors noted were hypotonia (53%), gastroesophageal reflux (30%), laryngomalacia 24%, Down syndrome 19%, craniofacial abnormality 16.5%, adenotonsillar hypertrophy 3%, epilepsy 5%, and neuromuscular disease 2%. As well as the infants with Down syndrome, genetic abnormalities were found in a further 34% of the patients.

Management

Polysomnography is now the investigation of choice for assessing apnea of infancy but may not be readily available in all areas. Also, the interpretation of these studies remains hampered by the paucity of normal data in this age group. Snoring in infants has not always been treated aggressively in the past, and it is not unusual for parents, who present to a pediatric sleep clinic with their child at an older age, to describe that the snoring has been present since birth. It has perhaps been considered that snoring in young infants is benign, but this is not clearly so. Piteo et al. [26] demonstrated increased risk of neurocognitive deficits in 16 infants who commenced snoring soon after birth and were snoring for 3 or more nights a week, when they were compared with 88 healthy non-snoring infants. Also, the increased work of breathing associated with upper airway obstruction in young infants can lead to failure to thrive. There are therefore cogent reasons to offer treatment for these infants. Otolaryngologists may be cautious about undertaking surgery in these young infants and require definitive evidence of obstruction on polysomnography before proceeding. Shatz reported outcomes for 24 infants who had adenoidectomy for documented obstructive sleep apnea [27]. There were no complications related to the surgery, and all infants had resolution of symptoms and failure to thrive resolved. Increasingly nasal CPAP is being successfully used to treat young infants with obstruction, although there are still limitations in mask suitability in this age group. This is a reasonable first step. For infants with severe retrognathia such as in Pierre Robin syndrome, mandible distraction is another option [28].

As with older children, the gold standard for documenting the severity of the sleep-disordered breathing is overnight polysomnography. At times, these studies can be challenging as young infants are less likely to tolerate nasal prongs and as they get older are more able to remove them. Oximetry can also provide useful information in the older infant if positive and consistent with REM-related OSA. However, there are still no clear guidelines for the interpretation of oximetry for infants in the first few months of life.

Apparent Life-Threatening Events (ALTE)

Definition

For many years, it has been recognized that infants in the first year of life may present with respiratory events concerning to their parents. In the 1970s when research into the reasons for sudden infant death syndrome (SIDS) was in its own infancy, these events were referred to as "near miss SIDS" events as it was thought they represented an aborted sudden unexplained infant death [29]. In 1986 the term "Apparent Life Threatening Event" (ALTE) was proposed to describe these events [30]. Although this term was an improvement, it has been clear over time that these events are most usually not "life-threatening." Therefore in 2016, the American Academy of Pediatrics recommended a change to the term brief resolved unexplained event (BRUE). A BRUE is defined as "an event occurring in an infant younger than 1 year when the observer reports a sudden, brief, now resolved episode of ≥1 of the following: (1) cyanosis or pallor; (2) absent, decreased, or irregular breathing; (3) marked change in tone (hyper- or hypotonia); and (4) altered level of responsiveness" [31].

Pathophysiology

It is now recognized that the causes of these events are multifactorial, and the pathophysiology of the event therefore depends on the specific cause. At one end of the spectrum, parents may be concerned about events that represent normal physiology. Examples would be the infant who has post-sigh apnea, or the infant who looks very pale during non-REM sleep with shallow and periodic breathing. A parent may observe these events, be concerned about the infant, and pick them up and then find the infant hard to arouse because of the characteristics of the sleep state at the time of observation. The term BRUE particularly applies to these sorts of events. At the other end of the spectrum are presentations that may indeed be potentially life-threatening such as inflicted head injury or infection or cardiac arrhythmias.

There have now been a number of reports regarding presentations considered life-threatening in infants in the first few days of life. Initially these were reported as deaths or very severe events in infants thought to be healthy and at low risk [32, 33]. In a number of these cases, an identifiable serious cause such as sepsis was found. For other infants, the event occurred in association with feeding. Espagne et al. in 2004 described two newborns who died unexpectedly in the delivery room [34]. They were sleeping prone on their mother. A number of reports have now been published describing apparent life-threatening events in infants in the prone position hav-

ing skin-to-skin contact with their mother in the delivery room or during breast-feeding on the postnatal ward [35–39]. In response, in 2016 the Academy of Pediatrics documented clinical practices intended to facilitate safe positioning of the infant during skin-to-skin contact [40].

Diagnostic Approaches: History and Examination

The critical component of assessment after an infant presents with a BRUE is a careful history to differentiate between a likely physiological event and an event of clinical significance that could potentially be life-threatening such as the acute onset of any infection. For example, apnea with cyanosis may be the initial presentation of an infant with bronchiolitis. In this case, symptoms are not likely to resolve but to persist with increasing evidence of respiratory distress. The Academy of Pediatrics Clinical Practice Guideline provides a comprehensive list of historical features to be considered [31]. In the older infant, it is important to understand exactly where the infant was at the time of the event as infant holding practices have been associated with ALTE presentations [41]. A precise understanding of the event and where and how it happened is critical to the diagnosis.

The examination needs to consider the clinical status of the infant at the time of assessment. If resuscitation is required, this should be the priority. When the infant is stable, a thorough examination needs to be undertaken. Documentation of acid-base balance on arrival to the emergency room can provide evidence of the severity of the event if significant resuscitation has been required, and the infant has not yet returned to their pre-event clinical state. There should be a low threshold for assessing sepsis, especially in the younger infant.

Differential Diagnoses: Causes

If the history, including careful review of the circumstances the infant was found in, and examination do not provide an explanation for the event, then a physiological variation in breathing pattern is the most likely explanation, and the application of the term BRUE would be appropriate. If the infant has not returned fully to normal, then other reasons for the event need to be considered. Particular diagnoses to be considered are infection, cardiac arrhythmias, and child abuse.

Management

The management depends on the information gathered from the history and examination. If serious illness has been ruled out, then reassurance can be given to the caregiver. The clinician needs to be aware that the experience of these events for parents can be quite frightening, so reassurance needs to be given carefully with a full explanation of the likely nature of the event. Enquiry should be made about a family history of sudden infant death or friends and acquaintances of the parents who may have experienced the death of an infant as this will affect their ability to be reassured that the event was not potentially life-threatening. If no concerning features are identified on history and examination, then infants are considered to be low risk, and any diagnostic procedures or tests are unlikely to be helpful. Cardiac testing is positive in less than 1% of patients [42]. If the initial clinical assessment reveals concerning historical features or examination findings, then the infant should be investigated in line with the most likely differential diagnosis appropriate to those findings. For example, if an infant was not fully alert on assessment and there was bruising noted on the trunk, then it would be appropriate to consider abusive head trauma as a possible reason for the presentation and investigate accordingly [43].

Infants considered at low risk of a recurrent event are those aged >60 days, infants with a gestational age ≥ 32 weeks and postconceptional age ≥ 45 weeks, infants experiencing their first BRUE, events lasting <1 minute, events with no CPR required, events with no concerning historical features, and events with no concerning examination findings [31]. Young term infants and premature infants are more likely to have a recurrent BRUE presentation.

Sudden Unexplained Death in Infancy (SUDI)

Although sudden death in infancy has been the subject of much research over the last three to four decades, it has been reported since the earliest times. The Bible documents a report of an infant being overlain and found dead ("And this woman's son died in the night, because she lay on him." 1 Kings 3:19 English Standard version).

With the increased use of the prone sleep position for preterm infants as neonatal intensive care developed in the 1960s and 1970s, this sleep position became increasingly used also for term infants, as infants were thought to sleep better in this position. The large epidemiological studies set up in the 1980s to try and establish the reasons for the increasing prevalence of sudden infant death syndrome (SIDS) found a strong association between use of the prone sleep position and the risk of SIDS [44–46]. Consequent research has provided some insights into the mechanisms by which the prone sleep position might contribute to the sudden and unexpected death of an infant. Numbers of infant deaths have dropped dramatically since the introduction of "Back to Sleep" public awareness campaigns internationally [47–49]. In the current era, the focus is on "Safe to Sleep." However, sudden infant death is still the largest

category of post-neonatal deaths, and the burden now lies with the most disadvantaged and socially vulnerable families [50].

Definition

The term sudden infant death syndrome (SIDS) was initially coined by Beckwith in 1969 [51] and then updated in 1989 [52] as follows: "the sudden death of an infant less than one year of age which remains unexplained after a thorough case assessment, including performance of a complete autopsy, investigation of the death scene, and review of the clinical history." In more recent years, the term sudden unexplained death in infancy (SUDI) has been used and will be used from here onward. This is a global term as depicted in Fig. 27.1 and includes all deaths of an infant not anticipated as a significant possibility in 24 hours preceding death. All such deaths are referred to local coronial services for investigation. One of the main reasons for autopsy is to rule out an organic diagnosis that would fully explain the sudden death. Possible diagnoses would be overwhelming infection, inflicted head injury, or previously unrecognized congenital anomaly [53]. The death would then be classified as "explained SUDI." As well as the autopsy, investigation of such deaths should include a death scene examination and a clinical history of the infant up to the time that they were found deceased as well as a full past medical, family, and social history. This information might provide further information to enable the cause of death to be classified as accidental suffocation. Information that would confirm this diagnosis would be a clear history that the infant was found wedged between an adult bed and a wall with the chest compressed or a history of the infant being observed by a reliable witness to have been found completely overlain by a co-sleeping adult or older sibling. As in the SUDI case illustration at the end of this chapter, for some deaths, there may be circumstantial evidence that accidental asphyxia was the cause of the death. In the case discussed, a reasonable diagnostic conclusion would be that the cause of death is possible accidental asphyxia in an unsafe sleeping position. If the death scene examination, clinical history, and autopsy are all non-contributory, then a diagnostic label of sudden infant death syndrome would be appropriate.

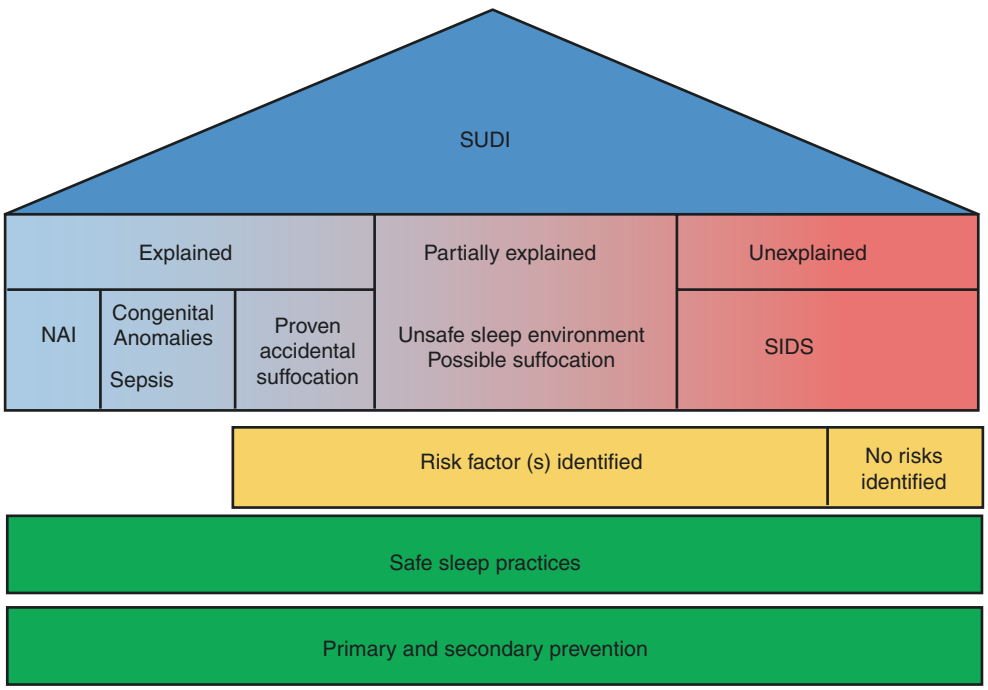

Fig. 27.1 Sudden unexpected death in infancy classification. Explained deaths are sudden deaths that are explained after investigation and include cases that are clearly attributable to factors which on their own alone would be enough to cause death, e.g., accidental suffocation, asphyxia, entrapment, infection, ingestions, metabolic diseases, arrhythmia-associated cardiac channelopathies, and non-accidental injury (NIA). Partially explained deaths (also called unascertained) are cases where a pathologist or coroner is unclear to what extent the deaths are explained, often because they do not have complete information about the circumstances of death in front of them. Unexplained sudden deaths remain unexplained after a thorough case investigation, including death scene investigation, autopsy, and review of the clinical history. SUDI risk factors are usually identified in the explained deaths involving accidental suffocation, partially explained deaths and unexplained deaths, but there will always be a minority who dies suddenly for whom no risk factors or reason can be ascribed. SUDI preventive measures and safe sleep practices apply to all infants to reduce risks of sudden death, regardless of SUDI risk

Pathophysiology

Research into potential biological mechanisms is severely compromised by the absence of a "disease state" and "natural history of disease." However, the epidemiologic approaches have been rigorous with consistent findings from many studies across the globe integrated into highly effective risk reduction strategies centered on "safe sleep" for all infants. The challenge remains to successfully integrate findings from the many other disciplines involved in SUDI research to "discover" a "cause," although all evidence to date points to a myriad of factors involved [54], and therefore a single "cause" is likely to be elusive.

The infant can die at any time of the day or night, but deaths occur most frequently at night, quietly during sleep, and mostly unobserved. There are no consistent warning signs to alert the caregiver to an impending death, as per the SUDI definition. The baby may have been a little unsettled or might have had a slight cold or tummy upset, or there might have been a change in circumstances as to where the baby slept on the night they died. The triple risk model, first described in 1972 by Wedgwood [55] and revised in 1994 by Filiano & Kinney [56], presents a hypothetical working model to help explain why SUDI may occur. The model suggests that an infant may succumb if three critical factors occur at the same point in time: (1) the infant has an intrinsic vulnerability that for the most part is not modifiable, e.g., male gender, prematurity, indigenous ethnicity, poverty, adverse prenatal exposures (e.g., maternal smoking, alcohol, illicit drug use, inadequate nutrition), and genetic polymorphisms, (2) an external stress is involved (e.g., the infant is in a bed with an adult, sleeping face down into soft bedding, an infection is present), and (3) a critical window in development where the vulnerable infant is most at risk of a fatal event brought on by an external stressor (e.g., young infants can be more at risk because of their inability to arouse or have the motor ability turn their head away from a potentially suffocating environment because of their postnatal risk of small size and physical or developmental immaturity).

Still robust in 2019, the model has rarely been challenged and has survived the many shifts in the epidemiological landscape of SUDI affecting the critical window of vulnerability (the mortality still peaks from the 2nd to 4th month of life [57], but there has been a shift in the median with more infants dying under the age of 2 months), change in seasonality (decreased from one historically observed more frequently in the colder months [57, 58]), predominance of risk factors (sleep position falling dramatically, while bed-sharing has gained more prominence [59, 60]), and an increase in the proportion of SIDS associated with poverty [50, 53, 60], alcohol consumption [61], and preterm birth [59, 60, 62]. Although SUDI is believed to occur as a result of the intersection of all three components of the triple risk model, reducing the risk from one factor may decrease the overall risk of SUDI. The "Back to Sleep" campaign has focused on this sleep position as the key factor and yet has resulted in a significant decrease in SUDI wherever it has been implemented.

For SUDI cases, where no specific cause is identified, causes may be varied, and several hypotheses overlap. Autopsy findings do exist but are usually inconclusive as to the mechanism of death. Multiple neural mechanisms may contribute to the final event, but these are still speculative. For example, subtle asphyxiation or airway obstruction may happen when a baby slips under adult bedding or finds him/herself face down into soft bedding, or any position that could squeeze the nostrils together or block the mouth compromising breathing can be hazardous. This includes anything in a baby's sleep space that can move into their breathing space, e.g., the domestic cat. Neural processes that could overcome this and restore airway patency or cardiovascular control via reflexive compensation may be impaired in infants that eventually succumb to SUDI. The evidence from early studies in SIDS cases ranges from subtle physiological signs related to impaired autonomic control [63, 64] to autopsy findings of altered neurotransmitter systems including the serotonergic system that plays an extensive homeostatic role in cardiovascular and respiratory control and thermoregulation [65, 66]. Processes may be altered by the vulnerability of the infant due to age or prematurity, or a genetic predisposition [67], or the infant may have a seemingly innocuous viral illness [68]. The fatal event may occur in a sleep state which can suppress muscle tone (REM sleep) [64] essential to restore airway patency.

Diagnostic Approaches

To be able to classify SUDI correctly, a careful clinical history needs to be undertaken, as well as a death scene investigation and an autopsy. The history needs to address the past medical history of the infant and the clinical history in the days before the death. Also, the history needs to document risk factors such as parental smoking and usual sleep practices. The death scene needs to consider carefully where the infant was found including detailed documentation of the sleep environment. The autopsy needs to be undertaken by a pathologist who has appropriate expertise and experience for this age group of children and who also understands the forensic role of the autopsy in the context of sudden infant death.

Differential Diagnosis

As discussed above, two important priorities are to rule our organic disease and inflicted injury. Then the issue is to consider whether there is evidence to suggest that accidental suffocation has definitely occurred or whether it is possible that this may have occurred. The diagram (Fig. 27.1) summarizes

the main differential diagnostic areas that need to be considered within the various levels of classification of SUDI.

Management

The immediate management issue is to manage the acute presentation of the death. Mostly this occurs in the community and police are notified, and the case is referred to the coroner or medical examiner depending on local practices. In jurisdictions where a medical practitioner is not required to certify death, a clinician may not be involved at this stage. Some hospital protocols recommend that a pediatrician or health worker have some involvement with the family at this stage. It is useful for a pediatrician to be able to meet with a family to discuss the results of the autopsy when they are available, but sometimes it can be difficult to get families to engage with a clinician they have not met previously.

Families may seek advice after the birth of a subsequent sibling. They should be made well aware of the primary prevention factors and may need some support with follow-up until the infant has passed the age of the deceased sibling. There is no evidence that cardiorespiratory monitoring prevents sudden infant death, but parents sometimes buy respiratory monitors for reassurance as well as using intercom systems for remote noise monitoring.

Primary Prevention

Those at greatest risk of SUDI are well described, but no objective marker exists for identifying the infant that may eventually succumb. Therefore, the key to SUDI "cure" lies in "prevention," capitalizing on the known risk factors that are modifiable, with a key emphasis on *safety in sleep*, i.e., a safe sleep environment for every sleep. Efforts at prevention must begin early in pregnancy in recognition of the heightened risk of maternal smoking in pregnancy.

SUDI prevention messages for parents can vary slightly by country, but consistent key messages are:

- Making sure baby is on their **back** for *every* sleep
- Keeping baby **smoke-free** from the start
- **No bed-sharing** or no bed-sharing if mother smoked during pregnancy, or baby is less than 1 month of age
- **Breastfeeding** baby
- **Immunizing** baby on time

Creating a Safe Sleep Environment

- *Face up and clear at all times*. Ensure the baby's head never becomes covered. Some SUDI infants have been discovered with the bedclothes covering the face and head. Using infant sleeping bags or placing the feet of the infant at the foot of the cot under a tucked cotton sheet reduces the possibility of head covering.
- *Use a firm sleep surface.* A firm cot/bassinet mattress, covered by a fitted sheet, is the recommended sleeping surface to reduce the risk of SUDI and accidental suffocation. Mattresses should be firm and maintain their shape even when the fitted sheet is used, so no gaps between the mattress and the side of the cot/bassinette occur.
- *Other infant bed types*. Baby boxes and clip-on cots have been developed to provide a separate sleep space for infants sleeping close to parents [69, 70], and for some communities where bed-sharing is common practice and considered culturally important, specialized infant safe sleep devices have been developed similar to the baby box. For example, in New Zealand, the wahakura (woven bassinet) and Pēpi-Pod on-bed baby beds [71, 72] are considered an acceptable alternative to having the baby in the parental bed [73].
- *Keep soft objects and loose bedding out of the cot* to reduce the risk of SUDI, suffocation, entrapment, and strangulation. Pillows or cushions should not be used in the cot, and other soft materials or objects such as pillows, quilts, duvets, or sheepskins, even if covered by a sheet, should not be placed under a sleeping infant.
- *Sitting devices, such as car safety seats, strollers, swings, infant carriers, and infant slings, are not recommended for routine sleep.* Infants who are younger than 4 months of age are particularly at risk because they can get into positions that create risk of suffocation or airway obstruction.
- *Tummy time.* Supervised, awake tummy time is recommended on a daily basis, beginning as early as possible, to promote motor development, facilitate development of the upper body muscles, and minimize the risk of positional plagiocephaly.
- *Keep the baby in the same room for the first 6 months.* SUDI mostly happens unobserved; therefore sleeping infants in the parental bedroom in the first 6 months of life reduces the risk.
- *Prevent overheating.* Dressing the infant in too many layers, using duvets/doonas and thick quilts, and having the sleeping environment too hot are all associated with an increased risk of SUDI. It is especially important that outdoor hats are not used indoors for sleeping; the inability of young infants to easily control their own body temperature means that the head is an important area for heat regulation/dissipation.

Illustrative Cases

Apnea of Infancy: Case 1

A male and a female twin born at 36 weeks gestation were followed up in the pediatric clinic. The male twin had hypoglycemia in the neonatal period because of intrauterine

growth restriction. It was noted at the first follow-up that he had an occasional blocked nose. At 3 months of age, it was noted that he was wakeful at night, but his parents thought that was due to wind. His blocked nose was less of a problem. At 6 months of age, his parents reported recurrent nasal snuffliness that still interfered with feeding at times. He demonstrated good catch-up growth. At 8 months of age, his parents reported nasal snuffliness by day and night. He was waking a lot at night, whereas his twin was now sleeping through the night. His parents thought he was waking with a cough. On examination, nasal snuffliness was noted, and some increased respiratory effort was noted. The tonsils were large in size. An overnight sleep study was undertaken which showed an AHI of 36.6 events/hr. This was initially treated with CPAP, but although this was established in the hospital, it was difficult for the parents to manage at home. An adenotonsillectomy was carried out at 9 months of age without complication. He was seen for follow-up at 10 months of age and was found to be eating well including eating more solid foods than he had been able to tolerate previously. His parents reported he was not as "grumpy" and was improving in his language skills. Snoring by night and noisy breathing by day had completely resolved, and there was some catch-up growth demonstrated.

Apnea of Infancy: Case 2

A male aged 10 months presented with parental concern with his breathing since the age of 4 months which had become progressively worse over the last 4–5 months. His parents observed snoring, increased respiratory effort, and respiratory pauses followed by a gasp and arousal. He was a restless sleeper and slept with his mouth open all the time and his neck hyperextended. He was waking 2-hourly through the night and was slow to wake up and tired by day. His growth had been progressing normally along the 50th centile for the first 4–6 months of life but had dropped off to below the 3rd centile. Perinatal history and other medical history are unremarkable. He was described as being snuffly in the first 6 weeks and was noted to periodically struggle to breathe through this nose right from birth. His 2-year-old brother and his father required adenotonsillectomy in early life for obstructive sleep apnea symptoms. Development was normal on initial history. On examination, he was thin with a weight of 7.3kgs (<3rd percentile) and height 74cms (<50th percentile). He had adenoidal facies with mild retrognathia and small nares which were obstructed. His oropharyngeal exam revealed a Mallampati score of 2–3 and tonsils that were grade 3. He had a small appearing posterior oropharynx. Oximetry was undertaken at home and showed evidence suggestive of REM-related OSA with a DSI3% of 25 events/hour and an oxygen saturation nadir of 83%. He had adenoidectomy and diathermy of his inferior turbinates just before his first birthday. There was some improvement in symptoms, but there were still symptoms of obstruction. In clinic, poor concentration was noted, and he continued to have poor weight gain. At 15 months of age, he had tonsillectomy. As he lived some distance from the hospital, the family was asked to stay locally to the hospital for a 2-week period post-surgery. One week after surgery, he had a hemorrhage from the tonsillar bed which was successfully managed under general anesthesia. At follow-up, his symptoms had completely resolved, and there was demonstrable improvement in his weight, daytime concentration, and behavior.

ALTE Case

A male infant was first admitted when he was 3 weeks of age. A family member had bought an apnea mattress for the baby when it was thought he was going to be born preterm after a presentation with threatened labor. He was born at term, but the parents started using the apnea mattress. There were no alarms until 3 weeks of age when the alarm went off, and he was noted to be pale and floppy and was thought to be not breathing. His parents were not able to say if he had a palpable heartbeat. They did not notice color change. They wondered if there was something wrong with the monitor but felt he was symptomatic. They did not notice any gasping breaths to resume breathing. He settled to regular breathing again, and then when they put him back to sleep, the alarm went off three more times that night. He did not take as long on those occasions to come back to what they thought was normal for him. He presented to hospital in the morning and was admitted. During the day, he had seemed his usual self. He was described as being a little fussy about feeding and to have some spilling. It was thought he might have gastroesophageal reflux. As he appeared well, he was discharged home 2 days later, and the parents were given advice about resuscitation. After they went home, the parents were informed about another type of monitor that had an abdominal sensor that monitors breathing. They therefore rang the hospital and were given one of these monitors. Five days after discharge, the alarm went off. He was seen by his primary care doctor and thought to be normal. He did not appear to need stimulation when the alarm went off. The monitor was alarming more frequently, and he would also appear to the parents to be apneic when he was awake. There was one time when he was on the breast and the monitor alarmed. He was not cyanosed at that time. He had another admission because of his monitor alarming more often and alarms were occurring every night. He had otolaryngology review as an outpatient and an awake endoscopy was normal. A slightly recessed jaw was noted. He was otherwise well and gaining

weight. His spilling had improved on thickened feeds. His developmental progress was normal. There was no family history of sudden infant death syndrome or recurrent miscarriage. There was no family history of known obstructive sleep apnea, but the father and paternal grandfather were snorers. At 4 months of age, the infant was reviewed by the pediatric sleep service, and an overnight polysomnography was arranged. The infant was kept on his usual home alarm during the study. There were alarms going off as the home alarm was set at 10 seconds over night, and it could be demonstrated that these alarm periods coincided with a sigh followed by a short period of central apnea, sometimes followed by a few breaths and another short respiratory pause. Some of these events were associated with a brief 3% oxygen desaturation. There were no findings outside the range of normal for age and in particular no evidence of obstructive apnea. Continued monitoring was not recommended, but the parents were advised that if they did intend to use the monitor, the breath indicator alarm should be set to 20 seconds.

SUDI Case

A 6-week-old male infant was found dead in a bed with his mother. He had reportedly been well previously. The infant had been born at term, but there was intrauterine growth restriction and the birth weight was 2.3 kgs. His mother smoked in pregnancy up to ten cigarettes a day. There had also been some marijuana use. Neither parent had been working, and the mother was 19 years of age and the father 21 years of age. They both came from families where there was a history of violence during their own childhood. The infant was growing well with some catch-up growth demonstrated. His mother was well but was very tired because the infant was feeding 3-hourly at night. Her BMI was 35. The evening before his death, the infant had been put down to sleep in his cot at 7.30 pm but woke for a feed at 10.30 pm. His mother was already in bed at this stage, so she brought him into her bed and fell asleep with the infant in her arms. When she next awoke, she expected she would need to feed him again. She found that his face was turned away from her, and when she brought the face back toward her, she found he was floppy, there was no observable breathing, and he was cool. There were some slight bloody secretions at his nose. This was about 1 am in the morning. The ambulance and police were called, and the case was referred to the coroner. There was no death scene investigation. At post-mortem, there were some petechiae found on the thymus and the lungs but no other relevant findings. The infant appeared to be well-cared for. The coroner's final verdict was sudden infant death in infancy in an unsafe sleep situation.

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Apnea of Prematurity

28

Christian F. Poets

Abbreviations

AOP	Apnea of prematurity
ATP	Adenosine triphosphate
AUC	Area under the curve
BPD	Bronchopulmonary dysplasia
CAP	Caffeine for Apnea of Prematurity
CI	Confidence interval
CO_2	Carbon dioxide
COT	Canadian oxygen trial
CPAP	Continuous positive airway pressure
ELGAN	Extremely low gestational age neonate
FiO_2-C	Automatic control of inspired oxygen fraction
FRC	Functional residual capacity
GA	Gestational age
GER	Gastro-esophageal reflux
HFNC	High-flow nasal cannulae
IH	Intermittent hypoxemia
IMV	Intermittent mandatory ventilation
IPPV	Intermittent positive pressure ventilation
NCPAP	Nasal continuous positive airway pressure
NHFOV	Nasal high-frequency oscillatory ventilation
NICU	Neonatal intensive care unit
NIPPV	Nasal intermittent positive pressure ventilation
NNT	Number needed to treat
OR	Odds ratio
PaO_2	Partial pressure of oxygen in arterial blood
pCO_2	Partial pressure of carbon dioxide
PCr	Phosphocreatine
PEEP	Positive end-expiratory pressure
PMA	Post-menstrual age
RCT	Randomized controlled trial
ROP	Retinopathy of prematurity
RR	Relative risk
SD	Standard deviation
SGA	Small for gestational age
SIMV	Synchronized intermittent mandatory ventilation
SpO_2	Arterial oxygen saturation measured by pulse oximetry
VLBW	Very low birth weight

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Introduction

Apnea of prematurity (AOP) is a developmental and thus self-resolving disorder, which nonetheless may cause serious long-term sequelae through its accompanying hypoxemia. Almost every infant born at less than 29 weeks gestation exhibits AOP. Isolated can be distinguished from recurrent events, i.e., periodic apnea. The latter, although associated with frequent brief, yet potentially profound desaturations, is probably benign and follows a different time course: while isolated events reach their peak occurrence at 2–3 weeks of age after largely sparing the first 2 postnatal weeks, periodic apnea is most common at 33–35 weeks post-menstrual age, independent of postnatal age (Fig. 28.1) [1, 2]. Because the latter has not been associated with impaired outcome, this review will focus on isolated events. Among these, central can be distinguished from obstructive apnea, and both may also occur combined (mixed apnea). It has been suggested that all three patterns (central, obstructive, and mixed apneas) occur at the minimum phase of spontaneous oscillations in ventilatory drive, suggesting that they have a common underlying mechanism and that obstructive components are also involved in apparently purely central apneas and vice versa [3].

Significance

Until recently, very little was known if and when the triad of apnea, bradycardia, and desaturation, commonly lumped together as AOP, becomes potentially harmful. Recently, we

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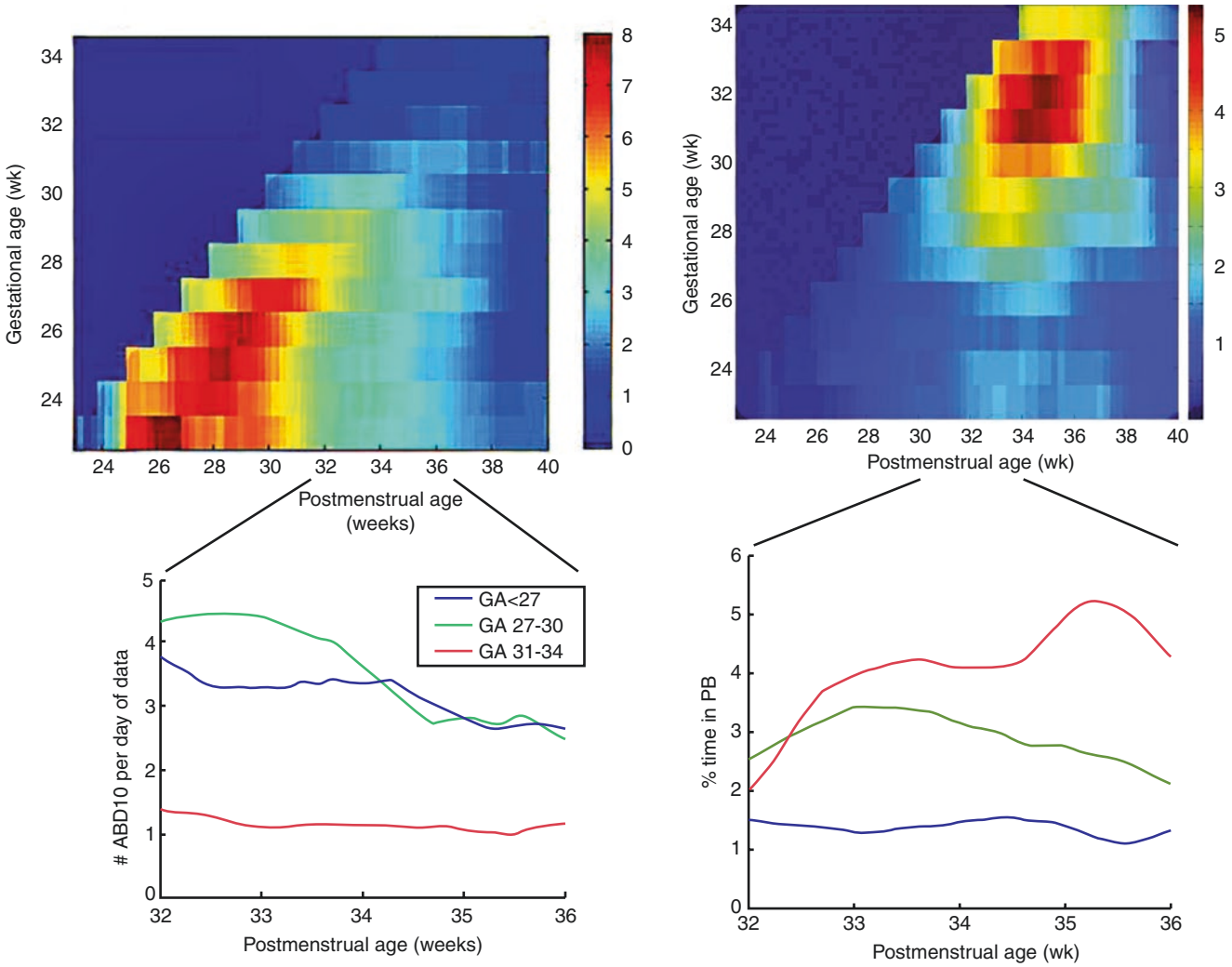

Fig. 28.1 Heat maps illustrating the mean number of central apneas (>10 s duration) with IH (pulse oximeter saturation < 80%) or bradycardia (heart rate < 100/min., both of any duration) per 24 h (left) and the mean daily % time spent with periodic breathing (right) in relation to postnatal and post-menstrual age. Data are based on recordings from 1211 infants <35 weeks GA, excluding periods of mechanical ventilation, and divided into each week of gestation. Color scale goes from blue (zero) to rad (eight) events per day. The line graph below shows mean daily such events for infants <27 weeks GA (blue), 27–30 weeks (green), and 31–34 weeks (red). (From Fairchild et al. 2016 [1] and Patel et al. 2016 [2], with permission from Springer Nature)

performed a secondary analysis of pulse oximeter saturation (SpO_2) and pulse rate data recorded for the first 10 weeks in 1035 participants in the Canadian oxygen tial (COT). This trial compared two target ranges for pulse oximeter saturation (SpO_2): 91–95% vs. 85–89% in infants born at 23–27 weeks GA. Our data helped to assess the long-term effects of these events by revealing the following associations [4]:

- Mean percentages of recorded time with hypoxemia (SpO_2 < 80% for at least 10 s) for the least and most affected 10% of infants were at 0.4 and 13.5%, respectively, while %time spent bradycardia (pulse rate < 80/min. without hypoxemia) was rarer at 0.1 and 0.3%.
- Being in the highest decile for %time with intermittent hypoxemia (IH) of at least 1 min. duration was associated with 3.4-fold increased odds of developing the primary outcome of death beyond 36 weeks or disability at 18 months, with this association being non-significant for shorter events.
- Odds ratios for secondary outcomes (motor impairment, cognitive or language delay, and severe retinopathy of prematurity) were three- to fivefold increased after prolonged hypoxemia.
- Bradycardia, in the absence of concomitant hypoxemia, did not significantly add to the risk of adverse outcome.
- The severity of IH, expressed as the area under the curve (AUC), and the rate with which desaturation occurred added little prognostic value.
- Associations between hypoxemic exposure and adverse outcomes were stronger at later postnatal ages (i.e., at 8–10 weeks) and for infants assigned to a target range of 91–95% compared to a target range of 85–89% SpO_2.

Investigators from the SUPPORT group had performed another large study comparing different target ranges for SpO_2 in extremely low gestational age neonates (ELGANs) and also looked at sequelae of IH but recorded SpO_2 data only during the first 3 postnatal days and associated these with 90-day survival. This was 47.4% for infants born small for gestational age (SGA) who had ≥15 episodes/day with SpO_2 < 80% for 20–60 s but 77.6% for SGA infants with less than 15 such episodes/day. A similar albeit smaller effect size was seen for longer IH events (1–5 min), but not for infants with normal birth weight. No increased mortality was seen in infants of normal birth weight with frequent IH [5]. These data thus confirmed an association between IH events occurring shortly after birth and mortality, albeit only for SGA infants.

More recently, the same group looked at associations between intermittent hypoxemia and bronchopulmonary dysplasia (BPD) in a smaller group of infants from their own center and found that this diagnosis was associated with an increased number/day of IH events between postnatal days 7 and 28 and a longer cumulative duration of IH [6].

Given these associations of long-term outcomes with IH, but not with bradycardia, it seems prudent to focus on the avoidance of IH, particularly of episodes lasting for 1 min or longer, if we want to reduce adverse sequelae of AOP as the main cause of IH in extremely preterm infants.

Although not fully in line with the above data, the approach taken in the author's institution has been to grade the intensity of the interventions provided for AOP based on a severity score that relies largely on the nurses' acute intervention to events (e.g., stimulation or bagging; Fig. 28.2). Neither this score nor any treatment threshold used with it has ever been validated. However, the low rates of retinopathy of prematurity (ROP; <2% for stage 3 or higher in infants <1500 g birth weight in 2010–15) and high Bayley scores [7] associated with implementation of this apnea scoring paradigm suggest its potential as a protocol that warrants further study. Such a severity score may serve as an example for how apnea severity may be assessed more objectively without documentation via continuous recordings, which would be preferable but is yet impractical in most units.

Pathophysiology

Hypoxic Ventilatory Depression

In the fetus, oxygen supply occurs via the placenta, and breathing happens only intermittently, with breathing efforts becoming a waste of energy if oxygen supply via the placenta is reduced. Thus, suppressing breathing efforts during hypoxia may be lifesaving for the fetus. While the opposite is true postnatally, the preterm infant continues this fetal behavior until approximately term-equivalent age [8]. The underlying molecular mechanisms of this behavior are yet unclear. One candidate is the creatine-phosphocreatine (PCr) system. In the absence of oxidative phosphorylation, provision of phosphate to generate adenosine

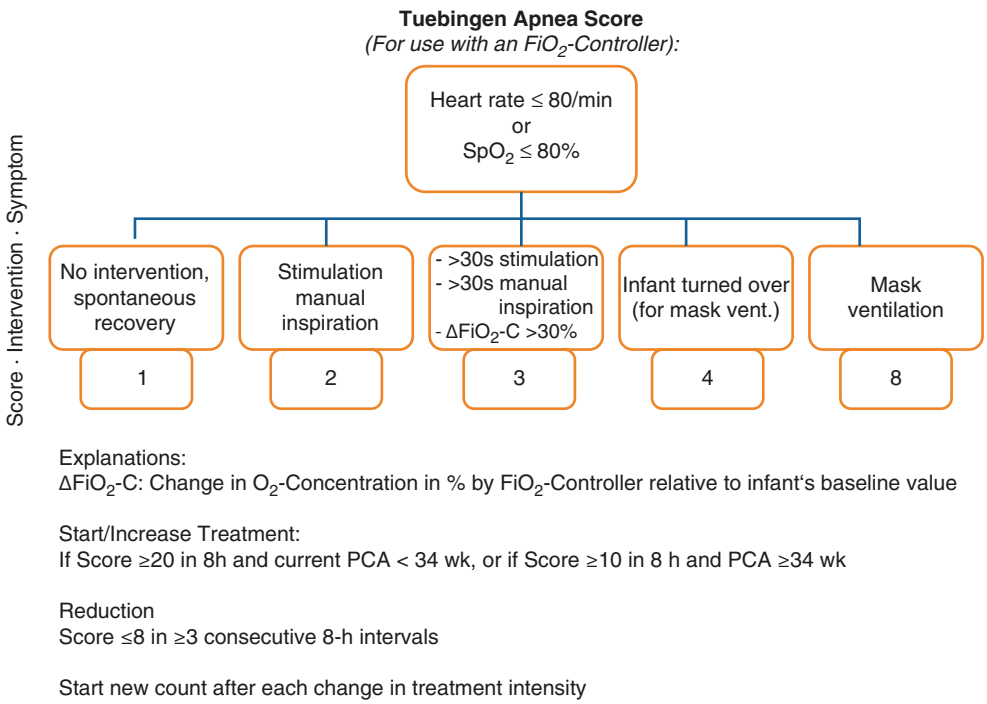

Fig. 28.2 Updated version of the apnea severity score to standardize assessment across different raters/infants and in use for >10 years in the author's NICU. In contrast to its earlier version, it now includes an increase in the fraction of inspired oxygen (FiO_2) as a potential intervention executed by an automated FiO_2-controller. The values in the lower row of boxes indicate the respective score. The threshold for an increase in treatment severity is lower in more mature infants as these are considered more vulnerable to the detrimental effects of intermittent hypoxemia

triphosphate (ATP) relies predominantly on the PCr pool. Investigations of the cytosolic levels of PCr during moderate hypoxia in adult rats showed that the occurrence of hypoxic ventilatory depression was preceded, by 30 s, by a significant decrease in PCr levels, which reached its minimum level 30 s after maximal respiratory depression [9]. Brainstem slices from pups of creatine-fed mice (2 g/kg/d) showed higher PCr content and less hypoxic ventilatory depression (−14 vs. −41%) than those from non-supplemented control animals. This corresponded to nearly constant cerebral ATP levels in the former vs. a 54% decrease in the latter animals after 30 min of anoxia [10]. Also, measurements of the maximal respiratory amplitudes in such pups during hypoxia showed an increase by 51%, compared to 22% in control animals [11].

A randomized controlled trial of 14 days of creatine supplementation (200 mg/kg/d) to preterm infants with AOP, however, starting at around 2 weeks of age, showed no effect at all on AOP [12], although this could have also been due to an insufficient dose and/or duration of treatment. Thus, it remains unclear how to avoid the hypoxic ventilatory depression in preterm neonates.

CO_2 Apneic Threshold

Respiratory drive depends not only on O_2 levels but at least as much on CO_2. If pCO_2 falls considerably below its eupneic baseline, apnea occurs. The pCO_2 value at which this occurs is called the apnea-hypopnea threshold; it is approximately 3.5 torr below eupneic pCO_2 in healthy adults [13]. The closer the eupneic pCO_2 is to apneic threshold pCO_2, the more unstable breathing becomes, as minor behavioral changes in ventilation would be sufficient to propel the pCO_2 to below threshold, inducing apnea. In term and preterm neonates, however, the spontaneous pre-apneic threshold is only 1–1.3 mmHg below eupneic values [13]. This closeness between eupneic and apneic levels likely de-stabilizes respiration in neonates, as minor oscillations in breathing may already induce apnea. Indeed, CO_2 inhalation to infants with AOP was shown to be almost as effective a respiratory stimulant as theophylline [14].

Relationship Between Apnea, Bradycardia, and Desaturation

One of the most striking findings in recordings of respiration, heart rate, and SpO_2 in preterm infants is the close temporal relationship between apnea, bradycardia, and IH [15]. When we analyzed the relationship between these three phenomena, we found that 86% of bradycardias (defined as a fall in heart rate by >1/3 of baseline) were accompanied by a fall in SpO_2 to ≤80%, 83% by an apnea of 4 s or longer, and 79% by both apnea and IH. Heart rate during bradycardia almost invariably began to fall *after* the onset of apnea (median interval, 4.8 s). In 86% of events, bradycardia onset was also *after* the onset of the fall in SpO_2 (median interval, 4.2 s). This was because the interval between the onset of apnea and that of IH, corrected for the time it takes for the blood to travel from the lung to the pulse oximeter sensor site, was extremely short (median 0.8 s; Fig. 28.3) [15].

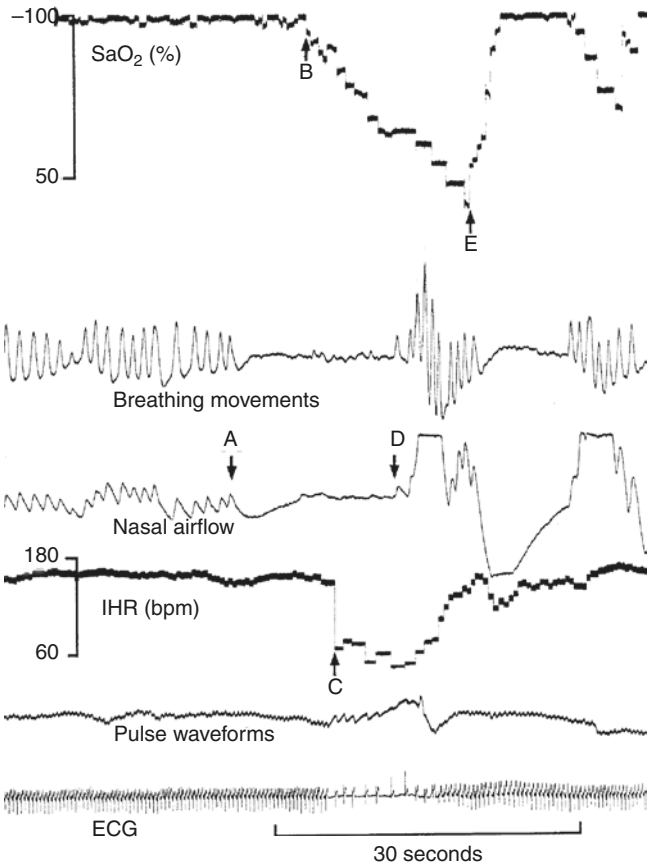

Fig. 28.3 Example for the close temporal relationship between apnea, bradycardia, and desaturation. The delay caused by the time it takes for the blood to travel from the lung to the pulse oximeter sensor attached to the foot can be estimated from the delay between the first breath following an apnea and the onset of the recovery in SpO_2 (**c**). This must be subtracted from the interval between the onset of apnea and that of desaturation (**a**) and from the interval between the onset of bradycardia and that of desaturation (**b**). (From Poets [62], with permission from Taylor and Francis Group LLC Books)

These temporal observations support the concept that hypoxemia causes bradycardia, e.g., via stimulation of peripheral chemoreceptors. Bradycardia coincides with apnea because a combination of apnea and hypoxemia excites arterial chemoreceptors much more than either apnea or hypoxemia alone. Thus, the appearance of bradycardia during apnea seems to depend upon there being no overriding effect from the pulmonary inflation reflex, which

is known to cause an increase in heart rate [16]. One possible explanation for the comparatively high frequency of bradycardia in preterm infants is, therefore, that bradycardia is primarily caused by hypoxemia (which is common in this age group) and that the hypoxemic effect on heart rate is potentiated by the concomitant cessation of lung inflation during apnea.

Changes in Lung Volume, Apnea, and Desaturation

A surprising finding in the above study [15] was the brevity of the interval between the onset of apnea and that of desaturation. This could be explained by a loss in functional residual capacity (FRC), which may be particularly relevant to preterm infants, whose relaxation volume is only 10–15% of total lung capacity and thus very close to residual volume, predisposing them to the development of peripheral airway closure [17]. To compensate for this disadvantage, young infants actively maintain their end-expiratory lung volume above relaxation volume (which is one reason for their high respiratory rate) [18], whereas lung volume falls if respiration ceases [19]. During repeated FRC measurements and concomitant recordings of breathing movements and SpO_2, we found that apneas resulted in a significant decrease in FRC: mean FRC was 20 ml/kg if measured in close proximity to an apnea, 26 ml/kg after a sigh ($p < 0.001$), and 24 ml/kg if there had been neither a sigh or an apnea ($p < 0.05$). The interval between apnea and the FRC measurement had no effect on FRC [20]. Thus, apneas resulted in a reduction in FRC, which was restored by a sigh. These findings provide further evidence for the hypothesis that one of the main functions of sighs in preterm infants is to reverse falls in lung volume caused by apnea.

What does this have to do with the interval between apnea and desaturation? The FRC serves as a buffer to stabilize oxygenation during brief periods of apnea. Lung volume is an important determinant of the speed with which desaturation develops during voluntary breath-holding. We found an inverse correlation between FRC and the speed with which SpO_2 fell during desaturation, i.e., the lower the lung volume, the more rapid the fall in SpO_2 during apnea [20].

During periodic apnea, SpO_2 falls twice as fast as during isolated apneas [21]. Although a transiently impaired mixed venous SO_2 following a prior fall in SpO_2 may also increase the rate of fall in SpO_2, the main reason for the more rapid fall in SpO_2 is a progressive fall in lung volume during the repeated apneas, resulting in peripheral airway closure. The complex interrelations of the factors influencing the speed of the fall in SpO_2 during apnea in preterm infants have been modeled mathematically [22].

The Role of Feeding and Gastroesophageal Reflux

Symptoms of AOP often increase during and after feeding. While hypoxemia *during* feeding may be caused by a reduction in minute ventilation due to an immature coordination between breathing, sucking, and swallowing, activation of the laryngeal chemoreflex, gastroesophageal reflux, or diaphragmatic fatigue, its occurrence *after* feeding, may be due to a reduction in FRC and an increased work of breathing resulting from gastric distension.

In own studies on the effect of bottle feeding, as compared to slow (1 h) and bolus (10 min) gavage feeding, on apnea, bradycardia, and IH, there were three times more desaturations to ≤80% with bottle feeding than with bolus gavage feeding, but no further reduction with slow gavage feeding and no difference in baseline SpO_2. With all three feeding techniques, there were significantly more desaturations in the hour the feeds were given than during the following 2 h. The deleterious effects of bottle feeding were most evident during the hour of feeding, but IH remained significantly more common than with gavage feeding during the following 2 h. In contrast, there was no significant effect of feeding technique on the frequency of apnea or bradycardia [23].

Thus, bottle feeding may confer a significantly increased risk of IH, which may be surprisingly long-lasting following each feed. It is puzzling that slow gavage feeding (over 1 h) offered no advantage over bolus gavage feeding. Gastroesophageal reflux (GER), occurring with either feeding method, might be an explanation for the observed increase in desaturation rate during and immediately after feeding, but when we studied the role of GER in apnea using the pH-independent multiple intraluminal impedance technique, we found a high rate of both apnea and GER, but no difference in the number of apneas occurring within ±20 s of a reflux episode compared to reflux-free epochs; the same was true for IH. Also, GER occurred similarly often within 20 s before as after an apnea. These data have since been confirmed, so that it is not surprising that anti-reflux treatment has no effect on AOP [24].

Chest Wall Distortion, Anatomic Dead Space, and Diaphragmatic Fatigue

Due to their highly compliant chest wall, preterm infants are disadvantaged with regard to their respiratory mechanics. Chest wall distortion, clinically apparent as paradoxical breathing, is common in infants and is especially visible in preterm infants. This distortion increases the volume displacement of the diaphragm during inspiration to almost

twice that needed for pulmonary ventilation [25]. This additional workload not only leads to a significant calorie expenditure in these infants but may also contribute to the development of diaphragmatic fatigue and apnea. Further contributing to this fatigue is that, because of their relatively large head size, anatomic dead space is approximately 45% of tidal volume in neonates compared to 25% in adults [26].

Treatment

In the following, interventions to improve IH and/or AOP will be sorted in the form of an incremental treatment plan (Textbox 28.1).

Textbox 28.1 Suggested Incremental Treatment Plan to Reduce IH in Very Low Birth Weight Infants

1st Step (while intubated/receiving additional O_2): SIMV; use of closed suctioning systems, use of an FiO_2 controller

2nd Step: 15° head-up tilt position

3rd Step: Caffeine*

4th Step: Variable flow NCPAP or synchronized NIPPV

5th Step: Intubation and mechanical ventilation**

*Consider caffeine as first-line treatment in infants <29 weeks GA. **Doxapram may be considered as an alternative in infants who continue to exhibit IH despite nasal ventilation.

Head-Elevated Positioning

While a Cochrane analysis demonstrated *no* advantage of the prone position in reducing apnea rates in preterm infants (data on intermittent hypoxia were not reported) [27], a head-elevated 15° tilt position was associated with a 49% reduction in desaturations to <85% in a study involving 12 preterm infants [28]. Two re-investigations of the effectiveness of this position, however, triggered by the observation that infants appear more comfortable when only the chest and head rather than the entire body are being tilted, showed only a modest and nonsignificant reduction in IH rates in the head elevated tilt compared to the horizontal position [29, 30] and also no significant advantage for the head-and-chest elevated position [29]. This much less clear advantage of the head-up tilt position may be due to the fact that several infants in the earlier study had received no other treatment for AOP, whereas in the more recent one, all had received methylxanthines and/or nasal continuous positive airway pressure (NCPAP) in addition to positioning. A head-up tilt position may thus be considered the first step in the above incremental treatment plan for AOP (Textbox 28.1), while this intervention may be less effective in infants already receiving caffeine or NCPAP.

Nasal Respiratory Support Systems

NCPAP has been shown to reduce extubation failure in preterm infants and can be applied via a nasopharyngeal tube or (bi-)nasal prongs. Reintubation rates are 40% lower with the latter (relative risk (RR) 0.59 [95% confidence interval (CI) 0.41;0.85], number needed to treat (NNT) 5) [31], suggesting nasal prongs as the preferred patient interface when applying NCPAP. An extension of NCPAP is nasal intermittent positive pressure ventilation (NIPPV), with better effectiveness than NCPAP in preventing extubation failure if used in synchrony with the infant's own breathing efforts [32]. Interestingly, gastric distension, a theoretical concern with nasal ventilation, was not an issue in the studies contributing to this meta-analysis [32].

NCPAP can be generated via a standard infant ventilator or using a variable flow system (Viasys, Conshohocken, PA, USA) that reduces work of breathing via a fluidic-flip valve [33, 34]. Two studies investigated different NIPPV systems vs. NCPAP and reported a decrease in bradycardia and IH rates with NIPPV compared to non-synchronized NIPPV and also for NCPAP via the above variable flow system [35, 36]. Thus, a reduced work of breathing and/or effective synchronization with an infant's own breathing efforts may be key to success for nasal respiratory support applied to ameliorate AOP.

Another form of nasal respiratory support that is gaining popularity is high-flow nasal cannulae (HFNC), where heated humidified gas is delivered at flow rates above 1 l/min. An initial crossover study compared NCPAP generated via a standard infant ventilator with HFNC at flow rates (1–2.5 l/min) to achieve a PEEP level of 4–5 cm H_2O in 40 infants <2000 g birth weight. Mean rates of apnea, bradycardia, and desaturation were quite similar with both systems [37]. Another study compared the Infant Flow system against HFNC from a non-heated bubble humidifier. With this setup, there were on average three times more episodes of apnea and bradycardia with HFNC [38]. Finally, in a large randomized controlled non-inferiority study comparing HFNC against NCPAP in 303 infants <32 weeks GA, apnea was the reason for treatment failure in 62% of 52 infants on HFNC, compared to 64% of 39 infants in the NCPAP group (n.s.), suggesting comparable effectiveness of both systems with regard to severe apnea [39].

Finally, some centers use nasal high-frequency oscillatory ventilation (nHFOV) as a nasal support mode, but data on its

effectiveness are yet very limited. In a recent crossover study involving 40 infants <30 weeks GA initially receiving NCPAP in whom recordings were started on either NCPAP or NHFOV after a 30-min. washout period on the assigned treatment, the mean number of IH to <80% SpO_2 was 5.5/2 h (IQR 0.5–13.5) on NHFOV vs. 8.5 (1.0–25.0) on NCPAP ($p = 0.001$). The cumulative duration of time with $SpO_2 < 80\%$ was 0.63 min (0.06–1.56) on NHFOV vs. 0.99 min (0.00–3.23) on NCPAP, $p = 0.05$ [40]. Mean FiO_2 was 0.03 higher on NHFOV, while pCO_2 was not significantly changed. Mean heart rate was 170/min. on NHFOV vs. 166/min on NCPAP ($p = 0.01$). In six infants and on seven occasions, oscillatory amplitude was reduced because heart rate had increased to >190/min; the latter decreased in all infants following this reduction. More evidence is needed before recommendations on NHFOV for preventing IH in VLBW infants can be made.

Caffeine

Methylxanthines increase chemoreceptor sensitivity as well as respiratory drive and can also improve diaphragmatic function. Of the substances available, caffeine has a wider therapeutic range and fewer side effects than theophylline. Its effectiveness in improving patient outcome was proven in the CAP study [41, 42], a large placebo-controlled randomized controlled trial (RCT) enrolling over 2000 infants. Caffeine (or placebo) was started during the first 10 postnatal days in infants of 500–1250 g birth weight at a dose of 5–10 mg/kg caffeine citrate in infants considered eligible for caffeine treatment and given until no longer considered necessary for AOP treatment. Mechanical ventilation, NCPAP, and oxygen could all be discontinued approximately 1 week earlier in infants treated with caffeine. Somewhat unexpectedly, and not a primary outcome, was the finding of a 40% lower risk of BPD (36% vs. 47%; OR 0.6; 95% CI 0.5;0.8), a 30% lower risk of developing a symptomatic patent ductus arteriosus (OR 0.7; [0.5;0.8]), and a 40% reduction in the risk of developing stage 4 or 5 retinopathy of prematurity (ROP) or requiring treatment for ROP in the caffeine group (OR 0.61 [0.42;0.89]) [42]. Most important, however, are the data on the primary outcome, showing a 23% reduction in death or disability at 18 months corrected age in addition to a reduction in cerebral palsy in infants in the caffeine group [42].

Results from the 5-year follow-up of this study still showed an effect of caffeine on death or disability, but this was no longer significant. Neonatal caffeine therapy, however, reduced motor dysfunction, defined as a gross motor function scale result of 1–5 (OR 0.66 [0.48;0.91]), but this was only a secondary outcome in that study [43].

At an 11-year follow-up investigation of this patient cohort, caffeine therapy, compared to placebo, was still associated with a reduced risk of motor impairment (OR 0.66 [0.48–0.90]; $p = 0.009$) [44]. Regarding other long-term (side) effects, sleep studies, performed in 201 former CAP participants at age 5–12 years, showed no difference in sleep disorders in subjects treated with neonatal caffeine compared to placebo [45].

In subgroup analysis, the effect of caffeine on the primary outcome was found to be restricted to those requiring ventilatory support at randomization, i.e., caffeine had no effect on death or disability in infants *not* requiring NCPAP or IPPV. Interestingly, the reduced duration of the need for ventilatory support was only evident in those who were randomized within the first 3 postnatal days, and the effect on death or disability was only significant for infants receiving at least 3.5 mg/kg/d of caffeine base (7 mg/kg/d caffeine citrate). Also, in secondary data analysis, a significant difference in the rate of cerebral palsy between caffeine and placebo group infants was only found in those receiving caffeine for at least 45 days [46, 47]. Thus, caffeine administration should be started within the first 3 days of age in infants <1250 g, requiring respiratory support and being likely to develop AOP.

It is important also to consider when to discontinue caffeine treatment. In the CAP study, caffeine was given until a mean PMA of 34.4 weeks. However, caffeine continues to be effective in reducing intermittent hypoxia rates until 35 weeks PMA [48]. With no current standards for discontinuing caffeine therapy, the use of an apnea severity score such as that proposed in Fig. 28.2 may provide a treatment guide in the clinical setting.

At what dose should caffeine be given? First, it must be remembered that caffeine is usually available as caffeine citrate, in which the active component (caffeine) comprises only 50% of the total dose. In this chapter, all data will be on this active component. In the CAP study, a loading dose of 10 mg/kg (iv or orally) and a maintenance dose of 2.5–5 mg/kg once daily were used. Two randomized controlled trials compared a loading dose of 40 mg/kg caffeine (maintenance dose 10 mg/kg/d) with a "conventional" 10/2.5 mg/kg regimen in 234 infants born at a mean GA of 27 weeks. Infants in the high-dose group had only half the risk of failing extubation within 48 h of caffeine loading or to require reintubation and mechanical ventilation or doxapram within 7 days of caffeine loading (15.0 vs. 29.8%, RR 0.51 [0.31;0.85]) [49]. They received mechanical ventilation for 14.4 days (SD 11.1), compared to 22.1 (17.1) days for infants in the lower-dose group. This better efficacy was not at the expense of an increased risk of side effects, including no difference in Griffith's mental development scales at age 12 months. However, the other RCT investigating high-dose vs. standard-dose caffeine was stopped prematurely because of a much higher incidence (36 vs. 10%) of intracerebellar hemorrhages in the high-dose group compared to the standard-

dose group [50]. This example reminds us that data on drug safety are only valid for the dose at which they have been tested.

Doxapram

Doxapram stimulates peripheral chemoreceptors at low and central ones at high doses. It shows a clear dose-response curve, with a 50% reduction in apnea rate occurring in 47, 65, 82, and 89% of infants at doses of 0.5, 1.5, 2.0, and 2.5 mg/kg/h, respectively [51]. An own longitudinal cohort study focused on IH rates to ≤80% SpO_2, which were reduced from a median of 8 to 2/h, with this effect continuing throughout a follow-up period of 6 days [52]. However, long-term data are sparse. An early study investigated factors associated with a Mental Development Index <70 in extremely low birth weight infants and found that the only significant factor was that infants with developmental delay had received a mean cumulative doxapram dose of 2233 mg, compared to 615 mg in matched controls. Whether this reflects a drug effect or the detrimental effects of IH (for which doxapram had been given) cannot be answered using a retrospective study design [53]. In the CAP study [42], placebo group infants not only were more likely to develop cerebral palsy but were also three times more likely to have received doxapram. A more recent study, however, analyzed 2-year follow-up data in 142 infants born at <1250 g or <30 weeks GA and 284 controls and found a significantly lower risk of the combined outcome of death or neurodevelopmental delay in the doxapram group after adjusting for confounders (OR 0.54 [0.37; 0.78]) [54]. Given these conflicting data in the absence of safe alternatives, doxapram is used in the author's institution on an individual basis in selected infants with very frequent IH despite nasal SIMV plus caffeine.

Most studies on doxapram used a continuous intravenous infusion, although some suggest that the iv solution may also be given orally at twice the dose with good effect (enteral absorption is approximately 50%) [52]. Short-term side effects become quite common at doses above 1.5 mg/kg/h and include irritability, myoclonus, elevated blood pressure, and gastric residuals. Given these data (or lack thereof), doxapram cannot be recommended as a standard treatment for AOP, although it seems to be rather widely used in some countries.

Interventions to Reduce IH Independent of Apnea

There are also other means to reduce IH with proven effectiveness, including suctioning with closed systems, synchronized instead of non-synchronized mechanical ventilation, and the use of oxygen controllers in infants receiving additional inspired oxygen.

Endotracheal suctioning traditionally involves disconnecting the patient from the ventilator, i.e., intermittent loss of positive end-expiratory pressure (PEEP). This loss of PEEP increases the risk of IH. Indeed, the relevant Cochrane analysis, including 241 infants, reported less events with SpO_2 < 90% (RR 0,48 [0,31; 0,74]) with the use of a closed suctioning system [55], so that this comparatively simple change in respiratory care may be included in the list of interventions aimed at reducing IH.

Synchronizing a baby's breathing efforts with the ventilator can by now be regarded standard of care; nonetheless, it is worth mentioning that this synchronization also reduces IH. In a crossover study on 18 infants <1250 g who were >14 days old, infants spent on average 3.0% (SD 0.9%) of the time with SpO_2 < 80% while receiving intermittent mandatory ventilation (IMV) but only 0.9% (SD 0.4) while receiving synchronized IMV [56]. No such effect could be seen for a comparison between volume- and pressure-targeted ventilation [57]. Volume-controlled ventilation, however, has other important benefits such as a reduction in BPD or in severe intraventricular hemorrhage [58].

The third approach to reducing IH in infants receiving ventilatory support is the automatic control of the inspired oxygen fraction (FiO_2). FiO_2 controllers are increasingly used with neonatal ventilators, where they result in an increased proportion of time spent in the desired SpO_2 target range [59]. Only few studies, however, looked specifically at the avoidance of IH. However, van Kaam et al. reported that, using an SpO_2 target range of 91–95%, %time spent at an SpO_2 < 80% was 2.0% with manual vs. 0.8% with automatic oxygen control [60]. Reanalysis of data from an own multicenter trial on the subject [61] also showed a reduction in %time with SpO_2 < 80% from 2.6 to 1.7% ($p < 0.01$; Urschitz MS; personal communication).

In summary, treatment for AOP/IH may follow an incremental approach, starting already in intubated infants with synchronized ventilation, automatic SpO_2 control, and closed suctioning and being continued, after extubation, with infant care procedures such as prone head-up tilt positioning followed by methylxanthines and NCPAP/synchronized NIPPV (Textbox 28.1).

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Disorders of Respiratory Control and Central Hypoventilation Syndromes

29

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Introduction

In normal individuals, adequate spontaneous ventilation is dependent on a respiratory balance between ventilatory muscle power and central drive that can overcome respiratory load. Control of ventilation through the neurologic system normally ensures adequate ventilation during all periods of the day, including sleep, wakefulness, and exercise [1]. Central hypoventilation is a result of inadequate central respiratory drive that can be congenital or acquired [2–5]. Congenital disorders include congenital central hypoventilation syndrome, Chiari malformations/myelomeningocele, achondroplasia, Prader-Willi syndrome, Leigh syndrome, Joubert syndrome, familial dysautonomia, and ROHHAD syndrome. Acquired etiologies of central hypoventilation include brain tumors, infection, infarction, or after neurologic surgery. Disorders of respiratory control may result in a range from hypoventilation only during sleep to the inability to maintain adequate spontaneous ventilation during sleep and wakefulness [4]. The ability to detect disordered breathing has been enhanced by technologies such as pulse oximetry, end-tidal carbon dioxide monitoring at the bedside, cardiorespiratory monitoring, and polysomnography. As a result of increased recognition with improved diagnostic modalities, health professionals are better equipped to optimize care for patients with disorders of respiratory control. Management of these patients requires a multidisciplinary team that includes pulmonologists, primary care providers, intensivists, neonatologists, otolaryngologists, neurologists, neurosurgeons, geneticists, and respiratory therapists.

In this chapter, we will discuss definitions, pathophysiology, diagnostic approaches, differential diagnoses including the various congenital and acquired etiologies of hypoventilation, management including the different modes of ventilation available to these patients, and illustrative cases. We will give special attention to congenital central hypoventilation syndrome and rapid onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD).

Definitions

Central hypoventilation is due to a failure of the neurologic system to adequately detect and respond to respiratory stimuli, resulting in inadequate ventilation to achieve optimal gas exchange. Central hypoventilation can result in chronic respiratory failure. Chronic respiratory failure is the result of inability to sustain adequate spontaneous ventilation. This may be due to ineffective mechanisms that control ventilation, ventilatory muscle function, and lung mechanics.

Pathophysiology

Normally, the brain dictates how frequently and deeply to breathe. This is referred to as central respiratory drive. In order to sustain adequate ventilation, ventilatory muscle power and central respiratory drive need to be sufficient to overcome the respiratory load. In normal individuals, ventilatory muscle power and central drive can increase substantially to overcome increased respiratory loads, as during exercise or pneumonia. Central hypoventilation syndromes are characterized by decreased central respiratory drive.

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Breathing is important, so there are complex, redundant mechanisms involved in central drive. To begin with, there are two types of ventilatory control: (1) behavioral or voluntary control of breathing and (2) automatic or metabolic control of breathing. The ability to take a deep breath or hold one's breath on command is an example of voluntary control of breathing. Voluntary control is anatomically housed in the cerebral cortex, and it is responsible for breathing during speech, laughing, crying, etc. It is not tightly linked to blood gases. Hence, when ventilation is controlled by the voluntary system, P_aO_2 and P_aCO_2 can fluctuate significantly, and ventilation varies considerably with respect to timing and amplitude. However, one does not think about breathing all the time. The automatic system is tightly linked to blood gases and other reflexes. When ventilation is controlled by the automatic system, the timing and amplitude of breathing are monotonously consistent, and P_aO_2 and P_aCO_2 remain relatively stable.

Minute to minute, breathing is controlled by central chemoreceptors, which are anatomically located in the brainstem. CO_2 can diffuse across the blood-brain barrier, but H^+ and HCO_3^- ions cannot. CO_2 diffusion into the cerebrospinal fluid (CSF) is driven by P_aCO_2. In the CSF, CO_2 combines with water to form carbonic acid, which increases H^+ concentration. CSF H^+ stimulates cells in the CSF, increasing minute ventilation (V_E). There is a very tight linear correlation between P_aCO_2 and V_E, and central drive can be quantitated by the slope of that line. Hypoxia will accentuate the central chemoreceptor ventilatory response, and hyperoxia will depress it. Similarly, acidosis increases the CO_2 ventilatory response, and alkalosis depresses it. CNS depressant medications and sleep also depress the CO_2 ventilatory response. The central chemoreceptor-mediated CO_2 ventilatory response is exquisitely sensitive. Small changes in P_aCO_2 will result in changes in V_E. Thus, central chemoreceptors are primarily responsible for breathing minute to minute.

In an anatomically distinct location, peripheral chemoreceptors are primarily responsible for the hypoxic ventilatory response. Peripheral chemoreceptors are located at the bifurcation of the internal and external carotid arteries, not in the brainstem. In contradistinction to the central chemoreceptors, peripheral chemoreceptors serve as a safety or backup system. Peripheral chemoreceptors have a tonic stimulation of respiratory centers, which can be suppressed by hyperoxia. However, their hypoxic ventilatory response is relatively insensitive, and ventilation increases exponentially with $P_aO_2 < 60$ torr. V_E increases linearly with arterial oxygen saturation of hemoglobin (S_aO_2). However, this means that peripheral chemoreceptors do not stimulate breathing until P_aO_2 is low. In a sense, peripheral chemoreceptors rescue breathing if central chemoreceptors fail. Hypocapnia and alkalosis depress the hypoxic ventilatory response, and hypercapnia and acidosis increase it synergistically. Peripheral chemoreceptors also stimulate breathing in response to large drops in pH and large increases in P_aCO_2.

While central and peripheral chemoreceptors provide the most important input to respiratory centers, there are several other receptors and reflexes that affect breathing. Intrapulmonary receptors (stretch receptors, irritant receptors, and J-receptors), chest wall receptors, cortical influences, and mechanoreceptors, to name a few, also have input to breathing.

Central hypoventilation syndromes are conditions where central respiratory drive is diminished or absent. The causes can be genetic, developmental, or acquired. Most central hypoventilation syndromes are characterized by decreased or absent chemoreceptor function. Thus, these patients do not have objective or subjective ventilatory responses to hypercapnia and/or hypoxia. When hypoxic and hypercapnic ventilatory responses are measured, they are absent or severely diminished in both sleep and wakefulness. However, because central respiratory drive is relatively decreased during sleep in everybody, clinical manifestations of apnea or hypoventilation are more severe during sleep. Nevertheless, these patients will not increase V_E in response to hypoxia or hypercapnia while awake or asleep. This causes one of the most difficult aspects of clinical management. We recognize hypoxia and/or hypercapnia in normal individuals because they exhibit tachypnea, agitation, nasal flaring, retractions, etc. These require intact ventilatory control, and therefore they are absent in central hypoventilation syndrome patients. Thus, these patients can be profoundly hypoxemic, yet not show outward clinical signs of this problem.

The redundancy of ventilatory control can allow some reflexes to compensate, to some extent, when others are absent or dysfunctional. For example, even though patients with congenital central hypoventilation syndrome (CCHS) have absent ventilatory responses to hypoxia and hypercapnia awake and asleep, both active and passive body movement will stimulate breathing in these patients.

Differential Diagnosis

Congenital Central Hypoventilation Syndrome (CCHS)

CCHS is a rare genetic disorder resulting in a failure in the autonomic control of breathing that begins from birth [6]. It is caused by an autosomal dominant mutation in the paired-like homeobox (*PHOX2B*) gene [2, 7, 8] which is important in the migration of neural crest cells and therefore in the development of the autonomic nervous system. In most patients, the mutation is spontaneous. However, affected patients have a 50% chance of passing CCHS with each pregnancy [7, 9].

The vast majority of PHOX2B mutations in this disorder result in an expansion from 4 to 13 copies in the 20-residue polyalanine region (23–33 alanine repeats). Approximately 10% of CCHS patients have non-polyalanine repeat mutations (NPARMS) [2, 10]. The severity of disordered ventilation and associated autonomic nervous system dysfunction are directly proportional to the number of expansion repeats, with the most severe presentation occurring in those patients with 33 alanine repeats in the polyalanine repeat expansion mutations (PARMs) [2]. CCHS patients typically have evidence of hypoventilation from birth, although some may present later in life, even into adulthood [11].

The majority of affected patients will present in the newborn period where they exhibit central apneas [12, 13], cyanosis, and small volume breaths [14]. They have worse hypoventilation and hypoxemia during sleep, which is most severe during NREM sleep when breathing is primarily dependent on the metabolic control of breathing, less prominent during REM sleep, and variable during wakefulness [15, 16]. Ventilation is most severely affected at sleep onset because breathing during non-rapid eye movement (NREM) sleep is primarily dependent on the metabolic control of breathing [16]. Neonates and young infants with CCHS may be unable to be extubated and weaned off from assisted ventilation. Older children may present with increased central apneas and arousals while breathing spontaneously in NREM sleep [15]. As they get older, some patients show more adequate spontaneous ventilation during wakefulness as other components of their respiratory system mature with age [2, 17–20].

Some patients will not initially present in the neonatal period but may have unrecognized severe hypoventilation resulting in life-threatening respiratory failure [21], right ventricular heart failure/cor pulmonale [22–24], and neurologic sequelae [22, 25]. Patients may live into adulthood without diagnosis of CCHS or need for assisted ventilation but may present with hypoventilation after respiratory infection [11, 26] or general anesthesia [27, 28], or they may be diagnosed in the context of genetic testing because of family members who have been diagnosed with CCHS [13, 22, 29, 30]. Some may present with unexplained polycythemia [22, 31] or elevated bicarbonate on routine blood testing [30].

Physiologic studies indicate that the primary abnormality in CCHS arises from the area in the brainstem involved in the integration of central and peripheral chemoreceptor inputs and not from abnormalities in the chemoreceptors themselves [32–34]. Mouse models support the key role of brainstem retrotrapezoid nucleus (RTN) in the control of breathing. RTN neurons are thought to function as central chemoreceptors regulating alveolar hypoventilation as well as the site of integration of inputs from the peripheral chemoreceptors, raphe, hypothalamus, and neighboring astrocytes that modulate respiratory drive [35–39].

When suspected, genetic testing for PHOX2B gene mutation must be performed to confirm the diagnosis [2]. There are three testing methods that are currently available: (1) *PHOX2B*-targeted mutation analyses (PHOX2B screening test) which identifies all PARMS and most NPARMS, thus identifying pathogenic variants in most CCHS individuals, (2) *PHOX2B* sequencing test which identifies all PARMS and currently all known NPARMS, and (3) *PHOX2B* deletion/duplication testing which identifies deletions of exon3 or of the whole PHOX2B. This test identifies <1% of patients with CCHS. Thus, when ordering the PHOX2B gene mutation analysis, it is crucial to specify that the targeted mutation and/or sequencing tests are performed. However, when clinical suspicion is high, all three tests may need to be done to confirm the diagnosis of CCHS [2, 40–42].

While awaiting confirmation of phenotypic presentation with genetic testing of mutations in the PHOX2B, it is prudent to workup patients with chronic respiratory failure suspected of having CCHS to rule out other causes such as ventilatory muscle weakness, cardiac disease, pulmonary disease, and intracranial pathology. The workup can include MRI and/or CT imaging of the brain and brainstem, chest X-ray, fluoroscopy of the diaphragms, and echocardiogram. Furthermore, a polysomnogram is a noninvasive method to establish sleep hypoventilation and assess for accompanying sleep related breathing disorder [2]. A daytime blood gas can document hypoventilation during wakefulness.

The cornerstone in the management of CCHS is to ensure adequate ventilation at all times [2, 43, 44]. At present, this is best provided by assisted ventilation particularly during sleep but may also be required during wakefulness [2, 43, 44]. Using supplemental oxygen without mechanical ventilation is insufficient because, while it results in improved PaO_2 and resolution of cyanosis, it does not treat hypoventilation. Trials with respiratory stimulants, such caffeine, doxapram, almitrine, and thyroxine, have been tried, but none have been found to be successful [45]. Recently, desogestrel, a potent progestin, has been found to improve the ventilatory responses to hypercapnia in two patients who had taken the drug for contraception, and animal data support its effect in improving basal ventilation [46, 47]. However, at present, it is too early to be adopted as the sole option in stimulating and sustaining sufficient respiration for adequate ventilation.

Modalities available for mechanically assisted ventilation include positive pressure ventilation via tracheostomy (PPV) [2, 20, 43, 44], noninvasive ventilation (NIV) via bilevel positive airway pressure or average volume assured pressure support ventilation [2, 3, 48, 49], negative pressure ventilators [19, 50, 51], and diaphragm pacing [2, 52–54]. PPV via tracheostomy is the most common mode of ventilatory support for CCHS patients [17, 19]. It is considered the most effective and safest particularly for infants and chil-

dren as they spend majority of the day sleeping. For older children who continue to require full-time mechanical ventilation, diaphragm pacing during the daytime with positive pressure ventilation via tracheostomy during sleep is an attractive option to allow for mobility and independence from the home ventilator [2]. Older CCHS patients who require ventilatory support only during sleep can be transitioned to diaphragm pacing or noninvasive positive pressure ventilation via nasal or face mask. Although noninvasive ventilation has been used as the sole ventilatory support in young infants and children [49, 50, 55], the ATS currently recommends transition to noninvasive ventilation when patients are older [2]. There is increasing evidence that prolonged use of noninvasive positive pressure ventilation affects facial growth resulting in midface hypoplasia and malocclusion [56, 57]. Thus, for patients who are placed on noninvasive positive pressure ventilation long term, particularly when started at a young age, close monitoring with lateral cephalometry and by a craniofacial team should be part of the management plan.

Diaphragm pacing (DP) is a mode of ventilatory support that uses the child's diaphragm as the respiratory pump. With DP, an external transmitter generates electrical energy similar to radiofrequency. The electrical energy is transmitted via external antennae placed over surgically implanted receivers. The receivers convert the energy to electrical currents that are conducted via electrodes surgically implanted under the phrenic nerves, resulting in stimulation and contraction of the diaphragm [2, 53]. CCHS patients are ideal candidates for diaphragm pacing as they have normal diaphragm function and intact phrenic nerves and generally have little or no lung disease. In addition to providing daytime ventilation for ambulatory CCHS patients who require full-time support, it does allow for the option of decannulation in patients who require only nighttime support after about 5 or 6 years of age [52]. Diaphragm pacing is generally used for a maximum of 14 hours per day to prevent diaphragm fatigue. Thus, in those patients who are being considered for diaphragm pacing but continue to require full-time ventilation, an alternate method for ventilation for the remaining hours must be available. Obstructive sleep apnea can be a complication of diaphragm pacing without tracheostomy, as synchronous upper airway skeletal muscle contraction does not occur with each diaphragm contraction [52, 58, 59]. This can be addressed by adjusting pacer settings to lengthen inspiratory time and decrease the force of inspiration [52, 59].

Negative pressure ventilation works by applying a negative pressure outside of the chest and abdomen during inspiration in order to generate ventilation. This form of ventilation may provide effective ventilation for children and adolescents, but there is no synchronous activation of the upper airway muscles, and therefore upper airway occlusion can occur when a negative pressure ventilator generates a breath during sleep. The use of negative pressure ventilators for CCHS has diminished, likely due to advances and portability of positive pressure ventilators and noninvasive positive pressure ventilators. However, it remains an option for those patients who desire to be ventilated noninvasively.

CCHS patients do not have normal physiologic responses to hypoxia and hypercapnia that stem from even minor respiratory illnesses, exposure to respiratory depressants such as alcohol and anesthetic/sedating medications, as well as activities that involve breath-holding like underwater swimming. The usual evidence of respiratory distress will not be present and therefore cannot be relied upon as a marker to evaluate for acute hypoxemic or hypercapnic respiratory failure. CCHS patients are exquisitely sensitive to the respiratory depressant effects of medications such as benzodiazepines, narcotics, and inhalational anesthetics. Thus, when they are given these medications in the perioperative period, they should receive full-time ventilatory support, and their gas exchange should be carefully monitored with pulse oximeter and capnography to mitigate respiratory morbidity [60, 61].

As part of monitoring for ventilatory status and ventilator requirements, children with CCHS should undergo polysomnography at regular intervals. They need periodic echocardiograms to monitor for the development of pulmonary hypertension [4]. When pulmonary hypertension is identified, it needs to be assumed to result from inadequate ventilation requiring need for increased ventilatory support.

All patients with confirmed diagnosis of CCHS require evaluation and monitoring for associated autonomic nervous system dysfunction, guided by the PHOX2B genotype as well as patient's age [2]. Twenty percent of CCHS patients have Hirschsprung's disease (HD), most prevalent in patients with NPARMs as well as 20/27 PARM. These at-risk patients require evaluation with barium enema and/or rectal biopsy, particularly when symptoms are present [2]. Patients with HD typically present in the neonatal period with abdominal distension, failure to pass meconium, constipation, or feeding difficulties, and 70% were diagnosed before 1 month of age in one case series [17, 18, 62]. Most patients have long segment HD (aganglionosis extending to above the splenic flexure or total colonic form), but there is currently no correlation between the length of aganglionic segment and severity of CCHS [17, 18]. Following surgical intervention, these patients benefit from continued follow-up by surgery or GI, as they many have persistent bowel dysfunction with soiling, constipation, or diarrhea [18].

Neonates may have difficulty swallowing, emesis, and gastroesophageal reflux [45, 62]. Esophageal dysmotility in the absence of symptoms has been described in adolescents with CCHS [63]. These GI manifestations suggest central swallowing dysfunction due to central pattern generator changes or to abnormal input from the brainstem regions.

Thus, dysphagia evaluation, as well as assessment of esophageal dysfunction with upper GI study and/or manometry, is indicated in CCHS patients both with and without symptoms.

CCHS patients may have cardiovascular abnormalities such as bradycardia, decreased heart rate variability, and blood pressure abnormalities (i.e., low normal daytime blood pressure, orthostatic hypotension, and no dipping blood pressure circadian pattern) [64–67]. They are at risk for life-threatening sinus pauses of >3 seconds and require cardiac pacemaker implantation [68]. These life-threatening arrhythmias have been described in patients with 20/25, 20/26, and 20/27 PARMs, as well as those with NPARMS. These patients with arrhythmias are often symptomatic with syncope, palpitations, and dizziness [29], but some have been asymptomatic, thus supporting the need for anticipatory arrhythmia monitoring. The American Thoracic Society recommends yearly 72-hour Holter monitoring, but the availability of Zio patch monitoring allows for longer assessments when necessary. The use of implantable cardiac monitoring has been reported in a patient with recurrent syncopal episodes with normal Holter recording [69], but its general use for CCHS patients is unclear at this time.

CCHS patients with NPARMS and longest PARMS (20/28–20/33 PARMS) are at risk for neural crest tumors, i.e., ganglioneuroma and ganglioneuroblastoma and neuroblastoma [2, 70, 71]. In general, frameshift and missense PHOX2B mutations predispose to neuroblastoma, while the longest PARMS are associated with ganglioneuroma or ganglioneuroblastoma [71]. For these patients, screening may include initial MRI and subsequent abdominal and pelvic ultrasounds.

Patients also warrant evaluation for ocular abnormalities, including pupillary and iris abnormalities, ptosis, strabismus, and convergence deficiency [72]. Other autonomic dysfunction abnormalities include endocrine abnormalities (i.e., hyperinsulinism, hyperglycemia, hypoglycemia) [73–76] and temperature dysregulation [77].

CCHS is a lifelong disorder. At this time, there is no known cure, but with early diagnosis and targeted management, patients can survive into adulthood and lead a productive life [14, 78].

An illustrative case highlighting the clinical presentation, confirming the diagnosis, and management of CCHS is presented at the end of the chapter.

ROHHAD/ROHHADNET

ROHHAD refers to a constellation of symptoms of rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation [79]. ROHHAD is an exceedingly rare disorder. The classic presentation is a previously healthy child with rapid weight gain due to hyperphagia after 2 years of age, followed by autonomic dysregulation at 3.5 years, behavioral derangements at 4.8 years, and alveolar hypoventilation at 6.2–7 years. Features of hypothalamic dysfunction include rapid onset obesity, impaired response to growth hormone stimulation tests, hyperprolactinemia, central hypothyroidism, diabetes insipidus, adrenal insufficiency, and alterations in pubertal development [79].

Respiratory manifestations include obstructive sleep apnea, snoring, cyanosis, alveolar hypoventilation with hypoxemia, and hypercapnia. Obstructive sleep apnea precedes the development of nocturnal hypoventilation and is the most common sleep-related breathing disorder at presentation [80]. Patients may also have central apneas with oxygen desaturation during wakefulness [80]. Exposure to sedatives may result in respiratory arrest, and when intubated, ROHHAD patients may fail weaning from assisted ventilation. Autonomic dysfunction may present as gastrointestinal dysmotility, thermal dysregulation, decreased pain sensitivity, ophthalmologic abnormalities (strabismus, pupillary abnormalities), and tachy-bradyarrhythmias. Neurobehavioral abnormalities are common and include personality changes, anxiety, depression, Tourette's disorder, obsessive compulsive disorder, and psychosis; and these maybe the symptoms that bring a patient to medical attention [79, 81, 82]. About 1/3 of patients with ROHHAD have neural crest tumors (ganglioneuroblastomas and ganglioneuromas) in the chest and abdomen. When neural crest tumors are present, the syndrome is classified as ROHHADNET [83, 84].

The pathogenesis of ROHHAD/ROHHADNET is unclear, although autoimmune alterations have been postulated [85–89]. At present, there is no genetic determinant or biomarkers to define the syndrome [82, 90–92]. Familial cases have been reported, suggesting that ROHHAD may be a monogenic condition [93].

Physiologic studies indicate that ROHHAD patients have diminished tidal volumes and inspiratory drive in response to hypoxic and hypercapnic challenges and have absent behavioral awareness to the physiologic compromise. Although their awake control of breathing deficit is more subtle than that found in CCHS, suggesting preservation of peripheral chemoreceptor drive, ROHHAD patients are markedly susceptible to hypoxemia and experience extreme inability to maintain adequate oxygenation. This physiologic compromise can be due to a combination of (1) reduced inspiratory drive and diminished tidal volume response to hypoxic hypercapnia, (2) effects of obesity on breathing such as decreased functional residual capacity, decreased tidal volume and restrictive lung disease, (3) absent perception of air hunger, and (4) altered hypothalamic input to respiratory circuits interfering with ventilatory control. This combination of factors predisposes ROHHAD patients to respiratory failure [94].

The diagnosis of ROHHAD is based on clinical presentation. Since rapid weight gain is the most consistent feature, it should be highly considered in all children with rapid and early onset obesity after the age of 2 years.

Patients with ROHHAD/ROHHADNET should be differentiated from congenital central hypoventilation syndrome which shares the same features of alveolar hypoventilation and autonomic dysfunction. CCHS is due to mutations in the PHOX2B gene, which is absent in ROHHAD. Furthermore, significant hypothalamic dysfunction is absent in CCHS. ROHHAD patients should also be differentiated from Prader-Willi syndrome which is also characterized by morbid obesity, hyperphagia, hypoventilation, and autonomic dysfunction. PWS patients also have short stature and behavioral issues. However, unlike ROHHAD who are generally healthy until the onset of obesity after 2 years of age, PWS patients present with hypotonia, feeding problems, and weak cry or inactivity from birth [95]. In addition, PWS patients have the characteristic facial features (i.e., almond-shaped eyes, narrow nasal bridge, thin upper lip, and down-turned corners of the mouth).

Clinical Management

The most dangerous feature of ROHHAD is profound hypoventilation and, if unrecognized, results in rapid deterioration to cardiorespiratory arrest and death. Therefore, early recognition and initiation of ventilatory assistance cannot be overemphasized. Ventilatory support, either during sleep only or for 24 hours, is the mainstay of care in all ROHHAD patients. This is provided by positive pressure ventilation via tracheostomy or noninvasive positive pressure ventilation. The use of AVAPS mode can be considered in ROHHAD due to their morbid obesity. Patients need close monitoring for central apneas and hypoxemia during wakefulness, as these may indicate worsening respiratory morbidity [80]. Since nocturnal hypoventilation may not be present initially but develop over time [80], ROHHAD patients require periodic sleep studies to ensure optimal oxygenation and ventilation, aiming for a goal of ≥95% and end-tidal carbon dioxide between 35 and 45 mmHg [79].

When ROHHAD is suspected, a patient must undergo evaluation of the hypothalamic axis and MRI or CT screening of the chest and abdomen as tumors of neural crest origin predisposition is high, up to 40% [83, 93]. Brain imaging should always be performed to rule out intracranial lesions causing hypothalamic-pituitary abnormalities [83].

Once the diagnosis is established, screening for tumors of neural crest origin with chest and abdominal imaging should occur every 12–18 months; if no tumor is identified in 10 years, screening can be performed every 2 years thereafter [79]. If a tumor is present, it must be removed. Immunomodulator therapies such as IV immunoglobulins, cyclophosphamide, Rituximab, and mycophenolate have provided symptomatic improvement in some patients [86, 96, 97].

A multidisciplinary approach is essential in the management of patients with ROHHAD. Due to the wide array of problems encountered by ROHHAD patients, the team should be comprised of but not limited to pediatrician, pediatric pulmonologist, sleep specialist, pediatric endocrinologist, intensivist, cardiologist, neurologist, pediatric psychiatrist/psychologist, and pediatric surgeon.

Chiari Malformation and Myelomeningocele

With Chiari malformation (CM), there is herniation of the medulla and cerebellum, which results in obstruction of cerebrospinal fluid from the fourth ventricles. These patients then develop hydrocephalus. In type I CM, there is caudal displacement of the cerebellar tonsils at least 3 mm into the upper cervical canal [98]. There is a type of CM known as 1.5, in which there is herniation of the cerebellar tonsillar along with brainstem and the fourth ventricle [99]. With type II CM, there is extension of the cerebellar tonsils as well as brainstem tissue into the foramen magnum. This is often in addition to a myelomeningocele, which is a form of spina bifida [98]. With brainstem involvement, central control of breathing is affected [84].

Clinical Presentation

Infants with CM can have central or obstructive sleep apnea as a result of hydrocephalus, which can cause compression of the brainstem. Hydrocephalus can also result in compression of the recurrent laryngeal nerve resulting in abnormal vocal cord movement. As a result, any patient with CM noted to have apnea or abnormal vocal cord movement should be presumed to have hydrocephalus until proven otherwise [99–105]. Infants can have sleep-related hypoventilation, obstructive apneas, and breath-holding spells [106]. Infants with myelomeningocele, hydrocephalus, and Arnold-Chiari malformation can have hypoventilation or apnea in up to 72% of cases unrelated to the level of the spina bifida lesion. Davidson Ward and coworkers found that infants were clinically asymptomatic but had abnormal sleep-related ventilatory patterns on polysomnography. They also reported abnormalities in the hypoxic and hypercapnic arousal responses in these patients [107, 108]. Swaminathan et al. found decreased hypercapnic ventilatory responses in both children and adolescents with CM2. Adolescents with CM have been found to have lower hypercapnic ventilatory responses [84]. Gozal and associates found some patients had abnormally low hypoxic responses, while most were normal when they studied peripheral chemoreceptor function [84, 109].

Clinical Management

Patients with Chiari malformation found to have central or obstructive sleep apnea or abnormal vocal cord movement should be evaluated for hydrocephalus and if found would require ventriculoperitoneal shunt (VPS). If VPS does not resolve their ventilatory abnormalities, posterior fossa decompression surgery can be considered. However, results from studies are mixed, and this technique does not always result in improved ventilatory function [110]. These patients require regular polysomnography, therefore, as part of their evaluation and management [111]. Patients should be monitored carefully for stridor while awake, as this may be a manifestation of vocal cord paralysis and posterior fossa herniation, and should therefore be evaluated by laryngoscopy and brain imaging, respectively. Tracheostomy may be required for vocal cord paralysis. Chronic ventilatory support may be needed for patients with sleep-disordered breathing and central hypoventilation, which can be by noninvasive positive pressure ventilation for patients who only need support during sleep, or positive pressure ventilation via tracheostomy for patients who require support during both sleep and wakefulness [112, 113].

Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is a genetic disorder caused by a deletion of the long arm of paternally derived chromosome 15 (15q11.2-q13) characterized by sleep disorders, hypotonia, obesity, hyperphagia, mental retardation, hypogonadism, and behavioral disorders. While patients early in life may have poor weight gain, they will later develop significant hyperphagia that results in morbid obesity if their dietary intake is not restricted. This disorder has a prevalence of approximately 1:10,000 to 1:25,000 [114, 115]. Patients have hypothalamic dysfunction, i.e., growth hormone and thyroid hormone deficiencies and autonomic dysregulation manifested by ophthalmologic problems, high pain threshold, and temperature instability. Children with PWS have cognitive disabilities and are delayed in reaching their language and motor milestones. They have characteristic behaviors that include temper tantrums, resistance to change, manipulative tactics, and compulsiveness. It is believed that dysfunction of the anterior hypothalamus results in the clinical manifestations of this disorder.

Clinical Respiratory Features

Patients with PWS often have excessive daytime fatigue, abnormal organization in REM sleep, abnormalities of arousal, obstructive sleep apnea, restless movements during sleep, hypoventilation, and hypoxia [116]. Risk factors for the development of sleep abnormalities include obesity, alterations in cranial structures, kyphoscoliosis, hypotonia, and impaired ventilatory control [116–118]. While obesity may further worsen the sleep-disordered breathing, these patients have absent or blunted hypercapnic ventilatory responses that are independent of obesity [119]. Gozal and colleagues found that patients with PWS have defective chemoreceptor ventilatory responses that are likely due to abnormal peripheral chemoreceptor function and/or defective afferent pathways to central controllers [120–122].

Clinical Management

Patients can be evaluated by polysomnogram to characterize sleep-disordered breathing and direct management. Obstructive sleep apnea may require adenotonsillectomy, supplemental oxygen, noninvasive positive pressure ventilation, or invasive positive pressure ventilation via tracheostomy, although the latter is rare in PWS patients [113, 116, 123]. Management of obesity through behavioral modification, nutrition counseling, and weight management can be helpful in decreasing the risk for OSA [116, 124]. Although bariatric surgery has been explored for these patients, outcomes have been poor [125].

There is a potential role for growth hormone therapy if precautions are taken. Growth hormone can be used to increase lean body mass and growth velocity, and one study found improvement in response to CO_2, ventilation, and central inspiratory drive [126]. However, caution should be taken prior to starting growth hormone as there is an increased risk of tonsillar and pharyngeal soft tissue hypertrophy, which can lead to obstructive sleep apnea. In rare cases, sudden death can occur in patients started on GH, and therefore, patients should undergo polysomnography and upper airway examination prior to starting treatment with this medication and should be closely monitored thereafter. The risk of sudden death is increased with previously existing OSA, respiratory tract infection, obesity, and other previously existing cardiopulmonary disease. If indicated, patients should have adenotonsillectomy prior to starting GH [127–132].

Achondroplasia

Achondroplasia is caused by autosomal dominant mutations in the fibroblast growth factor receptor 3 (FGFR3). It results in inhibition of normal proliferation and maturation of growth plate chondrocytes, which results in decreased growth plate size, reduced trabecular bone volume, and decreased bone elongation [133].

Clinical Respiratory Features

Patients with achondroplasia may present with obstructive sleep apnea, waking cyanotic episodes, and chronic respiratory insufficiency or failure. Characteristics of this disorder that increase the risk for respiratory compromise include

midface hypoplasia, upper airway obstruction, occipital dysplasia, cervicomedullary cord compression due to a small foramen magnum, and thoracic cage restriction. The latter can impact lung growth and result in insufficient ventilation [134].

Management

Various assessments may be indicated for these patients depending on their presentations. Testing may include imaging for hydrocephalus and cord compression, monitoring of gas exchange, overnight polysomnography, and pulmonary function testing [135]. Patients may require VPS placement for hydrocephalus, cervicomedullary decompression for disordered central respiratory control, supplemental oxygen for hypoxemia, adenotonsillectomy for adenotonsillar hypertrophy contributing to OSA, noninvasive positive pressure ventilation (NPPV) for hypoventilation and/or OSA, and tracheostomy for severe OSA. They may also require mechanical ventilation for hypoventilation with restrictive lung disease [134, 136].

Leigh Syndrome

Leigh syndrome, also known as subacute necrotizing encephalomyelopathy, is a hereditary neurodegenerative disorder of infancy and childhood. These patients have progressive brainstem dysfunction [137]. This disorder is caused by defects in mitochondrial enzymes [138, 139]. Patients are typically affected in infancy and early childhood [140].

Patients with Leigh Syndrome can have minimal abnormalities or may have severe neurologic impairment. They may present with poor feeding, emesis, apnea, alveolar hypoventilation, and developmental regression. Evidence of brainstem involvement include nystagmus, bizarre eye movements, pupillary changes, and hypotonia, seizures, and sleep-wake disturbances. Patients who have irregular breathing, deep sighing, unexplained hyperventilation, or hiccups with lethargy may be showing prodromal evidence of impending respiratory failure and should be evaluated with neuroimaging. Because of the poor prognosis with many of these patients, chronic ventilatory support with mechanical ventilation is often not offered [141, 142].

Joubert Syndrome

Patients with Joubert syndrome (JS) have distinctive cerebellar and brainstem malformation called the molar tooth sign, hypotonia, and developmental delay. These patients often have episodic tachypnea and apnea as well as abnormal eye movements. The respiratory abnormalities usually occur during wakefulness but are also common during sleep [143–145]. Breathing abnormalities tend to improve with age in some patients, while truncal ataxia develops over time, and patients may have delayed development of gross motor milestones [146]. Brainstem involvement results in short episodes of tachypnea up to respiratory rates of 200, followed by apnea [146, 147] that predominates in NREM sleep. Obstructive apneas can occur due to hypotonia and facial features [145]. The tachypnea is more common in the newborn period, with apnea becoming more common later.

Clinical Management

A brain MRI should be obtained as part of the workup for suspected Joubert syndrome to evaluate for the pathognomonic molar tooth sign, which is the result of cerebellar vermis hypoplasia, deep interpeduncular fossa, and thickened superior cerebellar peduncles [146, 148–150]. Once the diagnosis has been confirmed, further evaluation is necessary to look for multisystem organ involvement including the eye, kidney, liver, and thyroid involvement [151] as well as polydactyly, congenital heart defects, median line defects, and situs inversus [151]. Other brain involvements such as encephalocele, hydrocephalus, Dandy Walker syndrome, and absence of pituitary gland have been reported and should be looked for [151–153]. As sleep-related breathing disorder is prevalent in this population, patients need evaluation with overnight polysomnography [146, 149]. Home apnea-bradycardia monitoring can be considered for infants and children with abnormal breathing patterns. Some patients may benefit from caffeine or supplemental oxygen. Some severely affected infants may require assisted ventilation, possibly with tracheostomy [146, 149]. One study found resolution of central events, improvement in sleep quality, and normalization of oxygenation during wakefulness in patients treated with NPPV [144]. Initiation of NPPV should be performed with attended overnight polysomnography to determine the best settings to resolve the central and obstructive events [145, 154]. Some patients may require nutritional support via gastrostomy tube, especially those with hypotonia or oromotor dysfunction that places them at increased risk of aspiration [146]. Mortality is largely due to respiratory failure in children less than 6 years of age in one cohort [155], emphasizing the importance of high index of suspicion, close monitoring, and management of respiratory disturbances and aspiration in these patients.

Patients with Joubert syndrome are remarkably sensitive to the depressant effects of opioids, which can cause central apneas. In addition, their craniofacial features put them at risk for obstructive sleep apnea. Thus, when undergoing procedures or anesthesia, these patients should be vigilantly monitored during the perioperative period, and medications that do not affect the respiratory drive or short acting opioids should be highly considered [156, 157].

Familial Dysautonomia

Familial dysautonomia, also known as Riley-Day syndrome, primarily affects patients of Ashkenazi Jewish descent. The estimated incidence is 1:3600 in this population. It is a recessively inherited disorder. This disorder carries a high mortality. Autonomic dysfunction can affect multiple organ systems [158].

Clinical Respiratory Features

These patients typically present at birth and have a progressive course. They may initially have feeding problems and hypotonia and recurrent aspiration from swallow dysfunction and gastroesophageal reflux disease that contribute to chronic lung disease. Affected children can have episodes of the so-called dysautonomic crises characterized by agitation, tachycardia, and hypertension with vasomotor instability [158].

The most concerning respiratory abnormality is insensitivity to hypoxemia and hypercarbia. At high altitude or with respiratory illness, patients can have profound instability with hypotension, bradyarrhythmia, and syncope. Some patients require chronic mechanical ventilation if they have recurrent apneic episodes and hypoventilation. Because respiratory abnormalities may go undetected, these patients are at risk for sudden unexpected death, which is the most frequent cause of unexpected death during sleep. However, if patients are diagnosed and managed appropriately, they can live into adulthood [158–160].

Acquired Central Hypoventilation Syndromes

Central hypoventilation syndromes may develop secondary to underlying causes such as brain neoplasms, infection, and infarction, or following neurosurgical procedures when the brainstem is affected [161–165]. It is unlikely that affected individuals will have primary peripheral chemoreceptor dysfunction, given the anatomical distinction of these chemoreceptors from the brainstem. Instead, patients are likely to have central chemoreceptor and integration dysfunction. There is likely ventilatory muscle weakness or paralysis as a result of disruption of the motor tracts leading to ventilatory muscles [134].

Children with acquired central hypoventilation syndromes will typically require full-time ventilatory support, with variation depending on the initial insult and extent of injury. Particularly, following resection of craniopharyngioma, patients can have panhypopituitarism, OSA as a result of obesity, as well as central hypoventilation syndrome. Sometimes they can be managed with noninvasive positive pressure ventilation with a backup rate or in timed mode.

Management

Children with central respiratory control disorders are generally considered candidates for chronic home mechanical ventilation. Patients are at increased risk for the development of pulmonary hypertension if chronic hypoventilation is not managed adequately. Supplemental oxygen alone improves the PaO_2 and relieves cyanosis, but this treatment is insufficient to treat hypercarbia. These patients should be optimized with assisted ventilation, whether during sleep only or throughout the day.

We recommend optimizing ventilator settings to achieve a goal of $P_{ET}CO_2$ of 25–35 mm Hg and S_pO_2 greater than 95% [1, 4]. It is our experience that children who are hyperventilated at night have better spontaneous ventilation and maintain better gas exchange while awake.

There are several options for modalities of chronic respiratory ventilatory support for patients with central hypoventilation syndrome. These options include portable positive pressure ventilation via tracheostomy; NNPPVPPV via nasal, oronasal, or full-face mask (for patients who require support only during sleep); negative pressure ventilation; or diaphragm pacing.

For patients ventilated by positive pressure ventilation via tracheostomy, a relatively smaller uncuffed tracheostomy tube is recommended to prevent tracheomalacia and because the larger leak with a smaller tracheostomy is associated with improved ability to speak. For patients with central hypoventilation, the authors recommend the assist control mode, although some have used the SIMV with an appropriate backup rate.

With NPPV, the difference between inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) must be adequate to deliver adequate tidal volume, and EPAP must be adequate to maintain functional residual capacity. An attended polysomnography should be instituted for patients on noninvasive ventilation to determine the optimal treatment pressure settings [166]. NPPV should be used in spontaneous/timed or timed mode to guarantee breath delivery for optimal gas exchange. Average volume-assured pressure support ventilation (AVAPS) has been found to be successful in patients with CCHS and obesity hypoventilation syndrome. During acute respiratory illness, patients on NPPV may require intubation.

Negative pressure ventilation (NPV) can be an option for patients who cannot tolerate mask noninvasive positive pressure ventilation but want to be ventilated noninvasively. The downside to NPV is that it is more cumbersome and difficult to use than the current NPPV devices. In addition, NPV can predispose to obstructive apneas in those with neuromuscular and bulbar weakness due to absence of

coordination between upper airway muscle activity and ventilator cycle [167].

Regardless of mode of ventilatory support provided, patients with respiratory control disorders should undergo periodic overnight polysomnography to assess adequacy of ventilatory support as a result of the child's growth and development and associated conditions.

Other factors that can affect ventilation include electrolyte disturbances and medications. Chronic metabolic alkalosis can further inhibit central respiratory drive and should be avoided. Serum chloride concentrations should be kept at greater than 95 mEq/dL. Medications that cause sedation and/or central nervous system depression should be avoided or used with extreme caution when use is absolutely necessary.

Illustrative Case

The patient is a 5-month-old male who was born full term and presented with cyanosis, lethargy, and pallor. He was noted to have oxygen saturation of 50% on room air. He had been discharged from the newborn nursery at 3 days of life and appeared to be well until 4 months of age, when he became fussy, had decreased feedings, and had increased reflux symptoms. He was diagnosed with gastroenteritis and managed accordingly. He had poor weight gain that did not improve with formula change. His mother reported that, in retrospect, he may have had pallor or cyanosis during sleep and that his fingernails were occasionally blue. She also reported decreased stooling and sweating with feeds. Immunizations were up to date, and he was noted to become apneic with his immunizations.

At the time of presentation, he was cyanotic and pale and had abnormal movements concerning for a seizure. CBC showed elevated hemoglobin of 15, and CBG showed hypercapnia with a CO_2 of 80. A chest X-ray showed cardiomegaly and mild chronic lung disease. He was admitted to pediatric intensive care unit intubated and mechanically ventilated. An echocardiogram confirmed cardiomegaly, and a cardiac catheterization showed pulmonary hypertension without intrinsic cardiac disease. MRI of the brain showed matter hypoplasia.

A diagnosis of CCHS was suspected and therefore genetic testing was sent, which confirmed that he has a PHOX 2B 20/25 polyalanine repeat mutation (PARM), confirming the diagnosis of CCHS. He subsequently underwent tracheostomy and transitioned to home mechanical ventilation. He had G tube placed for feeding due to dysphagia.

With appropriate ventilatory support, alveolar hypoventilation improved. His pulmonary hypertension improved with sildenafil, in addition to full ventilatory support. His pulmonary hypertension gradually resolved with adequate ventilation.

This vignette illustrates CCHS presenting from birth and the consequences that occur with a delayed diagnosis, emphasizing a high index of suspicion, the role of *PHOX2B* gene testing to confirm the diagnosis, and the importance of optimal ventilatory support.

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Disorders of Excessive Sleepiness

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Introduction

Clinical and epidemiological studies have proven that sleep is necessary for the development of optimal cognitive and behavioral performance, for maintaining a stable mood and affect, and for overall well-being and health [1]. Sleep in children can be characterized both qualitatively and quantitatively. The American Academy of Sleep Medicine (AASM) has published an expert consensus recommendation for sleep duration per 24 hours in children at various ages. This consensus states that in order to promote optimal health, infants 4 months to 12 months should sleep 12–16 hours per 24 hours (including naps), children 1–2 years of age should sleep 11–14 hours per 24 hours, children 3–5 years of age should sleep 10–13 hours, children 6–12 years of age should sleep 9–12 hours, and teenagers 13–18 years of age should sleep 8–10 hours [2]. National and global sleep societies have increased their efforts to bring awareness to the adverse impact of sleep deprivation in children [3]. The main symptom of insufficient sleep is excessive daytime sleepiness (EDS), defined as the inability to stay awake or alert during the day [4]. EDS can be physiological when associated with insufficient sleep or can be pathological when associated with an underlying medical condition or sleep disorder [4].

The prevalence of EDS in children and adolescents ranges from 17% to 47% [5, 6], but in some populations, the prevalence of EDS has been reported to be as high as 68% [7]. The exact prevalence of EDS in children may remain unknown because families do not always seek medical evaluation for children with EDS. In fact, sometimes children suffering from EDS can be misunderstood to be inattentive, or lacking motivation [8] instead of perceived as being sleepy. In fact, the clinical signs of EDS in younger children can be irritability, moodiness, inattention, and hyperactivity, while in older children and adolescence, EDS can manifest as impulsivity, poor academic performances, and accident proneness [9]. Other more general signs of EDS include return to napping, prolonged sleep periods, intrusive sleepiness (represented by microsleeps (5–10 seconds) that cause lapses in attention, nodding off when sedentary, and REM phenomena (hypnagogic hallucinations) [10].

In this chapter, we will be focusing on central disorders of hypersomnia including narcolepsy, idiopathic hypersomnia, Kleine-Levin syndrome, and insufficient sleep syndrome. These disorders usually manifest during childhood or adolescence and persist into adulthood.

Narcolepsy

Definitions

Narcolepsy is a rare central disorder of hypersomnia characterized by sleep and REM dysregulation. Sleep dysregulation manifests as excessive daytime sleepiness during the day and significant sleep disruption at night. REM dysregulation may manifest as cataplexy, defined as a sudden loss of muscle strength in the legs, trunk, face, or neck, that can be triggered by emotions such as laughter or rage during wakefulness [4]. It is believed to represent intrusion of REM atonia during wakefulness. Other manifestations of REM dysregulation are the presence of sleep-onset REM periods (SOREMP) in naps or nocturnal sleep onset, hypnopompic (upon waking from sleep) or hypnagogic (at sleep onset) hallucinations and sleep paralysis, which is the brief inability to move upon awakening or while falling asleep [11]. As we will discuss below, in children, these manifestations present

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differently, or are not present at all contributing to challenges in the early diagnosis of narcolepsy [12].

The presence or absence of cataplexy further subdivides narcolepsy in two subtypes: narcolepsy type 1, characterized by the presence of cataplexy (NT1), and narcolepsy type 2 characterized by the absence of cataplexy (NT2) [4].

Epidemiology

The prevalence of narcolepsy in children is less studied than narcolepsy in adults, despite the observation that symptoms usually begin in childhood or adolescents [13], with 65% of patients presenting before the age of 20 years old [12, 14]. The mean age for onset of symptoms occurs approximately at 9–10 years old [15–21]. A large prospective study showed onset of symptoms occurring before puberty in 5% of children [22]. The accurate estimate of narcolepsy prevalence in childhood is not known partly due to a delayed diagnosis (up to 15 years) [12] despite early onset of symptoms. A European study estimated the prevalence of narcolepsy in children to be 0.13/100,000 in children less than 5 years old and 0.38/100,000 in children 5–19 years old [15, 16].

Pathophysiology

Narcolepsy in humans has been associated with low to absent levels of cerebrospinal (CSF) hypocretin. In NT1, there is loss of hypocretin-producing neurons in the hypothalamus [23]. This hypocretin system alteration underlying NT1 has been postulated to be secondary to an autoimmune process. Children with NT1 typically test positive for the HLA-DQB1*0602 antigen [24]. NT1 has also been associated with polymorphisms of immune-related genes including P2RY11, CTSH, and TNFSF4 [25, 26]. Other evidence to support the autoimmune theory includes the association between NT1 and influenza A virus subtype H1N1 after the influenza pandemic in China [27] and after the vaccination campaigns with Pandemrix in northern European countries [28]. These data have supported that the presence of the HLA-DQB1*0602 alone will not cause narcolepsy but needs an environmental factor to precipitate it such as illness, stress, and, recently, molecular mimicry to influenza [29]. Figure 30.1 further illustrates the immunologic mechanisms behind narcolepsy.

Narcolepsy type 2 is less well understood. Part of the diagnostic criteria for NT2 is normal or moderate levels of hypocretin [30]. It has been postulated that NT2 is still due to loss of hypocretin-producing cells, though just not to the degree as in NT1 [31].

The majority of narcolepsy cases are idiopathic; however, secondary narcolepsy has been reported in children with lesions of the posterior and lateral hypothalamus or midbrain. These lesions may be caused by tumors, stroke, and demyelination disorders such as multiple sclerosis, trauma, or inflammation. Due to the areas affected in the hypothalamus, children develop hypersomnia *and* overt neurologic deficits (e.g., abnormal eye movements, focal weakness, pituitary dysfunction, or obesity). The mechanism is associated with disruption of the hypocretin system/neurons or their connections to REM- and wake-regulatory regions.

In addition, children with narcolepsy often have one or more comorbid psychiatric conditions such as anxiety, depression, ADHD, eating disorders, or schizophrenia [32]. These comorbidities are likely not the result of sleep disturbance alone, but due to a shared pathophysiology. Hypocretin has a direct excitatory effect on serotonergic neurons and the noradrenergic system which are known to be involved in anxiety and depression [33, 34]. Hypocretin deficiency will lead to downregulation of noradrenergic and dopaminergic signals which are neurotransmitters of wakefulness and upregulation of cholinergic pathways involved in REM regulation [35]. An interesting fact is that the downregulation of dopaminergic signals may be responsible for the increased number of periodic leg movements seen in children with narcolepsy [36].

Seventeen percent of children with narcolepsy with cataplexy exhibit precocious puberty [37]. Although it is not proven that hypocretin deficiency directly affects puberty, studies have shown that hypocretin neurons have an effect on growth hormone, which is an important regulator of puberty [38].

Hypocretin deficiency can contribute to weight gain and obesity in children with narcolepsy. Hypocretin is also called orexin, which was termed in 1998 after the Greek word for "orexis" meaning appetite [39]. This neuropeptide not only regulates the sleep-wake cycle, but animal models show that it is a central mediator of energy metabolism [39–42] and food consumption. Obesity in patients with NT1 ranges from 25% to 74% [37] and is more prevalent in NT1, compared to patients with NT2 and normal hypocretin levels [43]. Studies also show that the basal metabolic rate in patients with narcolepsy is reduced by 25% compared to healthy controls, controlling for food intake and exercise, suggesting that obesity is related to basal energy metabolism [44].

Clinical Features

The classic tetrad of narcolepsy includes EDS, hypnagogic hallucinations, sleep-related paralysis [45], and in NT1, the pathognomonic feature of cataplexy. EDS is always present, and often the initial presentation, while cataplexy may present years later [46]. This is important for diagnosis as initially children may be given the diagnosis of NT2, and

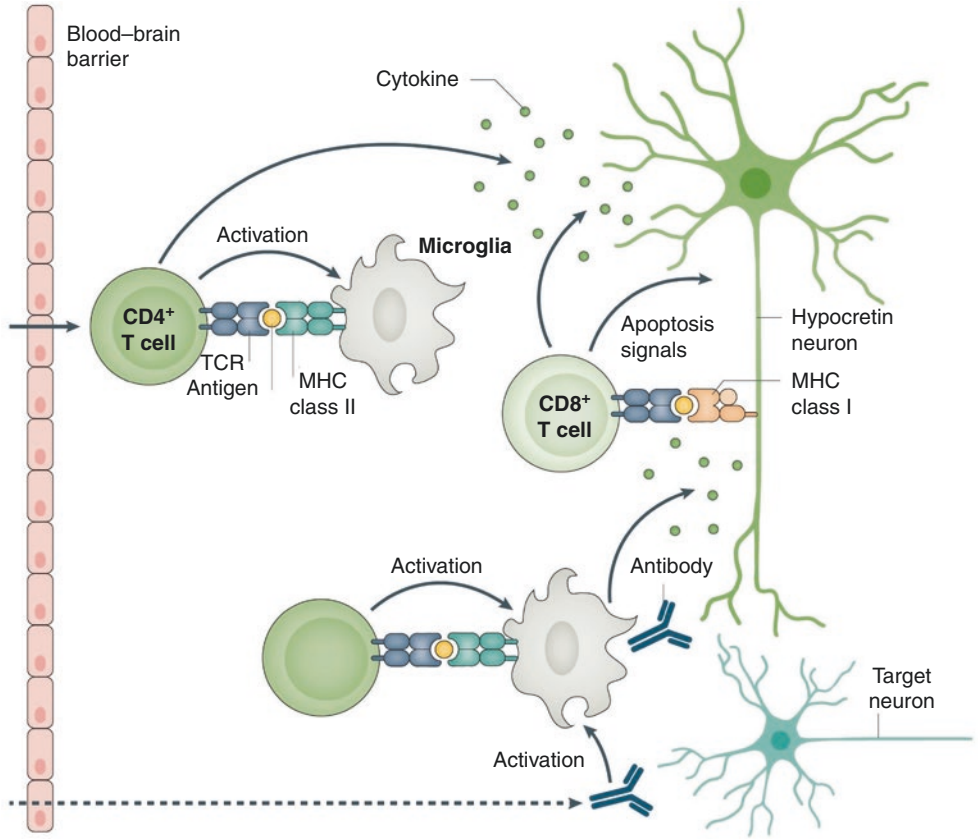


Fig. 30.1 Autoimmune hypothesis of narcolepsy type 1. (From Kornum et al. [109]. Reprinted with permission from Springer Nature) The most important elements in the current hypothesis of narcolepsy type 1 (NT1) pathogenesis include T cells, microglia, and antibodies. If autoreactive T cells and antibodies enter the brain, an immune reaction that leads to the destruction of hypocretin neurons in the lateral hypothalamus could be started. This autoimmune response could include the secretion of cytokines and chemokines by microglia or T cells, which could attract more immune cells and damage the hypocretin neurons or make them more susceptible to an attack from CD8+ T cells. The most likely mediators of the loss of hypocretin neurons are cytotoxic CD8+ T cells, which could provide proapoptotic signals to the hypocretin neurons, leading to neuronal loss. Although CD4+ T cells can enter the healthy brain, antibodies do not cross the blood–brain barrier under normal circumstances and only cross if the blood–brain barrier is compromised (dashed arrow) by a pathological event. In pathological conditions, autoantibodies can enter the brain, and, by binding to hypocretin neurons or their downstream targets, they could potentially have a role by activating the local microglia. TCR T-cell receptor

then when cataplexy ensues, the correct diagnosis of NT1 is attributed. The delayed onset of cataplexy may be secondary to disease progression. A study by Plazzi et al. demonstrated that cerebrospinal hypocretin levels progressively declined toward a complete deficiency, with levels parallel to clinical symptom presentation [47, 48]. This is particularly important in young children in whom CSF hypocretin levels may not show a significant deficiency. A lumbar puncture in children may need to be considered for adequate diagnosis [31, 49].

Cataplexy in childhood may also differ from cataplexy in adult patients. Close to disease onset, cataplexy often presents as a complex movement disorder, with negative and active phenomena [50, 51]. The negative component consists as a subcontinuous hypotonic condition, without a clear link to emotional stimuli and characterized by a general floppy aspect, altered gait, frequent and very brief (few seconds) falls to the ground, and a typical "cataplectic facies," with facial hypotonia, bilateral ptosis, mouth opening, and tongue protrusion [50, 51]. The positive component consists of hyperkinetic features involving mainly the face such as perioral/tongue movements, facial grimacing, eyebrow raising, but also in other body areas with stereotyped motor behaviors, and dyskinetic/dystonic movements [more evident in patients with a recent streptococcal infection] [52].

Close to disease onset, a clear link with emotions could be absent; "spontaneous" cataplexy gradually transitions into the picture of classical cataplexy triggered by strong often positive emotions [21, 51].

Recently, disrupted nighttime sleep (DNS) has been added as a core narcolepsy symptom consisting of patient report or frequent awakenings or polysomnographic evidence of fragmented sleep [53]. DNS has been reported to be more common than other manifestations of narcolepsy (sleep

paralysis and hypnagogic hallucinations) with prevalence ranging from 30% to 95% [53]. A retrospective polysomnography (PSG) analysis showed that the number of transitions from any sleep stage to wake or NREM stage 1 normalized by total sleep time (called the wake/N1 index) was associated with objective daytime sleepiness, daytime SOREMPs, self-reported disrupted sleep, and CSF hypocretin levels (p's < 0.003) and held highest area under the curve (AUC) for the diagnosis of NT1. When combined with a night SOREMP, the DNS index had greater accuracy for diagnosing NT1 [AUC = 0.91(0.02)] than a night SOREMP alone [AUC = 0.84, (0.02), LR test $p < 0.0001$). The authors concluded that the wake/N1 index is an objective DNS measure that can quantify DNS severity in pediatric NT1 and might be a useful sleep biomarker that improves recognition of pediatric NT1 using only the nocturnal PSG [54].

Clinical manifestations may vary by age. In very young children, identification of EDS may be difficult due to expected regular naps. The identification of cataplexy is of utmost importance in this age group. Consideration to measuring CSF hypocretin should be given to highly suspicious cases. In school-age children, return to napping in spite of adequate amount of sleep should raise a red flag. DNS can be present as well as increased periodic leg movements. School-age children also show more behavioral problems including hyperactivity and irritability during the day [15] that can be mistaken for attention-deficit hyperactivity disorder [12, 51]. A summary of the diagnostic features is found in Table 30.1.

Differential Diagnosis

The differential diagnosis for narcolepsy includes insufficient sleep syndrome, idiopathic hypersomnia (discussed below), and other primary sleep disorders that may cause excessive daytime sleepiness and disrupted sleep such as obstructive sleep apnea, periodic limb movement disorder, and, more recently described, restless sleep disorder [55]. This is complicated by the fact that these conditions may also be coexisting in narcolepsy; thus, if sleepiness remains despite treatment of these conditions, narcolepsy should not be overlooked. Idiopathic hypersomnia may also resemble narcolepsy though can be distinguished by lack of 2 SOREMPs on MSLT.

Other neurologic disorders, cardiac disorders, and psychiatric disorders are also on the differential diagnosis list for narcolepsy. For example, providers not well versed in cataplexy may diagnose it as syncope, a drop attack/seizure, or as part of a functional neurological disorder or other psychiatric disorder. It can also be difficult at times to distinguish subtle cataplexy such as cataplectic facies with features of other neuromuscular conditions such as ptosis seen in myasthenia gravis. Cataplexy may also be found in rare neurological conditions including Niemann-Pick type C, myotonic dystrophy, Moebius syndrome, Kearns-Sayre syndrome, and Prader-Willi syndrome.

Finally, one must not forget the contribution of prescription drugs, over-the-counter medication, and illicit drug use as a possible cause of EDS [56]. Common medications known to contribute to EDS include antihistamines [56], antiepileptics [57], antidepressants [58], and benzodiazepines [59].

Diagnostic Approach

A thorough history is of importance when evaluating children who present with excessive daytime sleepiness. This history should include questions about total sleep time including daytime naps, history of nocturnal sleep disruption, sleep hallucinations, and cataplexy.

In addition, non-sleep-related review of systems (ROS) should be completed to assess for the comorbidities associated with narcolepsy including questions regarding mood to assess for depression/anxiety, questions regarding attention/school performance to assess for ADHD, questions screening for precocious puberty, and questions screening for eating disorders.

It can also be useful to identify timing of onset of symptoms in terms of any relation to a potential trigger such as trauma, an upper respiratory infection, or streptococcal

Table 30.1 Diagnostic features of the various central disorders of hypersomnolence

Features	Narcolepsy type 1	Narcolepsy type 2	Idiopathic hypersomnia	Kleine-Levin syndrome	Insufficient sleep
EDS daily	At least for 3 months	At least for 3 months	At least for 3 months	From 2 days to 5 weeks at least once every 18 months	At least 3 months
Cataplexy	Present	Absent	Absent	Absent	Absent
Nocturnal sleep	Disrupted	Disrupted	Normal to prolonged	Not diagnostic	Less than required for age
MSLT sleep latency	8 minutes or less	8 minutes or less	8 minutes or less	Not diagnostic	Not diagnostic
SOREMP	2 or more	2 or more	Less than 2	Can occur	Can occur
Course	Chronic	Chronic	Chronic	Periodic/recurrent Can resolve	Resolves with adequate sleep

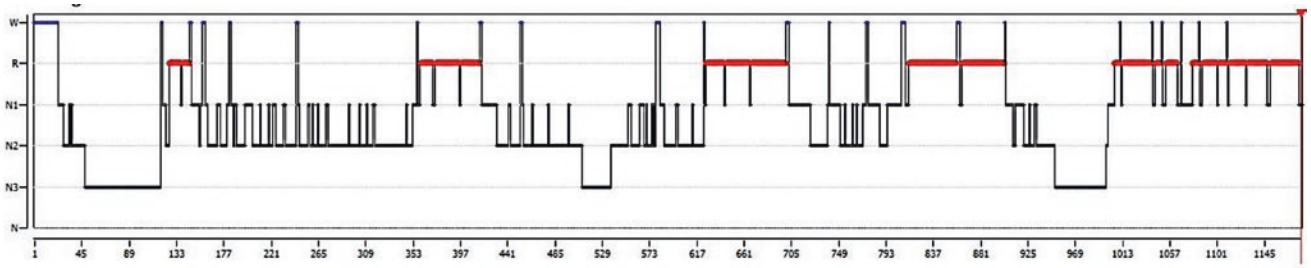
infection [52]. If symptom onset is explosive, then it could indicate secondary narcolepsy due to traumatic injury, for example.

Physical exam must include a note about the appearance of the child (i.e., "sleeping during the visit"), a note of appearance, Tanner stage, and vital signs including body mass index percent per age. A neurological examination assessing muscle tone and signs of cataplectic facies should be completed in every child presenting with excessive daytime sleepiness, since these features can predate distinct cataplectic episodes [50, 51].

If narcolepsy is suspected, objective evaluation with a PSG followed by multiple sleep latency test (MSLT) is recommended. The PSG is needed both to document adequate sleep the night prior to the MSLT and to assess for other sleep disorders [60]. During the MSLT, the child has 4–5 nap opportunities separated by 2-hour breaks. Both the mean sleep latency (MSL) and number of sleep-onset REM periods (SOREMPs) are used to diagnose narcolepsy [11, 61]. A study by Pizza et al. [62] recently validated the use of the MSLT in pediatric patients. They determined that an MSL of <=8.2 minutes and 2 SOREMPs are valid and reliable markers of pediatric NT1 diagnosis. It is important to note, however, that medications may interfere with interpretation of the MSLT, particularly REM suppressants. For example, children should wean and/or discontinue any antidepressants, stimulants, benzodiazepines, and/or antihistamines prior to their MSLT [61]. In addition, best practice is to obtain actigraphy accompanied by sleep diary for 1–2 weeks prior to the PSG/MSLT. This will better quantify total sleep time and differentiate narcolepsy from delayed circadian phase disorder or behaviorally insufficient sleep syndrome [61]. Figure 30.2 shows the MSLT results and hypnogram in a patient with NT1.

Although there is low specificity, if there is uncertainty of the diagnosis, especially if the history of cataplexy is questionable, then patients can be tested for the associated haplotype DQB1*0602. This haplotype is present in 95% of patients with cataplexy and 96% of those with hypocretin deficiency; however, it must be remembered that patients with NT2 are less likely to be positive and approximately 12–38% of the general population who will never develop narcolepsy are also positive [63].

The gold standard for diagnosing NT1 is measurement of cerebrospinal (CSF) hypocretin-1. A level of less than 110 pg/ml has a specificity of 99% and sensitivity of 88–94% [64].



Nap Summary

	Nap 1	Nap 2	Nap 3	Nap 4	Average
Lights Off	08:33:45 AM	10:31:10 AM	12:32:50 PM	02:28:39 PM	-
Lights On	08:49:52 AM	10:47:20 AM	12:48:22 PM	02:46:19 PM	-
Time In Bed	16.1	16.2	15.5	17.7	16.4
Sleep Time	15.3	15.3	14.8	17.2	15.6
Sleep Efficiency	94.8%	94.3%	95.2%	97.5%	95.5%
Sleep Onset	08:34:35 AM	10:32:05 AM	12:33:05 PM	02:29:05 PM	-
Sleep Latency	0.8	0.9	0.3	0.4	0.6
REM Onset	08:36:35 AM	10:32:05 AM	12:33:05 PM	02:31:05 PM	-
REM Sleep Onset Latency	2.0	0.0	0.0	2.0	1.0

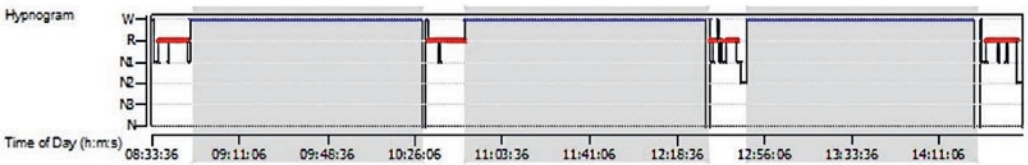


Fig. 30.2 Polysomnography hypnogram and multiple sleep latency test on a patient with narcolepsy type 1
Top section demonstrates a full-night hypnogram with early-onset REM and multiple brief nocturnal awakenings and sleep-stage shifts. The bottom part illustrates the results of a multiple sleep latency test showing SOREMP in all four naps with an average sleep latency of 0.6 minutes

The *International Classification of Sleep Disorders* third edition (ICSD-3) [4] has established clear diagnostic criteria for NT1. A patient must have daily periods of excessive sleepiness lasting for 3 months, and cataplexy and diagnostic findings in MSLT (sleep latency of 8 minutes or less with 2 or more SOREMPs) or CSF hypocretin-1 of 110 pg/ml or less (one third of the mean value for normal subjects can be an alternative criteria). For NT2, cataplexy must be absent, and hypocretin-1 does not have to be measured or is above 110 pg/ml (or above the level of one third the mean value for normal subjects). A SOREMP during nocturnal PSG prior to MSLT can replace one SOREMP during MSLT.

Management

Because of comorbidities noted above and common pathophysiology, it is recommended that treatment is provided by a multidisciplinary team formed by the general pediatrician, sleep physician, psychiatrist, psychologist, and endocrinologist to ensure appropriate treatment of comorbidities such as depression, anxiety, and obesity. In addition to systemic and mental comorbidities, comorbid sleep disorders can worsen symptoms of EDS in children with narcolepsy, and screening for obstructive sleep apnea, restless legs syndrome, and other sleep disorders is recommended.

Non-pharmacological treatment measures include changes in lifestyle habits and/or implementation of strict and appropriate sleep hygiene. This includes maintaining a normal sleep schedule that can include 1–2 brief daytime naps after school or after extracurricular activities. Adolescents should be made aware of the risks of drowsy driving and instructed to avoid driving when sleepy as well as engaging in potentially risky activities.

Medication is also frequently required to optimally control EDS and/or cataplexy in patients with narcolepsy. Common medications to treat EDS and cataplexy in narcolepsy are listed in Fig. 30.3, and specific medicines and doses

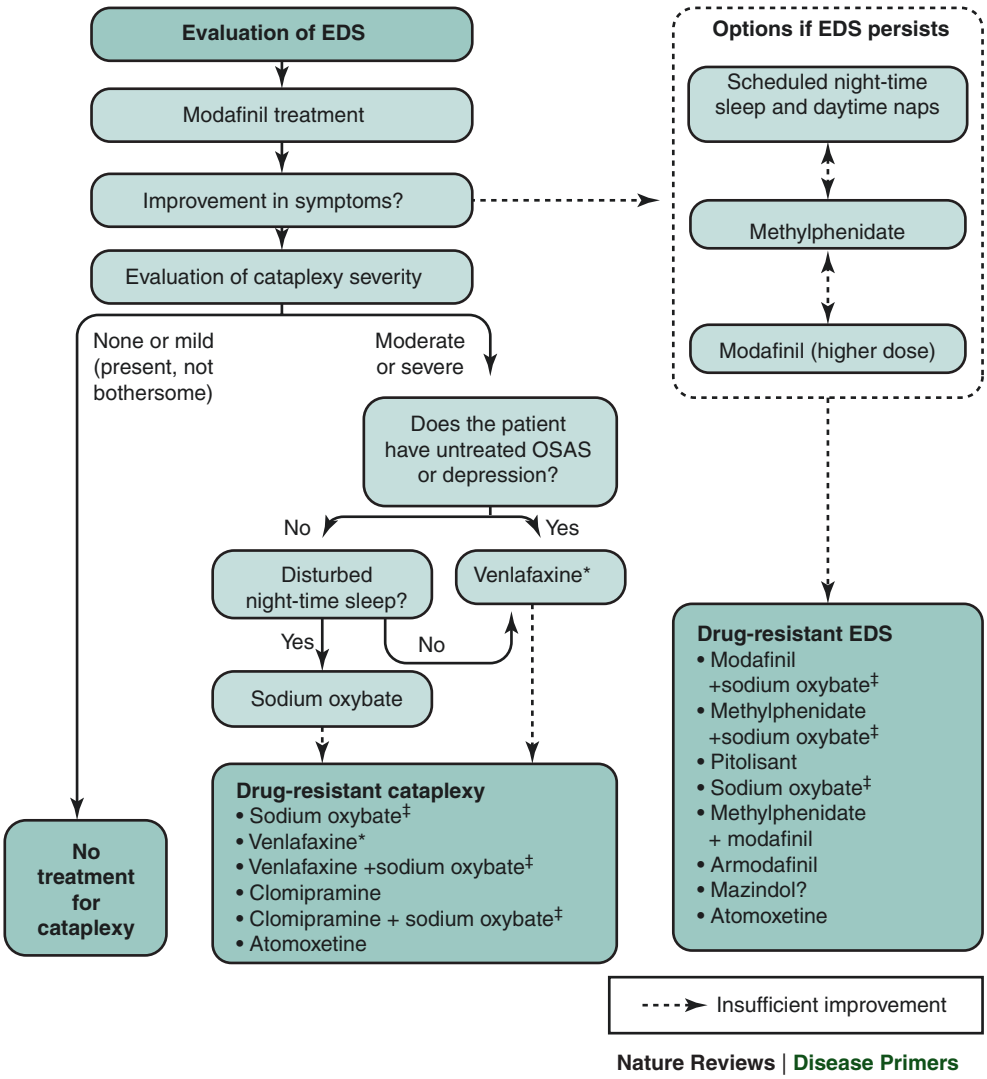


Fig. 30.3 Treatment of narcolepsy. (From Kornum et al. [109]. Reprinted with permission from Springer Nature)
On the basis of available evidence, the use of modafinil as a first-line treatment option for excessive daytime sleepiness (EDS) in patients with narcolepsy is rational. As second-line treatment options, modafinil doses can be increased or methylphenidate can be used. Treatment options for cataplexy should be considered after the evaluation of the severity of cataplexy and the presence of comorbid conditions. Venlafaxine and sodium oxybate should be the first-line treatment options for cataplexy, but in cases of insufficient therapeutic response or intolerable adverse effects, alternatives are suggested. For drug-resistant EDS, therapeutic options can include several drug combinations. *Consider doses that are sufficient for treatment of both depression (if present) and cataplexy. ‡Treatment of comorbid obstructive sleep apnea syndrome (OSAS) and depression is necessary before sodium oxybate can be considered

Table 30.2 Medications for treatment of narcolepsy [61, 110, 111]

Target symptoms	Medication class	Medication	FDA approval for children <18 years old (ages)	Dosing (total daily
Excessive daytime sleepiness (EDS)	Stimulants	Methylphenidate	Yes (6 and older)	10–40 mg
		Dextroamphetamine	Yes (6 and older)	5–60 mg
	Wake-promoting medications	Modafinil	No	100–400 mg
		Armodafinil	No	50–250 mg
		Pitolisant	No	10–40 mg
Cataplexy, hypnagogic hallucinations, sleep paralysis	Tricyclics	Protriptyline	No	5–60 mg
		Clomipramine	No	25 mg–75 mg
	SSRIs	Fluoxetine	No	20–40 mg
		Venlafaxine	No	37.5–150 mg
EDS + Cataplexy		Sodium oxybate	Yes (7 and older)	<=1 g twice nightly to 4.5 g twice nightly

in children are listed in Table 30.2. Although wake-promoting agents are considered first-line therapy in adults to treat EDS, these are not yet FDA approved in children; thus, stimulants are often tried first [61, 65]. Sodium oxybate recently gained FDA approval to treat both cataplexy and EDS in children. Solriamfetol and pitolisant are newer agents, and the overall favorable results in adults will likely transform them into first-line treatments for EDS in children [61].

Illustrative Case

We would like to share the case of a child who presented to a sleep physician at the age of 13 years old with a chief complaint of excessive daytime sleepiness. Her past medical history was significant for near syncopal episodes, anxiety, and depression with a history of self-cutting, and premature adrenarche. Medications included fluoxetine daily. On presentation, she reported that 1 year prior, she suddenly began feeling very sleepy and would fall asleep in class and while talking with friends. Despite these symptoms, she was getting 9–10 hours of sleep per night, though reported significantly disrupted sleep with frequent spontaneous nocturnal arousals. She denied any symptoms of sleep-disordered breathing. There was no precipitating trigger such as trauma, illness, or bereavement prior to the onset of her sleepiness. Associated symptoms included episodes occurring in association with laughter, described as her eyes rolling back into her head and chin quivering. Physical examination was notable for mild hypotonia.

We weaned her off her fluoxetine, and 3 weeks later she underwent a polysomnogram (PSG) that showed no evidence of obstructive sleep apnea (OSA). This test was followed by a multiple sleep latency test (MSLT) that showed a mean sleep latency of 2.1 minutes with 3 sleep-onset REM periods consistent with a diagnosis of NT1. She resumed fluoxetine, implanted a strict sleep schedule with a brief afternoon nap and was started on sodium oxybate with resolution of her symptoms.

Idiopathic Hypersomnia

Definitions

Idiopathic hypersomnia (IH) is a condition of overwhelming EDS with prominent non-REM features. Historically, two forms of IH have been defined based on nocturnal sleep duration (IH with or without long sleep time defined as a documented sleep period of less than or greater than 10 hours) both requiring confirmation of high sleep propensity on the MSLT. This division has been removed from the current ICSD-3 [4], and the current definition of IH represents a heterogeneous entity. In our opinion, the classification of both types of IH is still important in children and teenagers, in particular for school time and required activities. Recognizing a phenotype with an increased need for sleep from a phenotype without will help provide tools and social/school support [66]. It is unclear whether the currently defined disorders IH and narcolepsy type 2 are always separable entities. Moreover, it is not known if EDS in narcolepsy type 2 can be distinguished reliably from expressions of chronic sleep deprivation and narcolepsy type 1, but there are some features that can help identify IH. One prominent feature is sleep inertia (sometimes coined as "sleep drunkenness"), defined as an extreme awakening difficulty consisting of confusion, disorientation, poor motor coordination, and repeated return to sleep at waking up from nocturnal and daytime sleep, coupled with an abnormally prolonged sleep duration [67]. IH patients more frequently complain of prolonged nocturnal sleep duration, difficulties with morning awakening, and frequent occurrence of automatic behaviors compared with narcolepsy patients. Lacking a biological marker and being most often a diagnosis of exclusion of other sleep disorders causing EDS, IH remains a diagnostic dilemma. The characteristic findings of REM sleep-related symptoms (paralysis, hallucinations) and objective (SOREMPs occurrence) seen in narcolepsy are helpful in identifying both conditions.

Epidemiology

Idiopathic hypersomnia (IH) is a very rare disorder with unknown prevalence. Studies have suggested that symptoms begin at an average of 16.6 years old, with the majority of patients developing symptoms before the age of 18 [68]. Despite the early symptom onset, most patients are not diagnosed until the age of 30 [68]. Familial occurrence has been found in up to 30% [66, 69]. Female predominance has been reported [66].

Pathophysiology

The etiology of IH is still unknown. Various groups have contributed theories of the pathophysiology of IH. Hypocretin levels have been confirmed to be normal in patients with IH. Initial research focused on norepinephrine neurons in the locus coeruleus, but metabolites in the CSF were not abnormal [66]. Histamine levels may be low in the CSF of non-medicated patients with IH and narcolepsy, regardless of hypocretin levels, suggesting that CSF histamine levels could be a marker of EDS in hypersomnias of central origin [70]. Most recently, some promising theories have postulated a benzodiazepine/GABA abnormality [71]. Due to the increasing number of familial cases, the HLA system is an attractive potential marker [72, 73], but results have not been conclusive.

Clinical Features

The main clinical feature of IH is excessive daytime sleepiness and non-refreshing naps. In the setting of excessive sleepiness, children or adolescents may return to napping, with the characteristic that naps are not refreshing. Sleep inertia with difficulty waking up both in the morning and after naps occurs and is accompanied by reports of "cloudy mind" or "sleep drunkenness." Patients usually report disorientation and poor motor coordination [74]. EDS can also present with automatic behaviors, sleep paralyses, and hallucinations, demonstrating both non-REM and REM sleep manifestations [75]. Because SOREMPs are absent, children with IH usually do not report dream mentation during naps or during sleep, and because of the increase in slow-wave sleep, the refreshing quality of sleep is diminished, and sleep inertia upon awakening is prominent. A summary of the clinical features is found in Table 30.1.

Differential Diagnosis

Since the diagnosis of IH is often a diagnosis of exclusion, it is important to rule out medication effect, medical disorders, and chronic fatigue syndrome, among other conditions.

Sleep disorders are notoriously known to cause EDS. Especially at presentation, IH can resemble narcolepsy without cataplexy. In addition, other sleep disorders causing excessive daytime sleepiness should be considered, such obstructive sleep apnea, circadian rhythm disorders, and/or insufficient sleep syndrome. Children with psychiatric disorders such as atypical depression leading to poor energy or sleepiness may also present similar to those with IH [66]. In addition, post-viral or infectious hypersomnia may resemble IH. Finally, in children with epilepsy, anticonvulsant therapy is often a confounder when children present with symptoms of EDS.

Diagnostic Approaches

The first step in the diagnosis of IH is to rule out insufficient sleep syndrome. The Epworth Sleepiness Scale average at onset is 16.6 with an average overnight sleep time of 9.2 hours. Nighttime sleep did not correlate with Epworth scores [76]. Helpful tools to assess if total sleep is adequate for age include sleep diaries and actigraphy. The ICSD-3 [4] has established diagnostic criteria for IH which include EDS occurring for at least 3 months, absence of cataplexy, no evidence of SOREMP in the MSLT, and either MSLT showing an average sleep latency of 8 minutes or less, or documentation of total sleep time of 600 minutes or more in 24 hours [4].

Polysomnography with MSLT is therefore imperative for diagnosis. Studies of PSGs in children with IH have shown a sleep efficiency of 93% [75] to 94% [68]. The daytime sleep onset profile on the PSG differs in IH compared to narcolepsy, with IH patients showing a more prolonged fluctuation between wakefulness and NREM stage 1 sleep before entering into sustained sleep. Clinical features are mirrored by the evidence of high slow-wave sleep representation across the nighttime and, most notably, in early morning hours [77].

Because the diagnosis of IH includes exclusion of other neurologic, medical, or psychiatric conditions, neuropsychiatric testing, psychological evaluation, and/or magnetic resonance imaging may be included [78].

Management

IH is a chronic condition that can be debilitating. Treatment must be geared toward symptom improvement and quality of life. Behavioral therapies and sleep hygiene are often less effective because naps and overnight sleep are not refreshing, and irregular sleep pattern or inadequate sleep hygiene can worsen daytime symptoms; therefore, it is recommended to educate children and families of children with IH about sleep hygiene and sleep requirements. Part of the behavioral recommendations must include avoidance of medications

and drugs that can potentiate sleepiness. Pharmacological approaches include those used in narcolepsy (Fig. 30.3) including stimulants and alerting agents such as pitolisant and modafinil. Modafinil has been most widely studied in IH, including two randomized, double-blind, placebo-controlled trials [79, 80], and it is generally considered safe from age 6 and above. These studies showed modafinil improves MSL on MWT testing as well as driving performance. Other pharmacological approaches have been to use antidepressants known for insomnia side effects such as bupropion or protriptyline [66]. In pediatrics, sleep inertia specifically has been shown to respond to a nicotine patch applied to a patient's arm approximately 20 minutes before the desired wake time [81]. Newer therapies also include flumazenil, which is a benzodiazepine antagonist. Clarithromycin, a modulator of GABA, has also been tested and shown to improve subjective sleepiness in a study with 34 patients [82].

Prognosis

Once diagnosed, IH is usually stable and chronic [66]. When severe, those with IH may have debilitating complaints such as dismissal from work and/or poor performance in school due to recurrent tardiness or absences.

Kleine-Levin Syndrome

Definitions

Kleine-Levin syndrome (KLS) is a rare disorder characterized by unusual relapsing-remitting episodes of severe hypersomnia often associated with cognitive, psychiatric, and behavioral disturbances [4].

Diagnostic Criteria for Kleine-Levin Syndrome. (Adapted from AASM [4])

A. The child must experience two or more recurrent episodes of excessive daytime sleepiness and increased sleep duration, persisting for days to weeks.
B. Episodes recur more than once per year, at least once every 18 months.
C. The child has normal alertness, cognitive function, behavior, and mood between the episodes.
D. The child experiences at least one of the following symptoms during the episodes.
   1. Cognitive dysfunction
   2. Altered perception
   3. Anorexia or hyperphagia
   4. Disinhibited behavior (such as hypersexuality)
E. The child's symptoms are not better explained by another sleep, medical, or psychiatric disorder, substances, or medications.

Epidemiology

The prevalence of KLS is unknown, though estimated to be 1–2 per million with a male predominance [4]. In the United States, KLS is more prevalent in the Ashkenazi Jew population [83]. The disease most often manifests in adolescents, with a median age of onset of 15 years [83]. Most cases are sporadic, though familial cases are also known [84].

Pathophysiology

The cause of KLS remains unknown although many cases reportedly have followed an antecedent respiratory viral infection suggesting a potential local encephalitis [85]. KLS may have an autoimmune basis as there is a reported association with the human leukocyte antigen subtype (HLA) DQB1*02 [86]. Other possible triggers related to disease onset include head trauma, sleep deprivation, anesthesia, or mental stress [83].

Thalamic dysfunction is the primary hypothesis in KLS etiology, supported by neuroimaging studies. Asymptomatic patients with KLS have some degree of thalamic dysfunction, which worsens during periods of hypersomnolence [87]. Single-photon emission computed tomography (SPECT) measures cerebral perfusion, is the most common functional neuroimaging method in KLS research, and has shown hypoperfusion in the thalamus and in frontotemporal regions during symptomatic episodes, but also persisting to a lesser degree during asymptomatic periods [88]. Other neuroimaging studies focusing on metabolism and neural networks have also found significant differences in various brain areas as depicted in Fig. 30.4.

Clinical Features

The recurring episodes of hypersomnolence in KLS can last days to weeks and occur at a rate of every 2 weeks to every 72 months. Between episodes, patients report normal sleep, cognition, and behavior. Sleep duration during an episode is prolonged ranging from 15 to 24 hours without an obvious circadian rhythm [89].

Cognitive dysfunction includes difficulty reading, concentrating, and speaking, reduced attention span, and memory difficulties [90]. Patients also report a feeling of derealization during an episode in addition to disinhibited behavior in the form of hypersexuality and hyperphagia [90, 91]. Psychiatric manifestations include depression, anxiety, regressive behaviors, antisocial behaviors, and/or aggression [83, 92].

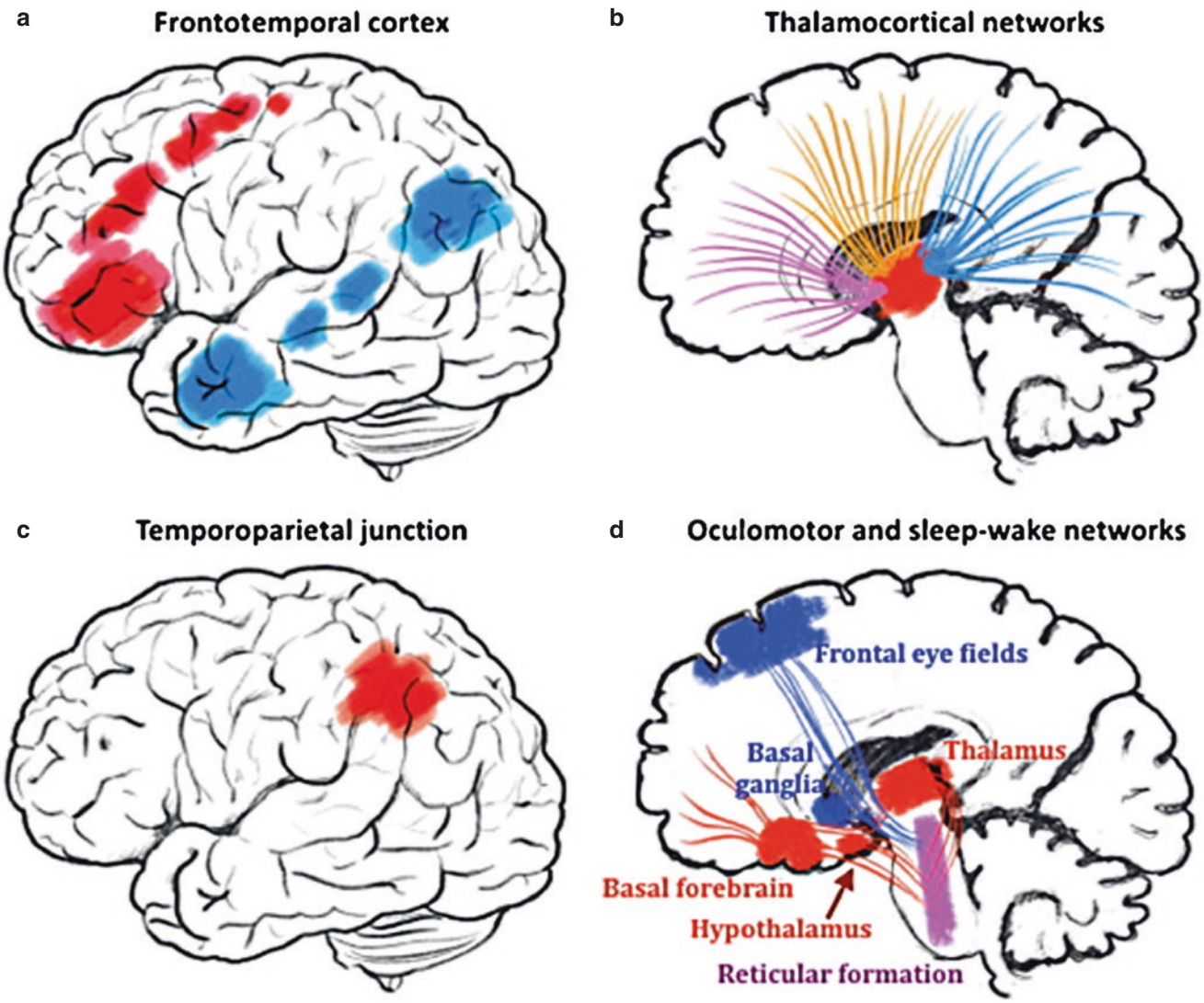


Fig. 30.4 Brain regions and networks involved in Kleine-Levin syndrome. (From Engstrom et al. [88]. Reproduced under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/) (no changes made))
Schematic overview of suggested brain regions and networks involved in KLS according to recent neuroimaging reviews. (**a**) Frontotemporal region with observed hypoperfusion and glucose hypermetabolism in KLS. (**b**) Thalamocortical networks with reported dysfunction in SPECT, PET, and fMRI studies. (**c**) The temporoparietal junction where cerebral perfusion is related to experiences of depersonalization and derealization in KLS. (**d**) Oculomotor and sleep-wake networks. Functional connectivity and perfusion studies show deviant function in the oculomotor network (blue) that involves nuclei in the brain stem reticular formation (*purple*) partially overlapping with the sleep-wake network (*red*)

Diagnostic Approach

There are no diagnostic biomarkers that have yet been discovered for KLS, and the diagnosis is largely based on clinical presentation and diagnostic criteria (see above). Laboratory findings are not indicated for the diagnosis of KLS but can help rule out other causes of hypersomnolence, particularly when facing the first episode. CSF analysis is equally not indicated for KLS but may be indicated if other conditions are suspected. EEG during attacks may be normal, but, in some cases, it has shown background slowing [93]. Brain imaging including MRI or CT scans are normal during and in between episodes. PSG abnormalities reported include slightly reduced REM sleep, increased total sleep time, and decreased sleep maintenance efficiency [94]. In some cases, prolonged PSG can show increased sleep time. MSLT has shown increased sleep propensity and SOREMPs [95].

Management

Treatment is geared toward improving symptoms during a hypersomnolence attack. Generally, medications tried to improve alertness, and prevention of recurrence has been found to be ineffective [96]. These medications include lithium, stimulants, antidepressants, antipsychotics, benzodiazepines, antiviral agents, and carbamazepine. There are no large randomized controlled trials evaluating any of these medications.

Prognosis

Most patients described in the literature meeting criteria for KLS return to normal between episodes, and the episodes become less frequent and less severe with time. There is often spontaneous resolution of symptoms without any sequelae. If KLS remains in older patients or worsens with age, one must consider secondary or superimposing conditions (stroke, sleep disorders). Older patients with persisting KLS have been found to have long-lasting cognitive deficits [97].

Insufficient Sleep Syndrome

Definitions

Sleepiness at the right time is a normal physiologic process that should be followed by the adequate amount of sleep for age. When sleep is shorter than what is required for age, daytime excessive sleepiness ensues, and inadequate sleep syndrome can develop. The American Academy of Sleep Medicine ICSD-3 includes [4] insufficient sleep syndrome under central disorders of hypersomnolence. The diagnostic criteria require evidence of EDS or, in the case of a child, behavioral abnormalities attributed to EDS. Sleep time must be less than expected for age, insufficient sleep must occur almost every day for at least 3 months, insufficient sleep occurs because of being awakened by an alarm or by another person, but when allowed to sleep ad lib, sleep is longer and symptoms of sleepiness resolve.

Epidemiology

Insufficient sleep syndrome affects a large number of adolescents. Less than a third of adolescents in the United States obtain the recommended amount of sleep for age. The Youth Risk Behavior Survey study revealed that 6.3% of children grades 9–12 reported sleeping less than 4 hours at night on school days, 10.5% reported sleeping 5 hours, 21.9% slept for 6 hours, 30.1% reported sleeping 7 hours, 23.5% reported sleeping 8 hours, 5.8% reported sleeping 9 hours, and 1.8% reported sleeping 10 hours or more [98].

Ranum et al. studied objective sleep amount using actigraphy in children ages and considered insufficient sleep when children slept less than 7 hours a night. Based on this definition, the prevalence of sleep insufficiency (<7 hours of sleep at night) was 1.1% at age 6, 3.9% at age 8, 4.2% at age 10, and 13.6% at age 12, confirming a steady decline in the amount of sleep during early childhood, achieving the highest prevalence of insufficient sleep during adolescence [99].

Etiology

The causes contributing to insufficient sleep in children can be subdivided into internal/biological factors and external factors [100]. Biological factors include circadian and homeostatic factors described below under pathophysiology. External factors typically include social demands, electronics, and behavioral practices [100]. Social demands can include extracurricular activities that can include sports, clubs, hobbies, and part-time jobs. With the increased accessibility to electronic devices recently, cell phones, computers, games, television, and other electronic devices in the bedroom have been shown to affect sleep onset and sleep continuity [101]. Finally, individual behaviors, such as caffeine consumption and heavy exercise into late hours of the night, can interfere with sleep [102].

Pathophysiology

Sleep time and length is regulated by two biological processes: process C and process S. The interaction between these two processes influences the timing and fluctuation of sleep and sleepiness across 24 hours, with the highest sleep propensity occurring when process S approaches the upper threshold of process C, and with wakefulness occurring when process S approaches the lower threshold of process C during nighttime hours, and, albeit of minor intensity, during early afternoon hours [103]. Process C is the circadian process, which is a roughly 24-hour sleep-wake cycle regulated by the suprachiasmatic nucleus (SCN) [104]. Process S is the homeostatic process, which is based on the previous amount of wakefulness or sleep and determines the propensity to sleep [105]. Insufficient sleep syndrome occurs when there is a dysregulation between these two processes, such as during adolescence. There is a circadian delay related to a delayed melatonin onset [106, 107] that occurs with puberty, manifested by the inability to fall asleep at an appropriate time for age (i.e., 10 PM). In addition to this delayed bedtime, the combination with an early awakening for school (6 or 7 AM) contributes to insufficient sleep for age.

Clinical Features

Children commonly present with symptoms of daytime sleepiness, fatigue, or poor school performance. In younger children, clinical presentation of insufficient sleep can include irritability, moodiness, inattention, and hyperactivity. In older children and teenagers, manifestations of EDS can include impulsivity, poor academic performances, accident proneness, intrusive sleepiness, or microsleeps (5–10 seconds). EDS can also cause lapses in attention, nodding off when sedentary, exacerbation of parasomnias, and REM phenomena (hypnagogic hallucinations).

Differential Diagnosis

It is important for the sleep physician to recognize physiological sleepiness from pathological sleepiness due to insufficient sleep. The differential diagnosis of insufficient sleep syndrome in a teenager includes medical comorbidities, medications, psychiatric comorbidities, and other sleep disorders such as obstructive sleep apnea and disorders of central hypersomnolence as discussed above.

Diagnostic Approach

The diagnosis of insufficient sleep syndrome can be made with a thorough sleep history and physical exam, but sleep diaries or actigraphy may be useful to assess for a comorbid circadian disorder. History should include bedtime routine, time of lights out at home, social environment, and potential sleep disruptors (such as pets in the bedroom).

Management

The disorder resolves when appropriate sleep amount for age is obtained. It is recommended to educate families on adequate sleep routine, consistent schedules, and sleep requirements for age as well as the consequences of not obtaining enough sleep [108].

Illustrative Case

Figure 30.5 illustrates actigraphy results for an 11-year-old boy who would stay up playing video games until 11 PM. He

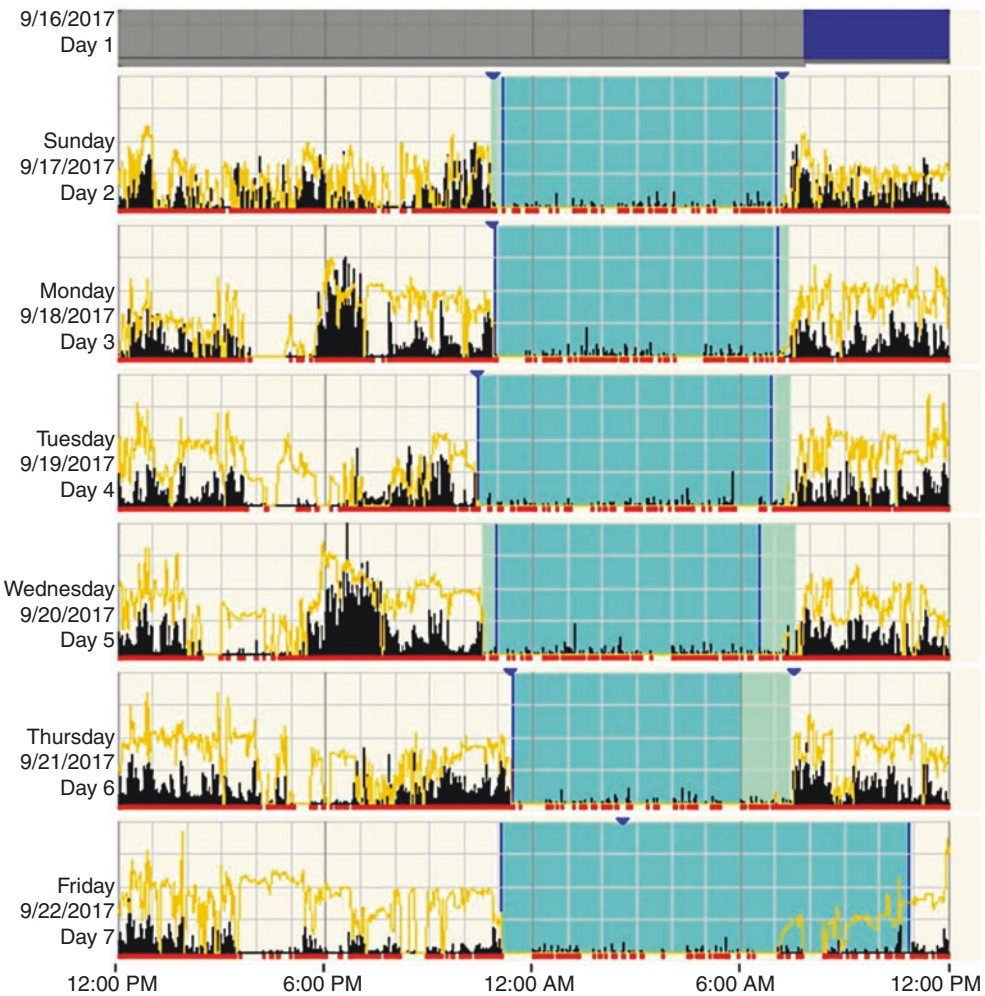


Fig. 30.5 Actigraphy in a child with insufficient sleep

used an alarm to wake up at 6:30 AM to go to school. He reported significant sleepiness during class and had episodes of dozing off in school and on short drives. Actigraphy is consistent with the history of sleep delay on weekdays, averaging approximately 7 hours of sleep during school days. On weekends that he did not need to wake up with an alarm, he would sleep for almost 12 hours. This is typical of insufficient sleep.

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Restless Legs Syndrome and Periodic Leg Movements of Sleep

31

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Abbreviations

AASM	American Academy of Sleep Medicine
ADHD	Attention deficit-hyperactivity disorder
AHI	Apnea/hypopnea index
CLM	Candidate leg movement
FDA	Food and Drug Administration
IMI	Intermovement interval
IRLSSG	International Restless Legs Syndrome Study Group
ISOLMS	Isolated leg movements during sleep
PLMD	Periodic leg movement disorder
PLMI	Periodic leg movements of sleep index
PLMS	Periodic leg movements of sleep
PSG	Polysomnography
RLS	Restless legs syndrome
RSD	Restless sleep disorder
SILMS	Short-interval leg movements during sleep

Definitions

Restless legs syndrome (RLS) is a clinical diagnosis characterized by an "urge to move the legs," worsening of symptoms during rest, worsening of symptoms in the evening, and improvement or resolution of symptoms after movement [1]. RLS, also known as Willis-Ekbom disease, was initially described in the 1600s by Thomas Willis as "restlessness," "tossing of the members," "not able to sleep," and "as if they were in the place of greatest torture." Later in 1944, Dr. Axel Ekbom described "a new syndrome consisting of weakness, sensation of cold and nocturnal paresthesia in the legs" [2]. In children, RLS was initially described by Dr. Ekbom in 1975 who reported a familial case of growing pains and restless legs which "convinced" him that both syndromes were different conditions [3]. Later on, Walters et al. described the first comprehensive case series of five children with RLS. The authors provided pedigrees with parents and family members affected. Polysomnographic data in two of the patients showed elevated periodic leg movements of sleep (PLMS) [4]. In this early report, the authors clearly described the features of pediatric RLS, which, when able to be expressed by the child, coincide with the typical presentation in adults: leg paresthesias/discomfort, nocturnal predominance, and relief with movement. In younger children, it was identified that other symptoms such as delayed sleep onset, bedtime struggles, and PLMS in polysomnography could aid in the diagnosis [4].

PLMS are a polysomnographic diagnosis first identified by Charles P. Symonds in a report of five cases of patients with leg twitches or involuntary jerking that occurred during sleep [5]. Since then the identification and criteria for scoring of PLMS during sleep polysomnography (PSG) have undergone several revisions, as discussed in the next sections. PLMS are universally reported as PLMS index (PLMI), which is the number of leg movements that fit PLMS criteria per hour of sleep. An elevated PLMI is defined by the American Academy of Sleep Medicine (AASM) as a PLMI >5 in children and PLMI >15 in adults [6]. An elevated PLMI by itself does not fit criteria for a sleep disorder.

The International Restless Legs Syndrome Study Group (IRLSSG) has added a few other definitions in the scoring of leg movements during polysomnography. A candidate leg movement (CLM) is a leg movement lasting 0.5–10 seconds long that is considered to be a part of a PLMS series.
Intermovement interval (IMI) is defined as the time from the onset of one CLM to the onset of the next CLM. Short-interval leg movements during sleep (SILMS) are CLM with IMI <10 second. Isolated leg movements during sleep (ISOLMS) are leg movements not included in the

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Table 31.1 Current criteria for the diagnosis of pediatric PLMD

1. Polysomnography shows repetitive stereotyped limb movements that are:
(a) 0.5–10 seconds in duration
(b) Minimum amplitude of 8 μV above resting electromyogram
(c) In a sequence of four or more movements
(d) Separated by an interval of more than 10 seconds (onset-to-onset) and less than 90 seconds (intermovement intervals often are short and variable in children)
2. The PLMI exceeds 5/h in pediatric cases
3. The PLMS cause clinically significant sleep disturbance or impairment in mental, physical, social, occupational, educational, behavioral, or other important areas of functioning
4. The PLMS are not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder (e.g., exclude from PLMS counts the movements at the termination of cyclically occurring apneas)

Adapted from: Picchietti et al. [8]

PLMS. Finally, periodicity index in sleep is defined as the ratio of the number of PLMS to the total number of CLM [7].

The AASM defines periodic leg movement disorder (PLMD) as an elevated PLMI associated with significant sleep disturbance or daytime impairment in any important area of functioning including mental, behavioral, social, physical, or occupational area [6]. Also the diagnostic criteria for PLMD in children [8] include the presence of clinical sleep disturbance and the absence of another primary sleep disorder or reason for PLMS (including RLS), but as explained above and differently from adults, a PLMI >5/h is considered to be pathologic in children. As excessive daytime sleepiness is uncommon in children with PLMD, the presence of this symptom might indicate other disturbances such as narcolepsy, as an example. Table 31.1 reports the diagnostic criteria for PLMD in children.

More recent data obtained by applying the latest evidence-based criteria for scoring PLMS [7] indicate that true periodic leg movements are rare in children [9], even in those with RLS or narcolepsy and that the cutoff value for the PLMI calculated following these new criteria suggests that an abnormal level in children should be 2/hour.

The diagnosis of PLMD is useful in younger children with language skills still insufficient to describe adequately their sensations; moreover, the sensory component of RLS seems to develop in early adolescence [10]. Pediatric PLMD has a prevalence of 8–12%, and PLMS have been found to be significantly more prevalent among Caucasian children than among African-American children [11]. A positive parental history of RLS can be found in 53% of pediatric RLS cases and in 52% of pediatric PLMD cases [12].

Several studies have reported a possible association between attention deficit hyperactivity disorder (ADHD), RLS, and PLMD in children and adolescents: 26–64% of children with ADHD meet the criteria for PLMD; conversely, 91% of children with PLMD have been reported to meet the criteria for ADHD. In addition, PLMI was found to be positively correlated with inattention/hyperactivity scores [13, 14]. Children with PLMD/ADHD have been reported to be significantly more likely to have enuresis, nightmares, and difficulty initiating sleep than children with PLMD only, as well as significantly more PLMS associated with electroencephalographic arousals. The relationship between ADHD, RLS, and PLMD is complex and not yet fully understood, possibly connected with a reduction of dopamine activity. Finally, ADHD, RLS, and PLMD seem to be all associated with low iron storages which might suggest that the improvement of ferritin levels is likely to also improve ADHD symptoms [13, 14].

It has also been reported that children with growing pains present a significantly increased probability to have a PLMI ≥5/hour than children without growing pains. In terms of RLS, data are confounding with some studies showing no relationship between both conditions while other studies show a higher incidence of growing pains in children with RLS. A genetic overlap between growing pains and RLS has also been suggested [15].

Pathophysiology

The pathophysiology of RLS includes genetic factors, dopaminergic dysfunction and decreased brain iron. In terms of genetic factors, 19 risk loci have been identified up to date for RLS [16]. The most common genetic associations have been attributed to homeobox gene MEIS1, BTBD9 and LBXCOR1 on chromosomes 2p, 6p and 15q, respectively with MEIS1 being the strongest genetic risk factor for RLS. The presence of each variant is associated with 50% risk of RLS [17]. Adult studies have found RLS to be familiar in about 60% of cases, with symptom onset at earlier ages than non-familiar cases [13, 18].

Early clinical studies in RLS demonstrated a response to dopaminergic medications leading to the understanding that dopaminergic neuronal pathways in the brain play a key role in movement disorders during sleep. Brain and spinal dopaminergic pathways postulated to be involved in RLS and PLMS include a deficiency in the inhibitory A-11 cell projections to the spinal cord, leading to increase sensory activation, input to the cortex, and increased sympathetic activity.

Adult studies have set the foundation for the pathophysiology of low iron storages in RLS and PLMS. Autopsy studies from adults with RLS have shown low brain iron storages [19]. Similarly, adult studies in which magnetic resonance imaging was used to assess regional iron brain concentrations have confirmed low iron levels in the substantia nigra and putamen [20]. Ferritin measurements in cerebrospinal fluid from patients with RLS have been shown to be low, in

particular those with symptom onset at an age younger than 45 years [21]. Iron is a cofactor for tyrosine hydroxylase in the dopamine synthesis pathway; therefore, it is postulated that low iron will also result in low dopamine levels.

Diagnostic Approaches

RLS affects approximately 2% of children [22]. Children with RLS do not always present with typical leg discomfort or "urge" to move the legs but often present with insomnia [22], sleep disruption, behavioral problems, neurocognitive deficits, and decreased quality of life [23]. In spite of these consequences, RLS is often misdiagnosed or underdiagnosed in children, in part due to the children's difficulty in expressing the symptoms and clinician's challenges assessing them. Children may not clearly verbalize the classic symptoms of RLS, and RLS has been demonstrated to present differently in children. PLMS, which are often seen in adults with RLS, also manifest differently in children. Furthermore, children often present with nonperiodic leg movements. Isolated leg movements may present earlier and disrupt sleep, months or years before the onset of RLS symptoms [24]. The IRLSSG has published guidelines for the diagnosis of RLS in adults and children. In children, the symptoms must be expressed in the child's own words. Basically, the diagnosis involves the following:

1. The urge to move the legs is usually accompanied by uncomfortable and unpleasant sensations in the legs.
2. The urge to move the legs is worse during periods of rest or inactivity such as lying down.
3. Walking or stretching partially or totally relieves the urge to move the legs.
4. The urge to move the legs is worse in the evening or night.
5. Symptoms are not due to a medical or a behavioral condition (leg cramps, positional discomfort) [1].

The diagnostic criteria of pediatric PLMD are detailed in Table 31.1. Just as in adults, PLMS in children has shown a significant night-to-night variability, and several measurements may be needed for the accurate identification and quantification [25].

Differential Diagnosis

As previously mentioned, studies identified some commonality between RLS, growing pains, and features of ADHD. Picchietti et al. studied 69 children diagnosed with ADHD and found that 27 reported leg movement activity at night. These underwent PSG with 18 showing elevated PLMS (defined as PLMI >5 per hour). From these 18 children, 8 had personal and parental history of RLS. The authors concluded that PLMS and RLS were common in children with ADHD and could contribute to the symptomatology of ADHD [13]. In a retrospective review of 129 children (ages 6–17) with PLMS >5/per hour, the same authors showed that 117 were previously diagnosed with ADHD. In this study, the mean PLMI was found to be 35.9/hour; interestingly, very few parents had noted that children kicked in their sleep, in spite of the high PLMI found. The authors then proposed an index of >25 PLMS/hour to be considered moderate/severe [26]. The authors also reported that two children with moderate to severe PLMS were initially diagnosed as having seizures [26]. PLMS and RLS in children with ADHD do not appear to be affected by stimulant medication. The authors concluded that PLMS, RLS, and ADHD could share a common pathophysiologic pathway. In agreement with this view, studies on iron supplementation in children with ADHD have shown improvement in both day- and nighttime complaints.

Growing pains have a peak prevalence at 4–6 years of age and occur intermittently in the evening, sparing the joints. The pain is not associated with erythema or swelling and occurs usually in both legs, thighs, and predominantly in the calf. Although growing pains share similar characteristics with RLS, the opposite does not apply. The urge to move the legs and the relief by movement are not characteristics seen in growing pains [27]. The challenge is the identification of both conditions in young children who do not understand "urge" but may identify RLS as a pain sensation. In this case, careful evaluation, including drawings and explaining of the symptoms in the child's own words, may help differentiate both conditions [15].

Painful nocturnal leg cramps can be confused with RLS in that they are alleviated by rubbing, massaging, or stretching the leg; however, there is no urge to move the legs, and they do not necessarily occur in quiet moments or in the evening prior to sleep [28].

Excessive motor activity during sleep can often be confused with RLS. Restless sleep disorder (RSD) has recently been identified in children with restless sleep and frequent movements or repositioning as it has been demonstrated that these children do not present with increased leg activity and do not have the urge to move the leg. Also, there is no family history of RLS [29].

Other musculoskeletal conditions can mimic leg discomfort but can be identified by articular involvement, inflammation, tender points or abnormal radiographs and include Osgood-Schlatter, acute injury, arthritis, connective tissue disorders, myopathy, sickle cell pain crisis, or neoplasms. A summary of the most common mimics with a comparison of symptoms with RLS and PLMD is found in Table 31.2.

Table 31.2 Differential diagnosis of RLS and PLMD

Condition	Symptoms	Diagnosis	Initial treatment
Restless legs syndrome	Urge to move the legs, worse in the evening or moments of rest, relieved by movement	History and physical exam	Iron
Periodic leg movement disorder	Nocturnal leg movements with or without night disturbance but must present with daytime impairment	Polysomnography	Iron
Restless sleep disorder [29]	Large muscle movements during sleep with daytime symptoms	History and physical exam, Polysomnography	Possibly iron
Growing pains [27]	Intermittent pain in both legs for at least 3 months	History and physical exam	Symptomatic care and over-the-counter analgesic [30]
Positional discomfort [31]	Can present as numbness due to temporary nerve compression	History and physical exam	Repositioning
Leg cramps [28, 31]	Painful contraction of leg muscles mainly calf, occur suddenly, short duration	History and physical exam	Massage, stretching
Ligament/tendon sprain/strain [15]	Localized pain worse with movement	History and physical exam	Conservative treatment: rest, compression, ice
Eczema [15]	Pruritus chronic or relapsing [32]	History and physical exam	Skin-directed topical treatment [32]
Juvenile idiopathic arthritis [31]	Joint discomfort without circadian pattern	History and physical exam, Labs radiography	Disease-modifying antirheumatic drugs [33] Varies per diagnosis

Management

Treatment of RLS in children includes non-pharmacological and pharmacological management (Table 31.3). Non-pharmacological management includes sleep hygiene, dietary modifications, and exercise.

Although the effectiveness of sleep hygiene has not been evaluated in children with RLS, it is important to have a comprehensive evaluation of the sleep environment to rule out comorbidities or mimics. Sleep hygiene refers to consistent activities and schedules around bedtime that promote sleep through appropriate environment and opportunity to sleep. General recommendations include keeping a cool temperature in the bedroom, comfortable mattress, and avoidance of electronics at least 1 hour prior to bedtime.

The most important dietary modification is avoidance of caffeinated products including tea, coffee, and chocolates after 3 pm [34].

The last non-pharmacological intervention is stretching exercises prior to bedtime. Stretching leg exercises decrease symptoms of RLS by 63% [35]. Exercise may improve RLS symptoms by improving circulation or by release of endorphins [36]. Adults who trained three times a week have also shown to improve their symptoms of RLS [37]. There is no data on rubbing or massaging the legs in children.

Pharmacological options for pediatric RLS include medications often used off-label because currently, there are no Food and Drug Administration (FDA)-approved medications for the management of RLS in children. Medication should always be combined with non-pharmacological treatment, elimination of factors that worsen or precipitate RLS and the evaluation of iron status [38, 39].

Although the IRLSSG guidelines on the use of iron supplementation as a treatment for RLS state that there is not enough evidence to recommend iron for RLS in children [40], clinically, most pediatric sleep specialists recommend supplementation with oral iron for children with RLS symptoms and serum ferritin levels below 50 ng/mL [41]. Oral doses range from 3 to 6 mg/kg/day and may take 3 months or more to achieve relief of symptoms [42]. Although the evidence is sparse, there are some studies that have reported improvement of symptoms after iron supplementation in children [34, 42, 43]. A longitudinal study on iron supplementation in 105 children (39% with RLS and 61% with PLMD) showed symptomatic improvement in 62.86% and objective decrease in PLMI after up to 2 years follow-up [44]. Intravenous iron supplementation has shown promising results in adults, and there is currently only a single study reporting improvement of symptoms in 62.5% of children [45]. Common side effects include constipation and teeth staining when liquid preparations are used [46].

When symptoms persist after iron supplementation, a second medication can be used or a new medication can be prescribed. In a study in 25 children with RLS and 28 controls, children with persistent symptoms after 2 months of iron supplementation were prescribed clonazepam or pramipexole [47]. Data on the use of dopaminergics for pediatric RLS is sparse [26, 48–52]. A small randomized, double-blind study

Table 31.3 Treatment of pediatric RLS

Non-pharmacological	Pharmacological
Sleep hygiene	Ferrous sulfate
Physical activity	Gabapentin
Stretches/massage	Clonazepam
Avoidance of caffeine	Clonidine
Avoidance of medications that exacerbate RLS such as antihistamines or antidepressants	Dopaminergics Levodopa/carbidopa Pramipexole Ropinirole Rotigotine

showed improvement in RLS and PLMS in children with ADHD and RLS treated with L-dopa [53]. A case series on five children with RLS treated with carbidopa/levodopa and two children with pergolide showed improvement in RLS, PLMS, and daytime symptoms of ADHD [48]. There are few case reports on the effective use of ropinirole [49, 54] and rotigotine in adolescents (13–17 years) [55]. An important consideration for treatment with dopaminergics is gleaned from data in adults showing effectiveness only in PLMS with periodicity between 10 and 90 seconds. This is important in children since they often lack periodicity in leg movements [56, 57]. Dopaminergics are notorious for causing augmentation, sleepiness, insomnia, compulsive behaviors, and hallucinations.

Gabapentin is another medication commonly used in adults with RLS showing improvement in slow-wave sleep and sleep-onset latency [58]. Gabapentin enacarbil is FDA approved for moderate to severe RLS in adults but not in children. A small cohort of two treated with gabapentin for RLS showed resolution of symptoms [34].

Clonazepam is a long-acting benzodiazepine known to pediatric sleep medicine for its use in the treatment of parasomnias. Polysomnography studies in RLS patients taking clonazepam have shown improvement in sleep and reduction in arousals, but no reduction in the motor and sensory manifestations of RLS [59, 60].

Clonidine is an alpha 2-adrenergic agonist commonly used for insomnia. Clonidine can be given in combination with iron supplementation to improve sleep onset [44]. In adults, clonidine has shown reduction in sensory manifestations of RLS [61].

Data is lacking on the utility of opioids in children.

Illustrative Cases

Case 1

A 2-year-old girl was referred to sleep medicine clinic for difficulty falling asleep and frequent nocturnal awakenings. Per her mother, she did not sleep more than 3 hours at the time at night. Her bedtime was 7 p.m. The parent noticed she was very restless, rubbed her legs, and had difficulty falling asleep. Sleep latency was about an hour. Once she fell asleep, the parent noticed frequent leg kicks and at least three nocturnal awakenings. There was no snoring and no parasomnias. There was no other past medical history and no medications. The mother had restless legs syndrome. A nocturnal PSG was performed which showed a sleep latency of 52 minutes, total sleep time of 458 minutes, and sleep efficiency of 78% due to a few awakenings, obstructive apnea/hypopnea index (AHI) 0.8, central AHI 0.5, and PLMI 7. A representative epoch with arousals and PLMS is seen in Fig. 31.1 (top panel), together with another PLMS alone (bottom panel).

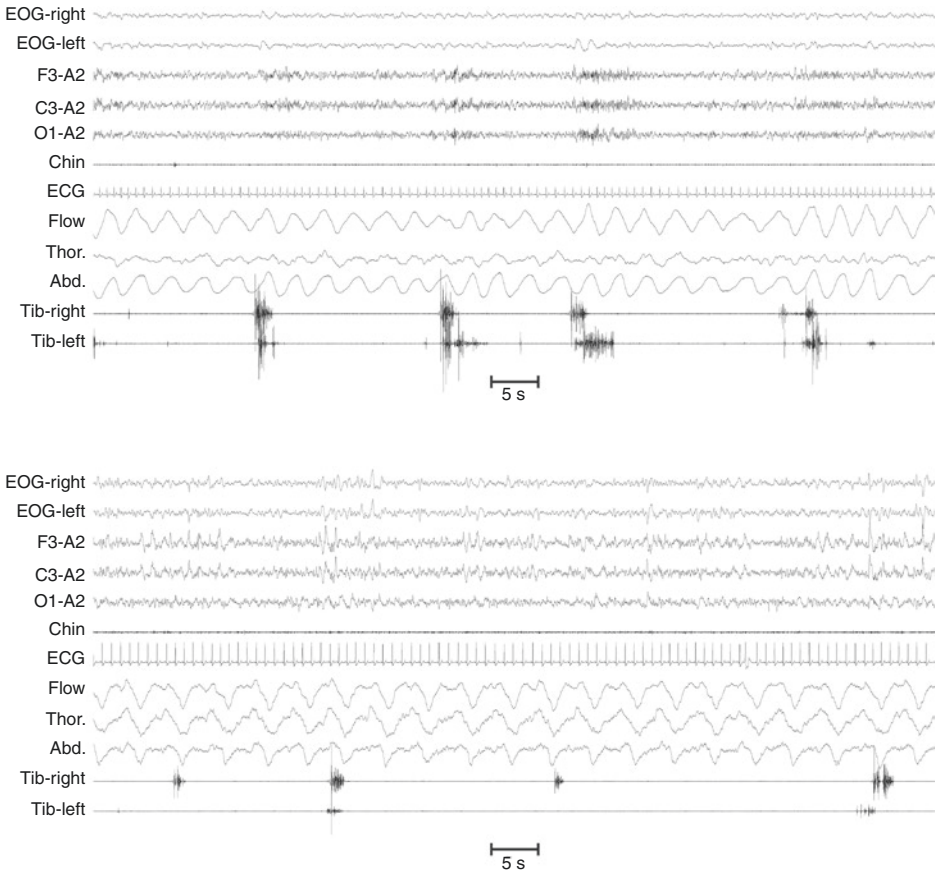

Fig. 31.1 Representative epochs of PLMS with arousals (top panel) or without arousals (bottom panel) obtained in Case 1

Question
What is the diagnosis and what is the next step in the evaluation of this child?

Answer
The child has restless legs syndrome. The next step is to check fasting iron profile and ferritin levels.

Case 2

A 17-year-old girl with restless legs syndrome presented for follow-up after 6 months of oral iron supplementation. The girl reported symptoms were worse and made it very difficult for her to fall asleep due to leg discomfort. Initially, ferritin level was 9 ug/dl. After 3 months of oral iron supplementation, ferritin levels were 12 ug/dl. After 6 months, ferritin was 10 ug/dl.

Question
What would be the next step in management of this patient?

Answer
We offered IV iron infusion with ferric carboxymaltose 750 mg one time. At the 2-month follow-up visit, ferritin level was 58 ug/dl. Symptoms of RLS resolved; there were no side effects.

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Circadian Sleep Disorders

32

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Definitions and Background

Circadian rhythm sleep–wake disorders (CRSWDs) are accompanied by a nomenclature that can make diagnosis and treatment more difficult. Some of the basic concepts of circadian physiology that were presented in Chap. 9 bear repeating before proceeding with a discussion of these disorders in children.

Circadian rhythms themselves refer to near 24-hour oscillations that are internally generated by the body. The mere presence of 24-hour rhythm in a biological parameter does not necessarily mean that it reflects an oscillation that is internally generated, however. Instead, some 24-hour rhythms may be evoked by changes in the environment or, more commonly, may represent the combination of internal and external oscillations.

Intrinsic circadian rhythms are ultimately the product of molecular clock work; intracellular translation/transcription feedback loops form the basis of these rhythms [1]. The rhythms are internally synchronized by the suprachiasmatic nuclei (SCN) in the hypothalamus. The SCN is considered to be the locus of the circadian pacemaker and is itself synchronized to the outside world via time cues (zeitgebers) that act to reset the timing of the pacemaker (referred to as *circadian phase*) [2]. Primary among these zeitgebers is light: a monosynaptic connection exists between intrinsically photosensitive retinal ganglion cells and the SCN (the retinohypothalamic tract) [3]. Light information transmitted from these retinal ganglion cells (as well as from the rods and cones) acts to reset the timing of the pacemaker (cause *phase shifts*) [3]. Shifts in the timing of the pacemaker to an earlier hour are called *phase advances* while shifts in the timing of the pacemaker to a later hour are called *phase delays* [4]. The magnitude and direction of phase shifts depend upon the timing and strength of a zeitgeber [4]. In the case of light, not only the intensity [5–7] but also the duration of exposure [8–12], wavelength [13, 14], and prior light exposure history [15] can all impact the magnitude of phase shifts.

The circadian pacemaker is functional at birth, and evidence from non-human primates indicates the pacemaker is responsive to the resetting effects of light at birth as well [16]. That said, consolidated bouts of rest and activity are difficult to detect in humans until about the first or second month of life [16].

Phase shifts are needed to synchronize the circadian pacemaker to the outside world because, as noted above, the circadian pacemaker has a periodicity that is not exactly of 24 hours [17, 18]. In a cohort of adolescent boys and girls aged 13.2–15.2 years, it was demonstrated that the pacemaker has a cycle length (*circadian period*) of approximately 24 hours and 20 minutes [19]. One consequence of a 24-hour and 20-minute circadian period is that circadian phase has a natural tendency to drift about 20 minutes later on average each day (to phase delay). Evening light exposure results in additional phase delays and the net tendency for circadian phase to shift later is counteracted by equivalent phase advances caused by morning light exposure. Circadian phase can thereby maintain a fairly constant relationship relative to the outside world—assuming that there exists a fairly consistent timing and intensity of light exposure.

The circadian pacemaker regulates the timing of a wide range of physiological parameters [2]. Most relevant here is the pacemaker's role in the regulation of sleep and wakefulness. The two-process model of sleep/wake regulation supposes that two counteracting processes interact to control the timing of sleep and wakefulness [20]. The sleep homeostat is responsible for increasing levels of sleepiness during wakefulness and decreased sleep drive during sleep: across the day sleep drive increases with extended wakefulness (peaking at the end of the wake period) and is then dissipated during sleep (decreasing in a non-linear fashion during sleep). The sleep homeostat is

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opposed by the circadian drives for wakefulness and sleep in such a way that relatively consolidated bouts of sleep and wakefulness can occur. Specifically, the circadian drive for wakefulness increases across the day, peaking at the end of the wake period, in such a way to oppose the increasing drive for sleep from the sleep homeostat. Conversely, during sleep the circadian drive for wakefulness is withdrawn allowing for continued sleep despite dissipation of homeostatic sleep drive. These two processes have been shown to have a non-additive relationship such that the strength of the circadian sleep/wake rhythm varies with the duration of prior wakefulness [2].

Pathophysiology

Most CRSWDs arise when there is a *mismatch* between the desired or required times for sleep and wakefulness and the endogenous circadian drives for sleep and wakefulness. CRSWDs are divided into extrinsic disorders that are the result of environmental perturbations (shift work disorder and jet lag disorder) and the so-called intrinsic CRSWDs [21]. The intrinsic CRSWDs include delayed sleep–wake phase disorder (DSWPD), advanced sleep–wake phase disorder (ASWPD), irregular sleep–wake rhythm disorder (ISWRD), and non-24-hour sleep–wake rhythm disorder (N24SWRD). Although children or adolescents can certainly suffer from jet lag disorder or shift work disorder, these are less commonly encountered in clinic and will not be addressed in this chapter.

In DSWPD, ASWPD, and N24SWRD, it has often been presumed that the primary defect relates to the timing of the circadian pacemaker (circadian phase) while in ISWRD it is believed that there is loss of coordinated circadian timing itself. Differences in response to phase advancing and/or phase delaying light as well as possible differences in circadian period [22] may play a role in the development of these disorders. Alternatively, circadian phase may be completely normal in individuals with CRSWDs [23] and the etiology may lay elsewhere (e.g., in the build-up and dissipation of homeostatic sleep drive).

As noted above, the genetic basis of circadian rhythmicity is well established and so it is not surprising that an evolving body of evidence indicates that morning and evening preference as well as CRSWDs themselves also have a genetic component [24–26] as epitomized by the familial form of ASWPD [27, 28].

Diagnosis

Summary of Disorders and Diagnostic Approaches

The diagnostic criteria set out in the third edition of the International Classification of Sleep Disorders (ICSD-3) share some commonalities across the different intrinsic CRSWDs [29]. All four disorders require at least 3 months of symptoms and at least 7 days of sleep diaries or actigraphy that document each disorders' particular sleep/wake pattern. The ICSD-3 states that 14 days of diary or wrist actigraphy data is preferred and that this must include both school days and weekends. One to two weeks of sleep diary or actigraphy may provide sufficient data for a diagnosis of DSWPD, ASWPD, or ISWRD. In practice, the diagnosis of N24SWD can require weeks or months of diary or actigraphy data for an adequate assessment.

In DSWPD, the main bout of sleep occurs late relative to the desired or required sleep time, with sleep onset insomnia and difficulty awakening when the individual attempts to sleep at an earlier time. Importantly, there should be no problems with sleep quality or duration when the patient is allowed to sleep at the preferred (delayed) times (Fig. 32.1).

Conversely, in ASWPD, sleep timing occurs early relative to the desired or required timing of sleep, with early evening hypersomnolence and early morning insomnia when the individual attempts to sleep at an later time. As with DSWPD, ASWPD patients should be free of insomnia or sleep quality complaints when allowed to sleep at their preferred (advanced) times.

N24SWD presents with a relapsing and remitting history of insomnia and/or hypersomnolence that is presumed to occur because the circadian pacemaker is no longer entrained (synchronized) to the 24-hour day. It most commonly occurs in blind children where light information is no longer conveyed to the SCN.

In ISWRD patients have irregularly timed sleep and wake episodes that occur throughout the 24-hour day, with symptoms of insomnia during the scheduled time for sleep and hypersomnolence during the scheduled wake period.

It is important to note that current diagnostic criteria do not require measurement of the timing of the circadian pacemaker (circadian phase) despite the fact that mistiming of the pacemaker is presumed to be the primary pathology for all but one of these disorders. This is somewhat analogous to diagnosing hypertension without measurement of blood pressure and is the result of the absence of a reimbursable test of circadian phase as well as the time, expense, and expertise currently required to measure circadian timing.

Differential Diagnosis

DSWPD must be distinguished from other causes of sleep onset insomnia (e.g., chronic or short-term insomnia) or daytime hypersomnolence (e.g., obstructive sleep apnea or narcolepsy). The primary differentiating factor is that children with DSWPD should have no problems with either insomnia or daytime sleepiness when they are able to sleep at later times. Similarly, ASWPD is distinguished by an absence of

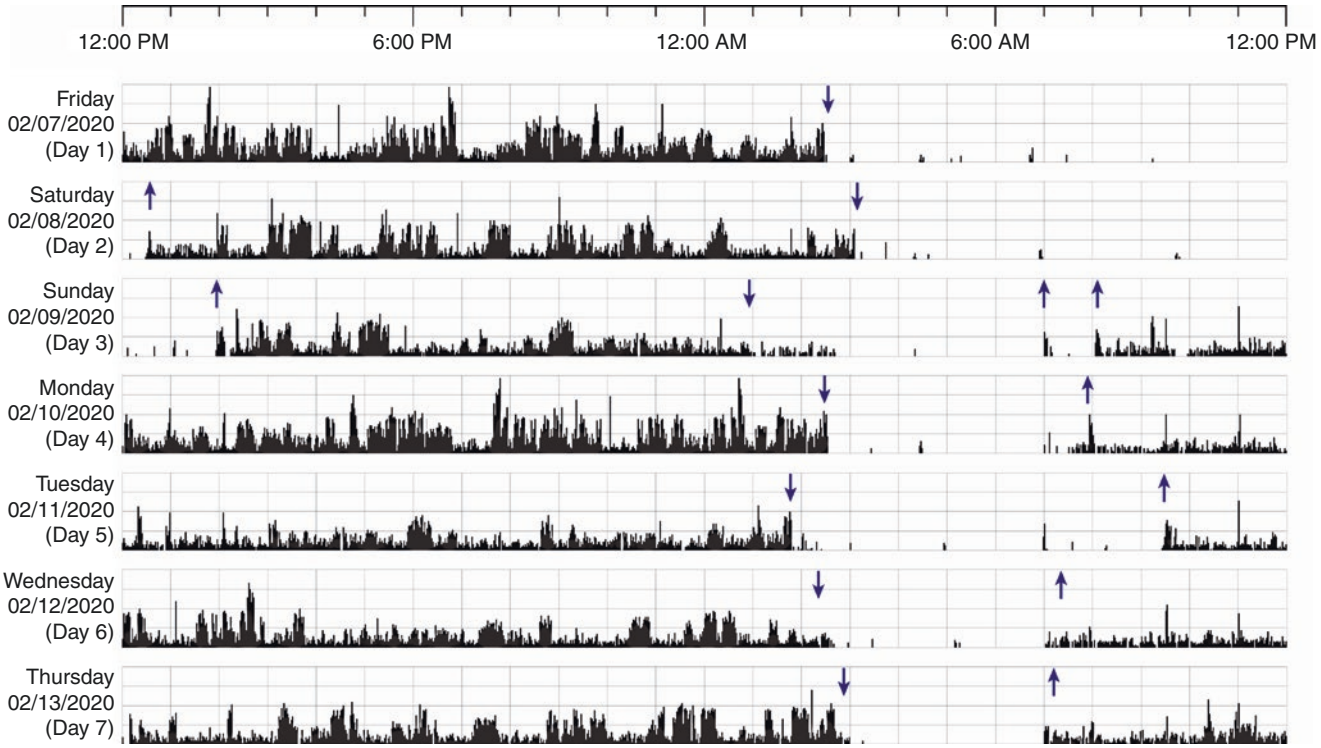


Fig. 32.1 Actigraphy. A schematic example of a week's worth of wrist actigraphy data. Successive days are plotted beneath each other. The black tick marks represent movement measured by a wristwatch-sized accelerometer. The blue arrows are times the patient pressed an event marker on the device to denote bedtimes (down arrows) and wake times (up arrows). The patient has delayed bedtimes and wake times on the weekends after 2 am and after 12 pm, respectively. On school days, bedtimes remain delayed and there are examples of the patient having insomnia when they attempt to go to bed at an earlier time (Sunday evening, third line) as well as oversleeping on school days (Monday and Wednesday mornings, third and fifth lines)

evening hypersomnolence or early morning awakening when patients are allowed to sleep at earlier times.

ISWRD must not be confused with poor sleep habits and a lack of a consistent schedule (e.g., inadequate sleep hygiene). In patients with ISWRD, irregularly timed sleep and wake episodes are not confined to times when the child is free of externally imposed schedules (e.g., summer vacation). In ISWRD, variable episodes of sleep and wakefulness occur even in the context of consistent timing of light and darkness, meals, and social contacts.

N24SWD can sometimes be difficult to diagnose and a non-24-hour pattern of sleep and wakefulness might be difficult to detect in the sleep diaries and actigraphy if a very regular schedule is imposed upon a child—as might occur in an institutional setting. The provider should inspect sleep diaries and actigraphy for a pattern of sleep timing, including naps, that tend to drift progressively later, or earlier, from day to day. In blind children lacking any light perception, a pattern of hypersomnolence and insomnia that has a relapsing and remitting pattern should raise a strong suspicion for N24SWD. The clinician should be aware that entrainment status, and therefore diagnosis, may change over time: if ocular disease is progressive, then it is conceivable that blind children might progress from normal entrainment to being entrained at a delayed or advanced time (with subsequent DSWPD or ASWPD, respectively) to a full loss of entrainment and N24SWD [30, 31]. Finally, there is evidence in adults that N24SWD may remit entirely for many months at a time before recurring (possibly due to changes in exposure to non-photic zeitgebers) and so diagnosis should be revisited as signs and symptoms warrant [31].

Treatment

There are a relatively small number of large-scale, well-controlled clinical trials of pharmacologic, behavioral, and light treatments of well-diagnosed CRSWDs in adults and the data are even more limited in children [21]. Therefore, it must be acknowledged that the evidence base for some of the treatment recommendations presented herein is limited. The most recent attempt to provide some guidance in this area was the American Academy of Sleep Medicine's (AASM's) updated clinical practice guidelines for the treatment of CRSWDs that was published in 2015. These guidelines were

based on a more rigorous assessment of the literature than was previously conducted (see table 3 in [21]) and the process resulted in CRSWDs practice guidelines that had remarkably few recommendations that were often weakly endorsed.

Nonetheless, both the literature and clinical practice reveal that there are a few general options for the treatment of CRSWDs: the timing of the *circadian pacemaker can be reset* to match that of the desired sleep/wake timing, *the timing of sleep and wakefulness can be changed* to match that of the circadian pacemaker (or to aid in resetting of the pacemaker), and/or *alerting and sedating medications* might be used to improve wakefulness and sleep, respectively [21, 32].

Consistent Light/Dark Timing

As noted above, light is the primary zeitgeber for the human circadian pacemaker and the first step in treatment should be the introduction of consistently timed and uninterrupted periods of light and darkness. A history of consistently timed periods of light and darkness ensures that the pacemaker's drives for sleep and wakefulness are occurring at the same times each day. Since even dim light can have a resetting effect on the pacemaker [7, 14], the clinician should consider the potential impact of even seemingly dim light—especially in the evening and during the night (e.g., from electronic devices). This can be especially difficult to put into practice in adolescents and a distinction must be made with patients and their parents between keeping a consistent sleep/wake schedule (which might not be possible, for example, due to insomnia) and maintaining a consistent *light/dark schedule* (which *can* be scheduled by either parents or older children themselves).

As noted above, the wavelength of light has an impact on circadian resetting with blue, shorter wavelength light having a greater resetting effect than red, longer wavelength light [13, 14]. Various electronic devices can shift their light emittance toward longer wavelength light with purported benefits for sleep and circadian functioning. However, it should be remembered that even dim indoor light [5–7] and light exposure on the order of seconds to minutes [8, 9, 11, 12] can reset the circadian pacemaker under the right conditions [15]. Furthermore, even longer wavelength light can have a resetting effect under conditions of low light intensity and shorter durations of exposure [14]. Therefore, we recommend more emphasis should be placed on achieving consistently timed "lights out" and "lights on" times with uninterrupted periods of darkness in children with CRSWDs than on the use of "blue-blocking" features on electronic devices.

Prescribed Sleep/Wake Scheduling

The AASM clinical practice guidelines did not find sufficient evidence to recommend prescribed sleep/wake scheduling alone for the treatment of intrinsic CRSWDs. That said, many of the controlled trials of light or melatonin treatment discussed below included a component of prescribed sleep/wake scheduling. Such scheduling, of course, also shapes light/dark timing and it is likely that any benefit derived from sleep/wake scheduling is at least partially a result of "gating" the timing of light and darkness. We recommend prescribed sleep/wake scheduling as a way of slowly shifting sleep/wake timing earlier or later in individuals with DSWPD and ASWPD, respectively. Shifts of approximately *15–30 minutes in bedtimes and wake times every 1–3 days* have been successfully used in clinical trials (also see clinical examples below) [21].

One exception to this recommendation would be the use of "chronotherapy" for DSWPD whereby sleep timing is progressively shifted later each day until desired bedtime is achieved (sleep timing is moved "around the clock"). This intervention is not recommended due to the increased risk that sleep/wake timing will continue to delay each day and the patient will develop non-24-hour sleep–wake disorder.

Resetting Agents

The clinician must select both a dose (intensity) and time of administration when attempting to reset the circadian pacemaker. Just as a dose–response curve allows a clinician to determine a drug effect based on *how much* is administered, a phase–response curve (PRC) tells the clinician what resetting effect to expect based on *when* a time cue is administered. The PRCs that are most clinically relevant are those to light [9, 33, 34] and melatonin [35, 36]. It is important to note that PRCs plot the magnitude and direction of a phase shift when a zeitgeber is administered relative to some marker of biological time (circadian phase) under controlled laboratory conditions and *not* relative to clock hour in an ambulatory setting. The most reliable marker of circadian phase is the onset of endogenous melatonin secretion under dim light conditions (the dim light melatonin onset or DLMO) [37, 38]. As noted above, however, circadian phase is not routinely measured in the clinical setting [39]. Circadian phase can only be very roughly approximated from sleep/wake timing and only then in individuals with the exact same light/dark schedule from day to day (the DLMO occurs approximately 2–3 hours before bedtime or lights out time on average under these conditions). Such consistency does not exist in many children with CRSWDs and so the clinician is left to administer resetting agents relative to sleep/wake timing with an unavoidable lack of precision.

With this caveat in mind, the PRCs to light generally show that light exposure in the early biological night (*before and after habitual bedtime*) causes phase delays while light exposure in the biological morning (*around habitual wake time*) causes phase advances [9, 33, 34]. In terms of light intensity, maximal resetting effects of light can occur at light intensities as low as 550 lux [6] in individuals living under conditions of very dim light [15]. Greater light intensities would be required to obtain maximal resetting effects in patients living under conditions of indoor electrical lighting or bright outdoor light and many clinical trials in CRSWD patients have used *exposures of ≥1000 lux for ≥30 minutes per day* [21].

The PRCs for melatonin indicate that administration late in the biological afternoon and evening causes phase advances, with the greatest advances approximately *5–7 hours before habitual bedtime*. Melatonin administration in the biological morning causes phase delays, with the greatest delays around *habitual wake time* [35, 36]. In terms of dose, melatonin likely has a therapeutic window for circadian resetting where doses of 0.5 and 3 mg have been shown to have roughly equivalent resetting effects [36] while higher doses (≥10 mg) have less resetting effect [40, 41]. Melatonin is administered during waking hours when given for circadian resetting and therefore lower doses are preferred to avoid soporific effects. A *0.3–0.5 mg dose* is recommended, and this can be decreased if somnolence occurs.

DSWPD

DSWPD has the largest number of well-controlled treatment studies utilizing resetting agents in children with CRSWDs, and both light (in combination with behavioral interventions) and orally administered melatonin are suggested treatments for children and adolescents with DSWPD in the AASM guidelines [21]. It should be noted that the recommendation for light treatment was based on just a single non-blinded study [42] that also incorporated behavioral interventions (educational sessions that included recommendations to reduce evening light exposure) and some degree of prescribed sleep/wake scheduling. The recommendation for orally administered melatonin was based on just three studies (including DSWPD patients both with [43, 44] and without [45] comorbid psychiatric illness). More recently, DSWPD has been shown to be successfully treated with prescribed sleep/wake scheduling in combination with melatonin and/or bright light in a randomized controlled trial in adolescents and young adults [46], with melatonin in a randomized controlled trial in adolescents and adults [47], and in an open trial of light therapy in young adults [48].

Timing and dose (or in the case of light, intensity) varied across studies. Light intensities of ~1000 to 10,000 lux were utilized for 30–120 minutes upon awakening (or in one case 8–8.5 hours after the DLMO) and rise times were advanced 30–60 minutes per day [42, 46, 48]. Similarly, melatonin was given in doses ranging from 0.5 to 5 mg (as well as 0.05–0.15 mg/kg) at either a fixed clock hour of 18:00 or 19:00, 1–2 hours before habitual or desired/required bedtime, or 12 hours after awakening [43–47]. Rise times were advanced 1 hour daily in some studies [46].

ASWPD

There is limited randomized, controlled data regarding the use of melatonin or light for well-diagnosed ASWPD in children. The AASM guidelines recommended light therapy in adults with ASWPD [21] based on a single controlled study that utilized white light of ~265 lux administered for 2–3 hours ending 1 hour before habitual bedtime. We recommend 1 hour of bright light exposure ending 1 hour before habitual bedtime.

N24SWD

There is very limited data on the use of melatonin or melatonin agonists in blind children with N24SWD, but orally administered melatonin [21, 40, 49, 50] and the melatonin agonist tasimelteon [51] have clearly been shown to entrain (synchronize) the circadian pacemaker to the 24-hour day in placebo-controlled studies of N24SWD. The early controlled studies of melatonin used 10 mg, 1 hour prior to preferred bedtime [40], and 5 mg at 21:00 [49]. Tasimelteon, 20 mg, was given 1 hour before the target bedtime.

We [40, 41, 52] and others [50] subsequently found that lower doses of melatonin (i.e., ≤0.5 mg) administered 5–6 hours prior to desired bedtime result not only in entrainment in patients with circadian periods >24 hours but also entrainment at a normal phase relative to sleep (i.e., the DLMO ~2–3 hours prior to bedtime) [53]. For patients with periods <24 hours (more common in females [18, 31]), melatonin administration at *wake time* is necessary to ensure entrainment at a normal phase [54]. Note that patients with periods <24 hours would have a tendency for sleep/wake timing to drift progressively earlier from day to day. For example, we have demonstrated successful entrainment of a 9-year-old female with N24SWD using 0.3 mg of melatonin. Her pretreatment observed period was 23.82 ± 0.07 hours (such that circadian phase advanced ~11 minutes earlier per day on average) and she entrained with a period of 24.00 ± 0.10 hours [31, 54].

ISWRD

The AASM practice parameters only recommended oral melatonin for the treatment of children with ISWRD and neurological disorders based on a single study that met criteria for inclusion as well as consideration of smaller open label trials that did not [21]. In a randomized controlled trial in children with autism spectrum disorder, 2–10 mg of melatonin was administered 30–40 minutes before planned bedtime with improvements in parents' reports of sleep latency and total sleep time [55].

Illustrative Cases

Case One

Clinical History

A 17-year-old healthy female presents for insomnia. Her parents are concerned due to daytime sleepiness, declining grades, and increasing impulsive behavior with binge drinking on weekends. When interviewed alone, the patient denies other substance use. The patient is concerned about her grades, as she was put on probation from her volleyball team and is at risk for losing her volleyball scholarship at the state university next fall.

Her weekday schedule includes volleyball practice after school followed by dinner at 7:00 pm and the finishing of homework until 10:00 pm. If she does not have practice, she often naps for 2 hours after school. Her parents are not involved in bedtime. She gets into bed at 11:00 pm and reports falling asleep at 1:00 am most nights but some nights she is up until 3:00 am. She sleeps in her own bedroom. She watches videos on her phone prior to bed, which she feels helps her fall asleep. Wake time on school days is 7:00 am for 8:00 am school start time. Weekend bedtime is 3:00 am, and she is able to fall asleep in less than 20 minutes. Wake time on weekends is between 12:00 and 1:00 pm. She has been frequently late to school, or misses school entirely due to sleeping in. She has been starting to drink one to two energy drinks in the morning prior to school.

During the summer, she fell asleep quickly at bedtime, denied nighttime awakenings, and was not tired upon awakening. Sleep schedule during the summer was 3:00–11:00 am.

She denies snoring, witnessed apneas, or sweating during sleep. She denies an urge to move her legs prior to sleep.

Physical Exam

On exam, her BMI is in the 60th percentile, blood pressure is normal, tonsils 1+, and she is Mallampati Class II.

- *What is your differential for her sleep disturbance? How can you help this teen be successful?*

Differential

- Delayed sleep–wake phase disorder
- Inadequate sleep hygiene
- Generalized anxiety
- Major depression
- Substance abuse

Work-Up/Results

- 14-day sleep log (Fig. 32.2)
- 14-day actigraphy (if available)
- PHQ-9 and SCARED screening (negative)
- Urine drug screen (negative)

Discussion

This teen presents with insomnia most likely due to DSWPD complicated by inadequate sleep hygiene. She has delayed sleep timing, with difficulty falling asleep before 1:00 am. The combination of a late bedtime and early morning school start time results in insufficient total sleep time and daytime consequences (concentration difficulties with school failure, erratic judgment with risky behavior, frank daytime sleepiness). When able to keep her ideal sleep schedule (e.g., summer sleep schedule), she wakes refreshed and denies sleep onset or maintenance insomnia. Electronics at bedtime are likely contributing to sleep difficulties by providing mental stimulation and reinforcement of a later bedtime due to evening light exposure (induces circadian phase delays).

Treatment Options

Address basic sleep and circadian hygiene with removal of electronics from bedroom and avoidance of caffeine and alcohol. Sleep schedule modifications should be reviewed with the patient and parent. Naps and sleeping in should be avoided.

Phase advancement (*moving bedtime and wake time earlier*, see Fig. 32.3a). This treatment requires significant parent support due to difficulty staying consistent and avoiding napping during treatment. The patient often reverses back to a delayed sleep schedule.

During phase advancement, low-dose melatonin can be given to advance patient's phase. General recommendations are for 0.3–0.5 mg melatonin 5–6 hours prior to bedtime.

For example, patient would take 0.3 mg at Step 1 at 7:45 pm, 0.3 mg at 7:30 pm at Step 2, 0.3 mg at 7:15 pm at Step 3, etc. Bright light upon wake time is also recommended. Ideally, a light box would be used with 20–30 minutes of bright (≥1000 lux) light exposure. Caution should be exercised using bright light therapy in patients with bipolar disorder and seizure disorders.

Phase advancement with sleep restriction (see Fig. 32.3b). Phase advancement can often be more successful with implementation of sleep restriction (move bedtime earlier but keep

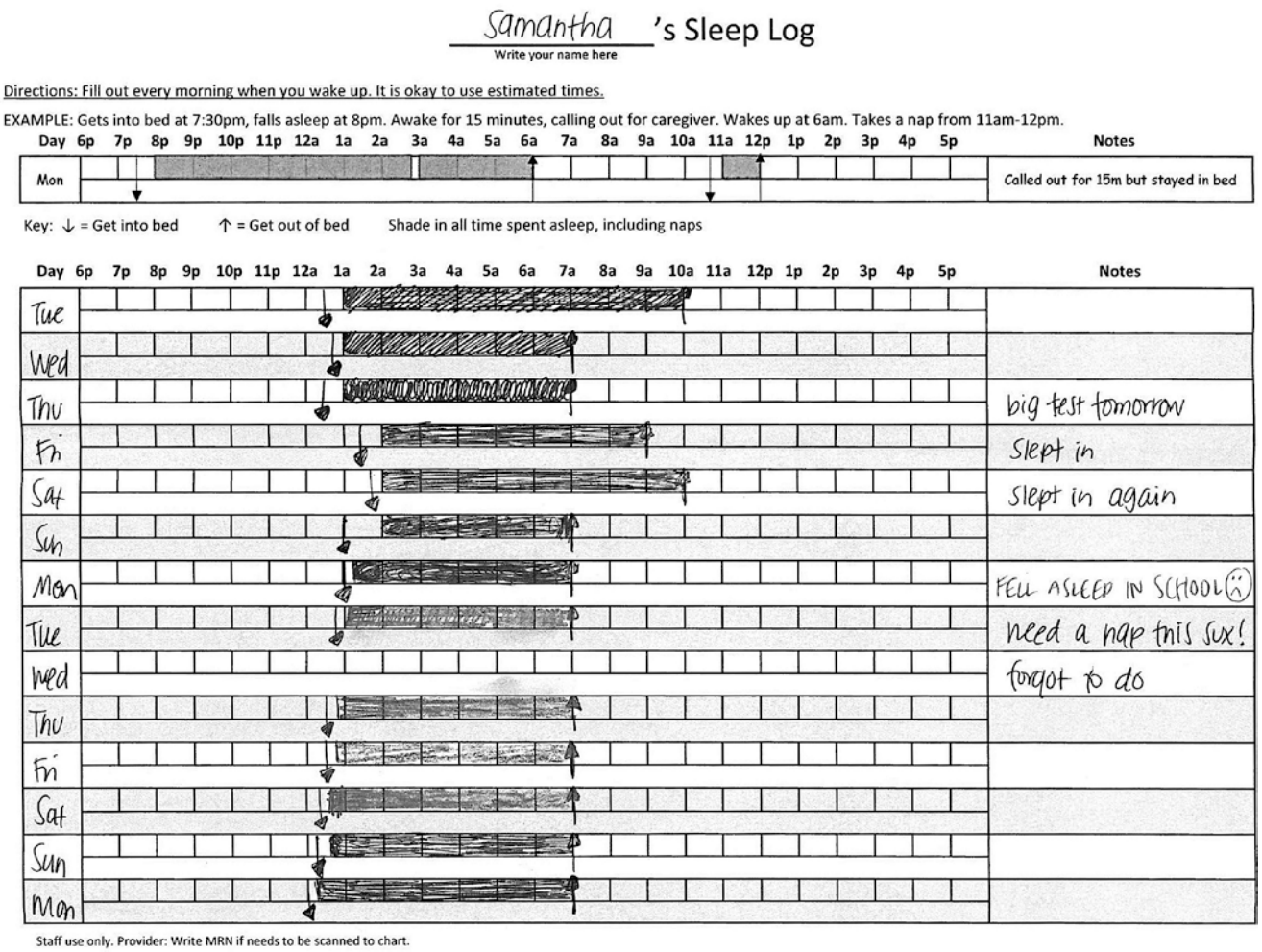


Fig. 32.2 Sleep log. In this example, our patient chose phase advancement with sleep restriction. Notably, she stayed up late on Friday and then slept in the next morning. This led to a further delay on Saturday night, and a return to her initial sleep pattern of waking at 10 am. Paying off her sleep debt over the weekend created difficulties falling asleep on Sunday night to get ready for another week of school. She got back on track and got up at 7 am on Monday morning even though she was tired. She was very sleepy over the next few days but continued to wake at the same time every day. At the end of the 2 weeks, she was falling asleep nearly an hour earlier than when she started

the wake time the same). Instead of slowly advancing wake time, patient would maintain usual wake time of 6:30 am on both weekdays *and* weekends. Sleep restriction can build up sleep drive, with the teen being sleepier earlier in the evening leading to successful sleep onset. It is not recommended to restrict sleep to fewer than 6 hours. As above, caution should be exercised using sleep restriction in patients with bipolar disorder and seizure disorders.

Outcome

In our case, the patient was very motivated for change due to significant complications of her delayed sleep–wake phase disorder. She stopped napping after school, cut out caffeine and alcohol, and plugged in her phone at night in the family's kitchen charging station. She worked on the phase advancement schedule with sleep restriction (see Fig. 32.3b) while simultaneously using low-dose melatonin and morning bright light therapy for 4 weeks. When returning to clinic 6 weeks later she was falling asleep at 11:00 pm, waking at 7:00 am. Her grades had improved enough that she was back on the volleyball team.

Behavioral interventions are inherently difficult for patients and their families to adhere to given they require a change in routine. Often treatment failures are secondary to a lack of adolescent engagement and behavioral change. Fortunately, the provider in this case was able to identify the patient's motivation to continue playing volleyball to promote adherence to the treatment plan. Overall, parent and adolescent involvement is crucial for success.

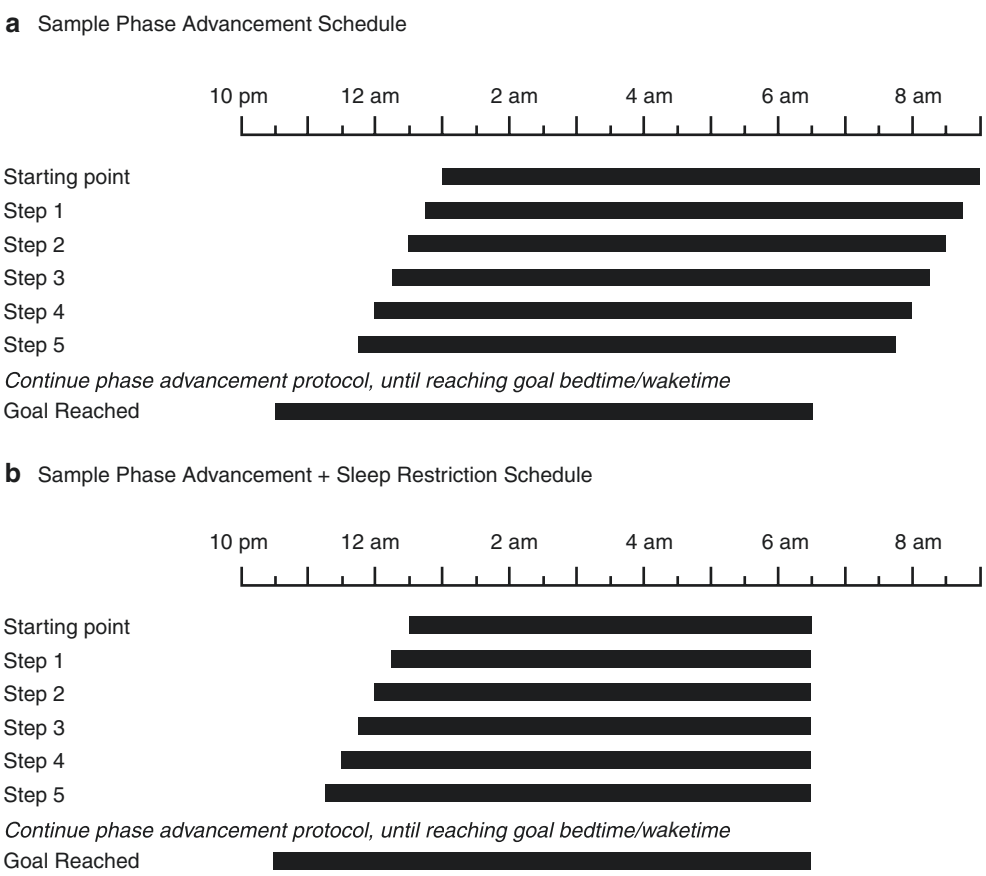


Fig. 32.3 (**a**, **b**) Sample sleep schedule modifications. Examples of prescribed sleep/wake scheduling to reset the circadian clocks of patients with delayed sleep–wake phase disorder

Case Two

Clinical History

A 5-year-old male with autism spectrum disorder presents with parents due to early morning awakenings. Bedtime is at 6:00 pm, wake time at 3:00 am. Patient naps most days at 10:00 am for 2 hours. Bedtime routine starts at 7:00 pm and ends with patient rocked by mother to sleep. He twirls his mother's hair, chews on a pacifier, bangs his head, and kicks and rolls. It typically takes him about 1 hour to fall asleep, with the mother present in his bed. Parents have tried moving bedtime later, but he still takes the same amount of time to fall asleep, resulting in less total sleep time.

He sleeps in his own room with a mattress on the floor. There are no electronics in his bedroom. Parents have not observed any snoring, witnessed apneas, or mouth breathing during sleep. Approximately, two to three times per week he will wake up crying, yelling, and thrashing between 11 pm and 1 am. At times he will settle back to sleep on his own, while other times he is awake for 1–2 hours during the night. If he wakes up and is unable to settle within 20 minutes, the parents will rock him back to sleep. Each morning, regardless of the time he falls asleep and time he spends awake at night, he will wake up at 3:00 am. He is irritable during the day, with worsening behavior after 2:00 pm.

Physical Exam

- General: Non-dysmorphic, NAD. Minimal eye contact with limited cooperation. Normal weight with BMI in the 55th percentile.
- HEENT: Normal-shaped head, no bruising or hematomas. Nares are clear. Tonsils 1+; Mallampati II with good dentition. Slightly high arched palate.
- Cardiac: RRR, no murmurs.
- Respiratory: Lungs are clear to auscultation; normal chest shape.
- GI: Abdomen is soft, non-distended.
- Skin/ MSK: Extremities are warm and dry. Skin without eczema. No swelling of knees or ankles. Normal scattered bruises on anterior lower extremities.
- Neuro: Non-verbal, with some arm flapping. Facies symmetric, normal gait.
  - *What is your differential for his sleep disturbance? What do you offer next?*

Differential

- Chronic insomnia (previously classified as behavioral insomnia of childhood, sleep onset association type)
- Sensory integration disorder and/or sensory processing difficulty
- Advanced sleep–wake phase disorder

- Night terrors/confusional arousal
- Restless legs syndrome (RLS)
- Sleep-related rhythmic movement disorder

Work-Up/Results

- Ferritin (normal = 52 ng/mL with reference range 14–80 ng/mL)
- 14-day sleep log
- 14-day actigraphy (if available)

Discussion

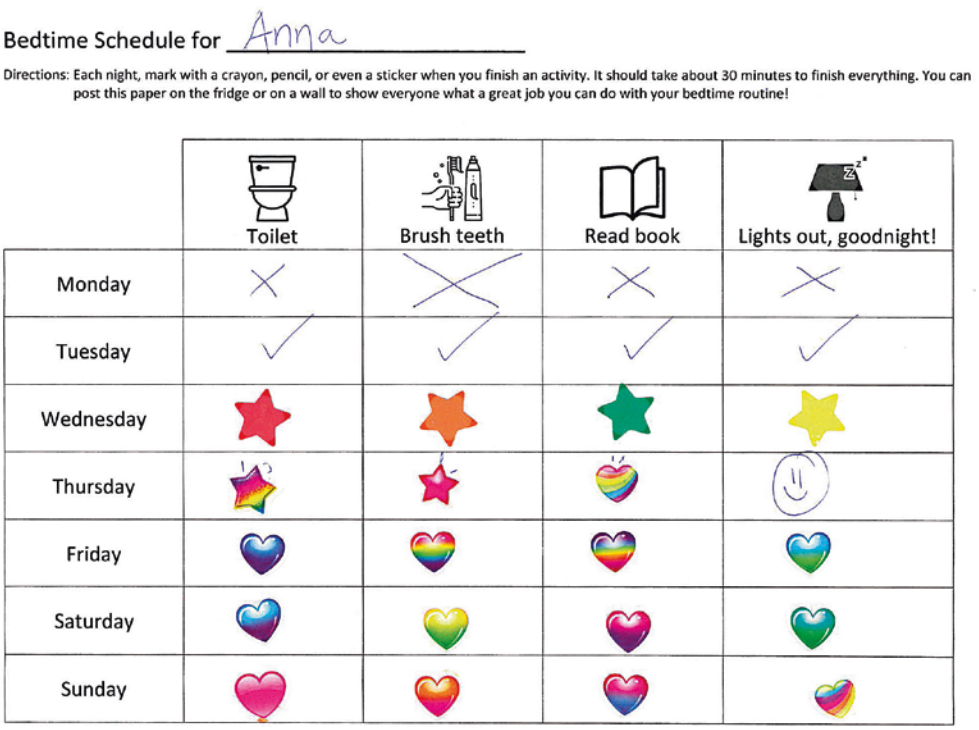
Upon review of 14 days of actigraphy, the provider noticed that the patient's naps were closer to bedtime and longer in duration than previously described, and bedtime was more variable (5:00–9:00 pm). Wake time was consistent at 3:00 am. The patient's movement prior to sleep may indicate self-soothing behavior as opposed to a movement disorder like RLS/PLMD in the context of a normal ferritin. Overall, this patient's sleep disturbance is most consistent with advanced sleep–wake phase disorder, complicated by behavioral insomnia of childhood, sleep onset association type, and sensory disorder.

Properly timed light and dark exposure can be helpful in treating advanced sleep–wake phase disorder. We recommend evening light exposure for 1 hour ending 1 hour before bedtime. For example, with this patient, he should receive timed light exposure from 5:00 to 6:00 pm with goal bedtime of 7:00 pm. Light restriction is also important. The patient should maintain a dark environment in the early morning between 3:00 and 5:00 am and during the middle of the suggested sleep period. Parent involvement will be necessary to limit electronic use and maintain a dark environment. Ideally, the child should stay in bed or relax in the dark. Incentives may be implemented to establish this schedule. Black out shades and avoidance of electronics are ways to achieve dark conditions. Avoid napping to increase sleep drive, when appropriate (most children do not need naps after age 5 years). Recommend adequate daytime activity to increase sleep drive.

It was reviewed with parents that the patient does have sleep onset association, with the mother needing to be present to soothe child to sleep at bedtime, and with the same requirement upon nighttime awakenings. This is likely contributing to prolonged nighttime awakenings, in which mother needs to rock child back to sleep again.

Behavioral interventions are a key part of the treatment plan. It was recommended that the parents aim to shorten the bedtime routine to 20–30 minutes with use of a timer and visual schedule (Fig. 32.4). All activities should lead to the bedroom, with the bedtime routine ending in the child's bedroom in dim light, with an enjoyable and relaxing activity like reading.

Reassurance was given regarding patient crying out in the middle of the night, which the provider presumes is a non-REM parasomnia (confusional arousal vs. night terror) in the context of chronic insomnia and insufficient sleep time. The parents were told that these usually resolve with age and with an appropriate sleep duration.


Bedtime Schedule for Anna

Directions: Each night, mark with a crayon, pencil, or even a sticker when you finish an activity. It should take about 30 minutes to finish everything. You can post this paper on the fridge or on a wall to show everyone what a great job you can do with your bedtime routine!

	Toilet	Brush teeth	Read book	Lights out, goodnight!
Monday				
Tuesday				
Wednesday				
Thursday				
Friday				
Saturday				
Sunday				

Fig. 32.4 Bedtime schedule. Having parents and children keep a bedtime schedule are a great way to make bedtime fun and reinforce healthy sleep habits

Outcome

At a follow-up appointment in 4 weeks, parent sleep logs demonstrate a later bedtime of 7:00 pm and a wake time between 4:00 and 5:00 am after making several changes: shorter bedtime routine, timed evening light exposure (discontinued once sleep onset delayed to 7:00 pm), consistent schedule with avoidance of naps, and use of a weighted blanket. Parent expectations were modified that child will wake between 4:00 and 5:00 am.

Parents continue to work on behavioral interventions, with the goal of him falling asleep independently at bedtime. Currently, the patient is falling asleep with the mother sitting on a chair in the room. Presumed parasomnias decreased in frequency with increased sleep time. The head-banging behavior persisted, but reassurance was given that this was likely a self-soothing behavior with no abnormal findings on initial or follow-up exams. A referral was made to Occupational Therapy for further treatment of comorbid sensory disorder.

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Parasomnias

33

Oliviero Bruni and Silvia Miano

Abbreviations

CAP	Cyclic alternating pattern
CPGs	Central pattern generators
DOAs	Disorders of arousals
HSD	Hypersynchronous delta
ICSD-3	International Classification of Sleep Disorders
RBD	Sleep behavior disorder
SHE	Sleep-related hypermotor epilepsy
SWA	Slow-wave activity
SWS	Slow-wave sleep
vPSG	Video-polysomnography

Definitions of Parasomnia

The International Classification of Sleep Disorders (ICSD-3) [1] defines parasomnias, which mean "around sleep", as "undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousal from sleep." Parasomnias are classified according to the sleep stages in NREM (confusional arousals, sleepwalking, sleep terrors, and sleep-related eating disorder) and REM parasomnias (REM sleep behavior disorder, recurrent isolated sleep paralysis, and nightmare disorder), or other parasomnias (exploding head syndrome, sleep-related hallucinations, and sleep enuresis) (Table 33.1). They occur during the night without altering the normal structure of sleep, as opposed to other major sleep disorders. The evolution is usually benign, given the tendency to spontaneous resolution at the time of puberty, even if the benignity is under doubt when the events persist into adulthood.

Table 33.1 Classification of parasomnias based on ICSD-3

NREM-related parasomnias
Disorders of arousal from NREM sleep
Confusional arousals
Sleepwalking
Sleep terrors
Sleep-related eating disorder
REM-related parasomnias
REM sleep behavior disorder
Recurrent isolated sleep paralysis
Nightmare disorder
Other parasomnias
Exploding head syndrome
Sleep-related hallucinations
Sleep enuresis
Parasomnia due to medical disorder
Parasomnia due to medication or substance
Parasomnia, unspecified
Isolated symptoms and normal variants
Sleep talking

Data from ICSD-3 [1]

Parasomnias have many features in common: clear and dramatic symptoms, not associated medical problems (although other sleep disorders may trigger parasomnias), spontaneous resolution, and unknown etiology. The prevalence is variable depending on the type of parasomnia and the age of occurrence. Parasomnias can have adverse and frequently overlooked consequences, including unintentional self-harm, harm to others (with potential legal implications), daytime sleepiness, and psychological distress [1].

NREM-Related Parasomnias

NREM-related parasomnias, commonly named disorders of arousal (DOAs), are a family of disorders that are thought to derive from incomplete arousal from NREM sleep, mainly

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slow-wave sleep (SWS), defined by ICSD-3 as recurrent episodes of incomplete awakening from NREM sleep, characterized by abnormal sleep-related complex movements and behaviors associated with various degrees of autonomic nervous system activation, inappropriate or scarce responsiveness to the external environment, limited or absent cognition or dream imagery. Subjects have partial or complete amnesia for the episode [1–3].

The clinical features of NREM parasomnia may be summarized as follows:

- Common in childhood
- Episodes in the first third of the night
- A state between sleep and waking during the event, disorientation, and confusion
- Presence of triggering factors
- Long episode duration (minutes)
- Minimal recall of the event
- Strong familial pattern

The events typically occur during the first third of sleep, at the exit of stage N3, usually once per night, and the subjects may appear confused and disoriented for several minutes or longer after. Sometimes, complex behavior with potentially violent or injurious features might occur, with some cases of defenestration that have been described [4].

DOAs are poorly understood and underdiagnosed, leading to inadequate management and underestimation of the consequences. These common disorders are especially prevalent during childhood, with sleep terrors reported in up to 34% of children at 1.5 years of age and sleepwalking in up to 13% of children at 10 years of age [5].

DOAs often resolve by puberty; however, they are far more common in adults than is generally acknowledged, with a 2–4% prevalence of sleepwalking or sleep terrors in both men and women. The same individual may experience more than one type of arousal parasomnia. Although one of the patterns might predominate, most sleepwalkers also experience sleep terrors and confusional arousals and considerable familial aggregation exists between sleepwalking and sleep terrors [6].

A strong familial occurrence has often been reported, in up to 60% of cases. Almost all children may have rare episodes of confusional arousals, in particular during the preschool age, characterized by minor episodes of partial awakening from sleep which might not come to the attention of caregivers. For this reason, epidemiological studies on confusional arousal are rare. Sleep terrors have the greatest incidence in preschool children, with a prevalence ranging from 17.3% to 39.8% in preschool age [6].

The prevalence of NREM parasomnias in adults is unknown, but mostly represents a continuation of episodes after adolescence, sometimes after having been symptom-free for several years.

A recent population-based cross-sectional study in 1000 randomly selected young adults (18 years and older) showed a lifetime prevalence of confusional arousals of 18.5% and prevalence in the last 3 months of 6.9%. For sleepwalking, prevalence was 22.4% and 1.7% respectively, and for sleep terrors 10.4% and 2.7%, respectively [7].

The natural course of DOAs is still unknown, and we cannot yet predict whether a DOA in any given child will resolve in adulthood or whether it will persist or even reappear after many asymptomatic years.

Diagnostic Approaches to NREM Parasomnia

Currently, the diagnosis of DOAs is based solely on clinical manifestations and history, in contrast to rapid eye movement (REM) sleep behavior disorder (RBD), which requires objective criteria (namely, REM sleep without atonia). However, polysomnographic recordings can be useful in difficult cases or when there is a comorbidity with other sleep disorders like sleep disordered breathing or narcolepsy or when there is a clinical doubt of nocturnal seizures [2].

Usually the manifestations of NREM and REM parasomnias can be differentiated simply on a clinical basis, and an accurate description of the episode according to a defined scheme is extremely important. Finally, the presence of a positive family history is another aspect helpful to identify NREM parasomnia.

Based on the ICSD-3, the following specific criteria must be met:

- Recurrent episodes of incomplete awakening from sleep.
- Inappropriate or absent responsiveness to efforts of others to intervene or redirect the person during the episode.
- Limited (e.g., a single visual scene) or no associated cognition or dream imagery
- Partial or complete amnesia for the episode.
- The disturbance is not better explained by another sleep disorder, mental disorder, medical condition, medication, or substance use.

Some researchers consider NREM parasomnias as a single continuum, ranging from confusional arousals with low motor and autonomic activation, on the one hand, to sleepwalking characterized by intense motor activity and mild autonomic activation, on the other hand. According to this theory, night terrors fall between these two, with intense autonomic discharge and mild motor activation. In addition, episodes sometimes combine elements of all three, and a child might display a sequence of different NREM parasom-

Table 33.2 Clinical features of NREM parasomnia

	Confusional arousal	Sleepwalking	Sleep terrors
Age of onset	2–10 years	4–12 years	18 months–10 years
Occurrence	First third of night	First third of night	First third of night
Ictal behavior	Whimpering, some articulation, sitting up in bed, inconsolable	Screaming, agitation, flushed face, sweating, inconsolable	Walking around, quiet or agitated, unresponsive
Motor activity	Low	Complex	Rarely complex
Autonomic activity	Low	Mild	Intense
Complications	Rare (aggressions)	Possible (violence)	Occasional (escape)
Amnesia	Yes	Yes	Yes
Threshold of arousal	High	High	High
Familiarity	High	High	High

Data from Proserpio and Nobili [9]

nias [8]. There are common features to these disorders (Table 33.2).

NREM parasomnias occur when there is an incomplete dissociation of NREM sleep into wakefulness: phenomena that deepen sleep and enhance sleep inertia promote NREM parasomnias by impairing normal arousal mechanisms; conditions that cause repeated cortical arousals lead to NREM parasomnias through sleep fragmentation; the impaired arousal mechanisms and the persistence of sleep drive result in a failure of the brain to fully transition into wakefulness [1].

During the episode, patients are usually unresponsive to the external stimuli, and completely or partially amnestic after the event, with little or no recall either immediately afterward or the next morning.

In clinical practice it is commonly acknowledged that the mental content of DOA episodes is less frequently reported by children than by adults. This phenomenon parallels the gradual development of dream imagery and cognitive abilities in children, and the less frequent reports of dreaming in young children than in adults [2].

An adequate general and hypnic anamnesis with the patient and bed partner or parents is vital, taken directly or supported by a questionnaire. There are no available standardized sleep questionnaires for parasomnias. Sleep screening questionnaires can be helpful to the physician to quickly collect data about sleep–wake habits [10, 11]. Sleep diaries can highlight irregularities of sleep/wake schedules to rule out whether episodes are triggered by sleep deprivation. In case of parasomnias, a videotape of a typical episode recorded by parents at home may be helpful to the clinician, and lately this is easily obtained and collected by the new smartphone.

On the other hand, some difficult cases need a video-polysomnographic (vPSG) recording to clarify the nature of the disorder. In agreement with international criteria, vPSG is not necessary for the diagnosis of arousal disorders, but it is recommended:

- In cases in which the clinical history is not completely suggestive of NREM parasomnia
- In the presence of injurious or extremely disruptive behaviors
- When there is a suspicion of other major sleep disorder associated (sleep apnea, periodic limb movement, nocturnal seizures, etc.)
- When the parasomnia is associated with medical, psychiatric, or neurological conditions [12, 13]

There are no specific features in terms of overall sleep architecture that can be highly suggestive of NREM parasomnia. However, some unusual sleep alterations have been described as characteristic of patients suffering from arousal disorders. These include hypersynchronous delta waves, irregular buildup of slow-wave activity, and NREM sleep instability.

The hypersynchronous delta (HSD) activity is defined as continuous high-voltage (>150 μV) delta waves occurring during slow-wave sleep (Fig. 33.1) or immediately prior to an episode. HSD has been considered a possible diagnostic sign of an NREM parasomnia, but this is still under debate, since HSD was absent in many sleepwalkers before episodes of complex behaviors [14–16], and it has also been described in patients without history of sleepwalking but with other sleep disorders [15–17] and finally in healthy controls, especially after sleep deprivation.

Three post-arousal EEG patterns have been described: (i) diffuse rhythmic and synchronous delta activity (<4 Hz), most prominent in bilateral anterior regions; (ii) diffuse and irregular moderate-to-high voltage delta and theta activity intermixed with, or superimposed by, alpha and beta activity; and (iii) prominent alpha and beta activity, at times intermixed with moderate voltage theta activity. The diffuse rhythmic and synchronous delta activity was preferentially associated with simple behavioral episodes [18].

The sleep of patients with arousal disorders is characterized by an increase in NREM instability of slow-wave sleep probably due to an abnormality in the neural mechanisms responsible for the regulation of this sleep stage [19]. The increased frequency of sleepwalking episodes during post-deprivation recovery sleep confirmed this hypothesis [20]. Polysomnographic recordings have shown that, compared with controls, sleepwalkers experience a higher number of microarousals and arousals during slow-wave sleep [21].

Cyclic alternating pattern (CAP) in place of, is a well-known and recognized endogenous rhythm, present in

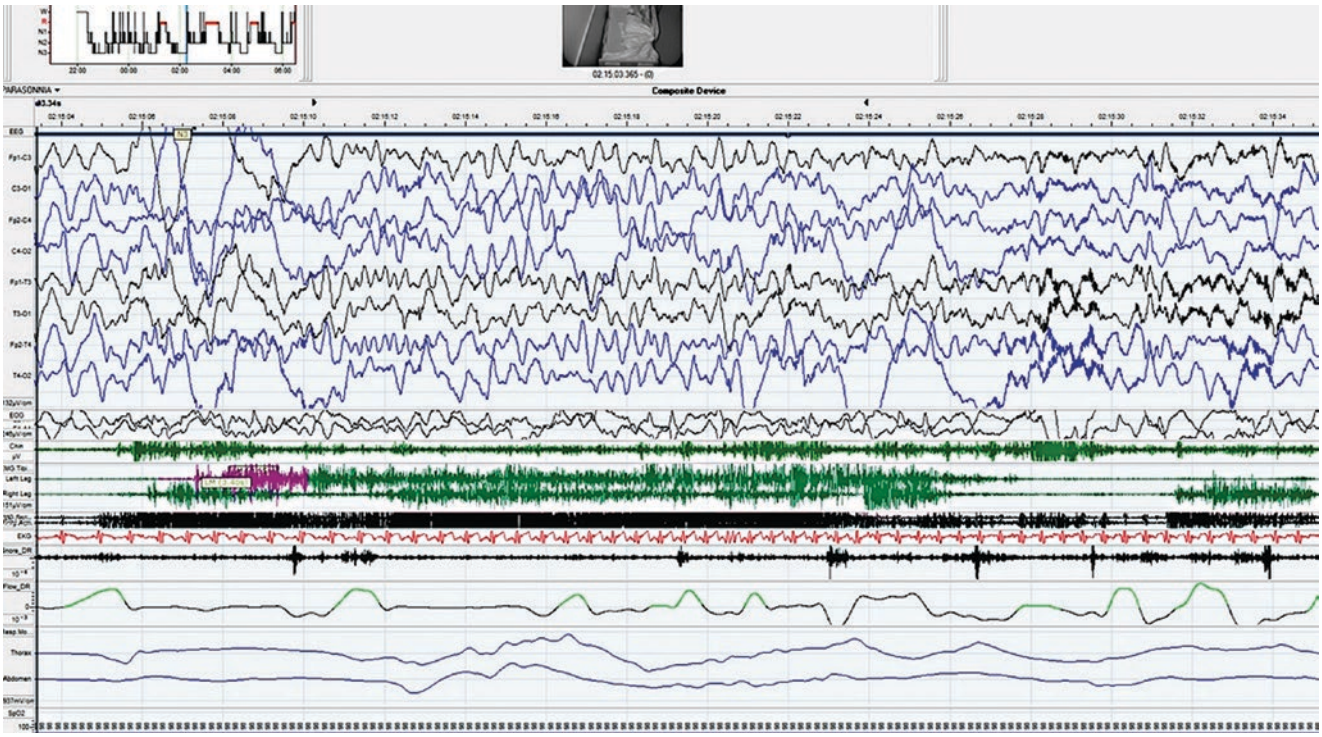

Fig. 33.1 Sleep EEG recording of the onset of an episode of confusional arousal in a 10-year-old child, occurring in N3 sleep stage. Notice the presence of a burst of delta waves immediately preceding the onset of the episode (corresponding to the increase of muscle tone) and the persistence of hypersynchronous theta-delta activity mainly expressed over the frontal regions. At nasal cannula, notice flow limitations

NREM sleep characterized by periodic EEG activity with sequences of transient electrocortical activations (phase A of the cycle) which are distinct from background EEG activity (phase B of the cycle). A subtypes alternate every 20–30 s and express the organized complexity of arousal-related phasic events in NREM sleep, thus representing a measure of NREM instability [22, 23]. Recently this pattern has been studied in patients with NREM parasomnia. The important finding was a higher CAP rate in patients with sleepwalking/sleep terrors in comparison with controls [20, 24, 25].

In summary, these data indicate that NREM parasomnias are characterized by an increase in NREM sleep instability and arousal oscillations together with an inability to maintain stable and consolidated slow-wave sleep, and the analysis of sleep microstructure, especially of NREM sleep, may be helpful for diagnosis.

Despite the well-known SWS instability in DOAs, relatively little attention has been devoted to the potential consequences of these parasomnias on daytime functioning. A series of studies supports the notion that around 40% of individuals with DOAs have excessive daytime sleepiness (EDS). DOAs were initially linked to psychiatric disorders, as supported by epidemiological studies, despite the cause–consequence relationship between psychiatric disorders and DOA is still being debated [2].

Disorders of Arousal From NREM Sleep

Confusional Arousal

Confusional arousals occur mainly in infants and toddlers and are defined as episodes characterized by mental confusion or confused behavior occurring in bed, without terror component or getting out of the bed [1].

The individual often sits up in bed and looks around in a confused and slow manner (opposed to night terrors, which begin suddenly). Somniloquy (sleep talking), with slow speech and blunted responses to questions, is frequently observed during confusional arousals [2].

An episode may progress to agitated and confused behavior with marked sweating, crying (but not screaming), calling out, or talking. Sometimes the child may fall out of bed, rarely with injuries. The child's eyes may be open or closed. The child is partially aware of the environment and combines reality with imagination. Although appearing to be awake, the child does not respond when spoken to and may seem to "stare right through" parents. Any attempts to intervene may trigger strong resistance or aggression. Each episode usually lasts 5–15 min (sometimes much longer) before the child calms down spontaneously and returns to sleep. Enuresis may occur during or after an episode.

Sleepwalking

Sleepwalking typically begins as confusional arousal but can also start abruptly, and the patient might exhibit inappropriate behaviors. Subjects may sit up with glass eyes, pick at the blankets, make body movements, mumble or moan, get up and walk to different rooms or even outside the house, may bump into a wall, go through a glass window, fall down the stairs, or urinate in a wastebasket after leaving the bed [3]. The ambulation may end spontaneously in an inappropriate place, or the individual might return to bed to continue sleeping without reaching conscious awareness at any point. Eyes are usually open, and the emotional expression can be calm up to extreme agitation. Given the variability of the episodes, the duration can fluctuate from few seconds to several minutes. Mental activity often includes misperception and relative unresponsiveness to external stimuli, confusion, perceived danger, and variable retrograde amnesia [26]. In many patients, brief, unpleasant dreamlike mental activity may occur during sleepwalking [27].

The onset is generally between 4 and 8 years, with a peak at 12 years and disappearing in adolescence. The prevalence is between 15% and 30% for sporadic episodes and 3% for frequent episodes. There is no difference between the two sexes.

A high level of familiarity is characteristic: around 80% have other family members with sleepwalking or other arousal disorders, with a chance of recurrence of 45% if one parent is affected and 60% if two parents are affected.

Some precipitating factors have been identified such as fever, sleep deprivation, obstructive apnea, bladder distension, external noises, and drugs (neuroleptics, chloral, some tricyclic antidepressants).

Episodes of sleepwalking in children are rarely violent and movements are usually slow. If restrained, the child tries to avoid the other person, but without aggressive behavior. On the contrary, in adulthood, the most serious complication is represented by injuries and violent behavior; the number of legal cases of sleep-related violence involving somnambulism is increasing [26].

Sleep Terrors

Sleep terror episodes are accompanied by behavioral manifestations of intense fear, frightening screams, and strong autonomic nervous system activation. It is commonly characterized by an abrupt awakening characterized by terror or intense fear, cries, sweating, confusion, and autonomic activation. The individual sits up in bed, unresponsive to external stimuli, with intense tachycardia, tachypnoea, mydriasis, increased muscular tone, and sometimes incoherent vocalizations [3].

The prevalence is up to 17.3% between the age of 3 and 13 years with a male prevalence. The onset is commonly between 3 and 12 years with a peak at 5–7 years. Symptoms and frequency of episodes tend to fade with growth: children under the age of 4 have on average one episode per week while children over 7 have an average of one to two episodes per month.

The precipitating factors are similar to those of sleepwalking. Sleep terrors usually last few minutes, but can range anywhere from 30 s to 30 min. They can occur more than once a night and up to several times per week. Patients are only partially responsive to the environment, and there is little or no recall of the event the morning after. As in sleepwalking there are no relationships with psychopathological pictures. Cases reported with violent behaviors appear related more to the attempts to block or restrain the individual [28, 29].

Sleep-Related Eating Disorder (SRED)

SRED consists of "recurrent episodes of involuntary eating and drinking during arousals from sleep, associated with diminished levels of consciousness and subsequent recall, with problematic consequences," which include the following: consumption of abnormal combinations of food or toxic substances, sleep-related injurious behaviors performed while in pursuit of food [30, 31], adverse health consequences (weight gain, various metabolic problems), and daytime sleepiness. Episodes occur during partial arousals from sleep during the first third of the night [32].

The prevalence of SRED in the general population is unknown. SRED is found predominantly in adult women, and the average age of onset is approximately 22–27 years [33, 34].

A history of other parasomnias during childhood, especially sleepwalking, is frequently reported. Patients with SRED share several clinical features with sleepwalkers plus eating behavior problems [35].

Several psychiatric conditions have been associated with SRED, including depression, bipolar disorder, anxiety, posttraumatic stress disorder, and history of repeated abuse. Finally, many drugs have been implicated in triggering SRED, including zolpidem, triazolam, amitriptyline, olanzapine, and risperidone [34]. Some drugs have been reported to be effective for the treatment of SRED, such as topiramate and dopaminergic agents alone, or in combination with benzodiazepines (mainly clonazepam) or opiates [36, 37].

Pathophysiology of NREM Parasomnias

NREM parasomnias seem to result from the co-occurrence of various predisposing, priming, and precipitating factors—the so-called 3-P model. The predisposing factor is likely to relate to the genetic background; the genetic contribution might be especially important for the persistence beyond adulthood. Two types of priming factors have been identified: first, factors that deepen sleep, such as sleep deprivation and various substances, including Z-drugs, lithium and sodium oxybate; second, factors that are known to induce or increase sleep fragmentation, such as fever, anxiety, and stress-induced insomnia, and any sleep comorbidities. The precipitating factors are less recognized as they show considerable interindividual and intraindividual diversity (noise, external and internal stimuli) [2]. Therefore, any factor that fragments sleep, increases sleep pressure (sleep deprivation, stress, febrile illness, medications, alcohol), or is associated with arousals (external or internal stimuli like the presence of sleep apneas, the transition to another sleep cycle, mental activity, or others) might act as precipitating factor [2]. A disorder of sleep maturation has been also hypothesized in the pathophysiology of NREM parasomnias [38].

The current pathophysiological theories consider parasomnias as state dissociation, characterized by the coexistence of wake- and sleep-like activity within cortical and subcortical areas of the brain.

Coexistence of wake-like and sleep-like EEG patterns in different cortical areas has been demonstrated with intracerebral stereo-EEG (S-EEG) investigations in epileptic patients during the presurgical evaluation [39]. Different S-EEG recordings during a confusional arousal showed the occurrence of a local activation in the motor, cingulate, insular, temporo-polar, and amygdala cortices, with a simultaneous persistence of slow waves in the frontal and parietal dorsolateral cortices as well as sleep spindles in the hippocampal cortex [40–42]. The electrophysiological patterns observed in these three cases are in accordance with data previously obtained with ictal SPECT in sleepwalking which showed decreased regional cerebral blood flow in the frontoparietal cortices associated with the activation of the cingulate cortex and the absence of a deactivation of the thalamus during sleepwalking [43, 44].

Therefore, the typical features of arousal parasomnias could be explained by the coexistence of an activation of the amygdalo–temporo–insular areas disengaged from the prefrontal control cortex (emotional activation, such as fear), with the persistence of the deactivation of the hippocampal and frontal associative cortices (amnesia for the event) (Table 33.3).

Apart from the phenomenon of state dissociation, other mechanisms seem to contribute to the appearance of these sleep disorders, such as arousal instability and activation of innate behaviors and locomotor centers.

A peculiar feature of subjects who experience NREM parasomnia is the presence of increased arousals and cyclic alternating pattern (CAP) rate during slow-wave sleep, even on nights without episodes [25, 45, 46]. These results suggested that a distinctive feature of DOAs is the abrupt and more frequent intrusion of the brief A phases of CAP during B phases, disrupting the homeostatic process that would be mediated by slow-wave activity (SWA).

An interesting theory suggests that part of the "emotional" and motor clinical features of NREM parasomnias could result from a release of inhibition of "central pattern generators" (CPGs). CPGs are "functional neural organizations" which regulate innate behavioral automatisms and survival behaviors and located in the spinal cord, mesencephalon, pons, and bulb [47].

Genetic factors are involved in the occurrence of arousal parasomnias. The probability of childhood sleepwalking has an incidence of 22% when both parents are unaffected, 45% when one parent has a DoA and 60% when both parents are affected [5]. About 80% of sleepwalkers have at least one family member affected by this parasomnia, and the prevalence of somnambulism is higher in children of parents with a history of sleepwalking [48]. A small series indicates that somnambulism may be associated with excessive transmission of the HLA-DQB1∗05 and ∗04 alleles [49].

Current data do not suggest a definitive association between parasomnias and concurrent psychopathology [50, 51]

Table 33.3 Sleep state dissociation in NREM parasomnias

	Main cerebral function	During slow-wave sleep	During wakefulness	During episode of parasomnia
Motor cortex	Control of movements	Slow-wave activity	Alpha and mixed activity	Alpha and mixed activity
Fronto-parietal association cortex	Consciousness, judgment	Slow-wave activity	Alpha and mixed EEG activity	Slow-wave activity
Limbic cortex and amygdala	Emotions	Slow-wave activity	Alpha and mixed EEG activity	Alpha and mixed EEG activity
Hippocampus	Memory	Slow-wave activity	Alpha and mixed EEG activity	Slow-wave activity

Data from Castelnovo et al. [2]

Differential Diagnosis of NREM Parasomnia

REM Parasomnias

RBD is typical of the adults and shows similar manifestations of NREM parasomnias. Nevertheless, the occurrence during the second half of the night, the dream enactment behavior, and the absence of mental confusion upon awakening are the features that permit a clear distinction. However, when the subject presents with the criteria for both NREM and REM parasomnias, the diagnosis to be considered is "parasomnia overlap disorder" [1].

Nightmares can be confused with sleep terrors, but some specific features allow an easy differentiation (Table 33.4).

Sleep-Related Hypermotor Epilepsy

Nocturnal frontal lobe epilepsy (NFLE), discovered in Bologna in 1981, has been recently renamed as sleep-related hypermotor epilepsy (SHE) [52] due to the typical clinical hypermotor pattern of seizures [53]. SHE is a rare disease, with an estimated prevalence of 1.8/100,000 individuals, without a gender predominance, with a peak onset during childhood and adolescence. Seizures are abrupt in onset and offset, typically brief, and have a highly stereotyped hypermotor pattern accompanied with vegetative signs, vocalization, emotional facial expression, and asymmetric tonic/dystonic seizures with or without head/eye deviation. Typically, several episodes per night occur associated with non-restorative sleep and daytime tiredness. Commonly, carbamazepine is effective at low doses in two-thirds of patients but in some cases a focal cortical dysplasia can be identified.

In some cases, the differentiation might be challenging between the behavioral patterns of NREM arousal parasomnias, REM behavior disorders, and SHE, because arousal disorders are often comorbid with SHE [54].

NREM sleep parasomnias and SHE also share the increase of sleep instability during slow-wave sleep responsible for triggering the episodes as well as the arousal patterns characterized by rhythmic non-epileptiform theta or delta activity over the frontal regions [55].

Moreover, interictal EEG fails to disclose epileptiform abnormalities in a substantial percentage of SHE patients. Even with video-EEG analysis the clinical features of the initial arousal behaviors might be indistinguishable between the two conditions [56]. In contrast, the clinical features of the evolution and the offset of the events could better differentiate SHE from parasomnias [57]. Table 33.5 summarizes some differences between SHE and NREM parasomnias [56].

A case report of an obese child with severe obstructive sleep apnea in whom nocturnal frontal lobe seizures, which were misdiagnosed as confusional arousals, started within a week after he began nasal CPAP therapy, corroborated the hypothesis about a complex relationship between DoA and SHE. In this case, CPAP treatment caused a rebound of slow-wave activity, with a significant increase of A1 component of CAP, triggering motor seizure. Magnetic resonance imaging disclosed signs of focal cortical dysplasia involving the right inferior frontal circumvolution [58].

Table 33.4 Differential diagnosis between sleep terror, nightmares, and post-traumatic reenactment

	Sleep terror	Nightmares	Post-traumatic reenactment
Occurrence	First third of the night (from slow-wave sleep)	Last third of the night (from REM sleep)	At any time (REM sleep or sleep N2)
Ictal behavior	Crying, screaming	Scary awakening, crying	
Consciousness	Disoriented, confused	Fully alert after awakening	Fully alert after awakening, with anxiety persisting
Autonomic activity, anxious behavior	Intense	Low/mild	Moderate to intense
Amnesia	Frequent	Absent	Absent
Dream recall in the morning	Absent	Good recall	Good recall
Familial history	Present	Absent	Absent
Complications	Potentially injurious and violent	Rarely injurious or violent	Related to post-traumatic stress disorders
Predisposing factors	Sleep deprivation, febrile illness	Stress, traumatic events, psychiatric disorders	Post-traumatic stress disorders
Treatment	Safety, avoid predisposing factors, or clonazepam, or melatonin, or L-5-hydroxytryptophan	None, psycho-/behavioral therapy, treatment of psychiatric disorders	Psycho-/behavioral therapy, treatment of psychiatric disorders

Table 33.5 Differential diagnosis between NREM parasomnia and sleep hypermotor epilepsy

	NREM parasomnia	SHE
Age at onset	3–8 years	Any age (peak in childhood)
Occurrence	During the first third	Any time during sleep
Sleep stage	NREM sleep (usually N3)	NREM sleep (usually N2 or N3)
Frequency during one night	One episode/night, if no other sleep disorders are associated	Several episodes/night
Frequency	Sporadic, if no other sleep disorders are associated	Almost every night
Duration	1–20 min	Seconds to 3 min
Evolution	Tend to disappear	Stable, increased frequency, rare remission
Predisposing factors	Frequent	Rare
Stereotypic motor pattern	Rarely	Yes
Consciousness	Usually impaired	Usually preserved
Amnesia	Frequent	Unconstant

Data from Proserpio and Nobili [9]

Management of NREM Parasomnia

When episodes are not frequent and benign and there is no risk for potential injury, it is often sufficient just reassuring the patient/family. However, DOAs might put the patients in a dangerous situation, with loss of judgment, awareness of environment, and reduced perception of risk. Parents or bed partners should be advised against attempting to awaken or intervene during the episode, as doing so may increase confusion and precipitate a dramatic or even violent reaction [59, 60]. It is preferable to wait until the episode is over and then guide the child quietly back to bed [61].

Attention should be paid to potential precipitating factors, such as sleep deprivation, stress, and environmental disturbances. Precautions should be taken to ensure a safe sleep environment (e.g., removing obstructions in the bedroom, securing windows, installing locks or alarms on outside doors, placing barriers in stairways, and removing sharp or otherwise dangerous objects).

Non-pharmacological Treatment

When parasomnia episodes become frequent and intractable or are associated with daytime mood or behavioral disturbance, the possibility of comorbid sleep disorders, especially sleep disordered breathing but also periodic limb movements, must be recognized and treated [61]. Treatment should always include instructions on sleep hygiene, avoidance of sleep deprivation, and stress management [62, 63].

In children, the preferred treatment for somnambulism consists of anticipatory or scheduled awakening. Parents keep a diary of their child's episodes and determine the approximate time at which the episodes typically occur and then awaken their child about 15–20 min before the episode's typical time of occurrence for a period of 1 month [64]. The mechanism of action was presumed to be related to an interruption of "faulty slow wave sleep" with a restoration of normal sleep patterns.

Psychotherapy is suggested when the clinician suspects that night terrors are manifesting as difficulty coping with frustration, conflict, and inwardly directed aggression and stress. Hypnosis has been found to be effective in both children and adults presenting with chronic sleepwalking or night terrors [65]. When DOAs are secondary to sleep respiratory events or other sleep disorders, treatment of the precipitating sleep disorder may result in a disappearance of DOAs [46].

Pharmacological Treatment

In general, medical treatment is not recommended for children with DOAs because of the benign nature and clinical course and should be considered only if the behaviors are hazardous or extremely disruptive or when they cause undesirable secondary consequences, such as excessive daytime sleepiness, or cause distress to the patient or family.

To date, current treatment recommendations are based only on small clinical trials as well as clinical and anecdotal evidence. Patients should be advised that prescribed drugs are considered "off-label."

Pharmacologic interventions include benzodiazepines such as diazepam 5–10 mg or clonazepam 0.5–2 mg and tricyclics such as imipramine or clomipramine [66]. The effectiveness of benzodiazepines may relate to sedative effects or to decreases in slow-wave sleep.

Other serotoninergic antidepressants, in particular paroxetine, have been reported to be particularly effective in the treatment of sleep terrors. On the other hand, paroxetine has been shown to favor episodes of sleepwalking [66].

An open pharmacological trial of L-5-hydroxytryptophan (2 mg/kg at bedtime) suggests its efficacy in the treatment of sleep terrors. L-5-Hydroxytryptophan is a precursor of serotonin that may modify central serotoninergic system dysfunction or enhance production of sleep-promoting factors [67]. Finally, some case studies have suggested that melatonin therapy, at 5 mg half an hour before bedtime, may be

helpful for patients with sleepwalking and sleep terrors [68]. Also, melatonin 5 mg dispensed 30 min before bedtime has been effective [69].

REM-Related Parasomnias

REM Sleep Behavior Disorder (RBD)

In RBD, normal atonia of REM sleep is lost, and patients have numerous episodes of dream-enacted behaviors that can vary from small hand movements to violent activities, such as kicking, or jumping out of bed. RBD-related behaviors range in severity from loud talking, swearing, laughing, and shouting to reaching, grabbing, leaping out of bed, and crawling. Dreams and nightmares recall is common. Often during the episode, the patient tries to defend himself from an attacker.

RBD is associated with an excess of muscle tone and/or an excess of phasic twitching activity. The ICSD-3 recommended vPSG to diagnose RBD [1], to demonstrate the occurrence of both REM sleep without atonia (RSWA), and video evidence of motor dream enactment in the form of increased physical activity, including aggressive or violent behaviors.

RBD occurs at all ages and in both sexes. In adults, there is clear association of RBD with synucleinopathic degenerative disorders such as Parkinson disease, dementia with Lewy bodies, and multiple system atrophy. In a minority of cases, RBD represents a side effect of treatment with drugs such as antidepressants (tricyclics, selective serotonin reuptake inhibitors (SSRIs), and selective noradrenaline reuptake inhibitors). During physiologic REM sleep, the serotonergic neurons descending to motor neurons cease firing, leading to hypotonia. In this perspective, drugs that stimulate the serotonin system can induce RBD, possibly because they prevent normal sleep-related hypotonia [70].

RBD is rare with an estimated prevalence of 0.05% of individuals and it is more common over the age of 50 years. RBD can occur in both children and adults with narcolepsy [71] with a prevalence ranging from 36% to 60% [72, 73] but clinical severity is usually less aggressive and violent. During childhood, RBD can represent the first manifestation of the disease [74] and in literature we found only single case reports or small case series of early-onset RBD [75, 76].

RBD in children is virtually never idiopathic and is usually associated with narcolepsy or idiopathic hypersomnia, neurodevelopmental–neurodegenerative disorders (autism, Smith–Magenis syndrome, Moebius syndrome, juvenile, Parkinson disease, Tourette syndrome, Neurofibromatosis type 1, pontine glioma, Chiari malformation type 1, or structural brainstem abnormalities), or a side effect of pharmacological agents [74].

RBD management includes the preventive measures, a reevaluation of drugs that can precipitate or worsen RBD, and the use of drugs aimed at avoiding the motor-behavior manifestations. Clonazepam (0.5–2 mg at bedtime) and melatonin (3–12 mg at bedtime) have been shown to be beneficial. Clonazepam seems to have a suppressing effect on phasic locomotor activity and a positive influence on mental dream activity. The mechanism by which melatonin can restore the REM-related muscle atonia remains unknown [76].

Recurrent Isolated Sleep Paralysis

Recurrent isolated sleep paralysis (RISP) is defined as "an inability to perform voluntary movements at sleep onset (hypnagogic form) or on waking from sleep (hypnopompic form) in the absence of a diagnosis of narcolepsy" [77]. During the episodes, consciousness is preserved, and full recall is present. Hallucinations, such as a feeling of the presence of others nearby, pressure on the chest or hearing footsteps, are common. A single episode usually lasts seconds to minutes and spontaneously resolves or can be stopped by external auditory or tactile stimulation from a bed partner. The sensation of being paralyzed can cause intense anxiety. Although diaphragmatic function is not affected, difficulties in breathing may be reported. RISP is considered to represent a condition of state dissociation, with a persistence of REM sleep into wakefulness [1].

RISP is such a vivid experience that it has been incorporated into popular folklore in many parts of the world, and may be interpreted as a supernatural experience, a nocturnal visitation of demons and devils, in a culturally distinct manner. Increased rates of RISP occur in adults reporting history of childhood sexual abuse and in post-traumatic stress disorder, and might be precipitated by stress, anxiety, panic disorder, sleep deprivation, or irregular or disturbed sleep–wake rhythm [77].

The lifetime prevalence of sleep paralysis, based on a large systematic review, is estimated to be 7.6% of the general population, 28.3% of students, and 31.9% of psychiatric patients. No consistent sex differences have emerged, and the mean age of onset is 14–17 years [78]. An association with anxiety/psychiatric disturbances has been described.

The management of RISP consists in reassurance about the benign nature of the episodes and in the avoidance of sleep deprivation and other triggering factors. Recurrent episodes may be treated with REM-suppressing agents such as low doses of tricyclic agents, clonidine, or clonazepam [1].

Nightmare Disorder

Nightmare disorder is characterized by "recurrent, highly dysphoric dreams, which are disturbing mental experiences, occurring during REM sleep and that often result in awakening" [2]. Full alertness upon arousal and full recall of the nightmare is characteristic. Nightmares occur within REM sleep and are therefore more prominent in the second half of the night; children arousing from a nightmare usually become fully alert quickly, respond positively to comforting, and may be able to describe in details the dream content the following morning. Compared to sleep terrors, nightmares are characterized by lower levels of autonomic activation, vocalization, but are often associated with much more anxiety and subsequently fear to get asleep [79]. Nightmare content seems vivid and real. Emotions are characteristically negative and most frequently involve anxiety and fear but also anger, rage, embarrassment, and disgust. Dreams of young children are characterized by monsters or other fantastical imageries, whereas adolescent and adults may experience more realistic images. Dream descriptions in preschool age children are usually short and simple, while older children may elaborate the dream content by adding fantastic features [67].

Occasional nightmares are very common in children, ranging from 60% to 75% [80]. Nightmare onset typically occurs between ages 3 and 6. In clinical practice, a frequency of one nightmare per week or more often has been used to identify the problem as clinically significant. The prevalence of children experiencing nightmares once a week or more often is estimated to be about 5% [78]. Nightmares are commonly seen in those suffering from posttraumatic stress disorder, as well as any kind of abuse and a strong association with anxiety disorders has been described.

Occasional nightmares do not require specific treatments but only reassurance of children about the unreal nature of dreams and avoidance of television viewing within 2–3 h of bedtime. Recurrent nightmares may benefit from psychological, pharmacological, or combined treatments, although studies in this field are scanty [1].

Re-scripting techniques, in which parents/therapist and children discuss the dream and invent less frightening ending, can be helpful. Encouraging children to write about or draw their dreams may also yield positive results [67].

Prazosin, risperidone, and trazodone are the most widely used drugs in treating nightmares. Antidepressants (e.g., selective serotonin reuptake inhibitors), acetylcholinesterase inhibitors, or antihypertensive medication can cause nightmares [81].

Other Parasomnias

Exploding Head Syndrome (EHS)

Exploding head syndrome is characterized by a "sudden, loud imagined noise or sense of a violent explosion in the head occurring as the patient is falling asleep or waking during the night" [1, 82]. The abnormal sensation usually lasts a few seconds and is usually accompanied by fear and sometimes perceptions of a flash of light or a myoclonic jerk. Patients range from having one episode in a lifetime to recurrent episodes per night leading to an insomnia complaint. Some subjects report increased numbers of attacks when under personal stress or overtired. EHS can precede other neurological conditions, such as migraine attacks or sleep paralysis.

The typical age of onset is over 50 years and is more common in women and in those suffering from RISP. A recent study conducted in 211 undergraduate students using semi-structured diagnostic interviews assessing for both EHS and RISP showed that 18% of the sample experienced lifetime exploding head syndrome and 16.6% presented recurrent episodes without a female prevalence. An association with RISP was found in 36.89% of subjects [83].

The neurophysiologic mechanisms underlying EHS are unknown. The management in EHS is reassurance and education, as this is a benign condition that remits over time. Some case reports describe the efficacy of therapy similar to that of migraine, such as tricyclic antidepressants or calcium channel blockers (flunarizine) [1].

Sleep-Related Hallucinations

Sleep-related hallucinations are "hallucinatory experiences that occur at sleep onset (hypnagogic) or on awakening from sleep (hypnopompic)" [1]. They are predominantly visual but may include auditory, tactile, or kinetic phenomena.

Hypnagogic and hypnopompic hallucinations can be associated with narcolepsy but can also be common in the normal population. Hypnagogic hallucinations may be repetitive but are not usually stereotypical. This lack of stereotypical feature distinguishes these events from seizures.

Studies reported a prevalence of 25–37% for hypnagogic hallucinations and of 7–13% for hypnopompic hallucinations. Both hypnagogic and hypnopompic hallucinations are more common in younger persons and occur slightly more frequently in women than in men [84].

Complex nocturnal visual hallucinations may represent a distinct form of sleep-related hallucinations. They typically occur following a sudden awakening, without recall of a preceding dream. They usually take the form of complex,

vivid, relatively immobile images of people or animals, sometimes distorted in shape or size. These hallucinations may remain present for many minutes but usually disappear if ambient illumination is increased. Complex nocturnal visual hallucinations are often associated with a variety of underlying disorders typical of the elderly, such as visual loss (Charles Bonnet syndrome), Lewy body disorders, and pathology of the mesencephalon and diencephalon (peduncular hallucinosis).

Little objective information is available regarding the management of sleep-related hallucinations. Most often reassurance is sufficient. Tricyclic antidepressants have been suggested for hypnagogic and hypnopompic hallucinations [85].

Sleep Enuresis

Sleep enuresis (SE) is characterized by "recurrent involuntary voiding" that occurs during sleep. In primary SE, recurrent involuntary voiding occurs at least twice a week during sleep after 5 years of age in a patient who has never been consistently dry during sleep for 6 consecutive months. SE is considered secondary in a child or adult who had previously been dry for 6 consecutive months and then began wetting at least twice a week. Both primary and secondary enuresis must be present for a period of at least 3 months [1]. Primary and secondary SEs are considered distinct phenomena with different etiologies and features. SE is defined monosymptomatic if there are no associated daytime symptoms of bladder dysfunction (such as wetting, increased voiding frequency, urgency, jiggling, squatting, and holding maneuvers) [86]. The clinical severity of the disorder can be defined on the basis of the number of events that occur during a week and, specifically, is defined as: infrequent (1 or 2 events per week), moderate (3–5 events per week), and severe (6 or 7 events per week) [87].

The prevalence of SE is between 6% and 10% at age 7, decreasing to 2% at 15 years and 0.5–2% in adults. Approximately 75–90% of patients with SE have a primary form, while 10–25% have secondary SE, with spontaneous annual remission during childhood of about 15%. SE is more frequent in boys than in girls under 11 years of age, after there is gender difference. The reported prevalence is 77% when both parents were enuretic as children and 44% when one parent has a history of enuresis [88].

Sleep disorders that fragment sleep, such as sleep apnea and periodic leg movements, are frequently associated with SE and treatment of these disorders may cure or reduce their incidence [86].

On the contrary, secondary SE can occur at any age, and it is commonly associated with organic factors such as urinary tract infections, malformations of the genitourinary tract, extrinsic pressure on the bladder (such as chronic constipation or encopresis), medical conditions that result in an inability to concentrate urine (diabetes mellitus or insipidus, sickle cell disease), increased urine production secondary to excessive evening fluid intake (caffeine ingestion, diuretics, or other agents), neurologic diseases (spinal cord abnormalities with neurogenic bladder or seizures), and psychosocial stressors (parental divorce, neglect, physical or sexual abuse, and institutionalization). Different studies hypothesized that children with primary SE should show a delay in achieving the normal increase in vasopressin release during sleep, thus developing nocturnal polyuria that exceeds the bladder capacity. In particular, children with enuresis are often described as "deep sleepers," and their arousal threshold seems to be more elevated in all sleep stages with respect to controls [86].

In SE, a correct diagnosis is essential for the success of treatment. A sleep diary for 2–4 weeks may be useful for a correct assessment of the habits and the application of sleep hygiene rules. Evening and daytime fluid intake which might contribute to nocturnal polyuria should be assessed carefully. Physical examination includes the observation of enlarged adenoids or tonsils, bladder distension, fecal impaction, genital abnormalities, spinal cord anomaly, and routine laboratory tests (urinalysis and possibly urine culture). Ultrasonography, bladder sphincter electromyography, and cystoscopy might be considered in some children who continue to be enuretic after 3 months of treatment or if organic causes are suspected. Nocturnal polysomnography is rarely required for the diagnosis of SE and should only be performed when other underlying sleep-related disorders (seizures and/or sleep-disordered breathing) need to be ruled out. It is essential to exclude other diseases and, in particular, medical conditions (e.g., diabetes), nocturnal seizures, neurogenic bladder (e.g., spina bifida), urinary infection, and sleep-disordered breathing [88].

Enuretic events happen mainly during the first part of the night, and can occur in all sleep stages; moreover, sleep structure is similar during nights when enuresis occurs and when it does not occur. The recent finding that patients with enuresis are subjectively sleepier than normal control patients and more difficult to awaken has been attributed to sleep fragmentation that might be responsible for the higher arousal threshold and is consistent with a large body of sleep research [89, 90]. A recent study using actigraphy and sleep logs evaluated sleep of children with sleep enuresis and found that natural sleep in these children is significantly more fragmented and that they experience higher levels of daytime sleepiness. Sleep fragmentation in children with sleep enuresis could cause an increased sleep pressure with a consequent higher arousal threshold [91].

A recent study indicated the presence of a disruption of sleep microstructure in children with sleep enuresis. The

decrease of CAP phase A2 and A3 indices (i.e., low- and high-power arousals) might reflect the impaired arousal threshold of individuals with enuresis reinforcing the parental belief of their children as "deep sleepers" [92].

Sleep enuresis has been related also to sleep disordered breathing, in both adults and children [93]. This association is supported by the improvement or full resolution of SE after treatment of sleep-disordered breathing (adenotonsillectomy or intranasal corticosteroids) [94].

The management of SE starts from some simple strategies, such as programmed awakenings, rewarding dry nights, bladder training (including retention control training), and fluid restriction. Conditioning therapy is the first-line treatment of primary SE based on the use of an alarm device. A small electrode is placed near the genitals and when the child voids in bed, the alarm is activated and triggers a considerable noisy sound, inducing a response of waking and, hopefully, inhibiting urination [95, 96].

Two approaches to drug therapy can be used: one to increase bladder capacity and the other to reduce the nocturnal polyuria. Anti-muscarinic medications such as oxybutynin and tolterodine improve bladder capacity [97]. Desmopressin acetate, a synthetic analog of the anti-diuretic hormone arginine (vasopressin), can decrease nocturnal urine production and increase urinary osmolality. The only serious adverse event reported is water intoxication. Desmopressin is particularly helpful for short-term use when a rapid response is needed and seems to have some positive effects in about 70% of treated children [96].

Tricyclic agents (such as imipramine, approved by the US Food and Drug Administration for children of 6 years of age and older) increase urinary osmolality and decrease detrusor tone while increasing sphincter tone [98]. The long-term cure rate is only approximately 25%; relapses are common. Tricyclic anti-depressants significantly affect sleep cycle and result in REM sleep suppression, which can lead to daytime sleepiness. Other adverse effects of these drugs are cardiotoxicity and constipation. Treatment can be started with a dose of 10 mg for children aged 6–8 years, and 25 mg for children older than 8 years. The dose can be increased by 10–25 mg every 5 days, until dryness [88, 96].

Nocturnal Panic Attacks

Nocturnal panic attacks consist in waking from sleep in a state of panic, with intense fear or discomfort and typically last 2–8 min. They almost always occur during the first half of the sleep period, usually within 3 h of sleep onset and are frequent in patients with panic disorder, with 44–71% reporting at least one nocturnal attack [99]. Sleep panic attacks may occur in school age children but are more frequent during adolescence in comorbidity with anxiety disorders.

Most patients did not report dream content or cognitions, but increased heart rate, chest discomfort or pain, sweating, choking sensations, and headaches were noted. There is no confusion or sleepwalking associated, but approximately two-thirds of patients with panic disorder report difficulty sleeping [99].

Sleep panic attacks occur during the first third of the sleep period from NREM sleep, either from stage 2 sleep or stage 3 sleep. Polysomnographic EEG does not show any epileptiform or other paroxysmal activity during these arousals [100].

The differential diagnosis is commonly with several abrupt events during sleep: nocturnal seizures, sleep paralysis, paroxysmal nocturnal dyspnea, nocturnal angina, nocturnal asthma, sleep-related laryngospasm, DOAs, RBD, nightmare disorder, and sleep apnea [101, 102]. However, the diagnosis might be easy with all these disorders because patients do not become agitated or aggressive during the attack; moreover, immediately after the episodes, they appear oriented, can vividly recall the episode, and usually have difficulty returning to sleep. The anxiety component of the episode is marked while most of the events described are not clearly accompanied with anxiety. In contrast to nightmares which might be accompanied by residual anxiety upon awakening, the nocturnal panic attack has its peak after awakening, usually accompanied by death anxiety and somatic symptoms of a panic attack, whereas the nightmare anxiety decreases upon awakening from the dream [103].

Cognitive behavioral therapy involves educating the patient about increased perception of physiological sensations, addressing maladaptive patterns of thinking including catastrophic thinking, and helping the patient change thinking patterns related to nocturnal panic attacks. Antidepressants like imipramine and nortriptyline, and benzodiazepines seem to be beneficial [103].

Illustrative Cases

Case 1

A 10-year-old obese child was referred to the Sleep Center of the Civic Hospital of Lugano for suspected sleep breathing disorder and sleep onset insomnia in a child with attention deficit hyperactivity disorder. Parents reported weekly episodes of nocturnal eating, sleep agitation, somniloquy, or somnambulism for almost 1 year. Some events were accompanied by injury with falling from bed.

An ENT consultation showed no significant adenotonsillar hypertrophy. The vPSG revealed an obstructive sleep apnea with an apnea hypopnea index (AHI) of 5.2/hour, snoring, and many brief episodes of arousal disorder during slow-wave sleep, preceded by high-voltage slow

wave and characterized by abrupt change of position from lying to sitting on the bed, of few minutes of duration, without autonomic involvement, but starring or looking around, associated with non-stereotyped movements (Fig. 33.1).

He started therapy with levetiracetam, with complete remission of NREM parasomnia and for OSA he started CPAP titrated during the second vPSG, since adenotonsillectomy was not indicated.

After few months, he withdrew levetiracetam for the presence of aggressive and bizarre behaviors at home and at school. After 1 year from the first visit, he underwent a third vPSG showing a clear improvement of OSA with CPAP (few hypopneas events, AHI=2.7/h) but still mild and brief episodes of NREM arousal disorder persisted. Parents reported a decrease in the frequency and severity of sleepwalking (twice per month) and did not report episodes of nocturnal eating from the start of ventilatory therapy. Finally, he started a diet to reduce weight.

For sleep onset insomnia melatonin treatment (2 mg, controlled release) was added at 7 PM, to anticipate bedtime and avoid sleep deprivation. A further amelioration of sleep quality and a remission of somnambulism were reported after 3 months, although the attention problems remain unchanged.

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Part VIII

Obstructive Sleep Apnea

Obstructive Sleep Apnea: Definition

34

Shannon S. Sullivan and Christian Guilleminault

First Description and Consensus Definitions for Obstructive Sleep Apnea in Pediatrics

In 1976, Guilleminault and colleagues authored the first definitive report of pediatric obstructive sleep apnea (OSA), describing a series of eight children ranging in age from 5 to 14 years who had loud snoring, breathing pauses in sleep, daytime symptoms including sleepiness, altered school performance, daytime behavior, morning headache, abnormal weight, and progressive development of hypertension as well as enuresis, in association with polysomnographic evidence of respiratory abnormalities similar to those seen in adult OSA [1]. In these children, respiration was reported to be normal during wake, but in sleep, marked abnormalities were observed, including apneas, or cessation of breathing, dozens to hundreds of times on a single night, in association with greatly disturbed sleep, a reduction of slow wave sleep, and sinus arrhythmia [2]. These early publications helped initiate use of the term OSA "syndrome," or OSAS.

About 20 years later, the American Thoracic Society described pediatric obstructive sleep apnea syndrome as "a disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction (obstructive apnea) that disrupt normal ventilation during sleep and normal sleep patterns" [3]. The most recent definition of pediatric OSA from the American Academy of Sleep Medicine (AASM) includes the following parameters: the presence of snoring; labored, paradoxical, or obstructed breathing during sleep; and/or sleepiness, hyperactivity, behavioral problems, or learning problems; plus polysomnographic evidence of one or more obstructive apneas, mixed apneas, or hypopneas per hour of sleep (i.e., an AHI ≥1), or a pattern of obstructive hypoventilation [4]. Obstructive hypoventilation is further given to be constituted by at least 25% of total sleep time with hypercapnia (PaCO2 >50 mmHg (*N.B.* a surrogate noninvasive measure for arterial CO2 may be used per AASM Manual for Scoring of Sleep and Associated Events) in association with either snoring; flattening of the inspiratory nasal pressure waveform, a phenomenon known as "flow limitation" (Fig. 34.1), and/or paradoxical thoracoabdominal motion [4]. These criteria apply to those under the age of 18 years.

Within this definition, several types of abnormal respiratory events are relevant, with the essential underlying factor of each being increased upper airway resistance. These include the following:

- *Apneas*, defined as a drop in oronasal thermal airflow peak signal excursion by ≥90% of pre-event baseline. Obstructive apnea is scored for pediatrics if the event is at least two breaths in duration and associated with respiratory effort throughout the entire period; if respiratory effort is absent for part of this duration, a mixed apnea is scored [5].
- *Hypopneas*, defined as a peak signal excursion drop of at least 30% from pre-event baseline using the nasal pressure or alternate sensor, for at least 2 breaths; associated with either a ≥3% oxygen desaturation or an EEG arousal. Unlike apneas, hypopneas need not be subdivided into obstructive or central etiology, as it is not possible to definitely determine contributions from reduced central drive or increased airway resistance without a direct quantitative measure of effort (such as esophageal manometry). Nonetheless, obstructive hypopneas in particular are suggested by presence of snoring, inspiratory flow limitation, which is characterized by flattening of the nasal pressure inspiratory waveform, or induction of paradoxical thoracoabdominal movement associated with the event [5]. Regarding hypopneas in particular, studies evaluating OSAS in children must be taken in the context of the era in which they were conducted, as the definition for hypop-

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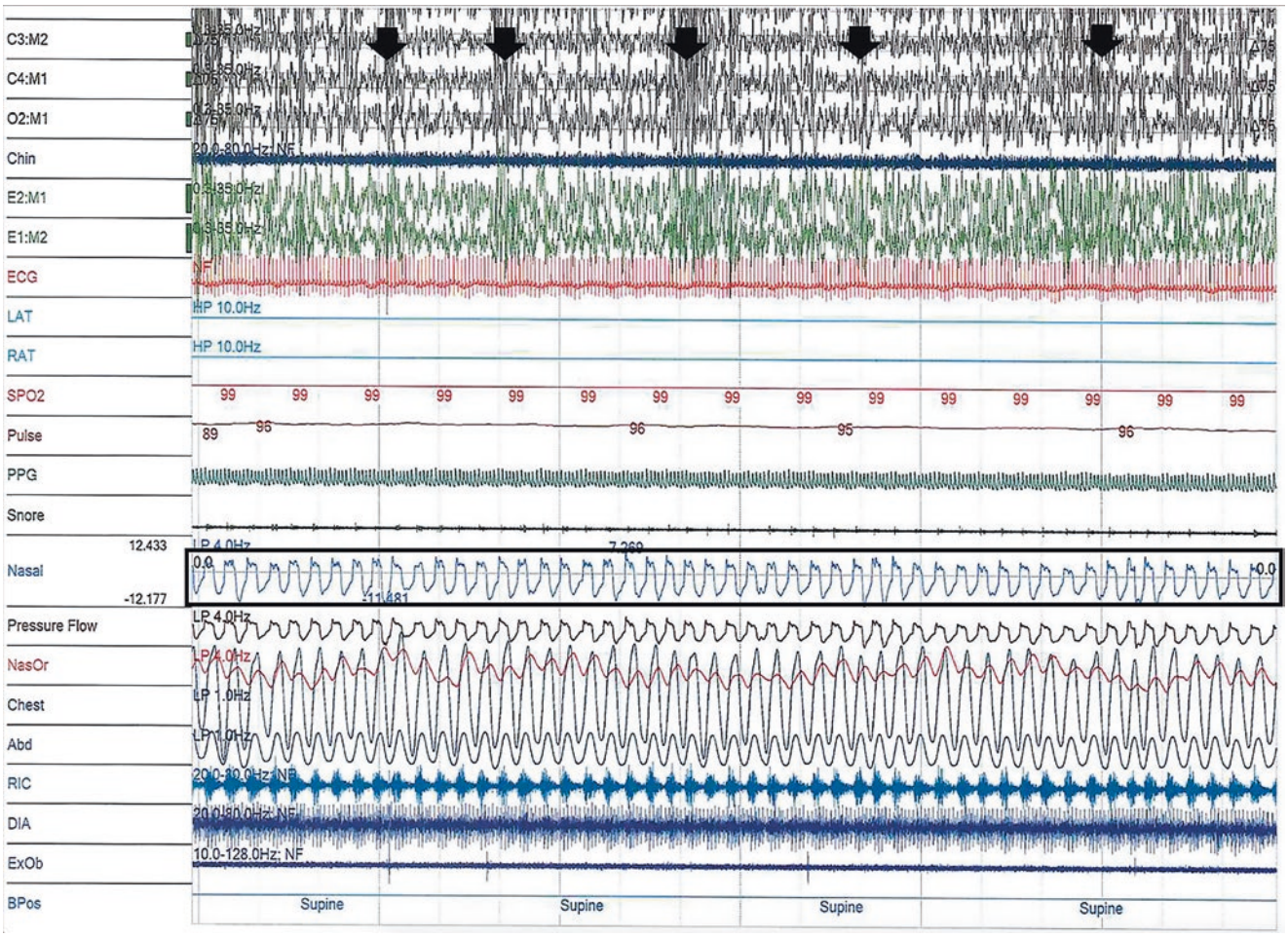

Fig. 34.1 Nasal flow limitation in a 10-year-old symptomatic child. There is sustained flattening of the inspiratory portion of the nasal waveform. Snoring is absent. Arrows indicate cyclic alternating pattern. (From Guilleminault et al. [19]. Reprinted with permission from Elsevier)

nea has undergone several iterations in the last 20 years, leading to substantial diagnostic impact. For example, in 2007, the AASM made a key change in terms of scoring hypopneas, altering the threshold for reduction in airflow (30 vs. 50%), which resulted in overall lower OAHIs and putatively reduced OSA severity by approximately 24% of cases in one study, and up to fivefold in another study of 209 children [6, 7].

- *Respiratory effort-related arousals,* or *RERA*s, defined as a sequence of at least two breaths that do not meet criteria for apnea or hypopnea, but are characterized by increasing respiratory effort (classically measured quantitatively by esophageal manometry, as other measures of respiratory effort are not quantitative); inspiratory nasal flow limitation; snoring; of an elevated end-tidal PCO2 above pre-event baseline, in association with an EEG arousal. Inspiratory flow limitation in children with abnormal nocturnal breathing has been shown to be associated with increased respiratory driving pressure (i.e., respiratory effort, as measured by esophageal manometry) and therefore elevated upper airway resistance in both NREM and REM sleep [8]. In fact by 1982, it was already recognized that apneas and hypopneas were inadequate to define the syndrome of OSA seen in children, and defining breathing abnormalities using snoring and "sleep-related respiratory resistive load" had been proposed [9]. Still, even now RERAs are not included in the calculation of *apnea-hypopnea index* (AHI), which represents the average of apneas and hypopneas recorded hourly over a single night recording. The *Respiratory Disturbance Index* (RDI) is more broadly defined, and represents the average of apneas, hypopneas, and RERAs recorded hourly over a single night recording. The presence of RERAs per se, in the absence of overt hypopneas and apneas, and with or without snoring, may give rise to the entity of upper airway resistance syndrome (UARS), in which clinical symptoms of sleep disturbance are associated with increased effort, sleep disturbances, respiratory arrhythmia, altered heart rate variability with altered parasympathetic activity. UARS was described in children over 20

years ago and remains relevant for understanding the clinical manifestations of, and developmental evolution of, sleep breathing disorders [10–12].

More recently, then, it has been understood that OSAS should be defined in the broader context of a spectrum of sleep disturbances due to altered upper airway resistance and consequent altered respiration, known collectively as "sleep disordered breathing" (SDB), a term that more aptly reflects diverse presentations. This spectrum may involve habitual snoring, overt apneas and hypopneas, obstructive hypoventilation marked by alterations in surrogate measures of PaCO2, or nonhypoxic increased respiratory effort associated with sleep fragmentation or autonomic nervous system alterations [13–16]. Increased respiratory effort is well-established as a way to measure to quantify the impact of increased airway resistance, but esophageal manometry, while insightful, is infrequently used in pediatric sleep laboratories, giving rise to interest in additional measures of impaired breathing in sleep.

Additional Elements of Sleep-Related Respiratory Disturbance Not in the Definitions

As noted above, apneas and hypopneas are now recognized to be an incomplete description of respiratory-related sleep disturbance. In 1985, Guilleminault and colleagues reported on 25 children who had daytime symptoms associated with sleep disturbance as well as heavy snoring. Polysomnography did not reveal OSAS or hypoxemia but did demonstrate increased respiratory resistive load during sleep associated with electrocardiographic R-R interval and esophageal pressure swings, with improvement on symptoms after upper airway surgery [9]. More recently, snoring severity itself has been found to correlate with poorer general behavioral and cognitive functional findings independent of AHI among a large cohort of community dwelling children [17].

More subtle but reliable and accessible measures of the breathing abnormalities associated with pediatric SDB exist. These include the presence of tachypnea, inspiratory nasal flow limitation measured by standard nasal pressure transducer; impairment of nasal breathing/habitual mouth breathing in sleep measured using a commercially available oral scoop, altered inspiratory-to-expiratory time ratio, accessory expiratory muscle activity measured by surface EMG, as nasal pressure transducer is an unreliable measure of expiratory flow limitation [13, 18, 19]. Whether these measures, which are generally available clinically in limited locations, can be extended into widespread practice and can be integrated into updates to the definition of pediatric sleep-disordered breathing remains to be seen.

Additionally, measures of sleep stability and fragmentation may also provide advances into defining the syndrome. The current definition of arousal from sleep, for example, is an abrupt shift of EEG frequency including alpha, theta, and/or frequencies greater than 16 Hz for at least 3 seconds, with 10 seconds of stable sleep preceding the change [5]. Arousals described this way are the key element of defining SDB-related sleep fragmentation but may not be sensitive enough to capture important disturbance. Additional, potentially more telling, sleep microstructural changes, that is, cyclic alternating pattern (CAP) rate changes, have been described [20] in association with pediatric SDB, for example [13, 21]. Using more refined measures of the sleep encephalogram in addition to AHI may become more practical with the advent of newer technologies capable of detecting the phenomenon in a less labor intensive and more consistent manner.

Finally, the diagnosis of pediatric OSA currently requires access to a qualified pediatric sleep laboratory, which poses potential access and cost challenges. While history alone has been shown to be insufficient diagnostically, and even recently, an AASM position paper reinforced the inadequacy of home-based sleep testing for the diagnosis of sleep apnea in children, evaluation of home-based assessments of breathing and sleep, in conjunction with clinical evaluation and validated tools, have been reported and may alter the landscape of pediatric OSA definition in the future, especially in resource-limited areas [22–26].

A Look Forward: Challenges to Define Early Signals of Pediatric OSA

While these respiratory abnormalities correspond generally to events scored in OSA defined for adult populations, it should be emphasized that the sleep-disordered breathing in children differs markedly from the syndrome seen in adults, in epidemiology, underlying proximal contributing factors, clinical presentation and associations, polysomnographic and physiologic findings, and largely, in treatment. It has been argued that the spectrum of pediatric sleep breathing disorders represents the earliest manifestations of airway dysfunction that will blossom in adulthood to fully manifested OSAS, with the epidemic of obesity either hastening or initiating this process [15]. Furthermore, the risks for pediatric SDB have been argued to occur as early as in utero, gaining steam throughout early and middle childhood if not corrected [27, 28]. To the extent that this occurs, the manifestations of SDB are not static and unlikely to be defined by simple "events" described by the consensus scoring criteria and manuals, but rather a spectrum of dynamic challenges to the airway and craniofacial complex, autonomic nervous system, and sleep stability. The dynamic interplay of structure and function in pediatrics in particular has given rise to

the argument that notion of OSA defined by apneas and hypopneas, and even UARS, are historical, if not just incomplete, as there is already enough knowledge to grow beyond these definitions by recognizing manifestations of sleep respiratory challenges differently, with a focus on secondary prevention [29]. In recognition of these factors, inclusion of degree of nasal flow limitation, oral breathing in sleep, stertor, CAP frequency, and other measures may be utilized clinically in the future to better define the syndrome of sleep disturbance associated with abnormal breathing, especially in those children without associated hypoxia.

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Pathophysiology of Obstructive Sleep Apnea Syndrome in Childhood

35

Raanan Arens, Sanghun Sin, and David M. Wootton

Introduction

Obstructive sleep apnea syndrome (OSAS) refers to a breathing disorder characterized by recurrent, partial, or complete episodes of upper airway obstruction, commonly associated with intermittent hypoxemia and sleep fragmentation [1, 2]. OSAS affects individuals of all ages, from neonates to the elderly. However, it is still not known whether OSAS represents a continuum of a disorder that places children at risk for the disorder also as adults [3], or whether OSAS during different stages of life comprises distinct clinical entities [4–7].

The structure and the neural control of the upper airway have evolved to serve three important physiological functions: (1) respiration (2) deglutition, and (3) speech. The upper airway is collapsible in order to accommodate these functions. The anatomic factors predisposing to OSAS differ over the lifespan. However, a smaller upper airway is noted in patients with OSAS in all age groups, and probably predisposes to airway collapse during sleep. Anatomic factors such as craniofacial anomalies, obesity, and adenotonsillar hypertrophy contribute to OSAS throughout life, yet a clear anatomic factor cannot always be identified. This suggests that functional factors altering upper airway neuromotor tone and the biomechanical properties of the upper airway could also play an important role in the etiology of OSAS [8, 9]. This chapter focuses on the anatomic, functional, and biomechanical aspects of the upper airway in the pathophysiology of OSAS during childhood as summarized in Table 35.1.

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Pharyngeal Development

The anatomy of the newborn pharynx is similar to the anatomy of other primates and mammals [10]. The uvula and epiglottis are in close proximity, creating a secure airway that allows for independent suckling and breathing. This anatomic relationship is maintained in other mammals throughout life, with discrete pathways for respiration and deglutition. However, in the human, at about 18 months of development the larynx descends to the level of the fifth cervical vertebrae. This anatomic formation develops because of the additional role of the human pharynx of phonation. For the purpose of deglutition, the pharynx functions as a flexible tube. The pharyngeal muscles, namely, the pharyngeal constrictors and tongue, force food from the oral cavity into the esophagus. For phonation, the pharynx functions as a muscular tube that can change its length and shape to alter the sounds generated by the larynx and passing through the pharynx. For respiration, the pharynx must remain as rigid as possible in order to allow air passage without collapse. However, despite the importance of respiration to sustain life, when one considers the muscles of the upper airway in the human, it becomes apparent that not one of these muscles has a primary function of pharyngeal dilation. It is speculated that the lack of such pharyngeal dilators in humans resulted from the absence of an evolutionary need in mammals and primates, because the anatomic orientation of the structures securing their upper airway is maintained throughout development, whereas in the human it is not.

Pharyngeal Anatomy

The pharynx is generally divided into three anatomic regions (Fig. 35.1):

1. *The nasopharynx*, located superior to the level of the soft palate and continuous anteriorly, through the choanae, with the nasal cavities.

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Table 35.1 Developmental aspects of obstructive sleep apnea syndrome

	Infancy	Childhood	Adolescence	Adulthood
Demographics:				
Estimated prevalence	?	2%	2%	4–9%
Peak age (years)	<1	2–8	12–18	30–60
Gender	M > F	M = F	?	M > F
Weight	Normal	Normal, may be underweight or obese	Mostly overweight and obese	Obese
Risk factors	Craniofacial anomalies Prematurity Gastroesophageal reflux Adenotonsillar Hypertrophy	Adenotonsillar hypertrophy Obesity	Obesity Adenotonsillar hypertrophy	Obesity Women-postmenopause
Level of obstruction	Nasopharyngeal Retropalatal	Nasopharyngeal Retropalatal	Nasopharyngeal Retropalatal Retroglossal?	Retropalatal Retroglossal
Anatomic findings				
Airway	Small?	Small	Small	Small
Craniofacial features	May have craniofacial anomalies: Midfacial hypoplasia Micrognathia	Majority normal	?	Retrognathia Micrognathia
Soft tissues	May have adenoidal hypertrophy; usually normal tonsils	Adenotonsillar hypertrophy Large soft palate	Adenotonsillar hypertrophy Other soft tissues?	Large lateral pharyngeal walls, tongue, soft palate, parapharyngeal fat pads
Functional findings				
Ventilatory drive: Normal subjects OSAS	High? ?	High Overall normal Some with subtle abnormalities	Moderate ?	Lower Studies conflicting
Arousability: Normal subjects OSAS	Low Very low	Very low Very low	Moderate ?	High High
Upper airway collapsibility: Normal subjects OSAS	Very low High	Very low High	Low High	Moderate High
Upper airway reflexes during sleep: Normal subjects OSAS	Brisk ?	Active Blunted	High Low	Low Low
Biomechanical findings				
Nasal resistance	?	Higher in OSAS	?	Higher in OSAS with obesity
Pharyngeal pressure drop	?	Higher in OSAS Lower after AT surgery	Higher in OSAS?	Lowered by MMA surgery
Pressure–area slope during tidal breathing	?	Sedated: more positive in OSAS Awake: more negative in OSAS		
Treatment				
Treatment of choice	Craniofacial surgery CPAP	Adenotonsillectomy	CPAP Weight reduction Adenotonsillectomy	CPAP Weight reduction
Treatment success	High	High	Moderate	Moderate

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2. *The oro*pharynx, located between the level of the soft palate and the larynx, communicating anteriorly with the oral cavity, and having the posterior one-third of the tongue as its anterior border. Based on a midsagittal view (Fig. 35.1a, b), the oropharynx is subdivided into retropalatal (bounded by the level of the hard palate and the caudal margin of the soft palate) and retroglossal (bounded by the caudal margin of the soft palate to the tip of the epiglottis) regions. In infants and young children, the oropharynx includes mostly the retropalatal region, since the soft palate and the epiglottis are in close proximity. The anterior oropharyngeal wall is

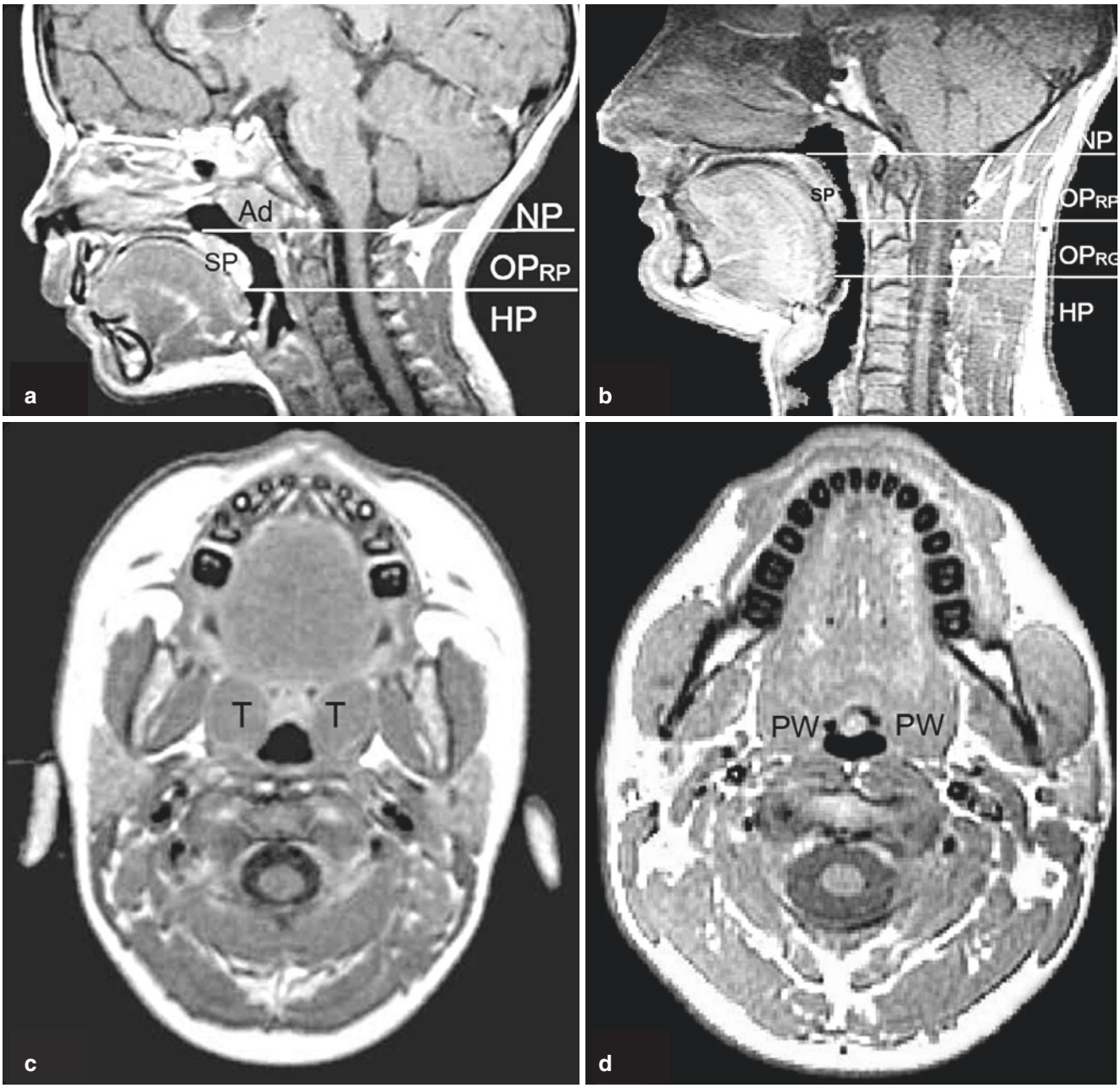

Fig. 35.1 Normal airway. A midsagittal MRI of the head of a child (**a**) and an adult (**b**) are shown. The airway is shown in black. Note the three main anatomical regions of the upper airway in the child: nasopharynx (NP), oropharynx adjacent to the retropalatal region (OP_{RP}), and hypopharynx (HP). The adult airway differs from that of the child by having, in addition, an oropharyngeal segment that is retroglossal (OP_{RG}). This anatomic difference is related to the descent of the larynx during the first 18 months of life. An axial MRI of the head at the retropalatal level of a child (**c**) and an adult (**d**) are shown. The airway is shown in black. The lateral pharyngeal walls (PW) in the child are formed mainly by the palatine tonsils (T). In the adult, the tonsils are usually absent or minimal in size and the PW is formed by a combination of muscles (see text for details). Ad, adenoid; SP, soft palate. (From Arens et al. [7]. Reprinted with permission from Oxford University Press)

formed primarily by the tongue and soft palate, while the posterior wall of the oropharynx is formed by the superior, middle, and inferior constrictor muscles [11, 12]. The lateral pharyngeal walls (PW) (Fig. 35.1c, d) are formed by several different soft tissues, including muscles (hyoglossus, styloglossus, stylohyoid, stylopharyngeus, palatoglossus, palatopharyngeus, and the lateral aspects of the superior, middle and inferior pharyngeal constrictors [13, 14]); lymphoid tissue, primarily the palatine tonsils (noted more in children, Fig. 35.1c) [15]; and adipose tissue (lateral parapharyngeal fat pads).

3. *The hypopharynx*, located posterolateral to the larynx, and communicating with the cavity of the larynx through the auditus. This includes the pyriform recesses and the valleculae.

Anatomic Considerations

Anatomic determinants of OSAS in children can be discussed in relation to broad age categories—infants, children, and adolescents.

Infancy

Infants are predisposed to obstructive events and oxygen desaturation during sleep because of high nasal resistance, reduced airway stiffness, and a highly compliant chest wall with reduced functional residual capacity [7, 16]. Spontaneous neck flexion can also result in airway obstruction in premature infants [17]. Nasal occlusion results in a switch to oral breathing only in a minority of infants [18] and therefore obstruction of the nasal passages from respiratory infection, craniofacial syndromes or choanal stenosis can result in significant OSAS. Upper airway obstruction may also occur as a result of airway edema, laryngospasm, and airway edema from gastroesophageal reflux disease (GERD). Intrinsic softness of the larynx from laryngomalacia in infants has been demonstrated to be associated with obstructive sleep apnea with improvement after supraglottoplasty [19]. OSAS in infancy is notable for its association with several important risk factors: (1) craniofacial anomalies, (2) altered soft tissue size, and (3) neurological disorders.

Common Pediatric Disorders Affecting Upper Airway Size and Associated with Obstructive Sleep Apnea Syndrome

I. *Craniofacial Anomalies*:
- Apert syndrome
- Crouzon syndrome
- Pfeiffer syndrome
- Treacher-Collins syndrome
- Robin sequence
- Stickler syndrome
- Nager syndrome
- Hallermann–Streiff syndrome
- Goldenhar syndrome
- Rubinstein–Taybi
- Down syndrome
- Beckwith–Wiedemann
- Achondroplasia
- Klippel–Feil syndrome
- Marfan syndrome
- Choanal stenosis
- Mucopolysaccharidoses (Hurler, Hunter)

II. *Neurological Disorders:*
- Cerebral palsy
- Syringobulbia
- Syringomyelia
- Myasthenia gravis
- Möbius syndrome
- Arnold–Chiari malformation
- Poliomyelitis

III. *Miscellaneous Disorders:*
- Obesity
- Polycystic ovary syndrome (PCOS)
- Prader Willi syndrome
- Melanocortin-4 receptor deficiency
- Congenital hypothyroidism
- Sickle cell disease
- Laryngomalacia
- Subglottic stenosis
- Airway papillomatosis
- Face and neck burns
- Gastroesophageal reflux

IV. *Postoperative Disorders*:
- Post-adenotonsillectomy leading to naso- and or oropharyngeal stenosis
- Post-pharyngeal flap: leading to naso- and/or oropharyngeal stenosis

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Craniofacial Anomalies

The relationship between craniofacial structure and OSAS is most compelling in infants with distinct craniofacial anomalies seen with craniofacial synostosis, such as Crouzon, Pfeiffer, and Apert syndromes [20, 21]; and with mandibulofacial dysostoses, such as Robin sequence [22–25] and Treacher-Collins syndrome [26]. Altered facial skeletal development, especially the association of maxillary and/or mandibular hypoplasia, may lead to airway narrowing due to crowding of adenoid, tonsils, and other soft tissues within the mid and lower face skeletal boundaries. Decreased neuromotor tone may further reduce airway size by inducing glossoptosis and hypopharyngeal collapse during sleep. Children with craniofacial anomalies may present with OSAS soon after birth and during the first years of life. In some cases, OSAS does not occur until the child is older and

develops adenotonsillar hypertrophy in conjunction with the narrow upper airway. Some craniofacial syndromes, such as Down syndrome, are also associated with hypotonia, which can contribute to upper airway obstruction. Children with associated central nervous system abnormalities may also have central hypoventilation.

Down syndrome is the most common genetic disorder associated with craniofacial anomalies. OSAS is present in 30–60% of these patients [27–30]. Anatomic factors related to the Down syndrome phenotype, including midfacial and mandibular hypoplasia, glossoptosis, adenoid and tonsillar hypertrophy, laryngotracheal anomalies, and obesity, are the most common causes for OSAS in this group [31, 32]. Reduction in neuromuscular tone may also play a role in the development of sleep-disordered breathing in these children.

Altered Soft Tissue Size

The size of the upper airway soft tissues (tonsils, adenoid, fat pads, and musculature) are determined by genetic factors. In addition, the size of these tissues may be affected by inflammation, infection, and infiltration by various metabolic or storage components. Finally, abnormal neuromotor tone may further alter the shape of upper airway musculature, predisposing to airway narrowing and collapse during sleep.

Inflammatory changes leading to adenotonsillar hypertrophy are seen in some infants prior to 1 year of age, leading to the full clinical spectrum of OSAS [33, 34]. Macroglossia can significantly reduce upper airway size. It commonly occurs in infants and children with Down syndrome, as well as in infants and children with various storage and metabolic disorders, such as mucopolysaccharidosis [35] and Beckwith–Wiedemann syndrome [36]. In patients with glossoptosis, the tongue may prolapse posteriorly and occlude the airway. Glossoptosis is commonly seen in patients with a small and retroposed mandible as in the Robin sequence [22–25], or in conditions associated with poor upper airway muscle tone such as Down syndrome [27–32]. Anomalies of the soft palate, such as cleft palate and velopharyngeal insufficiency, are not usually associated with OSAS. However, the surgical repair of these malformations by palatoplasty and pharyngeal flap, respectively, are associated at times with a moderate degree of OSAS [37, 38].

Neurological Disorders

Various central nervous system disorders have been associated with OSAS in young infants. All induce pharyngeal hypotonia and predispose to sleep-disordered breathing and airway obstruction. Common causes include cerebral palsy, increased intracranial pressure, brain stem compression/dysplasia such as Arnold Chiari malformations, recurrent laryngeal nerve palsy, palsies of the cranial nerves, and syrinx [39–42].

Childhood

In preschool children, the incidence of OSAS is estimated to be 2% [43, 44], whereas primary snoring is more common and is estimated as 6–9% in school-aged children [45]. Although the exact mechanism for OSAS in children is not fully understood, important anatomic risk factors have been identified, and are linked to the anatomical structures surrounding the airway that affect airway size, shape, dynamics, and mechanics.

Anatomical Assessment of the Upper Airway

Physical examination of the upper airway is important and should be performed in each child as part of the general assessment. However, in order to more thoroughly evaluate the airway, endoscopy [46] and imaging techniques such as lateral neck radiographs, cephalometrics, fluoroscopy, acoustic reflection, computerized tomography, and MRI are helpful [47–52]. The above modalities have all demonstrated that the upper airway of children with OSAS is smaller on average than that of the normal child.

MRI is a particular powerful tool because (1) it provides excellent upper airway and soft tissue resolution; (2) it provides accurate, reproducible quantification of the upper airway, and surrounding soft tissue structure; (3) imaging can be performed in the axial, sagittal, and coronal planes; (4) volumetric data analysis including three-dimensional reconstructions of upper airway soft tissue and craniofacial structures can be performed [15, 47, 53–55]; (5) dynamic images provide four-dimensional data of the size and shape of the airway during breathing [56, 57]; and (6) it does not expose subjects to ionized radiation. On the other hand, several limitations should be noted: (1) young children need to be sedated to avoid motion artifact; (2) studies in sleep are limited in the MRI environment because of noise, arousals, and movement artifact; and (3) MRI is expensive and not always available.

Airway Size

Using MRI, Arens et al. [47] studied the upper airway in 18 children with moderate OSAS (age 4.8 ± 2.1 years) with an apnea/hypopnea index of 11.2 ± 6.8 and compared these findings to 18 matched controls. MRI was performed under sedation with intravenous pentobarbital, and axial and sagittal T1- and T2-weighted sequences were obtained (Fig. 35.2a, b). The volume of the upper airway was smaller in subjects with OSAS in comparison to controls (1.5 ± 0.8 cm^3 vs. 2.5 ± 1.2 cm^3, $p < 0.005$). This finding was later reproduced by other investigators [58, 59] using similar techniques.

Region of Vulnerability and Overlap Region

In order to determine the anatomic region of maximal narrowing in children with OSAS, Isono et al. performed upper

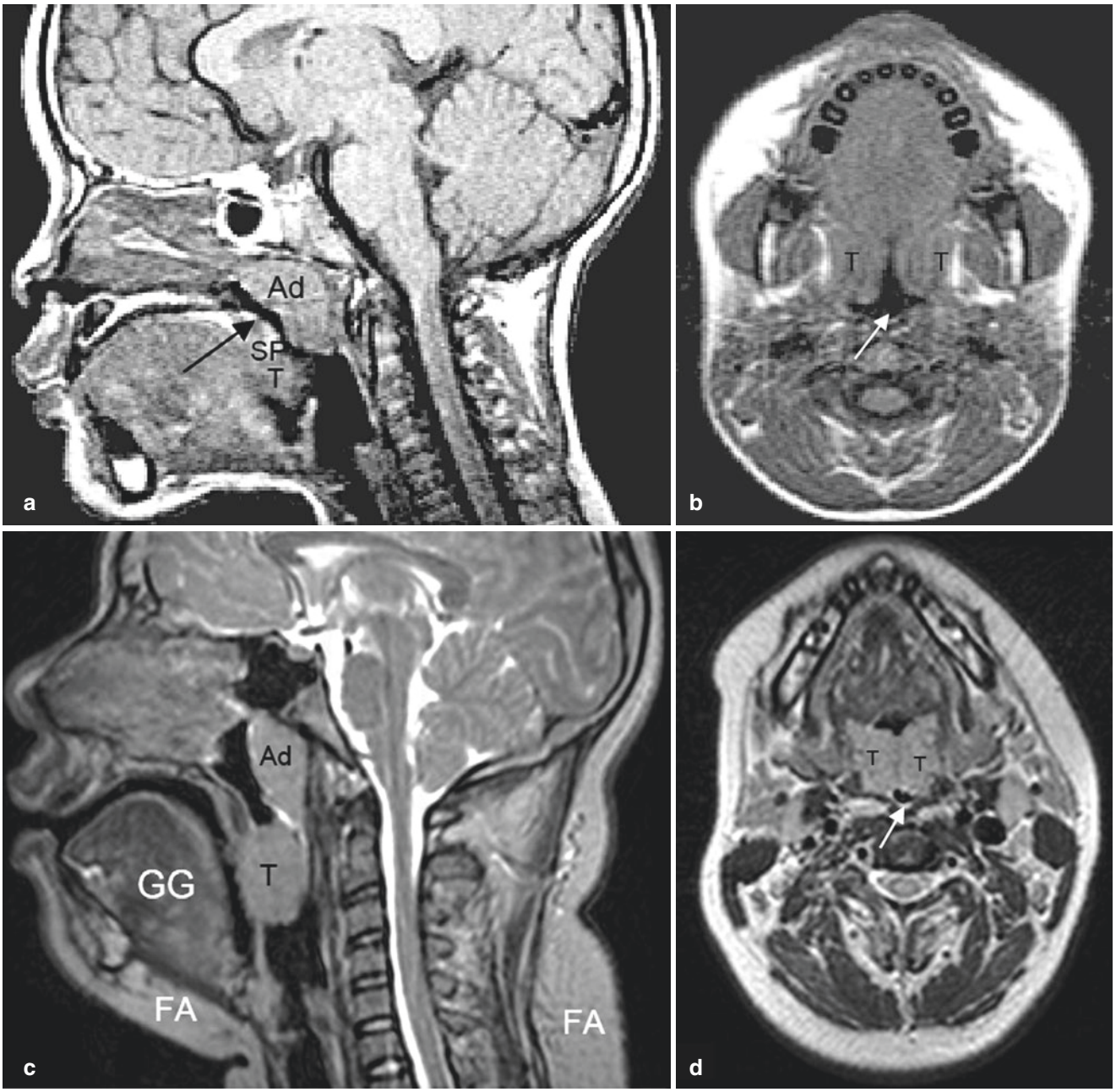

Fig. 35.2 Mid-sagittal image of a non-obese young child with OSAS (**a**). Black arrow points at narrow nasopharynx and overlap region between adenoid (Ad), soft palate (SP), and tonsils (T). Axial image of the same subject (**b**); white arrow points to a narrowed oropharyngeal airway by two tonsils (T). Mid-sagittal image of an obese adolescent with OSAS (**c**). Note complete occlusion of nasopharynx in the overlap region by large adenoid (Ad), soft-palate and tonsils (T). Axial image of the same subject (**d**); white arrow points to a very small oropharyngeal airway between both tonsils (T)

airway endoscopy under general anesthesia, evaluating discrete levels of the upper airway including the adenoid, soft palate, tonsil, and tongue [46]. The minimum cross-sectional area was found to be at the level of the adenoid and the soft palate. These findings, along with high closing pressures noted at these points in the same study, suggest that the superior upper airway segments are most involved in children with OSAS. These findings are supported by two recent studies evaluating upper airway shape with MRI. Arens et al. [53] showed that airway narrowing in children with OSAS occurred along the upper two thirds of the airway, and was maximal in the region where the adenoid overlap the tonsils and soft palate—"the overlap region" [53] (Fig. 35.3). Similar findings were noted by Fregosi et al. [59], who

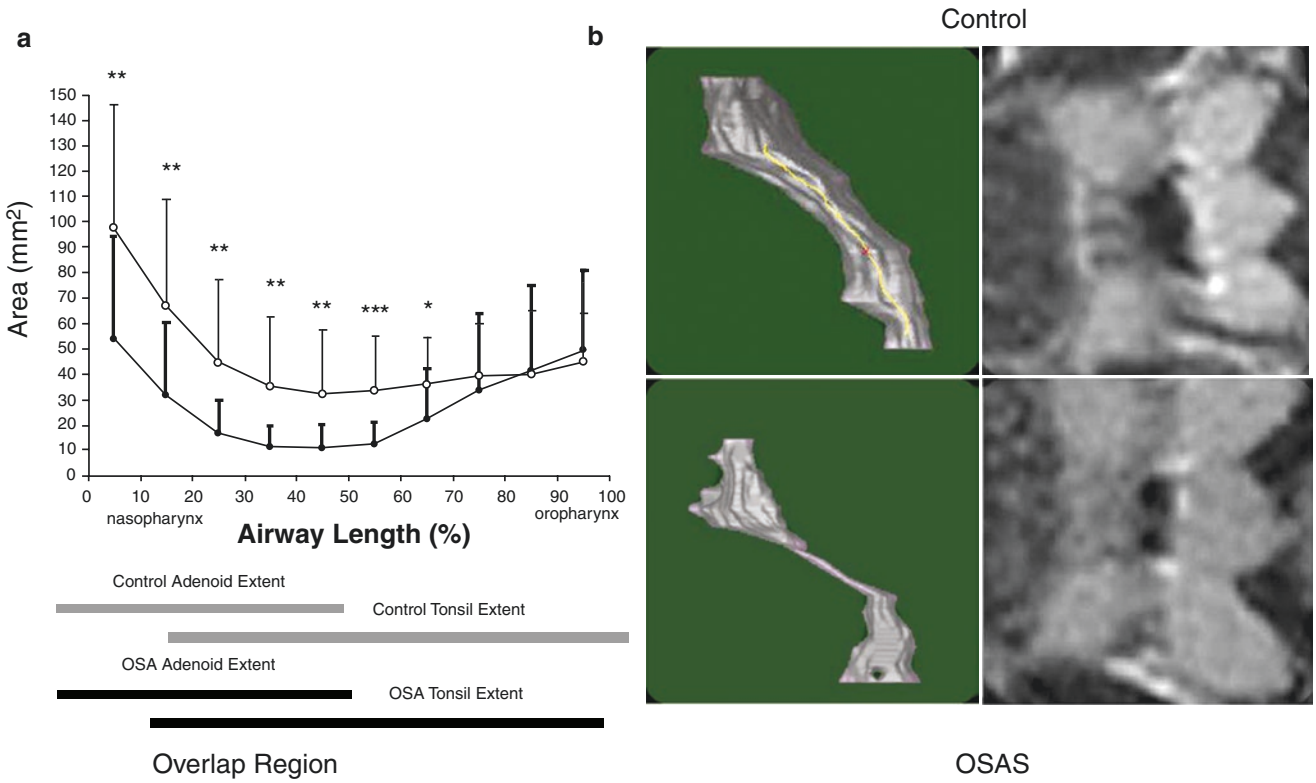

Fig. 35.3 Airway cross-sectional area from choana to epiglottis and the "overlap region." (**a**) Airway length versus cross sectional area in 20 control children (open circles) and 20 children with OSAS (closed circles). Data points are means ± SD. Horizontal bars show the regions of the adenoid and tonsils adjacent to the airway. Gray = controls, black = OSAS. *$p < 0.5$, **$p < 0.005$; ***$p < 0.0005$. Note that the *overlap region* of the adenoid and tonsils in both groups corresponds to the minimal airway cross sectional area. Modified from reference [53]. (**b**) 3D reconstruction of the airway and overlap region where the adenoid and tonsils overlap the soft palate in Control and OSAS

described maximal narrowing in the retropalatal region where the soft palate, adenoid, and tonsils overlap.

Airway Dynamics Depicted by MRI

Arens et al. used respiratory-gated MRI to demonstrate the dynamics of the upper airway during tidal breathing in sedated children with OSAS [56]. They showed that the maximum restriction in patients with OSAS occurred in mid-inspiration (Fig. 35.4), and that dynamic fluctuations in the airway overlap region were sixfold higher than in controls. They have speculated that such changes may have been induced by one of the following: altered upper airway motor tone, increased airway compliance, or excessive inspiratory driving pressures caused by proximal airway narrowing.

The above study demonstrated different size and shape configuration of the airway in children with OSAS in both inspiration and expiration as compared with control subjects. Subjects with OSAS exhibited an airway shape narrowed across the A–P axis. This could be caused by anatomic features influencing the width of the lateral pharyngeal wall and/or by neuromotor factors affecting upper airway dilator muscle activity along this axis (i.e., genioglossal activation). These differences, together with the magnitude of area changes during tidal breathing, may contribute to a more collapsible airway in children with OSAS during sleep, as suggested by functional studies [46, 50, 60].

Soft Tissues

Adenoid and Tonsils In normal children without OSAS, the soft tissues, particularly the tonsils and adenoid, grow commensurate with age maintaining a constant proportionality with the pharyngeal airway [7, 15]. It has been speculated that disproportional overgrowth of the adenoid and tonsils in children with OSAS results from inflammation and/or infections but the mechanisms leading to this process have not been elucidated [15].

Arens et al. measured the size of the adenoid and tonsils in children with OSAS compared to controls [47]. They found that both were significantly larger in the OSAS group; 9.9 ± 3.9 cm^3 and 9.1 ± 2.9 cm^3 versus 6.4 ± 2.3 cm^3 and 5.8 ± 2.2 cm^3 ($p < 0.005$; $p < 0.0005$, respectively). In addition, the combined size of the adenoid and tonsils correlated significantly with the apnea/hypopnea index ($p = 0.03$, $r = 0.51$), suggesting that volumetric measurements of these

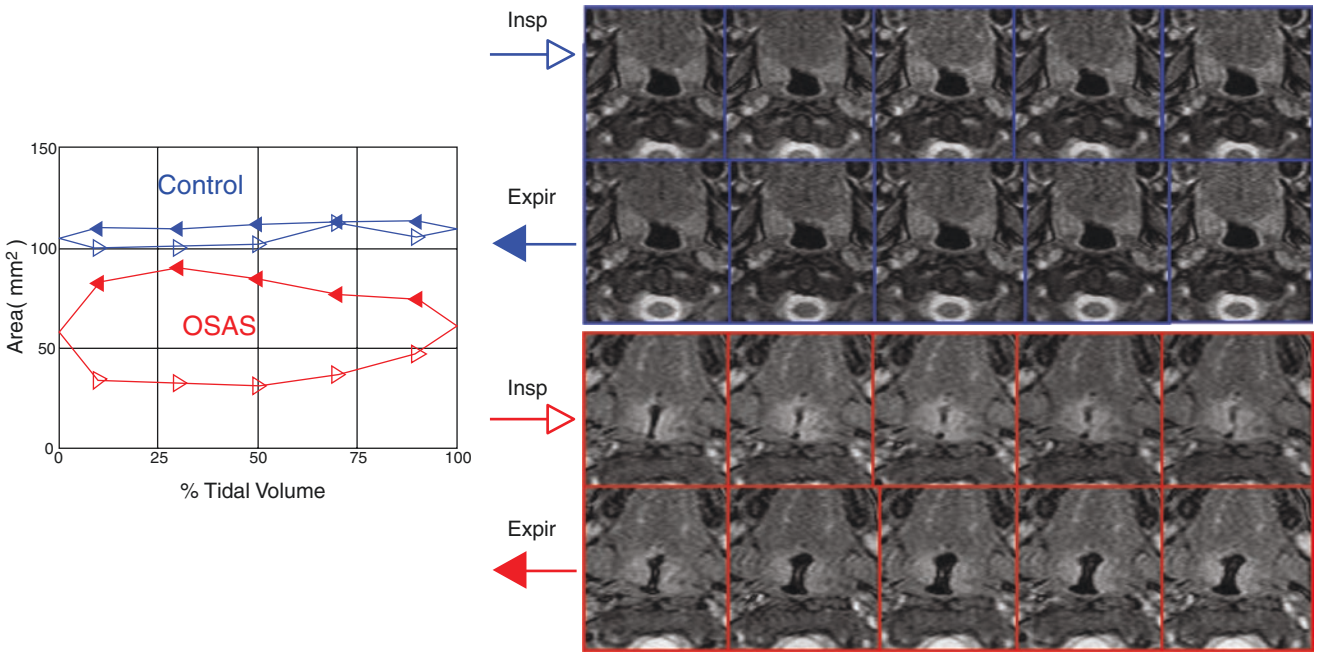

Fig. 35.4 Airway dynamics – cross-sectional area during tidal breathing in Control and OSAS. Dynamic changes in cross-sectional area at mid-tonsillar level during tidal breathing (TV), 5-vol increments of inspiration (Ins), 5-vol increments of expiration (Exp) in a control child (*top panels*) and a child with OSAS (*bottom panels*)

tissues may be useful in predicting the severity of obstructive sleep apnea in children.

In most cases, large tonsils and/or adenoid can explain the clinical symptoms of children with OSAS, and surgical removal of these tissues cures or ameliorates the disorder in the majority of cases [33, 61–63]. However, it is estimated that in 10–15% of otherwise normal children with OSAS, this disorder is not resolved by the simple removal of the tonsils and adenoid [64–66].

Although the importance of adenoidal and tonsillar hypertrophy in the pathogenesis of childhood OSAS is unquestioned, much remains to be learned. It is possible that the three-dimensional orientation of these tissues, and how they overlap in the airway, is a more important factor, and may significantly affect flow resistance during sleep [47, 53, 59].

Tongue Size The tongue is one of the largest structures defining the oropharyngeal airway and bounds its anterior aspect. It is composed of extrinsic muscles (genioglossus, hyoglossus, and styloglossus), which alter its position; and intrinsic muscles, which alter its shape; both of which can affect airway size and shape. Arens et al. found that the overall volume of the tongue in nonsyndromic children with OSAS did not differ from controls [47].

Soft Palate There are few data on the dimensions of the soft palate in children with OSAS. Using direct measurements, Brodsky et al. [67] did not find a correlation between soft palate length and severity of tonsillar hypertrophy in children with OSAS. Using MRI, Arens et al. [47] noted a 30% increase in the volume of the soft palate of children with mild to moderate OSAS compared to controls. They speculated that the larger palatal volume might have been due to edema and inflammatory changes secondary to chronic snoring, as described in adults [68–70].

Craniofacial Structure

Several studies using cephalometrics support the idea that children without distinct craniofacial anomalies have subtle craniofacial morphometric features associated with OSAS [49, 71–74]. Kawashima et al. [75] reported that children with OSAS and more pronounced tonsillar hypertrophy had retrognathic mandibles and increased posterior facial height compared to children with OSAS and less pronounced tonsillar hypertrophy. Shintani et al. [71] noted that the relationship of the mandible with respect to the cranial base was retrognathic in children with OSAS compared to normal children. Zucconi et al. [76] noted that children with OSAS had increased craniomandibular, intermaxillary, goniac, and mandibular plane angles, indicating a hyperdivergent growth pattern (angle between nasion-sella line and mandibular line >38°).

In contrast to the above, other investigators suggested that the craniofacial changes found in children with OSAS are mild, and are reversible following adenotonsillectomy [74, 77, 78]. This is supported by a study evaluating upper airway structure using MRI, showing no significant differences in

the size of the mandible and maxilla of children with OSAS versus controls [47]. Furthermore, in a more comprehensive evaluation of the mandible after three-dimensional reconstruction, the above authors found no difference in eight dimensions of the mandible between children with OSAS and controls, suggesting that mandibular size and shape does not play a significant role in the causation of childhood OSAS in nonsyndromic children [79].

Childhood Obesity

Earlier descriptions of childhood OSAS characterized children as being of normal weight, and failure to thrive was a common complication [33 m 80]. However, the dramatic increase in pediatric obesity [81, 82] is not reflected in most of literature characterizing risk for OSAS from early infancy to late childhood [44, 82–88] although a large epidemiological study involving 399 children between 2 and 18 years of age found that obesity was the most significant risk factor for OSAS, with an odds ratio of 4.5 [44]. The prevalence of OSAS was reported to be 46% by Marcus et al. in unselected obese children undergoing polysomnography [86]; Silvestri et al. reported a prevalence of 59% in obese children referred for evaluation of sleep disordered breathing [85]; and Kalra et al. reported a prevalence of 55% in morbidly obese children undergoing bariatric surgery [89]. The reason for such a high prevalence of OSAS in obese children compared to the 2% reported in the general pediatric population [44] is unknown. However, it may be related to a different underlying pathophysiology of the disorder distinguishing it from OSAS in nonobese children, and/or an augmented effect on regular causative factors, resulting from their obesity accelerating growth of upper airway lymphoid tissues [54].

In nonobese children with OSAS the most common treatment is adenotonsillectomy [90]. Adenotonsillectomy cures or ameliorates the disorder in the majority of cases [33, 61–63]. However, as noted earlier, it is estimated that in 10–20% of otherwise normal children, significant residual symptoms exist after surgery [64–66, 91]. Similarly, several investigators emphasize the role of adenoid and tonsillar hypertrophy in obese children with OSAS [86, 92–94]. A recent study suggests that 45% of morbidly obese children and adolescents with OSAS have evidence of adenotonsillar hypertrophy [95]. However, after adenotonsillectomy in obese children with OSAS, residual OSAS is noted in up to 50% of children [96]. This finding suggests that other anatomical and/or functional factors play a significant role in the pathophysiology of OSAS in this group.

Obese children may have excess deposition of adipose tissue within the muscles and tissues surrounding the airway, limiting airway size and increasing airway resistance as observed in adults [97]. Additional factors that may predispose obese children to OSAS include altered chest wall mechanics and reduced lung volumes due to altered body composition [54, 98], resulting in decreased oxygen reserves and decreased central ventilatory drive [83, 99]. However, the exact effects of weight gain or weight loss on upper airway structure and function have not been studied in obese children. Moreover, as mentioned above, other mechanisms affecting upper airway neuromotor tone and increasing upper airway collapsibility could have a compound effect in these children with an anatomically compromised airway.

Adolescence

There are few data related to the epidemiology of OSAS in adolescence. Only one study assessed the prevalence of the disorder in this age group and estimated it at 1.9% [100]. It is not known whether OSAS appearing in adolescence is an extension of the clinical disorder of childhood, with adenotonsillar hypertrophy as a major risk factor, or whether it represents an early manifestation of the adult form of OSAS, with obesity as a major risk factor.

Several studies have addressed the relationship between childhood OSAS and OSAS during adolescence. In a retrospective study, Morton et al. [101] found that sleep-disordered breathing in adolescence was more common in those who had undergone adenotonsillectomy during early childhood. Tasker et al. [102] noted a significant increase in inspiratory effort and snoring during sleep in adolescents 12 years after adenotonsillectomy, compared to controls. The latter authors speculated that airway narrowing could have originated in childhood and predisposed to OSAS during adolescence. Guilleminault and colleagues noted alterations in craniofacial morphology in three adolescents with OSAS and a history of upper airway obstruction in childhood. They hypothesized that both genetic factors altering craniofacial growth, and secondary modification of craniofacial growth secondary to adenotonsillar hypertrophy, predisposed these patients to OSAS [103, 104].

Another possibility is that OSAS during adolescence represents an early manifestation of the adult form of OSAS, especially when associated with obesity. It is well established that the antecedents of adult obesity begin during childhood and adolescence [81]. Childhood obesity in all age groups is currently on the rise, and the highest prevalence (15.5%) is seen in adolescent children between 12 and 19 years of age [105] also having all components of the metabolic syndrome [106–109]. Studies investigating the pathophysiology of OSA in this population have shown that upper airway lymphoid hypertrophy restricting airway size continue to be an important contributor to OSAS [54, 110] (Fig. 35.2c, d) though functional factors impacting airway collapsibility may also play an important role [111].

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders associated with overweight

and obesity. It affects 5–10% of adolescent girls and women of reproductive age [112]. PCOS usually presents during adolescence with irregular menstruation and clinical signs of hyperandrogenism and is associated with obesity and cardiometabolic abnormalities [113]. In recent years it has been shown that adolescent girls [114] and adult women with the disorder have a significantly higher prevalence of OSAS compared to women without the disorder [115–117], screening for OSAS has therefore been recommended in these subjects [118].

Summary of Anatomic Considerations

Various anatomic mechanisms may lead to OSAS in children. However, a smaller upper airway is noted in all age groups and probably predisposes to airway narrowing and collapse during sleep. OSAS is uncommon in infancy. However, children born with craniofacial anomalies are at increased risk for the development of a severe form of the disorder.

The most common type of childhood OSAS occurs in children between 2 and 8 years of age and is associated with adenotonsillar hypertrophy in most cases. Surgical removal of the adenoid and tonsils ameliorates the disorder in most but not all children, suggesting that other mechanisms such as those leading to altered upper airway neuromotor tone during sleep may contribute to OSAS in these children.

Recent data suggest that obesity may be a leading cause for OSAS during adolescent years. This form of OSAS probably shares much with the adult form of OSAS and particularly with the metabolic consequences of the disorder. However, in contrast to the adult form of OSAS, adenotonsillar hypertrophy commonly observed in early childhood plays an important anatomical contributor in this age group as well.

Functional Considerations

There are several arguments that suggest that functional attributes have an important role in limiting and influencing OSAS in children. The first is that the upper airway in children is smaller compared to adults. Since the prevalence of OSAS is much lower in children, it is probable that children have nonanatomical attributes that enhance airway stability during sleep. The second is that airway obstruction occurs during sleep and not during wakefulness, suggesting that neuromotor activation keeps the airway open during wakefulness but not during sleep, when activation is diminished. The third is that subjects with OSAS survive each night. Therefore, there must be overriding mechanisms that prevent unremitting airway obstruction and anoxia from leading to death.

Central Ventilatory Drive

The role of ventilatory drive in the pathophysiology of OSAS in adults and children with OSAS is not fully understood. The central ventilatory drive changes with age from infancy to adulthood. Methodological limitations in measuring drive and mechanical and anatomical differences across the age spectrum do not allow precise comparisons of ventilatory drive throughout the life span. However, it appears that ventilatory drive gradually declines from childhood to old age, possibly because of declining basal metabolic rate with age.

Some adults with OSAS have been reported to have increased ventilatory responses to hypercapnia and hypoxia leading to a high-gain ventilatory control system that could predispose some individuals to irregular or periodic breathing, ventilatory instability, and apnea [119, 120]. This relationship is not firmly established; normal or even reduced ventilatory responses have also been reported in adults [121].

In comparison, nonobese children with OSAS were shown to have normal ventilatory responses to hypercapnia and hypoxia during wake and sleep [7, 122, 123], and other studies in obese children showed a blunted ventilatory response to hypercapnia in sleep. Such studies suggest that OSAS in children is unlikely to be initiated through ventilatory instability and high chemical loop gain [124, 125].

Ventilatory Response to Inspiratory Resistive Loading

During wakefulness, addition of an external resistive load leads to an immediate compensatory increase in ventilatory effort that maintains gas exchange. In sleep, this compensatory response is not normally seen unless there is a complete airway occlusion. With partial occlusion, a decrease in minute ventilation ensues and compensation of ventilation is delayed; this eventual correction is believed to be in response to gas exchange abnormalities. In normal children, this compensation can be limited and delayed by 3 minutes or more as compared to adults [126]. Young children with OSAS have reduced arousal responses to inspiratory resistive loads during sleep that together with the aforementioned inadequate compensation of ventilation may explain the prolonged periods of obstructive hypoventilation observed in childhood OSAS [126]. Similar abnormalities in upper airway reflexes and diminished response to resistive loading have been described in adolescents with OSAS and particularly if were obese and during REM sleep [127, 128].

Arousals from Sleep

Arousals are a normal phenomenon of sleep and are defined as sudden shifts in EEG frequency lasting for 3 seconds. However, if arousals occur too often, they produce sleep disruption, and interfere with the restorative nature of sleep. It should also be pointed out that arousals may be considered protective to subjects with OSAS since they coincide with increased dilator muscle activity, reduced upper airway resistance, and restoration of normal ventilation.

Studies in children and adults have clearly shown that frequent arousals and sleep fragmentation often lead to decreased vigilance, sleepiness, and other neurocognitive impairments. Interestingly, children are much less prone to arousals due to respiratory events than adults and typically are less sleepy compared to adults with OSAS. The major stimuli for arousals from OSAS are thought to be mechanical stimulation of lung and chest wall stretch receptors due to increased respiratory effort. However, hypercapnia is also considered a potent arousal stimulus. Most obstructive events in adults are associated with arousals from non-REM sleep. In children most obstructive events occur during REM sleep, and associated arousals are less frequent than in adults. Normal children have a higher arousal threshold than adults; children with OSAS seem to have an even loftier threshold for arousal in response to inspiratory loading [126] and hypercapnia [123] compared to children without OSAS.

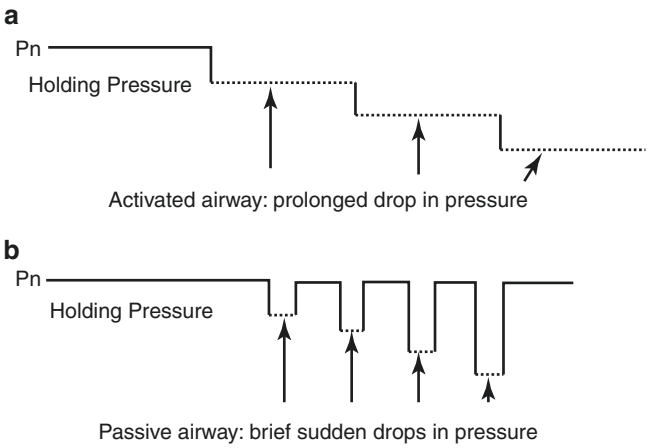

Fig. 35.5 Active and passive critical closing pressure protocols. Schematic of active and passive airway critical closing pressure protocols. Holding pressure (horizontal solid line) is maintained at levels just enough to abolish flow limitation. (**a**) Active protocol: To determine active critical airway closing pressure, nasal pressure (Pn) is reduced in 1–2 cm H_2O decrements (broken lines) and maintained for prolonged periods (1–10 min) to allow dynamic airway activation to occur and maximal inspiratory air flow is obtained at each pressure. Airway pressure is reduced until airflow approaches zero or arousal from sleep occurs. (**b**) Passive protocol: To determine passive airway critical pressure, pressure drops (broken lines) from holding pressure (horizontal sold line) are made for brief periods lasting five breaths, before dynamic responses are activated. Airway pressure is then raised to holding pressure rapidly for 1 or more minutes before dropping it further in increments of 1–2 cm H_2O pressure till zero flow is approximated or arousal occurs. Maximal inspiratory flow (Vi max) at each pressure setting is determined. Pressures employed span a range of positive to negative (sub atmospheric) values to estimate critical closing pressure

Upper Airway Neuromotor Tone

Flow through the upper airway depends not only on mechanical and anatomic factors but also the active dilation of the airway by neuromotor tone [8, 9]. Pressure–flow relationships based on the Starling model provide an understanding of airway stability in the "active" state with neuromotor activation and in the "passive state" before neuromotor responses are activated [7, 60, 129–131] (Fig. 35.5). Plotting a range of airway pressures against the resulting maximal inspiratory flows of breaths generates a pressure–flow line with the critical closing pressure (Pcrit) being represented by the intercept on the pressure axis (Fig. 35.6, adult). Airway pressure is applied by a nasal mask with the subject in a supine position and airflow is measured by a pneumotach; the pressures applied range from positive pressures to negative (subatmospheric) pressures. When pressure is maintained in a steady state, neuromotor activation occurs and the airway is in the active state; this active Pcrit is considered a measure of airway collapsibility. The nasal pressure at which the airway closes or is estimated to close by the pressure-flow line is typically lower for the active airway compared to the passive airway (Fig. 35.6). In children, the Pcrit tends to be very negative (i.e., motor tone is very high) such that extrapolation of the pressure flow line can become unreliable; the slope of the pressure–flow line is taken as the best estimate of upper airway collapsibility (Fig. 35.6, child). In addition, airflow in the first few breaths following a sudden drop in pressure, before neuromotor responses can occur, represents the "passive airway"; this passive Pcrit estimates mechanical and structural properties of the airway. A passive airway closing pressure can also be estimated by the pressure–cross-sectional area relationship endoscopically observed in anaesthetized subjects (in whom neuromotor activation is suppressed) analogous to the pressure–airflow relationship. Neuromotor activation can more directly be estimated by measuring the EMG activity of the genioglossus muscle, which is the major pharyngeal dilator.

The pediatric airway is very resistant to collapse compared to the adult airway, airway collapsibility increases with age during adolescence and is not a function of pubertal development [7, 129]. In children and adolescents with OSAS the critical closing pressure is much higher than non-OSAS children [7, 60, 128]. Childhood OSAS is most prominent in REM sleep which is associated with reduced pharyngeal tone and wide fluctuations of airflow, both of which probably contribute to OSAS. While closing pressure

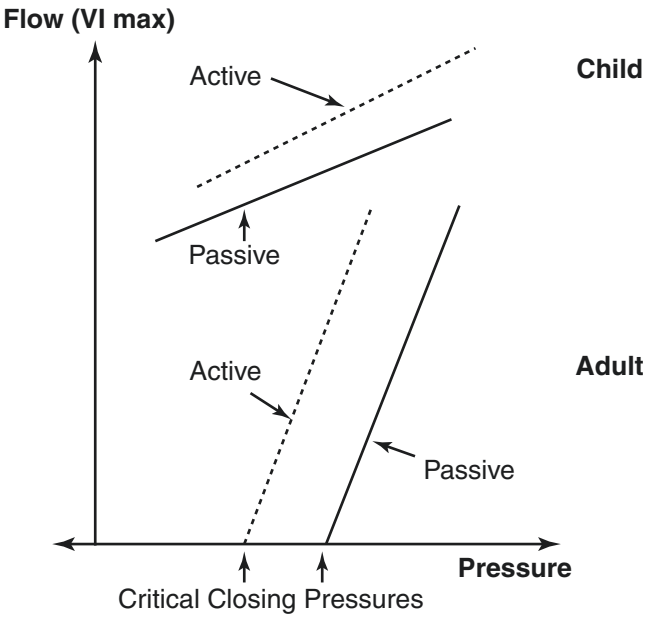

Fig. 35.6 Active and passive critical closing pressure (Pcrit) in a child and adult. Schematic representation of plots of nasal pressure (on *x*-axis) and maximum inspiratory air flow (Vi max) (on *y*-axis). Pressure flow lines calculated from flow at each pressure setting in the active or passive condition are used to obtain critical closing pressures; the intercept on the *x*-axis is the critical closing pressure. The activated pressure flow line (dashed line) has a lower airway closing pressure than the passive airway pressure flow line (solid line). Children tend to have very stable airways with a zero slope (dashed and solid line at top)

is difficult to measure in REM sleep for practical reasons, reduced airway tone can be demonstrated by EMG studies of the tongue muscles. Awake children with OSAS have higher baseline EMG tone than normal children, most probably to compensate for their narrower airways. With sleep onset these children have a rapid decline in EMG tone [132], with a further decline in REM sleep, predisposing them to airway obstruction during sleep [133].

Upper Airway Sensation

The afferent (sensory) loop of the upper airway negative pressure reflex also plays a role in promoting airway stability. During wakefulness, topical nasopharyngeal anesthesia results in increased upper airway collapsibility in both children [50] and adults [134]. Similarly, during sleep, the application of topical nasopharyngeal anesthesia in adults results in increased upper airway collapsibility, leading to obstructive apnea [135–138]. The resultant worsening of apnea appears to be due at least in part to changes in muscle tone [139], but also to blunting of the arousal response [135, 138]. These studies are supported by the study of Tapia et al. showing impaired sensation along of the tongue and hard palate and possible primary sensory function abnormality in children with OSAS during wakefulness. The latter authors speculated that this has been secondary to nerve damage and/or hypoxemia caused by OSAS [140].

Summary of Functional Consideration

The pediatric airway is very resistant to collapse compared to the adult airway, and airway collapsibility increases with age and during adolescence. This trend may explain the lower prevalence of OSAS in children compared to adults. Differences in ventilatory drive, arousal thresholds, airway reflexes during sleep, and active and passive properties of the upper airway also suggest different pathophysiological mechanisms in childhood OSAS compared to the adult form.

Active and passive techniques assessing airway collapsibility in sleep in children with OSAS show that the critical closing pressure is higher than in non-OSAS children. However, the overall ventilatory drive in response to hypoxia and hypercapnia is probably normal in OSAS children, although infants have a strong biphasic response to hypoxemia, and are more likely to develop central apnea when exposed to prolonged hypoxemia. The central ventilatory drive also plays a role in augmenting upper airway neuromotor reflexes and tone. Normal children have brisker upper airway reflexes during sleep than adults, perhaps due to their greater central ventilatory drive. These reflexes appear to be blunted in children with OSAS. Finally, children with OSAS are less likely to arouse in response to upper airway obstruction and do not compensate for prolonged increases in inspiratory resistive load. This may explain why patients in the pediatric age group often have obstructive hypoventilation rather than discrete, cyclic obstructive apneas.

Biomechanical Considerations

In recent years, biomechanical modeling of the upper airway has been developed to characterize the anatomical and functional mechanisms that play a role in the pathophysiology of OSAS in children. This approach, called image-based modeling, uses imaging modalities such as magnetic resonance imaging (MRI) with engineering tools such as computational fluid dynamics (CFD) to analyze individual subjects. Dynamic imaging and image-based flow models create a rich data set that may help to explain how anatomy, tissue properties, and muscle function contribute to flow limitation, hypopneas, and apneas. Upper airway pressure fields modeled by CFD have been validated in vivo [141] and in vitro [142, 143]. The pharynx in OSAS is often restricted where the adenoid, soft palate, and tonsils overlap [53], and CFD models can identify the location and quantify severity of anatomical restrictions. CFD model outcomes based on the drop

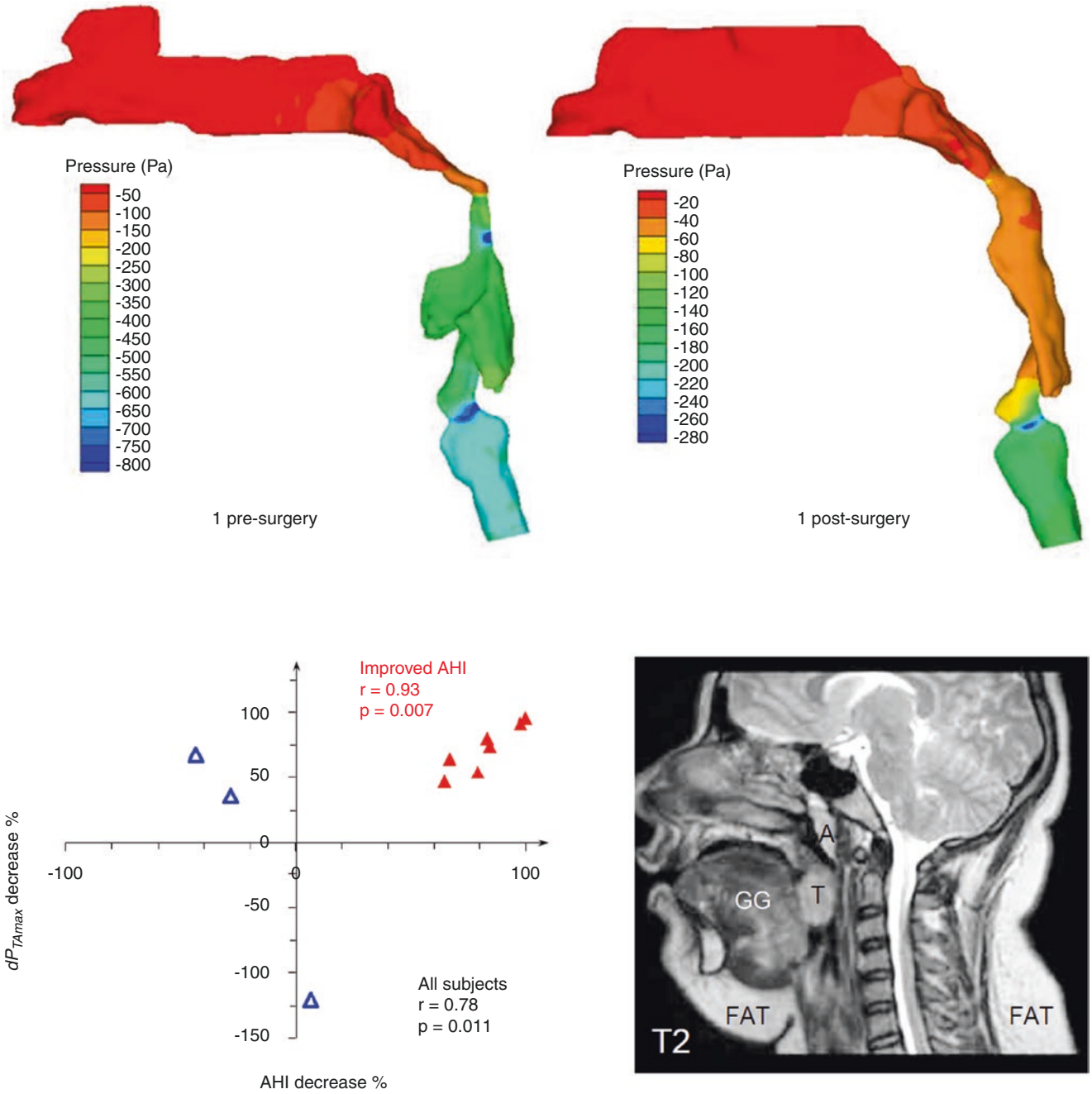

Fig. 35.7 Image-based CFD as a tool to assess surgical outcomes in children with OSAS. Top: CFD pressure fields at peak inspiratory flow, before (left) and after (right) adenotonsillectomy surgery, in a subject with 100% improved AHI postsurgery. Maximum pressure drop from choanae through the "overlap region" where tonsils and adenoids overlap (T and A on lower right image), dP_{TAmax}, was reduced by 96% after surgery. Bottom left: reduction in dP_{TAmax} after surgery correlates strongly with improvement in AHI, especially in patients with significant postsurgery improvement. Bottom right: sagittal centerline MR image before surgery showing enlarged tonsil (T) and adenoid (A) also overlapping with the soft palate

in pressure between the choanae and location of maximum restriction have been correlated to OSAS severity in obese children [141, 142, 144]. Such studies identified the drop in airway pressure between the choanae and the point of maximal narrowing at maximum inspiratory flow, dP_{TAmax}, as the CFD measurement that most consistently correlated with OSAS severity [141, 145]. Changes in CFD pressure drop correlate strongly to improvements in OSAS after AT surgery [145] (Fig. 35.7) or oral appliance placement [146, 147]. Compared to CFD biomarkers, correlation to strictly

anatomical biomarkers such as cross-section area or airway volume is often weaker or not significant [141, 148]. The above works show that CFD has matured as a robust and accurate method to compute the effect of anatomical restriction over the upper airway air pressure field.

An early study of pressure drops and flow resistance in the pharynx of individual children with OSAS [142] showed significantly higher airflow resistance in the upper airway of mildly sedated young children with OSAS. The same trend was observed in wakeful older obese children imaged during relaxed tidal breathing [141]. In a minority of OSAS cases, airflow resistance was lower [149], suggesting that in these children OSAS does not result from anatomical restriction, but rather from altered *functional* factors related to tissue compliance and neuromuscular tone during sleep. Deficits in these factors can be suggested by the Pcrit which measures collapsibility of the upper airway, but Pcrit cannot identify the location of collapse or the anatomical or mechanical causes of collapse. Thus, image-based CFD may help to identify different patient phenotypes (Fig. 35.8) if it is combined with a functional assessment.

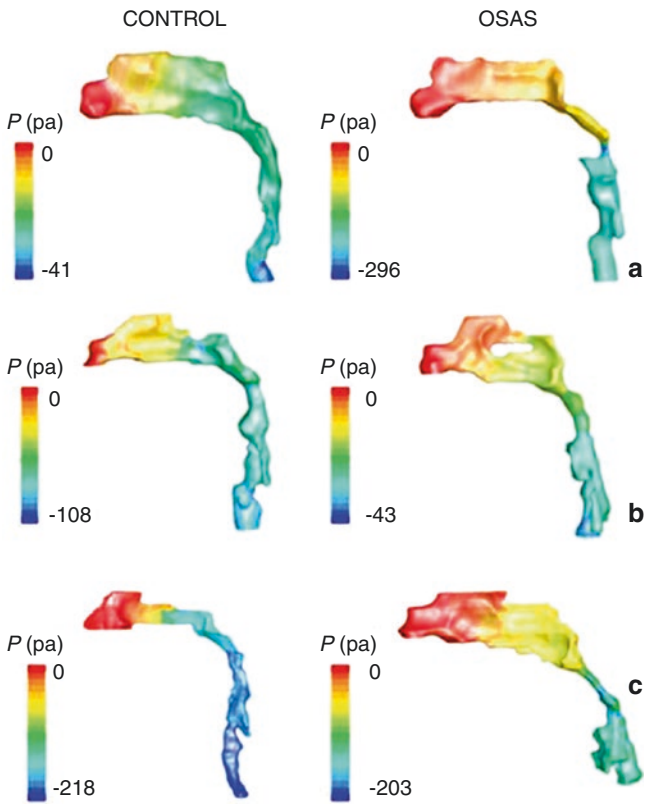

Fig. 35.8 OSAS phenotypes by computational fluid dynamics. (**a**) Anatomically driven OSAS: significant anatomical restriction in the "overlap region" leads to high pressure drop between choanae and minimum area of the pharynx in OSAS compared to controls. (**b**) Functional factor driven OSAS: OSAS with area restriction and CFD pharyngeal pressure drop similar to controls suggests loss of airway function during sleep. (**c**) Functional protection in control subject with anatomical restriction and high CFD pharyngeal pressure drop compared to OSAS. (From Wootton et al. [141]. ©American Physiological Society)

CFD analysis based on dynamic imaging may be used to characterize both anatomical and functional factors, using a novel noninvasive method to compute the effective regional mechanical airway compliance [150]. The effective compliance is the slope of a plot of cross-sectional area versus the local airway pressure, computed from image-based CFD. Effective compliance measures the combined effects of passive tissue properties and active airway muscle tone similar to Pcrit, but with the advantage of providing this data at any location along the airway in reference to the phase of the breathing cycle.

In a study of obese adolescent girls that combined dynamic MRI, CFD, and Pcrit, the effective compliance in the nasopharynx correlated significantly and negatively with both AHI and Pcrit [151], suggesting strong phasic airway dilator activation while awake, compensates for a collapsible airway, and loss of muscle tone during sleep leads to obstructions. An early study of sedated sleeping subjects showed positive effective compliance in subjects with OSAS, consistent with a passive, compliant pharynx susceptible to collapse [150]. CFD based on dynamic MRI of subjects before and after the onset of sleep has the potential to reveal both anatomical and functional factors to better identify OSAS phenotypes.

Airflow resistance of the nasal passages from nares to choanae is another important biomechanical factor that often determines the majority of the air pressure force in the pharyngeal airway prior to airway collapse. Nasal resistance measured using anterior rhinomanometry is significantly higher in children with OSAS than controls [152], and may be an important tool for screening and diagnosing OSAS.

Additional Considerations

Edema

Although increased soft tissue size surrounding the airway as a cause for OSAS is primarily related to obesity, chronic edema, and inflammation of the upper airway soft tissues may further restrict the dimensions of the upper airway. The mechanism for this effect is speculated to be the effect of chronic vibratory effects of snoring, and of upper airway soft tissue being tugged caudally during fluctuation in intrathoracic pressure, resulting in trauma to the upper airway soft tissues [69, 70]. Indeed, the therapeutic effect of CPAP is thought to be partially mediated through a reduction in upper airway soft tissue edema, and the use of CPAP has been shown to reduce soft palate volume [153].

Myopathy

It has been suggested that patients with OSAS have a primary myopathy. Several studies have demonstrated an

increase in type II fast twitch fibers in the genioglossus of patients with OSAS [154–156]. Type II fibers are less resistant to fatigue than type I fibers. It is possible that the increased number of type II fibers is secondary to chronic muscle injury which, in turn, may alter the size, length, and configuration of the affected muscles.

Gender

In adults, OSAS is far more common in males than females [157]. Considerable effort has been expended in trying to determine the mechanisms underlying this male predominance, but no clear explanation has emerged. Studies have not shown differences in pharyngeal anatomy resulting in a smaller pharyngeal lumen in males. On the contrary, females were found to have a smaller pharynx [158, 159], despite the presence of larger soft tissues in males [160]. It is therefore possible that the reduced occurrence of OSAS in females is due to a stiffer and less collapsible upper airway despite its smaller size [161–163]. Speculated mechanisms mediating differences in airway collapsibility include hormonal differences, differences in chemosensitivity, and differences in tissue properties [161, 162, 164].

In contrast, no gender differences have been noted in children with OSAS. Pillar et al. evaluated the upper airway length in pre- and post-pubertal non-OSAS children using CT images. They noted that airway length after normalization was significantly greater in males in post-pubertal years and speculated that such changes in length after puberty may predispose males to OSAS later in life [165].

As mentioned above, PCOS is one of the most common endocrine disorders associated with overweight and obesity and affects 5–10% of adolescent girls and women of reproductive age [112]. Screening for OSAS has therefore been recommended in these subjects [118].

Genetics

Genetic factors most probably play an important role in both the pathophysiology and health outcomes of OSAS in children and adults. However, genetic studies in the field of OSAS particularly in children lag behind other common medical disorders.

Evidence to suggest that OSAS is genetically mediated in children includes the following: (1) the strong association of OSAS with discrete craniofacial skeletal disorders restricting the upper airway such as Down syndrome, Treacher Collins, and Apert syndrome; (2) distinct genetic disorders associated with obesity that present with an extremely high prevalence of OSAS and sleep disordered breathing such as PWS, PCOS, and melanocortin-4 receptor deficiency. The above examples suggest that distinct genes regulating upper airway morphology, body composition, or ventilatory control also contribute to the pathophysiology of OSAS in such groups. However, so far, such genes have not been identified and it is unclear if such putative genes share similarities to genes responsible for OSAS on otherwise healthy children.

In adults, evidence to support that OSAS is a heritable disorder include the marked gender difference in disease prevalence and progression [157], familial aggregations of the disorder [166], and twin studies [167].

Genetic approaches to study OSAS have been utilized only in adults. Research in this area has been limited by the relatively small number of studies, small number of participants and the small number of replication studies. Standard genetic approaches include heritability studies to discover candidate genes using single nucleotide polymorphisms (SNPs) and OSAS phenotypes in case–control or cohort studies, or genome-wide linkage studies and genome wide association studies (GWAS) to identify causal genes without having a priori knowledge of functionality [168].

Nevertheless, several genetic association studies have identified candidate polymorphisms in genes linked to OSAS: the tumor necrosis factor alpha (TNF-α) gene (−308G/A) [169], the rs1409986 SNP in the prostaglandin E2 receptor (PTGER3) gene [170], and the rs7030789 SNP in the lysophosphatidic acid receptor 1 (LPAR1) gene [170].

Large-scale GWAS have identified loci for traits associated with OSAS such as: (1) polymorphism in the G-protein receptor gene (GPR83) [171] which is expressed in several areas of the brain including the hypoglossal nucleus, the dorsal motor nucleus of the vagus, and the nucleus of the solitary tract; (2) variants in the β-arrestin 1 (ARRB1) gene, which is an important regulator of hypoxia inducible factor 1 alpha (HIF-1α) [171]; (3) genes regulating obesity and body composition and insulin resistance [172]; and (4) genes regulating craniofacial structures [173]. It still remains to examine if these genes are applicable to risk for OSAS in children.

Research Questions

There are many pressing unanswered questions regarding the developmental pathophysiology of OSAS. In particular:

- What is the pathophysiology of the “idiopathic” OSAS often seen in infants?
- What is the natural history of childhood OSAS? Is childhood OSAS a precursor of adult OSAS, or a separate disease process? If the former, what is the recurrence rate during later life, and what are the risk factors for recurrence?

- What is the effect of childhood OSAS on craniofacial growth and structure? Does adenotonsillar hypertrophy per se result in craniofacial changes that could result in obstructive apnea later in life, or is the apparent adenotonsillar hypertrophy a result of overcrowding from a narrower upper airway? What is the potential role of treatments such as intraoral appliances and rapid maxillary expansion in changing craniofacial growth in children?
- When does the childhood pattern of OSAS transition into the adult pattern? What are the effects of puberty on upper airway function and structure?
- What roles do genetic, ethnic, and anthropometric factors play in the pathophysiology of OSAS?
- How can biomechanical studies using novel imaging modalities such as MRI improve diagnosis and treatment for children with OSAS?

Addressing these questions may improve diagnosis and provide optimal treatment outcomes for various phenotype of childhood OSAS in the upcoming years.

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Obstructive Sleep Apnea: Clinical Presentation and Differential Diagnosis

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Clinical Presentation

Clinical History

Children with obstructive sleep apnea (OSA) can present with variety of symptoms.

Clinical Presentation of OSA in Children

Nocturnal Symptoms
- Snoring
- Observed apnea
- Difficulty breathing
- Paradoxical breathing
- Snorting and gasping
- Mouth breathing
- Usual sleeping positions (sitting, hyperextended neck)
- Nocturnal sweating
- Restless sleep
- Enuresis

Daytime Symptoms
- Mouth breathing
- Recurrent upper respiratory tract infection
- Daytime tiredness and/or fatigue
- Inattention
- Hyperactivity
- Poor school performance
- Aggressive behaviors
- Behavior problems
- Hearing and speech problems
- Difficulty swallowing
- Morning headache
- Excessive daytime sleepiness

Snoring and noisy breathing are the most common presenting symptoms of children with OSA. Snoring is a low-frequency sound produced by vibration of the soft palate and tonsillar pillars, but snoring can have a higher pitch in a young child when enlarged tonsils and adenoids impede movement of the soft palate [1]. Snoring may not be present in infants or children with neuromuscular disorders due to inability to produce sufficient flow. Intermittent snoring alternating with respiratory pauses is a classic symptom of OSA in adult population. The adult pattern of snoring alternating with respiratory pauses can be seen in children with OSA; however, children often have continuous snoring, a pattern of prolonged partial airway obstruction [2]. Difficulty breathing is frequently observed by parents. Some parents may notice paradoxical breathing. Because young children have a compliant rib cage, paradoxical breathing is a prominent feature in these children [3]. Observed apnea during sleep is reported in 0.2–4% of epidemiological study but can be seen in up to 87% of children with OSA [4]. Mouth breathing, gasping, and snorting sounds during sleep are common symptoms. Some parents report shallow breathing or unusual breathing patterns during sleep in their child. These breathing patterns

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during sleep can be frightening to the parents and often lead to increased vigilance and the perceived need to intervene such as stimulate their child during sleep [1].

Children with OSA may sleep in unusual positions such as sitting up or on their elbows and knees with their buttocks in the air and the neck hyperextended in an attempt to promote airway patency. Obese children with OSA may prefer sleeping sitting upright [5]. Excessive nocturnal sweating is common and has been reported in 50–96% [6, 7]. Nocturnal sweating is likely due to increased work of breathing during sleep. Children with OSA may present with nighttime awakenings and/or restless sleep from frequent arousals at night. Bed-wetting (nocturnal enuresis) is relatively common in children with OSA [8], and adenotonsillectomy has been shown to significantly reduce enuresis [9].

In addition to nighttime symptoms, children with OSA can present with a variety of daytime symptoms. Excessive daytime sleepiness (EDS) is very common in adults with OSA but is present in only a small proportion of children with OSA [10, 11]. Although EDS is infrequent, objective findings from MSLT revealed shorter sleep latency in children with OSA [12]. EDS tends to be more common among children with more severe OSA or obesity [12, 13]. Children often complain of daytime fatigue or tiredness. Morning headaches have been reported in 16% of children with OSA, which tend to subside by late morning [6]. The mechanism may be related to changes in cerebral blood flow secondary to hypoxia, hypercapnia, and sleep fragmentation [14, 15]. Mouth breathing, recurrent upper respiratory tract infection, hearing and speech problems, and difficulty swallowing are frequently reported in children with OSA and adenotonsillar hypertrophy [1].

Children with OSA may present with consequences of OSA. The main consequences of OSA are cardiovascular and neurocognitive. For cardiovascular consequences, systemic hypertension and isolated diastolic hypertension have been reported in children with OSA [16–18]. Elevated blood pressure (BP), both asleep and awake, and increased BP load and morning BP surges have been observed in children with OSA [19–21]. Pulmonary hypertension is the main cardiovascular consequence of OSA in adults. There is limited literature on the prevalence of pulmonary hypertension in children. Based on recent literature review, the co-occurrence of pediatric OSA and pulmonary hypertension ranges from 0% to 85% depending on the studied population and the method to diagnose pulmonary hypertension [22]. Treatment of OSA by surgery or noninvasive positive pressure ventilation can reduce pulmonary artery pressure in a substantial number of cases [22]. If left untreated, pulmonary hypertension can lead to cor pulmonale which was previously reported in children with OSA especially those with Down syndrome [23, 24]. Due to early diagnosis and intervention, cor pulmonale as an initial presentation of OSA is quite rare nowadays in children. Other cardiovascular consequences of OSA in children include cardiac dysfunction (right and ventricular dysfunction), cardiac arrhythmia, and changes in heart rate variability [6, 25–27].

For neurocognitive consequences, children with OSA may present with inattention, hyperactivity, and aggressive behaviors [28–30]. There is an association between ADHD and OSA in children, but relationship is complex [31]. Other behavior problems (learning deficit, memory problem, poor school performance, and depressive symptoms) have been reported in children with OSA [32–36]. Other consequences include the effect on growth and respiratory morbidity. Although a significant proportion of children with OSA are obese, they may present with failure to thrive [6, 23]. The mechanism may be due to poor caloric intake, increased energy expenditure, or abnormal release of growth hormone [37, 38]. Increased respiratory morbidity and health-care utilization have been reported in children with OSA [39]. In addition, OSA may be a predisposing risk factor for community-acquired pneumonia [40]. Treatment of OSA by adenotonsillectomy has been shown to reduce health-care utilization [41].

Physical Examination

Possible physical examination findings in children with OSA are summarized below.

- *GA*
  - Overweight or obesity
  - Failure to thrive
- *HEENT*
  - Micrognathia or retrognathia
  - Steep mandibular plane
  - Triangular face
  - Mid-face hypoplasia
  - Adenoid facies
  - Allergic shiner
  - Hypertrophic nasal turbinate
  - Nasal polyps
  - Nasal septum deviation
  - *Adenotonsillar hypertrophy*
  - High-arched palate
  - Crowded oropharyngeal opening
- *Cardiovascular system*
  - Hypertension
  - Loud second heart sound (pulmonary hypertension)
  - Tricuspid regurgitation and peripheral edema (cor pulmonale)

Possible Physical Examination Findings in Children with OSA

- *Respiratory stem*
  - Pectus excavatum
  - Upper airway transmitted sound
- *Neurological*
  - Normal
  - Hypotonia (in children with neuromuscular disorder)

A physical examination can provide useful information, although the examination can be normal in children with OSA. Assessment of vital sign is often normal. A small number of children may have hypertension as a consequence of OSA [18]. Clinician should pay attention to body mass index (BMI) as obesity is one of the major risk factors for OSA. However, children with OSA may present with failure to thrive. Craniofacial examination is important as certain craniofacial features including micrognathia, retrognathia, steep mandibular plane, triangular face, and mid-face hypoplasia are highly associated with OSA [42]. These features are more common in children with genetic and craniofacial syndromes. Children with adenoid hypertrophy may have long and opened mouth face called adenoid facies. The nose should be examined to assess for sign of nasal obstruction including hypertrophic nasal turbinate, polyps, and nasal septum deviation. The presence of allergic shiner suggests the presence of allergic rhinitis, a possible risk factor for OSA.

Oropharyngeal examination is the most important part of physical examination in children with OSA. As adenotonsillar hypertrophy is the most common cause of OSA, the size of tonsils should be evaluated. The palate, tongue, and oropharyngeal opening should be carefully examined. High-arched palate, long soft palate, and narrowing or crowding of oropharyngeal opening are associated with OSA [42]. The opening of the oropharynx can be evaluated by Mallampati classification, a visual assessment of the distance from the tongue base to the roof of the mouth. Mallampati classification has been widely used in adults with OSA, but there is limited data in children [43–45]. One study demonstrated increased Mallampati scores in obese children and the interaction between tonsillar size and Mallampati classification. The more crowded the airway, the lesser the size of adenotonsillar tissues required to elicit OSA [43].

A cardiovascular examination is usually normal. In children with OSA and pulmonary hypertension, a loud second heart sound may be heard. In advanced cases with cor pulmonale, tricuspid regurgitation and peripheral edema can be detected as signs of right heart failure. A respiratory system examination may reveal upper airway transmitted sounds on auscultation. Pectus excavatum has been reported in children with OSA [46]. Examination of neurological system is normal except in those children with underlying neuromuscular disorders.

Although clinical history and physical examination can help in assessment of children with OSA, they are not sufficient to diagnose OSA in children. Several studies have shown that both history and findings from physical examination cannot reliably discriminate between primary snoring and obstructive sleep apnea [10, 11, 47, 48]. Many common symptoms of OSA are often used as a component of the questionnaire to screen for OSA. For example, Brouillette et al. used relatively sensitive and specific symptoms including snoring, difficulty breathing, and observed apnea in creating "OSA score" [7]. Later questionnaires such as Pediatric Sleep Questionnaire (PSQ) integrated questions related to both clinical symptoms and consequences of OSA to provide a better assessment of OSA [49]. These questionnaires have yielded a wide range of sensitivity, specificity, positive predictive value, and negative predictive value. A recent meta-analysis of clinical assessment of pediatric OSA has shown that both single and combined symptoms and signs do not provide satisfactory performance in predicting pediatric OSA [50]. Certain symptoms and signs such as snoring and tonsillar size have high sensitivity but low specificity. In contrast, excessive daytime sleepiness, observed apnea, and difficulty breathing during sleep have relatively high specificity but low sensitivity [50]. Therefore, clinicians should be aware of the limitation of relying on clinical presentation and screening questionnaire to make a diagnosis of OSA.

Differential Diagnosis

In considering the differential diagnosis of pediatric OSA, the diagnostic criteria must first be discussed. The International Classification of Sleep Disorders, third edition [3], defines pediatric OSA based on clinical presentation and objective data from an attended polysomnography (PSG). Clinical criteria include the presence of snoring; labored, paradoxical, or obstructed breathing; and/or sleepiness, hyperactivity, behavioral problems, or learning problems. PSG data must have one or more obstructive apneas, mixed apneas, or obstructive hypopneas per hour of sleep (the obstructive apnea hypopnea index (oAHI)) or obstructive hypoventilation defined as the presence of snoring, airflow limitation on nasal pressure waveform, and/or paradoxical thoracoabdominal motion in conjunction with $PaCO_2$

>50 mmHg (or surrogate) for at least 25% of the total sleep time [3].

The differential diagnosis can be described based on symptomatology and polysomnographic pattern.

Differential Diagnosis

Based on Symptomatology

- Isolated snoring
- Fixed upper airway obstruction
- Central sleep apnea
- Normal physiologic pauses
- Sleep-related laryngospasm
- Sleep-related reflux
- Obesity hypoventilation syndrome
- Narcolepsy
- Idiopathic hypersomnia
- Insufficient sleep syndrome
- Sleep-related movement disorder

Based on Polysomnographic Pattern

- Primary snoring
- Non-obstructive alveolar hypoventilation
- Central sleep apnea
- Sleep-related epilepsy

For symptomatology, the clinical presentation can help guide the differential diagnosis for OSA. In children who snore, isolated snoring is an alternative diagnosis. Children with isolated snoring do not have observed apnea, difficulty breathing, or daytime behavior problem. Noisy breathing during sleep can be due to snoring or stridor. The timing of noisy breathing can be insightful. Snoring occurs during sleep while stridor can occur during both awake and sleep. Noisy breathing from biphasic stridor may be indicative of a fixed airway obstruction such as subglottic or glottic stenosis or vocal cord paralysis, whereas inspiratory stridor may be due to laryngomalacia or other dynamic laryngeal pathologies. However, children with fixed upper airway obstructions can have coexisting OSA. Children with history of respiratory pauses may have normal physiologic pauses, central sleep apnea, or OSA. In children with history of choking and gasping during sleep, OSA should be differentiated from sleep-related laryngospasm and sleep-related reflux. Excessive daytime sleepiness can be a manifestation of OSA, obesity hypoventilation syndrome, primary hypersomnia such as narcolepsy or idiopathic hypersomnia, or insufficient sleep syndrome. In children with restless sleep, OSA should be differentiated from periodic limb movement disorder or other sleep-related movement disorders. In the appropriate context, OSA should be considered in children with sleep walking, confusional arousals, and night terrors.

The differential diagnosis of OSA based on polysomnographic pattern includes primary snoring, non-obstructive alveolar hypoventilation, central sleep apnea, and sleep-related epilepsy (see above). The diagnosis of primary snoring can be made in children who snore but do not have apneas, frequent arousals, or gas exchange abnormalities. Obstructive hypoventilation, one pattern of childhood OSA, should be differentiated from non-obstructive alveolar hypoventilation in children with chest wall deformities or parenchymal lung disease. Such patients would not be expected to have snoring but may have desaturation and hypercapnia. Paradoxical inward chest wall motion or thoracoabdominal asynchrony should not be present in non-obstructive hypoventilation. However, the presence of thoracoabdominal asynchrony is dependent on the severity of the chest wall deformity as thoracic cage compliance is diminished with altered rib structure. In addition, any neuromuscular weakness can further amplify thoracoabdominal asynchrony as intercostal muscles can be too weak to provide the necessary tone to withstand the more negative intrapleural pressure generated on inspiration. Therefore, children with neuromuscular weakness without airway obstruction or thoracic cage deformity can present with thoracoabdominal asynchrony [51, 52]. If the children with neuromuscular disorders have sufficient inspiratory muscle strength, the nasal pressure transducer and thermistor can help identify flow limitation, indicative of upper airway obstruction. This does not guarantee the alveolar hypoventilation is due to upper airway obstruction as non-obstructive hypoventilation can coexist with upper airway obstruction. Thus, thoracoabdominal asynchrony cannot be depended upon to determine whether hypoventilation is obstructive or non-obstructive in children with neuromuscular disorders.

Central sleep apneas can be differentiated from OSA by a lack of respiratory effort identified on chest and abdominal recordings. Similar to differentiation between obstructive and non-obstructive hypoventilation, obstructive events may be misidentified as central events in children with neuromuscular disorders. Children with sufficiently weak inspiratory muscles may have difficulty moving the abdomen and chest wall against an obstructed airway. Other events mislabeled as obstructive or central apneas, known as “pseudocentral events,” can be observed during phasic REM and are related to atonic intercostal muscles with increased load on a weakened diaphragm rather than airway obstruction or lack of neural impulse [53]. Esophageal manometry can further assist in detecting respiratory effort in these patients [54] but is not routinely measured during polysomnography.

Sleep-related epilepsy masquerading as OSA is another disorder where proper identification will guide treatment. Some degree of suspicion is needed as the limited EEG of polysomnography is not intended to identify and localize epileptiform activity. Thus, if a clinician has sufficient suspicion, a combination of full EEG and polysomnogram study should be performed. If this is unavailable, a bipolar EEG montage can be helpful. During the recordings, obstructive events occurring in conjunction with epileptiform activities can be identified. It is important to note that central apnea can also occur in conjunction with a seizure [55].

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Surgical Treatment of Pediatric Obstructive Sleep Apnea

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Abbreviations

AHI	Apnea hypopnea index
CPAP	Continuous positive airway pressure
CT	Computed tomography
DEX	Dexmedetomidine
DISE	Drug-induced sleep endoscopy
GA	Genioglossus advancement
HNS	Hypoglossal nerve stimulator
HS	Hyoid suspension
IV	Intravenous
MRI	Magnetic resonance imaging
OSA	Obstructive sleep apnea
PSG	Polysomnogram
T&A	Adenotonsillectomy
TBS	Tongue base suspension

Introduction

Adenotonsillectomy (T&A) is typically recommended as the first-line treatment for children with obstructive sleep apnea (OSA), and this procedure is performed 289,000 times annually in children younger than 15 years of age in the United States [1]. Nevertheless, nearly one third of children with OSA suffer from persistent disease after T&A [2]. This chapter describes the evaluation, surgical options, and perioperative management of children with primary and persistent OSA after T&A.

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Adenotonsillectomy

T&A is recommended as first-line treatment for pediatric OSA by the American Academy of Sleep Medicine, the American Academy of Pediatrics, and the American Academy of Otolaryngology-Head and Neck Surgery [1, 3, 4]. This procedure is most commonly performed using monopolar electrocautery; however, many other devices are also employed in an effort to minimize damage to surrounding tissues, bleeding risk, and postoperative pain [5–8]. In addition to the number of instruments that has been utilized for tonsil removal, multiple techniques exist for removal.

Tonsillectomy involves complete removal of the tonsil, including the underlying capsule. This technique has been the gold standard for many years. Partial intracapsular tonsillotomy, also referred to as tonsillotomy, involves the removal of tonsillar tissue while leaving the capsule of the tonsil in place. The rationale for tonsillotomy is that the capsule provides a "biological dressing" for the underlying pharyngeal muscle, thereby reducing pain and providing protection to the underlying vessels [9]. Two meta-analyses of tonsillotomy [10, 11] have shown a reduction in postoperative pain by 2.6 days and a 79% decrease in the odds ratio for secondary bleeding when compared to tonsillectomy. Although tonsillotomy is associated with lower pain and bleeding rates compared to tonsillectomy, there is a risk that residual lymphoid tissue may reproliferate. One meta-analysis comparing tonsillotomy to tonsillectomy for children with OSA determined that tonsillotomy increased the risk of residual or recurrent OSA symptoms 3.33 times (95% confidence interval 1.62–6.82, $P = 0.001$) [12]. Nevertheless, given that polysomnography outcomes comparing tonsillotomy and tonsillectomy are lacking, tonsillotomy is not yet recommended for the primary treatment of pediatric OSA [13].

The risks of T&A have been well described. According to a meta-analysis of 23 studies, respiratory compromise is the most common complication which includes pulmonary edema, aspiration, laryngospasm, airway obstruction, hypoxia, and hypercapnia [14, 15]. The risk of respiratory

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compromise is even higher in children younger than 3 years of age as well as in those with obesity, severe OSA, severe oxyhemoglobin desaturations, neuromuscular disease, Down syndrome, and craniofacial disorders [15–17]. Intraoperative complications include damage to the surrounding structures of the oral cavity and oropharynx as well as the rarer anesthesia-related complications such as difficult intubation, endotracheal tube fire, and cardiac arrest [14]. In addition, prolonged throat or ear pain and dehydration may also occur after surgery. Bleeding is the most studied complication and may occur up to 2 weeks postoperatively, with rates ranging from 0.1% to 3% [14, 15, 17, 18]. Although patients may develop nasopharyngeal stenosis or velopharyngeal insufficiency, these complications are extremely rare [14, 15].

According to the results of the 2013 landmark randomized controlled Childhood Adenotonsillectomy Trial (CHAT) [19], as well as multiple systematic reviews and meta-analyses [15–23], T&A results in significant improvement in OSA severity for the majority of children [2, 20–27]. All analyses report that T&A improves the apnea hypopnea index (AHI), behavior, and quality of life when compared to watchful waiting or continuous positive airway pressure (CPAP). One pooled fixed effect meta-analysis of 472 children in 3 studies (median AHI 4.8, 14.4, and 10.0 events/hour) showed a decrease in the AHI by 4.8 events/hour [22]. A second meta-analysis included 21 studies (n = 1046) which estimated that the resolution of OSA (defined as an AHI <1 event/hour) after T&A was 59.8% using a random effect model [2]. Obesity, age >7 years, black race, and the presence of genetic and metabolic syndromes (especially those associated with craniofacial and neuromuscular disorders) decrease the resolution rate of T&A to below 50% [2, 22]. In view of these findings, it is suggested that children with these risk factors undergo a postoperative polysomnogram (PSG).

Preoperative Evaluation in Children with Persistent OSA

For children with persistent OSA after T&A, CPAP is typically considered for treatment. For those who fail CPAP or prefer a surgical option [3], clinicians are focused on identifying the specific site(s) of obstruction in these patients. Office flexible endoscopy is helpful in identifying nasal obstruction, adenoid regrowth, lingual tonsil hypertrophy, tongue base position, and congenital laryngomalacia; however, because it is performed with the child awake, it requires some degree of cooperation and may miss dynamic obstruction that occurs only during sleep [28, 29]. A lateral plain film of the nasopharynx is a fast and painless alternative to endoscopy; however, small deviations of the head and palate position at the time of the X-ray can result in an overestimation or underestimation of adenoid size. Videofluoroscopy has been employed to capture anatomic information; however, this modality is rarely used due to the relatively high radiation dose [30].

Drug-Induced Sleep Endoscopy

Drug-induced sleep endoscopy (DISE) was first described in 1991 as a technique to evaluate the upper airway while the patient was in an anesthetized state intended to simulate sleep [31]. Presently, DISE is widely used to aid in surgical decision-making for children with persistent OSA [32]. In addition, it is sometimes employed prior to T&A for children with OSA who have not undergone previous surgery but are at high risk for persistent OSA (e.g., those with obesity, severe OSA, craniofacial anomalies, hypotonia, and neuromuscular impairment) [24, 33, 34]. The rationale for this is that it allows for identification of additional sites of obstruction that could be addressed concurrently or in a staged fashion. Other authors maintain that because airway dynamics can be significantly altered after surgery, DISE performed before T&A is not useful to plan for subsequent procedures [35].

DISE may also be considered in children who have small tonsils in order to identify alternative sites of obstruction that should be addressed concurrently or instead of T&A [36]. Finally, DISE is required for patients being considered for treatment with the Inspire® hypoglossal nerve stimulator (HNS) in order to evaluate the degree and pattern of velopharyngeal collapse. According to current US Food and Drug Administration guidelines, patients with complete concentric velopharyngeal collapse do not meet the established criteria for HNS implantation. Although HNS is not yet approved for children, clinical trials are underway in children with Down syndrome, 10 years of age or older, and preliminary results are promising [37].

DISE is commonly performed in the operating room with an anesthesiologist present for cardiopulmonary monitoring and sedation. During the procedure, some surgeons may place children into their preferred sleeping position to observe the effect of position on airway collapse. A jaw thrust and manual tongue protrusion can also be performed to approximate the effect on the airway by a dental appliance or tongue reduction procedures. Performing these maneuvers while visualizing the palate can also help the surgeon determine the effect of the tongue on palate obstruction.

Several scoring systems for DISE have been developed to aid in communication, uniform reporting, and the ability to compare outcomes within and between studies. The first six scoring systems seek to objectively determine the level and degree of obstruction at different sites in the upper airway [29, 38–42]. Table 37.1 summarizes the scoring systems that have been evaluated in children [39]. In general, all of these scoring systems evaluate the airway at the nasopharynx, pal-

Table 37.1 Summary of scoring systems used in pediatric drug-induced sleep endoscopy

	VOTE (2011) [40]	Bachar (2012) [41]	Fishman (2013) [29]	Boudewyns (2014) [39]	Chan (2014) [42]	SERS (2016) [38]
Nasal cavity	–	0: no obstruction 1: partial obstruction 2: complete obstruction	0: none 1: mild 2: moderate 3: severe obstruction	–	–	0: IT obstruction <90% 1: IT obstruction >90% (1 or both sides) 2: no visible patency at IT
Adenoid/ nasopharynx	–		0: none 1: mild 2: moderate 3: severe obstruction	0: no hypertrophy 1: <50% obstruction 2: 50–75% obstruction 3: >75% obstruction	0 1: 1–50% obstruction 2: 51–99% obstruction 3: complete obstruction	0: adenoids do not extend past ET 1: adenoids partially obstructing 2: complete obstruction
Palate/velum	0: no obstruction 1: partial obstruction/ palate flutter 2: complete obstruction Describe patterns as AP/lateral/ concentric	0: no obstruction 1: partial obstruction/ palate flutter 2: complete obstruction *Includes contribution from tonsils	–	0: no collapse 1: dynamic collapse	0: no obstruction 1: 1–50% obstruction 2: 50–99% obstruction 3: complete obstruction	0: <50% obstruction 1: >50% but incomplete obstruction 2: ≤1 mm or complete obstruction
Oropharynx/ lateral pharyngeal walls/tonsils	0: no obstruction 1: partial obstruction 2: complete obstruction Describe patterns as AP/lateral		0: none 1: mild 2: moderate 3: severe obstruction	0: absent 1: <50% obstruction 2: 50–90% obstruction 3: tonsils touch	0: no obstruction 1: 1–50% obstruction 2: 50–99% obstruction 3: complete obstruction *Includes contribution from tonsil	0: <50% obstruction 1: 50% but incomplete obstruction 2: ≤1 mm or complete obstruction
Tongue base/ hypopharynx	0: no obstruction 1: partial obstruction 2: complete obstruction	0: no obstruction 1: partial obstruction 2: complete obstruction	0: none 1: mild 2: moderate 3: severe obstruction	0: no obstruction 1: partial obstruction 2: complete obstruction	0: no obstruction 1: 1–50% obstruction 2: 50–99% obstruction 3: complete obstruction *Includes contribution from the epiglottis	0: able to see arytenoids 1: unable to see arytenoids 2: complete epiglottic effacement against posterior pharyngeal wall
Hypopharynx	–	0: no obstruction 1: partial obstruction 2: complete obstruction	–	0: no obstruction 1: partial obstruction 2: complete obstruction	–	–
Larynx	–	0: no obstruction 1: partial obstruction 2: complete obstruction	–	0: no obstruction 1: partial obstruction 2: complete obstruction	–	0: arytenoid prolapse causing <50% obstruction of the TVCs 1: prolapse causing >50% obstruction 2: prolapse causing ≤1 mm or complete obstruction
Supraglottis	–	–	0: none 1: mild 2: moderate 3: severe obstruction	–	0: no obstruction 1: 1–50% obstruction 2: 50–99% obstruction 3: complete obstruction *Scored during jaw thrust to resolve any tongue base obstruction	–

(continued)

Table 37.1 (continued)

	VOTE (2011) [40]	Bachar (2012) [41]	Fishman (2013) [29]	Boudewyns (2014) [39]	Chan (2014) [42]	SERS (2016) [38]
Epiglottis	0: no obstruction 1: partial obstruction 2: complete obstruction Describe patterns as AP/lateral	–	–	0: no obstruction 1: dynamic collapse	–	–
Hypotonia	–	–	–	0: absent 1: present	–	–
Laryngomalacia	–	–	–	0: none 1: present	–	–
Min-max value	0–8	0–10	0–15	0–12	0–15	0–12

SERS sleep endoscopy rating system, *IT* inferior turbinates, *ET* eustachian tube orifice, *TVCs* true vocal cords

ate/velum, oropharynx, tongue base, supraglottis, and glottis; however, the description of the level varies between systems, and the number of levels evaluated varies from 4 to 6. The trachea and main stem bronchi may also be evaluated concurrently if there is concern for tracheomalacia or bronchomalacia. Recently, Tejan et al. used videos taken during 68 separate DISE procedures to compare these scoring systems and to attempt to correlate the scores to OSA severity, age, obesity status, and oxyhemoglobin nadir [43]. These authors found no significant difference in scores between the scoring systems and no correlation between any of the scores and OSA severity, age, obesity, or oxyhemoglobin nadir. Although a universal scoring system will likely be adopted in the future, current best practice is to utilize one uniform system within an institution.

Many anesthetic protocols have been used to perform DISE. Because of the known respiratory suppression of inhaled anesthetics and opioids (especially in patients with OSA), these drugs are generally avoided during DISE. Propofol has a fast onset of action and rapid drug clearance and is commonly administered in adults and titrated with bispectral index monitoring [44]. It is known to have a dose-dependent effect on airway collapsibility and decreased genioglossus neuromuscular tone [44]. In children with severe OSA, one study found that using propofol administered during cine magnetic resonance imaging (MRI) resulted in the need for an oral airway more often than when dexmedetomidine (DEX) was administered. In a comparison of propofol and DEX during DISE in adults, collapse patterns were similar; however, there were more severe collapse and oxyhemoglobin desaturation using propofol [45]. This decreased respiratory suppression makes DEX a more desirable agent for this procedure for many pediatric otolaryngologists [46], who often pair it with ketamine for its amnestic properties and minimal effect on respiration. Drawbacks of DEX as compared to propofol include its longer onset of action and slower drug clearance, adding time to both procedure and post-anesthesia recovery and its increased cost [47].

Cine MRI

Both computed tomography (CT) and MRI have been used to image OSA patients both awake and asleep in order to assess their degree of airway narrowing and obstruction. Dynamic images can now be created with both modalities as sequential images are stacked at multiple slices per second to provide a "movie" or cine sequence that be gated to respiration and can be viewed in three dimensions (axial, coronal, sagittal) and reformatted together for a 4D view.

MRI avoids ionizing radiation and the need for contrast that is required with CT and provides superior soft tissue resolution. Cine MRI was first described in 1992 [48] in awake patients with known OSA. Since that time, its use has expanded to patients anesthetized to approximate sleep with sedation protocols similar to those discussed above. This modality allows visualization of the airway in its entirety, thereby enabling the surgeon to identify primary and secondary sites of obstruction such as a large tongue occluding the airway while causing palatal elevation and obstruction. Additionally, lingual tonsil size and morphology are easily quantifiable, enabling the surgeon to distinguish between macroglossia and lingual hypertrophy [49]. Cine MRI can also allow the surgeon to visualize the movement of the tongue during sedation in order to distinguish dynamic glossoptosis (i.e., abnormal posterior motion of the tongue) from macroglossia (i.e., a large tongue encroaching on the airway, thus causing more static collapse) [50]. Although cine MRI has been used in large academic institutions, its widespread use is likely limited by time constraints on the use of MRI scanners, cost, the expertise of the radiologist and technician who carry out the protocol, and the need for ancillary staff (including an anesthesia provider) to monitor the patient. Figure 37.1 is an example of a sagittal image taken during cine MRI to evaluate for obstruction. The colors indicate the anatomic areas that may be obstructive, and the text below summarizes the surgeries that address the obstruction.

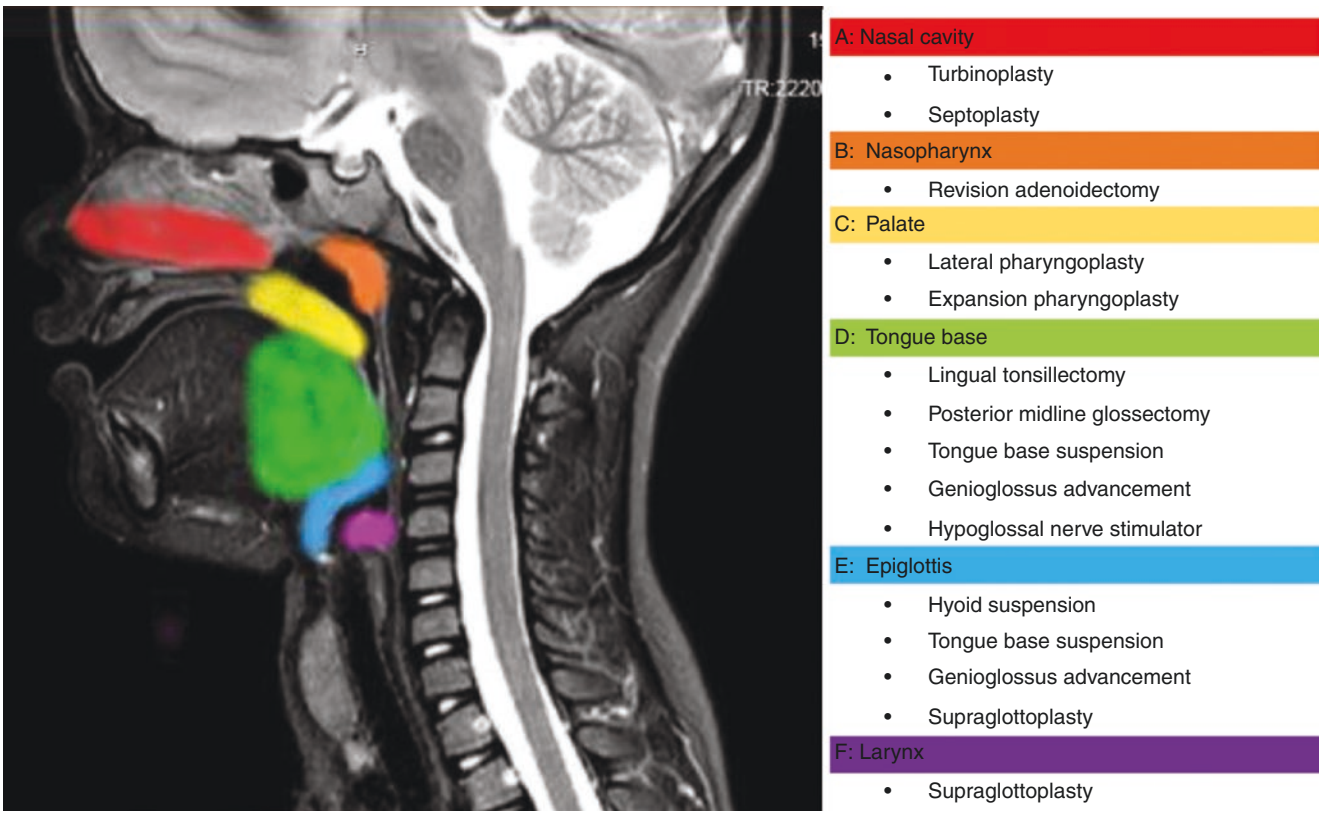

Fig. 37.1 Sagittal T2-weighted MRI of the upper airway with colors indicating the possible anatomic areas of obstruction that may be surgically addressed for obstructive sleep apnea

Nasal and Nasopharyngeal Surgery

Nasal breathing stimulates barometric reflexes that maintain airway patency during inspiration [51]. Mouth breathing due to nasal obstruction leads to an increase in airway resistance and reduces the size of the upper airway by retrodisplacing the tongue and soft palate [52]. In addition, chronic nasal obstruction has been shown to affect normal facial growth and to contribute to the development of OSA by reducing the vertical height of the mandible [53–57]. Although literature that supports addressing nasal obstruction in children with OSA is sparse, a meta-analysis of adult patients reported that nasal surgery can reduce the AHI by 11 events/hour [58]. Nasal surgery has also been shown to reduce CPAP pressures [59], potentially improving compliance.

Historically septoplasty has been avoided in children due to concerns about its effects on nasal growth based on animal studies. More recent literature has, however, shown that a limited septoplasty that spares all unobstructing cartilage and the bony septum can be safely performed, especially in children older than age 6 [60].

Turbinoplasty is a commonly performed procedure to improve nasal breathing in children with turbinate hypertrophy and signs of nasal airway obstruction. The goal of the procedure is to prevent turbinate swelling that can occur in response to supine positioning or allergic inflammation. It is generally considered a mucosal-sparing surgery in which an incision is made at the head of the turbinate and a volumetric reduction of the submucosal erectile tissue is performed to stimulate scarring. Reduction can be performed with a microdebrider, bipolar cautery, radiofrequency ablation, or turbinate wand or needle; no technique has been shown to be clearly superior [61]. An outfracture of the concha bone can also be performed to maximize airflow through the inferior nasal cavity. Although no studies have evaluated the efficacy of turbinoplasty alone on pediatric OSA, one study showed that T&A in combination with turbinoplasty resulted in a higher rate of OSA resolution compared to T&A alone in children with allergic rhinitis and nasal obstruction [62]. Turbinates are also frequently identified as a site of obstruction during DISE [63, 64]. The major risk of turbinoplasty is bleeding. Nasal crusting and rhinorrhea are expected for several weeks after surgery; less common complications include prolonged crusting secondary to infection or focal necrosis.

Though rare, scarring may lead to synechiae between the turbinate and septum. Finally, it is not uncommon for turbinate hypertrophy to recur 1–3 years after the procedure with a rate of 7.5% reported [61].

Adenoid regrowth is another cause of nasal obstruction. Revision adenoidectomy is commonly performed to address persistent pediatric OSA, although there is no data reporting the success rate of revision adenoidectomy alone. Retrospective assessment of adenoidectomy revision rates for any indication ranges from 0.5% to 2.5% [65–68]. Revision adenoidectomy is associated with age less than 5 years at the time of initial surgery, large adenoids, and extraesophageal reflux, although surgical technique was not [66, 69]. In two retrospective reviews of DISE-directed surgery to address persistent OSA, an adenoidectomy was performed in 42–57% of cases [63, 64, 70]. The risks of revision adenoidectomy are similar to those of primary adenoidectomy.

Oropharyngeal Surgery

Uvulopalatopharyngoplasty (UPPP), which involves removal of the excessive tissue of the lower soft palate and uvula, was first described by Fujita in 1981 as a treatment for OSA in adults [71]. However, complications such as velopharyngeal insufficiency (VPI), voice changes, globus, and airway stenosis have been shown to occur in up to 58% of patients [72]. Consequently, the traditional UPPP has undergone several modifications. Multiple techniques have been described which share the goal of expanding the airway while minimizing tissue excision.

The term lateral pharyngoplasty refers to suturing the palatopharyngeus (posterior tonsillar pillar) to the palatoglossus (anterior tonsillar pillar). Several studies have been carried out, but none have shown improvement in the postoperative AHI when performing this procedure concurrent with T&A compared to T&A alone [73–75].

Expansion pharyngoplasty was first described by Pang and Woodson to treat adults with OSA, small tonsils, and collapse of the palate and pharyngeal walls [76]. In contrast to traditional UPPP, this procedure involves transection and repositioning of the palatopharyngeus to a more superior/anterior position within the lateral soft palate, thereby reducing the bulk of the lateral pharyngeal wall and allowing the palatopharyngeus muscle to open the airway. Soft tissue is removed only when there is redundant mucosa elongating the uvula. In a 2014 retrospective review, 25 children with lateral pharyngeal collapse on DISE underwent T&A and expansion pharyngoplasty [77]. Demographics and preoperative and postoperative PSG results were compared to those of 25 children who underwent T&A alone. Although the pharyngoplasty group was older and had a higher body mass index, the median postoperative AHI was significantly lower in the pharyngoplasty group (2.0 vs. 6.2 events/hour), which also had a significantly higher cure rate (AHI <1; 64% vs. 8%). Neither VPI nor voice changes were noted in either group. In summary, newer techniques minimize the risks associated with the UPPP as described by Fujita; nevertheless, larger prospective studies are needed to verify the indications and outcome of pharyngoplasty in children.

Surgery to Address Tongue Base Collapse

Tongue base collapse can be secondary to macroglossia, glossoptosis, lingual tonsil hypertrophy, retrognathia, hypotonia, or a combination of these factors. The goal of tongue base surgery is to increase the retrolingual airway space either by volumetric reduction of the tongue base or by repositioning the hyoid or mandible to advance the tongue musculature. With the exception of lingual tonsillectomy, investigations of the techniques, risks, and outcomes of these procedures are more widely reported in the adult literature.

Tongue Base Reduction

Lingual tonsil hypertrophy is a frequent cause of persistent OSA and is most frequently reported in children with Down syndrome and/or obesity [50, 78, 79]. Lingual tonsillectomy involves removal of the lingual tonsil lymphoid tissue from the base of the tongue. Similar to T&A, this procedure can be performed using a variety of instruments. Two small meta-analyses [80, 81] that reviewed a total of 6 studies (n = 233 children) showed success rates of 51–52% to obtain an AHI <5 events/hour and 12.5–17% to obtain an AHI <1 event/hour, respectively. The small number of patients in these studies precludes the determination of a precise complication rate; however, tongue edema causing airway obstruction, intraoperative and postoperative bleeding, and pneumonia were encountered. The largest single institution study [82] reported an overall complication rate of 9.8%; complications included bleeding, dysphagia, decreased oral intake, and voice changes. Two of 92 patients (2.2%) required return to the operating room for hemorrhage control.

Posterior midline glossectomy is performed via posterior wedge resection or by submucosal volumetric reduction. Reporting of wedge resection outcomes in children is limited to 1 retrospective study of 16 patients (mean age of 14.2 years) in which the surgery was combined with a lingual tonsillectomy in some cases [83]. These authors reported a significant improvement in the AHI (from a mean of 47 to 5.6 events/hour) was found in children with a normal BMI. The improvement in AHI, however, decreased with

increasing BMI, and no postoperative improvement was found in obese patients. Lingual tonsillectomy results in significant postoperative pain similar to that seen after T&A. A meta-analysis in the adult literature [84] reported that the most common complications were bleeding (4.2%) and transient change in taste (5.85%), which sometimes persisted for 2 months after surgery. Oropharyngeal stenosis, a morbid and difficult to treat complication, occurred in fewer than 1% of cases.

The SMILE technique (submucosal minimally invasive lingual excision) was developed to minimize the morbidity of wedge resection [85]. The surgery begins with a small incision in the tongue. The tissue is then submucosally removed using a coblator; ultrasound and endoscopy are often used to aid visualization. The incision is left open to avoid hematoma or seroma formation in the remaining cavity. This technique was first used in children with persistent OSA, and changes in the AHI were reported for only two children.

Tongue Repositioning Procedures

Tongue base suspension (TBS) is a minimally invasive technique that loops a permanent suture through the tongue to form a sling that is suspended from a titanium screw inserted into the inner table of the mandible. This sling advances the genioglossus forward and prevents glossoptosis during sleep. One retrospective study of 31 children who underwent TBS along with adjunctive procedures for persistent OSA reported that 16 (52%) children had an AHI <5 following surgery [86]. Complications attributed to TBS were two seromas at the surgical site. Although dysphagia was also noted, the number of patients affected was not reported. A more recent study of children with cerebral palsy and OSA reported polysomnographic outcomes for seven patients who underwent TBS with UPPP and T&A [87]. Five (71%) of these patients exhibited an AHI <5 events/hour following surgery. There were no complications reported in this study. While it is difficult to determine the effect of TBS alone on persistent OSA, one meta-analysis in the adult literature [88] reported that average success is 48.7% (success for adults defined as a reduction in the AHI >50% and postoperative AHI <20). The complication rate ranged from 10% to 30.8% with postoperative pain, delayed wound infection, and transient dysphagia being the most common.

Hyoid suspension (HS) is a procedure performed to rotate the epiglottis forward and to prevent glossoptosis during sleep by advancing and stabilizing the hyoglossus, genioglossus, and geniohyoid muscles. The hyoid bone may be advanced to the mandible using a suture looped to a screw on the inner table of the mandible (similar to TBS). Alternatively, it may be brought forward and secured to the thyroid lamina [89]. In adults, this procedure has a success rate of 38.3–50.7%, depending on the suspension technique [90]. There are no reports analyzing the surgical outcomes of this technique in children, although the senior author (SLI) uses this procedure for children 6 years of age and older.

Genioglossus advancement (GA) was first described by Riley et al. in 1984 [91]. The procedure involves creating a rectangular osteotomy at the midline of the mandible. This rectangle of the bone includes the bulk of the origin of the genioglossus muscle. The rectangle is then advanced forward, turned 90 degrees, and screwed or plated in place to permanently advance the origin of the genioglossus. The outer table of the bone can be removed to avoid cosmetic defect. Similarly, the sliding genioplasty can be used for patients with permanent teeth with the lower portion of the mandible (including the genioglossal tubercle) pulled forward and plated into position. These procedures are rarely performed in children due to growth concerns of the mandible and damage to growing teeth. Complications include the floor of mouth hematoma, chin numbness, and rarely mandible fracture.

The hypoglossal nerve stimulator (HNS) is an implanted device that sends electrical stimulation to the hypoglossal nerve during sleep, causing tongue protrusion and relief of retrolingual airway collapse. The Inspire® HNS was approved in the United States in 2014 for use in adults 22 years of age and older with moderate to severe OSA. A relative indication for the implant was a BMI less than 32 kg/m^2. As discussed earlier, HNS is not recommended for patients with complete concentric collapse at the palate; thus, DISE is required prior to determining if a patient is a candidate. Additionally, it is not recommended for use in patients whose central apnea index is greater than 25% of the total AHI or those whose AHI is greater than 65 events/hour. Although this device is not currently approved for use in children, a prospective trial is underway to evaluate the efficacy of HNS on adolescents with Down syndrome who have been diagnosed with OSA. The initial outcomes of the first 20 patients (median age of 16.0 years) have been reported and showed a 75–92% reduction in the AHI with HNS and median nightly use of 9.21 hours/night [37]. These are promising results in a population of children with a high incidence of persistent OSA.

Supraglottoplasty

Laryngomalacia is a condition that causes intermittent obstruction of the larynx by supraglottic structures. Although it is more commonly diagnosed in awake infants by flexible endoscopy, it has also been identified in older children with OSA who have no daytime symptoms but have supraglottic collapse during DISE [79]. This type of laryngomalacia has

been termed sleep-dependent, state-dependent, late-onset, or occult laryngomalacia and is an indication for supraglottoplasty. Supraglottoplasty may include excision of redundant arytenoid tissue, incision of tight aryepiglottic folds, or pexy of the epiglottis to the tongue base based on the findings seen during DISE. Complications are rare and include recurrent or residual laryngomalacia, failure to extubate (requiring subsequent tracheostomy in some cases), aspiration, supraglottic granuloma and stenosis, and abscess.

Lee et al. analyzed PSG changes after supraglottoplasty in infants who underwent this procedure as the primary surgery for OSA and in older children who underwent the procedure for persistent OSA. These authors found a significant improvement in the AHI for both groups (primary change, −9.5 events/hour; 95% CI −14.8 to −4.3; change in persistent OSA, −7.1 events/hour; 95% CI, −10.9 to −3.3) [92]. A meta-analysis of supraglottoplasty in children with OSA reported that patients with neuromuscular disorders, cardiac disease, and laryngomalacia associated with complex medical comorbidities have a lower rate of success after supraglottoplasty [93].

Tracheostomy

Tracheostomy allows complete bypass of obstructive upper airway structures for the treatment of OSA. Although there are no guidelines regarding the indications for tracheostomy, it is generally considered a salvage treatment for children with severe OSA after other options have failed. It may, however, be considered a first-line treatment for infants with severe OSA and no identifiable site of obstruction, failure to thrive, or contraindications to other upper airway surgeries (especially those with neurologic impairment) [94]. In a meta-analysis of tracheostomy for pediatric OSA [94], all 196 patients from 11 studies (mean age, 4.2 years; range, newborn to 18 years) were found to have severe OSA and had either a congenital syndrome (in particular, syndromes that affect facial growth) or significant comorbidities, most commonly, neuromuscular disorders. Tracheostomy was successful in treating OSA in all cases that reported PSG results in this meta-analysis. This procedure is life-altering for both the child and family and is associated with a complication rate ranging from 43% to 77% of cases. These complications include bleeding, granuloma formation, and tracheoesophageal fistula [93, 95]. Although death (most commonly after accidental decannulation) is rare (0.7–3%) [95, 96], this possibility should be discussed when considering tracheostomy for a disease that is not immediately life-threatening.

A review of 29 patients from 4 institutions [97] showed that most patients remained tracheostomy-dependent 2 years after tracheostomy. Of the six patients who were successfully decannulated, five underwent a capped PSG prior to decannulation. Although this practice is not universal, it should be considered as part of the clinical evaluation to determine if decannulation can be safely attempted [98–100].

Perioperative Considerations in Pediatric OSA

OSA is associated with an increased risk for perioperative complications. The American Academy of Otolaryngology-Head and Neck Surgery thus recommends detailed communication between the surgeon and the anesthesia team, ensuring that there is an understanding of OSA severity so to appropriately tailor anesthesia [1]. Given that patients with OSA have an increased sensitivity to opioids and inhaled anesthetics, these drugs should be carefully dosed to avoid over-sedation and airway obstruction [46, 101, 102]. Following extubation, children with OSA are at a higher risk of airway obstruction, laryngospasm, oxygen desaturations, pulmonary edema, and respiratory failure than are those without OSA [103]. All children with OSA should be monitored for a period of time after surgery until they are fully awake and oxygen saturations are stable [104]. Postoperative hospital admission should be considered for children younger than 3 years of age, those with severe OSA, and those with OSA and hypoventilation. It should also be considered for obese children and children with comorbid conditions, including cystic fibrosis, genetic syndromes, asthma, and cardiac disease [103, 105, 106]. Children should be given adequate pain control medications; however, opioids should be cautiously prescribed and avoided if necessary due to their known respiratory depressant effects. Additionally, codeine should be avoided in all children, especially those with OSA, as some children are considered ultrarapid metabolizers, which may result in fatal respiratory depression [107].

Conclusion

Although T&A is the primary surgical treatment for pediatric OSA, studies show a high rate of persistent OSA in children with severe OSA, black race, obesity, and genetic and metabolic syndromes. Therefore, a postoperative PSG should be considered for these children. Surgical treatment of persistent OSA can be effective; however, the choice of surgical procedure depends on accurate identification of the patient's site(s) of obstruction. This can be determined by physical exam and procedures such as cine CT, cine MRI, and DISE. Surgeries that may be considered include revision adenoidectomy, turbinoplasty, septoplasty, palatoplasty,

tongue base reduction and repositioning, hyoid suspension, hypoglossal nerve stimulator, and supraglottoplasty (Fig. 37.1). Tracheostomy is usually considered a salvage procedure except in rare cases. In view of the elevated risk of complications in children with OSA, the surgical team should be cognizant of the severity of OSA so the team can plan a safe perioperative course that will optimize the child's outcome.

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Obstructive Sleep Apnea: Treatment – Anti-inflammatory Therapy

38

Pablo E. Brockmann and Katalina Bertran Salinas

Introduction

Obstructive sleep apnea (OSA) is a form of sleep-disordered breathing that occurs in children of all ages. Its characteristics are prolonged increased upper airway resistance and respiratory effort, with partial or complete upper airway obstruction, and various combinations of snoring, intermittent hypoxemia, hypercarbia, restless sleep, and increased numbers of arousals from sleep [1]. Estimations concerning the prevalence of OSA show highly widespread ranges from 0.7% to 10.3% with a peak prevalence of childhood OSA between 2 and 8 years of age [2, 3]. On the other hand, there is an increasing recognition that repeated arousal, sleep fragmentation, and intermittent hypoxia caused by OSA are possible mechanisms involved in neurocognitive impairment in young children leading to significant neurocognitive [4] and cardiovascular consequences [5]. Therefore, treatment of OSA seems to be urgent in children, especially in those showing daytime symptoms like hyperactivity, somnolence, or poor school performance [6]. Surgical removal of enlarged tonsils and adenoids (i.e., adenotonsillectomy) is the most commonly used treatment for OSA [7]. However, adenotonsillectomy may be painful and has the potential risk of complications such as bleeding, postsurgical apneas, and adverse anesthetic reactions. On the other hand, after adenotonsillectomy, up to 20% of the operated children may still have some degree of residual OSA [8].

Considering that local inflammation is present in adenotonsillar tissue children with OSA, the use of systemic or topical anti-inflammatory agents seems to be an option for reversing adenotonsillar enlargement. Children with OSA have increased inflammatory molecules in their upper airways, and these inflammatory mediators may lead to pro-proliferative pathways that finally turn into adenotonsillar hypertrophy [9]. There is currently consistent data for supporting the use of nonsurgical anti-inflammatory approaches in children with OSA and other forms of sleep-disordered breathing. The aim of the present chapter is to summarize the existing evidence that support the use of anti-inflammatory medications in children with OSA.

Mechanisms of Action

As in other inflammatory airway diseases like asthma, anti-inflammatory medications, like nasal corticosteroids and oral montelukast, inhibit the recruitment of inflammatory cells into the airway and the development of inflammatory processes. This effect is produced by suppressing the production of several cytokines, chemotactic mediators, and adhesion molecules (Fig. 38.1). In addition, anti-inflammatory agents reduce the survival of inflammatory cells like eosinophils, lymphocytes, and mast cells. Nasal corticosteroids have a proven effect on reducing symptoms associated with allergic rhinitis. Nasal itching, sneezing, and even ocular symptoms may be reduced after the use of such medications.

The major intracellular mechanism action of corticosteroids is to deactivate multiple inflammatory genes that encode for several mediators like cytokines, chemokines, and adhesion molecules. Nasal corticosteroids decrease inflammation on nasal mucosa and reduce the recruitment of inflammatory cells like basophils, eosinophils, neutrophils, and mononuclear cells. Cytokine release is also inhibited using nasal corticosteroids.

Cysteinyl leukotriene receptor-1 expression is elevated in the tonsillar tissues of children with OSA. Tonsils of children with OSA displayed show cysteinyl leukotriene receptors in specific cells like T lymphocytes. This enhancement of

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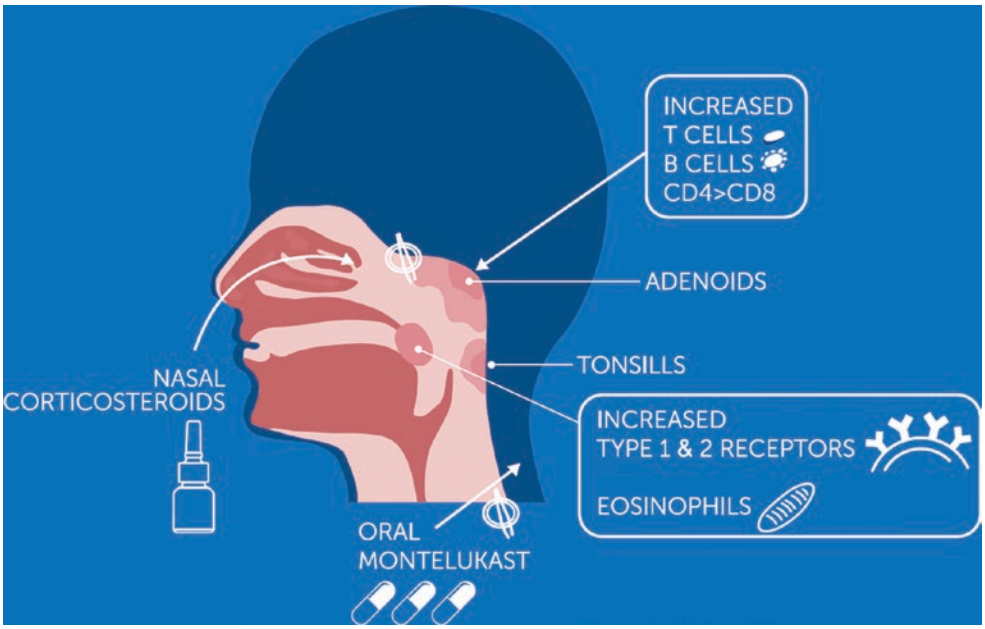

Fig. 38.1 Anti-inflammatory medications like nasal corticosteroids and oral montelukast inhibit the recruitment of inflammatory cells into the airway and the development of inflammatory processes. This effect is produced by suppressing the production of several cytokines, chemotactic mediators, and adhesion molecules. In addition, anti-inflammatory agents reduce the survival of inflammatory cells like eosinophils, lymphocytes, and mast cells

leukotriene receptors seems to be independent from systemic inflammation. Thus, overexpression of leukotriene receptor types 1 and 2 could potentially be involved in the enlargement of tonsils and adenoids in children with OSA by promoting the severity of the disease. An in vitro study has shown that addition of leukotriene D4 induces increased proliferative responses and release of proinflammatory cytokines in adenotonsillar tissue [10]. Furthermore, treatment with leukotriene antagonists seems to reduce cellular proliferation in a dose-dependent way [10].

Nasal Corticosteroids

The use of inhaled corticosteroids in inflammatory airway disorders is not novel, especially in asthma where its use has escalated. With that rationale in mind, it seems to be very reasonable to use corticosteroids in children with OSA, based on the abovementioned physiopathology. However, cumulative experience with such drugs in the treatment of pediatric OSA is limited.

After one initial study that failed to demonstrate benefits of the systemic corticosteroids' use on OSA [11, 12], Brouillette et al. launched the first randomized, triple-blind controlled trial in 2001, investigating the use of nasal fluticasone in children with OSA. They compared 6 weeks of treatment with nasal fluticasone versus placebo in 25 children with OSA. In that study, an important reduction of the apnea hypopnea index was seen in the fluticasone group: The AHI in the treatment group fell from 10.7/hour to 5.8/hour, while the apnea hypopnea index increased from 11.0/hour to 13.1/hour in the placebo group ($P = 0.04$) [12].

In adults, an effect on reducing snoring has already been demonstrated after the use of 1-week intranasal budesonide. In that study, patients showed a significant increase in REM sleep after that 1-week trial with nasal budesonide as compared with the nasal placebo [13].

In 2008, the use of intranasal budesonide for 6 weeks was proven in a randomized, double-blind controlled trial with a crossover design in a group of 62 children with polysomnographically diagnosed mild obstructive sleep apnea syndrome. That study showed a significant reduction in the apnea hypopnea index in children with mild OSA and the size of the underlying adenoidal hypertrophy. The effect persisted 8 weeks after discontinuing treatment [14]. The authors concluded the use of intranasal corticosteroids was therefore justified as an initial option in otherwise healthy children with mild OSA.

A long-term follow-up was conducted in one Italian study. Criscuoli et al. showed that on $n = 53$ children, there was a significant clinical improvement after 2 weeks of nasal corticosteroid therapy [15]. Initially, 45% of the children treated with nasal corticosteroids responded. Among these same responding children, an additional 24-week treatment showed a significant 52- and 100-week symptom reduction, compared with children (55%) who had not responded after the initial 2-week steroidal therapy. Nasal obstruction index was also assessed in that study. Children treated with nasal corticosteroids seem to have a higher reduction rate than those in the control group [15].

Most studies have so far included children with mild OSA. Cases with moderate to severe indices seem therefore not to be susceptible to a significant improvement using medications only.

Montelukast

Studies have identified the presence of cysteinyl leukotriene receptor-1 in tonsils and adenoid tissues in children with OSA. Therefore, the use of montelukast seemed promising in some patients with OSA. Several studies show significant improvement in the apnea hypopnea index, tonsil size, and even symptoms after the use of oral montelukast. In one of the first studies on this topic, Goldbart et al. performed a double-blind, placebo-controlled study showing that oral montelukast therapy improved nocturnal symptoms, reduced anatomical size of adenotonsillar tissues, and significantly reduced polysomnographic indices in $n = 46$ children with OSA [16]. That study used oral montelukast for a period of 12 weeks [17].

In another randomized controlled trial by Kheirandish-Gozal et al., polysomnographically diagnosed OSA in children ages 2–10 years, treated with either oral montelukast (4 or 5 mg daily) or placebo for 16 weeks, AHI decreased from 9.2 ± 4.1/hour total sleep time (TST) to 4.2 ± 2.8/hour TST ($P < 0.0001$) in montelukast-treated children, whereas in children receiving placebo the AHI did not change (from 8.2 ± 5.0/hour TST before to 8.7 ± 4.9/hour TST at completion of the trial) [17].

A recent systematic review on the efficacy of montelukast for OSA included six studies (in $n = 668$ children), five of these studies showing significant improvements in apnea hypopnea index and lowest saturation [18]. According to that review, in using oral montelukast alone ($n = 166$ patients), there was a mean reduction of 56% in the apnea hypopnea index (6.2 ± 3.1 events/hours versus 2.7 ± 2.7 events/hours after treating) [18]. Table 38.1 shows a non-exhaustive list of studies on anti-inflammatory medications in children.

Comparison of Treatment Efficacy: Nasal Corticosteroids Versus Montelukast

One study addressed the question concerning the better efficacy of therapies. After a trial of 12 weeks, using either inhaled corticosteroids or oral montelukast, there were similar reduction rates in children with mild OSA, the improvement rate being 62.4% and 63.1%, respectively [19]. There was no significant difference in improvement between the abovementioned treatments. Based on those results, both therapies seemed quite similar in terms of efficacy. In this systematic review, the use of oral montelukast and nasal corticosteroids showed a mean 70% improvement in the apnea hypopnea index (4.8 ± 2.1 events/hours to 1.4 ± 0.4 events/hours after the use of the medications) [18].

Table 38.1 Non-exhaustive summary of selected studies on montelukast and/or nasal corticosteroids (NCS)

Study	Design	Patients N (age)	PSG	Treatment	Dose	Duration	Control
Tuhaniouglu 2017	RCT	120 (4–10 years)		Mometasone Montelukast Both None	100 µg 4/5 mg	12 weeks	NCS
Barghawa 2014	RCT	100 (2–12 years)		Mometasone	200 µg	8 weeks	NCS
Barghawa 2014	RCT	60 (2–12 years)		Mometasone	200 µg	8 weeks	NCS
Kheirandish-Gozal 2014	Retrospective	752 (2–14)	Mild OSA	Montelukast and NCS	Variable	12 weeks	--
Cengel 2006	RCT	122 (3–15 years)		Mometasone	100 µg	6 weeks	NCS
Hassan 2014	RCT	65 (5–14 years)		Mometasone	100 µg	12 weeks	NCS
Hassanzadel 2013	RCT	40 (4–12 years)		Mometasone	400 µg	4 weeks	NCS
Rehman 2013	RCT	112 (3–8 years)		Mometasone	NR	8 weeks	NCS
Goldbart 2009	RCT	(2–10 years)	AHI 1–8/hour	Montelukast	4/5 mg	12 weeks	Placebo
Kheirandish-Gozal 2008	RCT, crossover	62 (6–12 years)	Mild OSA	Budesonide	32 µg × nostril	6 weeks, washout, 6 weeks	Placebo
Berlucchi 2007	RCT	60 (3–7 years)		Mometasone	100 µg	40 weeks	NCS
Yilmaz 2003	RCT	28 (12–18 years)		Mometasone	200 µg	6 weeks	NCS
Criscuoli 2003	RCT	53 (3.8 ± 1.3)		Beclomethasone	400 µg	2 weeks, 24 weeks	Placebo
Brouillete 2001	RCT	25 (1–10 years)	AHI >1/hour	Fluticasone	50 µg c/12 hours 1 week 50 mcg/24 hours 5 weeks	6 weeks	Placebo

Combination Therapy of Nasal Corticosteroids and Montelukast

The rationale for using montelukast and nasal corticosteroids in a combined therapy emerged after the success for reducing OSA after trials with each of these therapies. In a large retrospective study on $n = 752$ children with mild OSA by Kheirandish-Gozal et al., subjects received the combination of inhaled corticosteroids and oral montelukast. Overall, beneficial effects were seen in around 80% of the children. In those children, the apnea hypopnea index was reduced from 4.5 ± 2.0 to 1.4 ± 0.0.9 [20].

In the study by Yang et al., the combined used of nasal corticosteroids and oral montelukast showed a higher efficacy than each one separately: 73.7% versus 62.4% and 63.1%, respectively [19]. This is in line with another study by Bluher et al., who also found a significant impact of the use of fluticasone and montelukast on the quality of life in children with mild OSA [21].

Side Effects

Nasal corticosteroids and oral montelukast are FDA-approved for use in children, but nevertheless, side effects with the use of any medications exist and must be acknowledged. However, the frequency of such side effects seems to be extremely infrequent according to existing literature. In the study by Kheirandish-Gozal et al., which is – to our knowledge – the largest study on anti-inflammatory medications so far conducted, only 6 patients (0.7%) out of 752 enrolled subjects reported side effects that prompted them to discontinue the use of medications [20]. These side effects were headaches, nausea, vomiting, and epistaxis [20]. Other studies have not reported any side effects, and the recent systematic review informed only three minor adverse reactions in all included and reviewed studies (0.59% rate).

In comparison to the complication rate of adenotonsillectomy, these side effects seem to be very infrequent.

Anti-inflammatory Medications After Adenotonsillectomy

Nasal corticosteroids and montelukast have so far often been used as an alternative for surgical treatment. Much less has been published concerning the use of such anti-inflammatory medications after surgery, i.e., adenotonsillectomy. Considering that symptoms may persist even after adenotonsillectomy and abnormal polysomnographic-based indices may persist, the use of anti-inflammatory medications could be promising. However, their postoperative use is not common. Among the sparse literature on this topic, one study analyzed adenoid regrowth after adenotonsillectomy in $n = 35$ children using inhaled nasal mometasone and compared it with control using nasal fluid spray [22]. In that study, fiber-optic nasal endoscopy showed a significant reduction in adenoid tissue in the treatment arm. Also, the use of nasal corticosteroids showed a reduction in symptom scores following adenoidectomy.

Identification of Patients Susceptible for Medical Treatment

*M*ost studies have been conducted in children with mild OSA. The use of anti-inflammatory medications in moderate and severe forms of the disease seems not to be recommended so far. Notwithstanding the consistent evidence of the use of anti-inflammatory medications in children with mild OSA, there is still a need to develop tools that may predict which patient is susceptible for such treatment and who is not.

One study addressed the question of anti-inflammatory treatment success or failure. In the study conducted by Kheirandish-Gozal et al., two easily identifiable patient characteristics were detected. The presence of obesity and an age >7 years were negatively associated with a favorable response to nasal corticosteroids and oral montelukast therapy [20].

Another factor to consider is the detection of patients in whom an adenotonsillectomy can be eventually avoided with the use of anti-inflammatory medications. To our knowledge, no studies have analyzed the financial impact of the use of nasal corticosteroids considering that some adenotonsillectomies may be reduced by using them. In the study by Brouillette et al., a lower percentage of children undergoing adenotonsillectomy was reported in the groups of children who received nasal corticosteroids [12].

Conclusions

Nasal corticosteroids and oral montelukast seem to be a promising option for treatment of adenotonsillar hypertrophy and OSA in children. Despite the growing volume of studies on the topic, current literature leaves gaps in our knowledge regarding the role of medical treatment in pediatric OSA.

Identification of the ideal patient susceptible for treatment with anti-inflammatory medications is not completely defined. So far, only children with mild OSA seem to be responders. Obesity and older age apparently are factors associated with a higher failure rate of medical treatment. On the other hand, the length of treatment in all studies so far

ranges from 6 to 16 weeks. The optimal length of treatment is still unknown. Also, it is not completely understood if there is an after-treatment effect. Future well-designed, prospective studies are needed to unveil these answers.

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Pediatric Obstructive Sleep Apnea: Orthodontic Management

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The management of pediatric obstructive sleep apnea (POSA) is complex and still not fully agreed upon. Due to the likely involvement of the craniofacial area in POSA cases, oral health professionals can play an important role in screening and identifying signs and symptoms related to this medical condition and referring the patient to a sleep medicine/ENT specialist if there is a perceived high OSA risk. Later, and when properly indicated, oral health professionals can be part of a interdisciplinary management of this condition in a group of selected cases. An orthodontic approach in such cases, namely, through rapid maxillary expansion (RME) devices and maxillary and/or mandibular advancement (MAD) appliances, has been reported to be useful, at least temporarily, in reducing POSA signs and symptoms in selected mild and moderate cases [1, 2].

In this chapter, the potential contribution of the oral health professionals in the screening and management of POSA will be discussed, displaying the role of oral health professionals, more importantly, in POSA screening, as well as in the interdisciplinary management and follow-up of this disease when the orthodontic intervention is properly indicated. It must be noted that the concepts and findings discussed below are not equivalent for adult OSA cases.

Pathophysiology Assessment in an Oral Health Office

Even though the oral health professional should theoretically not be the first health-care provider to identify patients at high risk of POSA, they can contribute in identifying children at high risk of POSA as they examine children more frequently than pediatricians after children are older than 2 years of age. In addition, a subset of POSA patients exists in which altered craniofacial characteristics may be strongly associated [3]. It is becoming clear that although a subset of POSA patients has a set of craniofacial features linked to altered OSA such as long narrow fascia, convex profile, constricted palate, and anterior open bite, another subset of POSA patients do only have some or none at all of these craniofacial characteristics.

Having stated this, screening of craniofacial bony and soft tissues associated with OSA in the dental office, as well as general features such as weight, altered breathing symptomatology, and presence of craniofacial syndromes, can help dentists in narrowing the referral of possible POSA casuistic to those cases with a higher probability of having a confirmed full medical diagnosis [3]. The evaluation of medical and dental history, oral and facial clinical examination, and, when indicated, craniofacial imaging, such as the panoramic radiographs, lateral radiographs, and cone beam computed tomography (CBCT), can strengthen this assessment [4, 5].

Assessment of Craniofacial Features, Airway Space, and Weight

The assessment of craniofacial characteristics can be performed by the evaluation of clinical and cephalometric radiographic findings. Historically, it has been believed that POSA patients had associated increased total and lower facial height, decreased maxillary width, and retruded mandibular prominence [6, 7]. Nevertheless, the presence of these characteristics is not part of a definitive reason for referral.

Specific craniofacial features have been linked to POSA in cross-sectional and case-control studies, where cephalometric and clinical evaluations were performed. Some case-control studies have reported a lower position of the hyoid bone in POSA children aged 3–6 years old [8], as well as in a group of 6–12 years old [9], when compared to healthy controls.

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In addition, a reduction in SNB angle, suggesting a retruded mandibular position, and a reduction in Pg-NB measurement, indicating a retruded chin, were reported in a group of children from 6 to 12 years old, presenting POSA [9]. In a posteriorly positioned and posteriorly rotated mandible, increased gonial angle and longer facial height were also reported in a group of 3–5-year-old POSA patients [10].

A more recently explored area assessing craniofacial anatomical features with POSA is the exploration of cranial base dimensions. Inconclusive results regarding this portrayed association have been synthesized [11].

The initial screening for tonsil hypertrophy, clinically, and adenoid hypertrophy, through craniofacial imaging, when associated with a pertinent medical history, seems to be useful to support the referral to an ENT specialist by the oral health professional [12]. A definitive diagnosis in those scenarios by the ENT specialist will likely require a nasoendoscopy [13, 14].

The evaluation of the weight of the patient is also an important variable that can easily be completed in a dental office. Obesity has been recognized as a significant risk factor for SDB in children, as well as for the chronicity of this disease [13].

Differences in Syndromic Children

Patients with craniofacial syndromes present an increased risk of having sleep-disordered breathing (SDB). SDB etiology in these cases is different from that of non-syndromic patients [14, 15]. Factors commonly associated with sleep disorders in children, such as obesity and adenoid hypertrophy, are not typically present in children presenting craniofacial syndromes [16]. In these patients, midface and/or mandibular hypoplasia, macroglossia, and narrowed oropharynx can result in airway problems and OSA in severe cases [14, 15].

Other syndromes, such as Down [17] and Prader-Willi syndrome [18], can also present craniofacial involvement with a resulting OSA development. Due to the specific symptoms of each syndrome, it has been suggested that some otherwise useful tools in non-syndromic patients, such as the Pediatric Sleep Questionnaire (PSQ), may not be so useful on the evaluation of OSA in these syndromic cases [16].

Screening of POSA: Prediction of Likely Presence or Absence by Oral Health Professionals – Clinical and Imaging Assessment

The oral health professional can play an essential role in POSA screening. Even though they are not able to provide a full diagnosis and a treatment plan on these patients, they can identify signs and symptoms related to OSA and refer the patient to a sleep medicine/ENT specialist when justified.

Assessment of OSA signs and symptoms should be considered through the use of properly validated sleep questionnaires. In addition, the evaluation of craniofacial parameters, both clinically and through craniofacial imaging, could nicely complement this information. The use of validated questionnaires by oral health professionals represents an available tool for the assessment of OSA risk level. Focus lays in reported symptoms such as presence of snoring, breathing problems during sleep, daytime sleepiness, presence of risk factors (such as obesity, sex, or age), and presence of comorbidities. Among children, the Pediatric Sleep Questionnaire (PSQ) has been pointed out as the best available screening method for this task [19]. It must be noted that although this questionnaire suggested an excellent response in identifying positive results (97% positive predictive value) for sleep disorders but poor response for negative results (45% negative predictive value) [20], these numbers do change quite significantly when non-referred samples with strong POSA suspicion are considered. In other words, when used in individuals with previous suspicion OSA, the Positive Predictive Value (PPV) is quite high, while the Negative Predictive Value (NPV) is quite low, but when used among more general population, these values change significantly. If a prevalence of 3% (general population) is used, then the PPV goes down significantly to 43%, and the NPV goes up significantly to 99%. If orthodontic populations, with increased chances of anatomical craniofacial alterations, are considered with a suggested prevalence of 8%, then the PPV changes to 84% and the NPV to 97% [21]. In summary, PSQ could be quite useful when used by oral health professionals in their population samples, but not so much in highly selected pediatric samples with high suspicion of OSA. These samples are likely to benefit from a comprehensive assessment as they are already going to be evaluated in a more specialized environment.

During clinical and imaging evaluation, the presence of enlarged adenoids and tonsils is a common risk factor for upper airway obstruction among children and adolescents [5]. The assessment of adenoid and tonsils can be performed using subjective clinical evaluation, including the Brodsky grading scale [22] and Mallampati score [23]. However, the assessment of the size of these tissues is not a strong predictor of possible OSA severity [24]. For adenoid hypertrophy, a nasoendoscopy (NE) assessment is the current gold standard method to evaluate their size using a specific grading system [25].

There is no single accurate method that oral health professionals can use to evaluate these lymphoid soft tissues in clinical practice. However, it has been suggested that an initial screening can be performed in lateral radiographs or CBCTs, when combined with patient's medical history [12]. The lack of assessment of transverse airway dimensions is a major limitation when using 2D lateral cephalometry. More

recently available craniofacial imaging such as CBCTs provides a 3D evaluation of the upper airway when compared with 2D radiographs (Figs. 39.1, 39.2, and 39.3), allowing the measurement of the volume of airway space and its surrounding soft tissue [26]. The standardization of image resolution and the operator's expertise [27], as well as the poor training of some oral health specialists to evaluate the upper airway area [28], may be associated with limited accuracy. When these factors are controlled, the accuracy and reliability could be useful to improve proper referrals for full medical assessment [4, 29, 30]. It is important to note that this is not an implicit suggestion that CBCT imaging should replace NE or is an indication to justify its request. But when already available for other reasons, it could provide additional useful information to ENTs. A significant limitation is that CBCT imaging is taken with patients in supine position which does not reflect the influence of gravity on soft tissues when lying down while sleeping.

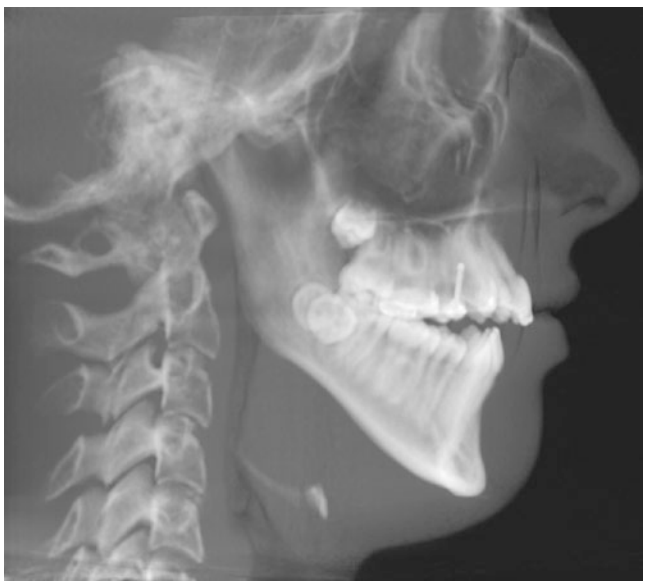

Fig. 39.1 Lateral cephalogram of a 13-year-old patient showcasing some of the sagittal and vertical malocclusion traits usually associated with the so-called long face syndrome that has been closely linked to pediatric OSA

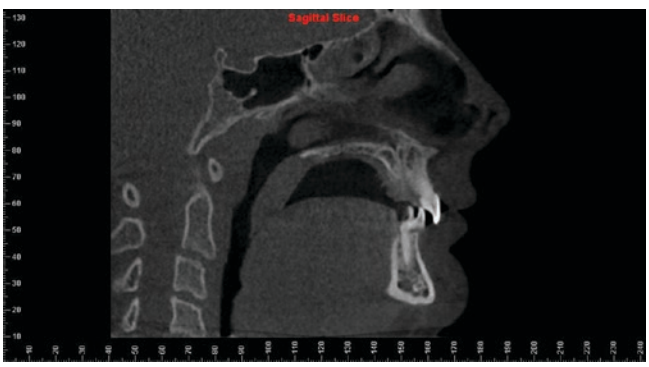

Fig. 39.2 Sagittal cut near the midface of CBCT imaging of a 14-year-old showcasing the intimate relationship of the posterior dorsum of the tongue and the soft tissue palate with the posterior wall of the oropharynx and nasopharynx

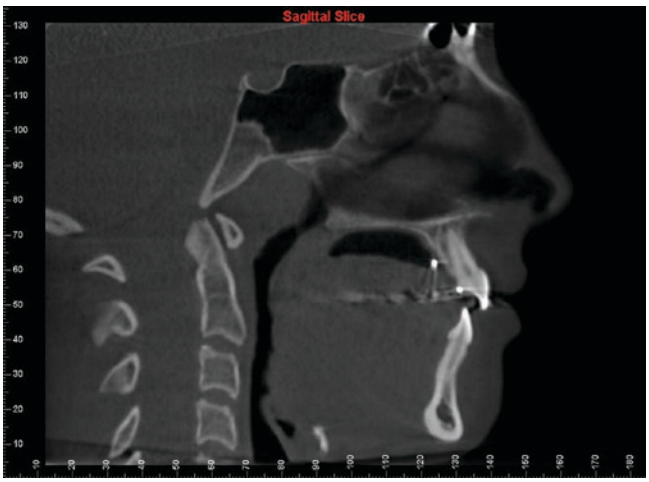

Fig. 39.3 Similar depiction to Fig. 39.2 but from a different individual, same age, but with what appears to be reduced sagittal dimensions of the nasopharynx potentially due to close proximity of the hypertrophic adenoids and the posterior wall of the nasopharynx

In summary, oral health professionals are uniquely positioned to screen for high-risk OSA pediatric patients as they do evaluate them semiannually. The use of the PSQ by oral health professionals should be encouraged for every pediatric patient as its strong PPV and excellent NPV in samples similar to those seen in dental practices make it the best available screening tool for oral health professionals. When indicated by PSQ responses, a referral to a sleep medicine specialist should follow for full medical diagnostic consideration.

Management of POSA by Oral Health Providers

In selected cases, some forms of orthodontic treatment may also be beneficial during the management of pediatric OSA patients. As noted before, some craniofacial features, including a narrow maxilla or a retrusive mandible or maxillary complex, are sometimes associated with OSA problems. The correction of these problems, including performing maxillary expansion through a RME device or the use of MAD appliances, may be useful in the interdisciplinary management of pediatric OSA [31].

Indication

In children with craniofacial problems or anomalies that also present a primary orthodontic indication for maxillary expansion, maxillary or mandibular advancement may show

some improvement in airway function parameters associated with a reduction of upper airway collapsibility on mild and moderate OSA cases [32]. Consistent reductions of about six points for AHI values after RMEs and MADs have been suggested in a few systematic reviews [31, 33–35]. At the same time, not all the OSA cases treated with these therapeutic approaches show improvements in OSA symptomatology. Some did not have changes in sleep parameters [36, 37], and some parameters got even worse [38]. In addition, even the positive changes were not necessarily maintained long term [39]. Even more importantly, there is still no strong evidence that supports the indication of oral appliances or functional orthopedic appliances without craniofacial problems that justify the use such appliances in every POSA case [32].

An important point – children are continuously growing, and increments in upper airway dimensions are going to happen. In some cases, careful observation is everything that is needed, as Mother Nature may take care of reduced upper airway dimensions. At this point, identification of such subset of patients has not been reached.

Maxillary Expansion

RME is indicated for the correction of skeletal transverse maxillary discrepancy, more specifically in the presence of maxillary constriction or posterior dental/skeletal crossbite (Figs. 39.4 and 39.5). In cases of children presenting mild to moderate OSA who also present maxillary constriction, RME can be indicated as an adjunct OSA treatment that may improve OSA symptomatology at least short term. An underlying hypothesis is that the correction of a narrow maxilla may improve nasal airway dimensions by simultaneous changes in nasal dimensions and adjacent structures [40, 41].

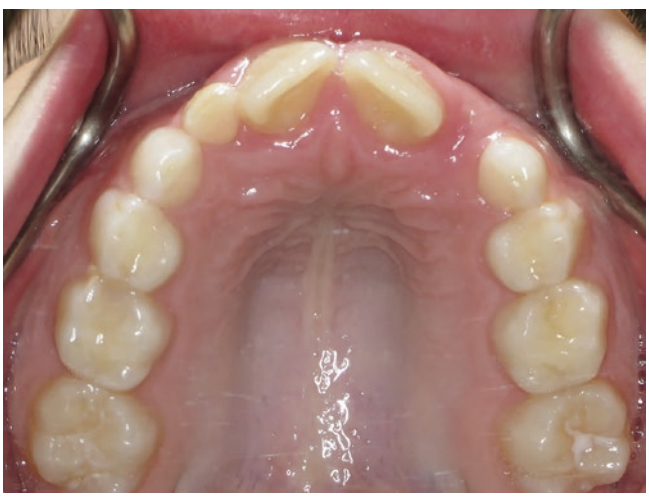

Fig. 39.4 Occlusal photo of the maxillary dentition depicting reduce transversal dimensions and potential lack of space for the eruption of the permanent lateral incisors

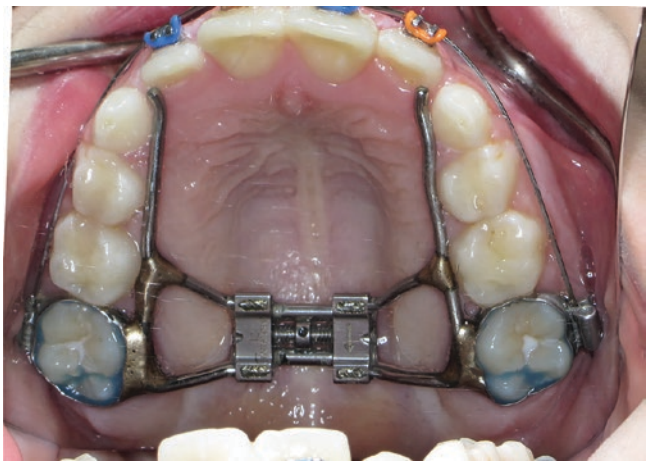

Fig. 39.5 Occlusal photo of the same individual (Fig. 39.4) but now showcasing the degree of maxillary expansion obtained with the use of a Hyrax-type expander. Note the increased transversal dimensions and now the permanent lateral incisors fully erupted and being aligned

The missing link is the fact that in these studies breathing function changes were not quantified but only anatomical dimensional changes. It should not be automatically assumed that increases in upper airway dimensions automatically generate sleep breathing improvements. Another potential hypothesis is that the significant forces needed to separate the palatal suture facilitate a significant inflammatory response from the body in the surrounding areas and the release of inflammation mediators may have beneficial effects in cases where the OSA obstruction is mainly due to inflamed upper airway surrounding soft tissues.

Mandibular Repositioning

The MAD devices may change the mandible to a more forward position, which may increase the sagittal dimension of the oropharyngeal area and reduce the collapsibility of the airway there (Fig. 39.6). This is due in part to the forward movement of the tongue insertion moving it away from the posterior wall of the oropharynx. Fixed and removable appliances, including custom-made appliances (Monobloc, Activator, Frankel, Herbst, Bionator, and Twin Block), have been suggested for this purpose [34, 40]. One factor that can influence MAD treatment results is the patient's compliance, especially with removable appliances [34].

Maxillary Advancement

An area that has limited information so far is the impact of advancement of the nasomaxillary complex in cases of deficient maxillary development. It can be argued that if orthodontic-orthopedic approaches that facilitate forward movement of the nasomaxillary complex in young children (such as reverse pull headgear with or without concomitant RME) are successful, then the sagittal dimension of the nasopharynx should be increased.

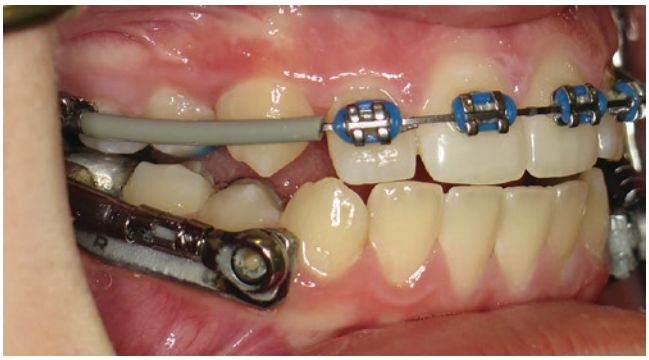

Fig. 39.6 Lateral right occlusal photo of a sagittal malocclusion being managed with a fixed sagittal corrector. This device forces the mandible forward improving the occlusal relationships

Other Considerations

Other adjunct approaches can be indicated for OSA treatment in children, mostly on cases where the adenotonsillectomy (A&T) is not indicated or residual OSA is measured. Myofunctional therapy (MT) is one of these options, conducted in cases with significant oral breathing and lip hypotonia. This technique consists of regular exercises, which can improve the position of the lips, tongue, soft palate, and lateral pharyngeal wall. Even though there is a still lack of substantial evidence on the results of this approach, it has been suggested that this management approach may reduce AHI in some OSA children [42].

Specific Craniofacial Diagnosis Prior OSA Management

As a part of a interdisciplinary approach, oral health professionals should refer patients to a sleep medicine specialist or ENT specialist when adenoidal/tonsillar hypertrophy is identified. If the treating physician considers that orthodontic approaches may be helpful in patients presenting craniofacial abnormalities, then the oral health professional should consider the possible treatment options identified above [2].

For both RME and MAD appliances, a regular set of records commonly required for orthodontic treatment are needed. A clinical intraoral evaluation, including a facial analysis, teeth condition, and occlusion evaluation, is required. As part of this analysis, an assessment reporting all teeth conditions and occlusions, obtained by panoramic radiographs, and X-rays reporting the facial profile, associated with a cephalometric analysis (teleradiographs), are also part of this initial screening. In addition, photos of the face and profile, as well as plaster models to evaluate the teeth occlusion, are necessary [43].

For RME treatment, a specific diagnosis of maxillary constriction or posterior crossbite is mandatory, beyond that of an OSA problem [44]. In MAD treatment, a significantly retruded mandible is the primary indication for this treatment [31]. Keep in mind that the mandible is going to grow forward and downward anyway as part of normal craniofacial growth and development. Other specific conditions may be considered prior treatment according to the type of appliance used, the patient compliance, and the number of primary or permanent teeth present.

Outcomes of Orthodontic-Orthopedic Approaches

In pediatric patients overall, some orthodontic-orthopedic approaches have resulted in reduction of airway collapsibility in addition to the craniofacial improvements provided by MAD and RME appliances.

MAD Appliances

In mild and moderate OSA patients, short-term improvement of AHI values has been reported by the literature in cases of mandibular retrognathism and the use of MAD appliances [31]. There is so far no consistent evidence showing the long-term effects of MAD appliances. The effects of other factors, such as performing of previous A&T, lifestyle, or previous treatments received for OSA, have also not been fully explored yet.

Some improvement in upper airway dimensions may be observed in some cases with mandibular retrognathia as an additional benefit after the use of the MAD appliance. The changes in pharyngeal airway dimensions in growing patients presenting mandibular retrusion were reported in some case-control studies, suggesting better results in the increasing of upper airway parameters in a group using an MAD appliance when compared to a control group without the treatment [45, 46].

In MAD appliances, the improvements in upper airway collapsibility were also associated with an increase in airway volume and airflow [47]. Changes in airway volume after the use of MADs were reported as an increase in the volume of the velopharynx. The skeletal and soft tissue changes can be a consequence of this process, including an increase in the lower anterior facial height, reduction in the distance between the hyoid and posterior nasal spine, and anterior movement of the tongue base muscles in adults with OSA [48].

Most of the studies evaluating the effects of MAD appliances focused on immediate polysomnography (PSG) results, pharyngeal width changes, and OSA symptoms. Different appliances have been tested, such as Twin Block, Herbst appliance associated with RME, Monobloc appliances, headgear, and custom-made appliances. The duration of use of these appliances varied from 6 to 12 months until the resolution of the retrognathism problem or end of treat-

ment. Mixed protocols were observed among the studies, varying from the usage during all day or only at night [31, 33, 34, 49]. Overall, these studies included patients presenting a mild to moderate OSA, according to the AHI classification. During a short-term evaluation, a reduction of up to 50% of AHI has been reported in the existing studies [31, 34, 50]. Other benefits, including a reduction in daytime sleepiness and improvement of sleep quality [39] and increase of pharyngeal width, have also been reported [51–53].

Most of the MAD studies evaluating their effectiveness in OSA children have not presented a control group [31]. When an untreated control group presenting OSA symptoms was considered to evaluate the effectiveness of this intervention, it was also suggested an improvement in AHI and daytime sleepiness after a 6-month treatment with oral appliances. No changes in OSA symptoms were detected in the untreated group after the same length of time [36]. It must be noted that the CHAD study suggested that some patients requiring A&T but were randomized to the careful watching group did improve with time without any intervention [54]. This may be the combined effect of normal lymphatic tissue shrinkage and normal craniofacial growth changes in the upper airway.

In summary, due to the lack of substantial evidence supporting the evaluation of MAD effects in OSA children, it is not possible to predict their effects or categorically imply consistent benefits of these appliances in this age group yet. Initial results may be considered promising.

RME Appliances

Among the RME appliances, a similar scenario is observed, including the improvement of OSA in mild to moderate severity cases and the limited association of OSA improvement as a direct consequence of maxillary expansion. However, for RME, some evidence that AHI improvements are maintained over a long-term period has been identified [41]. A normalization of AHI values (AHI <5) was reported after the use of the appliance in mild to moderate OSA children presenting an orthodontic indication for RME, when a follow-up of 12 months was considered [41]. Additional results, including the improvement of nasal septum asymmetry during childhood [55], a normalization of hyoid bone position by decreasing the distance of this bone to mandibular plane [56], and the reduction of nasal resistance [57], were reported as a consequence of RME procedure.

The results of RME expansions seem stable in the short term, after RME removal and retention period, as well as in a long-term evaluation, when the expansion of the maxillary arch is maintained [41]. There is no evidence supporting that additional factors such as sex or type of appliance can influence airway changes.

Some functional improvements in enlarged tonsils and adenoid tissue were reported after RME in nonrandomized studies [58]. However, it is not possible to predict the magnitude of these improvements after RME from these studies. In addition, a reduction in these lymphoid tissues after maxillary expansion was also associated with only a dimensional effect from palatal expansion and not a true reduction [59].

One of the hypotheses that may explain the RME effect in OSA patients is associated with the reduction of nasal resistance, which may increase oxygen saturation and allow air passage through the nose. The RME was associated with a decrease pharyngeal airway pressure and velocity, resulting in an improvement of nasal ventilation [60]. The maxillary expansion could also increase the oropharyngeal space and improves tongue position due to the enlargement of the nasomaxillary complex [41].

As mentioned earlier, another factor that could be related to the RME effect is the release of inflammatory mediators [61]. The OSA is a systemic inflammatory disease linked to an increase in serum inflammatory markers [62]. The increase on inflammatory mediators may influence OSA symptoms or disease stage, but specific details of the biochemical effect of this treatment have not been elucidated yet. However, there is no strong evidence supporting these theories or the direct association among OSA improvements and the indication of RME as a treatment option [41, 58].

In summary, due to the lack of substantial evidence supporting the evaluation of RME effects in OSA children, it is not possible to predict their effects or categorically imply consistent benefits of these appliances in this age group yet. Initial results may be considered promising.

Prediction of Orthodontic-Orthopedic Management Outcomes

Identified published evidence after use of some oral appliances as part of POSA management suggests an improvement in OSA symptomatology when using RME and MAD appliances [31]. However, these results came from a small number of studies with significant methodological issues and hence high risk of bias, which may compromise the predictability of these outcomes.

For MAD appliances, there were two studies evaluating their effectiveness. An improvement of AHI values was observed short term, presenting a similar result and a small response variability. When the changes in OSA symptoms were considered, a reduction was reported in both studies, using valid questionnaires [36, 39].

The outcomes of the RME treatment on sleep parameters presented a considerable variability as assessed through the AHI, according to the duration of follow-up among the stud-

ies. Even though a mean follow-up of 12 months were more prevalent, the current literature reported a period of 1–18 months after RME treatment, which may compromise the comparison of results among studies [31, 41, 58]. The presence of adenoid hypertrophy among the patients and performing adenotonsillectomy before or after RME were also reported in some studies, which can have an impact on OSA symptomatology changes [31].

Follow-Up

Treatment provided in childhood must be followed at least until the end of their craniofacial growing stage, observing craniofacial changes during this period, as well as the emergence of other factors that can influence OSA progression. It has been reported that a spontaneous resolution of OSA in pediatric patients is associated with mild to moderate severity of the disease, including a low AHI values, the absence of obesity, higher-positioned soft palate, smaller neck circumference, and non-black race. A reduction in tonsillar size and an airway enlargement that occurs naturally with growth have been pointed as possible causes of these results [63].

At the same time, the impact of orthodontic-orthopedic OSA management beyond the reduction of AHI values and craniofacial changes must be evaluated. The patient's experience with the appliances, the impact in the quality of life, the management of treatment, and the integration between physicians and orthodontists must be considered during the follow-up evaluation.

Success Rates of Treatment

When the sleep parameters were considered, MAD and RME appliances presented limited evidence in children patients. Retrospective and nonrandomized studies have shown an improvement in AHI varying from 40% reduction up to normalization of AHI values in mild and moderate OSA cases [31, 33].

Regarding the patient's perception of changes, there is also a lack of studies evaluating their perspective in regard to airway improvements after orthodontic-orthopedic management. In some case series studies, an improvement in nasal respiration was reported among RME patients presenting OSA [64]. Improvement of signs and symptoms, including daytime sleepiness, was reported after the treatment with oral appliances in children [31, 65].

In children, the presence of excessive salivation was described in a randomized controlled study after the use of MAD appliances as a side effect, with no pain or discomfort reported in temporomandibular joint [36]. These findings may change in adult patients, in which the presence of dry mouth, gum discomfort, myofascial pain, abnormal morning occlusion, and temporomandibular joint disorders were reported as MAD side effects in OSA patients [66]. However, since there are no more studies evaluating the side effects of these appliances among OSA children, it is not possible to establish their causes or association with a specific age group.

The intolerance or problems of compliance during MAD or RME treatment can also represent a barrier for the orthodontic-orthopedic management in OSA children. The main problems reported in this type of treatment that result in a discontinuation of the use of the MAD appliance were the presence of uncontrollable coughing, loss of the appliance, and self-esteem complaints, as the embarrassment for using the appliance in school. This is specifically linked to MAD approaches [36].

Recurrence of Craniofacial Discrepancies

As noted, there is a lack of studies evaluating long-term effects of orthodontic-orthopedic management effects in OSA patients. Long-term studies are essential due to the continuing growth of the maxilla, mandible, and adjacent bone structures and the impact in the soft tissues within the airway (i.e., soft palate, uvula, tonsils, tongue, epiglottis, pharynx) [63]. How much of the improvements are related to the therapeutic approach and how much are part of normal growth changes are still largely unknown.

In children without OSA, the relapse of craniofacial problems in RME patients presents a low prevalence. The increase of transversal dimensions seems to be maintained in 6 months to 7 years post-retention of follow-up [67]. Nasal changes, as the increase of nasal width after the opening of midpalatal suture, were also reported as stable after 12 months to 5 years of follow-up [68]. At the same time, it seems that only 20% of the initial expansion amount is actually skeletal in the long term [69]. As a regular expansion device is activated close to 10 mm, it means that only 2 mm are actually going to represent skeletal expansion. The impact of such amount over airway dimensions is a challenging concept. OSA is a multifactorial disease. Hence, it is not only about available upper airway dimensions but several other physiologic responses.

Regarding MAD appliances, no recurrence of problems in mandible or upper airway dimensions has been reported by case-control studies with a follow-up varying from 2 to 2.5 years [70, 71]. The long-term mandibular changes must be cautiously considered, due to their transient effects after growth reported in children using mandibular advancement appliances [72, 73]. Since the long-term available studies reporting pharyngeal and upper airway dimensional

changes present a retrospective design and are nonrandomized [70, 71], further studies are needed to answer this question.

The recurrence or appearance of new craniofacial discrepancies after orthodontic treatment in pediatric OSA patients, as well as the recurrence of OSA symptoms, can also be a result of malocclusions or skeletal problems manifested later in the growing phase. The follow-up of these patients until adulthood is recommended to evaluate this potential risk factor [74]. Again, how much of the improvements are related to the therapeutic approach and how much are part of normal growth changes are still largely unknown.

Guiding Recommendation on Long-Term Reassessments

Despite performing clinical exams during the follow-up of patients after orthodontic-orthopedic management of POSA, some other tools have been suggested involving the use of validated questionnaires [75], the combination of physical examination of the patient and case history [65], or the performing of radiological exams to evaluate further craniofacial changes [76]. However, currently there is no validated tool adequate for outcome prediction in pediatric OSA patients. Hence, mass management approaches implying indiscriminate use of orthodontic-orthopedic appliances among POSA individuals should be discouraged until more solid evidence is identified. In the future, it is hoped that our capability to identify a subset of POSA individuals that would definitively benefit from a multidisciplinary management of OSA in which oral health professionals may play a major evidence-based role is fine-tuned. Nowadays there are more questions than answers, but at the same time some initial evidence has been showcased that suggests that oral health professionals may be able to play a significant role in some selective cases.

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Myofunctional Approaches to Pediatric Sleep Medicine

40

Maria Pia Villa and Melania Evangelisti

Introduction

Recently there has been increasing evidence on the role of orofacial myofunctional treatment in children with sleep-disordered breathing (SDB) [1–3].

Obstructive SDB is an upper airway dysfunction that occurs during sleep and is characterized by snoring and/or increased respiratory effort caused by upper airway resistance and pharyngeal collapsibility [4, 5]. Obstructive SDB includes a spectrum of clinical entities from simple snoring and upper airway resistance syndrome to obstructive sleep apnea syndrome (OSAS). Adenotonsillar hypertrophy is the leading cause of OSAS; tough other risk factors include allergic rhinitis, craniofacial anomalies, neuromuscular diseases, laryngomalacia, and obesity [6–8].

From recent evidence in literature, we know that a stepwise therapeutic approach is needed to achieve the complete resolution of SDB. In 2010, both Bhattacharjee [9] and Ye [10] confirmed that adenotonsillectomy (AT) resolves OSAS in about 30% of children. In 2014, we also demonstrated that residual OSAS is present not only after adenotonsillectomy but even after orthodontic treatment with rapid maxillary expansion (RME) [11].

Mouth breathing and lip hypotonia are common symptoms observed in children with obstructive SDB and are related to altered nasal tone and increased nasal resistance. They are more often associated with a malposition of the tongue, thus constituting a possible interference with normal growth and development of the maxilla and mandible [12–15]. Mouth breathing could lead to deficits in orofacial muscles and directly affects the position and strength of the tongue, causing abnormal airway development and obstructive SDB [15].

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The multidisciplinary therapeutic approach to children with OSAS is based on surgery, orthodontic and medical treatments, as well as weight loss in children with obesity and noninvasive ventilation when required [5, 11–16]. Different treatment modalities are often combined in a stepwise intervention to achieve the complete resolution of obstructive SDB.

Orofacial myofunctional therapy helps to re-establish correct habits and functioning of orofacial muscles to avoid the residual SDB after surgical and orthodontic treatment. The treatment must be as early as possible for protecting airway health and sleep quality. Orofacial myofunctional exercises restore a correct stomatognathic function; educate or reeducate the orofacial muscles for optimal breathing, sucking, and swallowing; eliminate wrong habits; and correct orofacial muscle problems. Therapy should be considered with integrative treatments in children with SDB [2, 3].

Craniofacial Growth and SDB

A healthy development of the jaws and upper airways is essential for good sleep and starts in the very early years. By the ninth week of fetal development, the initial cartilaginous facial skeleton is well established. By the twelfth week of fetal growth, areas of ossification appear, and bone rapidly replaces the cartilaginous template forming the early cranial base. At the same time, the bones of the cranial vault, mandible, and maxilla develop through intramembranous ossification [17–19].

The maximum face growth occurs between birth and 2 years of age. After birth, there is a continuous interaction between orofacial functions and the growth of anatomic features. The movement of the fetal tongue between the sixth and tenth weeks of gestational age allows the closing (i.e., vertical, horizontal, and transverse planes) of the primitive mouth (stomodeum). The tongue's new placement below the palate changes from a previous vertical orientation to a horizontal orientation. This organization is under the control of

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the 39 homeobox genes (HOX). At this time in gestation, mutations involving these genes will lead to congenital orofacial syndromes such as Pierre Robin sequence. From the 20th week, the tongue grows and develops control from the brain stem, and the baby should be actively sucking and swallowing in utero from the third trimester. At birth, an infant is an obligatory nose breather. Abnormal nasal airflow also affects the palate and its maxillary alveolar dental development [20, 21]. Such changes interfere with maxillary dental arch growth which will disturb mandibular dental arch development secondarily. In particular, the changes lead to the disappearance of the diastasis (or interspace) between the deciduous incisive teeth, which in turn interferes with the placement of the permanent teeth. Nasal breathing does play a role not only in orofacial development but also in the coordination between nasal breathing and sucking which develops very early in life. Sucking and swallowing, as previously discussed, are very coordinated activities, and appropriate nasal breathing is a crucial point. Such coordinated actions (e.g., breathing and sucking) play a role in the stimulation of the structures involved in orofacial growth early in life. Mastication at close to 6 months of age is an added stimulus for such growth and must be promoted. Alterations in these functions increase the risk of abnormal development of bone structures supporting the upper airways, leading to an increased risk of collapsibility in the upper airways during sleep [12, 20]. The neurological network must be stimulated very early in life to prevent alterations in the form and function of craniofacial structures.

Orofacial Myofunctional Evaluation

Children with sleep-disordered breathing (SDB) present alterations in posture and mobility of the stomatognathic system components. Oropharyngeal muscle hypotonia is implicated in the pathogenesis of OSA, and oropharyngeal exercises may improve stomatognathic function and reduce neuromuscular impairment [2, 3].

Children with SDB more often present peculiar orofacial characteristics (Fig. 40.1):

- Long face (often asymmetric)
- Under-eye dark circles
- Mouth breathing
- Lip hypotonia
- Nasal cartilage hypotonia

Orofacial myofunctional disorders were defined as alterations/dysfunctions of the appearance, posture, and/or mobility of the lips, tongue, mandible, and cheeks and of respiration, deglutition, and mastication functions. An accurate oropharyngeal evaluation, targeted to explore the presence of mouth breathing, nasal disuse, orofacial muscle hypotonia, and an incorrect swallowing pattern, should be part in the assessment of children with SDB, in order to recognize potential improper oropharyngeal characteristics that must to be treated. In this regard, oropharyngeal exercises may help to resolve oropharyngeal muscle dysfunction that persists following the standard treatment of SDB and in this way reduce the possible contributing factors to airway collapse [22].

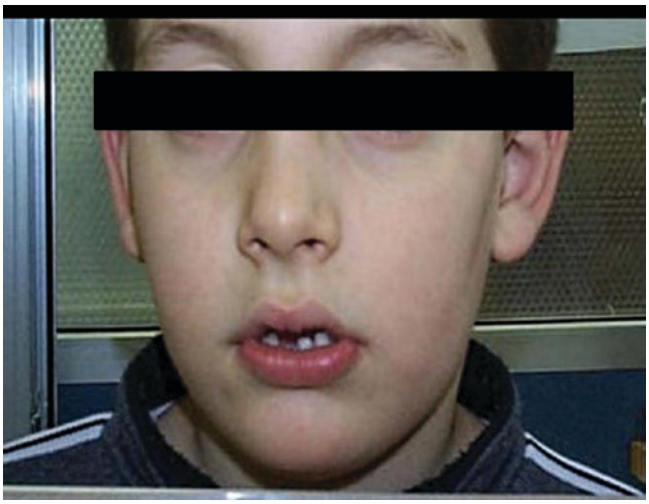


Fig. 40.1 Child with sleep-disordered breathing

Validated tools that enable identifying, classifying, and grading changes in oropharyngeal muscles and function status should be used. Currently, this is possible with the Orofacial Myofunctional Evaluation with Scores (OMES)-expanded protocol validated for children [23, 24]. A standard evaluation protocol is useful for the characterization of the orofacial myofunctional conditions of children [23, 24]. Specifically, the OMES protocol is an instrument for the clinical evaluation of orofacial structures and functions of children that will permit the examiner to express numerically his perception of the characteristics and behaviors observed and that can be administered without special equipment and in a brief manner [24].

OMES-expanded permits the assessment of appearance/posture and mobility of the stomatognathic system and of functions such as breathing, swallowing, and mastication [23, 24], using observations made on an ordinal level of measurement, as defined by the psychophysical principles of measurements [23, 24]. For the orofacial myofunctional evaluation of children with SDB, it's important to observe aspect/appearance/posture of the lips, jaws, cheeks, face, tongue, and palate; mobility of the lips, tongue, jaws, and cheeks; and functions—respiration, deglutition, and mastication [23, 24]. For respiration, the normal pattern was considered to be nasal when the subject presented labial closure without effort during rest. For deglutition, the pattern was

considered normal when the subject presented the tongue contained in the oral cavity, contraction of elevator muscles, and anterior sealing of the oral cavity without effort. For mastication, the subject was instructed to chew the food (a stuffed cookie) or water in his habitual manner [23, 24].

Moreover, objective measures of muscular strength/force [25] and electromyography [26] can contribute to the oropharyngeal muscle disorder diagnosis, following the assessment of the results of the treatment.

Orofacial Myofunctional Exercises

Orofacial myofunctional exercises are designed to achieve balance of the orofacial muscles and to correct stomatognathic functions such as swallowing, breathing, speech, and chewing. Orofacial myofunctional rehabilitation consisted of isometric and isotonic exercises involving all the stomatognathic apparatus and is based on promoting proprioception, mobility, coordination, and strength of orofacial structures [23].

In our study [3], we used a set of exercises divided into three categories:

1. Nasal breathing rehabilitation
2. Labial seal and lip tone exercises
3. Tongue posture exercises

Examples of exercises are described in Fig. 40.2.

In our study, children with residual OSAS were recruited and performed the orofacial myofunctional therapy for 3 months, exercised every day at home, at least three times a day, doing 10–20 repetitions each time. In the group treated with oropharyngeal exercises, the number of patients with a proper labial seal, increased lip tone, and re-established nasal breathing increased. In this study, oropharyngeal exercises led to a significant decrease in nasal obstruction and improved nasal patency, thereby allowing patients to regain nasal breathing; moreover, in the children with residual OSAS after adenotonsillectomy, seal lip exercises designed to strengthen the lips also allowed them to regain correct labial seal [3]. In another study conducted on subjects with primary snoring and mild to moderate OSAS, there was a significant increase in the objective measures of tongue strength, tongue peak, and endurance [25], as measured by the Iowa Oral Performance Instrument (IOPI), with the orofacial myofunctional therapy. Moreover, in the same study, the number of children with mouth breathing, abnormal tongue rest position, and lip hypotonia decreased after oropharyngeal exercises [25].

The purpose of these exercises is to increase the strength, tone, and coordination of the muscles. Added benefits include stability of treatment plans involving the upper airway. Normal muscle activity should be maintained for a lifetime; otherwise the gains in muscle strength and coordination can be lost.

The oropharyngeal reeducation involves strengthening of the tongue and orofacial muscles by teaching individuals how to assume the appropriate muscle and structure position. The tongue should be kept in a high position during sleep with its dorsal-terminal end in constant contact with the palatine striae located on the anterior aspect of the palate. Oropharyngeal reeducation may be initiated at the age of 5–6 years. The duration of treatment is variable but typically consists of 3–6 months of active therapy, followed by a maintenance period of the same duration, and it is largely related to the degree of effort parents make in reinforcing a subject to perform his or her exercises.

Usually, it is recommended that three series of exercises, with 10–20 reps for each exercise, be carried out two to three times per day at different times (at least 2 hours between sessions).

Nasal washes are most important and usually were performed two times, in the morning and evening during the entire period of treatment.

The early diagnosis and treatment of oropharyngeal muscle dysfunction in children with OSAS is mandatory to optimize the normal growth of the upper airways and to ensure a lasting impact in the treatment of obstructive SDB [2, 26].

Obstructive SDB and Orofacial Myofunctional Therapy

There are recent studies demonstrating the efficacy of orofacial myofunctional exercises as treatment for residual OSAS and as adjunct treatment in children with mild to moderate OSAS.

In a retrospective study conducted on oropharyngeal exercises in children with OSAS, Guilleminault et al. demonstrated the reduction of apnea hypopnea index (AHI) in children with residual disease [2]. The authors evaluated 24 children who were cured by the combination of adenotonsillectomy and palatal expansion (AHI 0.4 ± 0.3) [2]. Eleven children received oropharyngeal exercises (treatment group) and were compared with 13 children (control group). At the 4-year follow-up, the children who performed oropharyngeal exercises over the long term did not exhibit residual OSAS (AHI 0.5 ± 0.4 ev/h), compared to children who were never trained to perform the exercises and subsequently had a recurrence of OSAS (AHI 5.3 ± 1.5/h).

In our prospective study conducted in a small cohort of children with residual OSAS after adenotonsillectomy, we demonstrated a complete resolution of the disease [3]. Post-adeno-tonsillectomy children were randomized to either oropharyngeal exercises or control group. Fourteen patients

a

Re-education of the Nose

Inhale through the nose and exhale through a straw, trying to move a ping-pong ball. See how far you can blow the ball!

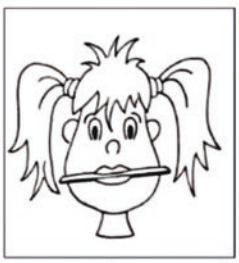
Place a straw in a cup of water. Next, inhale through the nose and exhale through the straw, making bubbles for as long as possible.

Inflate a balloon. Inhale through the nose and exhale through the mouth forcefully, so as to blow the balloon away from you.

b

Exercises for LIP SEAL

Insert two fingers to the corners of the mouth and exert a slight outward tension, at the same time contracting the inside of orbicularis muscle, thus counteracting the stretch.



Hold a tongue depressor between the lips using only the contraction of the perioral muscles, without the help of the teeth. Keep the stick for at least 20 seconds and repeat 8 times.

The Button Exercise: place a smooth button, about an inch in diameter and attached to a thread or string, inside the lips in front of the teeth and close the lips over the button. Pull the string in a forward and upward direction to strengthen the upper lip, forward and downward to strengthen the lower lip, while holding the button in place with the lips. Be sure to exert a gradual traction on the button, and avoid clenching the teeth.

Fig. 40.2 Examples of orofacial myofunctional exercises. (**a**) Reeducation of the nose. (**b**) Exercises for lip seal. (**c**) Tongue posture exercises. (**d**) Exercises for abnormal swallowing

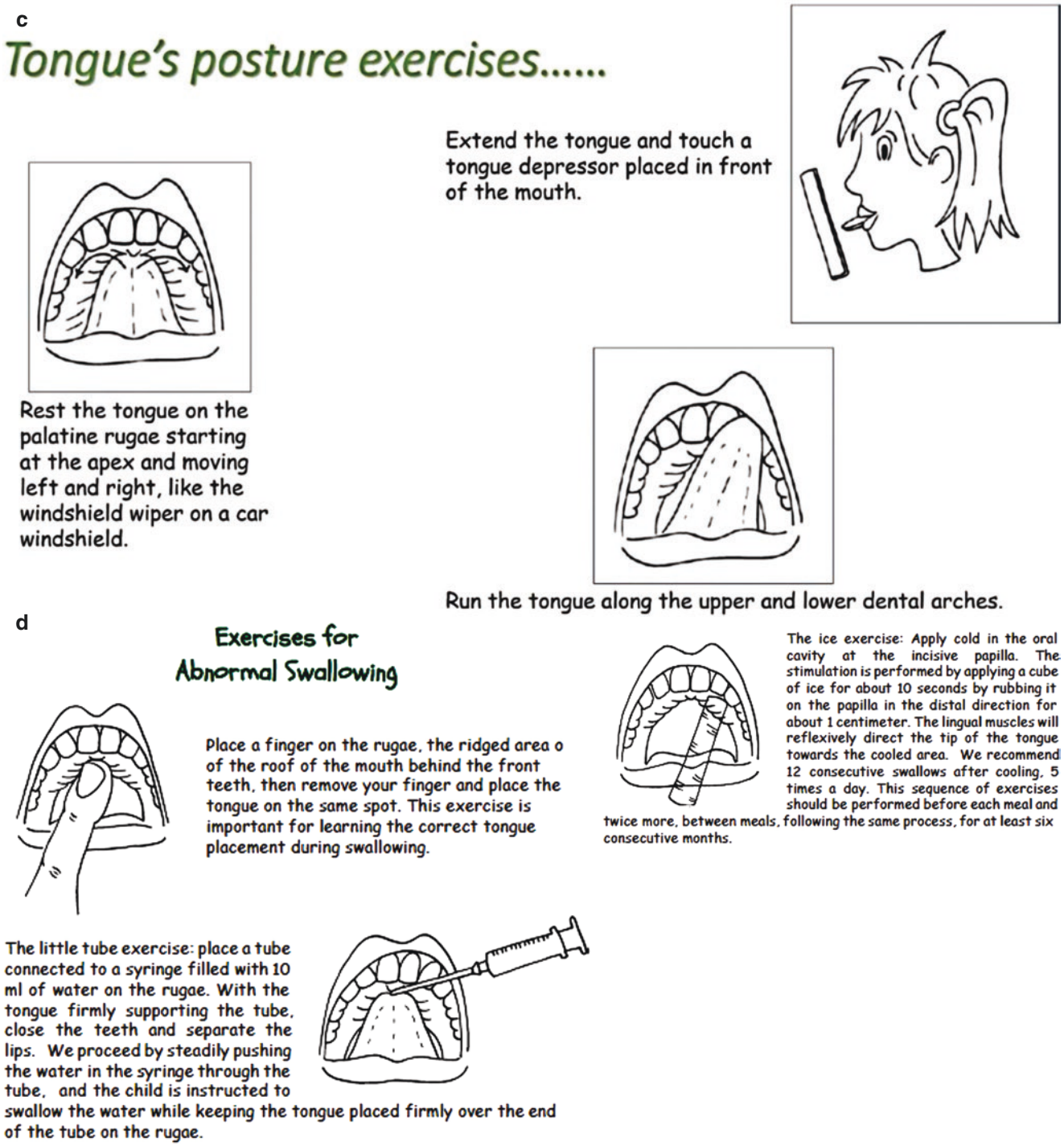


Fig. 40.2 (continued)

were assigned to the treatment group, and they performed PSG before and after 2 months of oropharyngeal exercises. We observed a 62% reduction in AHI (from 4.87 ± 3.0 ev/h to 1.84 ± 3.2 ev/h, $p = 0.004$) in the treatment group. Minimal change in AHI (4.56 ev/h to 4.11 ev/h) was found in the control group.

In another randomized control [25] on 54 children (mean age 7.1 ± 2.5 years, 29 male) with obstructive SDB, we demonstrated the efficacy of oropharyngeal exercises on sleep respiratory parameters. Mean oxygen saturation increased (96.4 ± 0.6 vs 97.4 ± 0.7, $p = 0.000$), and the oxygen desaturation index decreased (5.9 ± 2.3 vs 3.6 ± 1.8,

$p = 0.001$) only in children assigned to treatment group. Moreover, we evaluated in a randomized case-control study the effects of oropharyngeal exercises on tongue tone and symptoms in 54 children (mean age 7.1 ± 2.5 years, 29 male) with obstructive SDB [25]. Orofacial myofunctional characteristics, an assessment of tongue tone using Iowa Oral Performance Instrument (IOPI, IOPI Medical), and nocturnal pulse oximetry were performed at T0 and after 2 months (T1) in treatment and control groups. The IOPI objectively measures the tongue strength and endurance. Tongue strength is expressed as the maximum pressure in kPa exerted when an individual puts pressure with her tongue on a disposable, standard-sized tongue bulb against the roof of the mouth. The standard procedure and reference values for age have been previously validated by Potter et al. [27]. Maximum tongue pressure was measured in triplicate with each effort lasting approximately 1 second and with a rest period of 1 minute between trials. Endurance was measured by asking subjects to maintain 50% of their maximum pressure for as long as possible, and the duration of the endurance measurement was expressed in seconds.

In children who performed oropharyngeal exercises, oral breathing (83.3 vs 16.6%, $p < 0.0002$) and lip hypotonia (78 vs 33.3%, $p < 0.003$) were reduced, and normal tongue resting position (5.6 vs 33.4%, $p < 0.04$) was restored. Mean tongue strength (31.9 ± 10.8 vs 38.8 ± 8.3, $p = 0.000$), tongue peak pressure (34.2 ± 10.2 vs 38.1 ± 7.0, $p = 0.000$), and endurance (28.1 ± 8.9 vs 33.1 ± 8.7, $p = 0.01$) significantly increased in the treatment group. These data demonstrate that oropharyngeal exercises reduced respiratory symptoms during the night and mouth breathing, and increased tongue tone as measured by IOPI, in children with SDB. Moreover, subjects with SDB were found to have lower tongue strength as measured by the IOPI than healthy children, and authors have speculated that these aspects were probably due to the persistence of mouth breathing affecting tongue position and strength and possibly leading to orofacial muscle disorders and impaired growth of stomatognathic apparatus [15].

Cheng et al. [28] investigated the effects of an oropharyngeal motor training program on ten children with OSAS in Hong Kong. This reeducation training was performed to strengthen the tongue and oral-facial muscles by teaching individuals how to reposition muscles appropriately. Assessments were conducted at two time points: (a) before training and (b) 2 months post-training.

The training program consisted of ten individual mobilization exercises involving orofacial and pharyngeal area that required 45 minutes to complete. Each exercise had to be repeated ten times. Three outcome measures were chosen to study the effectiveness of the training program including tongue strength, tongue endurance level, and orofacial function. Tongue strength and tongue endurance level were assessed using the IOPI. The Nordic Orofacial Test-Screening (NOT-S) Assessment was used to assess the orofacial function. Seven out of ten participants completed the training program and attended the follow-up session after 2 months. The tongue strength (mean 38.00 vs mean 48.29 KPa, $p = 0.018$) and the scores of NOT-S of the seven participants were found to have significant improvement after training. Oropharyngeal motor training could improve the symptoms of children with OSAS such as oromotor function, including chewing, feeding, and reducing mouth breathing.

Mouth breathing and the resulting abnormal tongue position at rest and during sleep in children with SDB are more often associated with dento-skeletal malocclusions, as has been demonstrated by other authors [29, 30] for the consequent reduction in the modeling role of the tongue on the oral cavity [31]. The improvement in tongue function after 2 months of oropharyngeal exercises was accompanied by improved oximetry sleep parameters (mean oxygen saturation, reduced oxygen desaturation index). In children who followed the recommendations of oropharyngeal exercises with an aim to eliminate mouth breathing and recover nasal breathing, clinical and PSG improvements were achieved [32].

Other New Evidences

In a recent study, Chuang et al. [33] evaluated the short-term therapeutic effect of passive myofunctional therapy using an oral appliance during sleep in children with OSAS. The oral appliance is a one-piece, custom-made adjustable device for advancing the mandible. A bead is mounted on the lower part of the frame for the tip of the tongue to roll, which in turn places the tongue in a forward position, opening the airway [33]. The amount of mandibular advancement associated with the wearing of the device was 50%. Patients were instructed to wear their appliances and use their tongue to roll the bead (i.e., passive myofunctional therapy) during sleep every night. Twenty-nine children with OSAS were recruited and were divided into two groups: premature children and full-term children. All children wore an oral device to induce their tongue muscle activity during sleep for 6 months. Polysomnography during sleep was performed before and 1 week after the end of 6-month treatment. Both groups, full-term and premature children, had a significant decrease in the AHI. Prematurely born children had a significant decrease in the AHI during rapid eye movement sleep and in the mean heart rate during sleep [33].

Conclusions

Current literature demonstrates that orofacial myofunctional therapy plays an important role in the treatment of children with obstructive SDB and that orofacial myofunctional exercises could decrease AHI in children with residual OSAS. Oxygen saturations and SDB symptoms are improved when children perform orofacial myofunctional therapy. Treatment decreased mouth breathing, re-established nasal breathing, and improved orofacial muscle performance. Moreover, children with obstructive SDB have lower tongue strength, as measured by the IOPI, than healthy children, and oropharyngeal exercises can increase tongue tone.

Oropharyngeal exercise is repetitive muscle training, with specific gains in the coordination, tonicity, and endurance of the muscles, considering the specificity of the exercises adopted (isotonic and isometric). Oropharyngeal exercises represented a valid integrated treatment for children with mild to moderate OSAS and residual OSAS.

The objectives of orofacial myofunctional therapy are:

- Recover and improve dyskinetic orofacial muscle function
- Restore deficient orofacial muscle tone
- Reacquire correct posture (tongue, jaw, lips)
- Reeducate functions (swallowing, phonation, chewing, breathing)
- Reduce and eliminate habits such as thumb-sucking and pacifier use

When breathing problems during sleep are present, orofacial myofunctional therapy aims to restore the function of the nose as the main upper airway route for respiration. A multidisciplinary approach with standardized orofacial myofunctional evaluation in children with obstructive SDB is mandatory.

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Illustrative Clinical Cases

41

Oscar Sans Capdevila, Ehab A. Dayyat, and David Gozal

Case #1

ADHD and Delayed Sleep-Wake Phase Syndrome with RLS

Biographic Data

Michael is a healthy 13-year-old adolescent diagnosed with attention deficit hyperactivity disorder (ADHD) since he was 8 years old. Treatment for his ADHD is based on a multimodal approach: on one hand, the application of a series of methodological curricular adjustments at the school level and a specific reeducation work and, on the other hand, pharmacological treatment based on methylphenidate, which was started in progressively increasing doses until reaching a maintenance dose of 1.2 mg/kg/day, with excellent response in the control of the core symptoms of ADHD and good tolerability.

Chief Complaint

Michael and his parents came to the Sleep Clinic with the chief complaint of difficulties falling asleep, restless sleep, and unrefreshed sensation upon awakening, with lack of energy and stamina throughout the whole day. ("I am exhausted by the end of the day.")

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Family History

Father diagnosed with restless legs syndrome (RLS) at the age of 45. Father required evaluation and treatment in an adult sleep unit for his RLS.

Personal History

No past medical history (PMH) or past surgical history (PSH). In addition, he met all milestones appropriately with normal development.

Sleep-Specific History

Michael reports difficulties initiating sleep for several years, which have worsened in the past year. Parents report sleep onset latency of close to 2 hours, which is corroborated by a sleep diary record carried out during 14 days during Christmas holidays (Fig. 41.1). He falls asleep every night between 1:00 and 3:00 AM, and his wake-up time is between 12:00 and 13:00 early afternoon. On a regular school week schedule (Fig. 41.2), he goes to bed at 10:30 PM, with SOL of 2–3 hours. He must wake up at 7:30 AM in order to be in school at 8:00 AM. Bad sleep habits during sleep include the use of an electronic tablet or mobile phone to chat with friends or to watch series on TV until he falls asleep. Snoring is not observed, and no witnessed apneas are reported. No history of parasomnias, except for sporadic episodes of sleep-talking (somniloquy).

No frequent nocturnal awakenings, but for the last 4–5 months, he has been suffering from what he called "leg tickling, or heebie-jeebies, creepy spiders crawling up on my legs." This discomfort in both legs is usually located on the soles of both feet and calves. This unpleasant sensation appears predominantly in the evening hours (or the moments before falling asleep) and when sitting for a long time at school (daytime). This uncomfortable feeling on legs and feet has started to awaken him during the night. To relieve the discomfort, Michael moves, stretches, tosses, and turns his legs or even gets up and walks or runs around. Getting a massage in the affected area sometimes will provide a quick relief.

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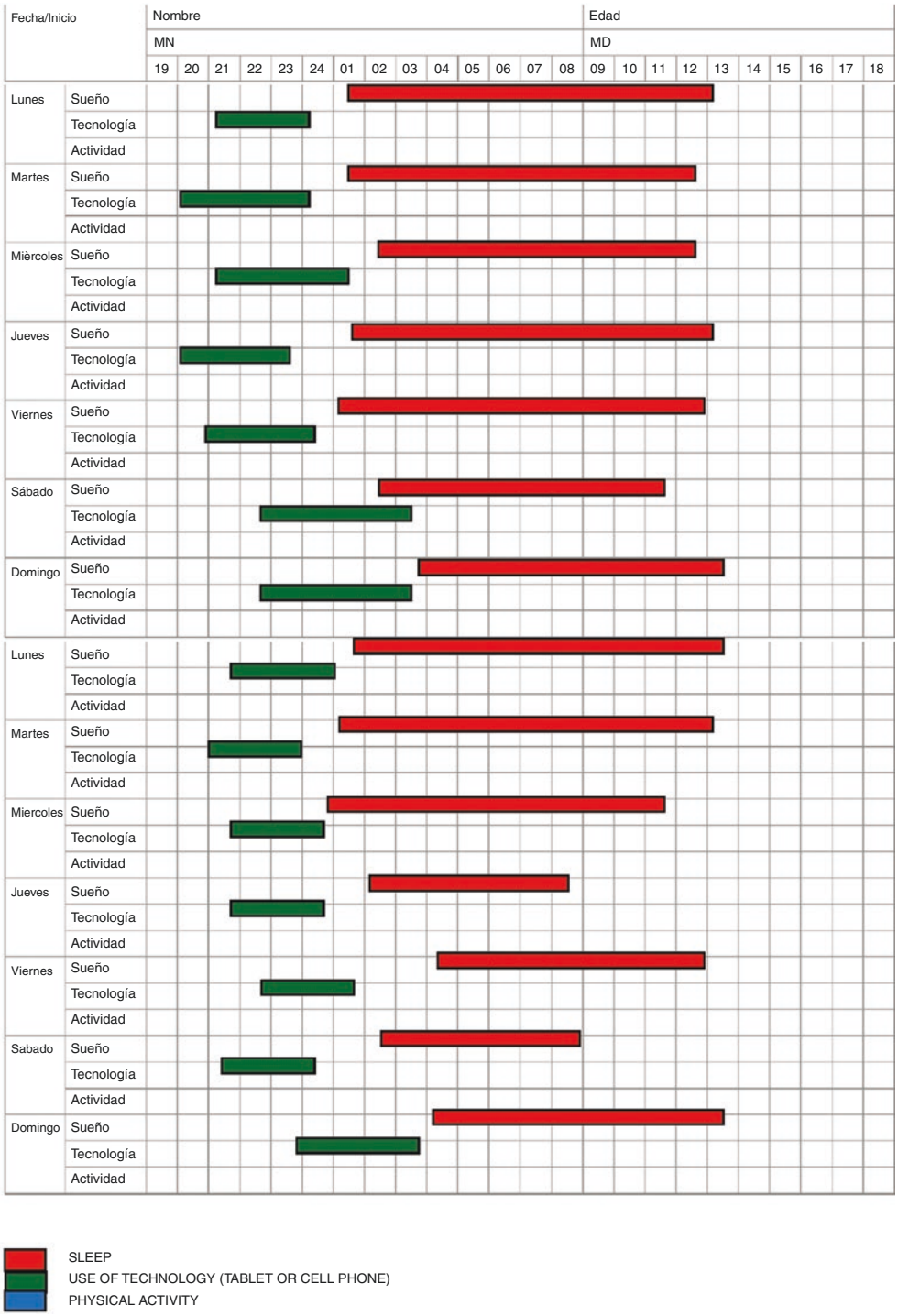

Fig. 41.1 Sleep diary during vacation (Christmas holidays)

General Examination

During the neurological examination, the patient is reactive and collaborative and establishes an adequate social contact. He is an active, restless boy who interrupts frequently during the consultation. The remainder of the physical examination is within normal for the patient's age.

Complementary Tests Performed

General lab work analysis includes study of iron and thyroid hormone profile. Serum ferritin level of 20 micrograms/liter was shown, without associated anemia. Normal T3, T4, and TSH levels are found.

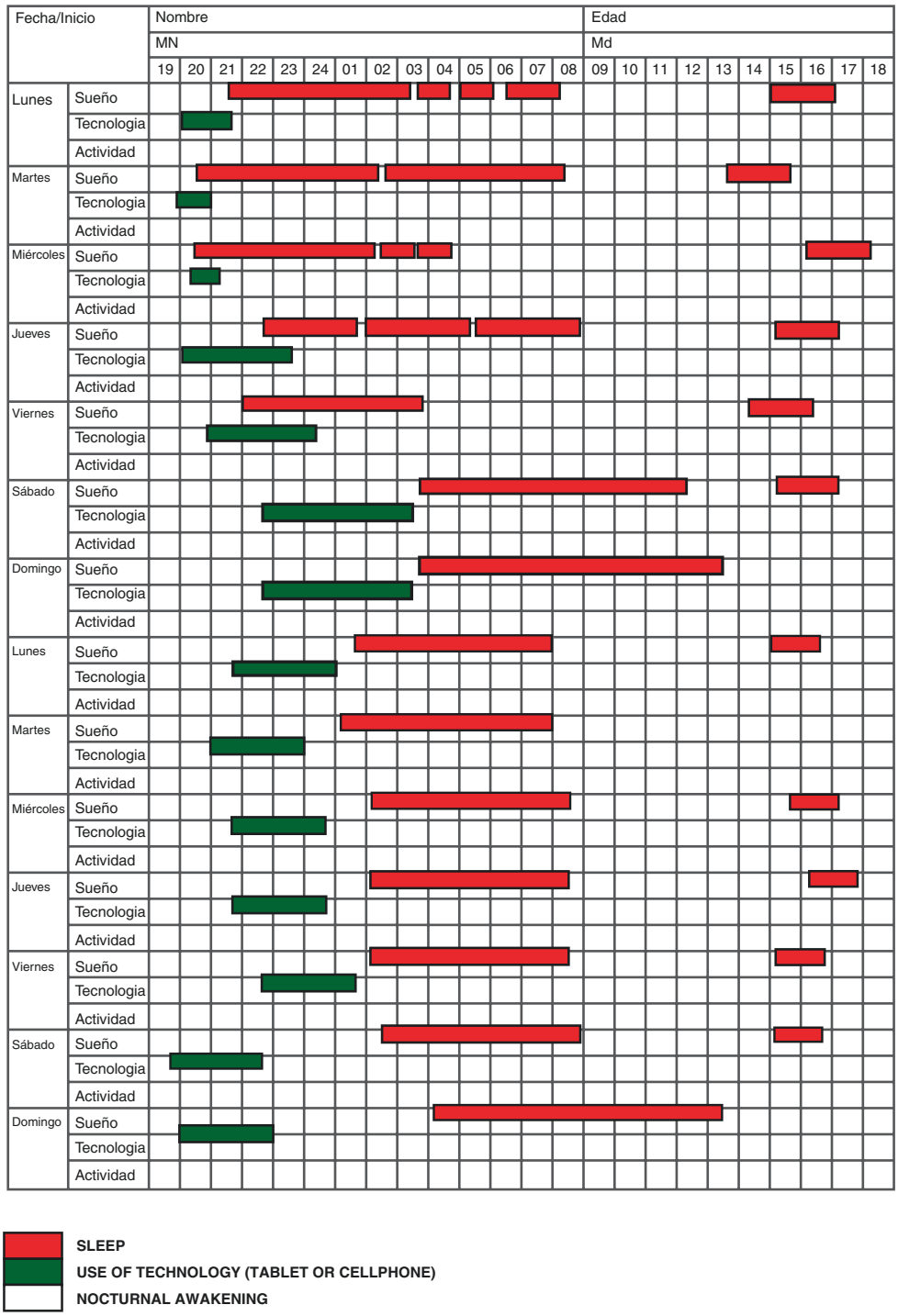

Fig. 41.2 Two-week sleep diary during school period

1. Looking at the two sleep diaries, what do you think is Michael's sleep onset problem condition?
   A. Sleep onset insomnia
   B. Irregular sleep-wake rhythm disorder
   C. Delayed sleep-wake phase disorder
   D. Non-24-hour sleep-wake rhythm disorder

Answer: C

This is one of the most common circadian rhythm disorders. Patients with delayed sleep-wake phase disorder (DSWPD) fall asleep later than they would like and find it difficult to wake up on time in the morning. DSWPD often interferes with work, school, or social responsibilities. Delayed pattern leads to chronic symptoms of insomnia and excessive sleepiness associated with impairment in daytime functioning [1]. As demonstrated by the sleep diary

(Fig. 41.1), Michael suffers from DSWPD, rather than from sleep initiation insomnia. The diagnosis of DSWPD is largely based on obtaining a detailed sleep history of a sleep and wake pattern that is chronically and stably delayed. A sleep diary and/or wrist actigraphy for at least 7 consecutive days (longer if possible) is indicated to establish the habitually delayed sleep/wake pattern. In addition, biological markers of circadian timing can be useful and are desirable if available. Dim light melatonin onset (DLMO) and nadir of core body temperature have been used in clinical practice and confirm the expected delayed phase. Nocturnal polysomnography is not indicated unless there is suspicion of concomitant disorders, such as sleep disorder and other causes of insomnia or daytime sleepiness [2]. DWSPD is strongly associated with anxiety and depression, so mood disorder screening should be considered in all patients [3].

Differential diagnosis with primary insomnia is needed in patients with DSWPD. As shown in our case, when patients with DWSPD can choose their natural preferred schedules (see sleep diary during winter holidays in our case), their sleep is usually of normal quality and duration for age [1].

In patients with ADHD, multiple studies have opened the possibility that primary insomnia is due, at least in part, to a circadian rhythm disorder (with delayed endogenous melatonin secretion during the evening compared to the general population). Behavioral factors, also, precipitate and perpetuate DWSPD. For example, the delayed sleep and wake times of patients with DWSPD are often associated with less light exposure in the morning and more light exposure in the evening, especially with the use of electronic devices—tablets and cell phones—whose blue/white light spectrum further delays melatonin secretion [1].

2. According to the treatment for the delayed sleep-wake phase disorder (DSWPD), pick the most appropriate statement:
   A. Sleep hygiene and good sleep habits must include avoidance of bright light at evening and night.
   B. Multimodal approach for the treatment of DSWPD includes the use of oral melatonin.
   C. Bright light therapy in the morning results in phase advance, improving sleep onset time.
   D. All the options above are correct.

   Answer: D

In ADHD, multiple studies have opened the possibility that insomnia is due in part to a circadian rhythm disorder (with delayed endogenous melatonin secretion during the evening compared to the general population).

The management of DSWPD requires a combined approach using behavioral techniques, strategic and planned progressive manipulation of light/dark exposures, and, in some patients, pharmacological agents. The treatment of DSWPD includes adherence to good sleep habits, regular sleep and wake times, chronotherapy, timed bright light therapy, and pharmacotherapy. Chronotherapy is a treatment in which the sleep and wake times are progressively delayed by about 3 hours every 2 days until a final earlier bedtime schedule is achieved and maintained. Although effective, adherence is generally poor due to the requirement for the strict scheduling of social, school, and work activities and careful control of the time of light exposure. Despite its challenges, chronotherapy is particularly useful in treating children and adolescents [1–3].

Timed bright light therapy is one of the most used treatments for DSWPD. Exposure to light in the biological evening or early night phase delays circadian rhythms, while exposure to light in the morning results in phase advances [1–3]. Therefore, bright light of 2000 to 2500 lux for 2 hours in the biological morning, combined with avoidance of bright light exposure in the biological night, can effectively achieve earlier sleep and wake times in DSWPD patients. Exposure to bright light between 7:00 and 9:00 AM is usually effective for most DSWPD patients. However, for patients who are more severely delayed (whose endogenous sleep time is after 3:00 AM and wake time is after 9:00 AM), the time of morning light exposure should be given later in the morning (shortly after awakening) to avoid light exposure before the nadir of core body temperature which could further delay circadian rhythms. Compliance with light therapy can be challenging due to the inability of patients to awaken in the morning for light exposure and the need to restructure their social and professional activities around the light regimen. Light therapy in the morning should be accompanied by avoidance of bright light in the evening by using sunglasses or decreasing ambient light intensity [2].

Due to some of the practical limitations of chronotherapy and timed bright light therapy, the benefit of taking melatonin in the evening has been investigated. The effectiveness of melatonin administration in the evening in the treatment of DSWPD has been demonstrated in several studies [4–9]. Appropriately timed melatonin (in the early evening) has been shown to decrease sleep latency, increase sleep duration, and improve function in DSWPD patients. One small placebo-controlled study in DSWPD patients showed that administration of melatonin 0.3 or 3 mg about 6 hours prior to their sleep time resulted in the largest phase advances of sleep and wake times [6]. Although melatonin is indicated as a treatment for DSWPD, large, randomized, placebo-controlled studies are still needed to establish a standard clinical approach for its use [1].

In addition to light and melatonin, treatment of DSWPD should also include proper sleep hygiene, such as adherence to regular sleep-wake times and structured social and physi-

cal activity schedules, and address other factors, such as comorbid psychopathology and other sleep disorders [1].

3. Regarding Michael's discomfort in legs and calves, which of these options seems to be more accurate?
   A. Due to his ADHD, he is extremely nervous and anxious, and the urge to move his legs is associated with this condition.
   B. From the clinical point of view, a diagnosis of restless legs syndrome (RLS) could be made, except that in children this condition has not been described.
   C. From the clinical point of view, a diagnosis of RLS can be made, especially with the association of a concomitant ADHD.
   D. From the clinical point of view, a diagnosis of RLS could be made, except that daytime symptoms should not be present in patients with RLS (it's a nocturnal phenomenon).

Answer: C

Restless legs syndrome (RLS), also called Willis-Ekbom disease, is a sleep disorder in which the child or adolescent reports an uncomfortable and irresistible urge to move his or her legs. This urge usually happens at bedtime but can occur at other times when the legs have been inactive, such as when sitting still for a long period of time (at school, during long car rides, or while watching a movie). In the pediatric age, it is a common disorder and is in many cases associated with attention deficit hyperactivity disorder (ADHD). Yet, it remains "the great unknown" in pediatrics. Pediatricians do not usually think of it when examining a child with sleep problems, and there is even a tendency to deny its existence in children [10]. Symptoms of restless legs include *leg discomfort*: uncomfortable leg sensations. Children may describe these sensations as "got to move, wiggle, or kick." These sensations usually occur at bedtime but can occur at other times of leg inactivity. *Urge to move legs*: To relieve leg discomfort, children and adolescents have an uncontrollable urge to move their legs, especially when resting, such as when sitting or lying down. *Sleep disruption*: Additional time is often needed to fall asleep because of the urge to move the legs to relieve the discomfort. Sometimes staying asleep may also be difficult. *Bedtime behavior problems*: Because children have a hard time falling asleep, they may not always stay in bed and sometimes need to get out of bed to stretch their legs to relieve discomfort. *Daytime sleepiness*: Problems with falling asleep and staying asleep may result in daytime sleepiness. *Behavior and school performance problems* may emerge in the child's academic performance or in daytime behavior (irritability, difficulty concentrating, hyperactivity, etc.) [10–15].

The exact cause of restless legs syndrome varies from child to child. In some cases, the cause is not known. In other children, RLS can be related to a low iron level or sometimes is associated with diabetes, kidney, or some neurological diseases. RLS sometimes runs in families, and there is thought to be a genetic link in these cases. Many different types of drugs including those used to treat depression, allergies, and psychiatric disorders, as well as nicotine and caffeine, may cause RLS as a side effect [10, 14]. The differential diagnosis includes other conditions associated with leg discomfort such as nocturnal leg cramps, positional discomfort, arthritis, Osgood-Schlatter, neuropathies, and various types of dermatitis. As mentioned earlier, several medical conditions can be associated with RLS including pregnancy, iron deficiency, renal failure, and children receiving dialysis. It is important to ask for the typical topographic distribution of RLS symptoms in taking the history. Although true RLS can exist in almost any part of the body, the typical distribution is in the thighs and calves [14]. Parents should be advised to avoid caffeine in these children. Regular sleep routines and good sleep hygiene are essential for the management of RLS in children [10, 14]. Sleep hygiene practices that should be encouraged include regular sleep and wake schedule, avoidance of heavy exercise and large meals close to bedtime, limiting exposure to bright light at night, and eliminating stimulating activities at night [14].

4. Regarding iron levels and symptoms of restless legs, pick the correct answer:
   A. In our clinical case, the patient had no anemia (normal iron plasma levels) with low ferritin levels, but within normal range. If there is no anemia, no action is required.
   B. Restless legs syndrome (RLS) is a common condition in children and adolescents. It is likely that if left untreated, it may lead to adverse cardiovascular and neurocognitive consequences.
   C. Non-pharmacological treatment of RLS (proper sleep hygiene and good sleep habits) is not as important as pharmacological measures.
   D. Dopaminergic medications are widely used and considered as the first line of treatment in pediatric patients with RLS.

Answer: B

ADHD and RLS have common symptoms and frequently share a common etiopathogenesis (low iron storage or iron deficiency anemia). Children with ADHD are more likely to have iron deficiency, and treatment with supplemental iron has been reported to improve sleep quality and subsequently decrease ADHD symptoms [11, 13–15]. Children with low iron storage, as defined by low-serum ferritin levels, may benefit from iron therapy. Several studies have suggested the benefit of raising serum ferritin above 50 ng/ml [14, 15].

The dose of iron therapy is 3 mg of elemental iron/kg/day. The duration of treatment used in our previous study was 3 months followed by slow tapering of the dose for a period of 1 year. The preliminary long-term follow-up of these children treated with iron therapy showed consistent evidence of sustained clinical improvements 1–2 years after iron therapy, with serum iron and ferritin remaining at adequate levels. *Iron therapy seems to lead to long-lasting improvement in clinical symptoms, and should be considered as the initial option, when serum ferritin levels are < 50 ng/ml* [14, 15].

While there is overall limited experience regarding the use of dopaminergic agents in children with RLS and PLMD, published reports suggesting efficacy of compounds such as levodopa, ropinirole, pramipexole, and pergolide have emerged. Other medications including benzodiazepine, anticonvulsants, and alpha-adrenergic and opioid medications have not been adequately studied in children [10, 14, 15].

A subsequent polysomnographic study on 55 ADHD children showed that ADHD children reported motor restlessness (50%), sleep walking (47.6%), night terrors (38%), confusional arousals (28.5%), snoring (21.4%), and leg discomfort at night associated with RLS (11.9%). The diagnosis of RLS was found in 14 children (25.4%) of the ADHD sample, and PLMS were recorded in 40%. The presence of RLS worsens ADHD symptoms, and strong significant correlations emerged for ADHD hyperactive subtype and RLS scoring, PLMS and PLMW indexes, and opposition scores [16].

Using Melatonin with Tryptophan and Vitamin B6

There is evidence that L-tryptophan levels are lower in children with ADHD. However, the intake of L-tryptophan supplements does not seem to improve the symptoms of ADHD, although they can improve latency at the onset of sleep in these patients. Tryptophan metabolism is complex and has many processes, requiring an adequate amount of biopterin, vitamin B6, and magnesium for its correct absorption and distribution. Vitamin B6 is involved in the conversion of tryptophan to serotonin and in the metabolism of other metabolites, for example, kynurenine. Sleep latency can be significantly reduced by orally administering melatonin with tryptophan and vitamin B6. In this case, we will administer the melatonin with tryptophan and vitamin B6 also between 4 and 6 hours before the actual conciliation time, determined by the sleep schedule [17].

Conclusion

Why is it important to ask about sleep in children with ADHD?

ADHD affects 5% of children and adolescents, while the different sleep disorders affect from 2–4% (obstructive apnea) to 20–30% (insomnia), so they can coexist. Thus, considering that between 25 and 50% of boys with ADHD may present sleep disturbances and that these affect their quality of life, emotional well-being, and school performance, systematic evaluation of sleep in the pediatric population is imperative. There is evidence of the effect of poor-quality sleep on increasing daytime sleepiness, on behavioral regulation, and on other functions of the prefrontal cortex, including attention. In addition, sleep disorders can not only produce ADHD-like symptoms, exacerbate ADHD symptoms from subclinical to clinical levels, or aggravate an established ADHD but also affect mood (which helps worsen behavior and decrease response treatment).

The relationships between sleep and attention deficit hyperactivity disorder (ADHD) are complex and are routinely overlooked by practitioners. Motricity and somnolence, the most consistent complaints and objectively measured sleep problems in children with ADHD, may develop as a consequence of multidirectional and multifactorial pathways. Therefore, subjectively perceived or reported restless sleep should be evaluated with specific attention to restless legs syndrome or periodic limb movement disorder, and awakenings should be queried with regard to parasomnias and sleep-disordered breathing. Sleep hygiene logs detailing sleep onset and offset quantitatively, as well as qualitatively, are required. More studies in children with ADHD are needed to reveal the 24-hour phenotype or its sleep comorbidities [12].

Case #2

Epilepsy and Sleep Disturbances (Insomnia)

Biographic Data

Jennifer is a 28-month-old baby girl who is followed in our department of pediatric neurology for a recent onset epileptic encephalopathy. She had no relevant perinatal history. She was the first child of non-consanguineous parents, with no family history of epilepsy or other sleep or neurological disorders.

Epilepsy began at 24 months of age as generalized tonic-clonic seizures. Later, the seizures increased in frequency until they became daily and were associated with others of different semiology: myoclonic, atonic, and atypical absences. These seizures were resistant to different antiepileptic treatments, including valproic acid, ethosuximide, lamotrigine, zonisamide, levetiracetam, clobazam, and ketogenic diet.

Electroencephalograms (EEG) showed normal baseline activity with spike-wave-type generalized epileptiform activity (Fig. 41.3).

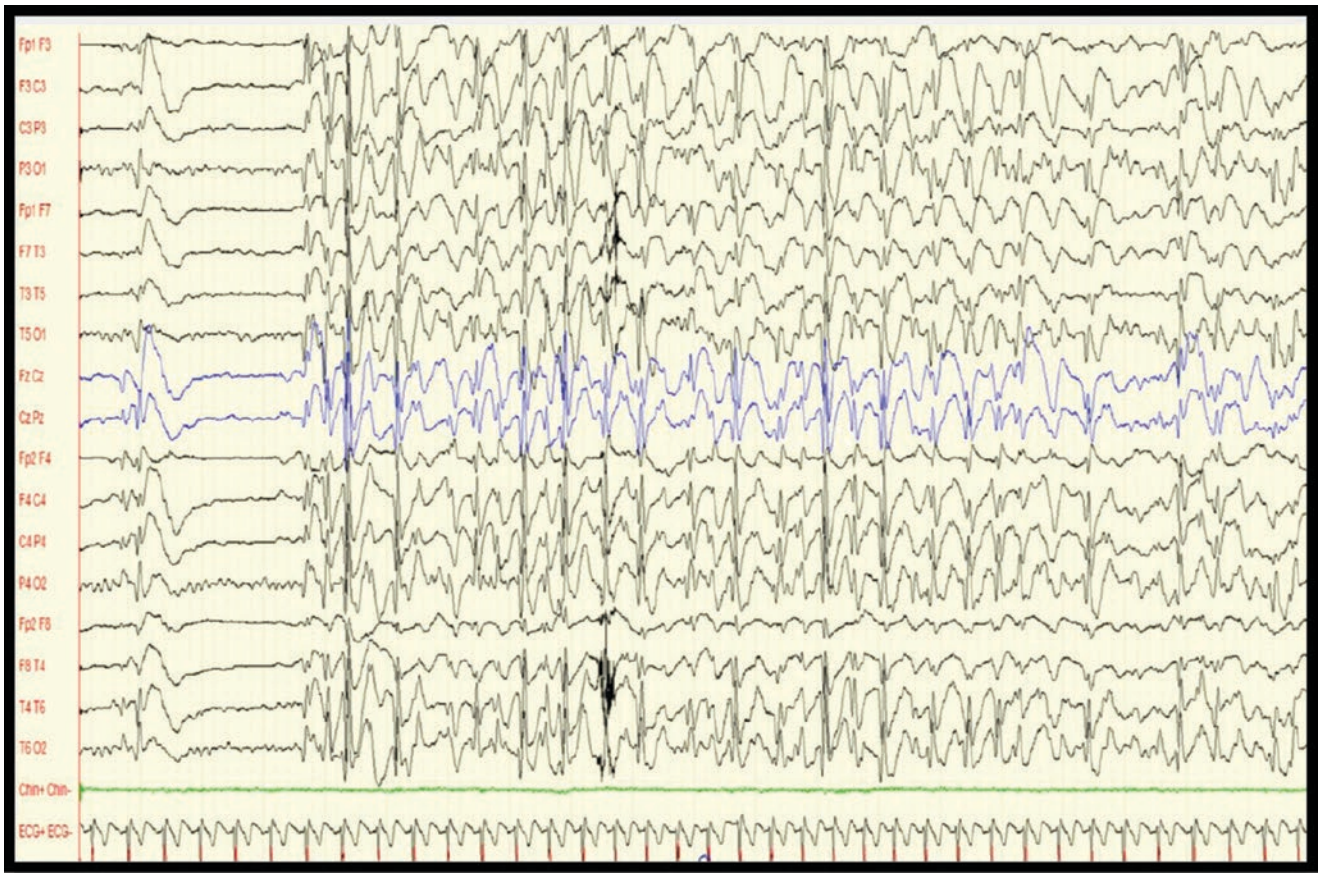

Fig. 41.3 Generalized spike-wake discharge in our 28-month-old patient (Case #2)

The psychomotor development of the patient prior to the onset of the seizures had occurred at the lower limit of normality; gait began at 19 months, emission of referential bisyllables after 22 months, and slight fine motor problems, without apparent impairments, as far as social interactions. Coinciding with the onset of the crises, there was a regression in these developmental milestones, with the emergence of a more unstable gait and loss of emission of referential bisyllables. The physical examination revealed a trunk ataxia, and the tendon reflexes were symmetrically increased without other neurological focus or abnormalities.

Brain MRI, intermediate metabolism studies, and genetic study using an expanded panel of epilepsy genes were normal.

Sleep-Specific History

The patient, prior to the onset of epilepsy, had inadequate sleep hygiene: Sleep onset took place in parents' room; they all slept in the same bed (secondary co-sleeping). After sleep onset, secondary co-sleeping continued because parents were afraid of not being able to be aware or detect a nocturnal seizure if Jennifer slept in her room. The patient had multiple awakenings (3–4 per night). "Awakenings" were short (less than 5 minutes); Jennifer appeared to be unconscious and little responsive to external stimuli except for the response to her parents' comforting strategies (gentle rocking or, more often, with bottle feeding).

Evolution

In consecutive follow-ups, it became evident that worsening of patient's sleep pattern is one of the factors that most compromises the family's quality of life. Since the onset of epilepsy, patient's sleep worsened both in conciliation and maintenance. She went to bed with the presence of her parents at 8:30–9:00 PM by her side and fell asleep within 30–45 minutes with parents using an electronic tablet with her preferred cartoons. After sleep onset, the patient presented 4–7 awakenings per night. All awakenings were relatively short with Jennifer taking 10–45 minutes to fall asleep again. In addition, she presented an early awakening around 5:00–6:00 AM, after which she did not go back to sleep. She took an occasional 30-minute nap (frequency 2–3 naps per week) without a specific scheduled time (any time from 2:00 to 5:00 PM). Parents did not report snoring or witnessed apneas. She presented motor restlessness during sleep but did not wake up with apparent pain. There was no family history of restless legs syndrome. The presence of gastroesophageal reflux, constipation, and other medical problems that could fragment sleep, such as pain or dermatological diseases, was ruled out.

Associated with this worsening in her sleep patterns, the patient showed greater irritability, motor restlessness, and a worsening of attention during the day. This sleep fragmentation was not explained by the presence of epileptic seizures. Although she had myoclonic seizures during sleep, most of the seizures occurred while the patient was awake.

Parents consulted other specialists for her sleep problems, and different pharmacological treatments, including antihistaminic drugs (alimemazine) and immediate-acting melatonin, were started without any benefits.

This sleep maintenance insomnia did not change as a function of the antiepileptic drugs being used. Blood tests were performed and showed that the CBC, renal profile, 25-OH vitamin D, anti-transglutaminase antibodies, and ferritin values (54 ng / ml) were all within normal limits. A 2-week sleep diary was obtained to assess patient's sleep pattern (Fig. 41.4).

Fig. 41.4 Sleep diary for 2 weeks illustrating sleep-wake activity patterns in Case #2

1. After analyzing the patient sleep diary, what would be the most probable diagnosis?
   A. Insomnia due to seizure disorder
   B. Insomnia due to circadian rhythm disorder
   C. Insomnia due to bad sleep habits (behavioral insomnia)
   D. Normal sleep pattern in a patient with a mild neurodevelopmental delay

Answer: C

After a thorough look at the sleep diary and realizing that nocturnal seizures were not the cause of the multiple nocturnal awakenings, we talked to the family, and sleep hygiene measures and behavioral techniques were implemented. The "three-step rule" was recommended to parents: introduction of a regular wake-sleep rhythm (going to bed and getting up at the same time), adjusting the hours for sleep onset and wake-up to individual needs (according to patient circadian rhythm), and instruction of helping the patient to fall asleep alone without the presence of parents and without the help of technology (tablet with cartoons). After explaining different behavioral techniques to the family, the initiation of gradual extinction techniques was chosen to be the most suitable technique for the parents to apply.

After 4 weeks of sleep hygiene and behavioral technique implementation, parents came for a follow-up visit. Nocturnal awakenings had decreased dramatically from 4–6 to 2–3 per night. They still had problems with sleep onset (more than 30 minutes). At this point, the use of oral immediate-acting melatonin (4–6 drops (1–1.5 mg total dose)) administered 30 minutes prior the desired bedtime was recommended along with the behavioral interventions.

Four weeks after the introduction of this treatment, the sleep diary (Fig. 41.5) showed an improvement in the patient sleep patterns. Sleep onset was achieved in 5 minutes or less, and the frequency of awakenings decreased to 1 or none per night. Jennifer sleep schedule went from 9:00 PM to 8:00–9:00 AM. Along with nocturnal sleep amelioration, daytime alertness and mood also improved. After improving the sleep pattern, an initial reduction in the number of seizures (> 30%) was achieved, although after 2 months the frequency of seizures returned to the previous frequency.

2. Regarding the treatment of behavioral insomnia in children, pick the correct answer:
   A. The treatment of choice for behavioral insomnia is the application of sleep hygiene measures and a cognitive-behavioral approach.
   B. The treatment of choice for behavioral insomnia is implementation of melatonin.
   C. The treatment of choice for behavioral insomnia is implementation of antihistaminic drugs.
   D. The treatment of choice for behavioral insomnia is implementation alpha-agonist drugs.

Answer: A

The International Classification of Sleep Disorders (ISCD-3) defines childhood behavioral insomnia as the one which occurs as a result of an inappropriate association for sleep onset (child depends on a specific stimulation with objects or certain adjustments such as the presence of parents for initiating sleep or going back to sleep after awakening) and/or the establishment of inadequate limits for bedtime (resistance of the patient to go to bed, reinforced by an inappropriate or inconsistent use of limits by the caregiver) [18].

It is estimated that ~30% of children between 6 months and 5 years of age suffer from insomnia, with 5% being secondary to medical causes, while the remaining 25% is of behavioral origin. Chronic sleep deprivation translates into behavioral, cognitive, and emotional impairments, as well as endocrinological or cardiovascular alterations, among others. The consequences of insomnia are more serious when it occurs during the first 6 years of life, coinciding with the period of greatest neuroplasticity. This need for early identification together with the possibility of diagnosing insomnia without the need for excessive complementary tests, like in our clinical case, which was carried out by means of a directed history-taking and sleep diary, means that the diagnosis and treatment of insomnia should be carried out at any level of care, in either primary or specialized care [19].

The treatment of choice for behavioral insomnia is the application of sleep hygiene measures and a cognitive-behavioral approach. Although hypnotics in isolation are not indicated due to the lack of efficacy in this type of insomnia, their use is unfortunately widely implemented in clinical practice. In a study among 671 pediatricians in the United States, 75% responded that their first option for insomnia titration was the use of sleep drugs: melatonin, antihistamines, or alpha agonists [20].

It is known that those children who manage to fall asleep autonomously will achieve longer sleep duration, fewer awakenings, and a shorter sleep latency compared to patients who are dependent on their parents to initiate sleep [21]. One of the most effective and widespread methods is application of extinguishing or reinforcement technique strategies based on published work by Ferber et al. [22]. Although these methods are safe, their implementation is often complicated because in the first 2 or 3 days there is usually a transitory increase in behavioral problems (crying and complaints from the child), which usually leads to the abandonment of this approach by family members.

It is important to point out that there are different behavioral techniques so we must individualize which one to choose, according to the patient and family. For that matter,

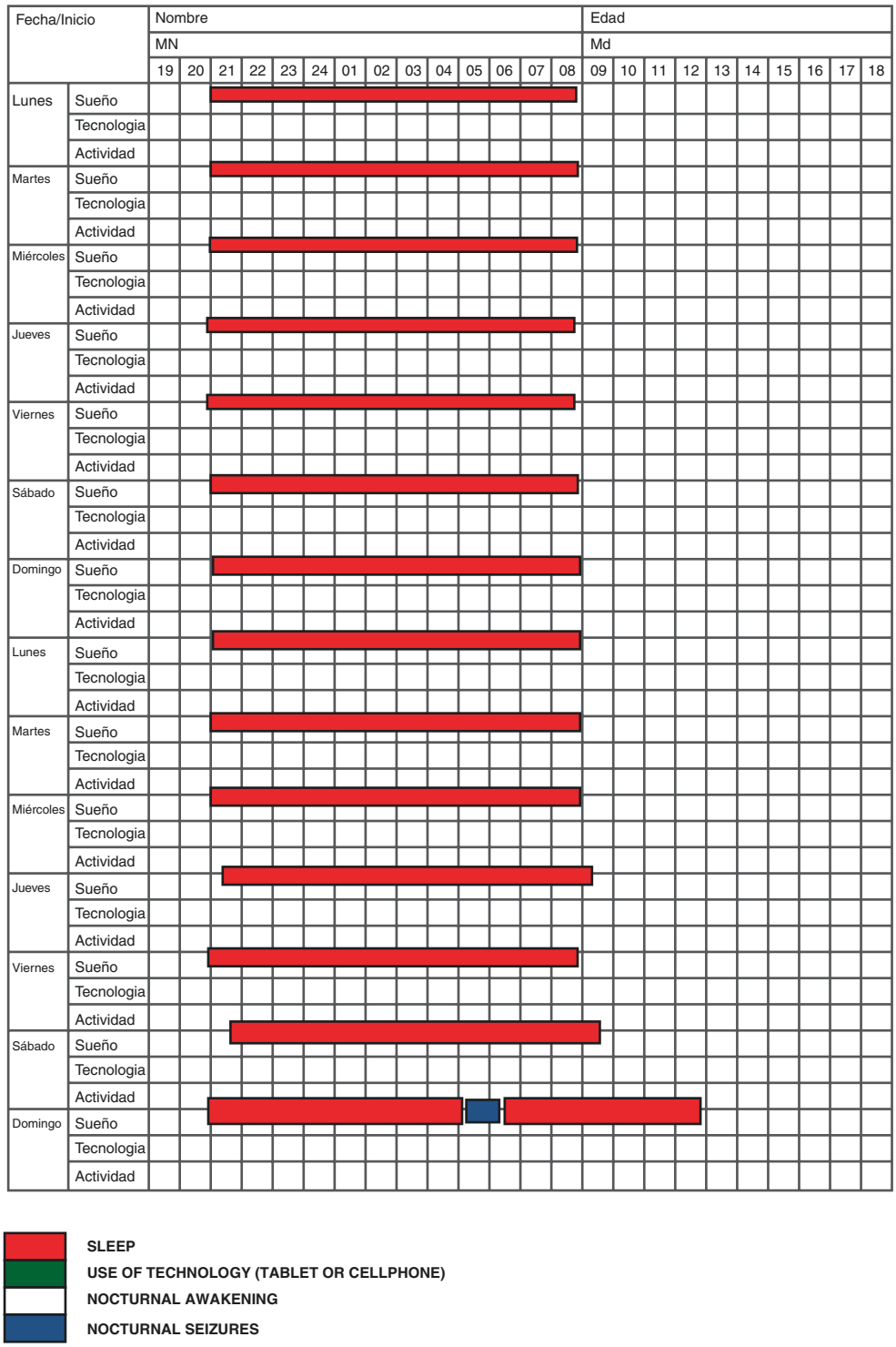

Fig. 41.5 Two-week sleep diary in Case #2 after intervention

the use of the "family tolerance questionnaire" may be particularly useful [23].

The use of hypnotics (especially melatonin) as an adjuvant to optimize implementation of behavioral techniques by the parents can be taken into consideration. Melatonin produces an increase in homeostatic sleep pressure making easier for parents to apply this behavioral approach. Effects must be evaluated after 4 weeks [24].

Conclusion

The relationship between epilepsy and sleep is bidirectional. It is common for patients with epilepsy to suffer from sleep disorders. In a recent study, Tsai et al. found that in 111 infants and preschool children with epilepsy, 78.9% had chronic sleep deprivation (slept less than 10 hours/day), 83.3% suffered from maintenance insomnia (more than an

hour awake during the night), and up to 32% had developed a poor sleep routine (non-regular hours, co-sleeping, and resistance to going to bed) [25]. Sleep in children with epilepsy as measured by polysomnography shows a shorter total sleep time, worse sleep architecture, as well as high sleep fragmentation due to frequent arousals, number of seizures, and epileptiform abnormalities [26, 27]. This impaired sleep quality is due to several reasons, such as the use of antiepileptic drugs that cause insomnia (lamotrigine or ethosuximide, among others), lower synthesis of melatonin, lower percentage of REM sleep, and decreased total sleep time [27].

On the other hand, sleep deprivation worsens the frequency and intensity of epilepsy. Thus, there are studies that suggest that adequate treatment of sleep apnea syndrome (which is estimated to affect 10–20% of children with epilepsy) translates into a reduction in the frequency of epileptic seizures [28].

In the clinical case, our patient had sleep onset and maintenance insomnia that was resolved with the application of adequate sleep hygiene, behavioral techniques, and melatonin. Although initially it was feared that melatonin could trigger seizures, the administration of melatonin has subsequently been shown to be safe in patients with epilepsy [29].

In our patient, the amelioration of her sleep pattern was accompanied by a decrease in the frequency of seizures, but this initial improvement was not sustained. This is probably due to the existence of other factors inherent to the etiology of the epilepsy (probably genetic) and to the progressive nature of epilepsy in her case.

Due to the uncertainty of having a nocturnal seizure, family members of children with epilepsy are four times more likely to sleep less (on average 30 minutes) than parents of children without epilepsy and therefore experience greater daytime sleepiness [30]. As in our case, the improvement in sleep quantity and quality of a child with epilepsy led to a clear improvement in the quality of life of the whole family.

Case #3

Central Congenital Hypoventilation Syndrome (Late Onset)

Alex is a 4-year-old boy referred to our sleep unit for a second opinion. He was seen at a different sleep center at the age of 3 years, where he presented with the chief complaint of habitual snoring and witnessed apneas. In the sleep study (video polysomnography) performed in that center, central and obstructive apneas and hypopneas were found. The apnea hypopnea index (AHI) was 12 (4.6 was the index for obstructive apneas and hypopneas, and 7.4 was the index for central apneas). Mean O_2 saturation was 97%, and the lowest O_2 saturation during sleep was 92% after an obstructive event. The percentage of time with $SpO_2 < 90\%$ (CT 90%) during the study was 0%, and no CO_2 measurements were performed.

With the results of this video polysomnography (vPSG), the patient was sent to the ENT for surgical removal of tonsils and adenoids. Surgery was done without complications. Eight weeks after surgery, a repeat vPSG was performed. Results showed an AHI of 10 (all central apneas). The mean O_2 saturation was 98%, and the lowest O_2 saturation during sleep was 91% after a central event. The CT 90% during the study was 0%. No CO_2 assessment was performed.

At the age of 4 years during his visit, parents were concerned about the elevated number of central apneas found in the control vPSG done 8 weeks after T&A surgery. Alex was a healthy boy with normal development. Medical history was positive for Hirschsprung disease, with successful surgery when he was 4 days old. Parents referred no problems prior, during, or after the two surgeries, as well as no problems recovering from anesthesia.

Specific Sleep History

Parents did not report problems initiating or maintaining sleep, no snoring or witnessed apneas were observed by parents, and no excessive movements during the night seemed to be present. He slept 10 hours per night on a regular basis, had no problems during the day, and showed no signs of excessive daytime sleepiness. No naps during the day.

1. Given that clinical case presentation, what would you do next?
   A. Nothing, patient is alright. There are no signs of altered quality or quantity of sleep, and there are no daytime symptoms.
   B. Repeat the vPSG.
   C. Repeat the vPSG with CO_2 monitoring, and perform a head and neck MRI to rule out Arnold-Chiari malformation.
   D. MRI to rule out Arnold-Chiari malformation.

   Answer: C

We have a normal 4-year-old boy with a central apnea index of ten events per hour of sleep on a vPSG with no other symptomatology. When we saw the patient, we decided to perform an MRI to rule out any neurological disorder, especially an Arnold-Chiari malformation, and repeat the sleep study but to make sure to include comprehensive CO_2 monitoring.

Central Sleep Apnea (CSA)

According to the American Academy of Sleep Medicine (AASM), a central apnea is defined as the cessation of airflow in the absence of respiratory effort and duration of more than 20 seconds or duration of more than 2 respiratory cycles associated with an arousal, awakening, or fall >3% in satura-

tion of oxygen. It may or may not be associated with hypoventilation, which is defined as the presence of CO_2 levels >50 mm Hg during >25% of total sleep time [31]. Central apneas with AASM criteria are generally associated with underlying diseases, predominantly neurological diseases such as Arnold-Chiari malformation, brain tumors, genetic diseases such as Prader-Willi syndrome and Down syndrome, laryngeal abnormalities such as laryngomalacia, gastroesophageal reflux in infants, and congenital cardiac defects. Premature infants frequently present with central apneas, although apneas with an obstructive component (obstructive or mixed) predominate and improve with age. Central apneas have also been described as part of the congenital central hypoventilation syndrome and associated with treatment with CPAP devices in obstructive sleep apnea.

A central apnea index (CAI) of ≥5/hour is clinically significant, although the value associated with morbidity is variable and may differ depending on the underlying pathology present. Its clinical presentation is nonspecific and variable, from the absence of symptoms to symptoms suggestive of OSAS or those of the underlying disease [32].

Several studies have shown the higher frequency of respiratory events, especially central apneas, and drops in oxygen saturation in healthy children with suspected sleep-disordered breathing (SDB) living in high-altitude areas (> 2000 meters above sea level) [33]. There are no extensive studies about pathological consequences of central sleep apnea (CSA), as there are for obstructive sleep apnea (OSAS), but they are possibly similar since intermittent hypoxemia, sleep fragmentation, and activation of the sympathetic system with changes in heart rate and blood pressure are involved [34].

In this clinical case, head and neck MRI in our patient was normal. The most common findings on the MRI associated with central sleep apnea (CSA) are Arnold-Chiari malformations (17–48% according to the series), and the most serious are CNS tumors, so it is recommended to perform MRI even if the yield is low. If coexistence of obstructive and central apneas is detected in the absence of adenotonsillar hypertrophy, MRI is also recommended [35, 36].

vPSG: The sleep study this time showed the presence of 12 respiratory events during the night, all of which were central apneas (AHI: 1.3). The mean O_2 saturation was 98%, and the lowest O_2 saturation during sleep was 89% after central event. The CT 90% during the study was 0.01%. CO_2 monitoring showed mean ETCO2 of 41 mmHg with a peak of 48 mmHg (Fig. 41.6).

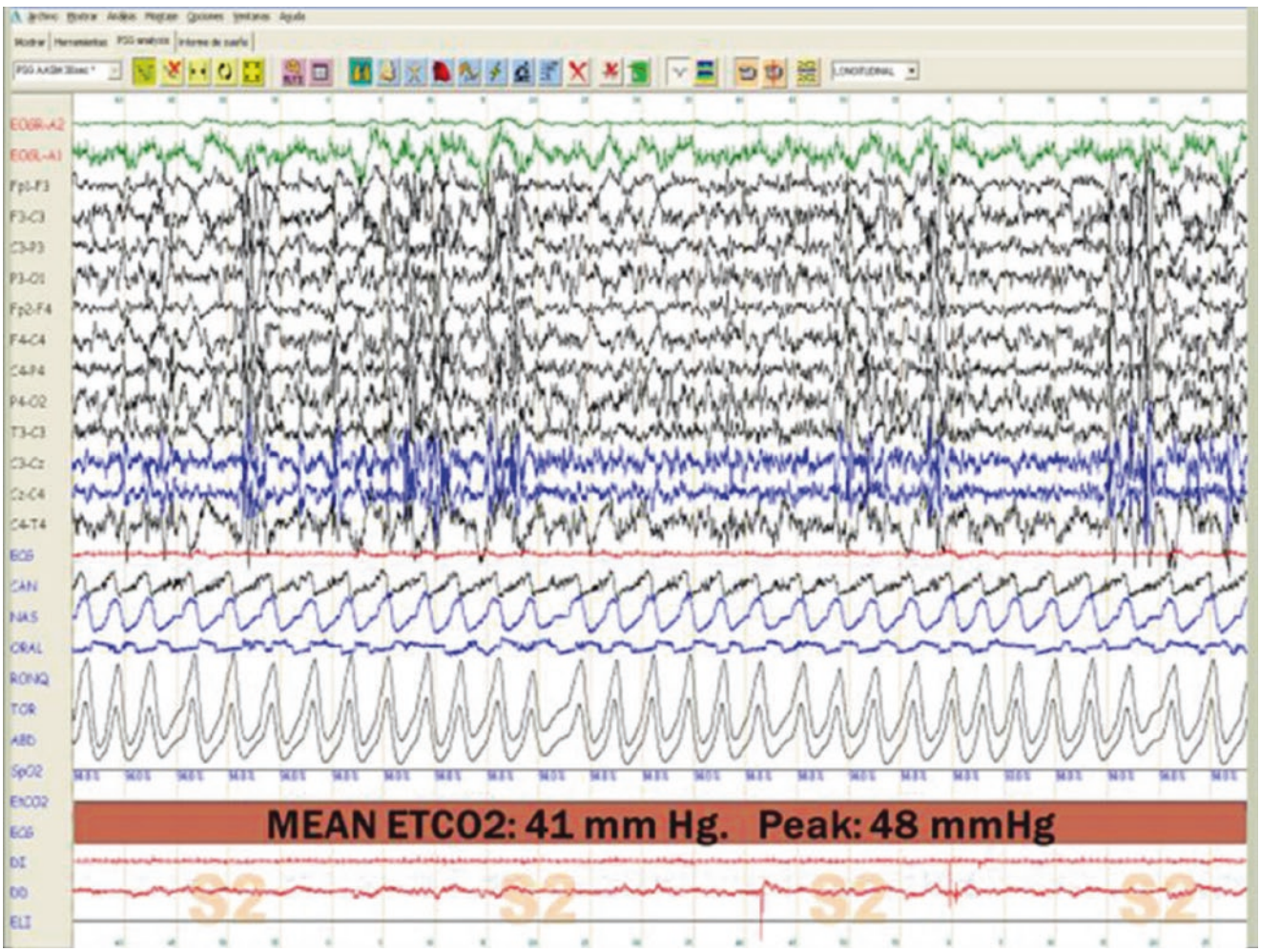

Fig. 41.6 Representative sleep tracing in Case #3 (please refer to text)

2. What would you do next?
   A. Nothing, patient is all right. MRI and vPSG are normal.
   B. Repeat a control vPSG with CO_2 monitoring in a year.
   C. Repeat the vPSG with CO_2 monitoring and the MRI in a year.
   D. Repeat the MRI in a year.

Answer: C

Why repeat the sleep study in a year? Although there is no objective reason based on our findings to do a follow-up sleep study, the presence of central apneas (although normal according to a central apnea index below five events per hour of sleep) and the parental concern level prompted the decision to repeat the sleep study within 1 year. Look what we found:

> The fourth sleep study showed the presence of 28 respiratory events during the night, all of them meet criteria of central apneas (AHI: 2.9). Mean O_2 saturation was 98%, and the lowest O_2 saturation during sleep was 90% after a central event. The CT 90% during the study was 0%. CO_2 monitoring showed mean $ETCO_2$ of 54 mmHg with a peak of 62 mmHg. $ETCO_2$ levels were above 50 mmHg during 90% of the total sleep time (see examples in Figures 41.7 and 41.8).

3. Which of the following conditions is the most likely diagnosis?
   A. Central sleep apnea with hypoventilation
   B. Obstructive sleep apnea with hypoventilation
   C. Study is normal because central apnea index is below five events per hour of sleep.
   D. Central congenital hypoventilation syndrome

Answer: D

Congenital Central Hypoventilation Syndrome (CCHS): Late Onset

CCHS is characterized by alveolar hypoventilation and decreased sensitivity to hypercapnia and hypoxemia, particularly during sleep in the absence of neuromuscular or lung disease, or an identifiable brain stem lesion. The symptoms of autonomic nervous system deregulation or dysfunction are frequently seen in CCHS. Associations of Hirschsprung disease and tumors of neural crest origin, namely, neuroblastoma, ganglioneuroblastoma, and ganglioneuroma, have been reported in some CCHS cases.

Mutations in the paired-like homeobox (PHOX) 2B gene, which encodes a highly conserved transcription factor, are

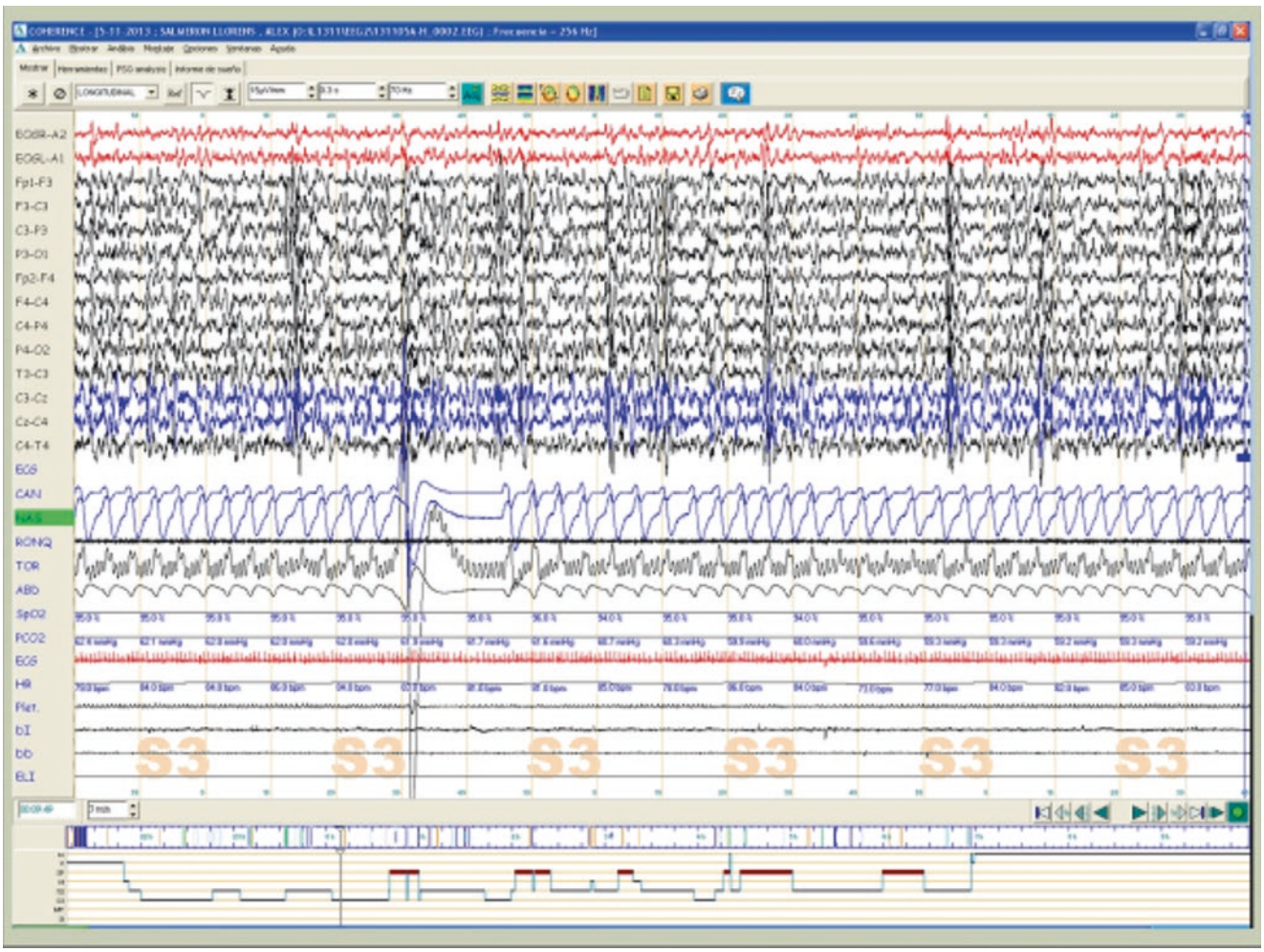

Fig. 41.7 Representative sleep tracing in Case #3 (please refer to text)

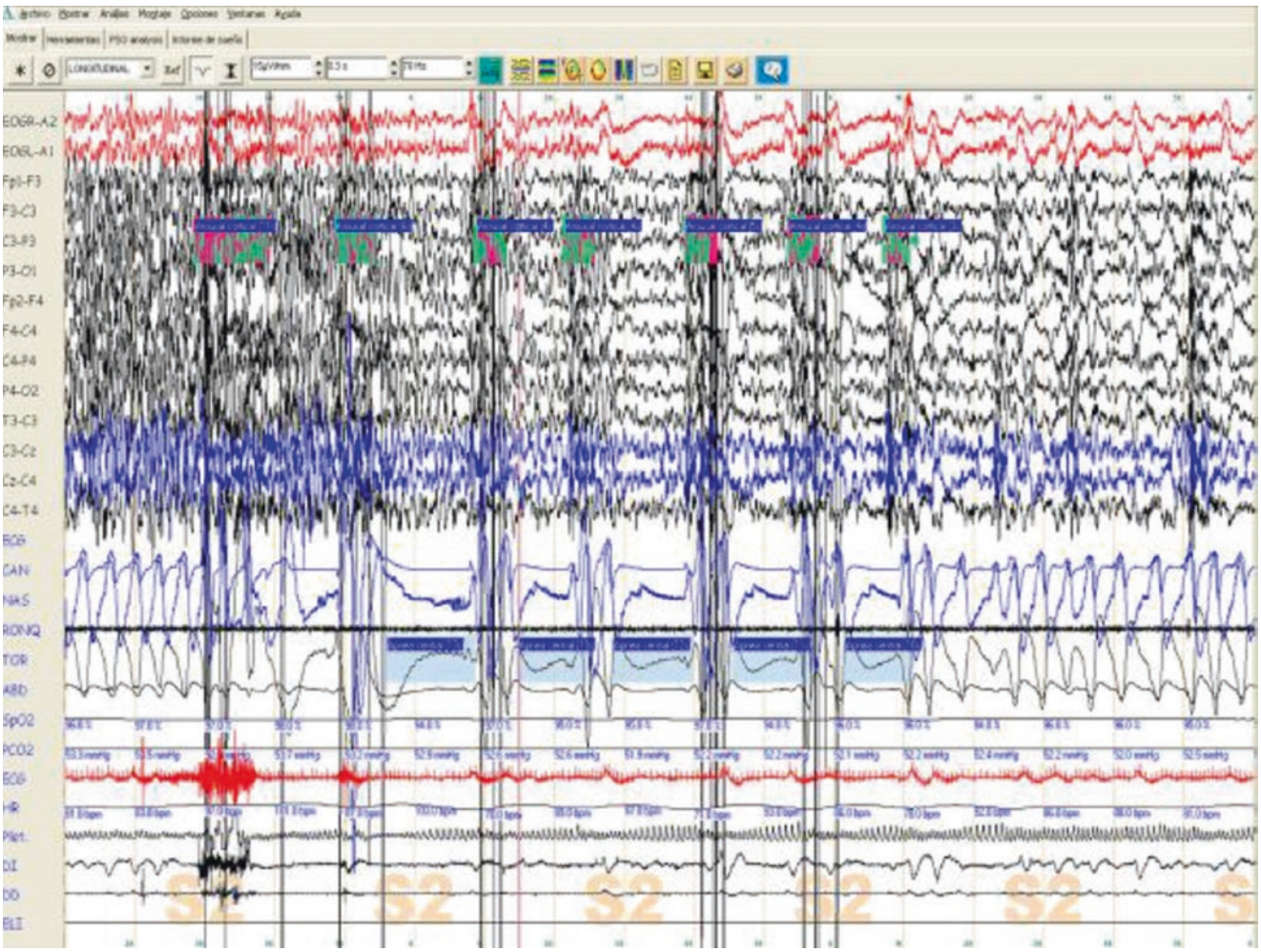

Fig. 41.8 Representative sleep tracing in Case #3 (please refer to text)

known to play a key role in the development of autonomic nervous system.

The great majority (>90%) of patients with CCHS are heterozygous for a polyalanine repeat expansion mutation involving the second polyalanine repeat sequence in exon 3 of PHOX2B. Expansions range from 15 to 39 nucleotide insertions, resulting in the expansion of the normal 20-repeat polyalanine tract to 25–33 repeats. Most expansion mutations occur de novo in CCHS probands. However, these mutations can be inherited as an autosomal dominant trait as identified in a small number of families.

Polyalanine repeat expansion size has been associated with the severity of several symptoms of autonomic nervous system dysfunction and ventilator dependence. Individuals with the smallest number of the PHOX2B polyalanine expansion mutations known to cause CCHS may survive into older childhood or even adulthood without manifesting the early respiratory failure classically associated with the CCHS phenotype.

Moreover, somatic mosaicism has been observed among the family members of probands with CCHS, thus explaining variable expression and incomplete penetrance of PHOX2B mutations [37, 38]. In our clinical case, Alex presented a heterozygous, de novo, missense mutation (c.382C > T, p.Arg128Trp). Now, at age 5 years, he uses nocturnal Bi-PAP with good adherence and complete resolution of respiratory disturbances during the night.

Case #4

Narcolepsy

A 13-year-old girl is referred to the pediatric neurology clinic with an unusual history. She had been lying on her couch, with her head propped up watching a comedy program on television. Her brother noticed that she had stopped breathing and had a bluish color but appeared to be awake

with her eyes wide open. She did not respond when he spoke to her. Her father immediately called 911 and then rolled her onto the floor to do CPR, when she suddenly started to breathe again. She was able to speak and was alert and oriented. She stated that she had never lost consciousness. The emergency medical technicians arrived within 5 minutes, quickly examined the patient, ascertained that all vital signs were normal, and suggested that the patient see a neurologist because they thought she might have had a seizure. The patient's past medical history includes severe daytime sleepiness, starting at approximately age 11 years, and recurrent episodes of buckling of her knees or subtle head drops especially when she is laughing or telling a joke. She was otherwise healthy.

1. Which of the following conditions is her most likely diagnosis?
   A. Seizure
   B. Cardiac arrhythmia
   C. Narcolepsy with cataplexy
   D. Transient ischemic attack

   Answer: C

Narcolepsy with cataplexy. An important clue that makes the first two answers unlikely is that she never lost consciousness. The features suggest the diagnosis is at the end of the vignette. She has severe sleepiness that began in the teenage years and recurrent episodes of buckling of the knees, a classic description for narcolepsy. What happened to this patient is that she developed cataplexy while watching a comedy program on television and lost tone of the strap muscles of her neck and the ensuing anatomical position of her head and neck led to an obstructed upper airway. It is important to remember that the correct name of the disease is "narcolepsy with cataplexy or narcolepsy type 1" to distinguish it from "narcolepsy without cataplexy," emphasizing that only in the former is hypocretin deficiency believed to be pathogenetic [39–43].

2. The patient has a scheduled 20-minute nap every day immediately after lunch break. Which statement about the naps is likely to be true?
   A. The patient feels refreshed for 1 to 3 hours after the naps.
   B. The patient will likely fall into REM sleep during naps.
   C. The patient is likely to stop breathing during these naps.
   D. The patient has been noted to twitch during naps.

   Answer: A

Naps have a very refreshing quality in patients with narcolepsy, and prescription of scheduled naps is an important aspect of treatment. Patients become more alert and energetic for up to several hours. That is in contrast to patients with sleep apnea or idiopathic hypersomnia, in whom the sleepiness generally does not improve that much with napping [42, 43].

3. Which symptom is the patient likely to have?
   A. Vivid dream imagery at sleep onset
   B. Cataplexy
   C. Sleep paralysis
   D. Disturbed nocturnal sleep (DNR)
   E. All of the above

   Answer: E

The classic tetrad includes sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations, but others also call pentad of additional symptoms include disrupted nocturnal sleep and automatic behaviors [43].

4. The patient had a sleep study followed by multiple sleep latency test (MSLT). Which set of findings would most strongly support the diagnosis of narcolepsy in this patient?
   A. PSG, sleep efficiency greater than 90%; MSLT, mean latency 4 minutes; 1 SOREMP
   B. PSG, REM latency 180 minutes, more than 6 hours of sleep; MSLT, mean latency 5 minutes; 1 SOREMP
   C. PSG, REM latency 45 minutes, more than 6 hours of sleep; MSLT, mean latency 5 minutes; 2 SOREMPs
   D. PS, REM latency 90 minutes, more than 6 hours of sleep; MSLT, mean latency 3 minutes; 0 SOREMPs

   Answer: C

In the context of a supporting clinical history, the finding during the MSLT of a mean sleep latency of 8 minutes or less and two or more SOREMPs is considered diagnostic of narcolepsy. Low hypocretin levels in the CSF are diagnostic of narcolepsy with cataplexy and may be used instead of the MSLT to confirm the diagnosis [42, 43].

5. The neurology resident working with you suggests performing a spinal tap as a workup for possible encephalopathy. What CSF abnormality is likely to be found in this patient?
   A. CSF hypocretin 1 level less than 110 ng/L
   B. High epinephrine level
   C. High leptin level
   D. High serotonin level

   Answer: A

A small number of cells in the lateral hypothalamus produce hypocretin (also called orexin). The hypocretin-

producing cells are markedly decreased or absent in patients with narcolepsy with cataplexy (narcolepsy type 1). The cells may be damaged as part of an autoimmune process. Hypocretin levels in the CSF are reduced (less than 110 ng/L) or absent in narcolepsy with cataplexy patients. Epinephrine is a wake-promoting neurotransmitter, and leptin is a hormone predominantly made by adipose cells and enterocytes that helps regulate energy by inhibiting hunger. Serotonin level is not changed in narcolepsy. However, low histamine levels have been reported in patients with hypersomnia [44, 45].

6. The patient was diagnosed with narcolepsy type 1. What medicine would be best to control her EDS?
   A. Modafinil
   B. Atomexetine
   C. Oxcarbazepine
   D. Atenolol

   Answer: A

Modafinil is the drug of choice for treating EDS in narcolepsy [44, 45]. However, new compounds, such as solriamfetol or pitolisant, are now being tested as alternative treatments [46–52].

7. The patient was treated with modafinil for her EDS, and despite sleeping 9–10 hours at night, her family reports she is falling asleep at school and has frequent spells of knee buckling that started to really affect patient's self-esteem, especially when occurring at school. What would be the best treatment for her?
   A. Sodium oxybate (Xyrem)
   B. Melatonin
   C. Prozac
   D. Ambien

   Answer: A

The best drug to address both her EDS and cataplexy episodes would be Xyrem, which has been approved for both indications [53, 54].

Case #5

OSA and ADHD

An 8-year-old boy with a 2-year history of ADHD (who is managed by his pediatrician) started on Ritalin (methylphenidate), then switched to Ritalin SR without significant improvement, and then placed on Adderall, and the dose was adjusted several times. Currently, he is on Adderall XR 15 mg in AM and Adderall XR 10 mg at 2:00 PM.

Patient is referred to Pediatric Neurology Office because he failed two stimulants, and Mom reports aggressive behaviors at school (patient is bullying other kids) and not sleeping well (restless sleep, snoring, and witnessed apnea). His BMI is 29 kg/m2 (>95%) and has +3 tonsillomegaly, but no retrognathia or micrognathia.

Patient was referred for an overnight polysomnography, and the results obtained from the overnight polysomnogram are as follows:

PSG #1: Snoring was documented during the sleep study. Total AHI, 11.5/hrTST (all events obstructive); $PETCO_2$, 28–45 mm Hg with peak $PETCO_2$ of 52 mmHg, nadir SaO_2 = 89%; mean SaO_2 = 93%, respiratory arousal index, 8/hr

1. What is the diagnosis that best fits these findings?
   A. Primary snoring
   B. Upper airway resistance syndrome
   C. Obstructive sleep apnea
   D. Sleep hypoventilation syndrome
   E. Normal findings

   Answer: C

Obstructive sleep apnea [41, 55–58]. Patient undergoes adenotonsillectomy and follows up with the clinic 3 months later. The caregiver reports that there is improvement in apneic events but also indicates that there is persistent light snoring and continued inattentiveness and hyperactivity. A second sleep study is scheduled to evaluate for residual sleep apnea.

PSG #2: AHI, 3.5/hrTST (majority of events were obstructive in nature); $PETCO_2$, 28–35 mm Hg, with peak $PETCO_2$ of 47 mmHg, nadir SaO_2 = 95%; mean SaO_2 = 97%, respiratory arousal index, 3/hrST.

2. You diagnose the patient with residual obstructive sleep apnea, which treatment would you choose?
   A. UPPP
   B. Intranasal corticosteroids and montelukast
   C. CPAP
   D. Bilevel PAP

   Answer: B

A large body of evidence supports the use of anti-inflammatory therapy using intranasal corticosteroids, with or without addition of montelukast [58–60].

Case #6

Behavioral Insomnia of Childhood

A young couple is seeking help with their 24-month-old son's sleep problems. The child has been a poor sleeper from birth and will not fall asleep by himself. The parents had him

sleep in their bed since the age of 4 months, when nocturnal crying started to interfere with their own sleep. Attempts to let him fall asleep in his own room have been unsuccessful. He falls asleep quickly in his parents' bed. When he is in his crib alone, he screams as if in fear. If he does fall asleep and then awakens (which can be any time during the night but usually occurs during the first third of the night), he cries and seems confused. For the past few months, the child moves a lot when he sleeps, and this is now keeping both parents awake at night. Parents are requesting a sleep study to figure out what is wrong with him. They report no snoring. The child's physical examination is entirely normal, and he has no features that suggest daytime sleepiness. There is no family history of sleep or neurological disorders.

1. The physician evaluating the child is considering the possibility of NREM parasomnia, namely, confusional arousals, and will explore this diagnosis by asking several questions. Which of the following is not a characteristic of confusional arousals in children?
   A. They occur in the first third of the night.
   B. There are stereotypical movements in each episode.
   C. Presence of a family history of similar parasomnias.
   D. The child typically has amnesia of the event and looks frightened when wakes up.

   Answer: B

Confusional arousals occur in about 20% of children younger than 13 years. When there are stereotypic movements with the episodes, one should suspect a seizure disorder. Confusional arousals mostly arise out of stage N3 or slow-wave sleep and therefore are more common in the first third of the night when most slow-wave sleep occurs. Since awakenings in this child occur throughout the night, confusional arousals are unlikely to be the sole cause of her problem, and a sleep study based on a lack of history of snoring and no other symptoms to suggest SDB seems to be not necessary, at least initially [41].

2. What is the most likely diagnosis of the child's sleep problem?
   A. Sleep terrors
   B. Behavioral insomnia of childhood: limit-setting type
   C. Behavioral insomnia of childhood: sleep onset association type
   D. Psychophysiological insomnia

   Answer: C

This is a classic presentation of behavioral insomnia of childhood, sleep onset association type. It occurs in 10% to 20% of children and starts when a child learns to fall asleep with inappropriate sleep associations, in this case sleeping in the parents' bed and relying on parent's presence to soothe him into sleep instead of relying on himself to fall asleep. The problem often begins shortly after a child starts to sleep most of the night (usually between 3 and 6 months of age). If the child awakens during the night with crying and a caregiver then comforts the child by holding, singing, rocking, etc., until sleep occurs, the child associates sleep with the caregiver's action and will not be able to fall asleep again until the same factor that helped him fall asleep initially occurs back again [61].

3. The preferred course of action is:
   A. Reassure the parents that the child will grow out of the problem and that no specific treatment is required
   B. Benadryl (diphenhydramine)
   C. Melatonin, which is a safe hypnotic in children
   D. Behavioral treatment

   Answer: D

Behavioral treatment is the correct answer. Behavioral treatment is helpful and does not involve pharmacological interventions with the attendant benefits of such approach. Behavioral interventions should result in two major positive outcomes. First, the child will be able to fall asleep with appropriate associations. Second, the parents will be able to sleep normally. Although answers B and C seem obviously incorrect, in fact young children have often been inappropriately treated with such medications for behavioral insomnia. Behavioral treatment involves changing the parents' behavior that reinforces the sleep association while at the same time changing it to positive associations and routines for bedtime. A key point is that the child should be put to bed awake and drowsy, not when asleep, to encourage the child to learn to fall asleep on his or her own [61–66].

Case #7

Sleep and Seizure Disorder

A 14-year-old otherwise healthy boy, without any daytime symptoms or snoring, displays strange behaviors at night, described by his mother as sudden awakenings with a scream, thrashing around, stiffness of the extremities, wandering around in the room, and occasionally falling of the bed with his eyes wide open. However, during those events, he does not seem to recognize anyone and is not aware of his surroundings. The patient himself has no recollection of the events, which can occur between once and four times a night.

1. What is the most likely diagnosis?
   A. Episodic wandering (frontal lobe epilepsy)
   B. REM sleep behavior disorder

C. Confusional arousals
D. Sleep terrors

Answer: A

This is a classic description of frontal lobe epilepsy, specifically episodic wandering. The other three conditions would be in the differential diagnosis [67–72].

2. Which medication is used to treat this condition?
   A. Clonazepam
   B. A selective serotonin receptor inhibitor
   C. Carbamazepine
   D. Dilantin

Answer: C

Carbamazepine, or its synonyms, in small doses leads to remission or improvement in patients with nocturnal frontal lobe epilepsy. In patients with a specific mutation of the CHRNA4 gene, genetic counseling should also be offered to the patient and the family.

Episodic wandering is one of the three diseases in the category of autosomal dominant nocturnal frontal lobe epilepsy (ADNFE): paroxysmal arousals, paroxysmal dystonia, and episodic wandering. Generally, in any of these conditions, one parent is affected, and patients present mutations in the CHRNA4, CHRNB2, or CHRNA2 genes [73].

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Part IX

Sleep in Other Disorders

Sleep-Disordered Breathing in Neuromuscular Diseases

42

Hemant Sawnani, Neepa Gurbani, and John E. Pascoe

Introduction

The broad categories of NMD that affect children include muscular dystrophies, congenital and metabolic myopathies, neuromuscular junction disorders, peripheral neuropathies, and anterior horn cell disease [1]. However, there are additional acquired pathologies such as acute transverse myelitis, flaccid myelitis syndromes, spinal cord injury, traumatic brain injuries (accidental and non-accidental), hypoxic ischemic encephalopathy and resultant cerebral palsy, etc. that result in altered muscle tone and carry subsequent respiratory implications. Lastly, central nervous defects (such as lissencephaly, myelomeningocele, spinal cord syrinx, etc.) can also result in unfavorable changes in muscle tone and/or respiratory drive. The related presence of sleep-disordered breathing (SDB) results from the combination of altered respiratory drive, upper airway muscle tone, respiratory compliance, and the presence of any associated underlying lung disease.

The incidence of sleep-disordered breathing in any specific neuromuscular disease is variable and depends on the degree of existing muscle weakness. It should be understood that progressive neuromuscular disorders are likely to be associated with sleep-disordered breathing at different time points in the disease progression. Sometimes, though, the underlying pathology may be a static insult (SMA types 1 and 2, congenital brain malformation, cerebral palsy, etc.), but the consequences of such disorders in growing children are progressive, and not infrequently, the onset of sleep-disordered breathing is a function of evolving growth and comorbidities (such as chronic aspiration, recurrent pneumonia, evolving thoracic dystrophy, etc.) and therefore delayed in its onset.

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Neuromuscular disorders have significant impacts on patient well-being. Psychological and psychiatric impacts echo on family relations and within the broader society; social implications abound with many patients and their families experiencing social isolation. High medical costs that relate to other morbidities develop as a result of primary neuromuscular disorders (such as feeding tube dependence, rehabilitative needs, predisposition to malnutrition and bedsores, recurrent infections, etc.). The financial costs are not trivial. In a comprehensive study of the costs associated with amyotrophic lateral sclerosis (ALS), Duchenne muscular dystrophy (DMD), and myotonic dystrophy (DM), it was determined that the total impact on the US economy inclusive of direct medical and nonmedical costs and loss of income was staggering [2] with annual per-patient costs approximated to be $64,000 for ALS, $51,000 for DMD, and $32,000 for DM. On a national scale, the population-wide costs were about $1.023 billion for ALS, $787 million for DMD, and $448 million for DM.

The landscape of pediatric NMD is changing as it relates to emerging novel treatments, and long-term survivorship is increasing. This makes the discussion of sleep-disordered breathing in these patients more relevant than ever.

Pathophysiology and Clinical Presentation

Respiratory complications in NMD occur due to respiratory pump dysfunction. The respiratory pump comprises the respiratory muscles, chest wall, and spine. At rest, the diaphragm is the major inspiratory muscle working as a piston to create an intrathoracic pressure gradient that determines the tidal volume. Other chest wall muscles involved in forceful inspiration include external intercostal muscles, pectoralis muscles, and anterior neck muscles. Exhalation is passive at rest occurring largely due to chest and lung recoil. With exertion or cough, there is additional recruitment of anterior abdominal musculature. The act of active inspiration plays a critical role in maintaining lung recruitment at rest and

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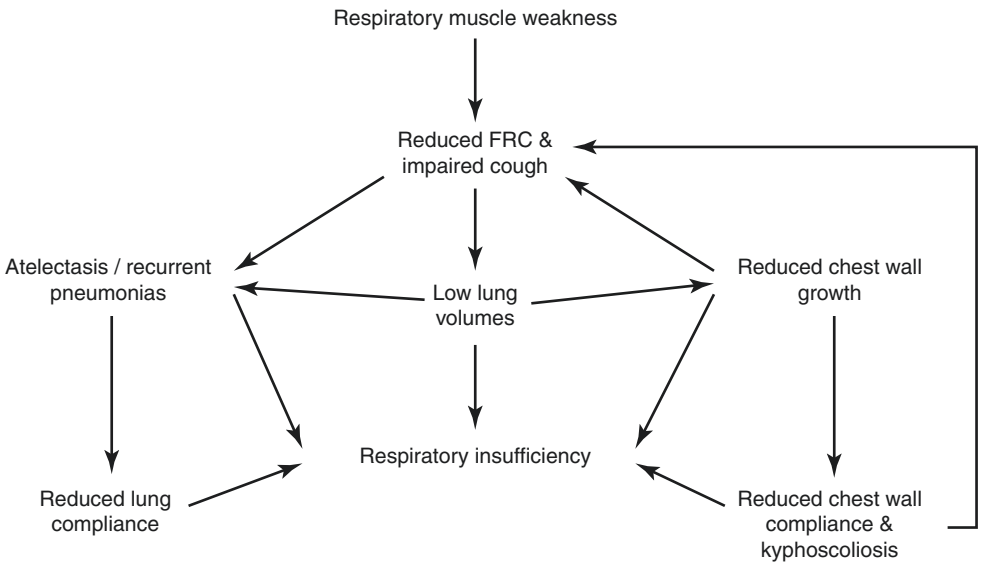

Fig. 42.1 Impacts of respiratory muscle weakness

secretion clearance when followed by a cough. With progressive weakness of respiratory muscles, these functions are impaired.

The impact of respiratory muscle weakness is summarized in Fig. 42.1. With progressive respiratory weakness, the "floor" of maximal expiration (expiratory reserve volume) to residual volume is progressively raised, while the "ceiling" or "height" of maximal inspiration (inspiratory reserve volume) is progressively lowered. Thus, the patient generally experiences narrowing of the range of vital capacity. It is therefore unsurprising that wheelchair-bound patients can lose 60–70% of vital capacity and not appear very symptomatic. Further, when low lung volume states and atelectasis become the norm for these patients, the lung compliance decreases [1], contributing to increased work of breathing and a generally increased catabolic state.

The normal chest wall is integral to normal respiratory function. The weakness of thoracic muscles as seen in SMA type I and other severe myopathies leads to loss of thoracic support. In these younger children, there is increased thoracic compliance in the early stage with obvious respiratory paradox as the negative intrathoracic pressure created by the relatively spared diaphragm is unopposed by the anterior chest wall muscles. The effect is further amplified with respiratory distress and upper airway obstruction (OSA). The persistent abnormal chest wall motion coupled with severe osteopenia of ribs drives subsequent thoracic dystrophy. The chest wall then eventually becomes fixed and poorly compliant with shortening of muscles and stiffening of tissues, resulting in persistent low lung volume states. Most often, there is severe caudal slant of the ribs with loss of anteroposterior depth of the chest (Fig. 42.2). The overall stiffness of the chest wall therefore not only limits vital capacity but also reduces the efficacy of spontaneous cough by reduced deformability. Lastly the spine requires normal muscle strength and tone to maintain its alignment, and the loss of supporting muscle predisposes the child to rotational spine deformities and diaphragm dysfunction. Inadequate vertical spine height translates into lower intrathoracic volumes, limited chest wall growth, and restrictive pulmonary defects (Fig. 42.3) [3].

Scoliosis negatively affects chest wall compliance, compresses or distorts bronchi, contributes to alveolar hypoventilation (Fig. 42.4), diminishes airflow, and decreases the effectiveness of cough [4]. This is generally seen in early childhood onset progressive respiratory weakness. If the onset of respiratory weakness occurs after the chest wall has been fully developed, as in the case in DMD, spinal muscular atrophy type 3, and mid- to late-adolescent spinal cord injury, the degree of thoracic dystrophy that ensues could be milder.

Normally, sleep onset is associated with reduced ventilatory control inputs from higher centers, attenuated sensitivity of central chemoreceptors, medullary and cortical arousal mechanisms, and reduced upper airway muscle tone. The reduction in tidal volume, minute ventilation [5], respiratory rate [6], chemosensitivity [7], and loss of the wakefulness drive [8] results in a 2 to 4 mmHg increase in $PaCO_2$. During rapid eye movement (REM) sleep, skeletal muscle atonia is most pronounced with preserved diaphragm and extraocular muscle function. In supine wake and non-REM (NREM) sleep, the rib cage contributes about 44% of the tidal volume. The atonia of phasic REM sleep reduces this contribution to 19%, decreasing functional residual capacity by 6% to about 15% [9] and rendering tidal volume in phasic REM sleep to be diaphragm-dependent [10, 11]. The load on the respiratory system is compounded by the increase in upper airway resistance during NREM sleep at sleep onset [12] that is fur-

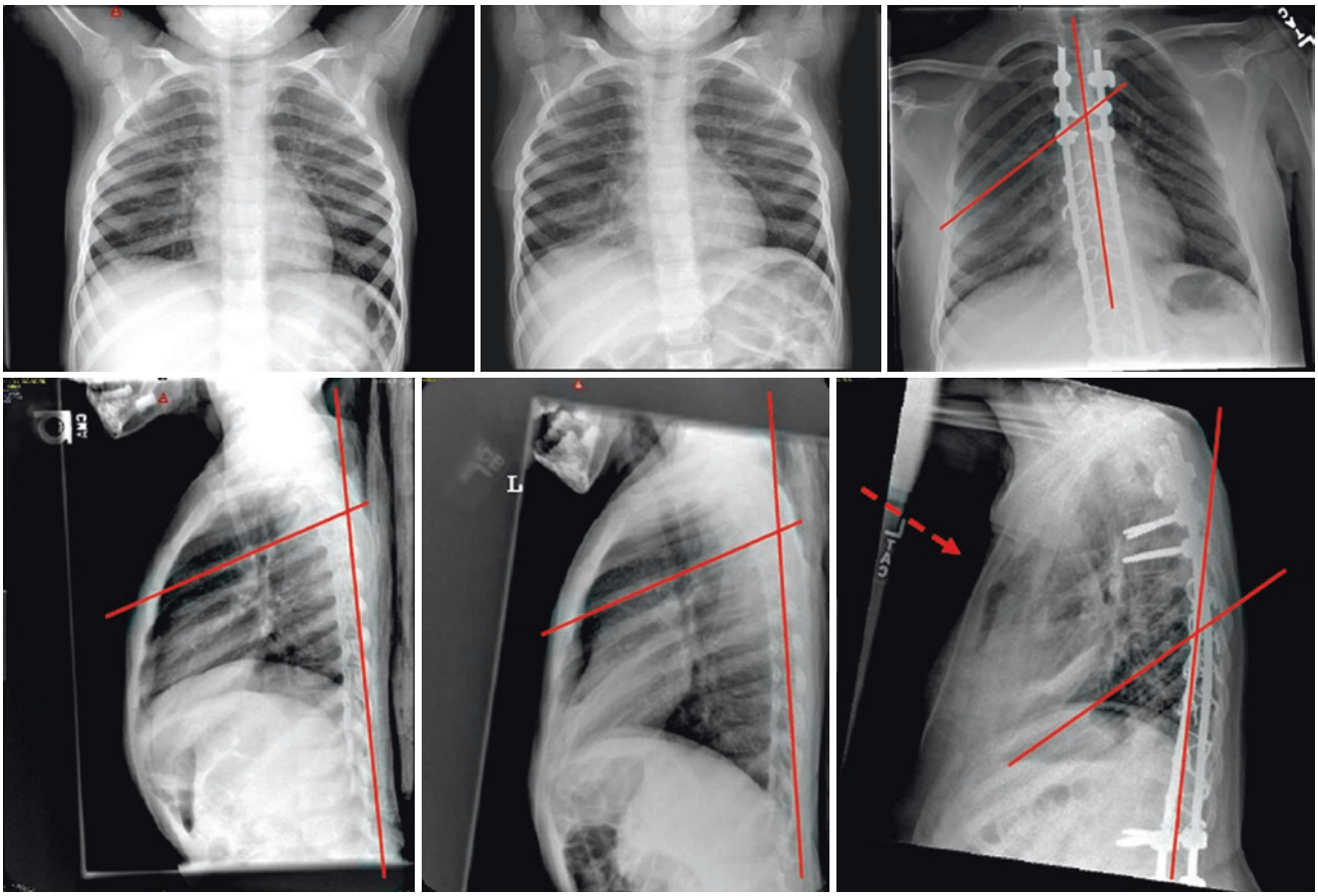

Fig. 42.2 Progressive chest wall changes in a patient with SMA II. Note the early scoliosis at 5 years and loss of antero-posterior diameter of the thorax and progressive sloping of ribs in relation to vertebral axis by 13 years

ther exaggerated during REM sleep with the decreased activity in pharyngeal and laryngeal dilators [13]. These normal phenomena are exaggerated in the presence of muscle weakness with emergence of respiratory instability initially in REM sleep and subsequently including NREM sleep. In severe cases, the instability is notable even while awake. Of course, the nature of the underlying disease will determine the degree of muscle group involvement.

Understanding normal sleep mechanics and chemosensitivity highlights the vulnerability of REM sleep in a patient who either is weak or has altered chest wall mechanics. The diaphragm may initially be able to generate enough negative intrathoracic pressure during REM sleep against a weak or atonic upper airway resulting in its narrowing (hypopnea) or collapse (apnea). Weak intercostal muscles can still contribute to tidal volume in NREM sleep but completely lose this ability in REM sleep. Hence, hypoventilation is initially isolated to REM sleep. With worsening degrees of weakness, there is additional NREM sleep involvement, finally progressing to continuous hypoventilation or respiratory failure [14].

Inherent to this discussion is the definition of hypoventilation. The American Academy of Sleep Medicine (AASM) defines adult nocturnal hypoventilation in two ways: (1) $PaCO_2$ or its surrogate of ≥55 mmHg for ≥10 minutes and (2) a ≥ 10 mmHg increase in $PaCO_2$ or its surrogate compared to wake to a value >50 mmHg for ≥10 minutes [15]. Using the first and second definitions, the prevalence of hypoventilation with daytime eucapnia in neuromuscular disease is 4% and 9%, respectively [16]. The AASM pediatric definition of hypoventilation is >25% of the total sleep time with $PaCO_2$ or its surrogate >50 mmHg. This definition captures 24% of children with neuromuscular disease [17]. Early in the process, symptoms of SDB are poorly perceived with roughly 64% having daytime somnolence, headache, snoring, or sleep disturbance. Notably, these symptoms do not predict the presence of SDB [18]. In a larger population of boys with DMD, only 17% of patients with abnormal PSG findings were noted to have related symptoms [19]. The insidious onset is partially due to impaired mobility and the inability to tax the respiratory system [20]. Subtle symptoms may include unrefreshing sleep, and multiple nighttime

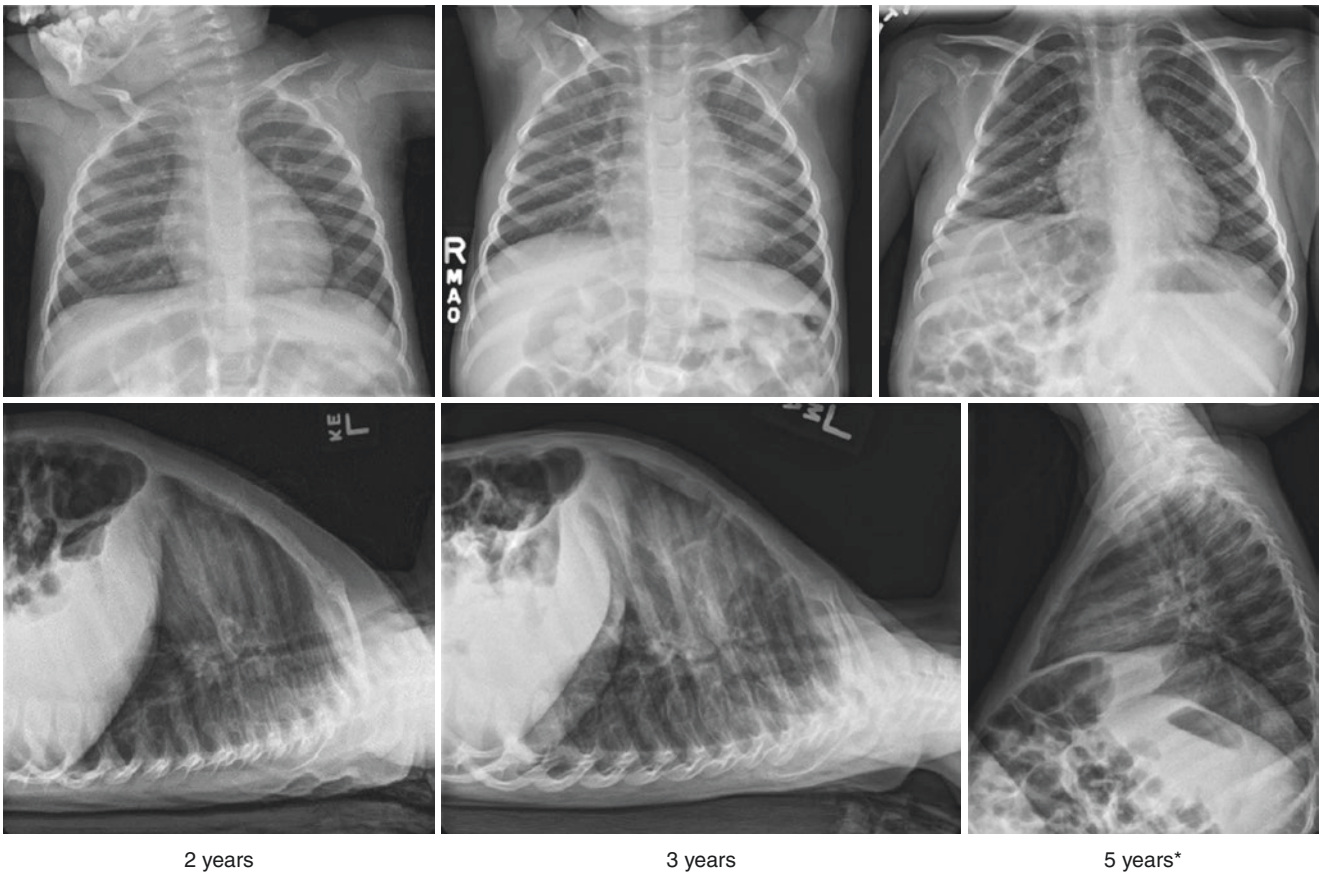

Fig. 42.3 Inadequate thoracic height despite growth, contributing to low lung volumes in a girl with SMA II

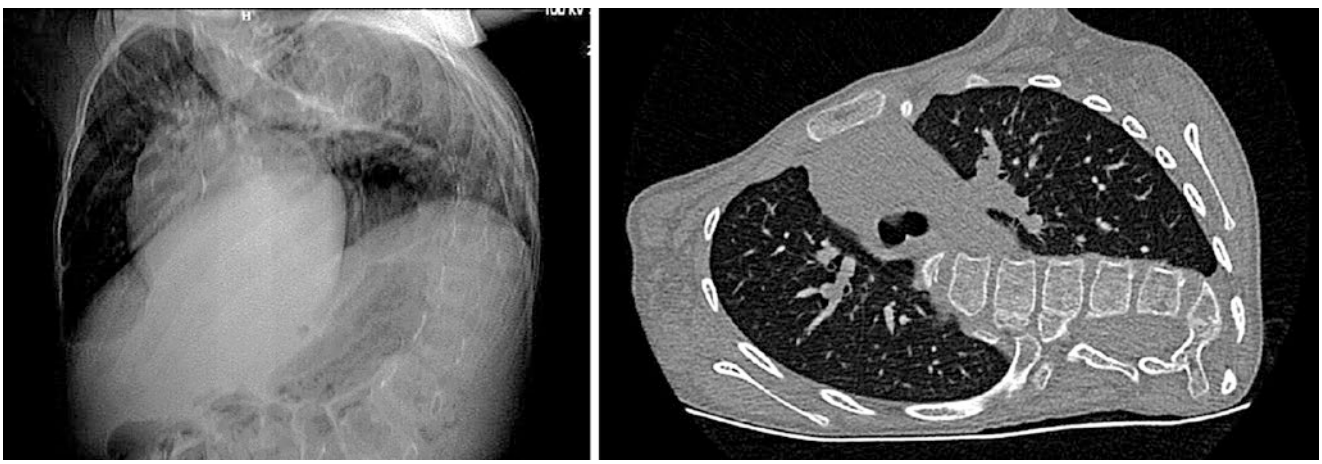

Fig. 42.4 Severe scoliosis in a young boy with congenital muscular dystrophy shown with X-ray (left) and chest CT scan (right). Note the severe rotational thoracic defect, levels of the diaphragm (left), and the multiple vertebral bodies running horizontally within a single frame (right). Asymmetric crowding of ribs is also noted

arousals due to sleep fragmentation. Parallel PSG findings include increased NREM1 [21, 22] and decreased REM sleep [23]. Such findings should raise suspicion for sleep-disordered breathing in patients with neuromuscular disorders.

In 2007, the portable monitoring task force of the AASM recommended that portable monitoring may be used as an alternative to in-laboratory PSGs for the diagnosis of OSA in adults with high pretest probability of moderate to severe OSA [24]. Thus far, studies on portable monitoring have been performed on otherwise healthy children. Children with NMD are at high risk for hypoventilation, and the lack of reliable capnometry monitoring may be a significant limiting factor to allowing for safe and reliable home studies.

In a study to assess the role of overnight pulse oximetry and daytime blood gases in accurately detecting nocturnal hypoventilation in children with long-term noninvasive respiratory support, it was observed that 42% of these subjects experienced nocturnal hypercapnia without nocturnal hypoxemia [25]. In fact, daytime capillary arterialized carbon dioxide levels were normal in 85% of these patients.

Therefore, capnometry monitoring is important in children in whom there is concern regarding nocturnal hypoventilation, regardless of the primary underlying issue (neuromuscular disease, underlying lung disease, or obesity hypoventilation). Most HSAT testing devices do not include any capnometry monitoring. This is a critical aspect of testing as nocturnal hypoventilation in NMD may occur in isolation, and not associated with classic clinical symptoms of sleep-disordered breathing, nocturnal desaturation, or daytime hypercapnia.

Finally, the American Academy of Sleep Medicine (AASM) recommends that HSAT for diagnostic evaluation of suspected OSA should be performed only in conjunction with a comprehensive sleep evaluation, preferably by a sleep medicine specialist, and may be used as an alternative to PSG in patients with a high pretest probability of moderate to severe OSA. As such, patients at risk for central apneas, hypopneas, or hypoventilation should not be tested with such devices. The accuracy of HSAT in these patients is unknown.

Sleep Studies in NMD: Findings

Sleep-disordered breathing in patients with neuromuscular disorders has been well established. However, the type of SDB, timing of onset, and treatment options can vary depending on the underlying disorder. A baseline understanding of the effect of neuromuscular disease on sleep is imperative to suspicion, timely evaluation, diagnosis, and treatment. The findings on polysomnography in a patient with a neuromuscular disorder can be subtle until respiratory insufficiency is more overt. In keeping with the history of non-restorative sleep and frequent nocturnal awakenings, the sleep architecture on PSG will likely reveal increased Stage 1 NREM sleep [21, 22] and decreased REM sleep [23]. Sleep-disordered breathing often manifests as obstructive sleep apnea that is REM sleep predominant. Oximetry on the hypnogram may have a sawtooth pattern versus the prolonged desaturations of hypoventilation [26]. As weakness progresses, the difficulty in polysomnogram analysis lies in differentiating obstructive from non-obstructive respiratory events. Snoring may be absent due to reduced ability to generate a high enough inspiratory flow to produce upper airway vibration. Additionally, thoracoabdominal asynchrony (paradoxical respirations) may be present at baseline, further limiting the ability to detect obstructive events. Respiratory events called "pseudocentral" events or diaphragmatic events are characterized by attenuated intercostal EMG and signals from chest/abdominal belts by the lack of respiratory muscle effort (Fig. 42.5). These events are not from the lack of respiratory drive but instead result from the combination of REM sleep atonia and chest wall muscle and diaphragm weakness [22]. These tracings are similar in appearance to central hypopneas, however, with differing etiologies. Esophageal manometry can facilitate differentiating between such events.

One of the difficulties of neuromuscular sleep medicine is detecting the onset of hypoventilation. Monitoring of ventilation via end-tidal or transcutaneous capnography in addition to respiratory rate is paramount. At the onset, hypoventilation is compensated by an increased sleep fragmentation preventing prolonged desaturations [26], slightly increased end-tidal CO_2 with mild tachypnea and clinical symptoms of unrefreshing sleep due to fragmentation, and morning headaches. Such findings on polysomnography often do not meet the current definition of hypoventilation, further highlighting the importance of recognizing compensatory mechanisms in play during sleep. Lastly, adaptive suppression of REM sleep occurs, thereby reducing the effects of REM-related sleep-disordered breathing in neuromuscular diseases [27].

Spinal Muscular Atrophy

The muscle weakness due to spinal muscular atrophy (SMA) can be a continuum spanning from fetal onset respiratory failure at birth to late-onset SDB in adulthood. In general,

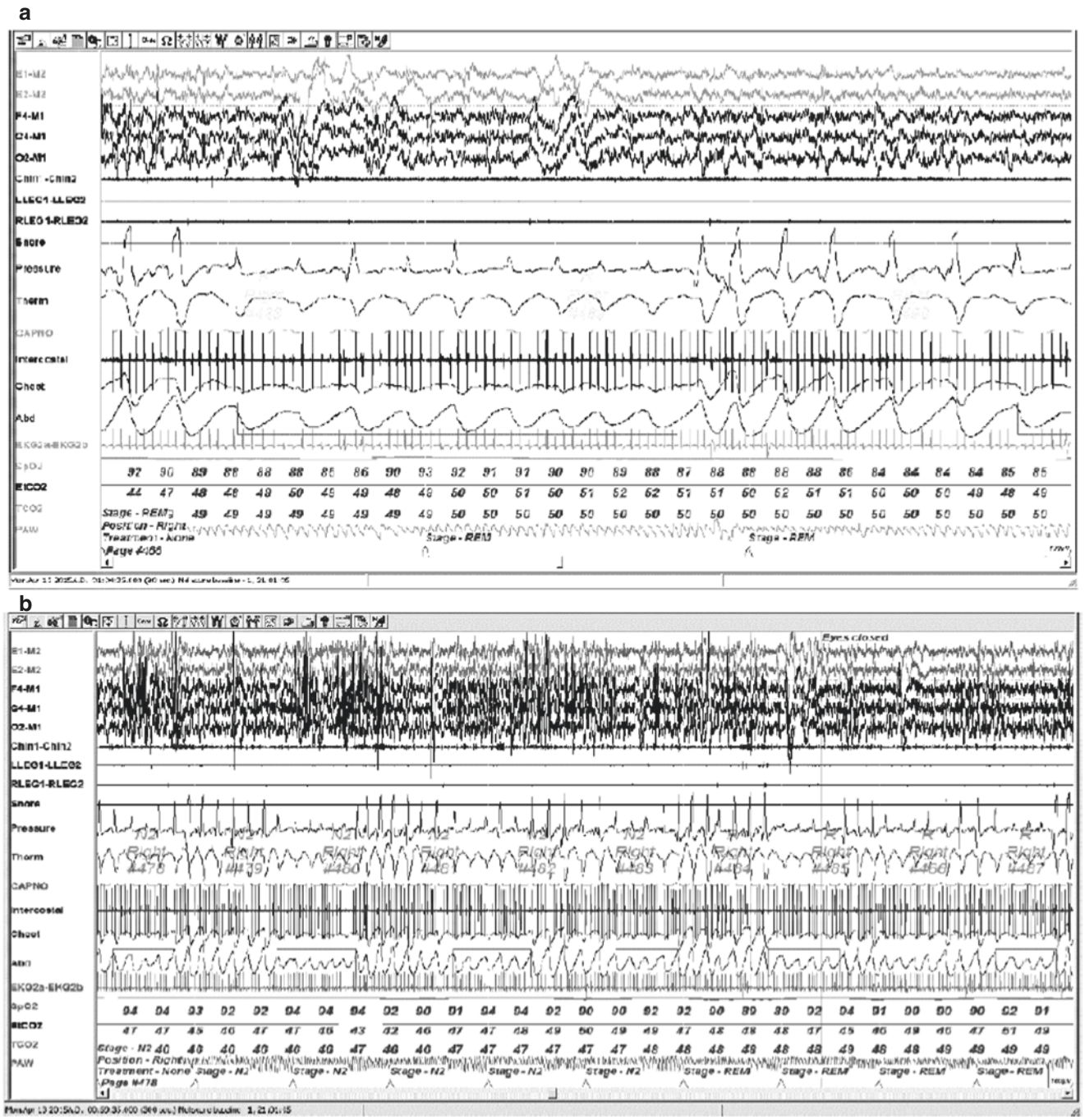

Fig. 42.5 (**a**) REM sleep portion (90 seconds) of a sleep study of a 15-year-old boy with Duchenne muscular dystrophy. Note the non-obstructive respiratory paradox with periodic reduction in intercostal activity during the event. The patient exhibits hypoventilation and hypoxemia at baseline, made worse by this event. (**b**) REM sleep portion (5 minute) of a sleep study of the same 15-year-old boy with Duchenne muscular dystrophy. Note the waxing and waning character of the events

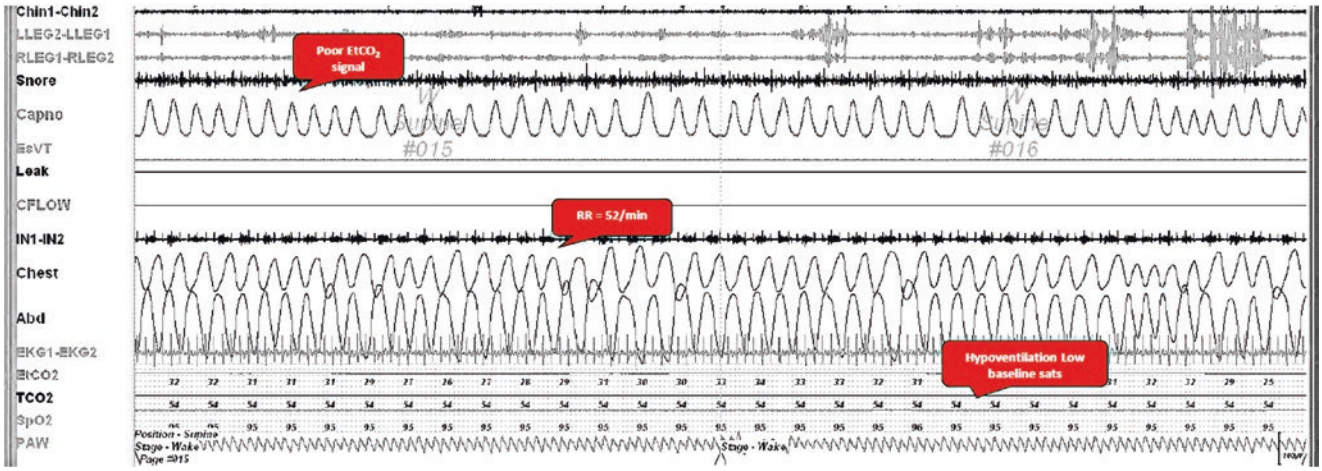

Fig. 42.6 Awake portion (1 minute) of a sleep study of a 5-year-old boy with SMA type I. Note the respiratory paradox, tachypnea, and consequent absence of plateau of end-tidal capnometry waveform (Capno channel) that produces lower related readings ($EtCO_2$) when compared to the transcutaneous CO_2 (TCO_2) channel. Low baseline saturations are also observed

the diaphragm is relatively spared, and remaining muscles are variably affected. Recommendations for children with SMA I, who are unable to sit on their own, are to have a very low threshold to obtain a polysomnogram [28]. The onset of SDB in SMA I is often manifested with upper airway instability, and in very severe cases, patients exhibit airway obstruction even while awake. While awake, patients with SMA I will often manifest tachypnea and respiratory paradox and with greater degrees of weakness also experience hypoventilation and hypoxemia (Fig. 42.6).

Duchenne Muscular Dystrophy

Sleep-disordered breathing in patients with Duchenne muscular dystrophy (DMD) has an anticipated progression. In young boys with DMD and treated with glucocorticoids, there appears to be initial presentation of SDB in the form of REM sleep-related OSA. Continuous nocturnal hypoventilation and ultimately respiratory failure are typically events of the second to third decade. The onset of SDB in steroid-treated patients with DMD has been reported as young as 12 years of age with corresponding FVC% predicted of over 70% [19]. The etiology is multifactorial as chronic glucocorticoid therapy generates obesity in addition to the relentless disease progression. The study affirmed that reduced FVC was associated with a greater risk of hypoventilation, showing that the odds of hypoventilation increased by 20% for every 10% reduction in FVC (OR, 0.80; 95%CI, 0.74–0.87; $P = 0.001$). Interestingly, 16.4% of DMD subjects experienced hypoventilation at a very young age (11.6 ± 3.3 years), and although not significant, this group tended to have lower FVC and respiratory muscle strength profiles compared to their normal or SDB peers. The identification of this small unique group of younger subjects with alveolar hypoventilation and without significant apnea raises the importance of capnometry measurement during PSG acquisition. In steroid-naïve patients with DMD, the decline in lung function occurs about 3 years earlier, and the onset of hypoventilation should be expected at a younger age [29]. DMD patients have normal respiratory drive and respond to hypercarbia and hypoxia by increasing their respiratory rate (Fig. 42.7) compared to age-matched controls who increased their tidal volumes [30, 31]. Using optoelectronic plethysmography, Lo Mauro et al. showed that DMD patients cope with the progressive impairment of the diaphragm by increasing the recruitment of the inspiratory ribcage muscles in order to maintain minute ventilation and do so by increasing their respiratory rate rather than tidal volume [32]. These findings provide evidence that diaphragm weakness in boys with DMD occurs early in the disease. Progression of weakness in DMD is variable, and diurnal hypoventilation occurs as inspiratory muscle weakness progresses [33, 34].

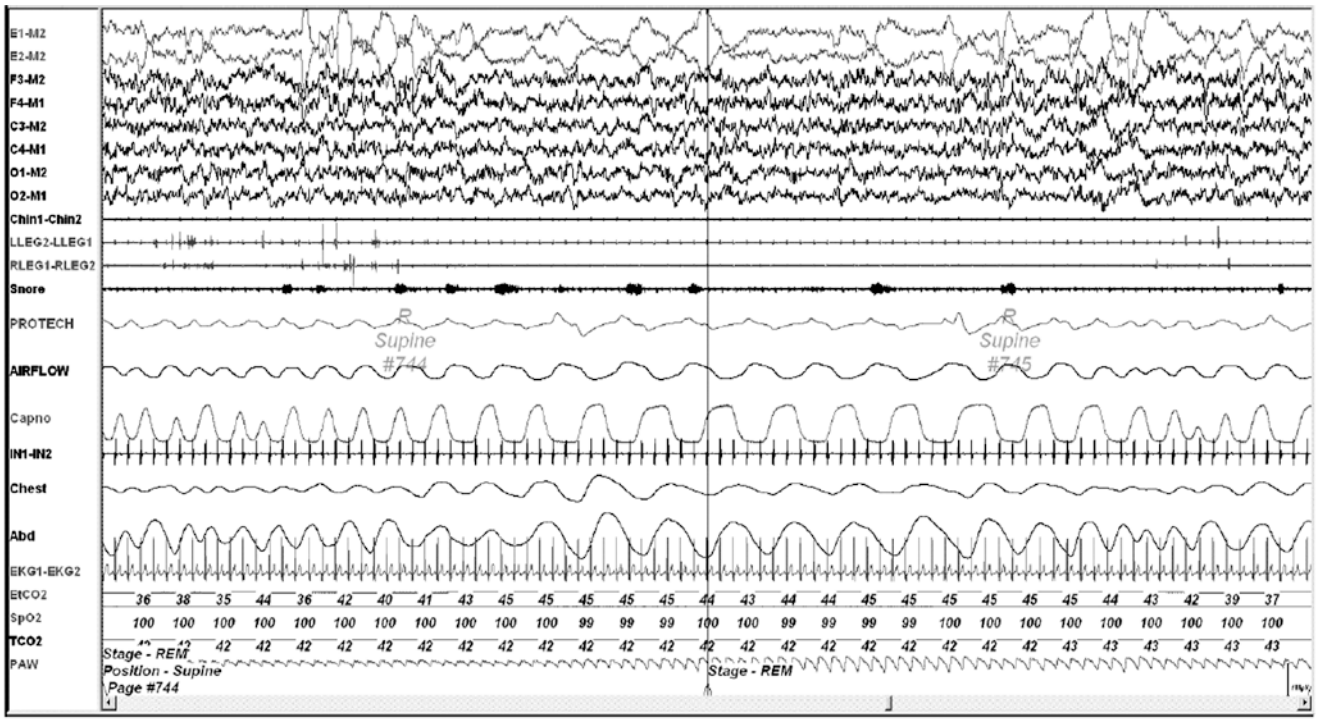

Fig. 42.7 REM sleep portion (1 minute) of a sleep study of a 15-year-old boy with Duchenne muscular dystrophy. Note the range of end-tidal CO_2 ($EtCO_2$) despite a respiratory rate of about 30/min. The $EtCO_2$ channel bears intermittent low values due to the absence of plateau of the related waveform. The respiratory rate is non-physiologic for this age and indicative of compensatory mechanisms at play. Phasic REM sleep exhibits greatest degree of respiratory variability

Congenital Muscular Dystrophy

Congenital muscular dystrophy (CMD) is a rare, inherited neuromuscular disease that comprises heterogeneous subgroups. CMD manifests clinically by early-onset progressive muscle weakness that presents from birth to up to 2 years of age [35]. Certain subtypes are known for early-onset weakness with the inability to sit unassisted, and others present in adulthood. Interestingly, patients with Col6-, LAMA2-, LMNA-, and SEPN1-related CMD are known to have significant diaphragm weakness and may experience hypoventilation even while they are still ambulatory [36]. Diaphragm involvement can be detected with sitting and supine spirometry, noting a fall in FVC% by greater than 20% [37]. In general, it is recommended that there be a low threshold to study these patients by polysomnography.

Spinal Cord Injury

Patients with spinal cord injuries (SCI) are also prone to SDB. Here, characterization of SDB is dependent on the level of the lesion, with higher cervical spine injuries more likely to involve the diaphragm. Patients with SCI may have SDB with or without hypoventilation. The disruption in neural control, abnormal respiratory mechanics with paralysis of intercostal muscles, resultant low lung volumes, and use of CNS suppressants in cervical SCI patients results in roughly 90% of patients with SCI experiencing SDB during the acute phase. The predilection toward central sleep apnea is due to a narrow window between eucapnic and hypocapnic apneic thresholds, sometimes resulting in a periodic breathing pattern [38]. In the setting of cervical (C5–C7) spinal cord injury, about 63% of subjects manifested central apneas, and 88% had periodic breathing. In the case of thoracic spinal cord injury (T1–T6), the incidences of central sleep apnea and periodic breathing were much lower (13% and 38%, respectively). Patients with thoracic SCIs are prone to risk factors suffered by the general population, namely, obesity and subsequent tendency to manifest OSA. The incidence of SDB in the long term is between 22% and 68%, with additional observations of natural loss of function over time and blunted CO_2 sensitivity and respiratory drive [39].

Other Diseases

Metabolic disorders can also present with significant, occult sleep-disordered breathing. SDB including OSA and hypoventilation is common in infants with infantile alpha-

glucosidase deficiency (Pompe disease) [40]. Infants and children with severe neurologic injury or developmental mishaps are very prone to developing chronic respiratory failure from either difficulty maintaining a patent airway free of secretions, abnormal respiratory drive, obstructive sleep apnea, or a combination of a variety of these factors. As they grow, their metabolic needs increase, and pulmonary morbidities from aspiration, infection, and bronchiectasis add to the pulmonary management challenges. These patients merit frequent assessments and warrant polysomnography evaluations repeatedly to optimize their ventilation and growth.

Management Approaches

The detection of respiratory insufficiency seems fairly straightforward if the presentation occurs during an acute crisis such as high spinal cord injury, infantile SMA with acute respiratory infection, etc. However, detection of occult respiratory insufficiency from respiratory weakness presents a greater challenge in wheelchair-bound patients who may present for an ambulatory visit. This rings especially true for young boys with DMD and glucocorticoid therapy. These patients can be quietly tachypneic and are yet able to hold conversations comfortably. Gentle rocking back and forth is subconsciously aimed at increasing inspiratory and expiratory capabilities. In patients with congenital muscular dystrophy, hypoventilation while still ambulatory has also been described. Physical examination of all of these patients often reveals tachypnea, reduced chest excursions with respiratory effort (or sometimes obvious respiratory paradox), and reduced breath sounds due to shallow respirations. Percussion of the lung fields in the mid-clavicular line can reveal hepatic dullness in a higher than usual position (second–fourth intercostal space) providing evidence of low lung volumes at rest (reduced functional residual capacity (FRC)).

Once a deficiency in ventilation or airway clearance is identified, it is critical that it be addressed expediently and effectively. There are, however, a variety of different approaches to doing so that are based on both the age and needs of the patient. Regardless, the goals are re-establishment of appropriate FRC, optimization of tidal volumes, and normalization of gas exchange. These goals are rewarded with maintenance of lung recruitment and prevention of progressive atelectasis.

Nocturnal Ventilation

The goals of initiation of NIV are to normalize ventilation, reduce the work of breathing and provide respiratory muscle rest, improve sleep architecture by reducing sleep fragmentation, and treat SDB. Initiation of NIV has been shown to enhance the quality of life and functional status of patients with NMDs, to prolong survival, and in some patients to attenuate the loss of FVC [41]. The optimal time to initiate NIV in NMD is not clearly defined and universally agreed upon, but consideration should be given to the fact that children may need a little more time to adjust to NIV. The delay in initiation of such support until the first lower respiratory illness-related admission is fraught with unnecessary increased morbidity and perhaps mortality risk.

Patients may be treated with pressure- or volume-cycled modes of ventilation. In pressure-cycled ventilation, a higher designated driving inspiratory pressure is delivered above the end-expiratory pressure until the ventilator cycles into passive exhalation to the designated end-expiratory pressure. In volume-cycled ventilation, flow is delivered until a specific tidal volume is reached; the inspiration then cycles off, and airway pressure returns to the end-expiratory pressure. Regardless of the patient's ability to trigger the ventilator and the chosen mode of ventilation, a backup rate (with a physiologic inspiratory time) must always be included to maintain minute ventilation and provide respiratory muscle rest (Fig. 42.8). Improvement in tidal volumes and minute ventilation may produce reflex central apneas, and the use of a backup rate prevents related respiratory arousals and sleep fragmentation.

The end-expiratory pressure increases resting lung volume to an appropriate FRC, improves ventilation by preventing airway collapse and atelectasis, and treats obstructive apnea by pneumatically stenting the upper airways at the end of exhalation. The inspiratory pressure optimizes minute ventilation and treats obstructive hypopneas and hypoventilation. Technically, the pressure difference between the peak inspiratory pressure and the end-expiratory pressure forms the degree of pressure support the patient receives for spontaneously triggered breaths. Therefore, it stands to reason that the spontaneous and the ventilator breaths need to be as similar as possible to harmonize respiratory rhythm. If the patient is unable to maintain acceptable spontaneous inspiratory time due to severity of weakness, the pressure support volumes will appear much lower. Adding a pressure control feature instead then allows the ventilator to guarantee the set inspiratory time for the triggered breath as well and, hence, an appropriate tidal volume. The level of positive pressure required to normalize gas exchange can be closely approximated at the bedside, but polysomnography would allow for finer adjustments with extended monitoring of carbon dioxide and oxygen levels and sleep architecture.

Isolated continuous positive airway pressure (CPAP) should *never* be used in an attempt to support ventilation in

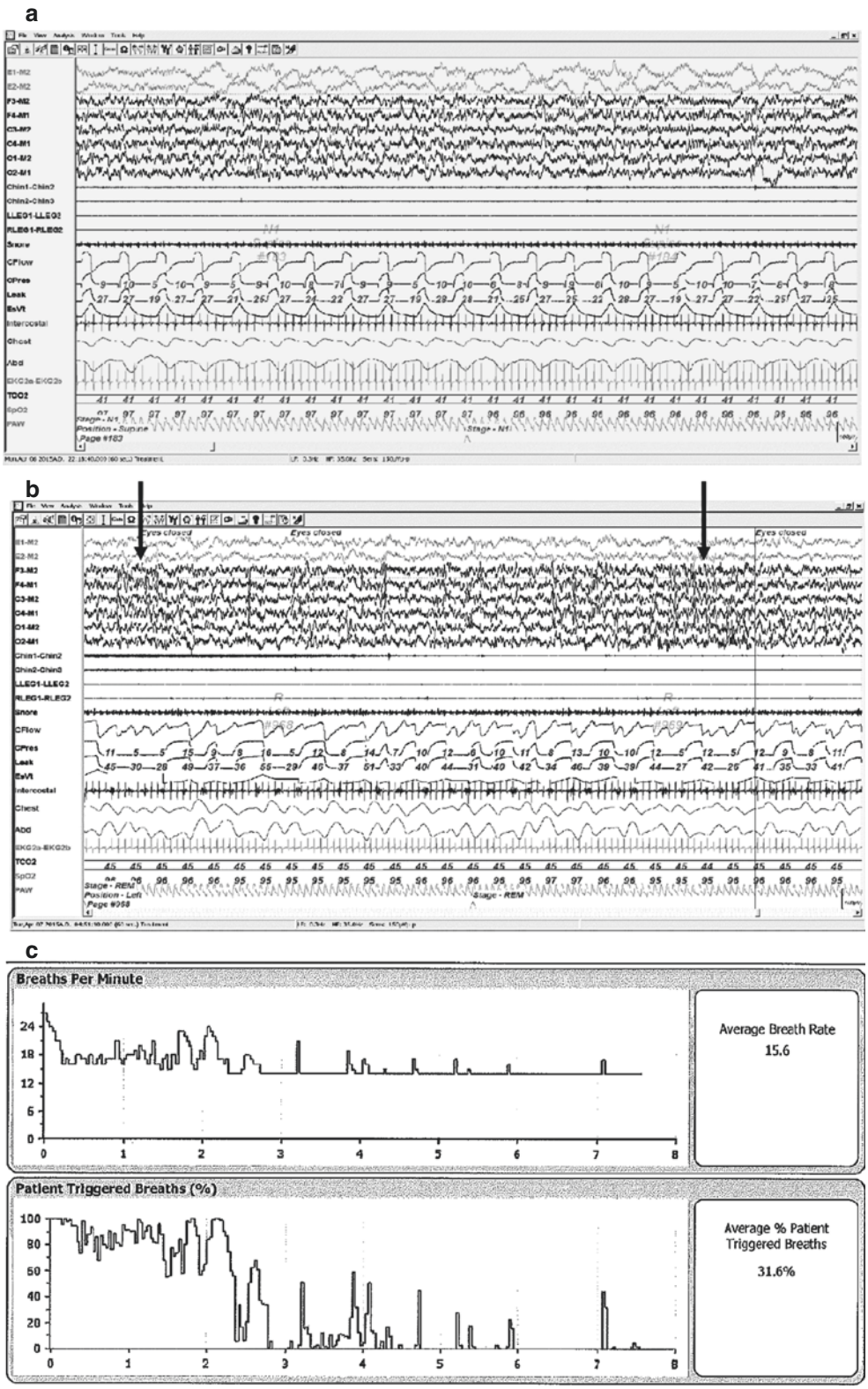

Fig. 42.8 (**a**) This is a 1-minute screen of a sleep study of a 15-year-old girl with SMA II. She appears fully supported with her current pressures and a full respiratory rate of 20/min with little additional spontaneous effort. The respiratory rate of the patient is entirely driven by the ventilator. (**b**) 1-minute screen of a sleep study of the same 15-year-old girl with SMA II, later in the study after withdrawing the backup rate. She appears to be in REM sleep, tachypneic (respiratory rate of 38/min) with acceptable capnometry, with arousals (arrows). Saturations are lower as well. (**c**) This is an overview of 8 hours of a ventilator download of a 20-year-old man with SMA II. Note the complete dependence on the ventilator rate following sleep onset. Occasional awakenings overnight are reflected with the increase in frequency of patient-triggered breaths

patients with NMD since it does not augment the tidal volume, nor does it allow for setting a rate to provide respiratory muscle rest. The only exception to this is a situation where obstructive sleep apnea exists in the presence of preserved respiratory muscle strength.

Titration of pressures or volumes in the sleep lab should be performed incrementally with careful documenting of the impacts on heart rate, respiratory rate and pattern, character of apneas, saturations and capnometry, tidal volume, leak, and sleep architecture. Higher pressures can lead to increased leak that could precipitate increased obstructive events, arousals, and ineffective ventilation. The management of these patients requires the careful follow-up with repeated assessments of ventilator downloads and periodic re-titration in the sleep lab to assure adequate ventilator support in the face of disease progression.

Diurnal Ventilation

Patients with progressive NMD often begin to spontaneously extend the use of nocturnal NIV into the day. This extension typically occurs many years after initiation of nocturnal NIV and is typically guided by the patient. Patients become increasingly symptomatic despite the use of assisted ventilation during sleep. In severe pediatric forms of NMD, such as congenital myopathies or SMA type I, patients may require 24-hour ventilator support from birth.

Past guideline from the American Thoracic Society (ATS) recommended starting diurnal ventilator support after the onset of daytime hypercapnia [42]. Subsequent studies have reported that 95% of patients with DMD complained about daytime dyspnea with the onset of hypercapnia [43, 44]. Clinical observations suggest that patients maintain normal PCO_2 by altering their position and breathing pattern to maintain ventilation as described earlier. Institution of diurnal ventilation has been met with resolution of dyspnea and symptoms and reducing the risk of respiratory fatigue and failure [45, 46]. For practical reasons, the type of respiratory support and existing wheelchair design need to be mutually compatible for successful use by the patient.

Interfaces for Ventilation

The options of interfaces for delivering daytime ventilator support include nasal and face masks (as a direct extension of nocturnal ventilation), mouthpiece (for sip or "sip and puff" ventilation), and tracheostomy.

Mask Interface

Suitable respiratory support for neuromuscular patients also warrants applying appropriate interfaces. There are a variety of different nasal masks and cannula interfaces, which are the most preferred. A nasal interface allows for continued speech, as patients learn to use the nasally provided ventilator breaths to speak during exhalation. A nasal mask may also protect against aerophagia, abdomen distension, and aspiration of vomitus. These issues are critical consideration for patients who lack the ability to spontaneously remove a full-face mask in the event of emesis. For patients with persistent oral air leak despite the use of a chinstrap, oronasal or full-face masks are considerations with the right precautions (venting gastric tubes, timing of feeds, etc.). Nasal masks can be used by patients too young and/or unable to tolerate upright position (e.g., SMA I infants and children) or mouthpiece ventilation. Some users of mouthpiece ventilation may prefer the nasal mask when travelling as it would be less prone to dislodgment and also allow for napping. Due attention must be paid to maintenance of related skin health. A mask interface can certainly be used for continuous ventilation [45].

Mouthpiece

Mouthpiece ventilation (MPV) is an on-demand system that is attached to the patient's wheelchair for daytime use. This system suits the wheelchair-bound patient best if there is a preserved ability to form a seal around the mouthpiece. The interface consists of a plastic or silicone tube that is held between the lips and teeth. Usually, a sipping action or tapping the tube with the tongue is sufficient to trigger the ventilator. MPV has gained popularity and is now being offered as the first mode of ventilation for daytime support. MPV is an effective interface that is inexpensive, easy to use, and safe. The preferred mode of ventilation in MPV is assist control with a larger desired tidal volume (about 2.5–3 times the inspiratory capacity).

Tracheostomy

Tracheostomy is the interface of choice in cases when the use of NIV (despite the wide variety of interfaces) provides less than ideal ventilator support and the need for such support is deemed to be continuous. This is especially true for infants and children under the age of 5 years or when bulbar symptoms are dominant and handling of oral secretions is

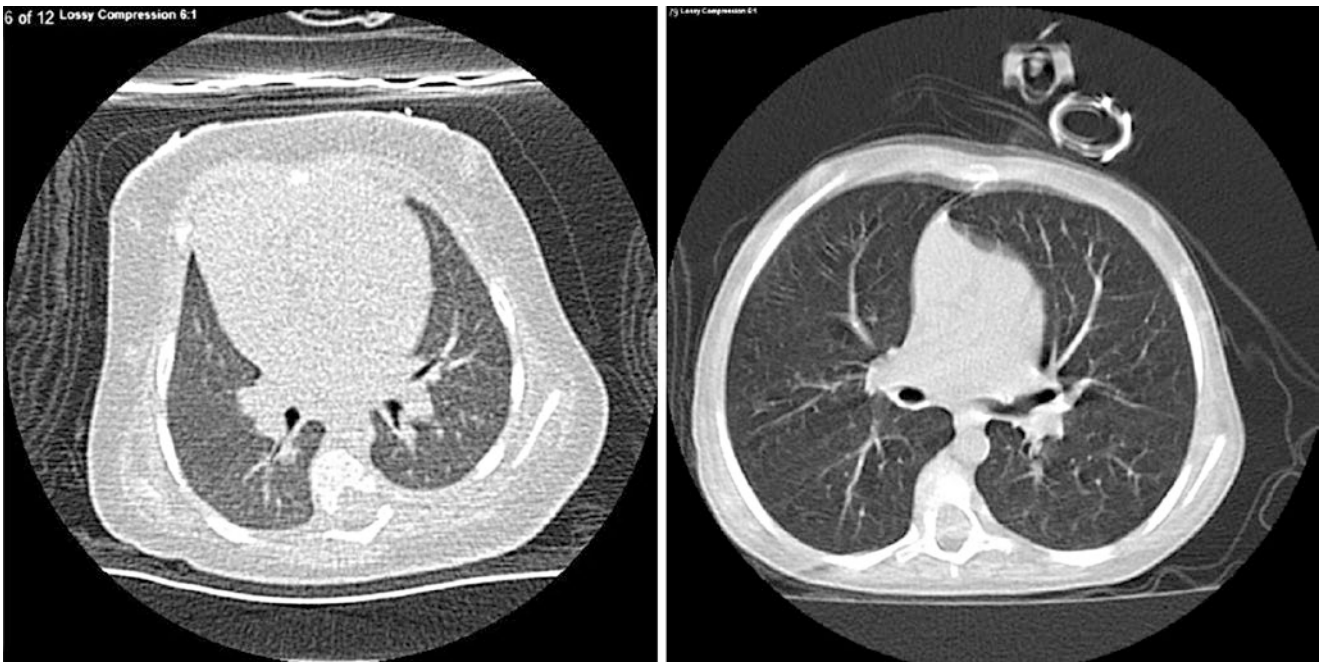

Fig. 42.9 These are CT scans of the same child at 8 months (left) and at 3 years (right). The patient has a congenital myopathy and received a tracheostomy shortly after birth. She presented with chronic respiratory failure at 6 months. Mechanical ventilation was instituted with clinical improvement. A CT scan at 3 years showed resolution of previously noted thoracic dystrophy

severely impaired. In the smaller growing child, it protects against the typical mid-face deformity that occurs from long-term NIV initiated at an early age, and allows for maintenance of normal thoracic architecture (Fig. 42.9). However, ventilation by tracheostomy requires focused care and maintenance, and is not without controversy, especially in NMD that are incurable or progressive.

Conclusions

The spectrum of neuromuscular respiratory disease in children is broad, and it is important that patients' diagnoses not be the only consideration when determining evaluation and management strategies. Rather, it should be their physiology state (or disruption) that needs to determine what the management course should look like. There are some diagnoses that are progressive and some that are static. However, in a growing child, the consequences are almost often progressive. This means that the testing and management strategies need to be adjusted based on their medical and social needs. There is constant discovery of novel treatment agents, and longevity of patients with SMA and DMD is increasing. It is therefore important that clinicians be aware of related guidelines and consensus statements that make recommendations to provide the best outcomes for these patient populations.

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Obstructive Sleep Apnea and Asthma

43

Maya Ramagopal and Steven M. Scharf

Abbreviations

AHI	Apnea Hypopnea Index
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
GERD	Gastroesophageal reflux disease
NAEPP	National Asthma Education and Prevention Program
OSA	Obstructive sleep apnea
PS	Primary snoring
PSG	Polysomnogram
PSQ	Pediatric Sleep Questionnaire
REM AHI	REM Apnea Hypopnea Index
SDB	Sleep-disordered breathing
T&A	Adenotonsillectomy

Introduction

Asthma and OSA are two commonly occurring conditions in children [1], and the prevalence of both these conditions is increasing worldwide [2]. There are several factors common to both conditions such as obesity, allergic rhinitis, and systemic inflammation. Some have even entertained the notion of calling this association of asthma and OSA the "alternative overlap syndrome" as a distinct entity from the more familiar "overlap syndrome" used to describe the association between asthma and COPD [3].

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Epidemiology

Prevalence of Asthma and OSA

Asthma is the most common chronic disease in childhood, affecting approximately six million children in the United States [4]. Although asthma cannot be cured, symptoms can be controlled by avoiding exposure to triggers and using daily controller medications [5, 6]. The overall prevalence of asthma has been stable over the last few years [4]. However, asthma disproportionately affects inner-city children living in poverty [7]. Furthermore, the impact of poverty on African American children with asthma is of a greater magnitude than is the case of Caucasian children in similar circumstances.

This is demonstrated by the Minorities' Diminished Return theory, which states that even with improvement in socioeconomic status (SES), health advantages in African Americans lag behind those seen among Caucasians [8].

Common asthma triggers include viral infections, allergies, and weather changes. Factors that may account for "hard to treat asthma" include obesity, gastroesophageal reflux disease (GERD), and OSA. The presence of OSA, determined by questionnaire data, has been associated with probable asthma and increased asthma severity. These modifiable comorbid factors should be addressed if asthma control is to be optimized [1, 9–11]. Furthermore, the NAEPP guidelines recommend assessment for OSA in patients with suboptimal asthma control. Although evidence was only grade D (Expert Panel), the influence of OSA on asthma control was clearly recognized [11].

In children, sleep-related breathing symptoms range from primary snoring, without physiological changes in oxygen and carbon dioxide levels, to full-blown OSA, which can be associated with important physiological changes such as hypoxemia and hypoventilation [12]. The prevalence of snoring in children from large cohort studies is estimated to range between 1.5% and 27.6% [13–15]. The prevalence of OSA from these same studies ranges from 1.2 to 5.7%.

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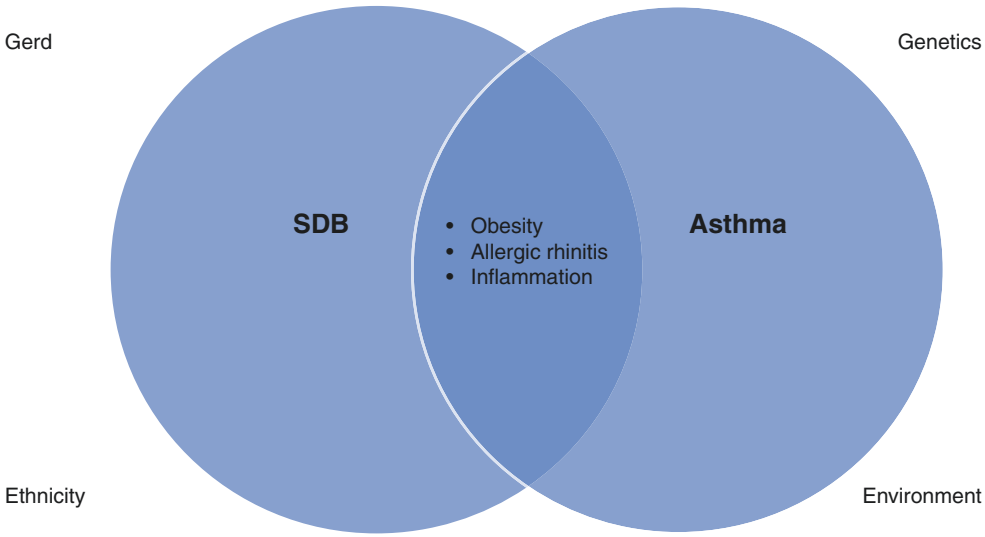

Fig. 43.1 Overlap of OSA and asthma

Both OSA and asthma are commonly associated with obesity, allergies, and both local and systemic inflammation and are seen more commonly in African American children and those from a lower socioeconomic status [16–18]. In addition to genetic and environmental factors, comorbid conditions like GERD play a role in the influence of one condition over the other (Fig. 43.1).

Additionally, nighttime symptoms like labored breathing and restless sleep can be common in both OSA and asthma, which may make it difficult to distinguish between these two entities. It is therefore important to be cognizant of the similarities and differences [19, 20].

The overlap and bidirectionality of both these entities have been well described [1]. There is evidence to suggest that asthma maybe a causal factor in OSA and OSA in turn maybe a causal factor in asthma. The united or one-airway hypothesis suggests that circulating Th2 effector cells in an allergic rhinitis model are responsible for promoting lower airway inflammation, both in a murine model [21] and in humans [22]. The increase frequency of wheezing with tonsillar hypertrophy suggests that the inflammatory process in the lower airways as is seen in asthma may promote lymphoid proliferation in the upper airways, which is a cardinal finding in OSA [23].

In the bidirectional relationship between OSA and asthma, there are reports that OSA predisposes to asthma, and some reports that asthma predisposes to OSA [24]. It is often difficult to ascertain which comes first, OSA or asthma. There are reports that OSA predisposes to asthma. OSA was identified as a modifiable risk factor for severe asthma after 1 year of specialty asthma care. In one study, after adjusting for obesity, race, and gender, children with OSA had a 3.62-fold higher odd of severe asthma at the 1 year follow-up compared to children without OSA [25]. In a survey of preschool children, almost half the number of children who snore had physician-diagnosed asthma [26].

Conversely, there is evidence that asthma predisposes to OSA. A community-based epidemiological study found that in children diagnosed with OSA by an in-home PSG, asthma was found more than twice as commonly as in those without OSA (28 vs 11.8%) [27]. This association was present even after adjusting for obesity and ethnicity.

Severity of Asthma and OSA

In a general pediatric clinic, the prevalence of snoring was higher in asthmatic children when compared to controls. A dose-dependent relationship was found – the more severe the asthma, the more likely to have OSA present [27]. Children with more severe asthma had increased odds of snoring and having a positive Pediatric Sleep Questionnaire (PSQ) score, which has been validated in children with asthma. The PSQ shows a high sensitivity but low specificity but maybe considered a first-line screening tool for OSA in asthmatic children [28].

Both asthma and OSA have been implicated as causes of behavioral problems including hyperactivity and inattention. Interestingly, children with both asthma and OSA have higher rates of behavioral and neurocognitive problems when compared to children with only asthma [29, 30].

There is some overlap in symptoms between asthma and OSA: poorly controlled asthma can cause nighttime symptoms such as cough, difficulty breathing, and possibly nighttime hypoxemia. Similarly, symptoms of breathing difficulty, like gasping and nocturnal hypoxemia, are prevalent in OSA. Though the mechanistic relationship between these two conditions has not been clearly elucidated, it is clear that

it is at nighttime when symptoms of both are most prominent. The nocturnal increase of symptoms in asthma has been attributed to an increase in vagal tone, decreased sympathetic activity, decreased functional residual capacity, and endogenous circadian system changes at night, making asthma a risk factor for worsening OSA [31–33]. Though excessive daytime sleepiness is a symptom that is more associated with OSA, the presence of asthma has an additive effect on poor daytime function [34, 35].

Common Clinical Features

Obesity, Allergic Rhinitis, GERD, and Inflammation

There are several common features between these two common conditions, which may account for the overlap: Obesity and adenotonsillar hypertrophy are considered the most important risk factors in the development of OSA. The rate of pediatric obesity has been steadily increasing and is currently at ~ 18% of school age children in the United States. There are environmental, genetic, physiological, and metabolic factors that are thought to play a role in this association. Although the overall prevalence of obesity has increased, it continues to be higher among minorities and is particularly more among non-Hispanic black children when compared to their Caucasian peers [36]. Concurrent with the increase in obesity prevalence, there is an increase in asthma prevalence as well, noticeably in the same minority populations. This relationship has borne out in several cross-sectional and longitudinal epidemiological studies. Prospective cohort studies found a twofold increased risk in the future development of asthma in obese children when compared to normal-weight children, suggesting that obesity is an independent risk factor for asthma [37]. Obesity-related asthma is an entity that is distinct from normal-weight asthma, which is associated with more poorly controlled symptoms and decreased response to medications [38, 39].

Rhinitis is another factor that is common to both OSA and asthma. It is estimated that 60–80% of children with asthma have comorbid rhinitis, and it is a common finding in children with OSA. The presence of rhinitis affects the quality of sleep. In overnight polysomnograms, rhinitis, and REM-related obstructive AHI was found to be independent of atopy, gender, age, BMI, and ethnicity [40].

Similarly, it is well known that in children, as in adults, obesity is a risk factor for the development of OSA. Each 1 kg/M^2 of BMI above the 50th percentile increases the risk of OSA by 12% [27]. Thus, with the current pediatric obesity epidemic, there is a concurrent increase in the prevalence of OSA [19].

Inflammation is the cornerstone of both OSA and asthma. The role of inflammation in the pathogenesis and consequences of OSA has been extensively studied [41]. Systemic inflammation and localized inflammation are implicated in the pathogenesis. Since both OSA and asthma share regional airway inflammatory pathways, each could mutually exacerbate the other [42].

C-reactive protein is an inflammatory mediator, produced by the liver in response to upstream interleukin-6 activity. Increased circulating levels of high sensitivity CRP (hs-CRP) are associated with increased severity of OSA. Continued elevated levels of this biomarker are indicative of residual OSA following adenotonsillectomy (T&A) [43].

Mechanisms of Increased Risk of OSA in Asthma

Upper airway vibration and airway collapse that occur during OSA have been postulated as a mechanism by which OSA worsens asthma. Upper airway vibration also leads to bronchoconstriction due to an increase in vagal tone. The increase in vagal tone in turn leads to an increase in nighttime asthma symptoms. Upper airway vibration also causes an inflammatory response, not just in the upper airways but also in the lower airways [44]. Plasma levels of proinflammatory cytokines like HS-CRP, TNF-α, IL-1β, and IL-6 are elevated in children with OSA [45]. This supports the concept that OSA induces a systemic inflammatory response activating the signal transduction pathway, leading to upregulation of inflammatory cytokines and downregulation of anti-inflammatory cytokines.

Vitamin D is known to modulate the innate and adaptive immune responses and has been implicated in several inflammatory conditions. Low levels of plasma 25-hydroxy-vitamin D have been reported in both OSA and asthma. Results from epidemiological studies suggest that vitamin D may play a role in the pathogenesis of asthma via its effects on innate and adaptive immunity. Several cross-sectional studies have reported associations between low vitamin D and increased disease severity [46, 47]. Similarly, low plasma levels of vitamin D have also been found in children with OSA, especially in obese African American children [48].

Clinical Implications

This bidirectional causal relationship between the two conditions has implications for the treatment and management of each of them. Adenotonsillectomy (T&A) is usually the first line of treatment of OSA in children according to the current American Academy of Pediatrics guideline [13]. It is curative

in majority of cases. In a multicenter trial evaluating T&A outcomes in the treatment of OSA, age and BMI emerged as the two main factors contributing to residual OSA following adenotonsillectomy. However, in non-obese children, the presence of asthma and severity of OSA prior to surgery played a role in residual OSA, implying that the presence of asthma could be a cause of treatment failure following a T&A [49]. The same study found a reduction in the number of asthma exacerbations, asthma-related emergency room visits, hospitalizations, and prescription refills in the T&A children, but none in the children who did not undergo T&A.

An overnight PSG is the gold standard to diagnose OSA in children and is recommended both by the American Academy of Pediatrics and the American Thoracic Society [50]. There are PSG differences [51] noted when asthma is present along with OSA. Comorbid asthma predicts increased severity of REM-related oxygen desaturation, REM-related obstructive AHI, and REM-related OSA when asthma was present. This was independent of asthma control, BMI, age, and gender [52, 53]. Overnight oximetry signal processing identified an REM sleep-related vulnerability trait that predisposes children with asthma to have more respiratory abnormalities during REM sleep. The maximal percentage of oxygen desaturation during REM but not NREM sleep was significantly higher in those with comorbid asthma, compared to those with OSA alone [54].

In instances where an overnight PSG is not readily available, a Pediatric Sleep Questionnaire (PSQ), which is widely used in clinical practice, can be used to screen for OSA in children with asthma. The PSQ is a 22-item questionnaire addressing both nighttime and daytime symptoms of OSA. The questionnaire has been validated in asthmatic children between 2 and 18 years of age. It has been translated into several languages and has a sensitivity of 0.85 and specificity of 0.87 for OSA screening [28]. While the gold standard for the diagnosis of OSA is an overnight PSG, the PSQ can be used for screening in resource-limited settings, recognizing that the similarity of nocturnal symptoms between OSA and asthma can complicate the use of this screening tool.

Treatment

Adenotonsillectomy is the first line of treatment of OSA in children and is curative in up to 80% of patients with no other comorbid factors [19]. However, residual OSA is frequently seen with obesity, severe OSA prior to adenotonsillectomy, older children (> 7 years of age), and children with asthma [49].

In cases where it is non-curative, continuous positive airway pressure (CPAP) is the recommended mode of therapy. In addition to the usual risk factors of craniofacial abnormalities, obesity, and neuromuscular disorders, asthma is a risk factor for the need for CPAP following a T&A, especially in cases of severe OSA. The likelihood of needing to use CPAP is higher in children with asthma even after controlling for gender, ethnicity, OSA severity, and a history of T&A [55].

The effect of T&A on asthma outcomes has been evaluated in several studies [49, 56]. Most have found that a T&A improves asthma symptoms, including the number of asthma exacerbations, degree of airflow obstructive on spirometry, medication use, and quality of life.

Leukotrienes are lipid mediators involved in the pathogenesis of asthma. They comprise a family of arachidonic acid metabolites that play a role in allergic and inflammatory diseases. Leukotriene synthesis is initiated in airway leukocytes in response to a variety of stimuli including allergens. Leukotriene antagonists are a class of anti-inflammatory medications that interfere with leukotriene production (5-lipoxygenase inhibitors) or leukotriene antagonist receptor antagonists [57]. Montelukast is a leukotriene receptor antagonist that selectively blocks binding of cysteinyl leukotrienes to the cysLT1 receptor through which most of their actions are mediated [58]. It has been used in the treatment of both SDB and asthma.

Leukotriene receptors have been identified in tonsillar tissue [59]. In fact, leukotriene receptor antagonists were found to be helpful in alleviating symptoms of mild OSA after a 16-week period, when compared to placebo [60]. Another nonsurgical treatment of OSA is intranasal steroids. Several studies have shown improvement in symptoms as well as polysomnographic findings like AHI and oxygen saturation nadir after a treatment period between 6 and 16 weeks [61]. Although leukotriene antagonists and nasal steroids are more beneficial in mild OSA, one study reported benefit even in severe OSA and was successful in decreasing severity of OSA [62].

Cysteinyl leukotriene receptor-1 expression is elevated in tonsillar tissues of children with OSA. Accordingly, cysteinyl leukotriene receptor-1, which interacts with leukotrienes and mediates the inflammatory pathway, was overexpressed in adenoidal tissue from children with adenotonsillar hypertrophy. Montelukast, an LTRA, has therefore been used successfully in the management of OSA. Additionally, there are reports of montelukast used as monotherapy in mild asthma, again demonstrating the common therapies used to treat both conditions [63].

Conclusion

Even if the relationship between OSA and asthma, two common pediatric conditions, is an association, not causal, the understanding of the relationship has significant clinical implications. Healthcare providers caring for children should be aware of the overlap in the symptoms, comorbid factors, and treatment between these two entities as they evaluate patients.

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Cystic Fibrosis

44

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Abbreviations

AHI	Apnea-hypopnea index
CF	Cystic fibrosis
CFRD	Cystic fibrosis-related diabetes
CFTR	Cystic fibrosis transmembrane conductance regulator
CO_2	Carbon dioxide
CPAP	Continuous positive airway pressure
FEV1 PPD	Forced expiratory volume in 1 second as a percent predicted
NIPPV	Noninvasive positive-pressure ventilation
OSA	Obstructive sleep apnea
PAP	Positive airway pressure
REM	Rapid eye movement
SpO_2	Oxygen saturation
WASO	Wakefulness after sleep onset

Case Vignette

John (name altered to preserve confidentiality) is a 15-year-old male with cystic fibrosis (CF) who complained of excessive daytime sleepiness during his quarterly clinic visit with his pulmonologist. He reported waking up feeling tired and unrefreshed despite an average of 9–10 hours of sleep per night over the prior 3 months. His father, who accompanied him to the visit, reported that he had heard John snore on occasion but denied any apneas, mouth breathing, or other significant breathing difficulties during sleep. John denied early morning headaches. In addition to the CF, John also had the following comorbidities: pancreatic insufficiency, moderate protein-calorie malnutrition, cystic fibrosis-related diabetes (CFRD), asthma, allergic rhinitis, gastroesophageal reflux disease, chronic abdominal pain, and reactive depression. His body mass index at the time of the clinic visit was in the 40th percentile (goal for patients with CF is >50th percentile). The rest of his vital signs were stable. He had normal lung function. Physical examination was significant for 2+ tonsillar enlargement and digital clubbing. He did not have evidence of copious rhinorrhea or postnasal drip. Lung exam was unremarkable. Standard in-lab polysomnography revealed an apnea-hypopnea index (AHI, apneas, and hypopneas per hour of sleep) of 13.1 (Fig. 44.1). His obstructive apnea index was 0.1, and his hypopnea index was 12.0. His baseline oxygen saturation was 94%, and he had an oxygen saturation nadir of 90%. He did not demonstrate sleep-related hypoventilation. Based on the abnormal AHI and the obstructive nature of his hypopneas, he was given a diagnosis of obstructive sleep apnea (OSA). John was subsequently evaluated by otolaryngology and underwent an adenotonsillectomy. Despite the adenotonsillectomy, John continued to report symptoms of excessive daytime sleepiness. A second in-lab polysomnogram obtained approximately 2 years after the adenotonsillectomy showed residual OSA with an AHI of 18.4 and an oxygen saturation nadir of 88%. This prompted a referral to a sleep specialist for initiation of positive airway pressure (PAP) therapy.

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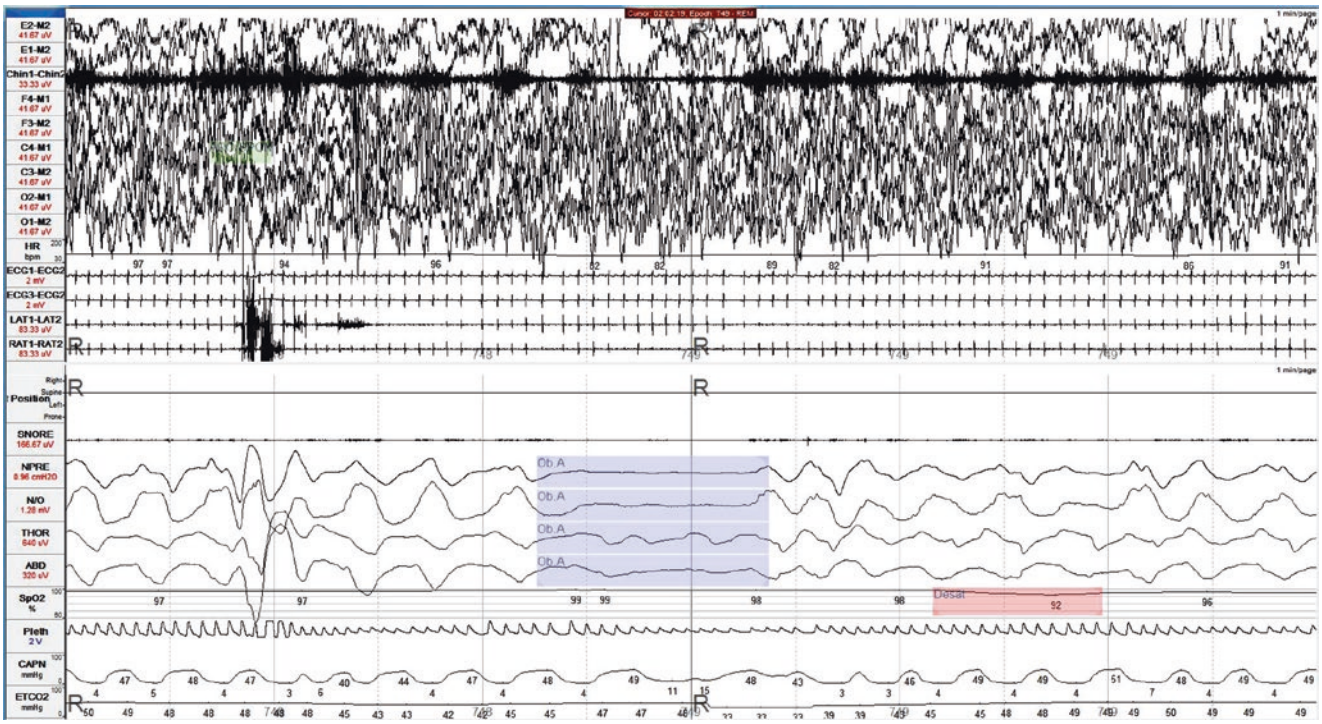

Fig. 44.1 One-minute epoch from the polysomnogram of a child with cystic fibrosis who has obstructive sleep apnea (though not the same individual described in the text). The transient absence of airflow in the setting of ongoing respiratory effort demonstrates an obstructive apnea. The event is associated with a desaturation characterized by ≥3% drop in the baseline oxygen saturation. As often occurs in children, no visible arousal follows the apnea

Introduction

Cystic fibrosis (CF) is a lethal genetic disease that affects approximately 1 in 3400 live births among Caucasian-Americans [1]. A combination of lower airway inflammation and recurrent respiratory infections results in a progressive decline in lung function over time and ultimately respiratory failure [2]. Pulmonary hypertension and right heart failure, frequently seen as sequelae of chronic hypoxemia in patients with advanced lung disease, also contribute to the significant morbidity and early mortality associated with CF [2–4]. Cystic fibrosis-related diabetes (CFRD), seen in up to 20% of adolescents, is linked to accelerated lung function decline, poor nutritional status, and reduced survival [4, 5]. The median age of survival for an individual with CF is currently around 47 years [1].

Multiple other organ systems including the pancreas, liver, and gastrointestinal tract can also be affected, resulting in fat malabsorption and protein-calorie malnutrition [2, 4]. Involvement of the upper airway and sinuses leads to chronic rhinosinusitis and nasal polyposis [4]. Cystic fibrosis transmembrane conductance regulator (CFTR), the protein affected in CF, has also been identified in neural cells within the spinal cord, thalamus, and hypothalamus, including areas within the anterior hypothalamus which houses the suprachiasmatic nucleus, the master circadian clock, although its role in these areas is still emerging [6, 7]. Dysfunctional CFTR has been linked to impaired ability of the retinal epithelial cells to respond to light, a process that is required for entrainment of the circadian rhythm, and a reduced capacity to phase shift in response to stimuli. Response to an acute increase in melatonin, which normally promotes sleep, is also impaired in CFTR-deficient neurons [6].

Sleep disturbances have increasingly been reported in patients with CF [8]. These include difficulties initiating and maintaining sleep, frequent arousals, and trouble breathing during sleep [9–14]. On polysomnography, children with CF, as compared to those without the disease, have reduced sleep duration, prolonged sleep-onset latency, and more fragmented sleep [10, 11, 15]. Frequency of obstructive sleep apnea (OSA) may also be higher in children with vs. without CF [16–19]. Abnormalities in gas exchange during sleep have also been observed with regularity among children with CF [12, 20, 21].

The detrimental effects of insufficient sleep on the mood, behavior, quality of life, and health of children are well-described [22–35]. Short sleep duration alone has been associated with higher levels of circulating inflammatory markers and an increased risk of hyperlipidemia and type 2 diabetes in otherwise healthy children [27, 29, 35]. Sleep disturbances may exact an even greater toll on the health of children with CF who already suffer from a life-limiting illness. Yet little is known about which patients might be at risk for sleep problems, when or how to screen these individuals, or what is the

best treatment strategy to address these issues. This chapter summarizes what is currently known about sleep disorders in children with CF and explores the potential impact that derangements in sleep might have on the quality of life and health of these children.

Insufficient Sleep and Poor Sleep Quality

Children with CF, as compared to their healthy peers, sleep less and have more fragmented sleep, characterized by frequent arousals and prolonged periods of time spent in wakefulness after sleep onset (WASO) [9, 10, 15, 16, 21, 36–38]. Sleep-onset latency may also be higher among children with vs. without CF [21, 38]. These findings from actigraphy and polysomnography are consistent with subjective patient complaints of difficulties initiating sleep, insomnia, frequent awakenings, and excessive daytime sleepiness [9, 10, 13, 14, 36–38]. Patients with poorer health also tend to report more sleep disturbances [21, 36, 39].

In children with CF, associations have been reported between a standard measure of lung function and disease severity (FEV1 PPD, the forced expiratory volume in 1 second as a percent predicted based on age, gender, race, and height) [40–42] and sleep duration, efficiency, and fragmentation [9, 10, 36, 43, 44]. Children with low FEV1 PPD (values <70%) vs. normal FEV1 PPD tend to have significantly lower sleep efficiency on actigraphy (Fig. 44.2) [36]. They also appear to have a shorter sleep duration, more prolonged sleep-onset latency, and longer WASO [9, 43, 44]. In multivariable models that included age, gender, and body mass index, both sleep duration and sleep efficiency independently predicted FEV1 PPD in children with CF [9].

Sleep efficiency is also lower among adolescents with CF who have pulmonary hypertension, as opposed to normal pulmonary artery pressures [3]. As patients with pulmonary hypertension tend to be sicker, with lower lung function, more radiographic abnormalities, and poorer exercise tolerance [3], whether the association with poor sleep may be due to the pulmonary hypertension itself versus the severe lung disease more directly still needs to be clarified.

Obstructive Sleep Apnea (OSA)

Although children with CF frequently endorse snoring, mouth breathing, and respiratory pauses while asleep [10–12, 18, 19], the extent to which OSA underlies these complaints remains uncertain. Polysomnographic data, mostly from outside the United States, suggest that the frequency of OSA is higher among young children with vs. without CF [16, 18–20]. Whereas OSA affects only 1–5% of the general pediatric population, this condition has been reported in

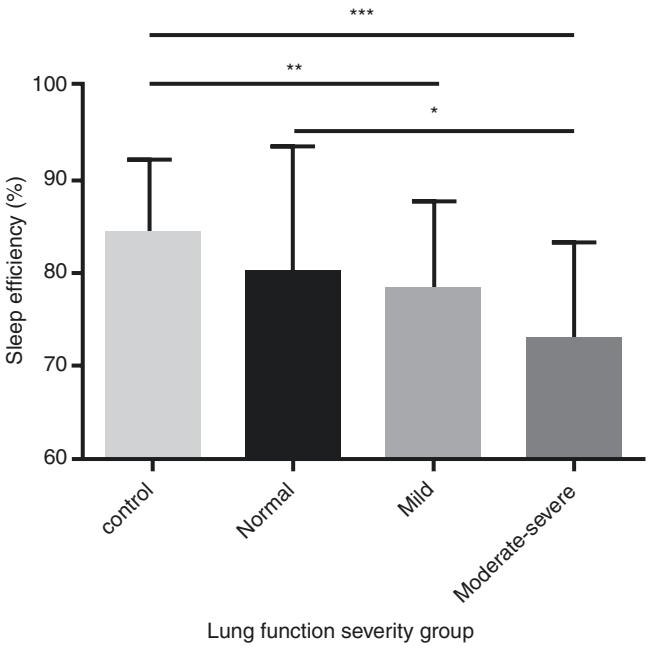

Fig. 44.2 Sleep efficiency of control children and children with CF across three different groups of FEV1 (normal [≥90%], mild [70%–89%], moderate-severe [<70%]). A significant difference was found in the children with CF across the 3 groups ($P = 0.03$) after controlling for sex, age, and SES (univariate analysis). A significant difference was measured between CF patients with normal lung function and CF patients with moderate-severe lung function (*$P < 0.05$). A significant difference also was measured between control children and CF patients with mild (**$P < 0.01$) and moderate-severe (***$P < 0.001$) lung function but not those with normal lung function ($P = 0.08$). (From Vandeleur et al. [36]. Reprinted with permission from Elsevier)

8–50% of children with CF [16, 19–21]. Both groups have similar risk factors for OSA, which include young age (typically <6 years), black race, and evidence of nasal or upper airway obstruction, most commonly due to hypertrophy of the adenoids or tonsils [16, 18, 21]. Children with CF can also have upper airway obstruction from dysfunctional CFTR in the nasal mucosa and sinuses, which results in recurrent inflammation and the development of nasal polyps [6, 18].

Not surprisingly, children who have CF with vs. without OSA have significantly lower nocturnal oxygen saturations (SpO_2) [12, 16–18, 20]. Both the Mean SpO_2, which is the baseline or average SpO_2 across the night, and the lowest SpO_2 attained during the night, or Min SpO_2, are reduced in the OSA group [12, 17]. Frequency of desaturation episodes and duration of hypoxemia, defined in children as $SpO_2 < 90\%$, as a percentage of the total sleep time, are both higher in the OSA vs. non-OSA group [17]. A moderate negative association has also been reported between the awake resting SpO_2 and OSA severity [11, 45].

However, OSA severity does not appear to be linked to any other daytime markers of CF lung disease severity, including FEV1 PPD [11, 12, 45]. Interestingly, in two out of

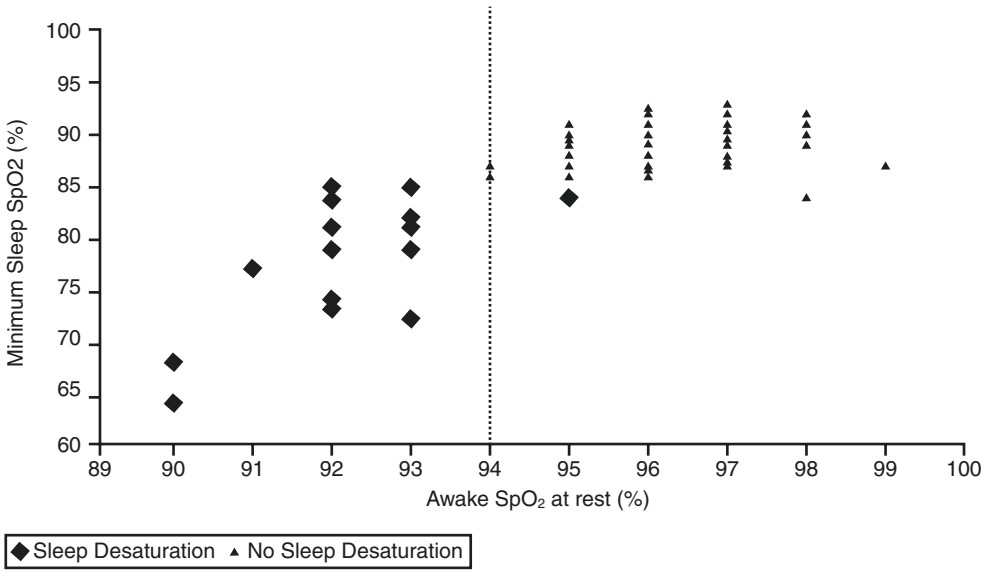

Fig. 44.3 Relationship between the minimum sleep SpO_2 and awake SpO_2 at rest in sitting position. The vertical line represents the threshold (awake SpO2 = 94%) that best separates patients who did desaturate (diamonds) from those who did not desaturate (triangles). (From Perin et al. [58]. Reprinted with permission from Springer Nature)

the three studies, the majority of the subjects had a normal apnea-hypopnea index (AHI) [11, 45]. Only one study, which included mostly children too young to perform lung function testing, found significantly lower FEV1 PPD values among those with vs. without OSA (77 vs. 82%, respectively) [16].

Impaired sleep duration, efficiency, and fragmentation have not been identified in association with OSA in patients with CF [17], raising the possibility that perhaps OSA might not explain the sleep complaints observed in these children. Emerging evidence suggests that children with OSA may have subtle microarousals, not readily observed on standard polysomnography, but nevertheless capable of adversely affecting sleep quality [46–49]. The application of some of these more advanced techniques in children with CF could improve our understanding of the impact of OSA on sleep in this population.

Abnormalities in Gas Exchange

Nocturnal Hypoxemia

Children with CF, and, in particular, those with moderate-severe lung disease, frequently experience a measurable decline in their oxygen saturation (SpO_2) during sleep [20, 21, 50]. This desaturation, most pronounced during rapid-eye-movement (REM) sleep, is thought to represent a potentially exaggerated response to a normal sleep-related reduction in lung volumes and ventilation [50–54]. Nighttime SpO_2 tends to be lower, on average, among children with vs. without CF, including among those with no clinical evidence of lung disease and irrespective of similar, normal daytime saturations [10, 15, 16, 21, 36, 37, 55]. The degree of nocturnal hypoxemia varies based on the severity of the underlying lung disease [11, 12, 19, 20, 36, 38, 55, 56]. The best predictors for the likelihood and severity of nocturnal hypoxemia, in both children and adults with CF, appear to be the awake resting SpO_2 (values <94%, Fig. 44.3) and the FEV1 PPD (values <64%) [19, 21, 57, 58].

Among adolescents and adults with CF, the frequency of pulmonary hypertension is higher among patients with vs. without nocturnal hypoxemia [3, 58]. The inverse has also been shown to be true, with worse daytime and nocturnal SpO_2, and prolonged periods of desaturation, both during sleep and exercise, among CF patients with vs. without pulmonary hypertension [3, 58].

Nocturnal Hypercapnia

The reduction in ventilation that occurs during sleep results in elevated carbon dioxide (CO_2) levels, often above normal physiologic levels, in children and adults with CF [12, 15, 38, 50, 58, 59]. Nocturnal hypercapnia, defined as an end-tidal or transcutaneous CO_2 value ≥50 mmHg, is observed with regularity among adults with CF, especially in the setting of supplemental oxygen for treatment of nocturnal hypoxemia [51, 60–62]. Although this is less of a concern among children with CF, who largely have normal CO_2 levels during wakefulness and sleep [11, 63], they nevertheless have higher CO_2 values than those found in age-matched, healthy peers [10].

As with nocturnal hypoxemia, severity of the nighttime hypercapnia is linked to CF lung disease severity [12, 38, 58, 59]. However, this relationship is not as straightforward. Children with CF who experience any increase in their CO_2 levels during REM vs. non-REM sleep, compared to those

whose CO_2 levels are unchanged, have a 15% lower FEV1 PPD [12]. However, nocturnal hypercapnia has also been reported in children with normal FEV1 PPD [15]. One study found no differences in nocturnal CO_2 levels between those with low vs. normal FEV1 PPD [11]. Whether the FEV1 PPD can adequately predict risk for nocturnal hypercapnia will require further investigation.

Nocturnal hypercapnia has been associated with lower nighttime SpO_2 levels among children with CF [11]. Nocturnal and diurnal hypercapnia has been observed in adolescents and adults with pulmonary hypertension [3, 58].

Effects on Sleep Quality

Both nocturnal hypoxemia and hypercapnia are associated with poor subjective sleep quality [21, 38, 64]. Nocturnal hypoxemia, and, in particular, the Min SpO_2, is linked to reduced sleep duration [36, 44], poor sleep efficiency [36, 65], frequent arousals, and prolonged periods in WASO [36].

Adult CF patients with vs. without nocturnal hypoxemia tend to have a higher respiratory rate during sleep [58]. The children and adults with CF who retain CO_2 breathe faster during sleep [12, 58]. This tachypnea during sleep is associated with low FEV1 PPD and poor nutritional status, at least in children with CF [12]. Whether the tachypnea has additional impact on sleep quality remains unknown.

An increased frequency of subjective sleep complaints is observed among CF patients with vs. without pulmonary hypertension [3]. Compared to those with normal pressures, patients with pulmonary hypertension tend to have poorer sleep efficiency and more prolonged sleep-onset latency. The percentage of sleep time spent in stage 1 (N1) sleep, often used as a measure of sleep fragmentation, is also higher in the pulmonary hypertension group [3]. Whether the derangements in sleep quality observed among patients with pulmonary hypertension arise because of underlying abnormalities in gas exchange awaits clarification.

Etiologies for Poor Sleep

Many reasons are likely to contribute to poor sleep in CF (Fig. 44.4). The presence of dysfunctional CFTR in the retinal epithelium and regions of the hypothalamus that regulate circadian rhythm could explain some of the phase delays, including the prolonged sleep-onset latency, observed in these individuals [6, 21, 38, 66]. Poor sleep hygiene, the presence of a behavioral condition such as attention-deficit/hyperactivity disorder, and delayed bedtimes or early rise times to accommodate the heavy treatment burden associated with the disease all have the potential to impair sleep in childhood CF [39, 44].

Insomnia is a known side effect of several medications routinely prescribed to children with CF including albuterol, prednisone, and certain antibiotics such as trimethoprim-sulfamethoxazole and levofloxacin. Children with CF frequently cough at night, and this has been associated with a reduced sleep duration and more fragmented sleep [9, 12, 44, 67]. Asthma often occurs concurrently with CF and can lead to poor sleep efficiency and prolonged WASO, possibly as a result of a frequent nocturnal cough [44, 68, 69].

Another common comorbidity observed in this population, CFRD, has also been linked to reduced sleep duration [44]. Although the temporal nature of this relationship has yet to be clarified, one study found two times greater odds of abnormal daytime glucose levels among children with CF who experienced nocturnal hypoxemia and, specifically, a Mean $SpO_2 < 96\%$ [15]. The mediator in this relationship between low nocturnal SpO_2 and elevated blood glucose levels might be insufficient sleep. Nocturnal hypoxemia has been shown to independently affect both sleep duration and efficiency in children with CF [36, 44], and both shorter sleep times and poorer sleep efficiency are linked to higher daytime glucose levels and reduced sensitivity to insulin in adolescents with CF [70].

Impaired CFTR function in the liver, pancreas, and gastrointestinal tract leads to significant protein-calorie malnutrition in children with CF [2, 4, 6]. Along with poor lung function, and the presence of CFRD, malnutrition is an important risk factor for early mortality in these children [71]. As a counter measure and in an effort to boost their nutrition, these children are frequently prescribed enteral feeds at night [72]. However, the use of nocturnal tube feeds is associated with shortened sleep times and more fragmented sleep in children with CF [44]. Other gastrointestinal symptoms frequently observed in these children, including abdominal pain [14, 73–75], acid reflux [76, 77], flatulence, and loose stools [2, 4], also have the potential for adverse impact on sleep [9, 44]. The presence of acid reflux, in particular, is associated with a greater frequency of respiratory symptoms, worse airway inflammation, more rapid decline in lung function, and earlier acquisition of *Pseudomonas aeruginosa*, factors independently linked to poor sleep [4, 44, 76].

Impact of Sleep Disturbances

Most of the literature on the adverse effects of poor sleep focuses on the impact of short sleep. In both children and adults, reports have often defined short sleep as a total sleep time under 7 hours per night, although teens are expected to get 8–10 hours of sleep per night and younger children 9–11 hours or more [34, 35, 70]. Children with CF, on average, sleep less than 7 hours per night [11, 12, 15, 17, 37, 38,

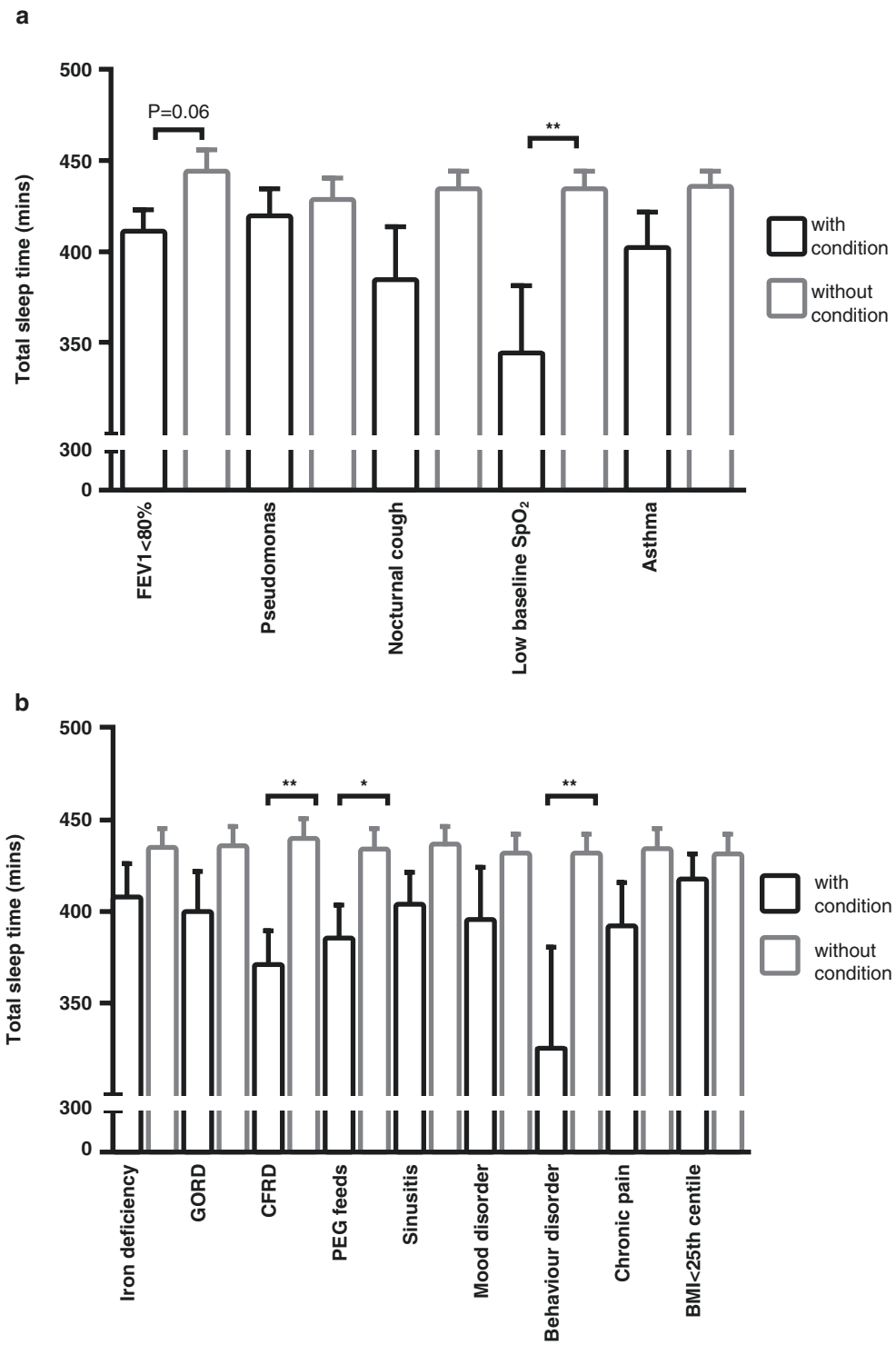

Fig. 44.4 Total sleep time of children with CF, with and without (**a**) respiratory comorbidities or (**b**) non-respiratory comorbidities. Data presented as mean ± SEM * $p \leq 0.05$, ** $p \leq 0.01$. (From Vandeleur et al. [44]. Reprinted with permission from Elsevier)

43, 50, 63]. Yet little is known about the impact of short sleep on the health and quality of life of children with CF.

Compared to those with normal sleep duration, otherwise healthy adults with short sleep have a relative risk of 1.38 for obesity, 1.37 for diabetes mellitus, 1.26 for coronary heart disease, 1.17 for hypertension, and 1.12 for overall mortality [78]. For every 1-hour reduction in total sleep time from 7 hours, the risk of all-cause mortality increases by 1.06 annually in these adults [34]. Insufficient sleep has been linked to an increased risk of obesity, hyperlipidemia, and insulin resistance among healthy children [27–29]. Reduced sleep duration, poor sleep efficiency, and prolonged sleep-onset latency have all been associated with higher daytime glucose levels among adolescents with CF [70]. Poor

sleep efficiency and increased sleep fragmentation may also worsen insulin resistance in patients with CFRD [70]. The presence of nocturnal hypoxemia, possibly due to its adverse impact on sleep duration and sleep fragmentation, has also been associated with impaired glucose regulation [15].

Although a lack of insulin is believed to be the primary cause of elevated glucose levels among patients with CF, these individuals also have a degree of insulin resistance, especially during periods of acute illness that is thought to be triggered by inflammation [5]. The presence of inflammation, more chronically, has also been implicated in the pathogenesis of CFRD [5]. The primary pathology in CF lung disease is chronic airway inflammation, involving the nasal mucosa, sinuses, and lower airways [2]. Among otherwise healthy adolescents, reduced sleep duration has been associated with higher levels of serum inflammatory markers [35]. Whether a similar relationship between sleep and inflammation exists among children with CF remains to be determined.

One of the main drivers for the chronic inflammation observed in individuals with CF is the presence of recurrent respiratory infections [2]. Each of these infective exacerbations is associated with an acute reduction in pulmonary function. Often, the lung function does not return to baseline even after adequate treatment of the exacerbation [79]. Loss of pulmonary function is a major risk factor for mortality among individuals with CF [71]. Frequency of pulmonary exacerbations has additionally been shown to independently predict 5-year survival in these patients [80]. Insufficient sleep has been associated with an increased susceptibility to viral infections among non-CF individuals [33]. This could be of importance to patients with CF since majority of the infective exacerbations are triggered by viruses [79, 81, 82]. Furthermore, recurrent viral respiratory infections are also associated with early *Pseudomonas aeruginosa* acquisition [81]. Yet no data exists on whether sleep disruption increases frequency of pulmonary exacerbations in children with CF.

Inadequate sleep, particularly in the setting of sleep disorders such as OSA, is linked to impairments in memory and executive function, inattentiveness, poor academic performance, an increased frequency of mood disorders such as depression and anxiety, and poor quality of life in otherwise healthy children [22–26, 31, 83, 84]. Impairments in health perception, vitality, and physical, social, and emotional functioning are reported by adolescents with CF who suffer from poor sleep [37]. These individuals also endorse more inattentiveness, hyperactivity, anxiety, and depressive symptoms [13, 14, 37, 85]. Although deficits in executive functioning, memory, and attention are all observed to a greater degree among children with vs. without CF [86, 87], how sleep disruption affect these outcomes is still largely unknown.

Treatment of Sleep Disorders

Treatment of sleep disturbances in patients with CF has largely focused on reversing the nocturnal hypoxemia, to reduce the risk for pulmonary hypertension and right heart failure. While effective in improving SpO_2, the addition of supplemental oxygen during sleep has not yielded any measurable improvement in sleep duration or degree of sleep fragmentation [51, 60, 61]. Several disease-specific outcome measures including mortality rate, nutritional status, lung function, frequency of pulmonary exacerbations, and daytime saturations are also similar between adults with severe CF lung disease who receive nocturnal supplemental oxygen vs. room air [88]. Exercise capacity, mood, and executive functioning are also not different [88]. Although sleep has not been formally assessed, the better school and work attendance observed with nocturnal supplemental oxygen has been attributed to improved sleep quality [88].

The use of supplemental oxygen, for either daytime or nighttime hypoxemia, has been consistently shown to worsen hypercapnia in patients with CF [51, 60, 61]. More than a third of adults with CF developed progressive hypercapnia within 1-year of initiation of supplemental oxygen [62]. Patients who had significant hypercapnia at baseline were also the ones most likely to fail oxygen therapy [62].

Noninvasive positive-pressure ventilation (NIPPV), which functions to prevent the fall in minute ventilation that normally occurs during the transition from non-REM to REM sleep, has been shown to improve nocturnal oxygen saturations without the unwanted side effect of worsening hypercapnia [51, 61, 89]. Adults with CF who were transitioned from supplemental oxygen to NIPPV saw an improvement in their hypercapnia within the first month [62]. While NIPPV does not appear to improve sleep duration or frequency of arousals [51, 61, 90], the frequency of apneic events might be lower on NIPPV vs. either supplemental oxygen or room air [51, 90]. Improvements in exercise capacity, dyspnea and other respiratory symptoms, and the rate of lung function decline are also reported within 1-year of NIPPV use [89, 91].

Interestingly, despite this promising evidence in support of NIPPV use for abnormalities in gas exchange during sleep, these are not the primary reasons for use of NIPPV in patients with CF. Rather, in both children and adults with CF, NIPPV is largely prescribed for daytime hypercapnia, whether it is in the setting of a pulmonary exacerbation or as a result of disease progression [91, 92]. In children with CF, NIPPV has been additionally used to promote airway clearance and as a bridge to lung transplantation [92]. Of note, OSA has not been cited, to our knowledge, as a reason for NIPPV use, despite recommendations for the use of positive airway pressure (PAP) therapy for persistent childhood

OSA. We were not able to uncover any data on the use of continuous positive airway pressure (CPAP) for OSA in either children or adults with CF.

A survey of pediatric centers in the United Kingdom and Australia found that a majority used pulse oximetry and/or capnometry to determine need for NIPPV; less than 50% performed polysomnography prior to starting NIPPV [92]. While polysomnography can be expensive, time-consuming, and sometimes technically difficult to obtain in children, nocturnal hypoxemia and hypercapnia can often precede any daytime abnormalities. Unfortunately, no guidelines currently exist on when or how to screen children with CF for sleep disturbances or the derangements in gas exchange parameters associated with them.

Although children with CF routinely complain of difficulties with sleep initiation and maintenance, there continues to be a paucity of information on how to effectively manage these problems. Despite emerging evidence on the effectiveness of cognitive behavioral therapy for the treatment of insomnia in children and adolescents, to our knowledge this treatment strategy has not been evaluated in children with CF. Given their propensity to adversely affect respiration, benzodiazepines should be used with caution in patients with CF. Zolpidem, a non-benzodiazepine hypnotic, has been associated with a higher risk for respiratory infections and should therefore also be used with caution [93]. Melatonin has proven efficacious to promote sleep in healthy children and in those with sleep-phase delays [94]. Among children with CF, melatonin has been shown to improve sleep efficiency and reduce sleep-onset latency [43]. Melatonin may also exert some anti-inflammatory effects in this population [43]. However, medications such as hypnotics are probably overused as most children and adults with chronic insomnia or circadian rhythm sleep/wake disorders can be treated effectively by behavioral approaches [95, 96]. Patients with CF may have added reasons to benefit from non-medication approaches, when available. Given the potential for phase delays and other circadian rhythm disturbances in children with CF, more work is clearly needed on ways to appropriately screen for and treat these conditions.

Conclusions and Implications for Clinical Practice

The significance of sleep disruption in childhood CF cannot be overstated. Poor sleep has the potential to adversely impact lung health, nutrition, cognitive function, mood, and quality of life in these children. When compared to those without CF, these children have been repeatedly found to sleep less and have more fragmented sleep, with frequent arousals and prolonged periods of wakefulness after sleep onset. Prolonged sleep-onset latency and phase delays have also been observed with greater frequency in this population. Emerging evidence suggests that children with CF might be inherently at risk for sleep problems, including circadian rhythm disturbances, due to defective CFTR function in the retinal epithelial cells and hypothalamus. Yet no guidelines exist on when or how to screen these children for sleep disorders.

Obstructive sleep apnea (OSA) has been shown to be both common and consequential in children with CF. However, few of these children are referred for polysomnography [8]. Only 15 polysomnographic studies have been published over the past 40 years that involve children with CF [8]. Although validated screening tools for OSA and other sleep disturbances of childhood are readily available [97, 98], none have been consistently used in the evaluation of children with CF. Children with CF do not currently undergo even routine overnight pulse oximetry monitoring despite knowledge that impaired gas exchange during sleep can precede any daytime abnormalities. As low lung function appears to be associated with more significant nocturnal hypoxemia, hypercapnia, and worse sleep quality, we believe that at minimum clinicians should consider screening all children with CF who have an abnormal baseline FEV1 PPD for sleep disturbances. Children who have an awake $SpO_2 \leq 94\%$ may also benefit from a similar evaluation or at least overnight pulse oximetry/capnometry monitoring to look for impairments in gas exchange during sleep.

Although guidelines recommend adenotonsillectomy as the first-line treatment for childhood OSA, no data exist on the benefits of this procedure in children with CF. A paucity of data also exists on the use of other treatment modalities including NIPPV and CPAP; sleep aids such as zolpidem, benzodiazepines, and melatonin; and cognitive behavioral therapy for insomnia. Treatment guidelines that address sleep in CF – evidence-based where possible and otherwise consensus-based – could help to improve care for these patients.

Timely detection and treatment of sleep disorders in children with CF would have the potential, even if still unproven, to improve quality of life, slow lung function decline, and increase survival.

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Bronchopulmonary Dysplasia

45

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Introduction

Bronchopulmonary dysplasia (BPD) is one of the most common morbidities of prematurity. It is a disease characterized by abnormal continued development and repair after premature birth and exposure to oxygen, mechanical ventilation, and inflammation. Outcomes reported from the National Institute of Child Health and Human Development Neonatal Research Network (NICHD NRN) over the last 20 years have shown modest but significant decreases in mortality and many major morbidities for even the smallest infants [1]. However, the incidence of BPD remains at approximately 50% for the smallest infants, which has remained steady or slightly increased over the previous two decades [1]. This trend has been seen across the country and across the world [2]. Infants with BPD continue to have lung disease into childhood with higher rates of viral infections, need for respiratory support, and increased risk for asthma [3–5]. They also are at higher risk for growth failure and neurodevelopmental impairment [4].

Definition of BPD

BPD was first described in 1967, but the definition has changed several times over the last few decades. An early definition of BPD was the requirement for supplemental oxygen at 28 days following the diagnosis of hyaline membrane disease in premature infants [6]. This original form of BPD was characterized by extensive inflammatory changes with fibrosis created in the setting of aggressive mechanical ventilation and exposure to high oxygen concentrations [7, 8]. When this definition was first accepted, the majority of infants diagnosed with BPD were born at over 32 weeks' gestational age. Over time, the term BPD has evolved to describe a very different disease. In more recent years, the infants diagnosed with BPD are born at much younger gestational ages, typically below 26 weeks' gestation. They have less severe initial respiratory distress syndrome (RDS) and exposure to less iatrogenic injury. These infants, born in the exogenous surfactant era, do not have the same extensive lung scarring that was seen in previous generations. In the modern era, some infants who develop BPD never had RDS or had only mild disease. The "new BPD" can be characterized as abnormal development in the setting of extremely preterm birth. The lungs of these infants, born just at the transition of canalicular to saccular stages of lung development, do not reach the ultimate branching complexity as is seen in the term newborn lung, leading to fewer and larger alveolae [7, 8]. The newer definition of BPD was defined as oxygen use at 36 weeks post-menstrual age.

The current NIH consensus definition was established in 2000. It defines BPD as lung disease in infants born at less than 32 weeks' gestation and requiring oxygen for at least 28 days and defines its severity based on level of oxygen requirement at 36 weeks post-menstrual age (PMA) (Table 45.1).

Table 45.1 Classic definition of BPD based on NIH consensus guideline published in 2001

Mild BPD	Infants who are breathing room air at 36 weeks' PMA or discharge, whichever comes first
Moderate BPD	Infants who are on less than 30% oxygen at 36 weeks' PMA or discharge
Severe BPD	Infants who require greater than 30% oxygen or positive pressure at 36 weeks' PMA

Data from Jobe and Bancalari [106]

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New Directions: New Definition, New Studies

Work continues as clinicians and researchers continue to improve the respiratory care of the smallest infants. A new definition of BPD is being discussed at this time which acknowledges the degrees of respiratory support which may be required at 36 weeks. It also provides a mechanism to compare the severity of BPD which infants may have. A common concern is that the definition of requiring oxygen at 36 weeks does not allow for variation in severity or allow a reasonable comparison of later pulmonary outcomes. Initial studies evaluating this new classification system were also able to predict later death and serious morbidity.

New BPD Definition (Table 45.2)

Pathophysiology

The original description of BPD was of moderately preterm infants who had severe respiratory failure due to hyaline membrane disease and required long-term ventilatory support [6]. The injury in these infants was due to mechanical trauma from the pressure needed to open these non-compliant lungs and from oxygen toxicity. Although the infants now diagnosed tend to be much younger and smaller, these same mechanisms remain important.

Inflammation

In the modern era of prenatal steroids and exogenous surfactant administration, inflammation from ventilation and oxygen toxicity continues to be seen despite lower amounts of both being used. How much of this inflammatory damage happens prenatally vs postnatally remains unclear. Higher concentrations of inflammatory cytokines have been found in the amniotic fluid of women whose infants went on to develop BPD; elevated IL1B, IL 6, and IL 8 in the amniotic fluid predicted the development of BPD in those infants [9, 10]. Increased levels of inflammatory cytokines, as well as increased inflammatory cells, have also been seen in the tracheal aspirates of infants who progress to development of BPD [11–17]. Experimental models have also shown that elevated cytokine expression, specifically increased IL 6 and TNF-alpha, cause an arrest of alveolar septation leading to larger alveolae with increased fibrosis [18].

Oxygen is essential for life and aerobic metabolism, but when delivered at high concentration can be toxic due to free radical production and subsequent injury. Discussion of the damage created by oxygen toxicity has continued since the first descriptions of BPD [6, 19, 20]. The toxicity of oxygen is associated with the formation of reactive oxygen species such as OH*, NO, H_2O_2, O_2^-, and LOOH [21]. It has been shown that premature infants have lower levels of antioxidants than adults or term infants, making them particularly sensitive to the damaging effects of oxygen. It is the imbalance of oxidant versus antioxidant species which has been proposed to be the cause of oxygen toxicity.

At the same time infections (both prenatal and postnatal) are both significantly associated with the development of BPD. Inflammation has therefore been hypothesized to be a primary actor by some investigators, but merely an associated mediator by others.

Infection

Infection and inflammation leading to BPD can begin prenatally. In mothers with both clinical and subclinical chorioamnionitis, the infants have an elevated risk of BPD. The inflammatory injury within the fetal lung either can be triggered by feedback from inflammatory cytokines from the placenta and fetal membranes or can take place in the setting of aspiration of infected fluid and direct injury [18]. Many clinical reports have determined that maternal colonization by ureaplasma urealyticum and other atypical bacteria increase the risk of BPD [22, 23]. Atypical bacteria such as ureaplasma urealyticum and ureaplasma parvum are commensal bacteria which colonize the genital tract and have been isolated in the placenta as well as in premature neonatal secretions (gastric, tracheal, etc.) [24]. Studies have demonstrated that, in premature animals injected with ureaplasma urealyticum and exposed to mechanical ventilation, those who were unable to clear the bacterial were more likely to have chronic inflammation and develop chronic lung disease [24]. In contrast exposure to these pathogens was associated with decreased severity of RDS and early lung maturation [18, 25–27]. This supports the theory that the exposure to atypical bacteria may predispose to abnormal lung develop-

Table 45.2 New proposed definition of BPD based on work by Eric Jensen et al. (2019)

No BPD	Grade 1		Grade 2			Grade 3	
Room Air	Nasal Canula <2 L/min		NC > 2 L/min		nCPAPA/NiPPV	Invasive PPV	
	<30%	>30%	<30%	>30%	Any FiO2	<30%	>30%

Data from Jensen et al. [107]

ment or may alter the way that the lung tissue responds to other pathogens. Other researchers were able to show that chronic ureaplasma infection in fetal sheep is associated with altered innate immune responses [28]. Despite an abundance of research into the association of infection or colonization with atypical bacteria, no study has been able to demonstrate causation. In addition, clinical studies looking at use of macrolides to treat ureaplasma infection have failed to demonstrate improvement in the rate of BPD [24, 29, 30].

Other studies have looked at colonization or infection after birth as contributing to the development of BPD. In one study evaluating tracheal aspirates taken in VLBW found an association of gram-negative rods in those infants who developed BPD [31]. It is likely that an interplay between exposures contributes to BPD.

Immaturity

A critical component to the development of BPD is the immaturity of the premature lung. The vast majority of infants who develop BPD are born at less than 26 weeks' gestation. At that developmental stage, the developing lungs remain in the "saccular" stage of development. The development of the lungs follows a staged process, and the transition from canalicular to saccular stages happens at approximately 22–23 weeks. Pathological studies in both animals and humans have shown that exposure to both oxygen and pressure causes arrest and atypical lung development with decreased septation – with fewer and larger alveolae [32–35]. In examining pathological samples, extremely premature infants have lower radial alveolar counts than control infants [32]. In the setting of extreme prematurity, exposure to oxygen and mechanical ventilation can adversely affect lung development and alter cellular differentiation [36–38]. A key to survival is rapid maturation and the ability of the premature lungs to function for gas exchange. However, it is possible that in that process, those early maturational changes lead to scarring which contributes to the development of BPD.

Ventilator Injury Pressure/Volume

The initial descriptions of BPD described the relationship of mechanical ventilation with BPD. Further research has shown that even a few breaths of positive pressure can cause damage leading to increased risk of BPD [39]. Cyclic stretch and overdistension of the lung tissue cause direct inflammation and injury. This promotes further inflammation and inhibits normal lung growth and differentiation. Great debate exists on whether the mechanical injury is more from the direct effect of pressure or whether it is the changes in volume, from the pressure that caused the primary injury. In experimental animal models exposed to high levels of positive inspiratory pressure, either with or without a rigid external chest wall cast (to limit pressure changes), the pressure alone, without changes in lung volume, resulted in significantly fewer cases of BPD. Given concern about the injury caused by volume changes, newer ventilation strategies have emerged.

Avoiding mechanical ventilation is associated with lower rates of BPD. Multiple large, multicenter studies have shown the benefit of avoiding mechanical ventilation to decrease development of BPD [40–45]. Applying noninvasive positive pressure rather than intubation and mechanical ventilation decreases the rate of BPD [41, 42, 44].

In some cases, intubation and mechanical ventilation cannot be avoided. In those cases, exogenous surfactant should be given to decrease the damage from positive pressure ventilation. Providing early selective surfactant (within 2 hours of delivery) to infants with worsening respiratory distress syndrome decreases the risk of air leaks and neonatal morbidity and chronic lung disease [46–48] (Fig. 45.1).

Current Management Strategies

As our understanding of the pathophysiology of BPD has increased, strategies have been adopted to try to decrease the incidence of BPD. Central to this is the early respiratory management of extremely premature infants. To successfully accomplish transition from fetal life to extrauterine breathing, the lungs must rapidly expand, clear themselves of fluid, and begin gas exchange. This requires the establishment of functional residual capacity (FRC). Surfactant is a naturally occurring substance which decreases the surface tension in the lungs, increases compliance, facilitates gas exchange, and allows the maintenance of FRC. Prophylactic and selective surfactant administration decreases both mortality and pulmonary air leaks when administered in the first hours of life. Prophylactic surfactant is defined as giving surfactant to all infants at risk of RDS, typically defined by a specified birth gestational age or birth weight criteria, in the delivery room, typically within 30 minutes of birth or ideally prior to positive pressure ventilation. The clinical practice of selective surfactant administration involves placing at-risk infants on noninvasive positive pressure in the delivery room and then intubating and giving surfactant only if certain clinical criteria are met. Over the last decade, further studies have evaluated different delivery room strategies, particularly comparing these two approaches. Use of early nasal CPAP with selective surfactant administration if certain oxygen needs or hypercarbia limits were met resulted in decreased BPD [40, 41, 44]. A meta-analysis of several of these trials showed that prophylactic intubation and surfactant adminis-

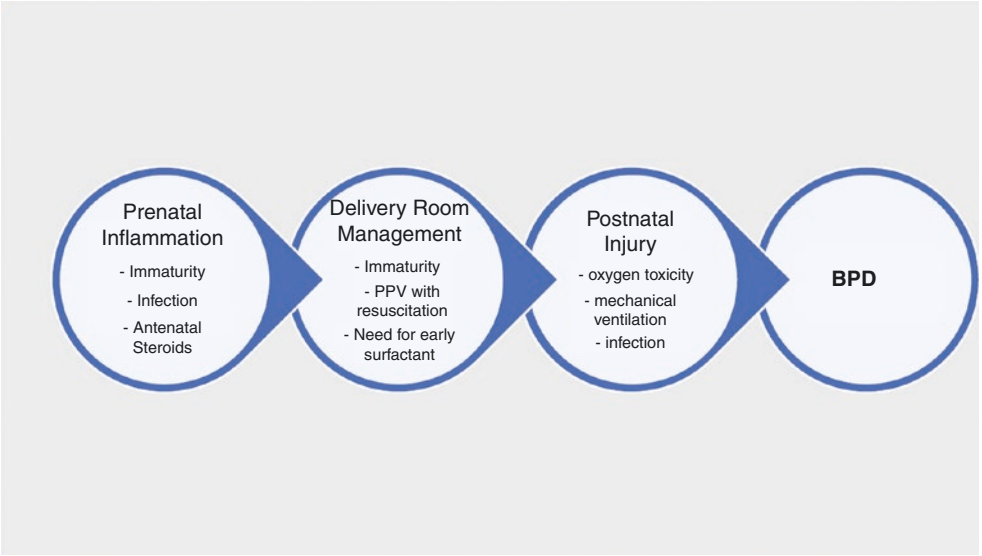

Fig. 45.1 Conceptual model of pathogenesis of BPD

tration with extubation to CPAP resulted in increased risk of death or BPD (RR 1.12 with number needed to harm 17). If intubation and mechanical ventilation is needed, earlier surfactant (i.e., within 2 hours of delivery) is preferable to delayed administration [48–50].

If intubation and mechanical ventilation is needed, a gentle ventilation strategy with permissive hypercapnia decreases the rate of BPD without increasing other morbidities. Permissive hypercapnia (targeting CO2 > 52 compared to <48) was evaluated in a multicenter trial by the Neonatal Network. In this trial permissive hypercapnia resulted in decreased need for ventilation at 46 weeks from 16% to 1% [51]. However another study comparing even more permissive hypercapnia up to 75 mmHg on day 7–14 did not show any benefit [52]. Some animal research suggests that CO2 may have direct benefit on the lung. However, much of the benefit appears to come from a more conservative approach to intubation and a more aggressive attitude toward extubation [43]. A more permissive attitude toward CO2 also allows a gentler approach to ventilation, with lower minute ventilation typically through lower inspiratory pressures.

Traditional pressure-controlled ventilation risks change in volume and resulting volutrauma. Rapid changes in compliance may be caused by clearance of fetal lung fluid and/or surfactant administration and other changes in the first hours of life. As a result, newer forms of mechanical ventilation have come to be favored which target a specific volume and decrease both volutrauma and atelectrauma. Several trials have evaluated volume-targeted ventilation of premature infants who require mechanical ventilation. A meta-analysis of these showed decreased BPD and mortality in the use of volume-targeted strategies [53, 54]. Other studies have evaluated the effectiveness of high-frequency ventilation to decrease BPD. There are two modes of high-frequency ventilation – the high-frequency oscillator (HFOV) and the high-frequency jet ventilator (JET) which are widely available in the United States and have been extensively studied. Both rely on an open lung strategy with high mean airway pressure to maximize oxygenation. The trials of these ventilators have shown mixed results regarding decreasing mortality or BPD [53, 55–57].

Management Strategies to Reduce Lung Injury and Development of BPD

Currently best recommendations based on the available evidence:

- Provide nasal CPAP to establish FRC in the delivery room.
- Provide selective surfactant within 2 hours of birth if needed.
- Extubate to nasal CPAP as soon as possible.
- If continued intubation and mechanical ventilation is necessary, use gentle ventilation with an open lung strategy and volume-targeted approach which minimized volutrauma and atelectrauma.

Medications

Despite extensive research over many years, few medications have been identified which impact BPD. The most important of these is caffeine. Caffeine is a methylxanthine, commonly used to decrease apnea of prematurity. In the Caffeine for Apnea of Prematurity (CAP) trial, over 2000 infants with birth weights between 500 g and 1250 g were assigned to caffeine versus placebo. The infants who received

caffeine had a significantly lower rate of BPD, were able to come off positive pressure on average 1 week earlier, and had improved neurodevelopmental outcomes [58, 59]. Additional research has shown that earlier caffeine is associated with improved rates of BPD compared with later administration. In post hoc analyses of the CAP trial, infants who started on caffeine before 3 days were less likely to develop BPD compared to those who started later [60–62]. In a large retrospective study of more than 62,000 infants, the rate of BPD was significantly lower in infants who received early caffeine. They were also exposed to significantly less mechanical ventilation [62].

Vitamin A is another medication which has shown promise in decreasing BPD. In 1999, Tyson et al. published the results of their placebo-controlled randomized trial of prophylactic vitamin A. In this study, 807 infants with birth weights between 400 and 1000 g received either 12 IM injections of vitamin A or a sham procedure over the first 4 weeks of life. Use of vitamin A was associated with a significantly decreased rate of BPD; 55% of the infants receiving vitamin A developed BPD compared to 62% in the placebo group (NNT = 14–15 infants) [63]. Follow-up data at 18–22 months continued to show a mild but not statistically significant improvement for the infants in the vitamin A group, without evidence of harm [64, 65]. Despite initial interest in this treatment, the small benefit in risk of BPD must be balanced against the acceptability of the intervention, which required 12 intramuscular injections in the first weeks of life [66].

Inhaled corticosteroids are another therapeutic modality which has been evaluated as a potential preventative treatment of BPD. In a large multicenter randomized placebo-controlled trial of inhaled budesonide to prevent BPD, 863 infants were randomized to budesonide versus placebo. Budesonide was associated with a small but significant decrease in the primary outcome, the combined outcome of death, or bronchopulmonary dysplasia. However, this was due to a significant decrease in the rate of BPD (27.8% vs 38%) but a slight increase in mortality (16.9% vs 13.6%) [67]. Another trial using fluticasone showed similar results. In this trial 211 infants were randomized to inhaled fluticasone within the first 24 hours compared to placebo [68]. This study also showed a decrease in the incidence of BPD with an increase in the incidence of pre-discharge death. Based on these studies and a few other very small trials, inhaled steroids cannot yet be recommended for the prevention of BPD.

Steroids

Systemic corticosteroids have been used in the treatment and prevention of BPD for many years. Prenatal steroids are one of the most effective therapies in neonatal medicine. Prenatal steroids have been shown to decrease RDS, improve survival, and decrease intraventricular hemorrhage [69]. In the 1980s, clinicians observed that premature infants treated with corticosteroids had improved respiratory status. Use of dexamethasone was associated with decreased need for mechanical ventilation, decreased need for supplemental oxygen, and decreased BPD [70]. A review in 2010 found 20 studies involving 2860 infants treated with early (started at <7 days) to prevent BPD. These studies involved a range of doses and durations of therapy. Early dexamethasone treatment was associated with decreased rate of BPD, defined by need for oxygen or positive pressure at either 28 days or 36 weeks. It was also associated with earlier extubation and decreased severe retinopathy of prematurity. Importantly, dexamethasone was also associated with increased risk of several important adverse in hospital events including GI bleeding, GI perforation, hypertension, and hyperglycemia [71].

Later outcomes were reported in 7 of the studies involving 921 infants. Most significantly, the combined outcome of death or cerebral palsy was significantly increased in the infants exposed to dexamethasone [71]. Similar findings were seen in trials of later dexamethasone. Use of dexamethasone after the first week of life was associated with a decrease in the length of mechanical ventilation, decrease in infants failing extubation, and decrease in BPD. However, this was offset by an increase in cerebral palsy [72]. In a large study of dexamethasone in a 42-day tapering course, the rate of cerebral palsy was 25% in the treatment group compared with 7% in the placebo, and 45% of infants had an abnormal neurological exam compared to 16% [73]. These findings led to statements by the American Academy of Pediatrics and the Canadian Paediatric Society and the European Association of Perinatal Medicine recommending against the routine use of systemic dexamethasone for prevention or treatment of BPD [74]. These recommendations and the increased recognition of the adverse long-term neurological effects of postnatal steroids led to a dramatic decrease in their use. In a review of a national database, steroid use decreased from 23.5% to 11% between 1997 and 2004 [75]. This was also associated with an increase in BPD during the same period. As BPD is associated with worse neurological outcomes, independent of gestational age, some researchers and clinicians have speculated that, in a specific cohort of infants, there could be a balance where the benefit from steroids may outweigh the potential risks, particularly for later administration of steroids [4, 74, 76].

Other investigators have looked at the role of other systemic corticosteroids, specifically hydrocortisone. Early prophylactic hydrocortisone was studied in a group of over 1000 ELBW infants between 24 and 28 weeks in the PREMILOC trial. This study showed a modest decrease in BPD in the intervention group without any difference in neurological outcomes at 18–22 months [77, 78]. Interestingly, this study

also looked at later respiratory outcomes in the infants at 18–22 months and did not find any difference. A pilot study evaluating stress dose hydrocortisone administered to ventilator-dependent ELBW infants between 10 and 21 days postnatal age with a tapering course over 7 days did not show any significant differences in either respiratory or neurological outcomes [79]. One study which is ongoing is the SToP BPD study which is a randomized controlled trial of hydrocortisone given over a 22-day tapering course [80]. Taken together there is some promise for the use of hydrocortisone to prevent or treat BPD, but its safety and efficacy remain uncertain.

Long-Term Implications

Despite improved neonatal care focused on prevention of BPD, the incidence of BPD, particularly among the smallest infants, continues to be significant [1]. These infants continue to exhibit respiratory symptoms long after discharge from the NICU [4, 5, 81]. Studies of former premature infants have shown that infants with BPD continue to have increased respiratory symptoms and increased need for respiratory medications for years [5, 82, 83]. Infants with BPD are more likely to be discharged home on oxygen and more likely to be rehospitalized within the first 2 years with a respiratory complication than premature infants without BPD [84–86]. In one series 73% of infants with BPD were rehospitalized within the first 2 years, and 27% had more than three readmissions [87]. Infants with BPD are more likely to be seen by both pediatric and specialty providers more often. They are more likely to be on chronic respiratory medications, such as inhalers [84, 86, 87]. When examining pulmonary function testing results, premature infants have significantly worse FEV_1 both in the pre-surfactant era and in the post-surfactant era [88]. Studies have also shown an increased risk of airway reactivity in former premature infants and a decreased exercise tolerance [88]. Both appear to improve over time but may not completely resolve.

Infants with BPD are more likely than age-matched premature infant controls to have neurological and developmental impairment. In one study of infants with severe BPD, they found that those infants had some neurological impairment in 71% of infants compared to 19% of control premature infants [89]. In larger cohort studies of the NICHD, BPD has been shown to be an independent risk factor for cerebral palsy [90, 91]. In more recent work, "severe BPD" as defined as the need for mechanical ventilation at 36 weeks was a predictor for cerebral palsy [92]. Infants with BPD had increased risk for multiple different types of neurological impairment. They were at increased risk for cerebral palsy, language delay, cognitive delays, and even attention and behavioral problems [4, 81, 90, 93]. These differences persist into school age. Infants with BPD continue to have increased academic challenges. Infants with BPD were more likely to have lower IQ scores, need increased special education services, and have poorer organizational and academic (mathematics and reading) skills compared to premature infants without BPD at 8 years of age [94].

Growth outcomes are also affected by BPD. Infants with BPD had significantly lower weights and head circumference at 18–22 months compared to premature age-matched controls [93]. Some studies have shown that linear growth is more affected than weight in infants with BPD [91, 95]. Growth can be improved in infants with BPD through use of oxygen supplementation as an outpatient. In studies where infants were compared between having oxygen with improved saturations compared to without oxygen, growth was significantly better [96].

Infants with BPD are frequently also affected by recurrent episodes of intermittent hypoxia. This can affect extremely premature infants both with and without BPD. Intermittent hypoxia is related to immature respiratory control and inconsistent stimulation from the respiratory control centers in the brain [97]. This is combined with immature and weaker musculature of the upper airway which combine to create apnea of prematurity, a form of apnea which has central and obstructive components [98]. Apnea of prematurity typically resolves between 36 and 40 weeks post-menstrual age. However, intermittent hypoxia and apnea frequently last even until 42 or 43 weeks, particularly in those extremely immature infants [99, 100]. Apnea of prematurity is typically treated with methylxanthines. Caffeine has been shown to be an effective treatment for apnea and has been shown to decrease BPD [59] and can also decrease intermittent hypoxia [99]. However, these alterations do not completely resolve as the infants mature. Studies have shown that sleep-disordered breathing may persist for many years. A study conducted in the United States found that premature infants were 3–5 times more likely than their term counterparts to have sleep-disordered breathing at 8–11 years of age [101]. In a Swedish cohort study, young adults who had been former low birth weight infants were twice as likely to have sleep-disordered breathing compared with those who had been born at term [102]. In addition, former premature infants who have sleep-disordered breathing later in life are more likely to experience more negative cognitive effects [103]. Infants who had been born premature are at higher risk of obstructive sleep apnea (OSA) during childhood [104, 105]. Where in the general population of children approximately 4% may have OSA, the rate is more than double that in former premature children [104]. They are also more likely to have other sleep disorders such as periodic limb movements of sleep compared with their term counterparts [104]. Given the high rate of exposure to methylxanthines, particularly caffeine which can affect sleep, researchers have

looked back at the infants who participated in the CAP trial and found no difference in sleep disorders between infants exposed to caffeine compared to placebo [104, 105]. This is still an area of active research as infants born premature are at risk for learning and behavior difficulties and sleep disorders is an additional risk.

Outpatient Management Strategies

Infants with BPD frequently continue to need significant care and management after discharge. As BPD is partly defined by the need for oxygen and respiratory support at 36 weeks, many of these infants are being discharged from the NICU on oxygen. The physiological need for this oxygen can come from a variety of causes. In some infants, it is related to poor diffusion across the alveolar capillary membrane resulting from the inflammation and scarring from earlier injury. While in others, the oxygen requirement may be related to the intermittent hypoxia from immature respiratory patterns. Pulmonary hypertension is another common diagnosis which complicates pulmonary outcomes for infants with BPD. Infants with BPD should be provided with supplemental oxygen to maintain saturations greater than 95% to support growth and improved neurodevelopment. Infants should be kept on pulse oximetry monitors to monitor oxygen saturations. Weaning off supplemental oxygen at home is a complicated problem, and currently there are not clear guidelines. Practice varies and may involve echocardiogram, blood gas, or polysomnography. Infants with BPD have increased nutritional needs and generally have increased caloric requirements. Ideally infants with BPD should be followed at a multidisciplinary clinic with expertise in the care of former premature infants. In this way these complicated and still vulnerable infants can be monitored and well supported in an outpatient setting. Critical components of this clinic would include pulmonary, nutritional, and developmental expertise.

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Down Syndrome

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Kate C. Chan and Albert Martin Li

Introduction

Down syndrome (DS) is the most common chromosomal cause of intellectual disability, with an incidence of 1 in 700–800 live births [1, 2]. It was first clinically described in the medical literature by Langdon Down in 1866 [3]. In 1959, trisomy 21 was discovered as the underlying genomic abnormality in DS by Lejeune-Gautier-Turpin [4]. Individuals with DS have multiple congenital malformations, medical conditions, and intellectual limitation because of the presence of extra genetic materials from chromosome 21 [4, 5]. Approximately 95% of patients with DS have trisomy 21 as a result of meiotic nondisjunction, which is sporadic [6]. Roughly 3–4% of DS are caused by unbalanced chromosomal translocations. In these cases, there are unbalanced translocations between chromosome 21 and another acrocentric chromosome, usually chromosome 14 or 15. The majority of these unbalanced translocations are de novo, but some of them can be familial translocations [6, 7]. The remaining 1–2% of individuals with DS phenotype suffer from a condition called mosaicism, in which there is a mix of two cell lines, one normal and another with trisomy 21 [6, 7]. The diagnosis of DS is made by chromosomal analysis, which can be performed prenatally due to identified risk factors or postnatally due to the characteristic facial appearance and/or other features of the infant [5]. Nowadays, the widely adopted prenatal screening with maternal blood tests and fetal ultrasonography helps to identify pregnancies at an increased risk and leads to subsequent definitive chromosomal analysis prenatally [2].

Individuals with DS are at an increased risk of having congenital heart defects, hearing impairment, otitis media, respiratory tract infection, gastrointestinal atresias, eye diseases, obstructive sleep apnea (OSA), thyroid disease, leukemia, and neurologic dysfunction [5, 7, 8]. The degree of cognitive impairment is variable and may range from mild to severe [7, 8]. Guidelines for the medical management of patients with DS have been developed [7–9]. Assessment, monitoring, prevention, and vigilance for various medical disorders are the foundations of these guidelines [7–9].

Sleep Disturbance in Children with Down Syndrome

Majority of studies that examined sleep disturbance in children with DS used parent-reported sleep questionnaire; the one most frequently used is Children's Sleep Habits Questionnaire (CSHQ). It is long recognized that children with DS have altered sleep architecture. In an early study that included 23 children with DS and 13 children with primary snoring, all underwent a 6- to 8-hour sleep study. The children with DS had significantly more sleep fragmentation as reflected by frequent awakenings and arousals, which were only partially accounted for by their OSA [10]. Children with DS have also been found to have higher prevalence of problems in initiating and maintaining sleep that can lead to inadequate amount of sleep and hence daytime sleepiness. However, often the extent of such sleep problems is underrecognized by parents [11]. Bedtime resistance, sleep anxiety, and parasomnias are present at higher rates in children with DS compared with typically developing peers [12, 13]. These sleep problems in children with DS usually begin at a young age, and their severity fluctuates with age [14]. In addition, self-regulation of emotional reactivity and behavior is also affected in DS children who exhibited sleep problems [14]. Similar findings are reported in studies using objective measures of sleep quality such as actigraphy. Developmental trajectories of circadian rhythms were demonstrated to be comparable between children with DS aged 5–67 months and their typically developing peers, despite increased sleep fragmentation and lower sleep efficiency as documented by 7-day actigraphy [15]. Sleep efficiency as assessed by actigraphy was not found to correlate with either parental or teacher

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reports of behavior or executive functioning, but parental reports of restless sleep were [16, 17]. Poor and restless sleep has also been linked with greater deficits on parental reports of language, which included vocabulary and syntax [18].

Sleep-Disordered Breathing in Children with Down Syndrome

Epidemiology

Children with DS are at higher risk of developing sleep-disordered breathing (SDB) of which OSA is the most common, and they also tend to have more severe disease. A recent study that recruited 106 children with DS aged between 2 and 18 years reported a prevalence rate of 90%, of whom 46 (44%) had severe disease as defined by an apnea hypopnea index (AHI) >10. Not surprisingly, obese patients had a higher chance of having more severe disease (56% vs. 35%) when compared with nonobese patients [19]. The prevalence of OSA has been found to be higher in boys (64.7%) than girls (38.5%) and in younger children with DS [20]. It is also important to note that among children with DS and without history of snoring or other symptoms suggestive of OSA, a majority (53%) were found to have OSA on overnight polysomnography (PSG). Furthermore, the classic risk factors, namely, tonsils size and body mass index, were not related to the presence or severity of OSA [21].

In a retrospective review of 144 sleep studies carried out in subjects with DS over a period of 10 years, central apnea was demonstrated to be prevalent in younger children, which may be related to their lower muscle tone and immature respiratory control [22]. In the same study, 22% of subjects were found to exhibit hypoventilation with significant hypercapnia on end tidal or transcutaneous measurements. The degree of hypoventilation was associated with the subjects' body mass index [22].

The increased prevalence of OSA and other sleep-related breathing abnormalities in individuals with DS is the result of the presence of multiple risk factors leading to upper airway obstruction. On top of the common anatomical abnormalities like laryngomalacia, macroglossia, midface hypoplasia, short palate, and enlarged lymphoid tissues, other factors such as obesity, increased secretions, hypotonia, hypothyroidism, and gastroesophageal reflux also play a part. This is also the reason why OSA in subjects with DS is more challenging to tackle [23]!

Evaluation and Diagnosis

In real life, it is difficult to recognize and accurately pinpoint clinical features that accompany OSA in subjects with DS as many also exhibit behavioral sleep disturbances which may mask the presence of OSA. For parents, studies have documented that they also find it difficult to accurately perceive the quality of their child's sleep. They may not seek medical help for even significantly disturbed sleep patterns if they believe it is part of their child's underlying developmentally impaired condition [24, 25]. Absence of OSA symptoms in a child with DS is not a true reflection of his/her OSA status [21]. As a result of high OSA prevalence in children with DS and the inability to predict its presence based on symptoms and/or physical findings, in 2011, the American Academy of Pediatrics recommended routine PSG for all children with DS by the age of 4 years [7]. Despite this recommendation, a retrospective study of 954 subjects with DS aged between 5 and 21 years demonstrated only 47.7% had undergone PSG assessment. The reason for failing to comply with the recommendations is likely multifactorial, namely, parental anxiety/reluctance related to their child having to be hospitalized, lack of awareness among clinicians, and lack of access to pediatric sleep diagnostic service with experience working with this population of children [26].

Early recognition of specific symptoms and signs remains an essential component of any OSA evaluation. Typical nighttime symptoms like snoring, witnessed apneic episodes, unusual sleep position, restless sleep, and gasping are common in DS patients with OSA. Furthermore, daytime neurocognitive and behavioral problems (e.g., daytime tiredness, poor attention, and irritability) may suggest underlying OSA. Physical examinations of children with DS suspected to have OSA may reveal either failure to thrive or obesity, and muscle tone is typically reduced. Thorough assessment of the craniofacial structures is essential to detect abnormalities such as midface hypoplasia, nasal patency, micrognathia, or retrognathia. Equally important is a proper evaluation of the oral cavity including the tongue, tonsillar size, and the position of the teeth, palate, and uvula. There may also be evidence of long-standing upper airway obstruction such as chest wall deformity and even evidence of pulmonary hypertension.

Polysomnography (PSG) remains the gold standard diagnostic test for OSA in patients with DS. As symptoms and signs are unreliable to predict presence and severity of OSA in this population and availability is one of the barriers to PSG, alternative predictive tools are being investigated. A model using a logic learning machine, which combined data from screening questionnaire, personal and medical history, anthropometric parameters, and physical examination findings, yielded a negative predictive value of 73% for mild OSA and 90% for moderate-to-severe disease, despite having positive predictive values of 55% and 25%, respectively [27]. The same group of investigators examined the feasibility of using urinary biomarkers for OSA in DS children. A combination of four urinary biomarkers predicted AHI >1

with a positive predictive value of 90% and a negative predictive value of 68% [28]. A study evaluated predictors for OSA in children with DS which found that home-based assessment is acceptable to most families and can be an alternative approach to in-hospital PSG [29]. A more recent study by the same group demonstrated that oximetry parameters that assess baseline oxygen saturation variability can sensitively pick up most children at risk of clinically significant OSA. According to the authors, using this oximetry screening test could potentially halve the number of children needing confirmatory PSG at specialist centers [30].

Another option to traditional PSG to assess OSA is near-infrared spectroscopy (NIRS) that uses near-infrared light in the 700–1000 nm range to noninvasively evaluate hemodynamic processes based on optical properties of the tissue being monitored [31]. A low-cost portable wireless system that can simultaneously record NIRS-based cerebral hemodynamic changes and head movements to predict the presence of OSA in children with DS was recently tested [31]. The monitor was well tolerated and obtained sufficient information on various physiological signals such as respiratory rate, heart rate, and cerebral and arterial blood oxygenation to aid in the diagnosis of OSA [31].

Until further research and confirmation, current data remain insufficient for these newer predictive tools to replace PSG in the management of children with DS suspected to have OSA.

Morbidity and Management

Children with DS can suffer from significant sequelae as a result of unrecognized and untreated OSA. We shall concentrate on neurocognitive and cardiovascular complications as these are the areas that have attracted much research focus.

Children with DS exhibit a wide spectrum of neurocognitive deficits affecting various domains, namely, short- and long-term memory, visual perception skills, and speech. Reduced executive function secondary to prefrontal and frontal cortical abnormalities is said to cause these deficits [32]. It is therefore not surprising to note that DS children with OSA tend to have poorer neurocognitive outcomes than those without. In an un-referred community-based study of 38 children with DS, mean verbal IQ score as assessed by the Arizona Cognitive Test Battery was 9 points lower in those with comorbid OSA (defined as AHI >1.5) than in those without, and performance on measures of cognitive flexibility was also worse [33]. This verbal IQ difference will translate to significant functional language impairment for these children with lower cognitive skills to begin with, emphasizing the importance of early recognition and intervention. In an online survey completed by 110 parents of children with DS and 29 parents of children with typical development (TD), age 5–18 years, sleep disturbances and especially SDB are negatively related to accomplishment of daily life functions [34]. In 29 subjects aged 14–31 years, parental rating of OSA was associated with poor verbal fluency and inhibition [35]. However, worse neurocognitive function in DS children with comorbid OSA is not demonstrated across all studies. No significant difference in cognition between those without OSA (defined as AHI <1.5) and those with (defined as AHI >5) was documented in a study that involved 25 subjects, aged between 7 and 19 years. Interesting to note that parental report of OSA symptoms did not differ between the two groups [36]. In a study of preschool children with and without DS, presence of OSA in children with DS was associated with increased language understanding and the use of actions and gestures [37]. Current literature linking presence of OSA in children with DS and neurocognitive function remains conflicting; more research including effects of treatment in this area is necessary.

Congenital heart disease (CHD) is prevalent in individuals with DS, and up to 54% of infants with DS are born with CHD [38]. The most frequent types of cardiac problems encountered include complete atrioventricular canal, ventricular septal defect, and atrial septal defect [38]. These underlying cardiovascular and associated pulmonary abnormalities, as a result of increased left-to-right blood flow leading to pulmonary over-circulation and hence risk of pulmonary hypertension, may be exacerbated by comorbid SDB [39]. Sixty-four subjects aged 2–17 years, 32 with DS and 32 TD children matched for age and SDB severity, underwent beat-by-beat heart rate (HR) analysis over the course of respiratory obstructive events. Time for oxygen re-saturation post events and overnight urinary catecholamines were also examined. Children with DS had significantly reduced HR changes post-events, and they also took longer time for oxygen re-saturation. In addition, children with DS had significantly reduced overnight urinary noradrenaline, adrenaline, and dopamine levels. Children with DS and SDB do exhibit reduced acute cardiorespiratory response and weakened sympathetic response to SDB [40]. Heart rate variability (HRV), a noninvasive assessment of autonomic control of the heart, measures the beat-to-beat changes in heart rate. Using power spectral analysis, activity of sympathetic, parasympathetic, and sympathovagal balance can be evaluated. Studies have consistently documented autonomic dysfunction in DS children with and without SDB [41, 42]. Abnormalities in autonomic control do place children with DS at increased risk for cardiovascular complications, including pulmonary hypertension.

Subjects with DS often have multiple factors causing upper airway obstruction and gaseous exchange abnormalities during sleep. It is not unexpected that merely removing enlarged lymphoid tissues, the currently recommended first-line treatment for OSA, does not result in complete cure. A

systemic review documents an average of 51% reduction in the preoperative AHI following adenotonsillectomy (T&A) in children with DS. However, in many cases, the intervention does not lead to a total cure as up to 75% will have residual OSA [43]. Persistent OSA is found to be more likely in those with hypothyroidism and congenital heart disease [44]. Furthermore, surgery does not lead to improvements in sleep efficiency or architecture. This information is important for counseling and patient management. It also emphasizes the need to obtain a postoperative sleep study, as many of these patients will need nighttime airway support or secondary sleep surgery [43]. Potential surgical risks also need to be conveyed to patients and parents. Previous work suggested higher rates of respiratory complications following T&A in patients with DS [45]. A more recent review involving more than 350 children with DS undergoing T&A has refuted that claim; DS patients having T&A did not have increased risk of respiratory compromise compared to patients without DS [46]. However, the authors did find increased incidence of postoperative bleeding (2.8% vs. 1.2%) [46]. Another retrospective study including 30 subjects with DS undergoing T&A documented late-onset bleeding that occurred between 7 and 10 days in 10% of their cohort [47]. DS patients receiving T&A should therefore be referred to specialist centers with expertise in dealing with medically complex cases.

In patients with DS, there are multiple causes for persistent OSA following surgery. A magnetic resonance imaging study revealed causes such as macroglossia, malposition of the tongue leading to downward displacement, presence of lingual tonsils, and reappearance of adenoids and tonsils individually or in combination leading to residual disease [48]. Recent studies suggested that drug-induced sleep endoscopy (DISE) provides a better delineation into the pattern of upper airway obstruction, and DISE-directed surgical intervention leads to better outcome in PSG parameters in this group of patients [49–51]. In subjects with residual OSA following surgery, direct visualization of the airway during sleep will be invaluable in guiding suitable additional treatment strategies.

Positive airway pressure (PAP) therapy is a noninvasive and effective option for individuals with OSA who are unsuitable for surgery or with residual disease. Data on PAP use in children with DS is limited; a randomized controlled study in adults showed improved daytime sleepiness, depression, and cognitive function with continuous positive airway pressure (CPAP) treatment [52]. Compliance is always a concern with the use of PAP, and in children with DS, this issue will be even more significant. Contrary to popular belief, a recent study has provided evidence-based information that satisfactory adherence to respiratory support is possible in children with DS [53]. In this retrospective study from a tertiary respiratory center, data from 60 patients with DS, median age of 1.5 years (0.7–5.3 years), was reported. Forty-two were diagnosed to have SDB: 27 (61%) with OSA, 11 (25%) central apneas, and 19 (32%) nocturnal hypoventilation. Twenty-six had baseline oxygen saturations <95%. Thirty-nine patients started respiratory support (14 oxygen supplementation, 18 CPAP, 7 other forms of noninvasive ventilation). After a 1.9 years' follow-up, just under 50% continued to have satisfactory adherence to CPAP/noninvasive ventilation (average use 8 h/night) [53]. Efficacy of PAP therapy in children with DS has also been demonstrated. Six children with DS were included in a cohort of ten children with neurodevelopmental impairment in a study that evaluated the effects of PAP therapy on neurobehavioral outcomes. After 3-month PAP use, significant improvements were documented in internalizing and total behavioral scores, quality of life, and daytime sleepiness [54]. The beneficial effects of PAP therapy on daytime sleepiness in children with DS were immediate and sustained, whereas a more gradual and progressive improvement was noted following T&A [55]. Studies examining PAP therapy on cardiovascular outcomes are very limited. Negative results were recorded in a study that examined awake blood pressure, plasma brain natriuretic peptide levels, and echocardiographic findings after 4-month use of CPAP, but compliance was a likely culprit [56].

In addition to CPAP and surgery, other adjunctive treatment regimens include intranasal corticosteroids and leukotriene receptor antagonists, both of which have been demonstrated to be effective in milder forms of OSA [57]. As muscle hypotonia is a contributing factor to upper airway obstruction in patients with DS, oropharyngeal exercises, also known as myofunctional therapy, may be a possible solution. A pilot study using a protocol with specific exercises demonstrated improved orofacial and nasal functions, together with correction of atypical swallowing, restoration of lip competence, breathing improvement, and reduction of nasal rhinorrhea [58]. In a recent study that specifically examined effects of myofunctional therapy in DS children with OSA, 42 children underwent cardiorespiratory sleep studies immediately before and after a 1-week intensive training camp consisting of three daily 45 min sessions of myofunctional exercises. Eighteen recordings which had ≥3 hours of artifact-free recording in both the pretreatment and posttreatment sleep study were included in the analysis. The 1-week intense myofunctional training had only a marginal effect on OSA. Whether a longer follow-up period or duration of intervention would yield stronger effects remains to be determined [59].

Significant mandibular hypoplasia in children with DS is another important factor predisposing them to OSA. A retrospective review of 35 DS patients with such facial abnormality and upper airway obstruction (UAO) documented mandibular distraction to be effective in all who underwent the procedure [60, 61]. Similarly, in DS children with nar-

row, high-arched palates, rapid maxillary expansion (RME) is an effective treatment option as it provides significant increase in upper airway volume [62, 63]. One study of 24 children with DS who underwent RME found improvements in hearing loss, rates of upper respiratory tract infections, and parental-reported symptoms of UAO [61]. A systematic review and meta-analysis of PSG outcomes in non-syndromic children who underwent RME for OSA reported an improvement in the AHI and oxygen desaturation nadir, especially in the short term (<3-year follow-up) [64].

Other newer therapies are also being introduced for refractory OSA in patients with DS, one of which is hypoglossal nerve stimulation (HNS). The procedure involves an implantable device that produces an electrical impulse to the anterior branches of the hypoglossal nerve, resulting in tongue protrusion, thus relieving UAO in response to specific variations in respiration. In adults, beneficial effects have been documented in patients who are noncompliant to CPAP [65, 66]. A substantial subjective as well as objective improvement of OSA (63 to 100% decrease in AHI and 77% decrease in ODI), translating into an overall satisfactory outcome, was recorded [65, 66]. The first pediatric HNS implantation was carried out in an adolescent with DS and refractory severe OSA (AHI = 48.5 events/hour). The patient could not tolerate CPAP and required a long-standing tracheotomy. HNS was well tolerated and effective, resulting in significant improvement in the patient's OSA. Five months after implantation, patient underwent de-cannulation of his tracheotomy, and he remained well with nightly HNS therapy [67]. A subsequent case series of six adolescents with DS, aged 12–18 years with severe OSA despite prior T&A and they were unable to tolerate CPAP. All tolerated well with HNS with a mean usage of 5.6–10.0 h/night and the therapy was effective, resulting in significant improvement in OSA [68]. At 6- to 12-month follow-up, a 56% to 85% reduction in AHI, with an overall AHI <5 events/h in 4 children and < 10 events/h in 2 children, was documented. A clinically significant improvement on the OSA-18, a validated quality-of-life instrument, was also recorded [68]. Overall, HNS is well tolerated and effective, representing a potential therapeutic option for patients with DS and refractory OSA after T&A who are unable to tolerate positive pressure airway devices.

Any treatment for patients with DS should be individualized as multiple factors come into play that will affect feasibility and efficacy of each treatment option.

Conclusion

Screening for sleep disorders in children with DS should be routinely carried out, and parents and clinicians should be made aware of the increased risk of sleep problems in this special population. Management and treatment options should be individualized and consider the likely multifactorial etiology. Successful treatment can be expected to significantly reduce the burden, social impact, and future health risks of both child and family.

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Sleep in Obese Children and Adolescents

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Introduction

Sleep curtailment and obesity are interrelated concurrent epidemics in children and adolescents posing a major public health challenge. Short sleep duration and poor sleep quality that are increasingly common in children were found to be linked to overweight and obesity [1]. Further, obstructive sleep apnea (OSA) is more common among overweight and obese children. In the last decade, the phenotype of childhood OSA has changed to bear a resemblance to the adult form of OSA. Although adenotonsillectomy remains the first line of treatment for childhood OSA, evidence from recent years indicates that obesity poses a risk for residual OSA post-surgery. Since obese children are at increased risk for residual OSA necessitating additional therapeutic measures, it may be warranted to change the clinical approach to this population.

Identifying behaviors that lead to weight gain in children is imperative, as childhood obesity is a strong predictor of adult obesity. Given that poor sleep could be a modifiable risk factor in the prevention of childhood obesity, the sleep/obesity connection has stimulated significant research activity. Improving sleep could potentially pave a new avenue for halting the weight gain cascade and its metabolic outcomes. However, whether sleep interventions can improve pediatric obesity and cardiometabolic health is yet to be determined.

Sleep duration as a risk factor for obesity has been the focus of most of the published research. Associations between obesity and other sleep-related variables, such as timing, variability, and quality, have also been explored. In this chapter, an overview of the existing literature on the associations between sleep and obesity in children and adolescents will be presented.

Sleep Duration and Obesity

Sleep requirements in childhood vary substantially by developmental stage. The most recent recommendations of the National Sleep Foundation are 9–10 hours of sleep per day for children 6–13 years of age and 8–10 hours for adolescents aged 14–17 years [2]. In 2016, the American Academy of Sleep Medicine (AASM) published a consensus statement. The AASM recommends sleeping 8–14 hours per 24-hour period, with age-specific recommendations decreasing as age increases [3]. Sleeping the number of recommended hours on a regular basis, according to the AASM, is associated with better health outcomes including improved attention, behavior, learning, memory, emotional regulation, quality of life, and mental and physical health [3].

The National Sleep Foundation (NSF) and the AASM position statements are the product of the epidemic of insufficient sleep in children and adolescents and increased awareness of the consequences. Epidemiological data has found that children and adolescents in both the USA and other countries are not getting enough sleep [1]. Ninety-five percent of high school students in the USA are not meeting published sleep recommendations [4]. Moreover, a secular decline in sleep duration by more than an hour over the past 100 years has been reported across all childhood age groups [5]. The declining sleep time in children and adolescents has been attributed to various aspects of modern society. One of the proposed plausible mechanisms for extending waking hours are the introduction of electricity and corresponding exposure to artificial light [6].

Population-based, experimental, and intervention studies provide robust evidence that short sleep duration is a risk factor for obesity in children and adolescents. Meta-analyses

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of observational studies reported significant increased risk for overweight and obesity in short sleepers compared to longer sleepers [7, 8]. Short sleep durations were found to be associated with a 58% increased risk of being overweight or obese. Moreover, each hour increase in sleep duration was associated with 9% reduced risk of being overweight or obese. Longitudinal studies strengthened these observational findings that short sleep duration is associated with an increase in BMI over time. Fatima et al. reported in a meta-analysis of 22 longitudinal studies that short sleepers had 2.15 higher odds of overweight/obesity [9]. Similarly, other meta-analyses that included only prospective and longitudinal studies supported these findings [10].

Cumulative exposure to short sleep throughout adolescence and early adulthood exhibited a dose-response relationship with obesity [11]. In a large prospective study with 15 years follow-up, participants who reported short sleep duration at all 4 waves of study follow-up were nearly 1.5 times more likely to be obese and have an elevated waist circumference [11]. These findings were supported by other large-scale prospective longitudinal studies [12–14].

Although the majority of research supports a link between short sleep duration and overweight/obesity, a few studies contradict these findings. In a study conducted in infancy, short sleep duration at 9 and 18 months did not predict adiposity at the age of 3 years [15]. Similarly, in another study in early childhood, short sleep duration at 12–36 months did not predict obesity or cardiometabolic risk at 36–96 months [16]. Possible explanations for these findings are the very young age of the participants and the relatively short duration of follow-up. A temporal interaction between short sleep duration and obesity is a plausible speculation.

Experimental studies provide the causal link between sleep restriction and weight gain, increased calorie consumption, and metabolic changes in children and adolescents. In a randomized crossover trial, adolescents consumed more calories under a sleep restriction condition (6.5 h in bed) compared to normal sleep length condition (10 h in bed) [17]. In another study, school-aged children had lower reported food intake, lower fasting leptin levels, and lower weight with increased sleep duration [18]. In another randomized crossover study of adolescents, calorie intake was 11% higher during sleep restriction compared to normal sleep duration with increased consumption of carbohydrates [19]. Contrastingly, in a randomized crossover trial of 21 adolescents involving sleep restriction over 3 nights, sleep restriction was not associated with a positive energy balance [20].

The precise mechanisms linking sleep and obesity are yet to be elucidated. Several potential pathways have been suggested [21]. Short sleep duration may lead to changes in hormonal regulation and increased food intake [22]. Indeed, experimental studies have demonstrated that short sleep leads to self-reported and biological changes in hunger and appetite [23–25]. Leptin and ghrelin are key hormones involved in appetite regulation. In individuals with sleep restriction, leptin levels are decreased, while ghrelin levels are increased resulting in subjective hunger. Partial sleep loss has been shown to alter leptin, ghrelin, cortisol, and insulin levels [23, 26–28]. However, the role of leptin and ghrelin in children with short sleep duration is less apparent [29].

Diet quality is another possible mediator between sleep duration and obesity. Short sleep duration has been shown to be associated with unhealthy dietary habits including larger portion sizes, increased perceived hunger, higher calorie food choices, and increased food and sugar-sweetened beverage intake [30–32]. Indeed, in a self-assessment survey study of approximately 2000 fourth and seventh graders, insufficient sleep was associated with more frequent soda consumption and less frequent vegetable consumption [33]. In adolescents, participants exposed to sleep restriction rated sweet and desert foods more appealing consistently and significantly compared to sufficient sleep [19]. Sleep restriction was associated with an 11% increase in overall food intake and 52% increase in sweet/desert servings [19]. In addition, short sleep duration was associated with consumption of energy drinks and sugar-sweetened beverages among adolescents [34, 35].

Decreased physical activity and increased sedentary activity is another possible mediator between sleep duration and obesity. Insufficient sleep may cause fatigue, decreased physical activity, and increased sedentary activity, which could in turn lead to obesity. In a study objectively assessing sleep duration with attaining physical activity guidelines of 60 minutes per day, children with shorter sleep duration were less likely to reach guidelines [36]. Short sleepers spend more time engaging in sedentary activities such as watching TV and use of screens [36]. Interestingly, screen time, especially in the evening, has been linked to reduced sleep duration in children and adolescents [34, 37–39]. Decreased sleep duration, decreased physical activity, and increased sedentary activity/screen time are interrelated modifiable risk factors in childhood obesity. Hence, interventions promoting physical activity combined with reducing screen time and extending sleep duration in children and adolescents might have a cumulative positive effect on weight status.

Non-appetite mediated eating behavior also links short sleep duration to obesity. In a crossover study of 11 healthy participants, increased snacking behavior was observed during sleep restriction, particularly during times when study participants would normally be sleeping [26]. Short sleepers may also eat more in attempt to offset the fatigue associated with sleep deficit. Short sleepers frequently report fatigue and daytime sleepiness, and it has been hypothesized that sleep-restricted individuals might increase calorie intake in an attempt to counteract the fatigue associated with sleep loss [40]. Thus, relationships between short sleep duration

and sugar-sweetened beverage consumption are most probably bidirectional. Although short sleepers may consume more sweet drinks hoping to offset fatigue, the sugar and caffeine present in these drinks could likewise lead to poorer sleep quality and/or delayed sleep onset. Short sleepers may also have more opportunities to eat because they are awake for more hours in the day.

The long-term effects of sleep loss during childhood on later weight gain is yet to be determined; however rodent models suggest that sleep perturbations during development may have implications on the risk for obesity and metabolic complications later in life [41].

Sleep Quality, Sleep Timing, Sleep Variability, and Obesity

Although most of the published literature has focused on sleep duration as a risk factor for obesity, research also has explored associations between obesity and other sleep-related variables, such as sleep timing, sleep variability, and sleep quality.

Sleep Timing and Obesity

The integrity of the circadian system plays a crucial role in hormonal regulation and metabolic health. Misalignment of circadian rhythms as exemplified by shift work has been identified as a critical mechanism underlying the development of obesity [42]. Altered circadian timing characterized by a preferred later sleep onset, known as "adolescent chronotype," contributes to shortened sleep duration and associated obesogenic behaviors. The natural circadian shift, with late bedtimes and a preference to late wake times, together with the tendency to complete schoolwork and socialize during evening and nighttime hours, places adolescents at risk of constant "social jet lag" due to misalignment between their natural circadian rhythms and social and environmental factors [1, 43]. Social jetlag has been linked to increased odds of being overweight and obese [44]. Adolescents with later bedtimes are more likely to have higher BMIs and exhibit poor nutritional choices [31, 45]. A UK study in 11–13-year-old adolescents found that later chronotype was associated with higher BMI and higher frequency of consuming unhealthy snacks, nighttime caffeine consumption, and inadequate daily intake of fruits and vegetables [46]. In an Australian study of 2200 children and adolescents 9–16 years of age, compared to participants with early bed/early rise sleep pattern, participants with late bed/late rise sleep pattern had higher BMI z scores, higher energy intakes, and poorer diet quality [47]. Participants with a late bed/late rise pattern also exhibit less moderate to vigorous physical activity and more screen time [48]. Moreover, increased sugar-sweetened beverage consumption and food preoccupation were associated with late bedtime shift and wake time shift in overweight and obese adolescents [49]. Sleep timing may influence obesity by shifting the time of eating patterns. Compared to those with earlier sleep times, those with later sleep times are more likely to engage in breakfast skipping and after dinner snacking [50].

"Bedtime shift" is another circadian/behavioral characteristic of adolescents. Bedtime shift describes later bedtimes on weekends compared to weekdays and may also affect the circadian rhythm as the circadian clock cannot adapt quickly to shifts in sleep onset. Independently of sleep duration, later bedtimes and greater bedtime shifts were found to be associated with obesity severity [31].

Sleep Variability, Sleep Quality, and Obesity

Additional putative sleep-related measures linked to obesity include the degree of regularity in sleeping schedules [51] and sleep quality. Maintaining a regular sleep pattern is important. Research suggests that greater sleep variability, usually defined as the standard deviation of actigraphy-assessed sleep duration, is associated with obesity in both children and adolescents [51–53]. In a study of 305 adolescents, higher sleep variability as assessed using actigraphy was associated with abdominal obesity measures. This observation could be partially explained by increased caloric intake, especially from carbohydrates, suggesting that maintaining regular sleep patterns is important in preventing weight gain and obesity in adolescents [53]. High sleep variability has been associated with sugar-sweetened beverage consumption [54] and irregular levels of physical activity [55].

Studies on the relationship between sleep quality and obesity are inconclusive. In a cross-sectional study of students from nine US universities, poorer sleep quality was associated with being overweight or obese [56]. Although this study used the Pittsburgh Sleep Quality Index, a validated questionnaire, to assess sleep quality, the conclusions are limited by this subjective tool. In contradistinction, a study using an objective assessment of sleep (actigraphy) and parental questionnaires, sleep quality was not associated with either obesity (BMI) or measures of adiposity (body fat percentage and waist circumference) [57]. Nevertheless, in a recent systematic review and meta-analysis, poorer self-reported sleep quality (defined as higher sleep onset latency, more sleep disturbances, recurrent awakenings, and lower sleep efficiency) was found to be associated with higher odds of being overweight and obese, independently of sleep duration [9].

Finally, part of the complexity derives from the bidirectional relationships between sleep quality and obesity; excess weight may adversely affect sleep quality; conversely, poor sleep quality could result in weight gain.

Obstructive Sleep Apnea (OSA)

OSA is a condition consisting of repetitive episodes of upper airway obstruction during sleep leading to recurrent oxyhemoglobin desaturation (intermittent hypoxia), hypercapnia, sleep fragmentation (frequent arousals), and significant swings in intrathoracic pressure. Thus, OSA can also lead to insufficient and disrupted sleep. In children, untreated OSA was found to be associated with increased risk of systemic hypertension, accelerated atherosclerosis, pulmonary hypertension, and, more commonly, learning and behavioral problems [58].

OSA in children classically results from adenotonsillar hypertrophy and has been associated with impaired growth and failure to thrive in infancy and early childhood. However, over the last 20 years with the epidemic of obesity, children with OSA have increasingly resembled their adult counterparts – overweight and obese rather than underweight [59]. It has been proposed that pediatric OSA should be classified into type 1 and 2; to date, a consensus has not been reached [60].

Similar to the adult population, there is higher prevalence of OSA in obese children and adolescents [61]. Excess body weight may exacerbate OSA through different pathways. By displacing the diaphragm upward, abdominal adiposity reduces lung volume and therefore downward tracheal traction leading to greater upper airway collapsibility. In addition, intra-muscular deposition of fat in areas such as the tongue has been shown in imaging studies. This fat deposition may not only narrow the upper airway but may also interfere with the dilating function of the upper airway muscles [62]. However, there is inconsistent evidence linking the degree of obesity or fat distribution and the severity of OSA [63–65] suggesting that other factors may play a role in the pathogenesis of OSA among obese children. Moreover, studies on the role of adenotonsillar hypertrophy in OSA among obese children are also conflicting [65–67].

Another means in which the pathophysiology of obesity and OSA overlap is inflammation. Indeed, both conditions were found to be independently associated with increased levels of various inflammatory markers that was further increased in children with both conditions [68].

The relationship between obesity and OSA, however, may be bidirectional. In a large longitudinal cohort study, it has been shown that children with OSA were at a greater risk for developing obesity [69]. One possible explanation is that the increased energy expenditure in sleep triggers overly compensatory hormonal changes to increase hunger and energy intake. Indeed, increased resting metabolic rate and high leptin resistance and ghrelin levels were found in adults with OSA [70]. In children, one study found that obese children with OSA had higher ghrelin levels and unhealthier diets and physical activity compared to non-obese children with OSA and obese children without OSA [71]. Another study conducted on obese children has shown decreased exercise performance in obese children with OSA independent of their weight providing another explanation for the contribution of OSA to obesity [72].

The association between OSA and type 2 diabetes in children and adolescents is not as clear as in adults [73]. Previous studies have shown inconsistencies across studies in childhood. In a recent systematic review and meta-analysis of ten studies conducted in adolescents only, Patinkin et al. found that OSA was independently associated with dyslipidemia, hypertension, and insulin resistance [74]. Several studies have shown that obese adolescents with OSA are at increased risk for altered glucose homeostasis and metabolic syndrome [75, 76]. In contrast, others have not found a link between OSA and increased markers of metabolic risk in obese children [77, 78]. Our group reported that the frequency and severity of OSA was similar in obese youth with type 2 diabetes and BMI-SDS-matched obese youth without diabetes [79]. However, our findings should be interpreted with caution due to the relatively small sample size. Further studies are warranted to elucidate the association between OSA and glucose metabolism in obese children and adolescents.

The effectiveness of surgical treatment for obese children with OSA has been studied in recent years. Despite initial improvements in the apnea-hypopnea index (AHI), several studies have discovered persistent symptoms in obese children after adenotonsillectomy [80–82]. A recent systematic review showed that obese children are more likely to have persistent OSA after adenotonsillectomy than normal weight controls [83]. There are several possible explanations for the lower effectiveness of adenotonsillectomy in obese children. First, children who were overweight or obese before surgery still often gain weight or at least fail to lose weight after surgery [84, 85]. Thus, adenotonsillectomy does not address the obesity component of OSA when present. Second, although adenotonsillectomy improves the apnea-hypopnea index scores in obese children, normalization of the breathing disorders occur in about 40% [86] of patients with little effect on CRP levels, suggesting continuation of the chronic inflammatory process [87]. Third, obese children may have upper airway obstruction in a different anatomical site such as the base of the tongue [88]. Taken together, it is important to critically examine the one-size-fits-all adenotonsillectomy

approach to treating OSA and inform the patients and families regarding the possibility of further care after surgery. Since adenotonsillectomy may be less effective in children with obesity, there may be a role for more individualized surgical treatment. One way to optimize surgical success may be through drug-induced sleep endoscopy (DISE) which offers direct visualization of upper airway obstruction in conditions similar to natural sleep [89]. A recent study examining DISE findings in children with persistent OSA post adenotonsillectomy found obese/overweight children were more likely to have obstruction at the tongue base and adenoid regrowth than normal/underweight children [88].

Persistent OSA post-surgery can be treated by continuous positive airway pressure (CPAP). CPAP has been shown to effectively reduce AHI in children and treat some of the morbidities associated with OSA in obese children such as hypertension and hyperlipidemia [90, 91]. However, CPAP usage in children is a challenge for the child, family, and the personnel with limited adherence.

Several studies have shown efficacy of anti-inflammatory agents like montelukast and budesonide in children, but thus far no studies have examined efficacy in obese children with residual OSA and over long periods of time [92, 93].

Weight reduction is an alternative approach in obese children and adolescents. In a study conducted on obese adolescents with OSA, a weight-loss program that included diet and exercise led to resolution of OSA in 62% of participants [94]. Surgical weight loss is another alternative treatment to improve OSA in obese adolescents. Studies on obese adolescents that underwent bariatric surgery demonstrated rapid improvement of OSA severity [95, 96]. There has been only one study in prepubertal children (ages 5–12 years) that found improved OSA symptoms that was sustained at 3 years postoperatively [97].

Obesity Hypoventilation Syndrome

Obesity hypoventilation syndrome also known as "Pickwickian syndrome" is defined as the presence of awake alveolar hypoventilation (partial arterial pressure of carbon dioxide [$PaCO_2$] >45 mmHg) in an obese individual with a BMI >30 kg/m^2, which cannot be attributed to other conditions associated with hypoventilation. Obesity hypoventilation syndrome should be considered in obese patients that have severe hypoxemia and spend a high percentage of sleep time with SpO_2 < 90%. The clinical symptoms are nonspecific and more reflective of the manifestations of obesity and coexisting OSA or the related complications such as pulmonary hypertension. The therapeutic approach includes initiation of noninvasive PAP therapy, along with lifestyle modifications for weight loss.

Sleep Interventions and Health in Youth

Interventions that aim to address obesity by improving sleep have been developed in recent years. These interventions include educational programs targeted to parents and/or children or policy changes such as later school starting times, decreased evening exposure to electronic media, and reduced academic workload and caffeine consumption [1, 98]. In an intervention study on obese adolescents, sleep extension exhibited lower BMI following treatment [99]. Sleep extension through earlier bedtimes resulted in consumption of fewer high glycemic index foods posttreatment and reduced calorie intake [17, 100]. Another approach for preventing obesity in children and adolescents is replacing time spent in sedentary activities with time sleeping [101, 102]. Taken together, preliminary studies in youth are promising since improved sleep may improve obesity risk and are relatively inexpensive [103, 104]. Further studies investigating the effect of sleep interventions on obesity are needed.

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Sleep in Sickle Cell Disease

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Alex Gileles-Hillel

Abbreviations

ACS	Acute chest syndrome
AHI	Apnea-hypopnea index
ANS	Autonomic nervous system
CPAP	Continuous positive airway pressure
hs-CRP	High-sensitivity C-reactive protein
LV	Left ventricle
NFκB	Nuclear factor-κappa b
NO	Nitric oxide
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
PFTs	Pulmonary function tests
PLMS	Periodic leg movements
PSG	Polysomnography
RBC	Red blood cell
REM	Rapid eye movement
SCD	Sickle cell disease
SDB	Sleep-disordered breathing
TRV	Tricuspid regurgitation jet velocity
TST	Total sleep time
VOC	Vaso-occlusive crisis

Introduction

Sickle cell disease (SCD) is a group of genetic conditions caused by pathogenic variants in the *HBB* gene encoding the hemoglobin β subunit. The annual global incidence of SCD is between 300,000 and 400,000 neonates, the majority of them in sub-Saharan Africa [1]. SCD is characterized by a wide range of clinical manifestation including recurrent pain attacks, acute chest syndrome, pulmonary hypertension, and upper and lower airway obstruction. Hypoxemia, especially at night, and sleep-disordered breathing (SDB) are emerging as risk factors for increased prevalence and severity of sickle cell disease manifestations and even mortality. Moreover, SCD patients are prone to poor sleep not just as a consequence of SDB, but other factors such as chronic pain and restless leg syndrome.

Sickle hemoglobin (HbS) is caused by a mutation in the β-globin gene in which the 17th nucleotide is changed from thymine to adenine causing a change of the 6th amino acid from hydrophilic glutamate for the hydrophobic valine. This mutation creates a hydrophobic binding between the beta chains, producing an expanding polymer that fills the red blood cell (RBC), disrupting its structure and elasticity (i.e., "sickling"), and promoting cellular dehydration, the latter being exacerbated by physical activity and by oxidative cellular stress. The degree of hemoglobin deoxygenation and the concentration of HbS in the RBC ultimately determine the rate of HbS polymerization and sickling, the main determinant of disease severity [2]. Clinical manifestations of SCD, both acute and chronic, can be categorized by their underlying pathophysiological process – i.e., vaso-occlusive or hemolytic [3]. Vaso-occlusive complications include acute pain crises, acute chest syndrome (ACS), and osteonecrosis. Hemolytic complications, on the other hand, comprise pulmonary hypertension, priapism, and leg ulcers. The most common reason for emergency room visits and hospitalization in patients with SCD of all ages are acute pain crises, which, although not usually and immediately associated with end-organ damage, are severely debilitating and have been associated with increased mortality in adult SCD patients. ACS, i.e., a new focal lung infiltrate, is the second most common cause of hospitalization in SCD patients. The pathophysiology of ACS includes pulmonary vaso-occlusion, infection, or fat embolism in some cases, but in many others, it remains unknown. Other less frequent complications of SCD include increased incidence of stroke, heart disease, pulmonary hypertension, renal disease, and hyper-hemolysis [2].

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Pathophysiology

SCD and SDB share some common pathogenic cascades that may lead to similar downstream clinical manifestations (Fig. 48.1). In the following several paragraphs, we will describe the similarities between these two conditions and the available data linking those pathways between SCD and SDB.

Nocturnal Hypoxemia

Hypoxia in sickle cell disease is one of the major modifiers of disease severity. At the cellular level, low oxygen levels promote HbS polymerization and RBC sickling, which obstructs blood flow in the capillaries, thereby causing a vicious cycle of hypoxia, sickling, hemolysis, and further vaso-occlusion [4, 5]. Sickling of cells under hypoxia also promotes RBC adhesion to endothelial cells [6]. In addition, hypoxia results in increased reticulocyte output from the bone marrow which, in comparison to mature erythrocytes, have greater adhesive properties to endothelium and further aggravate vaso-occlusion [7, 8]. Traditional pulse oximeters may overestimate the true oxygen saturation by 3–7% in patients with SCD. Therefore, hypoxemia may be present in SCD, even when pulse oximetry appears to be in the normal range, and any detected desaturations should be viewed as a marker for more severe disease [7].

Intermittent nocturnal hypoxia is one of the main components in SDB pathophysiology, driving many of morbidities associated with SDB, through oxidative stress, systemic inflammation, and sympathetic hyperactivity [9–15].

Nocturnal hypoxemia in SCD, even without concomitant SDB, has been associated with higher disease morbidity manifesting with higher degree of anemia [16, 17], increased pulmonary artery pressures [18], impaired pulmonary function [17], increased left ventricular (LV) hypertrophy and LV diastolic dysfunction [19], increased incidence of priapism [20] and nocturnal enuresis [21], increased incidence of CNS events [22], worse executive cognitive function [23], and vitamin C deficiency [24]. As discussed below, nocturnal hypoxemia may not be associated with an increased incidence of pain attacks [25]. Conversely, the reduction of SCD disease burden by hydroxyurea is associated with improvements in awake and nighttime oxygen saturation [26].

Oxidative Stress

Hemolysis causes increased oxidative stress, which in turn increases hemolysis. In addition to the accelerated auto-

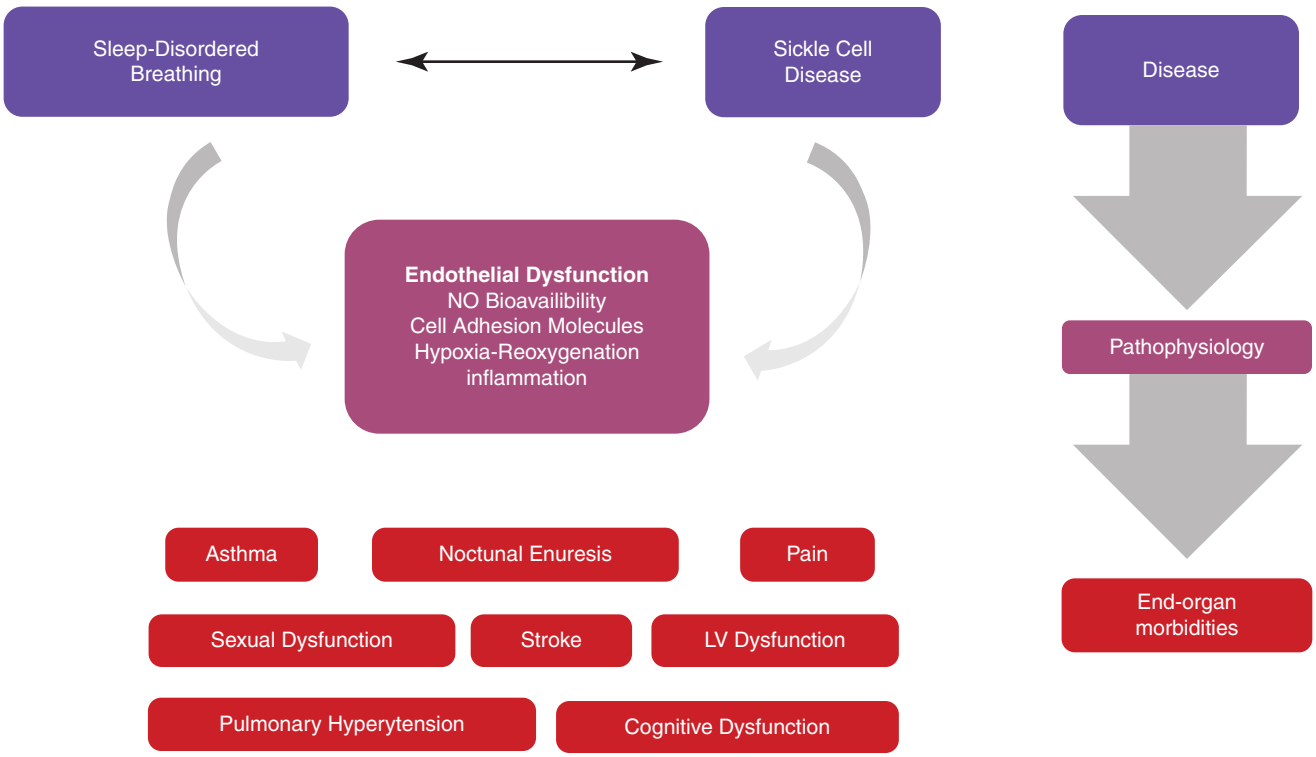

Fig. 48.1 Sleep-disordered breathing and sickle cell disease share common pathophysiological pathways leading to similar clinical manifestations. (Adapted from Whitesell et al. [89] with permission from Elsevier)

oxidation of HbS, reactive oxygen species (ROS) are generated by increased expression of pro-oxidative enzymes along with recurrent ischemia-reperfusion of tissues. ROS also deplete anti-oxidant substances leading to an overall increased oxidative stress [1]. In SDB, recurrent events of oxygen desaturation are a source of constant ROS generation that drive some of the pathophysiological consequences of SDB [27]. Although plausible, the contribution of SDB to increased oxidative stress in SCD has not been evaluated yet.

Nitric Oxide Bioavailability

Nitric oxide (NO) is one of the most potent vasodilator agents. Decreased NO bioavailability causes endothelial dysfunction which exacerbates adhesion of sickled RBCs to blood vessel lining [28]. NO bioavailability is reduced both through increased consumption and decreased synthesis. Consumption is increased by cell-free hemoglobin released from RBCs during hemolysis [29, 30]. NO is a key factor in SCD-associated endothelial dysfunction, and consequently, its bioavailability is a major determinant of disease severity and of the frequency of vaso-occlusive crises (VOC) in SCD [31].

Similar to SCD, endothelial dysfunction is a well-recognized consequence of OSA with a pivotal role in the pathophysiology of OSA-associated cardiovascular diseases, such as hypertension, atherosclerosis, coronary heart disease, and myocardial infarction, as well as cerebrovascular disease and ischemic stroke. Altered NO synthesis has been implicated in OSA-associated endothelial dysfunction [32–36].

Despite the reports involving similar pathways in the decreased NO bioavailability of SCD and SDB, we are unaware of any studies examining the contribution of SDB to the already deficient NO bioavailability in SCD, although some data show that endothelial dysfunction in SCD is aggravated by coexistent SDB: a recent study found that children with SCD have a higher degree of endothelial dysfunction and have more complaints of SDB. The subgroup of SCD with endothelial dysfunction in this study had slightly more SDB complaints, as compared to children without endothelial dysfunction [37]. Another study found that nocturnal hypoxemia was associated with increased adhesion of sickled RBCs and increased endothelial activation in SCD patients [38].

Inflammatory Cascade Activation

Chronic VOC and cellular hypoxia lead to chronic low-grade inflammation in sickle cell disease, with increased systemic levels of cytokines such as IL-6, TNF-α, GM-CSF, M-CSF, as well as the number of circulating leukocytes [39]. High-sensitivity C-reactive protein (hs-CRP) levels at steady state may serve as predictors of VOC and pain attacks [40].

Similar to SCD, circulating levels of inflammatory cytokines, such as hs-CRP, TNFα, IL-6, and INF-γ, are increased in OSA and have been implicated in the end-organ morbidity of OSA [41–43].

Cell Adhesion Molecules

Activation of cell adhesion cascades through ICAM-1, VCAM-1, P-selectin, and E-selectin plays an important role in the endothelial dysfunction of SCD and contributes to the pathophysiology of VOC [44–46]. RBC sickling and leukocyte adherence are enhanced by the expression of these molecules on endothelial cells and aggravated even further by hypoxia [6]. Abnormal RBC and leukocyte adherence to the endothelium and circulating levels of adhesion molecules may serve as markers of morbidity and mortality in SCD [47, 48], and anti-adhesion therapies for SCD are currently being developed [49].

Similar to SCD, SDB has been also associated with increased generation and expression of cell adhesion molecules, which leads down the road to OSA-associated morbidities, most notably cardiovascular disease [50, 51].

Autonomic Nervous System Imbalance

The autonomic nervous system (ANS) is a major regulator of microvascular blood flow, and many of the triggers of VOC affect the autonomic balance. ANS can also modulate the inflammatory response [52], which in turn feeds back to ANS activity through vagal afferents [53].

SCD is associated with impaired ANS balance, with reduced parasympathetic activity in basal state and dampening of the parasympathetic response during both physical and psychological challenges. Moreover, in SCD children, increased parasympathetic withdrawal in response to a challenge is associated with a more severe clinical phenotype [54, 55]. Similarly, OSA patients exhibit an ANS imbalance characterized by increased sympathetic and decreased parasympathetic activities [56], and this imbalance improves after CPAP treatment [57]. Interestingly, sigh breathing triggers vasoconstriction in SCD patients but not in controls, suggesting a more responsive ANS. It may be speculated that the intrathoracic pressure swings induced by recurrent episodes of apnea in SDB may trigger the same chest-wall receptors as sigh breathing, thereby providing a neurally mediated ANS link between SDB and VOC [58].

In summary, given the similarities of the various pathophysiological pathways activated in SCD and SDB (oxygen

desaturation, oxidative stress, inflammation, cellular adhesion, NO bioavailability, ANS imbalance) (Fig. 48.1), and the involvement of the endothelium, it is plausible to surmise that SDB exacerbates the clinical manifestations of SCD and that such common pathways may serve as common therapeutic targets.

Clinical Manifestations

Sleep Quality and Duration

Patients with SCD complain of various sleep disturbances – children report difficulty falling asleep, frequent nighttime awakenings, and increased daytime sleepiness, as well as symptoms of SDB, as compared to healthy controls [59–61]. Sleep architecture changes may include shortened REM phase [62], which improves following adenotonsillectomy [63]. Periodic limb movement syndrome (PLMS) and restless leg syndrome have been reported in 23–42% of children with SCD and are associated with sleep disruption [64–66]. Expectedly, a correlation was found between PLMS and lower iron and HbS concentration and more importantly with a cerebrovascular disease on MRI [67].

Pain and Sleep Quality

SCD is characterized by recurrent painful episodes, such that issues pertaining to chronic pain and its management have received substantial attention. Approximately 70% of patients with SCD suffer from frequent and recurrent bouts of VOC, approaching 10–13 times a year during childhood and adolescence [68, 69]. Accordingly, SCD patients are expected to suffer from sleep disturbances, as it is well established that sleep is disrupted in individuals who suffer from chronic pain in general [70].

The vast majority of the children and adolescents with SCD report some degree of sleep disturbance during the preceding month, while 18.2% require sleeping medications [71]. Poor subjective sleep quality during the preceding night is related to high pain intensity the following day, and higher pain severity is related to poor subjective sleep quality that night. The strength of the relationship between poor continuous subjective sleep quality and high pain severity increases with advanced age [72]. The negative mood might play a role in this bidirectional interaction between pain and sleep quality [60, 61, 73]. The association of SCD with disturbed sleep quality in middle-school children and adolescents is similar to the patterns reported for other chronic pain syndromes (e.g., juvenile idiopathic arthritis and headache) [74, 75]. In adults with SCD, sleep disturbances are also highly prevalent (70%) and are associated with depression, older age, more days of pain, and more acute pain events [76]. Interestingly, SDB may reduce the pain threshold, thereby potentially increasing the frequency and severity of pain episodes in patients with SCD [77, 78].

Respiratory Manifestations

Upper Airway Obstruction and OSA

Hypoventilation and upper airway obstruction are common reasons for hemoglobin desaturation during sleep. Young patients with SCD are at increased risk for airway obstruction due to compensatory adenoid and tonsillar hyperplasia following splenic infarction, reactive enlargement of upper airway lymph-adenoid tissues due to repeated infections, and increased extramedullary hematopoiesis due to hemolytic anemia [79]. In fact, the upper airway in SCD children is narrower, when compared to controls, due to hyperplasia of surrounding lymphoid tissues (tonsils, adenoids, deep cervical and retropharyngeal lymph nodes) [80].

Despite the higher prevalence of both daytime and nighttime oxygen desaturation in patients with SCD, until recently, the association of SCD with SDB has not been all that clear. A prospective multicenter study by Rosen et al. provided strong support to this previously expected assumption [19, 63, 65, 80–86] and demonstrated the increased incidence of OSA in children with SCD [87]. In this study, out of 243 children with mostly mild-moderate SCD, OSA was found in 41% (defined as an apnea-hypopnea index (AHI) $\geq$ 1/hr. total sleep time (TST)). Moderate to severe OSA (AHI $\geq$ 5/hrTST) was found in 10% of the patients. The diagnosis of OSA was strongly associated with waking $SpO_2 < 96\%$ and habitual snoring, two easily obtainable measurements during a regular clinic visit. Another large retrospective study evaluated a clinic-based sample of 641 children with SCD aged 14.2 ± 5.2 years, of whom 136 (22%) were identified as having OSA by PSG [88]. In this case, the higher prevalence of OSA could reflect referral bias, such that the actual prevalence may revolve around 10% or so as suggested by Rosen et al. [87]. Multiple other small or biased studies, summarized in [89], have generated the overall impression that the prevalence of OSA in children with SCD is probably higher than the 2–4% of the general pediatric population, approaching 10% for moderate to severe OSA (Table 48.1). The prevalence of habitual snoring or other conditions within the spectrum of SDB is certainly much higher, around 20–40%. Moreover, the predictive value of snoring or other SDB-associated symptoms for the presence of OSA seems very high, thus confirming the need for high clinical suspicion for the occurrence of OSA in this vulnerable population.

In adults with SCD, the data on the prevalence of OSA is scarce. One recent small prospective study of 20 patients

Table 48.1 Findings in PSG studies of patients with SCD

First author and publication year [ref]	*N* (total)	Control group	Age (yr)	Design	Key findings
Samuels 1992 [82]	103 (50 control)	Age matched	1.9–16.5	Case-control	SDB in 36% of SCD, no clear definition of OSA.
Raj 2006 [79]	23 (6 controls)	Matched for age, sex, ethnicity	4–16	Case-control	OSA diagnosed 10% in SCD vs. 25% in controls. SCD patients without OSA showed signs of cerebral hypoxia during wakefulness, which was exacerbated during sleep.
Souza 2007 [62]	50	N/A	10–18	Cross-sectional	In SCD adolescents without a prior diagnosis of OSA, TST and REM were shorter, while awakening, stage changes, and movements in sleep were higher for age. Most did not fulfill the criteria for OSA
Kaleyias 2008 [81]	29 (10 controls)	Matched for age, sex, ethnicity, and AHI	6–13	Case-control	79% of SCD patients with a history suggestive for SDB had OSA. More severe nocturnal desaturation and hypercapnia compared to no-SCD OSA
Spivey 2008 [86]	20	N/A	1–19	Retrospective	In a cohort with onetime day desaturation, all had nocturnal desaturation. 35% had OSA; 20% had asthma
Salles 2009 [16]	85	N/A	2–19	Cross-sectional	10.6% had OSA. Higher desaturation time was associated with a lower mean annual Hb
Rogers 2010 [65]	55	N/A	2–18	Retrospective	65% of children referred for SDB evaluation were diagnosed with OSA. SpO_2 was lower in HbSS vs. HbSC. PLMS were frequent
Johnson 2010 [19]	44	N/A	4–18	Cross-sectional	33% had lower SpO_2, and 19% had higher AHI than the population average. 46% had LVH; LV mass and diastolic function negatively correlated with lower SpO_2
Warrier 2010 [85]	28	N/A	N/A	Retrospective	28% of children with snoring history had OSA
Rogers 2011 [66]	64	N/A	2–18	Cross-sectional	PLMS are common (23%) and are associated with sleep disruption and symptoms of RLS
Goldstein 2011 [84]	64	N/A	2–14	Cross-sectional	23% had SDB and 50% of them had asthma. Cerebral blood flow was similar in SDB and no-SDB groups
Mullin 2012 [165]	45	N/A	4–18	Prospective	SDB symptoms remained stable or improved over a 1-year follow-up in clinically stable SCD patients
Lehman 2012 [21]	221	N/A	4–19	Prospective	AHI ≥ 2 was significantly associated with the presence of enuresis. Severe enuresis was associated with habitual snoring and SDB
Roizenblatt 2012 [20]	34 (16 control)	SCD patients w/o Hx of priapism	16–57	Case-control	History of priapism was associated with PLMS and oxygen desaturation
Rogers 2012 [64]	20	N/A	2–18	Cross-sectional	In SCD patients with PLMS on PSG or RLS, the ankle-activity monitor is a valid screening method for PLMS. PLMS were associated with higher ferritin level post-PSG and higher CRP levels overall
Strauss 2012 [80]	72 (36 control)	Matched for age, sex, ethnicity, weight& height	2–12	Case-control	19% of SCD had OSA. SCD had reduced upper airway size on MRI due to the overgrowth of surrounding lymphoid tissue
Hollocks 2012 [23]	10	N/A	8–16	Cross-sectional	Lower nighttime SpO_2 and higher arousal index were associated with worse executive function
Finch 2013 [63]	13	N/A	2–16	Retrospective	Adenotonsillectomy was associated with increased SpO_2 and REM sleep and reduced AHI on post-PSG as compared to pre-PSG
Katz 2014 [88]	272 (136 control)	Matched for age, gender, genotype, Hb levels	14 ± 5	Mixed retro/ prospective	22% of selected SCD children had OSA. SCD + OSA had more ACS, as compared to controls, but did not differ in overall cognitive (not including executive) function
Mascarenhas 2014 [166]	130 (65 control)	Matched for age, sex, AHI	2–17	Retrospective case-control	SCD children with OSA had lower mean and nadir SpO_2 and higher enuresis incidence (35%), as compared to AHI-matched controls

(continued)

Table 48.1 (continued)

First author and publication year [ref]	*N* (total)	Control group	Age (yr)	Design	Key findings
Salles 2014 [167]	85	N/A	2–19	Retrospective	Increased abdominal and cervical circumference is associated with nocturnal hypoxia
Rosen 2014 [87]	243	N/A	4–18	Prospective	41% of unselected for symptoms patients had OSA. 10% had mod-severe OSA. Habitual snoring and waking $SpO_2 < 96\%$ were strongly associated with moderate-severe OSA
Sharma 2015 [91]	32	N/A	35–47	Cross-sectional	In symptomatic patients referred to PSG 44% had OSA (AHI ≥ 5)
Whitesell 2016 [90]	20	N/A	22–28	Cross-sectional	OSA was present in 50%. OSA patients had higher systolic blood pressure, more LV diastolic dysfunction, and lower health-related quality of life scores
Al-Otaibi 2017 [168]	65	N/A	8 ± 5	Cross-sectional	82% had OSA. 7.7% moderate-severe OSA. Enuresis and habitual snoring were common
Katz 2018 [93]	272 (136 control)	Matched for age, sex, genotype	9.2 ± 4.7	Retrospective Case-control	Children with SCD and OSA had higher overall rates of SCD complications than low OSA-risk controls with SCD; lung morbidity showed the largest effect size
WIllen 2018 [25]	140	N/A	10.8 (IQR-7.2)	Multicenter prospective cohort	Over 4.9 years of follow-up, higher mean nocturnal SpO2 was associated with slightly higher rates of pain episodes. Neither low nocturnal SpO2, higher obstructive AHI, nor higher ODI were associated with increased incidence rates of acute severe pain episodes
Lin 2019 [67]	129	N/A	≤18	Retrospective	42% had PLMS. PLMS was associated with greater rates of cerebrovascular disease as detected by MRI

Modified from Whitesell et al. [89] with permission from Elsevier
SCD sickle cell disease, *PSG* polysomnography, *SDB* sleep-disordered breathing, *OSA* obstructive sleep apnea, *AHI* apnea-hypopnea index, *ACS* acute chest syndrome, *PLMS* periodic limb movements, *RLS* restless leg syndrome, *LVH* left ventricular hypertrophy; * most studies recruited stable patients without chronic transfusion of hydroxyurea, some reported HbSC patients in their cohort, but usually in small numbers

found a prevalence of 50% for any OSA (AHI ≥ 5/hrTST). In this unbiased study, snoring and sleep complaints were not predictive of OSA, but OSA was associated with lower quality of life, higher blood pressure, and diastolic dysfunction [90]. Another study in 32 adults referred for PSG due to clinical sleep complaints found a similar prevalence of 44% for OSA [91].

The ATS has recently published research gaps in SCD, identifying SDB and hypoxemia as research priorities [92]. Specifically, two main questions requiring attention remain:

1. How do SDB and repeated arousals during sleep impact SCD morbidity and mortality?
2. What is the impact of treatment of hypoxemia and SDB on short- and long-term outcomes in SCD?

Until recently, the association of nocturnal hypoxemia and/or SDB with increased disease severity in SCD has been undisputed, based on the strong biological plausibility derived from basic laboratory findings and on retrospective or cross-sectional clinical studies. For example, in one such retrospective study, OSA was associated with higher rates of a broad range of SCD complications, including pneumonia and acute chest syndrome [93]. However, the prospective data provided recently by Willen and colleagues is contradicting – this study has carefully followed 140 children with SCD over a period of almost 5 years, looking exactly for such association between SDB and hypoxemia and SCD morbidity. Surprisingly, higher, rather than lower, nighttime SpO2 levels were associated with a higher incidence of pain episodes, and SDB severity did not predict a higher occurrence of VOC [25].

Regarding the effect of treatment, in one retrospective study, children with SCD who underwent adenotonsillectomy ($n = 256$) had more baseline visits for OSA, recurrent tonsillitis, and stroke, as compared to matched controls with SCD but who did not require adenotonsillectomy ($n = 512$) [94]. After adenotonsillectomy, there was a significant decrease in the number of clinic visits for OSA or for cerebrovascular ischemic events, but not for VOC or ACS events, suggesting that at least some clinical aspects of SCD may be modifiable by treatment of OSA. Other smaller studies have reported improvement in AHI and oxygen saturation following adenotonsillectomy, but not on clinical severity parameters, possibly due to a short follow-up period [64. 66. 83]. One 6-week pilot trial of auto-adjusting continuous positive airway pressure in 24 children with SCD and OSA demonstrated good adherence and improved sleep parameters, oxygen saturation, and reported pain days [95]. A larger trial evaluating CPAP for OSA in SCD is currently underway [96].

Lower Airway Obstruction and Asthma

SCD and SDB share to a certain extent some similarities in their pulmonary comorbidities, most notably the presence of an increased incidence of asthma. Asthma is common in children with SCD and is associated with an increased incidence of VOC, ACS episodes, and a 2.4-fold increased risk of earlier death [97–100]. The association of asthma with SDB has also been repeatedly documented. In a recent meta-analysis [101], 23.9% of children with asthma reported symptoms of SDB as compared to 16.7% in the general population, and a diagnosis of asthma was associated with a two-fold increase in the risk of SDB. Studies in adults are less conclusive, although there seems to be an increased incidence of SDB in adult asthma patients as well, and the presence of SDB in adult OSA patients may be associated with a more severe asthmatic clinical phenotype [102–104]. Two recent studies have also shown that treatment of SDB in children is associated with significant improvements in asthma control [105, 106].

Do SCD patients with SDB have an increased prevalence of asthma? The strong association of each condition separately with asthma would suggest a positive answer to this question. However, the actual data to support this hypothesis is scarce – in one study asthma was present in 50% of the children with PSG-diagnosed SDB, as compared to 17% of the no-SDB group [84]. Two subsequent studies did not find similarly increased asthma prevalence [86, 87]. Notably, no studies have looked at asthma in the context of SDB in adult SCD patients.

Cardiovascular Disease

Cardiovascular causes account for up to a quarter of premature death in adults with SCD [107]. Cardiovascular manifestations of SCD include pulmonary hypertension, LV systolic and diastolic dysfunction, myocardial infarction, and venous thromboembolism [108]. Similarly, cardiovascular disease in SDB shares many pathophysiological factors involved in SCD (i.e., endothelial dysfunction, reduced NO bioavailability, increased inflammation, and oxidative stress). SDB has been extensively associated with endothelial dysfunction and increased risk for systemic and pulmonary hypertension in both adults and children, as well as increased prevalence of arrhythmias, atherosclerosis, myocardial infarction, and heart failure in adults [32, 109–118].

Pulmonary Hypertension

Pulmonary hypertension (PH) is a well-recognized comorbidity of SCD. An elevated tricuspid regurgitation jet velocity (TRV) by echocardiography (defined as ≥2.5 m/s) is present in approximately one-third of hemoglobin-SS adults, 10–20% of hemoglobin-SC adults, and 10–20% of HbSS children and adolescents [92]. Right heart catheterization studies find a much lower prevalence of 6–11% [119–122]. The pathophysiology of PH in SCD includes increased hemolysis, decreased NO bioavailability, increased expression of cell adhesion molecules, and increased activity of pro-coagulants all of which potentially leading to pulmonary thromboembolism, airway hyper-responsiveness, and possibly SDB [123, 124]. PH in adults with SCD is associated with early mortality [125–127]. In children, elevated TRV is not associated with increased mortality risk, but rather with reduced exercise capacity [128, 129].

PH may occur in patients with SDB, and similarly to SCD, the presence of PH conveys increased mortality risk [130–132]. Some data suggest that SDB may contribute to the PH in SCD – children with nocturnal hypoxemia had higher TRV, although AHI did not correlate with the severity of PH [133, 134]. In adults, no such association has been found [90].

Left Ventricular Dysfunction

LV dysfunction is a well-recognized complication of SCD [135]. The major systolic variables increased in SCD patients are load-independent, such as cardiac index, LV dilatation, and LV end-systolic stress index. Conversely, load-dependent variables are usually not altered. Diastolic dysfunction is present in 10–20% of adult SCD patients and is associated with mortality [136].

Few studies have examined the direct contribution of SDB to LV dysfunction associated with SCD. In children, LV hypertrophy and diastolic dysfunction are negatively associated with nighttime oxygen saturations and possibly also with awake oxygen levels [19, 134]. In young adults, PSG-diagnosed SDB may be associated with higher systolic blood pressure and diastolic dysfunction [90]. In adults with SCD and congestive heart failure, nighttime hypoxia, rather than apnea or arousals, predicted hemodynamic stress [137].

Future studies will need to examine the occurrence of LV dysfunction and SDB in larger pediatric and adult cohorts, and the potential benefits of CPAP or oxygen therapy in adults, or of adenotonsillectomy and supplemental oxygen in children as far as achieving improvements in cardiac function.

Neurological Complications

One of the most devastating complications of SCD is a stroke, with first-stroke incidence of 1:100 patient-years between 2 and 5 years of age. By the age of 20, 11% of the patients have

already sustained one stroke episode, and 60% of them will suffer from recurrent events. Most cases are associated with a vasculopathy of the internal carotid and middle cerebral arteries, in which aggravating factors include hypoxemia, decreased NO bioavailability, anemia, and hemolysis [2]. Increased cerebral blood flow (CBF) velocity as measured by a transcranial Doppler is a surrogate marker for the risk of stroke in SCD. Healthy children with SDB have increased CBF [138], and in children with SCD, CBF is reduced following adenotonsillectomy [139]. This seems to translate to an increased risk of stroke in SCD children with OSA, with risk reductions occurring following adenotonsillectomy [94].

Patients with SCD even without stroke show signs of impaired cognitive function as early as infancy, suggesting ongoing microvascular CNS pathology due to constant hypoperfusion to vulnerable brain areas, such as those involved in executive function [140]. Accordingly, increased CBF is associated with executive dysfunction in children with SCD [141] and in healthy children with SDB [138, 142]. In addition, nocturnal hypoxemia and sleep fragmentation have been also associated with worse executive function in SCD [23, 143].

In summary, there is evidence supporting the idea that SDB accounts to some degree for the adverse neurocognitive outcomes seen among SCD patients, as both an increased risk of stroke and an increased risk of cognitive dysfunction.

Urological Complications

The urological manifestations of SCD include priapism (a medical emergency), nocturnal enuresis, and erectile dysfunction [144]. Endothelial dysfunction, tissue hypoxemia, chronic hemolysis, and acute VOC all contribute to the damage to the genitourinary system.

Priapism

Priapism is a prolonged and unwanted penile erection lasting more than 4 hours, which is a medical emergency. The most common cause of priapism in children is SCD [145]. The mechanism for priapism in SCD is tightly associated with reduced NO bioavailability, endothelial dysfunction, and hypoxemia [146]. Patients with priapism have more sleep fragmentation and PLMS, and more severe SDB, with higher AHI and ODI [20].

Nocturnal Enuresis

Nocturnal enuresis is a common and challenging problem in both children and adults with SCD. Compared to 1–15% of the general population, as much as 20–69% of children and 9% of young adults with SCD suffer from nocturnal enuresis. Nocturnal enuresis is associated with lower self-esteem and reduced quality of life in patients with SCD [147, 148]. A strong relationship exists also between nocturnal enuresis and SDB [149–154]. Accordingly, the treatment of SDB by adenotonsillectomy in children is often curative for nocturnal enuresis as well [155–158]. CPAP treatment in adults with enuresis and SDB may benefit both conditions [159].

Underlying presence of SDB is linked to the presence of enuresis in SCD patients. Parental self-reported SDB symptoms and habitual snoring are strongly associated with enuresis in children with SCD, as are other disturbances in sleep quality, such as parasomnias and total sleep time [59]. Similarly, enuresis is more common in SCD children with PSG-diagnosed SDB – 56% of children with moderate-severe OSA – as compared to 27% in controls [87] and the prevalence of enuresis increases in a dose-dependent manner from habitual snoring to frank SDB [21]. Therefore, children with SCD suffering from enuresis should be screened for the presence of SDB.

Erectile Dysfunction

Erectile dysfunction is not uncommon in SCD patients with recurrent episodes of priapism [160]. Endothelial dysfunction and NO bioavailability, key components of SCD pathophysiology, also account for the erectile dysfunction in these patients [161–163]. Erectile dysfunction is common in the OSA patient population, and endothelial dysfunction, an early component of cardiovascular disease, may similarly underlie the pathophysiologic link between OSA and erectile dysfunction [164]. No study to date has examined the contributing effect of SDB to the erectile dysfunction occurring in SCD, although, clearly, such relation is plausible.

Summary

In summary, sleep is disrupted in patients with sickle cell disease, in part due to chronic pain and in part due to sleep-disordered breathing. SDB is more prevalent in patients with SCD. Both SCD and SDB share common pathophysiological pathways: recurrent episodes of hypoxia-reoxygenation with the generation of reactive oxygen species, reduced nitric oxide bioavailability, endothelial dysfunction, chronic inflammation, and autonomic nervous system imbalance. SCD and SDB share common end-organ morbidities such as asthma, pulmonary hypertension, cognitive dysfunction, LV diastolic dysfunction, and nocturnal enuresis. Treating SDB may improve some SCD outcomes, but the currently available data is inconclusive.

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Epilepsy and Sleep, Common Bedfellows

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Abbreviations

ADNFLE	Autosomal dominant frontal lobe epilepsy
BECTS	Benign focal epilepsy of childhood with centro-temporal spikes
BMAL1	Brain and muscle Arnt-like protein-1
CAP	Cyclic alternating pattern
CHRNA2	Neuronal acetylcholine receptor subunit alpha-2
CHRNA4	Neuronal acetylcholine receptor subunit alpha-4
CHRNB2	Neuronal acetylcholine receptor subunit beta-2
CLK5	Cyclin-dependent kinase 5
CLOCK	Circadian locomotor output cycle kaput
CPAP	Continuous positive airway pressure
DEPDC5	DEP (Dishevelled, Egl-10 and Pleckstrin) domain-containing 5
DLMO	Dim light melatonin onset
EEG	Electroencephalogram
EFHC1	EF-hand domain-containing protein 1
ESES	Electrical status epilepticus in slow wave sleep
GATOR1	GAP (GTPase-activating protein) towards Rags
GTCS	Generalized tonic-clonic seizure
ICK	Intestinal cell kinase
IED	Interictal epileptiform discharge
ILAE	International League Against Epilepsy
JME	Juvenile myoclonic epilepsy
KCNT1	Potassium channel subfamily T, member 1
MME	Minor motor events
MRF	Medial reticular formation
mTOR	Mammalian target of rapamycin
nAChR	Neuronal nicotinic acetylcholine receptor
NPRL	Nitrogen permease regulator-like
NREM	Non-rapid eye movement
OSA	Obstructive sleep apnea
PA	Paroxysmal arousals
PNES	Psychogenic nonepileptic seizures
PCCA	Post-convulsive central apnea
PCDH 19	Potential calcium-dependent cell-adhesion protein 19
PGES	Postictal generalized EEG suppression
PLMDS	Periodic limb movement disorder of sleep
PS	Panayiotopoulos syndrome
PSG	Polysomnography
REM	Rapid eye movement
RLS	Restless leg syndrome
RNS	Responsive neurostimulation system
SEEG	Stereoelectroencephalography
SHE	Sleep-related hypermotor epilepsy
SUDEP	Sudden unexplained death in epilepsy patients
TMS	Transcranial magnetic stimulation
VNS	Vagal nerve stimulation

Introduction

A bedfellow is a person or thing who shares a bed or is closely allied or connected to another. Since ancient times, epilepsy and sleep have been known to be bedfellows. Aristotle in the treatise *De Somno et Vigilia* conflates epilepsy and sleep, "sleep is similar to epilepsy and, in some way, sleep is epilepsy" [1]. In 1885 Richard Gowers reported that seizures occurred exclusively during sleep in 21% of institutionalized patients with epilepsy [2].

Electroencephalography, first recorded on a human by a human by Hans Berger in 1924 and refined over the follow-

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ing decades, became a powerful tool to study both epilepsy and sleep [3]. The first laboratory for the study of sleep was developed by Alfred Lee Loomis, a wealthy Wall Street lawyer and inventor, at his home in Tuxedo Park, New York, in 1935. Mr. Loomis and his colleagues developed the kymograph, an 8-foot-long drum allowing inscription of recorded data on a single piece of paper. The continuous recording of the electroencephalogram during sleep for 8 hours paved the way for sleep staging [4].

Further development of the electroencephalogram in the study of neuropsychiatric disorders, especially epilepsy, during the 1930s and 1940s at Harvard was conducted by Hallowell Davis and Frederic and Erna Gibbs [4]. In 1947 the Gibbs reported that while 36% of epileptic patients had interictal epileptiform discharges during wakefulness, 82% exhibited this activity during sleep [5].

Sleep-Wake State and Circadian Rhythm Effects on EEG, Seizures, and Cortical Excitability

NREM sleep is a state of hypersynchrony in neuronal networks and is known to activate IEDs. The thalamic reticular nucleus directs the progressive synchronization of the thalamocortical network during NREM sleep. Similar circuits are also involved in the hypersynchronous cerebral electrical activity generating spike and wave discharges in generalized epilepsy. The cyclic alternating pattern (CAP) represents a normal component of NREM sleep based on the finding that features of sleep architecture such as K complexes, sleep spindles, and delta activity are nonrandomly distributed during the sleep cycle. This endogenous rhythm of sleep is divided into A (A1, A2, A3) and B phases. The A phase represents cortical activation that is distinct for the background (B phase). IEDs (interictal epileptiform discharges) are noted to occur most commonly during the A1 phase of the CAP [6, 7].

Adenosine, the neurotransmitter that likely promotes the homeostatic sleep drive, increases over the course of the waking day demonstrating an antiseizure effect. The reduction of adenosine during sleep may result in the activation of IEDs [8, 9]. Therapeutic augmentation of adenosine is being explored as an antiseizure treatment [10]. In 1998 orexin A and B or hypocretin 1 and 2 were identified by two research groups concurrently, hence the two names. Orexins are hypothalamic peptides that promote wakefulness. Marked loss of hypothalamic orexin/hypocretin-producing neurons is the cause for narcolepsy [11]. Reduced activity of orexin is associated with REM sleep onset, resulting in decreased IEDs and seizures. Orexin antagonism has an antiseizure effect in animal models [12].

REM sleep is characterized by desynchronization of the EEG due to depolarization of the thalamus by cholinergic MRF (medial reticular formation) neurons. Spike frequency is reduced during REM sleep, especially during phasic REM related to cortical desynchronization [13]. REM sleep has a protective effect with regard to seizure occurrence. Multiple studies indicate a very low proportion of seizures occur during REM sleep (~1% of less). Seizures occur most often during N1, N2, and N3 sleep [14]. Frontal lobe seizures are more likely to be sleep related than temporal lobe seizures [15]. Temporal lobe seizures are more likely to evolve to bilateral tonic-clonic seizures during sleep [16]. Psychogenic nonepileptic seizures do not occur during sleep which often can be a helpful clinical clue to distinguish PNES from epileptic seizures [17]. In the course of video EEG monitoring for PNES, it is very important to note if the patient arouses from sleep prior to the onset of clinical seizure-like activity or if pseudo-sleep (patient quiet with eyes closed but awake) is present [18].

Multiple cellular clocks located in cells, tissues, and organs comprise the mammalian circadian system. The molecular basis of the circadian clock is based on the oscillation of posttranslational modification of proteins by phosphorylation and a feedback loop involving alternating activation and inhibition of transcription [19]. Based on clinical observation alone, it has been known since antiquity that epileptic seizures exhibit a circadian pattern. The use of prolonged video EEG monitoring for the presurgical evaluation of refractory epilepsy and, more recently, the use of closed loop implanted, responsive neurostimulation systems for refractory epilepsy (RNS) can quantify seizure distribution over the sleep-wake cycle for days to weeks. RNS allows for continuous recording of cerebral electrical activity over months to years. This has not only provided important data regarding circadian patterns of seizure activity but also on ultradian and multidien patterns [20]. Using these monitoring modalities, it has been demonstrated that IEDs peaked during sleep regardless of location [21]. Seizures, in distinction to IEDs, occurred with a circadian pattern that was related to the seizure onset zone as noted previously, for example, frontal lobe seizures tended to occur during sleep, while temporal lobe seizures occurred during wakefulness [22, 23]. The evidence to date would support that timing of seizures is related to behavioral state (i.e., wakefulness versus sleep or NREM sleep versus REM sleep) rather than environmental conditions such as light-dark cycles [23]. In frontal lobe epilepsy, seizures tend to occur during sleep whether this occurs during the night or day (daytime naps) [24]. Peak times for frontal lobe seizures were from 5:15 AM to 7:30 AM. Temporal lobe seizures clustered between 6:45 PM and 11:56 PM [25]. Dim light melatonin onset is an important biomarker of the circadian rhythm. Temporal

lobe seizures occurred 6 hours prior to DLMO and frontal lobe seizures 6–12 hours after DLMO [26]. Seizure types also exhibit circadian patterns. Tonic-clonic and tonic seizures tend to occur during sleep [27]. Clonic, absence, atonic, and myoclonic seizures occur more often during waking hours [28].

RNS has allowed the identification of multidien patterns of seizure occurrence in patients with refractory epilepsy. In a study of 37 patients who underwent RNS implantation and were monitored over months to years (3 months to 9.9 years), multidien patterns of interictal epileptiform activity that were quite specific to individuals and stable over years were identified. The most common periodicity was 20–30 days in duration. Seizures tended to occur during the rising phase of multidien interictal epileptiform activity. Patterns were similar in men and women suggesting that catamenial cycling does not fully explain the multidien pattern of interictal epileptiform activity and seizure activity. These multidien periodicities were identified even in those patients that did not exhibit clinically apparent periodicity to their seizure patterns [29].

The molecular basis for that mediate circadian effects on neuronal excitability are being elucidated. Clock genes and circadian variation in the mTOR (mammalian target of rapamycin) pathway have been implicated [20]. CLOCK (circadian locomotor output cycle kaput) is a transcription factor which regulates circadian rhythm in the suprachiasmatic nucleus. In a conditional mouse model in which the CLOCK gene is deleted in excitatory cortical neurons but is intact in the inhibitory neurons and suprachiasmatic nucleus, seizure threshold is decreased. It is important to note that the excess excitability was due to loss of CLOCK function in cortical neurons as it was preserved in the suprachiasmatic nucleus in this mouse model. In human tissue samples obtained from therapeutic surgical resection of focal cortical dysplasias and tuberous sclerosis complex, CLOCK protein was significantly reduced [30]. BMAL1 (brain and muscle Arnt-like protein-1) is another transcription factor that is a core element of the molecular circadian clock that binds with CLOCK to form the CLOCK-BMAL1 complex. BMAL-1 knockout mice exhibited significantly lower seizure thresholds at all times, supporting a role for this factor in modulating neuronal excitability [31].

mTOR is a molecular sensor system that regulates protein synthesis by enhancing mRNA translocation of genes that control cell proliferation and survival. Multiple lines of evidence indicate that the mTOR pathway has an important role in epileptogenesis. The paradigmatic conditions in which mTOR pathway dysregulation contributes to the etiopathogenesis of epilepsy are tuberous sclerosis and focal cortical dysplasia [32]. The close interaction between the mTOR pathway and circadian molecular clock systems is likely to play a critical role in epileptogenesis. Both the aforementioned CLOCK and BMAL1 genes are modulated by key molecules in the mTOR pathway. An overactive mTOR pathway changes the function of the BMAL1-CLOCK complex resulting in abnormal cortical neuronal excitability [33].

The unpredictable nature of seizures results in significant adverse economic, social, physical, and psychological consequences for patients with epilepsy [34]. The identification of the circadian pattern of seizures in patients with epilepsy allows for improved seizure prediction allowing for targeted treatments based on these patterns. One relatively simple intervention that has demonstrated efficacy is differential dosing of antiseizure medications. In patients with sleep-related or early morning seizures, a higher dose of antiseizure medication in the evening resulted in improved seizure control (64.7% seizure free, 88.2% with greater than 50% reduction in seizures). This effect is likely achieved by a slight increase in nocturnal peak levels of the antiseizure medication [35]. Vagal nerve stimulation (VNS), an implantable neurostimulator, is an effective treatment for drug-resistant forms of epilepsy resulting in a significant reduction in seizure frequency in the majority of patients [36]. The most recent iteration of this device (*SenTiva*®) has new programming feature that allows one to vary stimulus parameter during the day and night. Increased stimulation may be delivered during the night to patients with principally nocturnal seizures. It also allows one to detect prone versus supine position in sleep which is of importance given prone positioning as risk factor for SUDEP [37].

Epilepsy Syndromes and Sleep

The definition of epilepsy was refined in 2013 by the ILAE to the following:

Epilepsy is a disease of the brain defined by any of the following conditions:

1. At least two unprovoked seizures occurring >24 hours apart
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years (assessed via an abnormal EEG, MRI, or neurological examination)
3. Diagnosis of an epilepsy syndrome [38]

There is not yet a formal ILAE classification of the epilepsy syndromes. An epilepsy syndrome denotes a collection of features that occur together including seizure type, EEG, and imaging findings. It often indicates age-dependent qualities such as age of onset and remission. Comorbid conditions

including intellectual disability or behavioral disturbances can be specified. An epilepsy syndrome has implications for etiology, natural history, prognosis, and treatment [39]. Epilepsy syndromes that exhibit a distinct sleep profile include "benign" focal epilepsy of childhood with centrotemporal spikes (BECTS), Panayiotopoulos syndrome, and autosomal dominant nocturnal frontal lobe epilepsy. Epileptic encephalopathies may also exhibit characteristic sleep patterns [40].

Benign focal epilepsy syndromes of childhood affect 25% of children with nonfebrile seizures. The diagnosis and treatment of these syndromes comprise a substantial part of the practice of any pediatrician, pediatric neurologist, or epilepsy specialist [41]. It should be noted that the most recent ILAE classification recommendations regarding epilepsy syndromes speaks against using value-laden terms such as "benign" or "catastrophic." Specifically, with regard to the use of the term "benign" in childhood epilepsies, it is felt that this designation may underestimate the burden of these milder epileptic syndromes. The condition known as benign focal epilepsy of childhood with centrotemporal spikes (formerly benign Rolandic epilepsy) for some affected children carries substantial transient and sometimes longer-term adverse cognitive effects. It is important to note that this cognitive impairment may be related to disordered sleep physiology which will be discussed in greater detail later in this chapter. The ILAE suggests that the well-recognized benign features of the childhood epilepsy syndromes may be described more appropriately by the terms "self-limited" and "pharmacoresponsive," although it is important to emphasize that not all are pharmacoresponsive [39].

Benign focal epilepsy of childhood with centrotemporal spikes (BECTS) presents with childhood onset seizures between the ages of 1–14 years with a peak onset in early school age children, 7–10 years of age. Ictal features consist of hemi-facial sensorimotor seizures, oropharyngolaryngeal, ictal manifestations, arrest of speech, and hypersalivation. The majority of children retain awareness during the seizures. Centrotemporal spikes that are markedly activated by sleep are the hallmark of BECTS. The centrotemporal interictal epileptiform activity exhibits a highly stereotyped diphasic or triphasic morphology and occurs independently or bisynchronously over both hemispheres with maximal electronegativity often demonstrated at the T3 and T4 electrodes. Most seizures occur during NREM sleep just after falling asleep or sometimes just prior to awakening, with 55–59% of patient having seizures exclusively during sleep. The sleep-related seizures may evolve to bilateral tonic-clonic seizures. Status epilepticus and postictal paralysis are rare in this syndrome [41]. Atypical features abound including falls due to epileptic negative myoclonus and transient oromotor dysfunction [42, 43]. Prognosis is almost uniformly favorable with remission within 2–4 years of onset and before the age of 16 years [41]. The North American SUDEP registry identified three patients with apparent BECTS who had SUDEP-related deaths (two definite and one probable) between the years of 2011 and 2016 [44] (Fig. 49.1).

Panayiotopoulos syndrome (PS) is another self-limited and pharmacoresponsive epilepsy of childhood with distinct sleep-related features. Onset is between ages 1 and 14 years with most cases presenting between ages 3 and 6 years.

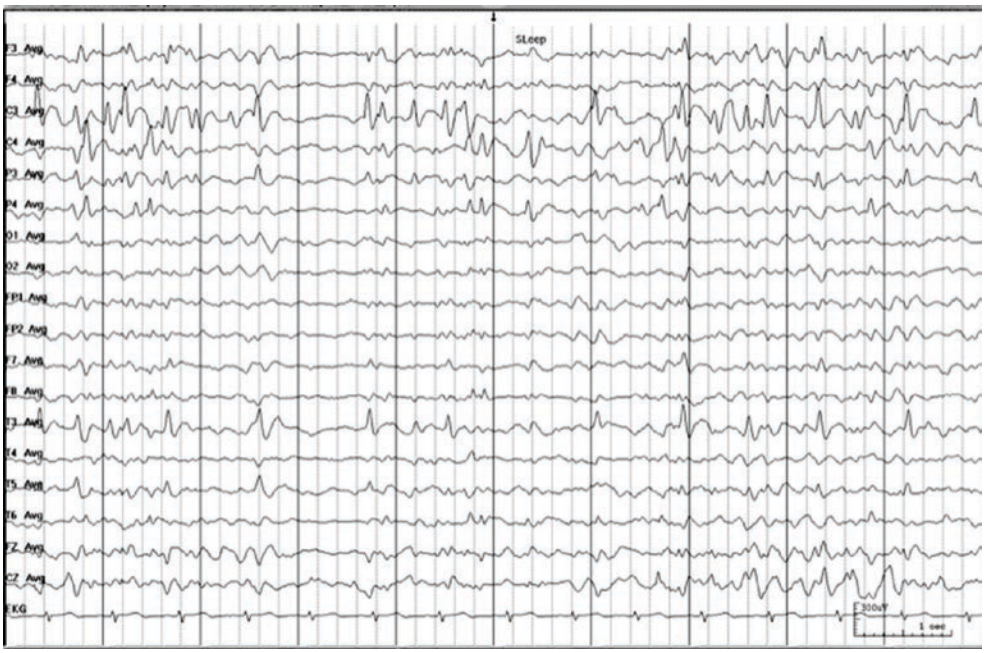

Fig. 49.1 Centrotemporal spikes activated by sleep that are characteristic of a self-limited, pharmacoresponsive focal epilepsy of childhood

Autonomic features are characteristic of the ictal presentation including ictal emesis, pallor, cyanosis, urinary and fecal incontinence, mydriasis, miosis, hypersalivation, coughing, thermoregulatory changes, diarrhea, changes in breathing patterns, apnea, and tachycardia. Ictal syncope is common, that is, limp unresponsiveness. Cardiorespiratory arrest has been reported rarely. Impairment of consciousness is frequent with only a minority of patients exhibiting preserved awareness. Eye deviation, hemiconvulsions and evolution to bilateral tonic-clonic seizures can occur. Prolonged seizures with autonomic features and autonomic status epileptic occur in this syndrome. Multifocal interictal epileptiform activity is reported although occipital spikes predominate [41]. The synchronous appearance of spikes over the occipital and frontopolar regions is quite characteristic of Panayiotopoulos syndrome (Fp-0 spikes) [45–47]. Centrotemporal spikes characteristic of BECTS and generalized spikes can occur. Interictal epileptiform activity is markedly activated by sleep. Most seizures are sleep related. As is the case with BECTS, the prognosis for PS is favorable with 25% of patients experiencing only a single seizure and remission within 1–2 years of onset [41].

Nocturnal frontal lobe epilepsy is characterized by sleep-related seizures sometimes with bizarre manifestations. In 2014, based on recommendations from a consensus conference, the name was changed to sleep-related hypermotor epilepsy (SHE) reflecting the fact that these seizures are associated with sleep rather than time of day. It also recognized that these seizures may originate from areas of the brain other than the frontal lobes [24, 48]. A small percentage of sleep-related hypermotor seizures have a genetic basis and are known as autosomal dominant frontal lobe epilepsies (ADNLFE). The first pathogenic mutations associated with ADNLFE were identified in the genes coding for subunits of the neuronal nicotinic acetylcholine receptor (nAChR), specifically CHRNA4, CHRNA2, and CHRNB2. The phenotypes are virtually indistinguishable. More recently other gene mutations have been identified including DEPDC5 and NPRL2 and 3. These genes are all associated with the GATOR 1 complex which regulates with mTOR pathway [49]. Mutations in the KCNT1 gene which encodes a sodium-gated potassium channel have also been associated with SHE. The phenotype is different from that displayed by the patients with mutations in the nAChR genes in that the majority exhibit intellectual disability and psychiatric symptoms. KCNT1 mutations have been associated with a severe epileptic encephalopathy, malignant migrating focal seizures of infancy [49, 50]. A very small percentage of patients with ADNFLE have mutations in the corticotropin-releasing hormone gene [51].

Seizures in SHE are sleep related and occur very frequently, with 1–20 events per night. Minor motor events (MME) and paroxysmal arousals (PA) occur even more frequently. PA last 5–10 seconds and are characterized by stereotype movements typically consisting of trunk and head elevation. MME are very brief (2–4 seconds) stereotyped movements involving appendicular or axial musculature. Sleep-related hypermotor seizures are also brief, almost always less than 2 minutes in duration, with abrupt onset and offset. The features may be bizarre with hyperkinetic automatisms but are highly stereotyped. The bizarre nature sometimes results in confusion with psychogenic nonepileptic seizures or confusional arousals as part of NREM parasomnias. Ictal features can include asymmetric tonic or dystonic posturing. Interictal and ictal scalp EEG recordings may be unrevealing. Inadequacy of scalp ictal recordings is due to inaccessibility of much of the frontal lobe to scalp EEG and the presence of obscuring muscle artifact [24, 48, 49]. Stereoelectroencephalography (SEEG) performed in patients with drug-resistant SHE has provides some important insights into the nature of epileptic disorder. SEEG recordings have improved electroclinical correlation. Some of the complex behaviors noted during sleep-related seizures occur without clear epileptic activation. These may represent a release of innate behavioral automatisms and survival patterns produced by central pattern generators. SEEG studies have also confirmed that paroxysmal arousals have an epileptic basis. MME, on the other hand, are likely nonepileptic events representing a manifestation of sleep instability. Sleep is very fragmented in SHE, creating a vicious cycle in which sleep deprivation results in activation of interictal epileptiform activity and worsened seizures [52]. SUDEP does occur in SHE but not at a higher rate than other epilepsies [49].

Parasomnias are sleep disorders that result in behavioral or experiential phenomena during sleep that are undesirable. NREM parasomnias are considered to represent partial arousals from sleep [53]. Sleep disruption in SHE also leads to parasomnias which occur in significant portion of patients with SHE. The clinical distinction of parasomnias from sleep-related seizures is very difficult based on comorbidity and common clinical features [54, 55]. Structured assessments have been developed to attempt to distinguish these disorders clinically including the frontal lobe epilepsy and parasomnia (FLEP) scale and the structured interview for nocturnal frontal lobe epilepsy (SINFLE). These assessments are based on some of the distinguishing clinical features such as the very short, frequent events that occur in SHE and exhibit good specificity [56, 57]. The cholinergic system has a critical role in arousal. Functional studies of ADNFLE-associated pathogenic variants in the nAChR suggest increased sensitivity to acetylcholine. Dysfunction in the arousal system may represent the common pathogenic mechanism for both SHE and parasomnias [58].

Electrical status epilepticus in slow wave sleep (ESES) is characterized by marked sleep potentiation of epileptiform activity during NREM sleep of such a degree that this activ-

ity is virtually continuous and associated with acquired neuropsychological deficits [59]. The terminology regarding ESES is so variable that a recent review made reference to the "Tower of Babel" [60]. Tassinari, who was one of the early describers of ESES, has made the case for the name "Penelope syndrome" [61], based on Homer's *Odyssey* which has Penelope, the faithful wife of Odysseus, weaving a funeral shroud during the day and unraveling it a night as a ruse to delay eager suitors. She would not remarry until it was finished [62]. This designation has not caught on perhaps because the unraveling performed by Penelope was volitional, which is not the case for the unraveling of neural networks that occurs in ESES during sleep. Although EEG criteria vary, many authorities define ESES by continuous epileptiform activity during NREM sleep occupying 85% or more of the recording [59]. Onset is typically between ages of 2 and 14 years with a peak at 4–8 years. The majority of patients have seizures, but these may be infrequent. The most disabling feature of the syndrome is the significant cognitive decline that is associated. Landau-Kleffner (LKS) is characterized by continuous epileptiform activity during sleep associated with regression in language, typically an acquired verbal auditory agnosia. Spontaneous remission of the epileptiform activity occurs in the mid-teens and is associated with stabilization and sometimes improvement in the cognitive, linguistic, and behavioral manifestations [41]. Halasz et al., in multiple publications, have advanced a hypothesis that the self-limited and pharmacoresponsive focal epilepsies of childhood (BECTS, PS) and ESES represent a continuum of dysfunction in the shared circuitry of a perisylvian epileptic network [63]. The presence of abundant epileptiform activity, continuous in ESES, in these epilepsy syndromes is posited to interfere with the plasticity functions of sleep [6, 64, 65]. The continued experience during wakefulness is known to increase synaptic strength between cells that encode information (Hebb rule). This process may well become saturated leading to impaired information storage. NREM sleep is theorized to promote the downscaling and renormalization to maintain plasticity [66]. This process has been demonstrated to be disrupted in ESES and is also impaired in mesial temporal lobe epilepsy [6, 64, 65]. The spectrum of severity associated with cognitive impairment in childhood focal epilepsies, milder but potentially disabling in BECTS [67, 68] to severe and disabling in ESES, reflects the degree to which NREM sleep is altered by epileptiform activity [6]. The optimal treatment for ESES has not been established by large prospective studies [69]. Most authorities agree that decreasing or eliminating the continuous epileptiform activity during NREM sleep is necessary for improvement in the cognition. Treatments employed include various antiseizure medications, high-dose benzodiazepine, immunomodulatory treatments such as corticosteroids and intravenous gamma globulin, and epilepsy surgery [70, 71]. The natural history of the condition is such that resolution of the epileptiform activity is associated with improved cognition [72, 73] (Fig. 49.2).

Severe epileptic encephalopathy of infancy is characterized by epileptic spasms. Epileptic spasms consist of brief bilateral tonic contractions of the axial and limb musculature. The duration is between 0.2 and 2 seconds, slower than myoclonic and faster than tonic seizures. Onset is between 3 and 12 months. Most cases are related to significant structural, genetic, or metabolic disorders of the brain. In a small percentage of cases, the cause cannot be identified. The pathognomonic interictal EEG finding is hypsarrhythmia characterized by high amplitude, poorly synchronous slow wave activity with abundant multifocal interictal epileptiform discharges. Hypsarrhythmia often appears first during NREM sleep. Ictal recording of a spasm is characterized by marked diffuse attenuation in electrical activity, an electrodecremental response. Onset of spasms is often associated with developmental regression. The long-term neurodevelopmental outcome is poor in most affected infants with a substantial risk of developing epilepsy [41]. Infantile spasms do exhibit a distinct circadian pattern tending to occur upon awakening in clusters [74]. Slow wave sleep is impaired in

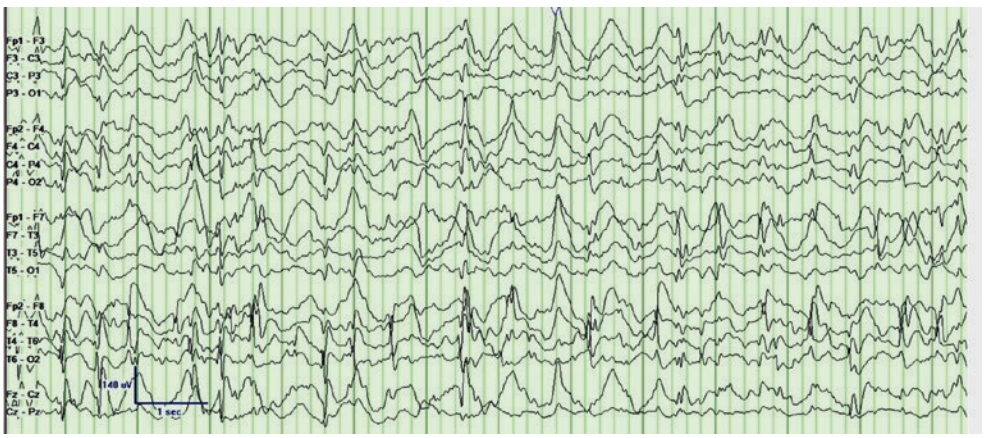

Fig. 49.2 Continuous epileptiform activity during NREM sleep characteristic of ESES

infants with infantile spasms. The restorative function of NREM sleep may be related to downscaling, a phenomenon marked by diminishing slope of slow waves during the course of the night [75]. There is significant reduction in the diminishing slope of slow waves in infantile spasms patients. This is restored in patients who are effectively treated [76] (Fig. 49.3).

Juvenile myoclonic epilepsy (JME) is a generalized epilepsy syndrome of unknown cause but with a presumed genetic basis. A total of 23 chromosomal loci have been associated with susceptibility to JME. The most common is EFHC1 (EF-hand domain-containing protein 1), and the most recent is ICK (intestinal cell kinase) [77, 78]. JME exhibits onset in adolescence with three seizure types: myoclonic (required for diagnosis), absence, and generalized tonic-clonic. Interictal EEG demonstrates generalized 3.5 to 6 Hz spike and wave discharges. Focal spikes can occur in up 30% of patients. Photosensitivity occurs in more than 30% of patients [41]. Myoclonic seizures tend to occur in the morning, related to increased cortical neuronal excitability during that time, as measured by transcranial magnetic stimulation [79]. Sleep deprivation is a very potent trigger for seizures in patients with JME. This can be shown to be related to increased corticospinal excitability in motor areas as measured by TMS (transcranial magnetic stimulation) parameters such as decreased short latency intracortical inhibition and increased short latency intracortical facilitation [80]. JME patients may have a chronotype described as "evening type" or "night owl," preferring to go to bed later and sleep late, although this is disputed [81]. It is clear that individuals with JME have significant sleep disturbances characterized by disrupted night sleep and excessive daytime sleepiness [82] (Fig. 49.4).

Epileptiform abnormalities can be identified on polysomnography in 1.5% of healthy children without epilepsy [83]. In severe epileptic disorders such as epileptic encephalopathy of infancy, electrical status epilepticus in slow wave sleep, and Lennox-Gastaut syndrome as well as in some developmental and epileptic encephalopathies such as Rett syndrome, the interictal EEG recording is so very abnormal

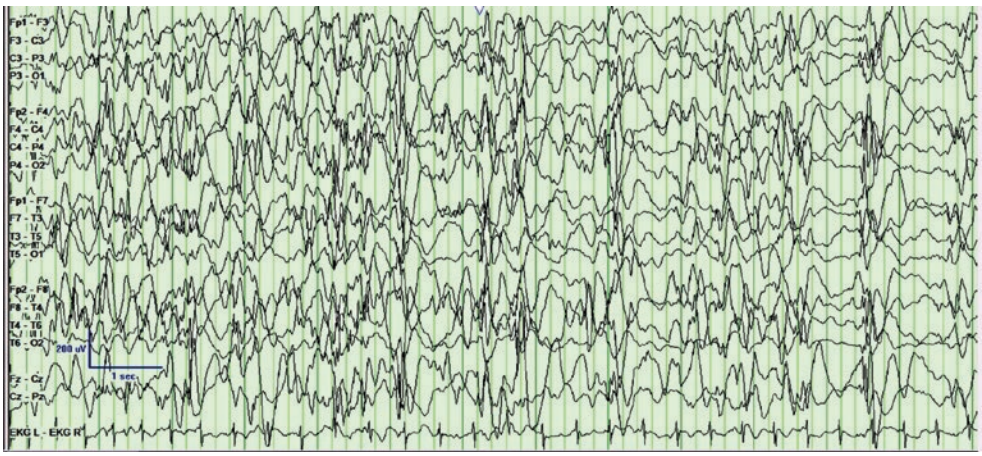

Fig. 49.3 Hypsarrhythmia

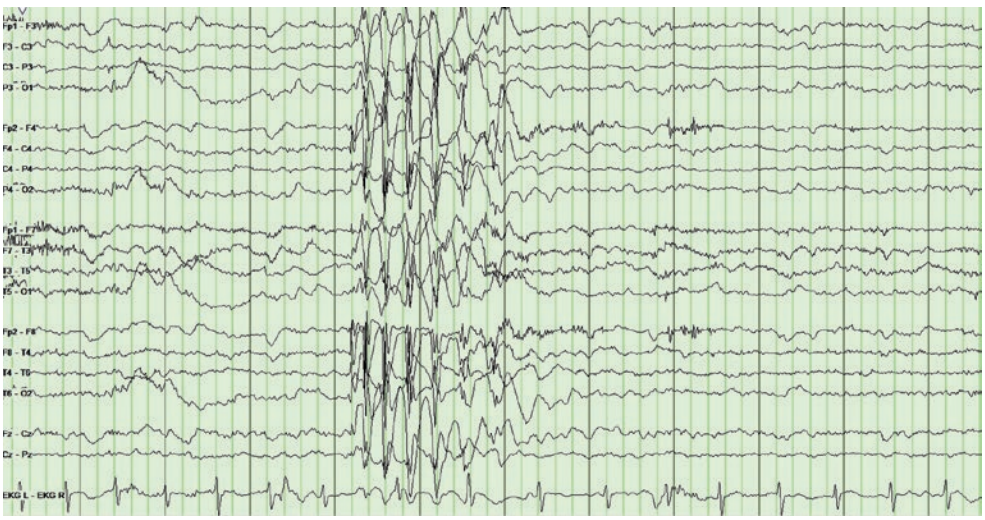

Fig. 49.4 Interictal generalized spike and wave discharge characteristic of JME

during sleep due to abundance of epileptiform activity that sleep staging of a polysomnographic recording may be difficult or impossible. Miano et al. have proposed simplified staging guidelines, but it may be necessary to stage recordings as wake or sleep only [84].

Epilepsy Treatment and Sleep

Most antiseizure medications have effects on sleep architecture. These effects can be variable. Gabapentin, tiagabine, pregabalin, clobazam, and carbamazepine have been shown to decrease sleep latency and improve sleep efficiency. Slow wave sleep was increased by pregabalin, carbamazepine, and gabapentin. Levetiracetam reduced slow wave sleep and at higher doses with resultant increase in daytime sleepiness. REM sleep is suppressed by phenobarbital and phenytoin but augmented by ethosuximide and gabapentin. Excessive daytime sleepiness was not caused by topiramate, lamotrigine, zonisamide, or vigabatrin based on objective measures such as multiple sleep latency test. Phenobarbital and valproate did result in daytime sleepiness [85, 86]. Twelve studies of cannabis-based products were reported to improve or impair sleep in a recent comprehensive review of their use in children [87]. Ketogenic diet improves slow wave sleep [88]. Sleep architecture is disturbed in pediatric epilepsy patients as a function of the number of antiseizure medications that are being administered. Sleep efficiency and REM sleep are reduced in patients on polytherapy [89].

Vagal nerve stimulation results in an increase in respiratory rate and decreases respiratory amplitude, tidal volume, and hemoglobin saturation during periods of device activation [90]. This can result in clinically significant obstructive sleep apnea in some patients [91]. Patients with VNS should be evaluated with polysomnography if the clinical history is suggestive of obstructive sleep apnea, e.g., snoring or excessive daytime sleepiness. Some authorities recommend screening patients after implantation [92, 93]. Changes in stimulation parameters can help ameliorate OSA in VNS patients, specifically, lowering the stimulus frequency below 30 Hz, reducing pulse width to <250 micro-seconds, and increasing the off time/decreasing the on time [94]. Continuous positive airway pressure (CPAP) treatment is helpful but may not always be effective [95] (Fig. 49.5).

Sudden Unexplained Death in Epilepsy Patients

SUDEP is the most fear inducing sleep-related phenomenon that occurs in epilepsy. SUDEP is defined as the "sudden, unexpected, witness or unwitnessed, nontraumatic and non-drowning death, occurring in benign circumstances, in an individual with epilepsy, with or without evidence of a seizure and excluding documented status epilepticus (seizure duration greater than or equal to 30 minutes or seizures without recovery in between), in which postmortem examination does not reveal a cause of death" [96]. Definite SUDEP is established with an unrevealing autopsy. Probable SUDEP meets the same clinical criteria, but no autopsy is performed. Possible SUDEP means that a competing cause of death is identified [96]. Although occurrence during sleep

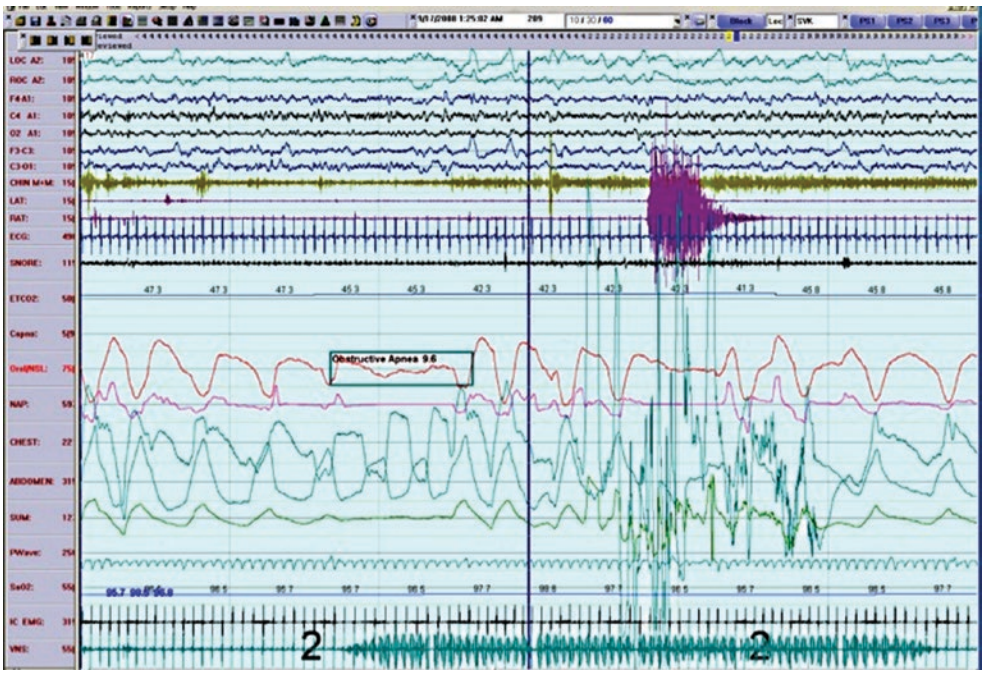

Fig. 49.5 Obstructive apnea induced by vagal nerve stimulation

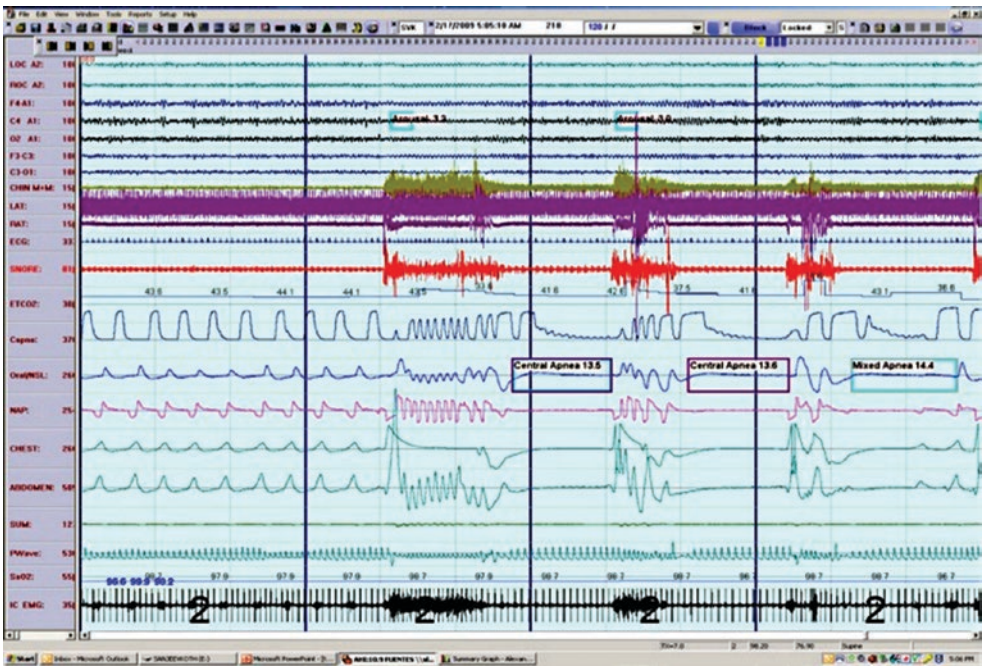

Fig. 49.6 Central apneas induced by tonic seizures

is not in the definition of SUDEP, the preferential occurrence of SUDEP during sleep is supported by numerous case series and reports [97]. The SUDEP risk in adults is 1.2/1000 patient-years (95% CI 0.64–2.32). In children it was thought that the risk was much lower until a recent report by Keller et al. who reviewed cases of pediatric SUDEP in Ontario, Canada, from 2014 to 2015 determining an overall incidence of 1.17 per 1000 pediatric epilepsy person-years (95% CI 0.68–1.88), a rate quite comparable to adult epilepsy patients [98, 99].

A very well-established risk factor for SUDEP is the presence of generalized tonic-clonic seizures (GTCS). Patients with three or more GTCS per year have a 15-fold increase in the risk of SUDEP. This is the basis of the recommendation for clinicians to undertake appropriate and patient preferred management strategies to reduce the risk of GTCS [100]. Early onset of epilepsy, refractory epilepsy with poor response of multiple antiseizure medications, and developmental delay/intellectual disability are putative risk factors in children [101, 102]. Genetic epilepsies are a risk factor for SUDEP. Dravet syndrome due to SCN1A mutation is a well-described genetic epilepsy with a higher risk for SUDEP. Other genetic syndromes that can be associated with SUDEP include 15 q duplication, CDKL5, PCH19, and ring chromosome 20 [102].

The pathophysiologic mechanism of SUDEP is still unknown despite extensive research [103]. In a prospective multicenter epilepsy monitoring study, post-convulsive central apnea (PCCA) but not ictal central apnea was associated with SUDEP [104]. PCCA occurred concomitantly with asystole. Postictal generalized EEG suppression (PGES) likely represents augmented activity in inhibitory neuronal networks as a response to seizure activity. This can occur in both focal and generalized seizures. Although some association between prolonged PGES after GTCS and SUDEP has been noted, the relationship remains uncertain [105, 106]. SEEG confirms the absence of cerebral electrical activity during PGES. In a SEEG study by Marchi et al., PGES was associated with upper extremity tonic posturing and oral tonicity (mouth opening and/or tonic vocalization during the tonic phase). The authors hypothesize that a tonic discharge affecting the bulbar nuclei in the brainstem results in laryngospasm [107] (Fig. 49.6).

Attempting to understand the mechanisms that lead to SUDEP are important for establishing strategies to mitigate the risks. First and foremost, improved seizure control achieved with optimization of medical management, dietary therapy, neurostimulation, or epilepsy surgery does reduce the risk of SUDEP [100, 108]. Some studies have demonstrated decreased risk of SUDEP over time with VNS, while others have not [36, 109]. A reduced SUDEP rate of 2/1000 patient stimulation years has been demonstrated with RNS compared to rate of 6.3–9.3/1000 in patients considered for epilepsy surgery [110]. The role of patient supervision has been well established and is the basis for the recommendation in this regard in the SUDEP practice guideline. This may include direct supervision or a listening device [100]. A variety of seizure detection devices are available exhibiting varying degrees of sensitivity and specificity [111, 112]. Multimodal devices that include electrodermal activity and accelerometry are optimal [113, 114]. Evidence supports prone positioning during sleep as risk factor for SUDEP

[115]. This finding has promoted some to call for a "Back to Sleep" movement for epilepsy similar to the highly successful campaign that reduced deaths due to sudden infant death syndrome (SIDS) [116, 117]. Asphyxiation from face down positioning with obstructed breathing due to bedding material may be factor in SUDEP related to prone positioning. Low air flow lattice pillows slow the rise of CO2 compared to conventional pillows during simulated rebreathing which may mitigate the risk of asphyxiation [118].

Epilepsy and Comorbid Sleep Disorders

Insomnia is common in epilepsy patients occurring over one half of patients surveyed. It is important to evaluate for circadian rhythm disorders such as delayed sleep phase syndrome which can present as insomnia [119, 120]. Melatonin can improve sleep in children with epilepsy without adversely affecting seizure frequency [121]. Treatment should be focused on sleep hygiene and cognitive behavioral therapy for insomnia [120].

Obstructive sleep apnea (0SA) occurs in epilepsy patients with a prevalence ranging from 7.7% to 75.7% based on a recent meta-analysis of 19 heterogeneous studies [122]. Eighty percent of children with epilepsy screened by clinical history and questionnaire exhibited sleep disruption due to OSA [123]. OSA can be associated with worsened seizure control. Worsening epilepsy in adults has been associated with a higher apnea hypopnea index and evidence of excessive daytime sleepiness. Onset of OSA symptoms coincides with increased seizure frequency and status epilepticus [124]. CPAP treatment can result in reduced interictal epileptiform activity [125]. Improved seizure control has been documented in many studies with CPAP treatment with 50% responder rate of greater than 70% in one study [126–128]. Improved seizure control was confirmed with CPAP treatment in a meta-analysis by Lin et al. [122]. Surgical treatment of OSA (tonsillectomy/adenoidectomy) in children with epilepsy resulted in seizure freedom in 37% [129].

In patients with epilepsy daytime sleepiness is very commonly reported. This is often attributed to the effect of antiseizure medication, but when studied it is more likely related to comorbid sleep disorders [130]. Factors associated with epilepsy such as number and type of antiseizure medications, seizure type, and seizure frequency were not correlated. Similar findings for children with epilepsy are noted [131].

In adult patients with epilepsy, 15% met criteria for periodic limb movement disorder of sleep (PLMDS) and 17% exhibited periodic limb movements. Restless leg syndrome (RLS) occurs in 18–35% of adult epilepsy patients [130]. In a study of 40 children with epilepsy who underwent polysomnography due to various sleep complaints, 10% had periodic limb movements of sleep [132]. Sleep disturbances in epilepsy patients are common and result in significant quality of life impairment. These conditions are often treatable resulting in improved quality of life [133, 134].

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Autism Spectrum Disorder

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Abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
ASD	Autism Spectrum Disorder
ASHS	Adolescent Sleep Hygiene Scale
ATN	Autism Treatment Network
BEDS	Behavior Evaluation of Disorders of Sleep
BRQ	Bedtime Routines Questionnaire
CBT-I	Cognitive Behavioral Treatment for Insomnia
CSHQ	Children's Sleep Habit Questionnaire
EEG	Electroencephalogram
FISH	Family Inventory of Sleep Habits
GABA	Gamma-Aminobutyric Acid
GI	Gastrointestinal
IQ	Intelligence Quotient
MSPSQ	Modified Simonds and Parraga Sleep Questionnaire
OSA	Obstructive Sleep Apnea
PLMS	Periodic Limb Movement in Sleep
PSG	Polysomnography
REM	Rapid Eye Movement
RLS	Restless Legs Syndrome
SDSC	Sleep Disturbance Scale for Children
SOL	Sleep-Onset Latency
SSRI	Selective Serotonin Reuptake Inhibitor
TD	Typically Developing

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Autism Spectrum Disorder Defined

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by impaired social interaction and communication and restricted/repetitive behaviors and interests [1]. Individuals with ASD experience high rates of co-occurring medical and psychiatric conditions [2–5], with over 95% of children with ASD experiencing at least one significant co-occurring condition and most experiencing multiple comorbidities [6–8]. In particular, children with ASD experience high rates of co-occurring sleep disorders [1], which can exacerbate core symptoms. There is considerable variability within the ASD population in terms of symptom severity and associated language and cognitive functioning. Approximately 30% of children with ASD have intellectual disability, with minimal language or verbal communication [9, 10], while 44% have average/above-average intellectual functioning [9]. Significant heterogeneity in clinical phenotypes makes identifying etiologic underpinnings and broadly effective treatment options challenging. ASD has an estimated prevalence [11] rate of 1 in 59 children [9] and annual costs (medical, direct non-medical, lost productivity) are estimated at $268 billion for 2015 and $461 billion for 2025 [12].

Epidemiology of Sleep Problems in ASD

Prevalence

Between 50% and 80% of children with ASD experience sleep problems [13–16]. Recent results from the largest epidemiological study of ASD risk factors and health found that 78% of children with ASD (aged 30–68 months) experienced parent-reported sleep problems [17]. A recent meta-analysis found that children with ASD experienced worse sleep efficiency, received ~32.8 fewer minutes of total sleep per day, and took ~10.9 minutes longer to fall asleep (assessed by actigraphy and polysomnography) than typically developing

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(TD) children [18]. Similar conclusions were reported in another meta-analysis: children with ASD demonstrated significant sleep disturbance as assessed by both objective and subjective measures [19].

Insomnia, defined as difficulty falling asleep or maintaining sleep, is the most common sleep disorder in children with ASD [15, 18, 20], with ~50% of children with ASD experiencing significant difficulty falling asleep [21, 22]. Although some research suggest that children with ASD may experience circadian rhythm disturbances [23–25], supporting evidence remains limited. A recent study examined rates of specific sleep disorders by reviewing military system health record data from 48,762 children with ASD (2–18 years of age). Results indicated that sleep disorder not otherwise specified and insomnia were the most common diagnosed sleep disorders (21.7% and 9.5%, respectively), followed by sleep-disordered breathing (9.3%), parasomnias (1.5%), restless legs syndrome (RLS;0.7%), and circadian rhythm disorder (0.6%) [26].

Developmental Course

Difficulties with sleep emerge in early childhood and persist across the ASD lifespan. A 10-year prospective longitudinal study found no differences in sleep between infants with and without later ASD diagnoses. However, children with ASD demonstrated significantly shorter sleep duration and more nighttime awakenings than TD children by 30 months of age. Although both groups demonstrated decreases in total sleep time over childhood, the ASD group continued to obtain less sleep than the TD group at each subsequent time point [27]. A 6-month longitudinal study also found that young children (aged 24–66 months) with ASD received less total sleep over time than TD children or those with intellectual disabilities without ASD [28].

Persistent sleep problems in school-aged children and adolescents with ASD have also been demonstrated. A longitudinal population-based study of school-aged children found that children with ASD experienced higher prevalence of sleep problems (39%) than TD children (3.6%), and those problems were less likely to remit over 4 years [29]. In a 2-year longitudinal study, among children with ASD with sleep problems at baseline (78%), the vast majority (91%) experienced persistent difficulties at follow-up [30]. Similarly, in children aged 6–12 years, chronic sleep problems were more prevalent in children with ASD (76%) than in those without ASD (30%), with decreases in sleep duration and sleep efficiency over 1 year [31]. In a recent longitudinal study, 68.4% of young children (aged 2–3 years) scored within the clinical range for sleep problems at baseline, compared to 70.8% of older children (aged 4–10 years). Across the entire sample, 22.9% showed worsening of sleep problems over 3½ years, 45.6% had stable sleep, and 31.5% showed improvement [32]. Although the majority of studies focus on younger children with ASD, evidence suggests that sleep disturbance persists into adulthood. Prevalence of sleep disorders in adults with ASD may vary as a function of age. For instance, in young adults (aged 15–25 years) with ASD, one study showed that 80% experienced objective sleep disturbance [33], while another evaluating slightly older younger adults (aged ~27 years) reported that 75% experienced disturbed sleep. In a study on adults with ASD across the lifespan (aged 23–50 years), reports of sleep disturbance were lower (41%) [34]. Despite some inconsistences in the literature, it is clear that sleep disturbance is a lifelong problem in ASD.

Correlates

Understanding factors associated with sleep problems among children with ASD may offer insights into their causes and consequences. Several cross-sectional studies have identified such factors (see Table 50.1; for a review, see [35, 36]). Regarding diagnostic features, studies report significant cross-sectional associations between sleep problems and overall ASD symptom severity [37–40]. Specifically, sleep difficulties are correlated with social impairment [37, 39, 41, 42], communication difficulties [39, 43], and stereotyped and repetitive behaviors [44–46]. Finally, sensory difficulties, particularly over-responsivity, are linked to various sleep problems [47, 48]. Although the direction of effect is unclear, children with ASD who experience sleep difficulties are characterized by more severe ASD symptom profiles.

Emotional and behavioral problems are associated with sleep difficulties in children with ASD. Difficulties across both internalizing and externalizing symptom domains are correlated with poor sleep in children with ASD [38, 49]. Regarding internalizing symptoms, anxiety is strongly associated with a wide range of sleep problems in children and adolescents with ASD [47, 50–52]. Anxiety and hyperarousal may play a causal and maintaining role in insomnia among children with ASD [36, 47, 53], similar to findings in the general population. Depression and affective problems [54], as well as behavioral dysregulation [50, 55–57] (e.g., challenging behaviors, inattention, hyperactivity, and aggression), are also correlated with sleep difficulties in children with ASD.

In the general population, sleep problems are related to decreased cognitive functioning among children [58]. However, similar evidence in children with ASD is limited and somewhat mixed. Some studies report associations between shorter sleep duration and poor sleep [43, 59]. However, some studies report no significant associations between sleep problems and IQ [32, 56], while others found

Table 50.1 Summary of studies evaluating correlates, predictors, and long-term outcomes of sleep disturbances in children with ASD

	Cross-sectional studies	Longitudinal studies	
	Correlate of sleep problems	Predictor of sleep problems	Consequence of sleep problems
Diagnostic features			
Autism symptom severity	[37–40, 49, 148]		
Social impairment	[37, 39, 41, 42, 56]		[50]
Communication impairment	[39, 43]		
Repetitive behavior	[32, 44–46, 56]		
Sensory problems	[32, 47–49]	[32]	
Cognitive functioning			
IQ	[43, 49, 59]		
Medical comorbidities			
Gastrointestinal problems	[49, 149]		
Emotional functioning			
Anxiety	[38, 47, 49–52]	[31]	[50]
Depression	[42]		
Behavioral functioning			
Aggression	[32, 38, 75, 150]	[61]	
Hyperactivity/inattention	[32, 56, 75]		[32]
Challenging behaviors	[75, 151]		[60]

that higher IQ predicts greater sleep difficulties [49]. Future research is needed to clarify these issues and more fully examine the sleep/daytime cognition relationship in children with ASD.

In a hierarchical regression analysis of cross-sectional registry data from children with ASD enrolled in the Autism Treatment Network (ATN), Hollway and colleagues [49] evaluated 45 potential demographic and clinical correlates of sleep disturbance. Anxiety had the strongest relationship to sleep disturbance (with IQ, ASD symptom severity, sensory sensitivities, and GI problems also being associated) [49]. Overall (see Table 50.1), cross-sectional studies provide preliminary information regarding potential predictors and consequences of sleep disturbance in children with ASD, garnering interest in understanding causality and direction of effect.

Predictors and Consequences

Despite high prevalence of sleep problems among children with ASD, only a few studies utilized longitudinal designs to better understand the relationship between sleep and other factors. In two small studies of children and adolescents with ASD, sleep disturbance predicted anxiety at 1-year follow-up [50], and reductions in anxiety over 1 year were associated with improved sleep [31]. In a study monitoring 14 days of sleep, Cohen and colleagues [60] found that variability in sleep predicted daytime challenging behavior among individuals with ASD.

Another recent study in a large sample of 1045 children with ASD used predictive modeling to identify longitudinal relations among sleep problems and other variables. Aggressive behavior independently predicted the development of sleep problems over 1 year among children with no sleep concerns at baseline [61].

In another recent longitudinal study, associations between sleep and other variables were examined in 437 young children with ASD followed up over 3½ years. Path analysis revealed that sensory over-responsivity predicted the development of sleep problems over time for younger children (ages 2–3 years at baseline). However, sleep problems at baseline predicted later development of ADHD symptoms in younger children (aged 2–3 years at baseline) and somatic complaints in older children (ages 4–10 years at baseline) [32]. Aggression was correlated with sleep problems in cross-sectional analyses, but was not a significant independent predictor or outcome in longitudinal analyses [32]. Findings suggest that sleep quality is highly associated with daytime behavior among children with ASD; however, findings across studies are not entirely consistent with regard to timing and directionality. Further research is needed to disentangle the complex and potentially bidirectional relations among sleep and other clinical characteristics and indicators of functioning in children with ASD.

Sleep in Autism – Ontogeny of Sleep Problems in ASD

It is unknown whether ASD and sleep problems share underlying causal mechanisms, ASD symptoms contribute to greater sleep problems, or vice versa. The etiology of sleep problems is multi-factorial, involving a number of genetic, neurobiological, environmental, and behavioral factors (Fig. 50.1).

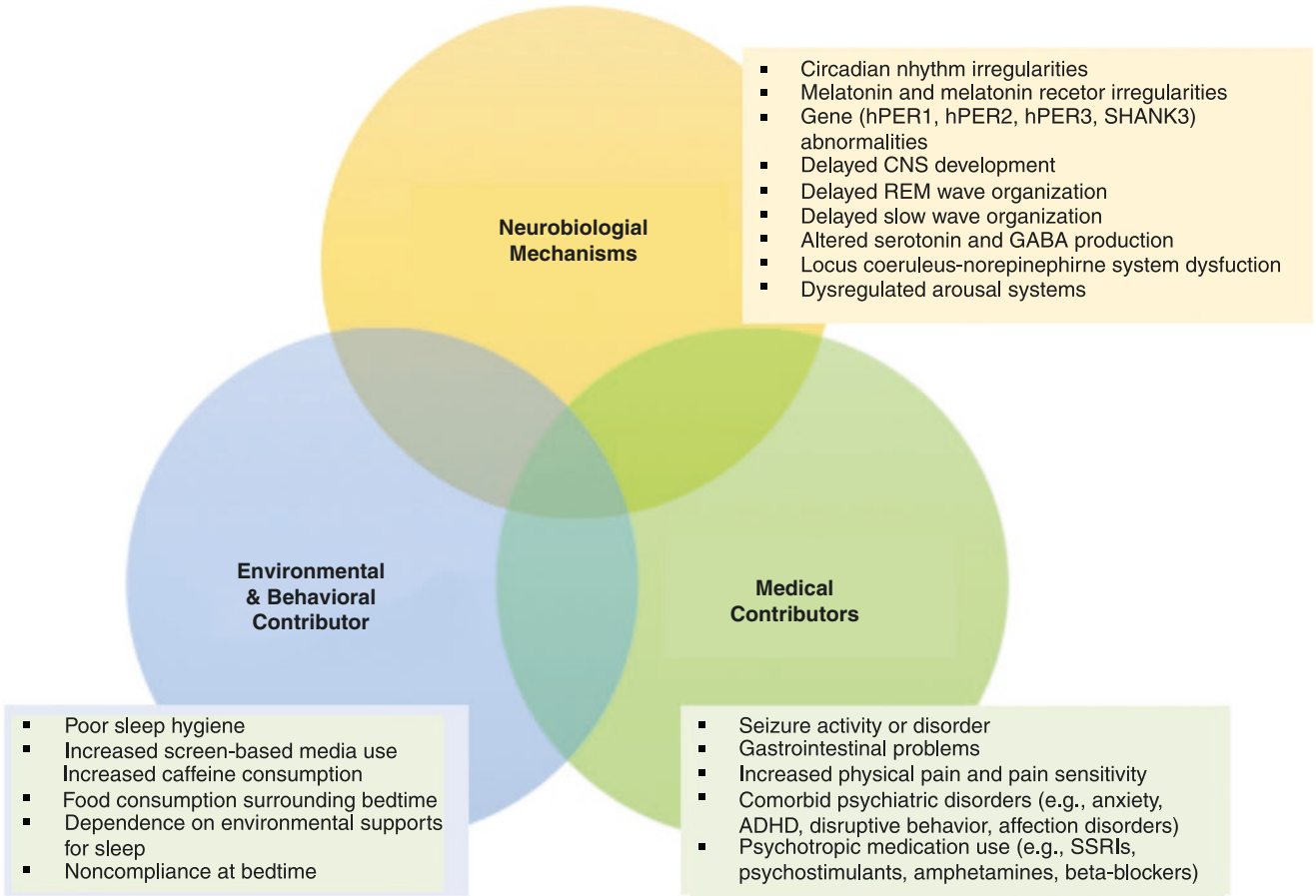

Fig. 50.1 Summary of etiological factors contributing to sleep problems in children with ASD

Neurobiological Mechanisms

Irregularities in genes affecting circadian rhythms and melatonin levels, sleep architecture changes, and sensory and arousal dysregulation are associated with sleep problems in ASD [62]. Sleep problems are linked with lower levels of melatonin/melatonin metabolites, variances in genes regulating melatonin, modified melatonin synthesis pathways, and altered responding in melatonin receptors [62, 63]. Irregularities in melatonin rhythm synchronization predict longer sleep latency, and low melatonin levels predict increased night awakenings. Sleep problems in ASD are associated with abnormalities in genes regulating synaptogenesis, synaptic pruning, circadian rhythms, and social communication, specifically hPER1, hPER2, and hPER3, and SHANK3 [63–65].

Sleep problems are partially attributed to delayed maturation of the central nervous system, slow wave, and rapid eye movement (REM) wave patterns [66–70]. Electroencephalogram (EEG) data suggest poor sleep stage differentiation in children with ASD compared to TD controls, based on findings of sleep spindles during rapid eye movement (REM) sleep [68]. This likely contributes to longer sleep latency, increased night awakenings, increased stage 1 sleep, and decreased non-REM sleep in ASD versus non-ASD controls [69]. Altered REM cycles are linked with changes in dream frequency and content [67, 68].

Physiological arousal may contribute to sleep problems [62]. The locus coeruleus-norepinephrine system, which provides the majority of the brain's norepinephrine, is strongly associated with executive functioning, hyper/hypoarousal, and sensory stimuli responsivity [71, 72]. Consequently, dysfunction in this system is also associated with sleep problems and, more broadly, may explain a specific profile of ASD with sleep problems, impulsivity, inattention, hyperactivity, and anxiety [62]. Sleep problems in ASD are associated with altered functioning in serotonin and GABA; regulation of these neurotransmitters is particularly important for regular sleep–wake cycles [70, 73].

Medical Contributors

Several physical and mental health disorders commonly experienced by children with ASD are associated with higher incidence of sleep disorders. Examples include seizures,

sleep apnea, and acid reflux, often a side effect of gastrointestinal issues, a common ASD medical issue [73]. Conditions associated with physical pain are associated with poorer sleep; one parent-report of youth with ASD found that pain predicted increased sleep problems, specifically sleep duration, parasomnias, and sleep-disordered breathing [74]. Psychiatric disorders associated with increased neurological attention, arousal, and sensory over-responsivity (e.g., attention-deficit/hyperactivity, anxiety, and disruptive behavior) are associated with increased sleep problems in ASD [47, 60, 75]. Regarding sensory arousal, sensory aversions to and avoidance of specific environmental stimuli have been linked with ASD and sleep problems [47, 48]. Some prescription medications targeting psychiatric disorders (e.g., psychostimulants, amphetamines, SSRIs) also interfere with falling/staying asleep. Given the high number of individuals with ASD taking prescription medications [76], their effect on sleep is important to consider. One study in 4- to 10-year-olds ($n = 1518$) found that prescribed sleep medications were associated with worse parent ratings of daytime behavior and quality of life [54].

Environmental and Behavioral Contributors

Behavioral causes of insomnia are the most common extrinsic cause of sleep problems in ASD across the lifespan [16, 77, 78]. Noncompliance surrounding bedtime, resistance of transitions, or attention-seeking behavior can delay bedtime and prevent caregivers from maintaining regular bedtime routines. Many parents practice poor sleep hygiene or implement multiple strategies to attempt to facilitate sleep in their children with ASD, such as lying in bed with them or including television or video games in the bedtime routine. This can unintentionally stall sleep, particularly when a child becomes dependent on these strategies to fall asleep [16]. Poor sleep hygiene has been associated with poor sleep in children with ASD to a greater degree than in children with ADHD or TD children [79]. In older children, daytime and bedtime screen-based media is problematic; it was associated with longer sleep latency and shorter duration in children with ASD [57], above and beyond children with ADHD or TD children [80].

Assessment

Objective Measures

Polysomnography

Although overnight polysomnography (PSG) is considered the "gold standard" objective measure of sleep, the invasive procedure proves difficult for youth with ASD and sensory-related difficulties [26, 54]. Primeau and colleagues [81] evaluated a systematic desensitization PSG protocol in children and adolescents with ASD (aged 2–25 years old). Features included pre-exposures to the equipment, in-home setup, and delayed hookup until parental approval of PSG equipment tolerance. Researchers also allowed ~2 hours for electrode application, applied leg/belt electrodes prior to more difficult placements (e.g., nasal cannula), and disguised conductive gels by covering them with colorful materials or using plastic caps instead of metal [81]. While this protocol was successful (PSG recording obtained for 144/161 children with ASD), replication is warranted.

Actigraphy

Actigraphy is a minimally invasive (i.e., traditionally a wrist-worn device) objective method for estimating sleep–wake patterns based upon physical activity. In children with ASD with sensory sensitivities, this objective sleep measure is often favored over PSG. Reed and colleagues [82] established an adapted actigraphy protocol for children with ASD aged 3–10 years and varying levels of cognitive functioning. Parents of older children with higher IQs were instructed to place the Actiwatch on their child's dominant wrist. Parents of younger children or children with lower IQs were instructed to place the Actiwatch on their child's dominant ankle (previously validated for TD children [83]). Malow and colleagues [84] evaluated a structured parent training program for actigraphy placement in children with ASD aged 2–10 years. This training included a hands-on demonstration with visual supports (e.g., graphic/descriptive details), post-assessment knowledge quiz, and follow-up telephone feedback to ensure proper actigraphy placement. In addition, this study tested a method for alternate actigraph placement in a t-shirt pocket on the child's nondominant shoulder [84, 85]. Studies utilizing actigraphy in ASD youth report minimal data loss (<20% [82]) and adequate compliance [16, 45, 84, 86–88].

Subjective Measures

Questionnaires

The Children's Sleep Habit Questionnaire (CSHQ) [89] is a widely used, comprehensive pediatric sleep assessment, originally intended for TD children. It has good psychometric properties, with internal consistency index (Cronbach alpha) of five subscales ranging from 0.50 to 0.87 for children with ASD aged 2–10 years [90]. Katz and colleagues [91] modified the CSQH into an abbreviated 23-item four-factor version using a large ATN sample of 2872 children aged 4–10 years. Despite potential clinical utility of the abbreviated CSQH [91], and its adoption by ATN as a primary sleep measure, further validation of its psychometric properties (validity/reliability) with ASD populations is needed. The Modified Simonds and Parraga Sleep

Questionnaire (MSPSQ) [92] is another sleep assessment tool for youth with ASD. When evaluated in 124 children with ASD aged 2–16 years, the MSPSQ had adequate psychometric properties (specificity = 0.70, sensitivity = 0.86) and was strongly correlated with the CSQH (r = 0.70, $p < 0.01$) [93].

The following sleep questionnaires are occasionally utilized in TD children, with promising psychometric properties within ASD populations: Sleep Disturbance Scale for Children (SDSC [94]), Behavior Evaluation of Disorders of Sleep (BEDS [95]), the Family Inventory of Sleep Habits (FISH [96]), Bedtime Routines Questionnaire (BRQ [97]), and Adolescent Sleep Hygiene Scale (ASHS [98]).

Sleep Diaries

In child ASD populations, daily sleep diaries are usually based on parent report. Variable standards exist regarding the duration that parents should use diaries to adequately capture their child's sleep behavior: 3 days [99, 100], 7 days [101], and 14 days (recommended and widely used approach [102, 103]). Lambert and colleagues [102] found that relative to PSG, parents reported significantly longer sleep-onset latencies (SOL) on sleep diaries. Prior studies in TD children found that compared to actigraphy, parents typically over report nighttime sleep duration and number/duration of nighttime awakenings, yet this pattern has not been observed in ASD caregivers [104].

Assessment Considerations

Assessing the function of sleep-related behaviors can be helpful for treatment planning. Assessment examines relationships between setting events (e.g., hyperaroused state), antecedents (e.g., pre-bed screen time), and consequences (e.g., parental co-sleeping) that may be maintaining sleep-related problems [105]. Prior studies demonstrate the benefit of using function-based assessment to inform development and tailoring of behavior sleep treatment [106, 107]. In conjunction with other subjective/objective measures, functional assessment could help clinicians and researchers identify factors associated with bedtime and sleep-related disruptive behaviors [108].

Treatment – Practice Pathway

Malow and colleagues [88] outlined a practice pathway for healthcare providers to address potential sleep difficulties in children with ASD (Fig. 50.2). Guidelines are based on a systematic review of 20 studies indicating that educational and behavioral interventions, as well as prescription melatonin, are most effective in treating sleep difficulties in ASD. Approaches such as massage therapy, weighted blankets, aromatherapy, and medication treatment with Risperidone or Mirtazapine did not have adequate evidence to support use. When the pathway was tested with providers at four medical sites, barriers identified included lack of time during medical visits for sleep screening and provider discomfort with sleep assessment. In response, additional provider resources were developed, including a short set of sleep screening questions, a checklist for medical contributors to insomnia, and a parent education pamphlet [88]. Further research should examine pathway effectiveness with these modifications.

The pathway recommends initial screening of all children with ASD. Children without sleep difficulties are recommended to be scheduled for one-year follow-up. Otherwise, providers are encouraged to gather information about possible medical contributions to sleep challenges (e.g., physical/psychiatric health, and medications), and refer patient to an appropriate professional. Simultaneously, providers determine whether families are good candidates for parent sleep education. Some parents may be experiencing circumstances that render them unable to deliver behavioral interventions without greater support. Furthermore, a child who is in crisis, at risk for nighttime injury due to sleep difficulty, or already taking multiple sleep medications may require referral to a sleep specialist. For well-suited family situations, however, parent education constitutes a free pamphlet outlining strategies for sleep hygiene and behavioral intervention, including worksheets to facilitate data collection on sleep behaviors [88]. Providers are recommended to reassess patients for sleep improvement using a standardized screening tool and parent report. Malow and colleagues [84] showed that children with ASD aged 2–10 years benefited from behavioral interventions by falling asleep more quickly. Persisting sleep problems, however, warrant referral to a sleep specialist and/or initiation of medication. The practice pathway recommends regular follow-up (e.g., 2–4 weeks later) to monitor progress. Once sleep problems resolve, follow-up frequency may be reduced to once per year [88]. More work is needed to evaluate pathway recommendations in youth with ASD.

Sleep Disorders

Insomnia

Development and Risk Factors

As described earlier, insomnia is highly prevalent among children and adolescents with ASD, impacting the quality of life of children and their families [94, 109]. Factors associated with manifestation of insomnia symptoms in children with ASD include inconsistent sleep schedules/bedtime routines, environmental factors (e.g., light exposure, noise), nightmares or night fears [110, 111]. As previously described, compared to TD youth, those with ASD may uniquely develop insomnia symptoms due to an increased predisposi-

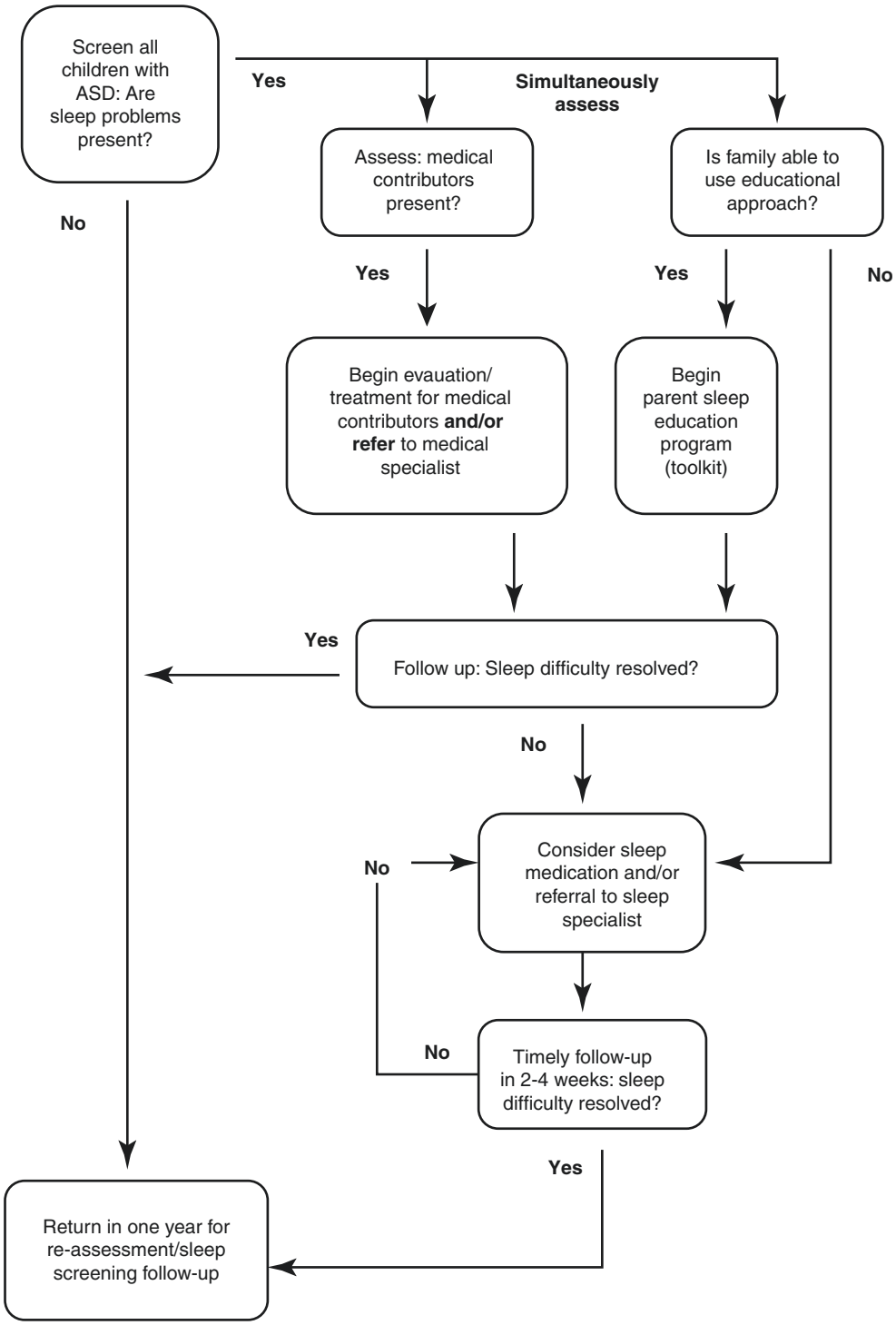

Fig. 50.2 Summary of practice pathway guidelines for children with ASD and insomnia

tion for hyperarousal and anxiety [48, 112]. Other risk factors associated with insomnia include severity of autism symptoms, gastrointestinal disturbances, allergies, iron levels, uncontrolled pain, developmental regression, conduct disorder, emotional problems, hyper and hypo-sensitivity to thermal stimuli, and hyperactivity [49, 61, 74, 109, 113–115].

Assessment

Initial assessment of insomnia (Table 50.2) in ASD populations should include a semi-structured interview to gather a detailed sleep history [116]. The following factors should be assessed: predisposing factors (hyperarousal, sensory difficulties), precipitating factors (e.g., worsening of comorbid symptoms, environmental stressors), and perpetuating fac-

Table 50.2 Summary of sleep assessments in children with ASD

Pediatric sleep assessment	Type of measure	Advantages for ASD populations	Disadvantages	Prior studies
Clinical sleep interview	Subjective	With the wide-ranging symptomology among youth with ASD, clinical interviews allow for clinicians and researchers to assess the unique factors precipitating and perpetuating sleep problems Assess for cultural and demographic (e.g., SES) barriers	Parents of youth with ASD are inundated with caregiving demands and an interview may be more of a strenuous time commitment Diagnostically, interviews are a beneficial measure, but they only capture subjective sleep history Clinical sleep interviews do not allow for clinicians or researchers to daily assess the sleep functioning of youth with ASD	[88, 118]
Sleep questionnaires	Subjective	Self- and parent-report measures are both cost- and time-efficient and place minimum burden on parents of youth with ASD Questionnaires are appropriate measures for screening sleep problems and for examining measuring treatment-related outcomes	There are only a few available pediatric sleep questionnaires that have been modified with strong internal consistency for ASD populations Like interviews measures, questionnaires provide great diagnostic information but are not adequate progress monitors of daily sleep functioning	[93, 103]
Sleep diaries	Subjective	Sleep diaries parents to efficiently report additional information related to antecedents, behaviors, and consequences Allows for the subjective report of sleep quality in addition to other aspects of nighttime sleep Able to include information relative to ASD and other comorbid symptoms impacting nighttime routines and sleep daily	Daily use of sleep diaries may be laborious for families already inundated with demands, particularly those overwhelmed with bedtime problems Past studies have found discrepant reporting of sleep patterns (e.g., SOL) by parents when compared to objective measures	[84, 102]
Polysomnography	Objective	Gold standard approach for identifying sleep-related problems that may not be detectable, or less reliably detected by other measures, including problems specific to stages of sleep, sleep latency, total sleep duration, and sleep-disordered breathing Used typically within clinical practices Ambulatory PSG allows for children to use measure within the home setting	Given the sensory difficulties among youth with ASD, it is often difficult for many youths to tolerate the placement, and maintenance during sleep duration, of several electrodes attached to the scalp and face Typically conducted within an unfamiliar laboratory, since portable PSG is less commonly used with this population PSG abnormalities may occur if a desensitization process to foster acclimation to the novel environment is not introduced Younger children take longer to acclimate to the PSG equipment and experience higher levels of intolerability	[26, 59, 67, 81]
Actigraphy	Objective	Allows researchers to obtain objective measure of children's home functioning relative to timing, duration, and continuity of sleep when parent reports on daily diaries are discrepant Less intrusive than PSG and tolerance is higher in the ASD population	Past studies have highlighted that Actiwatches may malfunction and result in data loss	[82, 84, 152]
Videosomonography	Objective	Allows for researchers to behaviorally code both child and adult behaviors within the home environment. This method is the most beneficial for behavioral sleep problems that are difficult for parents to convey or monitor	This measure is only typically used to assess parent–child interactions within the context of research and not clinical practice This objective measure has been primarily utilized with young children with ASD.	[83, 153]

tors (e.g., ASD-related behaviors that modulate chronicity) [117]. Goldman et al. [118] and Malow et al. [116] recommend that information should be gathered related to developmental, psychological, or complex medical histories common within ASD populations (e.g., hyperactivity, seizure disorder, and gastrointestinal issues). Inquiring about precipitating factors may include exploring acute occurrences that may trigger insomnia, such as current medications, new life stressors, newly onset illnesses or hospitalizations, or recent changes in their routine [116, 118–120]. Although perpetuat-

ing factors can be assessed using other measures like questionnaires and sleep diaries, a clinical interview allows for in-depth understanding of co-sleeping, parent behaviors, and daytime functioning [88, 118, 121].

Treatment

Behavioral treatments for insomnia have been widely adopted and evaluated in ASD (see Table 50.3; for an in-depth review, see [122]). Such treatments include sleep hygiene education, graduated extinction/extinction, bedtime fading/sleep restriction, visual support, bedtime pass, and chronotherapy [79, 123]. Given associations between nighttime anxiety/hyperarousal and sleep disruption in ASD, prior research has evaluated scheduled calming periods within bedtime routines, relaxation strategies, and distraction-based strategies [124, 125]. For ASD children and adolescent populations, sleep hygiene is the most widely used intervention, often delivered alone or within a multicomponent behavioral treatment protocol [56, 84]. Other treatment approaches (e.g., pharmacological, alternative therapies) for insomnia in

Table 50.3 Summary of sleep interventions currently used in children with ASD

Pediatric sleep interventions	Purpose of intervention	Relevance for ASD Populations	Future Directions	Prior Studies
Sleep hygiene	Sleep hygiene addresses important bedtime factors for pediatric populations with ASD that include food intake, caffeine consumption, environmental noise, light exposure, exercise, electronic and media use, and temperature/thermal comfort.	Sleep hygiene is a sleep intervention that has been widely used with young children to adolescents with ASD. For younger children with ASD, they notably have hyper-responsivity to sensory stimuli causing temperature sensitivity. Conversely, adolescents with ASD have been found to have reduced thermal sensitivity that impacts their perceptions of their thermal comfortability level during sleep. In addition, excessive use of electronic devices is a relevant issue impacting bedtime for both adolescent and children as young as 2 years old with ASD. Beyond the harmful artificial light exposure, the content of television shows and video games may uniquely induce nighttime arousal in youth with ASD. Gastrointestinal issues (GI) are very common among ASD populations and have caused notable sleep difficulties.	Opposed to the standard implementation of sleep hygiene recommendations, a health alternative could be incorporating the use of unstimulating media close to bedtime into sleep hygiene. However, the direct causation of sleep disruption due to media content versus light exposure from devices, has not been separately analyzed and should be considered in future research. Modifications to sleep hygiene recommendations addressing GI issues may include consuming smaller but more frequent meals and an elevated head position.	[82, 84, 87, 124, 154, 155]
Extinction/ Graduated extinction	Extinction is a behavioral strategy that requires parents to ignore all bedtime disruptions. Additionally, the parent places the child back into their bed while minimizing interactions with their child throughout the night. For graduated extinction/fading, parents as a stimulus are gradually faded out of their child's sleep environment to help them sleep independently at night.	Extinction has been employed as intervention to reduce problem behaviors in ASD youth populations. Relative to sleep problems, this intervention has been employed in multicomponent sleep interventions (e.g., integrated into parent sleep education and training).	This intervention has been primarily utilized with youth (ages 2–10) with ASD. Future studies may be employed to assess the effectiveness of this intervention component with children and adolescents aged 10–17.	[82, 84, 108, 125]
Relaxation strategies	Relaxation strategies may include breathing, mindfulness, or distraction-based strategies.	Anxiety and hyperarousal may uniquely play an integral role in maintaining insomnia symptoms among ASD pediatric populations. So far, relaxation has been incorporated into a brief sleep education and brief clinical consultation for children (ages 5–12) and adolescents (ages 13–18) with ASD.	Further research is warranted to examine clinically embed calming activities (e.g., relaxation/distraction strategies) that are both brief and predictable into bedtime routines.	[56, 124, 125]

(continued)

Table 50.3 (continued)

Pediatric sleep interventions	Purpose of intervention	Relevance for ASD Populations	Future Directions	Prior Studies
Sleep restriction/ bedtime fading	Faded bedtime occurs by using sleep diary data to determine whether a bedtime should be earlier, or delayed due to response cost, by 15–30 minutes until the desired bedtime is achieved.	Faded bedtime has been used in isolation, and within a multicomponent sleep education intervention, for youth with ASD This standalone intervention has been shown to be effective for youth with ASD, sleep problems, and severe problem behaviors (e.g., self-injury) within an inpatient unit. Additionally, standalone bedtime fading was robustly effective in reducing sleep problems in children 2–8 years old using an in-home behavioral parent training framework delivered by day treatment staff. Two multicomponent studies embedded bedtime fading into sleep education didactics and brief consultation, and another study compared bedtime fading to positive routines (basic sleep hygiene).	Bedtime fading has been primarily used with smaller sample sizes, so results may not generalize to a larger population. Also, bedtime fading has not been implemented with older adolescent populations. For ASD populations, it would be beneficial to see if adolescents or their parents would effectively implement bedtime fading strategies.	[87, 125, 133, 154, 156–158]
Chronotherapy	Chronotherapy involves systematically delaying a child's bedtime until the desired bedtime has been established.	This strategy is typically reserved for adult populations but was previously utilized with a young 8-year-old girl with ASD, delayed sleep–wake schedule, and food refusal within an inpatient setting.	Only an individual case study has been conducted using this method to treat circadian rhythm disorders among ASD populations. It is recommended that this area is further explored.	[133]
Visual supports (bedtime routine)	In the context of sleep, visual schedules are used to help children and adolescents with ASD anticipate and maintain a regular bedtime routine. Social stories use pictures organized into a brief story format to teach and establish a new social routine.	Pediatric populations with ASD have relevant heterogeneity related to symptom severity, communication difficulties, developmental delays, and cognitive functioning. For those with communication difficulties and decreased cognitive functioning, visual schedules and social stories are established interventions for teaching new social routines. Tailored multicomponent behavioral interventions addressing sleep concerns have begun to incorporate visual schedules to support adherence to bedtime routines. In addition, a prior study utilized a tailored social story to help a young child with ASD, language delays, and a learning disability learn a new bedtime routine.	Though included within multi-component interventions, visual supports have not been directly evaluated relative to treating sleep problems. Future studies conducting comparative analyses of standalone visual supports and multicomponent sleep interventions are warranted.	[87, 159]
Bedtime pass	Parents use a bedtime pass to address bedtime resistance. The pass is a small card that is given to the child to redeem one nighttime request (e.g., a hug or kiss from their parents, a drink of water, or a brief moment outside of the bedroom to use restroom). This strategy is often used in tandem with extinction (e.g., ignoring a child's requests, the bedtime pass has been returned).	Similar to extinction, the bedtime pass has been employed in multicomponent sleep interventions (e.g., integrated into parent sleep education and training).	Further research is warranted to examine whether the bedtime pass is a useful intervention as a standalone intervention for adolescent populations.	[82, 84, 125]

children with ASD are generally not recommended [116]. However, melatonin is the most widely used pharmacological intervention [36, 123, 126–128]. Massage therapy has also been evaluated as a potential treatment, but findings documenting its effects on sleep are inconsistent, with one study showing no post-treatment sleep improvement in children with ASD aged 3–10 years of age [129], and another showing reduction in disruptive sleep behaviors (e.g., self-stimulating, getting out of bed) in young children with ASD aged 3–6 years [130].

Within the extant literature on insomnia treatment in children with ASD, there are several limitations and methodological weaknesses (Table 50.4). Limitations include a lack of sample diversity (e.g., race, gender, age, cognitive levels, and comorbid conditions), and a lack of comparison to adequate treatment controls. Thus, in order to more fully understand the impact of sleep across the spectrum of youth with ASD, future research should explore treatment within more diverse samples, and compare treatment efficacy to control groups matched on non-specific treatment factors (e.g., expectancy, time spent with therapist). Finally, we argue that there is a need to explore other combination treatments for insomnia beyond strictly behavioral programs. For instance, while no published studies have evaluated the well-established Cognitive Behavioral Treatment for Insomnia (CBT-I) in youth with ASD, pilot work conducted in our lab [131] suggests that CBT-I is efficacious for improving sleep and associated problematic behavior in school-aged youth with ASD. Evaluations of CBT-I with appropriate control groups will improve understanding of insomnia treatment-specific components that alleviate sleep disturbance and associated core symptoms in youth with ASD.

Circadian Rhythm Disorders

Development and Risk Factors

Delayed sleep phase is the most common circadian rhythm disorder in ASD [24]. Relative to children with less severe ASD symptoms, children with more severe ASD may be at increased risk of developing a disordered circadian phase due to neurobiological mechanisms (e.g., increased light sensitivity, increased abnormalities in melatonin secretion, and lower nocturnal melatonin levels). Additionally, the timing phase of melatonin may lead to advanced sleep phase or irregular sleep–wake syndromes [92]. Unfortunately, distinguishing between circadian rhythm factors and insomnia is difficult in ASD [23] due to unclear differentiation between delayed sleep phase and insomnia symptoms. For example, actigraphy and sleep diaries may reveal delayed sleep onset and final awakening, but also multiple nighttime awakenings and early morning awakenings [24, 92].

Assessment and Treatment

Circadian rhythm disorders are widely examined in adult populations and treated through pharmacological interventions (e.g., melatonin), chronotherapy, and sleep hygiene. Further research is necessary to better understand the prevalence of circadian rhythm disorders in youth with ASD prior to development and evaluation of valid treatment strategies in this unique population [100, 132, 133].

Sleep-Disordered Breathing

Development and Risk Factors

Childhood sleep apnea is primarily caused by hypertrophy of the adenoid/palatine tonsils [134]. Obstructive sleep apnea (OSA) is more common in the ASD population than in community samples [135, 136]. OSA involves upper airway obstruction and is characterized by snoring, choking, mouth opening, leaning back the head, and difficulty breathing while sleeping. Some children with ASD may be predisposed to OSA, as a large tongue, enlarged tonsils, and obesity are known risk factors [137]. In youth with ASD, sleep-disordered breathing predicts levels of autism symptomatology, including social interaction problems and stereotyped behavior [37].

Assessment and Treatment

Best practice for assessing sleep apnea is nocturnal PSG. However, as described earlier, it may be important to modify PSG procedures (e.g., disguise conductive gels, obtain parental approval of equipment tolerance) in youth with ASD, to account for sensory difficulties. Providers should also consider assessing for inattention and hyperactivity, as some children with sleep apnea exhibit ADHD symptoms that resolve with sleep apnea resolution [37, 137]. Interventions for OSA include surgical removal of tonsils and adenoids. Murata and colleagues [138] found that sleep and ADHD symptoms improved following this procedure, as did withdrawal, social symptoms, hypersensitivity, and stereotyped behaviors [54]. Given evidence showing OSA impairs frontal lobe functioning [139], surgical treatment of OSA likely reduces disruptions to frontal lobe activity and leads to associated improvements in these areas of functioning [138].

Table 50.4 Demographics of study samples in intervention studies in youth with ASD

Reference	Setting/Format	Sample	Cognitive level	Age	Design	Treatment approach	Race/Ethnicity/ Nationality
[1]	In-home/parent training	6 children with developmental delays and ASD	Not reported	2.5–6.5 years old	Single case design: MBL	Bedtime fading and positive routine	Not reported
[2]	Inpatient unit/staff implementation	1 child with developmental delay and ASD	Not reported	4-year-old	Single case design: AB design	Bedtime fading	Not reported
[3]	Outpatient clinic/parent training	3 children (1 typically developing and 2 with ASD)	Not reported	9-year-olds	Single case design: Non-concurrent MBL	Graduated extinction and sleep education	Not reported
[4]	Outpatient clinic/Parent training	33 children which with ASD	*n* = 13: IQ >70; *n* = 20: IQ <70	2–6 years old	Randomized control trial	Multicomponent intervention: Sleep hygiene, Graduated extinction, Bedtime fading, and Visual supports	Black: 4; Asian Indian: 1; White: 24; Hispanic: 2; Multiethnic: 2;
[5]	Pediatric clinic/parent training	23 adolescents with ASD	All IQ >70	11–18 years old	Pilot study (pre-post)	Multicomponent intervention: Sleep hygiene, Visual schedule (bedtime), Relaxation strategies	White: 22 Other: 1
[6]	Pediatric clinic/parent training (individual and group)	80 children with ASD	*n* = 42: IQ >70; *n* = 38: IQ <70	2–10 years old	Randomized control trial	Multicomponent intervention: Sleep hygiene, Visual schedule, Bedtime pass, Extinction	White: 63 Other: 17
[7]	Remote/parent training (telehealth)	3 children with ASD	*n* = 3: IQ >90	8–9 years old	Case-series design	Multicomponent intervention: Sleep hygiene and bedtime fading	White: 3
[8]	Remote/Parent training (telehealth)	1 child with ASD, learning disability, receptive speech/language delays	Not reported	4-year-old	Case study	Social story (bedtime routine); graduated extinction	Not reported
[9]	Pediatric clinic/parent training	61 children with ASD and co-occurring ADHD	Not reported	5–13 years old	Randomized control trial	Multicomponent intervention: Graduated extinction; relaxation strategies; Bedtime pass	Not reported
[10]	Inpatient unit/staff implementation	4 children with ASD	Not reported	5–8 years old	Not reported	Bedtime fading with response cost	Not reported
[11]	Inpatient unit/staff implementation	1 child with ASD	Not reported	8-year-old	Case study	Chronotherapy	Not reported
[12]	Pediatric clinic/parent training (group)	15 children with ASD	Not reported	3–10 years old	Pilot study	Multicomponent intervention: Graduated extinction, Sleep hygiene, Visual supports, Extinction	Black: 4 Asian: 1
[13]	Pediatric clinic/parent training (group in-person or online)	23 children with ASD	Not reported	4–12 years old	Pre-post quasi-experimental	Sleep hygiene	Not reported
[14]	In-home/parent training	3 children with ASD	Not reported	4–8 years old	Single case design (non-concurrent MBL)	Bedtime fading	White: 3

Sleep Movement Disorders

Development and Risk Factors

Periodic limb movement in sleep (PLMS) is characterized by involuntary, stereotyped leg movements while sleeping. RLS causes uncomfortable sensation in the legs while still awake, stimulating an uncontrollable impulse to move the legs, often disrupting sleep onset. Relative to children without ASD, children with ASD have increased prevalence of PLMS and RLS [140, 141]. Youssef and colleagues [140] reported a prevalence of PLMS of 47% in ASD compared to 8% in TD children. PLMS is often found in RLS, but the reverse is not true [142].

Assessment and Treatment

Sleep movement disorders are first assessed through a thorough sleep–wake history to determine possible underlying causes. Gathering information about medication is also critical, as common ASD medications (e.g., Risperidone, SSRIs) may exacerbate PMLS or RLS [137]. Iron supplements show some promise in treating PMLS and RLS in children with ASD. In one study [143], 24 young children with ASD and RLS and low iron levels were given 6 mg of elemental iron per kg per day over 8 weeks. Parent reports indicated that 29% showed improvement in sleep quality, but more work is needed to validate these results [143].

Parasomnias

Development and Risk Factors

Parasomnias include sleepwalking and sleep terrors, confused arousals, nightmares, and REM sleep behavior disorder [144]. REM sleep behavior disorder involves violent dream enactment without loss of muscle strength, resulting in aggressive limb movement, crying, and/or yelling during REM sleep [145]. Parasomnias are more common in younger and school-aged children with ASD, but less common for adolescents with ASD [32, 146].

Assessment and Treatment

Assessment of parasomnias should include gathering of information regarding child awakenings/crying at night, verbalization of having scary dreams, struggle to calm when awoken, waking at small sounds [135]. Parasomnias are associated with daytime affective problems in children with ASD [15]; therefore, thorough assessment of daytime emotional difficulties is warranted. Comorbid ADHD symptoms are more likely in children with ASD and should also be assessed [136]. While further research is needed to determine optimal treatment of parasomnias in children with ASD, Thirumalai and colleagues [145] demonstrated preliminary effectiveness of clonazepam or melatonin at bedtime in treating REM sleep behavior disorder.

Bruxism

Development and Risk Factors

Bruxism refers to teeth grinding or clenching when an individual is asleep or awake. Bruxism is more common in children with ASD than in the general population [135]. There is some evidence that bruxism may be linked to increased stress in this population [147].

Assessment and Treatment

While research is limited, it is recommended that in children with developmental disabilities such as ASD, first-line assessment for bruxism should include dental screening, following by behavioral assessment (e.g., presence of teeth grinding) [147]. Recommended treatments include dental/medical interventions (e.g., prosthodontics) or behavior modifications (e.g., praise following sustained period of no bruxism) [147].

Summary, Conclusions, and Future Directions

Children with ASD experience a range of core neurodevelopmental and behavioral, and co-occurring symptoms. Sleep disruption, a major co-occurring symptom (particularly insomnia and sleep-disordered breathing), can exacerbate core ASD symptoms. While still unclear, the etiology of sleep disturbance in childhood ASD is likely multifactorial, as several factors are associated with worse sleep in this population, including social, communication, mood, sensory difficulties, hyperarousal, repetitive behaviors, neurotransmitter and hormone regulation, and genetics.

Development and evaluation of effective treatments for insomnia and other sleep disorders in children with ASD are critical. Unfortunately, heterogeneity in clinical phenotypes and high prevalence of medical comorbidities contribute to challenges in the assessment, treatment, and understanding of etiology of sleep and other disturbances in ASD. The current practice pathway for children with ASD [116] recommends behavioral and pharmacological treatments, but treatment for persistent sleep problems requires additional evaluation.

Future research should assess sleep problems and tailor treatments to more diverse samples of ASD children, taking into account ethnic, cultural, age, and family environment differences related to ASD symptomatology. Further, sleep treatments should be evaluated relative to appropriate control

groups to understand treatment-specific components of outcome efficacy. To date, insomnia treatments in ASD children have largely examined parent-reported sleep. Thus, future work should assess objective measures of sleep such as actigraphy, to better understand mechanisms underlying intervention efficacy. Finally, prospective longitudinal clinical treatment trials are needed to increase understanding of causes and consequences of disturbed sleep in children with ASD. Together, these considerations will improve understanding of etiology of sleep disorders, reduce sleep disparities, and inform sleep treatment development and dissemination in children with ASD.

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Sleep and Attention-Deficit/Hyperactivity Disorder

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Silvia Miano

Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
BD	Bipolar disorder
BECTs	Benign epilepsy with centrotemporal spikes
CAP	Cyclic alternating pattern
EF	Executive functioning
fMRI	functional magnetic resonance imaging
HLA	Human leukocyte antigen
IED	Interictal epileptiform discharge
MPH	Methylphenidate
MSLT	Multiple sleep latency testing
OSA	Obstructive sleep apnea
PFC	Pre-frontal cortex
PLM	Periodic limb movement
PSG	Polysomnographic
RLS	Restless legs syndrome
SCT	Sluggish cognitive tempo
SDB	Sleep-disordered breathing
SDPS	Sleep Delayed Phase Syndrome
SOI	Sleep-onset insomnia
SWA	Slow-wave activity
ToM	Theory of Mind

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders affecting about 5% of children and adolescents worldwide, persisting into adulthood in two-thirds of patients, especially when other psychiatric and sleep disorders are comorbidly present. Its symptoms usually start before 12 years of age, must be present in two or more settings, and negatively affect the child's social, academic, or occupational functioning [1]. Recent studies have focused on identifying endophenotypes that can assist in the early detection and prevention of ADHD. One of the most extensively researched areas in this domain concerns sleep issues. Interestingly, potential links between sleep and ADHD were first published in 1957 by Laufer and Denhoff [2], who wrote: "Generally, the parents of hyperkinetic children are so desperate over the night problems that the daytime ones pale in significance." Notably, high nocturnal activity was initially included (omitted in later revisions) in the criteria for diagnosis.

Children with ADHD are found to have a variety of sleep problems with a prevalence in the range of 50–74% [3]. Emerging evidence suggests a similarly high prevalence of sleep problems in adults with ADHD [4]. The ADHD symptomatology and possible comorbidities may disrupt sleep by increasing the probability of bedtime struggles or resistance; inadequate sleep hygiene; insufficient sleep disorder or poor sleep quality, and alternatively, each of these sleep perturbations may result in ADHD-like daytime behaviors. Contrary to adults, a sleepy or sleep-deprived child may display hyperactive, impulsive, inattentive, and disruptive behaviors [5]. Extant research has focused primarily on the impact of three sleep problems: sleep deprivation, sleep-disordered breathing, and circadian rhythm disturbances. Longitudinal studies suggest that sleep disturbances in early childhood may be an initial symptom of later ADHD or may be a causal factor in the development of future ADHD symptoms. Not just the presence of sleep disturbance, but also the stability of sleep disturbance over time, appears to be important in determining to what extent it is a risk factor for ADHD [6]. As such, although the relationship between sleep disturbances and ADHD appears to be bidirectional, there is support for the role of sleep disturbances as a predecessor to the disorder [6].

The most consolidated theory is that sleep deprivation and circadian disorders would lead to a deficit in pre-frontal cortex (PFC) executive functions, which would manifest as ADHD symptoms [7]. Sleep loss has similar daytime cogni-

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tive and behavioral costs caused by the occurrence of cerebral local "islands of sleep" in behaviorally fully awake subjects [7]. The more severe the daytime cognitive and behavioral consequences are, the more severe and chronic the sleep disorder is, as it has been demonstrated in several experimental human and animal studies on sleep deprivation [8]. Studies showed that even 1 hour of sleep restriction resulted in significant event-related potential changes in children across attentional tasks; they were more alert to negative stimuli and more susceptible to exaggerated aggressive impulses [9]. Executive functioning (EF) and emotional information processing are essential for the effective use of Theory of Mind (ToM). Cognitive ToM refers to inferences about others' beliefs and intentions, while affective ToM refers to inferences about others' emotions and feelings. Neuroimaging studies support the existence of a 'core neural network' for ToM, including the medial prefrontal cortex and the bilateral posterior temporal-parietal junction: the medial part controls affective ToM, while the dorsal part is engaged in the cognitive ToM [10]. EF is an umbrella term that describes the cognitive processes that enable one to engage in deliberate, goal-directed thought and action. EF and ToM are reported to be dependent on the prefrontal cortex, and they both develop in a similar fashion from early to middle childhood. A great deal of evidence directly links sleep duration and efficiency with all three EF subcomponents: working memory, inhibitory control and cognitive flexibility. Neural networks disrupted by poor sleep also correspond to brain areas involved in the affective and cognitive ToM network [10]. Preschool years are a critical period for the development of the PFC [11]. In past years, sleep-related slow-wave activity (SWA) has been recognized as having a crucial role in neuroplasticity, either in short-term synaptic downscaling, which sustains learning process, or in long-term plastic changes across the physiological development. Studies using high-density electroencephalography showed a task-related local increase of SWA during sleep after daytime learning [12]. The general topographical scalp distribution of SWA mirrors cortical maturation, with a maximal of SWA shifting from posterior regions of the scalp in early childhood, toward the frontal cortex in late adolescence [13]. This shift is specific for the SWA frequency range and remains stable across the night. In a small, non-naïve sample of children with ADHD, Ringli et al. [14] showed a maximum local increase of SWA over central brain regions rather than the frontal ones and interpreted this result as possible neuro-maturational delay in cortical activity. Children with ADHD display altered sleep-dependent memory consolidation, that is, sleep in children with ADHD benefits procedural memory more than in healthy children, whereas sleep did not benefit declarative memory in healthy children [15]. Moreover, it has been recently demonstrated that also contrast recognition performance was not improved after sleep, compared to wakefulness [16]. All these findings are in line with the hypothesis of an alteration of cortical maturation of both EC and ToM network in children with ADHD. Sleep loss may play an important pathogenetic role, inducing alteration of SWA in a crucial period of development.

In agreement with this view, several studies have demonstrated a causative role of early sleep deprivation and ADHD. Recently, in a large longitudinal study, the authors found that sleep problems at 3 years old predicted greater teacher-rated inattention and hyperactivity symptoms in elementary school [17]. A cross-sectional study conducted in a large sample of 15, 291 pre-schoolers in China found that delayed bedtime was significantly associated with a high risk of ADHD symptoms [18]. Scott and colleagues also found that age-specific reduction in sleep duration of >1 SD across a one-year time interval in pre-schoolers was a significant predictor of ADHD diagnosis, largely related to a later bedtime and more night-time awake [19]. The Quebec Longitudinal Study of Child Development indicated that sleep duration <10 h per night, especially before the age of 41 months, was associated with ADHD symptoms and lower cognitive functioning at age 6 years [20]. In a population-representative sample of 514 Chinese pre-school children recruited when in kindergarten, and reassessed after 3 years, the risk of probable ADHD was 15.5 per 100 for children with <8 h of sleep in kindergarten [21]. Gregory and O'Connor [22] found that sleep disturbances in early childhood (age 4 years) predicted attention problems in adolescence (age 15 years). The prospectively collected data from the Avon Longitudinal Study of Parents and Children showed that children with ADHD slept on average 13 mins less than the rest at night during infancy and continued to have shorter sleep during preschool and school years, although the difference was less marked. The ADHD group had more night-waking at every age, significantly from about 5 years [19].

Apart from unspecific data about sleep loss, the occurrence of specific major sleep disorders, such as obstructive sleep apnea (OSA) or increased motor activity as a precursor of restless legs syndrome (RLS) during preschool age, may predict later ADHD symptoms. Iron deficiency starting from infancy may induce increased numbers of periodic or nonperiodic limb movements during sleep (PLMs) in childhood, with increased risk of developing ADHD [23]. In addition, early respiratory problems during sleep may result in possible neuronal injury, specifically in the hippocampus and prefrontal cortex [24], and later manifest as behavioral dysfunction, much like ADHD [25]. Chervin and colleagues [26] found that snoring predicted hyperactivity 4 years later. Notwithstanding the well-established relationship between ADHD and interictal epileptiform discharges (IEDs) during sleep, there are no longitudinal studies assessing the effect of early IEDs or epilepsy affecting sleep on later ADHD symptoms (see below for further details). Moreover, the conse-

quences of these sleep problems (and any associated detrimental effects on brain development) may be most evident later in elementary school as that is when ADHD symptoms tend to become apparent as the academic and behavioral demands increase [17].

Importantly, relatively little is known about sleep among adolescents with ADHD. Deviations in biological processes occurring during this period may contribute to clinical outcomes. Given the significant alterations in sleep occurring during puberty, abnormalities in the developmental course of sleep changes in adolescence may have a profound impact on ADHD trajectories [4]. Notably, both high caffeine intake and overuse of electronics/internet have been associated with ADHD in adolescents [4]. In addition, studies investigating sleep and ADHD in adolescent-specific samples confirm that specific sleep disturbances (RLS, OSA, delayed sleep phase, and insomnia) are associated with ADHD symptoms. Teens diagnosed with ADHD may exhibit greater self-reported sleep problems than healthy peers [4]. Disrupted sleep may contribute to neuro-maturational abnormalities, neurocognitive deficits, and increased stress during a critical developmental period which in turn may worsen ADHD core symptoms and support the persistence of ADHD into adulthood [4]. Longitudinal studies of individuals with ADHD have provided evidence for neuro-maturational delays across adolescence, specifically, peak cortical thickness and surface area is delayed by 2–5 years, particularly in frontal, temporal, and parietal [4].

Several genes implicated in regulation of sleep have been investigated in ADHD population. In humans, the CLOCK genes have already been associated with the evening chronotype, as well as with some circadian and sleep disorders such as delayed sleep phase syndrome. Nevertheless, the CLOCK gene was neither associated with ADHD nor with chronotype, sleep duration, or sleep disorders in the most comprehensive and genome-wide association study [27]. It is plausible to expect that the relation between sleep/circadian rhythm phenotypes and ADHD may arise from a polygenic complex mechanism, involving several clock genes [27]. Furthermore, evidence for dopamine role in ADHD and the sleep-wake cycle comes from genetic studies examining catechol-O-methyltransferase, a gene that encodes for a dopamine-degrading enzyme. Children with ADHD having the low activity Met-Met polymorphism had poorer sleep continuity than their counterparts [28].

Summarizing literature data about sleep and ADHD, the available evidence from polysomnographic (PSG) studies is concordant for associations of ADHD with apnea/hypopnea and PLMs/nocturnal motor activity, whereas actigraphic studies reported evidence for insomnia and sleep phase delay (longer sleep latency, lower total sleep time, increased awakenings, and night-sleep variability, compared to controls). Subjective measures described bedtime resistance, insomnia, daytime sleepiness, and sleep-disordered breathing. Disconnections between parent-report instruments and objective measures are not contradictory, but that questionnaire measures are sensitive to problems not detected by objective measures [29]. It is notable that most literature data assessing sleep disorders in ADHD did not take into account the role of IEDs during sleep and epilepsy. To address the complexity and heterogeneity of sleep disorders in children with ADHD, five sleep ADHD phenotypes have been proposed [30]:

(a) Hypo-arousal state, resembling narcolepsy which may be considered a "primary" form of ADHD
(b) Sleep-onset insomnia as a marker of a later development of delayed sleep phase syndrome
(c) Sleep-disordered breathing (SDB)
(d) RLS and/or PLMs
(e) Epilepsy/or IEDs during sleep

A dysfunction of one of the three main sleep regulatory processes may be hypothesized in each sleep phenotype. An alteration of the circadian process is implicated in insomnia with delayed sleep onset; an alteration of the homeostatic process may be implicated in all sleep phenotypes associated with sleep fragmentations (OSA, RLS/PLMs, epilepsy); and lastly, an alteration of the ultradian process might be implicated in the "primary" form of ADHD [30, 31] (see Table 51.1). Cyclic alternating pattern (CAP), a marker of sleep instability and arousal, was found to be lower in children with ADHD selected without sleep disorders, suggesting a state of hypo-arousal in ADHD, correlated to a selective decline of the subtype A1 during N2 sleep stage [32, 33]. A similar decline was also found in children with narcolepsy, dyslexia, and with benign epilepsy with centrotemporal spikes (BECTs) [34]. However, others have reported no differences in CAP [35]. All sleep phenotypes, except for the primary form of ADHD and those related to focal benign epilepsy or focal EEG discharges, are associated with an increased level of arousal during sleep [30]. Considering ADHD is a 24-hour disorder [36] excessive doses of stimulant medication may be problematic in children exposed to stressors. If the stressors remain unidentified, children may be treated inappropriately with stimulants, exacerbating their condition. Major sleep disorders must be considered a form of chronic stress, inducing a persistent increase of arousals and an altered homeostatic process, expressed by neurobehavioral problems during wakefulness [30]. Numerous arousal systems, including the ascending monoamine systems (dopamine and norepinephrine), cholinergic neurons and the more recently discovered orexins, implicated in the pathogenesis of narcolepsy, project to the cortical mantle [37]. Moderate levels of dopamine and norepinephrine improve PFC function, whereas high levels, such as those

Table 51.1 Sleep disorders in ADHD, arousal, sleep process, treatment

	Sleep process	Arousal	Comorbidity	Treatment
Excessive daytime sleepiness-narcoleptic type	Ultradian process	Decreased	Slow cognitive tempo, depression	Stimulants
Sleep-onset delay insomnia/advanced sleep phase disorder in ADHD	Circadian process	Increased	Anxiety, bipolar disorder	Melatonin, light therapy
Sleep-disordered breathing (snoring and sleep obstructive apnea)	Homeostatic process	Increased	Oppositional defiant disorder, learning disorders	Adenotonsillectomy, orthodontic treatment for malocclusions and narrow palate, continuous positive airway pressure during the night, hypocaloric diet and/or elimination diet if co-morbidity with obesity
Restless leg syndrome and periodic limb movements during sleep, sleep hyperkinesia	Circadian process and homeostatic process	Increased	Bipolar disorder	Iron supplements, anticonvulsants, benzodiazepines, dopamine agonists (only if RLS is diagnosed)
Sleep ictal and interictal epileptiform discharges	Circadian process and homeostatic process	Increased/or decreased	Learning disorders	Antiepileptic drugs, elimination diet

released during stress, impair working memory [37]. High catecholamine levels may turn on more primitive brain structures to achieve more automatic behavior control when exposed to danger. The same mechanism may explain the PFC dysfunction found in conditions of hypo-arousability. A systematic review of task-based fMRI studies of sleep deprivation vs. ADHD vs. healthy controls revealed that ADHD and sleep deprivation share a common neural signature: hypoactivation of executive function neuroanatomy. In contrast, sleep loss was associated with thalamic hyperactivations as a potential compensatory response [38].

ADHD and Sleep-Onset Insomnia/Sleep Delayed Phase Syndrome (SDPS)

Approximately one-third of nonmedicated children with ADHD suffer from chronic sleep-onset insomnia. Several studies using subjective parent report rating scales, questionnaires, and screening instruments confirmed the high prevalence of sleep-onset insomnia [39]. In a meta-analysis of subjective studies of sleep in ADHD, six main parent-reported sleep issues were higher. The most common impairment was bedtime resistance, then difficulty with morning awakenings, sleep-onset difficulties, sleep-disordered breathing, night awakenings, and daytime sleepiness [40]. Other sleep questionnaire studies demonstrated that sleep-onset insomnia associated with bedtime resistance in ADHD children is increased especially in those who had anxious and depressed symptoms [29, 41]. In addition, PSG and actigraphic studies showed contradictory results, mostly not confirming difference in sleep-onset latency and sleep efficiency compared with controls or confirming differences only in those with other psychiatric diagnoses [42].

To date, the contributing elements leading to the higher frequency of reported increased sleep-onset difficulties remain to be fully explained. The child may be sent to bed when not yet sleepy because of a delayed endogenous circadian rhythm potentially expressed as bedtime refusal and daytime somnolence [5]. In line with this hypothesis, many studies showed delayed secretion of melatonin [43] more evident and significant in adolescents with ADHD [44]. In adolescents with ADHD, inattention was significantly associated with eveningness chronotype, which seems to be a possible endophenotype of ADHD [45]. An important and remarkable factor contributing to the shift of circadian rhythm in ADHD is internet addiction. Computer and videogames can serve to stimulate children and adolescents with ADHD who suffer from reward deficiency syndrome. One questionnaire study found more students with ADHD diagnosis spent more than 6 hours a day on the internet compared to those without ADHD diagnosis (20% vs 2%) and more ADHD students went to sleep after 2 a.m. than non-ADHD students (about 60% vs 15%) [46]. The same association between electronic media, evening type, and ADHD was found recently in 44 school-aged children [47]. In addition, technology use is associated with teacher-rated daytime sleepiness only in adolescents with ADHD [48].

Short sleep duration in relation to sleep-onset delay should be differentiated from a decreased need of sleep, which is, on the contrary, a red flag for pediatric bipolar disorder (BD). In comparing 100 youths at high-risk of BD, Shaw and colleagues [49] demonstrated that decreased need for sleep differentiated those at high vs. low risk, during a 10-year follow-up period. In a recent actigraphic study, decreased sleep duration and markedly increased nocturnal activity in the course of bipolar illness were found to be a relatively specific indicator of BD [50]. Moreover, consistent with data available on circadian phase preference in adults, BD adolescents, ages 13 years and older, endorsed significantly greater eveningness compared to their normal controls [51].

ADHD and Narcolepsy-Like Symptoms

Debate and skepticism have surrounded the notion of a connection between ADHD and hypersomnias. Nevertheless, hyperactivity seen in ADHD may be a compensatory response to sleepiness. Looking at the microstructure of sleep, children with ADHD showed a lower CAP similar to those found in children with narcolepsy, supporting the hypothesis of the existence of a hypoarousal state in these patients [32]. The "hypoarousal state" is further confirmed by multiple sleep latency testing (MSLT) studies, demonstrating that children with ADHD are about eight times more likely to fall asleep in comparison with controls [52]. In a study from our group, we found a narcolepsy trait in 4/30 children with ADHD investigated by MSLT [53].

One study found that self-reported daytime sleepiness significantly predicted parent-rated homework problems and academic impairment in 100 middle school-aged youths with ADHD [54]. Langberg et al. [55] found that in college students diagnosed with ADHD, sluggish cognitive tempo (SCT) was a significant predictor of daytime sleepiness, even after controlling for ADHD, anxiety, and depression symptoms. The construct of SCT is characterized by sluggish, undermotivated lethargic, slowed, and/or forgetful, daydreamy behavior [56]. There has been limited research on the relationship between ADHD, SCT, and sleep. More critically, if SCT symptoms are due, at least in part, to reduced quality of sleep, targeted interventions may help to reduce these symptoms and improve clinical outcomes [56].

An overlap in symptoms have been observed between central hypersomnia and ADHD (Fig. 51.1). Narcolepsy and hypersomnia can cause ADHD-like symptoms and ADHD, especially the inattentive subtype can resemble hypersomnias. Pharmacological treatment for ADHD overlaps with treatment used for narcolepsy, potentially masking symptoms of narcolepsy [57]. The presence of ADHD symptoms in children and adolescents with narcolepsy was found to be about two-fold higher than in controls, in 35.3% of children with narcolepsy type II and in 19.7% of narcolepsy type I [58]. In another study, Modestino and Winchester provided evidence of a significant retrospective childhood history of ADHD symptomatology among adult narcoleptics, found in 37% of cases [59].

ADHD and OSA

Attention deficits have been reported in up to 95% of children with OSA, whereas habitual snoring or OSA has been reported in up to 30% of children with ADHD [40, 60–62].

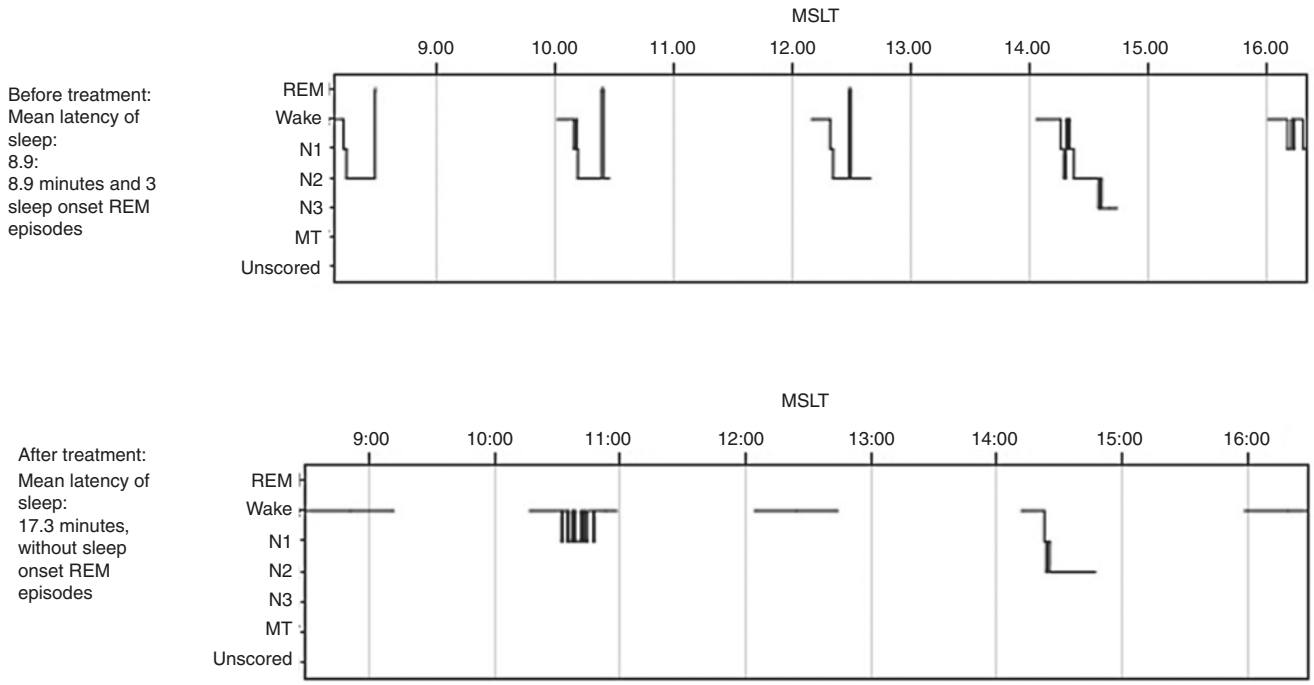

Fig. 51.1 The multiple latency tests (before and after 2 years of treatment with sodium oxybate) of a 16-year-old girl admitted to our Sleep Center for excessive daytime somnolence, with multiple sleep attacks, treated with methylphenidate for a previous diagnosis of ADHD and learning disability from elementary school. Excessive daytime somnolence started abruptly 3 years ago. She described hypnagogic hallucinations and suspected episode of cataplexy. The HLA was negative for narcolepsy, whereas the liquor assessment confirmed the diagnosis of narcolepsy type I, because orexin was undetectable. She started therapy with sodium oxybate, with amelioration of daytime somnolence, disappearing of cataplectic attack, but no evident effect of methylphenidate and/or modasomil on attention disorder. She will start therapy with pitolisant

One recent PSG study showed a mild OSA in 42.6% of 61 nonmedicated children with ADHD and a significant decreased amplitude of the P300 wave, which measures auditory attentional integrity [60]. In contrast, another study failed to find differences in respiratory parameters between Danish children with unmedicated consecutively recruited ADHD and controls [63].

Based on a community cohort of 1115 children (aged between 5 and 10 years) who underwent overnight PSG and cognitive and behavioral phenotyping, it has been recently demonstrated that indirect effects of SDB through behavioral problems predicted cognitive changes, while a direct effect of SDB status failed to predict cognitive findings. Behavior and psychiatric problems that often occur among children with SDB, such as inattention, emotional pathology or conduct issues, may potentially disrupt natural learning processes during early formative years [64]. In another study, among the SDB children, those with a high level of arousal had a higher degree of protection against the cognitive consequences of sleep respiratory problems; in other words, the higher the arousability, the higher the intelligent quotient, the latter also being accompanied, however, by higher diurnal hyperactive and inattentive levels. On a hypothetical scale of cognitive processes, the attempt to preserve global intelligence in children with SDB has a diurnal cost due to sleep deprivation [65]. The results of the Childhood Adenotonsillectomy Trial clearly confirmed that neurocognitive and behavioral dysfunctions in children with OSA are consistent and partially reversible. The adenotonsillectomy did not significantly improve attention or executive function, but it did reduce symptoms and improve secondary outcomes of behavior, quality of life, and PSG [66]. The partial reversibility of executive dysfunction may be explained by the literature findings regarding a damage of blood brain barrier. OSA is associated with sleep intermittent hypoxemic state and sleep fragmentation, inducing systemic inflammation and oxidative stress. This inflammatory process leads to disruption of the blood–brain barrier through alterations in microvessel permeability [67]. Recent functional magnetic resonance imaging studies have revealed aberrant cerebral perfusion, reduced grey matter, and altered patterns of intrinsic regional brain activity in children with OSA [9, 68]. Indeed, US guidelines recommend that children undergoing evaluation for ADHD must be assessed for sleep apnea [69]. An emerging body of the literature suggests that youths diagnosed with ADHD have especially high rates of being overweight/obese (up to 58%), which may be mediated by sleep disruptions [22]. Excess adiposity is associated with leptin resistance and reduced hypercapnic responses, implicated in mechanisms involved in hypoventilation and appears to greatly impact sleep respiration in obese individuals. Taken together, substantial evidence points to the possibility that obesity may trigger sleep respiratory-related changes which in turn contribute to ADHD-related symptoms [25]. Both short sleep duration and OSA causing intermittent hypoxia and inflammatory reactions induce obesity [9]. Obesity, per se, impact negatively, cognitive outcome and ADHD symptoms of children with OSA [70], creating a vicious circle.

ADHD Sleep and Epilepsy

The number of studies available specifying the relationship between sleep/ADHD/epilepsy are still scarce. The prevalence of ADHD is at least 2.5 times higher in children with epilepsy and symptoms of ADHD usually precede the onset of epilepsy [71]. Among 196 children with BECTs, 31% had ADHD, 21.9% had cognitive deficits, and 11.7% had behavioral abnormalities [72], while another study found in 21/32 children with BECTs, a diagnosis of ADHD. Children younger at epilepsy onset seem to have a low IQ and severe ADHD. An abundant occurrence of IEDs on nocturnal EEG worsens the severity of ADHD symptomatology [73] (Fig. 51.2). When treating a child with BECTS, one of the most important parameters for deciding whether to use a new drug is a formal psychological evaluation proving cognitive decline [74].

In a prospective study, symptoms of ADHD preceded the occurrence of the first seizure in 32% of patients: on average, ADHD preceded idiopathic focal epilepsy or other forms of genetically determined generalized epilepsies [75]. In line with these findings, a large body of literature data points to a high prevalence of interictal or ictal activity during sleep in ADHD children. A review demonstrated that the prevalence of interictal or ictal discharges is higher in children with ADHD, if evaluated via sleep and sleep-deprived recordings, with the proportion reaching more than 25% of the subjects evaluated, compared to 7% occurring in the prior wake recording [76]. An Italian group explored the prevalence of interictal or ictal discharges ADHD children. A higher prevalence (53.1%) of IEDs was found [77], demonstrating that long sleep recording can detect IEDs in more cases.

ADHD and RLS/PLMs

Higher levels of nocturnal activity or restlessness have commonly been described in children with ADHD and confirmed by subjective and objective methods [5]. The prevalence of PLMs in children diagnosed with ADHD is estimated to be as high as 7–44%, compared with a prevalence of only 1.2–2.0% in pediatric populations [42]. PSG studies found that 10.2–14.7% of children with ADHD had PLMs [42]. Crabtree et al. [78] showed that children with PLMs and ADHD were more likely to have PLMs-related arousals inducing sleep fragmentations.

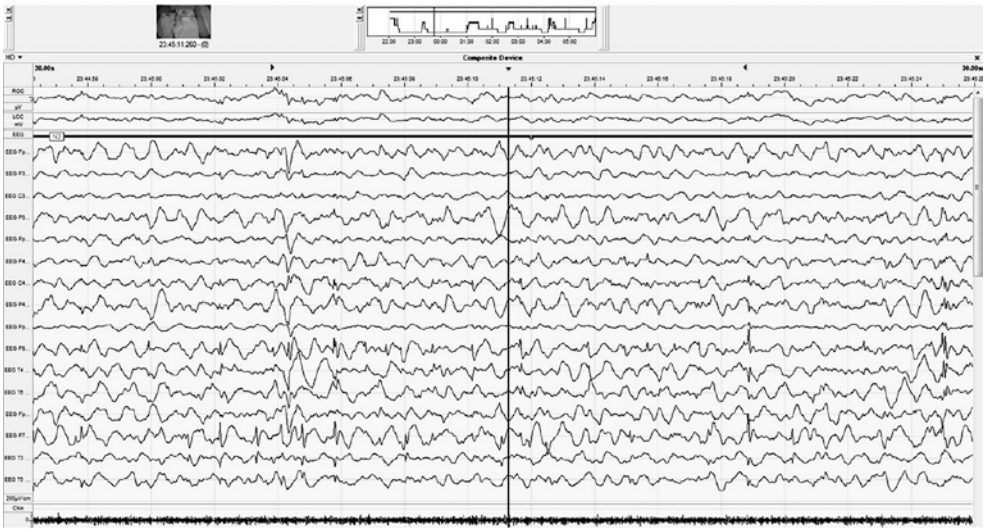

Fig. 51.2 Video-PSG with multichannel EEG recording of a nonmedicated boy aged 12 years and 6 months, with a diagnosis of ADHD, with abundant sharp waves, over right frontal-temporal regions, without any ictal episodes during sleep or during wakefulness. He started therapy with lamotrigine, a mild reduction of interictal epileptiform discharges and a mild effect on attention deficit. After 2 years, the antiepileptic therapy was stopped, the interictal epileptiform discharges during sleep disappeared, and he started therapy with long release methylphenidate, obtaining also beneficial on sleep-onset insomnia

Up to 44% of the ADHD population may experience RLS symptoms compared to 10% in the general population, with up to 26% of those with RLS possibly having ADHD symptoms, as RLS can mimic ADHD symptoms during the day [79]. A retrospective study on 374 children who met the criteria for RLS revealed ADHD in 25% of cases [80], while a recent questionnaire-based study found a definite diagnosis of RLS only in two of 56 Korean children and a probable diagnosis in four [81]. Konofal and colleagues investigated the impact of RLS on ADHD severity in 5- to 8-year-old children and found that ADHD symptoms were more severe in children with both ADHD and RLS [82].

The literature shows a positive correlation between iron deficiency and ADHD symptoms as well as between iron deficiency and RLS or restlessness during sleep. Cortese and colleagues [40] found that serum ferritin levels <45 μg/L might indicate a risk of sleep–wake transition disorders in children with ADHD. A recent personal study reported ferritin levels lower than 60 μg/L in a sample of 30 children with ADHD and sleep disorders [53].

Effect of ADHD Therapy on Sleep and the Effect of Sleep Therapy on ADHD Symptomatology

Both European and US guidelines recommend assessment of sleep disturbance during evaluation of ADHD and before initiation of pharmacotherapy [83]. Pharmacological treatment for ADHD includes both stimulants such as methylphenidate (MPH) and nonstimulants, such as atomoxetine and alpha-2 agonists such as clonidine. Stimulants are all likely to affect sleep, reducing total sleep time, increasing sleep-onset latency, reducing sleep efficiency, increasing motor activity during sleep, and inducing a phase-delay of daily rhythm [84, 85]. Children will also be more vulnerable to adverse sleep effects if they have a preexisting sleep disorder prior to stimulant treatment, or a comorbid condition also associated with sleep disorders such as depression or anxiety [36]. Nevertheless, the effect of stimulants may also be paradoxical; for instance: MPH administered in the late afternoon reduced nocturnal activity and consolidated sleep, thus improved sleep quality, prevented worsening of hyperactivity and behavioral difficulties at bedtime [5]. Moreover, prospective, placebo-controlled trials did not confirm that MPH causes sleep problems in children with ADHD assessed by PSG or actigraphy [86]. In contrast to stimulants, somnolence is the most common sleep-related adverse event associated with atomoxetine, guanfacine, and clonidine [83]. Limited open-label and retrospective studies of clonidine in ADHD have reported reductions in sleep latency and nighttime awakenings [87, 88].

Alternative treatments to drugs have postulated the improvement of sleep structure and background EEG frequency oscillations in children with ADHD by applying neuro-feedback or transcranial oscillating current stimulation, regardless of comorbid sleep disorders. EEG-neurofeedback training in ADHD increases the production of beta activity (16–20 Hz) while suppressing the production of theta activity (4–8 Hz). There is some evidence of

long-term benefits of neurofeedback training in children with ADHD, although one randomized study did not find any differences with the placebo group [89]. In line with these treatments, in children with ADHD, transcranial oscillating current stimulation for 10 minutes at 0.75 Hz during stage N2 (delivered during the first part of sleep) induces an increase of SWA over frontal regions, an enhancement of sleep declarative memory consolidation and of behavioral inhibition [90, 91].

Many studies have evaluated the efficacy of treatment of sleep disorders and the impact on ADHD symptoms. Melatonin significantly improves sleep-onset insomnia and it is well tolerated. One long-term follow-up study with a mean follow-up period of 3.7 years conducted in ADHD children with sleep-onset insomnia confirmed the efficacy of melatonin without notable adverse effects [92]. Furthermore, studies have demonstrated that melatonin administration advances circadian rhythms and endogenous melatonin; it is consequently associated with enhanced total duration of sleep in children with ADHD, even if failing to improve problem behaviors, cognitive performance or quality of life [93–95]. Another important intervention in line with these results is the beneficial effects of delaying school start times. The American Academy of Paediatrics strongly supports delaying school start times to improve chronic sleep deprivation among students [96]. In adolescents with ADHD, the potential effectiveness of light therapy as add-on therapy has been proved after 4 weeks of treatment [97] and recently confirmed [98]. In addition, one double-blind, placebo-controlled, parallel-group study in ADHD males demonstrated through actigraphy that L-theanine produced a significant increase seen in sleep efficiency, as well as a reduction in nocturnal activity [99]. On the contrary, a 12-week, randomized, double-blind, placebo-controlled trial of high- or low-dose eszopiclone in patients with ADHD and another randomized double-blind controlled trial of zolpidem both failed to demonstrate the efficacy on insomnia [100, 101]. The childhood co-occurrence of SOI and ADHD symptoms should prompt clinical exclusion of bipolar disorder. Although there is no clear evidence that stimulants accelerate or exacerbate the development of BD in children with ADHD, in children at risk of developing mood disorders, it is preferable to use firstly melatonin and/or light therapy to treat a circadian rhythmic disorder [30].

Although Walters et al. [102] indicated that treatment of PLMs with dopaminergic agents, in the absence of psychostimulant use, resulted in marked improvements in both sleep disorder and ADHD, a recent randomized placebo trial of carbidopa/L-dopa on 35 patients showed improvement of RLS/PLMs, without improvement of ADHD symptoms [103]. Several studies have highlighted the potential benefit of raising serum ferritin above 50 ng/ml and a case report showed a clear benefit also in ADHD diurnal symptoms, after morning oral iron administration [8]. Konofal et al. [104] reported improvement in sleep problems, assessed by parental interview and sleep diaries filled out by the parents, in a child with ADHD after iron supplementation for low ferritin levels. Another study reported improvement in total score, hyperactive/impulsive and inattentive subscales of the ADHD rating scale, and restless leg symptoms after iron supplementation [105].

Appropriate recognition and surgical treatment of underlying OSA in children with ADHD might prevent the need for long-term stimulant treatment. A longitudinal study has shown that ADHD improvement was maintained 2.5 years after surgery [106], whereas a randomized clinical trial that included 464 children demonstrated great improvements after adenotonsillectomy across behavioral outcome measures and some cognitive measures after 7 months [66, 107].

Few uncontrolled studies, conducted on a small sample of children with ADHD and IEDs, reported a positive effect of antiepileptic drugs on sleep quality [108, 109]. In addition, a clear improvement of ADHD symptoms has been demonstrated after treatment with ACTH in children with continuous spike waves during sleep and ADHD [110]. On the contrary, in a multicenter observational prospective study among a large sample of children with both epilepsy and inattentive-ADHD, MPH resulted in a small decrease of ADHD symptoms for 75% of patients, while 25 did not respond [75]. Whether or not severity and/or evolution of ADHD symptoms during follow-up (was) were associated with the abundance of IEDs remained an important open question. Considering the impact of ADHD on quality of life in children with epilepsy, alternative therapeutic strategies to MPH are warranted [75].

In children with narcolepsy, in contrast to narcolepsy symptoms, ADHD symptoms appeared to be largely unresponsive to psychostimulant therapy and use of higher doses of modafinil or MPH at any dose might be associated with elevated hyperactive-impulsive symptoms [58].

Finally, a randomized clinical trial with an elimination diet of 5 weeks, consisting only of a limited number of hypoallergenic foods, demonstrated improvement of physical and sleep complaints, together with a reduction of ADHD symptoms in a group of nonmedicated children with ADHD [111]. This surprising result should be confirmed and evaluated in those with comorbid OSA and/or IEDs during sleep.

Conclusion

A large portion of children with ADHD have problems regarding school performance, obesity, psychiatric comorbidities, and parent–children interactions, warranting more clinical attention. The aforementioned issues are frequently

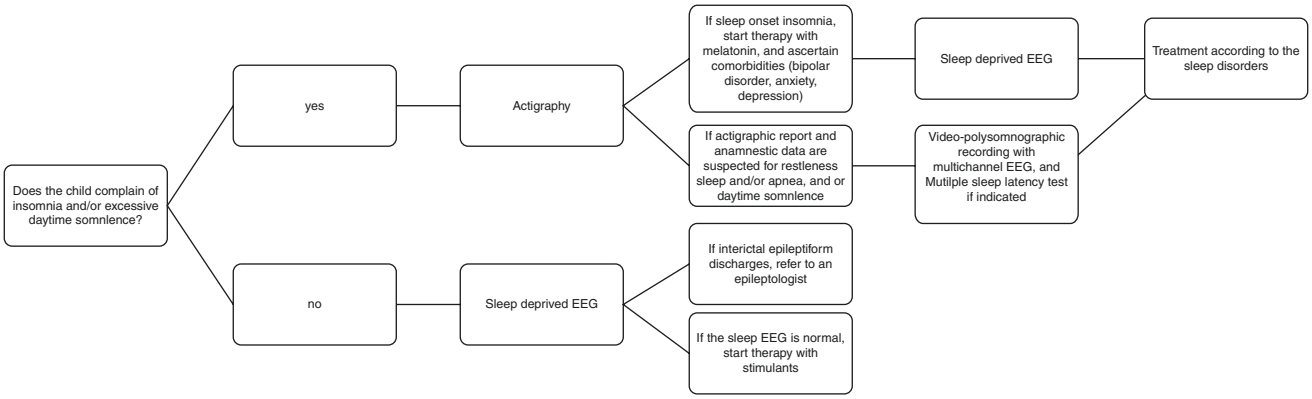

Fig. 51.3 Algorithm for management of sleep disorders and comorbidities

consequences of sleep problems or in turn affect sleep patterns and have a significant impact on long-term prognosis. The association between sleep and ADHD has yet to be fully understood. One reason for the limited knowledge available is the heterogeneity of the sleep studies conducted to date which differ considerably with regard to the methods adopted (questionnaire, actigraphic, and polysomnographic studies), the subjects' age (ranging from childhood to adulthood), the diagnosis (ADHD with and without comorbidities), and the type of sleep disorders investigated [30]. Many studies come from cross-sectional studies of school-aged children with limited controlling for confounding factors. Consideration of the longitudinal sleep trajectory and its temporal relationship with the onset of ADHD symptoms should be determined, thus offering more insight regarding possible direction of causation [19]. Furthermore, evidence-based treatments for sleep disturbances in children with ADHD remain limited [112]. It is recommended that health-care providers assess and treat early sleep problems to mitigate risk of inattention and hyperactivity occurrence [17]. As recommended in current guidelines, primary sleep disorders (specifically SDB/OSA and PLMs/RLS) should be ruled out before diagnosing or treating ADHD [84]. Obesity and psychiatric comorbidities (e.g., anxiety and depression) can also lead to sleep problems and must be identified and treated appropriately [83]. Many promising reports regarding the "sleep phenotypes" of ADHD, such as sleep deprivation, OSA, and circadian rhythm disturbances, suggest the possibility of identifying predictors of ADHD [6].

In one of our recent studies, we confirmed the hypothesis of sleep phenotypes and that a past and present history of chronic sleep deprivation is present in children with ADHD [53]. All children, prospectively recruited and drug free, underwent a full sleep assessment (questionnaires, video-PSG, MSLT, and actigraphic recording) and 28 out of 30 ADHD children received a diagnosis of sleep disorders. Sleep-onset insomnia (SOI) was found in five males, OSA was found in 15 children, PLMs were found in eight, without reaching criteria for RLS diagnosis. The narcoleptic-like phenotype was found in four children, while EEG interictal or ictal epileptiform discharges were found in 10 subjects: continuous spike and waves or sharp waves during sleep were found in three subjects (see Fig. 51.1). Three subjects had sleep arousal disorder, in association with OSA in two cases. Only two children were not affected by any sleep disorder. Many subjects received more than one diagnosis of sleep disorders. All children with ADHD slept less than 9 hours actigraphic recording, and had higher AHI compared to controls. We also found a negative correlation between the ADHD score and sleep fragmentations [53]. A similar study in a group of 26 children and 56 controls, without sleep disorders and psychiatric comorbidity, did not find any differences in actigraphic, PSG, and MSLT parameters, compared to controls [113]. Our study did not exclude children with sleep disorders, aiming to include a real-life sample of children with ADHD. According to the sleep phenotypes of ADHD described above, treatment with stimulants appears to be the first choice for the primary form of ADHD, while in other cases, treatment should focus on the underlying sleep disorders as well as comorbidities [30] (Fig. 51.3).

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Sleep and Mood Disorder

52

Maria Cecilia Lopes and Lee Fu-I

Introduction of Sleep, Behavior, and Mood

Mental health is a fundamental part of human well-being. The overall prevalence of mental disorders contributes to more than 10% of the age-standardized years lived with disability; it usually begins during adolescence and persists into adulthood [1]. Therefore, the promotion of mental health among young people should be seen as a priority, and environmental determinants – derived from specific cultural and geographic contexts better understood by locals – must be identified. The prevalence of suicidal ideation and non-fatal suicidal behavior in adolescents in low- and middle-income countries has increased dramatically. There are possible differences in adolescent suicidal thinking patterns and behavior between adolescents and adults. Further, in high-income countries, most young people reporting suicidal ideation do not make a tentative attempt, which is not the case in low- and middle-income countries.

Sleep has a relationship with quality of life. There are 70 million Americans who have been affected by sleep complaints at an annual cost of $15 billion in health expenses and $50 billion in lost productivity, according to the National Institute of Health [2]. Insomnia is a common complaint across the population [3]. It is present in all age groups, and can be associated with symptoms of pain, and with clinical and neurobehavioral manifestations in various healthy conditions [4]. It can be worse during adolescence, and discussion about the subjectivity of adolescence in the contemporary world is clearly necessary for professionals who intend to participate in their care. There are several specialized publications on the subject; the first book referred to in the Index Medicus addressing the theme adolescence dates from 1904 is the work of G. Stanley Hall, entitled *Adolescence: Its psychology and relation with physiology, anthropology, sociology, sex, crime, religion and education* [5]. According to Hall, the developing human being goes through various stages that correspond to those that occurred in the evolution of the human species, from animal primitivism to civilized life, which characterizes maturity. Also, the stages of development described in this theory form a universal, unavoidable, and immutable pattern which, controlled exclusively by heredity, is independent of the environment. As noted above, Hall perceives adolescence as a period of storm and tension, with expected turbulence [5]. According to Prof. Carskadon and colleagues [6, 7], the storm of adolescence can affect sleep due to a complex model of bidirectional effect in this age group. According to this idea, adolescence is a transitional period characterized by intense somatic and behavioral modifications that is followed by the evident storm. Hormonal changes initiate a chain of changes in the sleep/wake cycle. These changes lead to delays of phase and sleep deprivation, with important consequences in the life of the adolescent. At this stage of development, it can be said that the sleep pattern is a result of a "perfect storm": the combination of behavioral (psychological, social, and cultural) and biological conditions that predispose individuals to delayed sleep phase syndrome and consequent chronic sleep deprivation. Moreover, insomnia can occur in the developmental stages of adolescence and chronic sleep deprivation can lead to sleep pressure as a protective effect [6]. There are, however, common symptoms in insomnia patients, which are also observed in reports of adolescent sleep-deprived patients. Excessive daytime sleepiness is a frequent complaint and requires a differential diagnostic investigation with depression in adolescence.

Sleep disorders are very common in children and can be followed by behavioral problems. Most sleep disorders can improve when properly treated. Recommendations for improving sleep hygiene in children include maintaining a consistent bedtime for children and parents and discouraging bed sharing. Often, behavioral complaints may be intensified by untreated sleep disorders, and similarly, sleep disorders may exacerbate psychiatric symptomatology, and an abrupt change in sleep habit may be an early marker of bipolar disorder in children and adolescents. Further studies may

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prove the importance of the interaction between sleep and psychiatry.

Sleep is a cyclic neurophysiologic state, characterized by the alternation of two periods of NREM sleep and REM sleep, which differ according to the EEG pattern, together with behavioral changes evidenced by the presence or absence of rapid eye movements and changes in posture and in cardiorespiratory patterns. The study of sleep has made great advances recently, and several areas of medicine and sleep science, including examination of the interface with behavioral science, have been emerging. Some behaviors that have been observed during sleep have caused surprise and curiosity [8]. The presence of childhood somnambulism, as well as nocturnal terrors are common, together with behavior problems [9–11]. Panic attacks can occur at night as well as ruminations of anxious processes. The behavior of raiding the refrigerator (night eating disorder) is a frequent complaint in clinical practice. It is important to determine when these behaviors begin to be considered pathological. Hyperactivity and sleep disorder is a good example of a sleep disruption associated with behavioral changes [12–16]; it can be found in children with chronic snoring, and is referred to by some authors as: mild sleep-disordered breathing (SDB) with airflow limitation without classic apneas. These disorders have been associated with inattentive and hyperactive behaviors in children [12, 17]. A study by Gozal and colleagues [18] examined the hypothesis that domains of neurobehavioral function would be selectively affected by SDB. These authors concluded that an unusually high prevalence of snoring was identified among a group of children designated as showing mild symptoms of hyperactivity based on the specific tests [18].

There is evidence that the pre-frontal cortex is involved with the clinical expression of these behavioral changes [19]. The frontal cortex has the most interhemispheric connections. While there is a posteroanterior direction in neocortical development, in other way, there is an anteroposterior direction for brain waves from light sleep to deep sleep. This fact indicates the immaturity of the prefrontal cortex, making it more sensitive throughout development to sleep disorders. Respiratory disturbances are also likely to interfere with sleep stability, as can be demonstrated by the increase in the alternating pattern, particularly in slow-wave sleep. Sleep instability can be mapped by observing the alternating cyclic patterns in children and adults. Slow brain wave components that permeate sleep instability are associated with hemispheric synchronization [20], which in turn has a clear relationship with interhemispheric connectivity. The disorganization of brain waves in areas that depend on synchronization, such as the prefrontal cortex, explains typical behaviors such as hyperactivity, aggression, inattention, and even school difficulties. These executive dysfunctions tend to be recovered after treatment of sleep-disordered breathing [21]. Although sleep apnea occurs in children, it is more difficult to diagnose obstructive events in this population than in adults [22]. The relationship between SDB in children and neurobehavioral disorders is well established [15, 23, 24]. However, a major problem in identifying risk factors for childhood psychiatric morbidities is the fact that sleep-disordered breathing measures need to be optimized [16, 23]. Conventional polysomnographic measures such as the apnea and hypopnea index (frequency per hour of sleep), even when adapted for children, may underestimate the diagnosis of sleep disturbances in children with behavioral changes. Other evaluations have been reviewed such as the specialized staging of respiratory awakenings or not, as well as the quantification of EEG changes detected at each abnormal respiratory event [16]. The existence of sleep instability in children with respiratory manifestations (such as snoring, tachypnea, flow limitation without evident airway obstruction and/or hypoxia) has been described [25, 26]. The clinical implications of snoring frames (not necessarily associated with severe sleep-disordered breathing in children) have been described and include changes in craniofacial development [27] and neurobehavioral developmental changes. There is a possibility that partial obstructions of the upper airways may produce brief awakenings, which cannot be visualized, but may have an impact on cortical activity and neurobehavioral evolution. Sleepiness pattern is another important topic to analyze the interaction between sleep and mood. Wakefulness can change night performance, also awakenings during the night can change wakeful activity, and sleepiness is a symptom that can be a diagnostic tool to suggest that adjustments to sleep processes and behavioral changes are needed to help sleep recovery.

Daytime sleepiness in childhood may be the first symptom of a sleep disorder. Causes of excessive sleepiness in childhood (see also Table 52.1):

Table 52.1 Narcolepsy in children

Cataplexy	Easily recognizable in most narcoleptic children Often occurs while playing with other children Frequently the first symptom to be recognized Differential diagnosis with other causes of drop attacks in children
Excessive daytime sleepiness	Sometimes may be difficult to recognize Common symptom is falling asleep in class Sleepiness can be hidden behind other abnormal behavior, such as hyperactivity
Hypnagogic hallucination	Symptoms such as nightmares and hypnagogic hallucinations were considered a part of normal childhood May be difficult to diagnose
Sleep paralysis	Frequently accompanied by hallucinations Children dislike talking about these events
Disturbed nocturnal sleep	This symptom may not affect children and sometimes is a transitory complaint

Data from Pelayo and Lopes [19]

- Obstructive sleep apnea syndrome
- Parasomnias
- Insomnia
- Narcolepsy
- Sleep phase delay syndrome
- Kleine–Levin syndrome

Sleep apnea has been commented on before. Narcolepsy should always be considered when treating a child with significant drowsiness. A child with narcolepsy may fall asleep while talking, eating, or even riding a bicycle. They have irresistible attacks of sleep several times a day and may experience auditory or visual hallucinations (hypnagogic hallucinations) when they fall asleep. They may also experience episodes of sleep paralysis at bedtime or when they wake, as well as bouts of sudden muscle weakness usually triggered by laughter or strong emotion (cataplexy). These attacks can last from a few seconds to up to 30 minutes. During the early stages of narcolepsy, children often have great difficulty waking up early. When awake, they can become confused or aggressive. It is important to diagnose narcolepsy early because drowsiness can affect school performance. It can also lead teachers, as well as the child, to attribute the symptoms to laziness or deafness. Children with narcolepsy often benefit from regular sleep schedules and stimulant medication. There are important differences between narcolepsy in children and in adults.

Kleine–Levin syndrome (KLS) is a disorder characterized by episodes of recurrent drowsiness. Typically, the child presents episodes of hypersomnia, mood changes, hyperphagia, psychic alterations, and prolactin increase. The episodes last from 12 hours to 3–4 weeks (4–7 days is the most common), and the intervals between episodes can be from months to years. During the episode, the patient sleeps for long periods (6 pm to 8 am), usually waking up to eat voraciously. It can be accompanied by changes in sexual behavior, aggression, memory disorder, depressive symptoms, and even hallucinations. During the intervals between episodes, patients are absolutely normal and usually report amnesia around the critical time. KLS is rare, more common in males and its etiopathogenesis is unknown. A differential diagnosis of KLS should be made based on disturbances that occur with intermittent somnolence, such as third ventricle tumors, encephalitis, cranioencephalic trauma, and psychiatric disorders. SKL treatment consists of stimulants such as methylphenidate, dexedrine, amphetamines, and tricyclic antidepressants and lithium carbonate.

Delayed sleep phase syndrome (DSPS) is a circadian rhythm disorder. Children affected by the syndrome, usually teenagers, complain that they cannot fall asleep before 3 am and then have difficulty getting up to go to school in the morning [28]. This causes problems for family members who have to wake their child in the morning. Teenagers often benefit from weekend "shock" treatment: if they stay up all night on Friday and all of Saturday, they will sleep on Saturday night. This makes them wake up earlier on Sunday and should be followed by a strict bedtime routine 7 days a week. This circadian rhythm disorder may be manifested by insomnia, as well as by irresistible sleep attacks. Characterized by the difficulty of chronic daytime sleepiness and an inability to wake up at an appropriate time in the morning, it can sometimes be associated with depression and should be considered when evaluating teenagers with depression. A study in Japan attempted to define the psychological characteristics of patients with phase delay [29]. DSPS is not difficult to diagnose, once clinical suspicion is raised, but achieving a satisfactory response to treatment is more difficult. Attempts to correct sleep time are often unsuccessful unless the adolescent is motivated to change the lifestyle factors that influence late bedtime, particularly at weekends [30]. The treatment originally proposed was chronotherapy, described by Weitzman (1981) [28]. Chronotherapy reorients the patient's sleep cycle through a series of consecutive late bedtime adjustments over several days. To maintain the sleep model adjustment, the patient is encouraged to remain strictly awake. In this treatment, the child should be constantly supervised to avoid falling asleep at inappropriate times.

Insomnia seems to have the most obvious link between mood and sleep and to understand changes in sleep processes, we need to elucidate the environmental activities and the regular habits of the patients, including their families' routine. Sleep can provide a clear picture of brain development (Fig. 52.1).

Biological, cognitive, psychodynamic, etiological, familial, social, economic, and cultural factors are critical and determinant in the natural course of psychiatric illness. The effects of early development deficits can be opportunities or barriers. The family and/or social environment may amplify and aggravate disorders of childhood and adolescence. The adult outcome of early childhood pathologies is a result of the interaction between therapeutic approaches, risk and protector factors and prognosis may depend on the ability of the

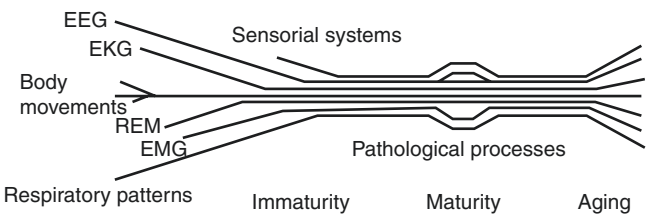

Fig. 52.1 Schematic figure showing the effects of early processes in sleep. The "cordon" analogy to illustrate the phenomenon of sleep entanglement. The first manifestations seem to be independent of rhythms, which gradually merge into a recognizable set of "state" parameters. EKG electrocardiogram, EEG electroencephalogram, EMG electromyogram. (Adapted from Kohyama J [31])

child and family to deal with the disorders. According to Jun Kohyama [31], sleep can be a window on brain development, where biological processes lead to pathological changes. Often, sleep problems indicated by parents' complaints to pediatricians are changes in physiologic processes.

Sleep medicine can be the key to accessing important information on the individual to establish the correct diagnosis in the mental health of childhood and adolescence. We cannot be secure in the interpretation of psychiatric symptoms without a comprehensive idea of sleep processes. Sleep medicine may improve sleep habits worldwide and across the entire life span.

Sleep and Psychiatry

Sleep has been analyzed as an endophenotype marker of psychiatric disorders in children and adolescents. A biological pacemaker regulates sleep, and pathophysiologic processes can be followed by multiple changes in the circadian rhythms. Sleep fragmentation in bipolar disorder can be followed by a mania episode. Insomnia can be caused by the biological pacemaker coupling disorders with sleep-promoting neurophysiology. The role of insomnia as a risk factor for psychiatric illness remains unclear. Also, sleep instability can explain the internal noise in our physiologic systems during sleep [32]. The relationship between sleep and psychiatric disorders has been addressed in several studies developed by sleep medicine and psychiatry, but unanswered questions remain. A longitudinal epidemiological study has shown that patients with sleep disorders are at increased risk for major depressive disorder, anxiety disorders, drug abuse, and nicotine dependence, with a strong relationship between sleep disorders and major depression.[33]

Study of Sleep in Psychiatric Disorders

Patients with psychiatric disorders often have problems with sleep. There is evidence that sleep disorders may play a critical role in the pathogenesis of psychiatric disorders [34]. However, these changes in electroencephalogram sleep may be obscure, a fact that increases the importance of recognizing sleep disorders in major depressive conditions in children and adolescents through subjective analysis, such as the application of questionnaires. Generally, subjective sleep analyses are based on questionnaires with questions about sleep problems and daytime complaints. Objective studies of sleep in depression in all age groups have been carried out by several authors. Interestingly, depressive disorders in adult patients cannot be differentiated from other psychiatric disorders through objective sleep studies [35], but the presence of a reduction in REM sleep is associated with suicidal ideation in adolescents with depression. REM sleep regulation is modified by the pathophysiology of depression, and there are two hypotheses to explain changes in REM sleep: one is associated with catecholamines and the other with acetylcholine receptors. There is evidence that anxiety disorders may increase the production of catecholamines and may alter the progression of depression associated with anxiety. There is a limit to the interaction between questions about sleep and daytime complaints in adolescents with depression, whether in the presence of anxiety disorder or not. Anxiety disorder has been associated with early insomnia and wakefulness throughout the night, but with a decrease in daytime complaints and sleepiness as well as in learning disabilities. Depressed children and adolescents with anxiety disorders often have impaired performance as a result of anxiety symptoms. However, there is some evidence that children with anxiety may have reduced ability to learn [36].

Depressive symptoms after a night of deprivation can be improved due to increased 5-HT levels [37]. As anxiety disorder can cause sleep deprivation, there may be a natural compensatory process in the body which relieves the symptoms of depression. Early insomnia has been described as the sleep disturbance most associated with early-onset depression [38]. A longitudinal follow-up study of adolescents indicated more sleep latency in childhood as a recurrent major depressive disorder course marker [39]. Depression and associated factors such as anxiety can gradually change the regulation of sleep and changes in the amount of sleep. Sleep loss due to restriction at bedtime in children may be followed by changes in cognitive and emotional functions. More studies are needed to elucidate the interaction of sleep and psychiatric symptoms.

Sleep and Depressive Disorders

The Diagnostic and Statistical Manual of Mental Disorders by DSM-5 [41], categorizes depressive disorders in children as follows: major depressive disorder, persistent depressive disorder, disruptive mood dysregulation disorder, premenstrual dysphoric disorder, substance/medication induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder. In this part of chapter, we will focus on major depressive disorder.

Depression in children is characterized by sadness or irritable mood, decreased interested and lack of enjoyment, change in social or school performance, decreased capacity to have fun, decreased self-esteem, and sleep disturbance. Sleep patterns can help us to understand abrupt behavior changes, and the disruption of sleep habits in childhood can be followed by physiologic changes in motor and cognitive

activities with future consequences until adulthood. According to DSM-5 [41], the diagnostic criteria for major depressive episodes include insomnia or hypersomnia and excessive fatigue. The literature has hypothesized that early recognition of and intervention into sleep disorders can prevent recurrent depressive symptoms. This hypothesis was based on results such as those from a prospective epidemiological study that demonstrated that people with insomnia symptoms with one-year follow-up presented a higher risk for the development of depressive symptoms. In addition, episodes of recurrent depression are usually preceded by subjective complaints of sleep disorders, particularly in children and adolescents [42]. Such observations favor the theory that sleep physiology disorder may precede the development of affective disorder, as well as providing evidence of the importance of sleep. Now that sleep disorders fall within the diagnostic criteria for bipolar depression, it has become imperative to study the coexistence of affective disorder and sleep disorder.

An estimated 90% of depressed adult patients have neurophysiologic changes in sleep [33]. Depression is a pathological condition believed to be present in all age groups with specific diagnostic criteria applied to children. The prevalence rate has been reported in epidemiological surveys in very varied proportions, ranging from less than 1.9% to more than 60% [42]. Therefore, there are indications that this disorder may be underdiagnosed in childhood and adolescence. There is an argument that the diagnostic criteria are not specific for children and adolescents and, therefore, prevalence rates are generally different from those in adults; speculations about the impact of age and degree of development on the phenomenology of depressive disorders persist. Although some studies suggest that it was not necessary to develop a specific diagnostic criterion for depressive disorders in 7- to 16-year-olds since the clinical pictures may be compatible with the DSM-IV criteria [42], this does not mean that the manifestations are identical for different age groups. DSM-IV itself recognizes that frames may be different according to different stages of development. According to DSM-IV, major depression in childhood may have features such as depressive or cranky mood, somatic complaints with no detectable cause, psychomotor agitation, failure to present expected weight gains for age, and symptoms of separation anxiety, phobias and avoidance are also common. Although neurophysiologic alterations of sleep in depressed adults are quite frequent, the studies developed in children have been controversial. Some authors have noted few neurophysiologic changes in sleep in children compared to the control group according to Dahl et al. in 1996 [38]. Nevertheless, there is a description of reduced rapid eye movement (REM) sleep in depressed children [38]. Although consistent, neurophysiologic changes in the sleep of depressed adults are not pathognomonic of major depressive disorder. The few studies carried out among the pre-pubertal age group are still controversial, which is possibly justified by the diagnostic difficulties discussed above. In addition to the scarcity of work in this age group, there are few sleep study data on depressed children in the population and in relation to childhood bipolar disorder, the neurophysiologic data suggest a greater fragmentation of sleep, as has been described in the adult population. Generally, the exclusion criteria in the study of depression in adolescents should be: (1) chronic medical illness or physical handicap; (2) psychoactive substance use or dependence in the last 2 weeks; (3) pervasive development disorder; (4) schizophrenia or severe psychotic disorder; (5) institutionalized subjects or homelessness; (6) mental retardation, and substantial learning difficulties or academic failure; (7) inability to complete all clinical interview procedures. There has been an increase in depression in recent years, linked to the use of electronic devices. An elegant study of 506,820 adolescents published by Twenge et al. in 2017 [43] showed that symptoms of depression, particularly in girls, can be increased as a result of using electronic devices (Fig. 52.2), and this can be followed by suicidal behavior. More studies of depressed children and adolescents are needed to understand the relationship between sleep habits, electronic devices, and mood.

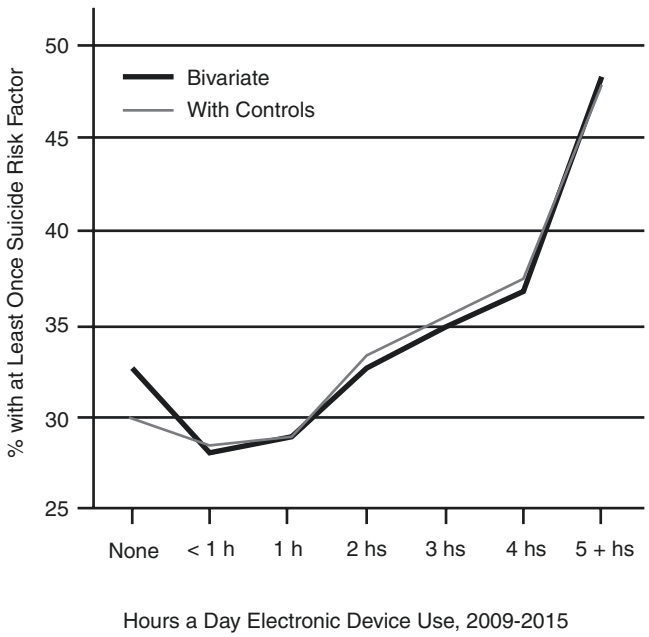

Fig. 52.2 The interaction between suicidal behavior and electronic device use. The relationship between electronic device use showing at least one suicide-related outcome, bivariate and with demographic controls for race, sex, and grade, 9–12th graders, Youth Risk Behavior Surveillance Survey (YRBSS), 2009–2015. (From two nationally representative surveys of U.S. adolescents in grades 8 through 12 in Twenge et al. 2017 [43], reprinted with permission from SAGE Publications)

According to Twenge et al. (2019) [44], the rates of major depressive episodes in the last year increased by 52% in 2005–2017 (from 8.7% to 13.2%) among adolescents aged 12–17 years and by 63% in 2009–2017 (from 8.1% to 13.2%) among young adults 18–25. Severe psychological distress in the past month and results related to suicidal behavior (suicidal ideation, suicide plans, suicide attempts, and deaths) in the last year also increased among young people aged 18–25 years from 2008 to 2017 (a 71% increase in severe psychological disorders). Cultural trends that have contributed to increased mood disorders and suicidal thoughts and behaviors since the mid-2000s, including increased electronic communication and use of digital media and declining sleep duration, may have a greater impact on young people. Moreover, the relationship between sleep and psychiatric disorders has been addressed. A longitudinal epidemiological study has shown that patients with sleep disorders are at higher risk for major depressive disorder, anxiety disorders, drug abuse, and nicotine dependence, with a greater relationship between sleep disorders and major depression [32].

Sleep and Bipolar Disorder

There have been changes in the classification of mood disorders between DSM-IV [42] and DSM-5 [40], and the category bipolar and related disorders and depressive disorders has been introduced. However, sleep-related complaints may not be present among children aged 1–6 years [45]. Sleep disorder is one of the cardinal symptoms for bipolar disorder. Poor-quality sleep may be present before the disorder is diagnosed and during the mania episode [46]. During acute mania, patients frequently present reduced total sleep time and reduced sleep requirements. Even during the euthymic period, sleep disorder is common. Recent studies have shown that 55% of euthymic patients suffer from chronic insomnia [47]. In a sleep study of 13 children with bipolar disorder, frequent complaints of sleep, difficulty in starting sleep, non-repairing sleep, nightmares, and morning headaches were reported [48]. Polysomnography showed that children with bipolar disorder (who had rapid ultradian cycling) had reduced sleep efficiency and frequent nocturnal awakenings; they also had reduced REM sleep and increased delta sleep [48].

Bipolar disorder in childhood tends to be an entity that is difficult to assess due to clinical polymorphism. Early identification tends to change the natural course of the disease. Sleep-related complaints are not among the symptoms in children aged between 1 and 6 years [45]. It is possible that there is a change in the characteristics of symptoms through brain maturation and it has also been suggested that bipolar subtypes that may have specific clinical characteristics. A differential diagnosis is essential for attention deficit disorder [49].

It is possible that a neurophysiologic marker may identify the disorder. It is still unclear whether sleep disturbances may be predictors of recurrence of symptoms in bipolar disorder [50], as well as for attempted suicide [51]. Hormonal issues have also been explored in adults as factors of symptom worsening, and there is evidence that hormonal changes in puberty may also influence the symptoms of bipolar disorder in adolescence. There are changes in the neurophysiologic pattern during development [52] and this finding may be correlated with changes in the neural network and synaptic reprogramming with changes in metabolism. These changes may influence the neurophysiologic pattern of affective disorders according to age, gender, and pubertal stage. There are also alterations of the circadian rhythm in affective disorders. Among children and adolescents with bipolar disorder, this characteristic is more pronounced and similar to adults than in other psychiatric disorders in childhood. These data suggest that sleep disorder may be a possible early marker of bipolar disorder in childhood. Further studies in the area of sleep and bipolar disorder in childhood are necessary for further clarification of the neurophysiologic findings. However, sleep quality in terms of brain wave rhythms, as well as autonomic changes during sleep and its stages, has not been studied. Spectral EEG data have been more widely explored in the population with major depressive disorder, but there are no data on the bipolar population. The quest to understand sleep as an endophenotypic marker has been encouraged [47]. Investigation of brain rhythms during sleep in bipolar children may contribute to the elucidation of an endophenotypic bipolar disorder pattern. Instability of the circadian rhythm has been pointed out as an important endophenotypic factor [50].

In a 2006 study [53], children and adolescents with bipolar disorder were compared with controls, who presented altered circadian rhythm through studies with actigraphy. The importance of sleep in modulating the emotions of children with bipolar disorder has also been studied [54]. The relationship between a genetic predisposition to bipolar disorder and sleep disorders is still unclear.

The manic episode that appeared in the description of mood disorders and disruptive behavior disorders/oppositional defiant disorder in DSM-IV [42] has been changed to disruptive mood dysregulation disorder (DMDD), which is in the depressive disorder class in DSM-V [40]. Copeland (2013) [55] has described a DMDD that occurs in children between the ages of 2 and 5 years, whose parents report high rates of recurrent temper outbursts and irritable mood. According to DSM-V, it needs to occur at least three times a week and cannot be diagnosed in children under 6 years old. Waxmonsky et al. (2017) [56] suggest that sleep deprivation impairs emotional regulation, which could increase the rates of DMDD symptoms, especially in those with pre-existing regulatory deficiencies, as seen in attention deficit hyperac-

tivity disorder. There has been little examination of the relationship between chronic sleep problems and the symptoms of DMDD, and the associations between parent-reported sleep complaints and DMDD symptoms seem to be a shared relationship with other behavioral problems. Chronic sleep problems do not appear to be a primary source of DMDD symptoms. Sleep appeared to be fragmented in the study population of young people with DMDD. Moreover, REM density was different in the bipolar group compared to the attention deficit hyperactivity disorder group and seems to be associated with high pathogenesis of pediatric bipolar disorder. The bipolar group was also associated with a higher rate of depressive symptoms than the DMDD or hyperactivity groups [57]. Sleep can be a key to understand theoretical framework to better of the pathogenesis of pediatric bipolar disorder.

Sleep and Suicide

Adolescents who are depressed and have also shown sleep complaints can have more suicidal ideation. More studies need to assess the role of multiple sleep variables on suicidal behavior. The presence of sleep complaints was associated with suicidal behavior in adolescents with severe depression [58, 59]. Sleep complaints can be a marker for suicidal behavior in children and adolescents [60]. Two other studies reported nightmares [61] and fatigue [62] as predictors of suicidal behavior in adolescents. Young people with bipolar disorder and nightmare comorbidity appear to be at high risk for suicide [63]. Implications for evaluation of nightmares and treatment approaches need to be discussed. Overall, Uddin et al. (2019) [1] showed that nearly one in five young people had had suicidal thoughts, planned suicide, or attempted suicide in the past 12 months (16.9%, 17.0% and 17.0%, respectively). These numbers are much higher than the 12-month prevalence reported in high-income countries. In the US National Comorbidity Survey, 3–6% of adolescents reported suicidal ideation, 0.6% reported a suicide plan, and 1.9% had attempted suicide in the past 12 months. This raises questions about the typical trajectory of suicidal behavior among this population and whether the models developed and validated in high-income countries, such as the integrated motivational-volitional model of suicidal behavior or the interpersonal suicide theory, could help to better understand suicide in low- and middle-income environments [64, 65]. The findings about suicide and sleep are mixed, but a growing body of research suggests that sleep problems may be a unique risk factor for suicidal behavior in youth. Sleep complaints may be particularly important because they are easily assessed across healthcare settings and are amenable to treatment.

Sleep, Mood, and Early Intervention

Sleep has a bidirectional interaction with affective disorders. The most common sleep complaint in children and adolescents is initial insomnia. This differs from the data that have been described for adults where maintenance insomnia is more frequently associated with major depressive disorder. The anxiety state can be followed by sleep deprivation, and it may be a compensative natural process to improve depression symptoms. Prolonged sleep onset has been described as the most reliable sleep macro-architectural abnormality in early onset depression. This suggestion was also supported by a longitudinal follow-up study of adolescents that indicated longer sleep latency in childhood as a marker of recurrent major depressive disorder course. There are many studies of sleep disorders and depression in adults, but fewer in pediatric cases, despite possible interaction between both types of health problems. Subjective analysis of sleep revealed sleep disturbance in children; however, there is a need to access the sleep changes by objective parameters such as EEG spectral analyses. The interaction between depression and anxiety in children and adolescents can be assessed by sleep analyses. Further studies are needed to clarify this interaction.

Many studies have hypothesized that the early recognition and intervention of sleep disorders may prevent recurrent depressive disorders. Such observations favor the theory that sleep physiology disorder may precede other symptoms in the development of affective disorder, particularly in children and adolescents, in addition to the evidence of the high prevalence of sleep disorders in depression and mania. This makes it imperative to study the coexistence of depressive disorder and sleep disorder. In relation to bipolar disorders in childhood, neurophysiologic data suggest greater sleep fragmentation and changes in the sleep-wake cycle of children and adolescents with bipolar disorder, and this can be followed by an increase in the magnitude of the symptoms.

Conclusion

Insomnia, hypersomnia, sleep continuity problems (awakening at night), and sleep–wake reversal are common sleep complaints in pediatric affective disorders. There is evidences that sleep disturbance may be a critical component in the pathogenesis of psychiatric disorders and some studies have indicated that clinical profiles differ between depressed children without and with sleep disturbance and with more severe depression in the latter. In adults, the sleep macro-architecture could not be used as diagnostic marker of depression; however, data on this issue in children and adolescents are not currently available. Questions about sleep

and daytime complaints in children and adolescents with major depressive disorder and bipolar disorder can be very helpful in the clinical assessment of these patients. Depression and other associated factors such as anxiety may gradually change the regulation of sleep and sleep habits, although anxiety disorders can be more associated with sleep onset problems. There are fewer daytime complaints and less somnolence in the pediatric population compared to adults and sleep disturbances in children are often followed by learning disabilities. Sleep deprivation can improve depressive symptoms after one night of deprivation due to the increase in the serum levels of serotonin. Usually, sleep in children and adolescents is characterized by deeper, protective sleep, increased delta sleep, less awake time, and increased arousal threshold. Sleep loss in children might be followed by changes in cognitive function in children. The goal of this chapter was to explore the power of sleep complaints in young individuals with mood disorders.

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Prader–Willi Syndrome

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David Gozal

Introduction

Prader–Willi syndrome (PWS; OMIM 176270) was initially described in 1956 by 3 pediatricians, Andrea Prader, Alexis Labhart and Heinrich Willi, who reported on nine children with four major common features, namely short stature, intellectual disability, obesity, and small hands and feet [1–3]. The phenotypic spectrum was expanded over time, further revealing the rather intrinsic complexity of the condition, which affects several organ systems to affect cognitive, behavioral, and neurologic functioning in addition to endocrine regulation and metabolism. With the expansion of genetic studies on these patients, it became apparent that PWS is the first human disease for which genomic imprinting errors were identified and is also the first condition caused by uniparental disomy [4, 5]. PWS has a prevalence of 1 in 10,000–30,000 live births with both males and females being similarly affected among all ethnic groups [6].

Genetics

The PWS critical region on chromosome 15q11-q13 is exclusively mono-allelically expressed by paternally inherited genes. The absence of expression of one or more of these genes contributes to different phenotypes of PWS, with three main mechanisms having been identified as determining the occurrence of the disease: paternal deletion of the 15q11-q13 region; maternal uniparental disomy 15; or imprinting defects. On the other hand, in the same region, the loss of expression of the UBE3A gene (preferentially maternally expressed) fosters the emergence of Angelman syndrome, with completely different clinical characteristics. By their common implicated region and mechanisms, both syndromes are considered sister imprinted disorders [7–11].

Clinical Manifestations

Clinical manifestations are rather stereotypic but will evolve and change with age while affecting multiple body systems. Fetal size and birthweight are usually within the normal range. However, prenatal hypotonia may be prominent and lead to decreased fetal movements along with a higher risk for problematic delivery or cesarean section [12]. It is the hypotonia, a clinical hallmark feature of PWS, that promotes the risk for failure to thrive during infancy since infants are lethargic and exhibit poor sucking ability. Decreased movements, reduced awakening, weak cry, thick saliva, and poor reflexes are all frequently encountered but of varying severities [13]. Toward the end of the first year of life, hypotonia and feeding usually improve, but reduced muscle mass and tone persist throughout the lifespan. As a corollary to such issues, physical and developmental milestones, such as crawling, sitting, walking, speech, and later reading, are usually delayed, and usually persist [14]. Of note, characteristic behavioral issues such as unusual oppositional behaviors, stubbornness, manipulation, compulsiveness, self-injury, and resistance to novelty are all very common [14–16].

Hypothalamic dysfunction is the endocrinological core problem of PWS and leads to hyperphagia, temperature instability, high pain threshold, sleep-disordered breathing, and multiple endocrine abnormalities [17]. In particular, uncontrollable hyperphagia will frequently result in morbid obesity with increased risk of developing type 2 diabetes mellitus, the latter being reported in up to 25% of adult PWS patients [17]. In uncontrolled cases, obesity and its complications are the major causes of morbidity and mortality: respiratory insufficiency, cardiovascular problems, metabolic syndrome, sleep apnea, and type 2 diabetes mellitus, as

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well as mortality (1.25–3% per year) [17–19]. In addition, increased risk for central adrenal insufficiency (in about 60% of cases) [20] and hypothyroidism (20–30% of children) [21] are common. Clitoral and labia minora hypoplasia in females and micropenis with hypoplastic scrotal sac in males are also very frequent, and hypogonadism with either complete or partial pubertal failure due to hypothalamic-driven reductions in LH, FSH, and gonadal sex steroids is characteristic. Short stature, another hallmark characteristic of PWS, will inevitably be present unless GH replacement therapy is initiated in a timely fashion [22].

Sleep and Respiration in PWS Patients

A common feature in PWS is sleep disruption, related to sleep apnea that impairs the quality and efficiency of sleep, frequently associated with excessive daytime sleepiness, and sedentary behavior with a higher predisposition to obesity [23]. Several abnormalities have emerged over the last several decades regarding sleep per se and breathing during sleep among PWS-affected patients.

The major principles regarding control of breathing have been reviewed in more detail in the previous chapters. However, studies from our group and others uncovered significant abnormalities in respiratory control among patients with PWS. Here, we will briefly review some of the salient abnormalities frequently encountered in children affected with PWS.

A rather frequent abnormality found in 60–70% of PWS is the attenuation of the hypoxic ventilator response (HVR). Exposures to a reduced oxygen concentration among PWS patients unaware of such occurrence showed the absence of the anticipated increases in minute ventilation, while a markedly blunted HVR occurred in the remainder when compared to age-matched controls [24]. Conversely, exposures to hyperoxic gas (100% oxygen), which normally will rapidly reduce ventilation through shutting down of peripheral chemoreceptors, actually resulted in increased ventilatory output among PWS subjects [25]. Similarly, when hypercapnic ventilatory responses (HCVR) were examined in PWS, those patients who had maintained a near-normal body mass index (BMI) showed evidence of near-normal or normal responses, while those who were obese exhibited significant attenuation of their HCVR [24]. Blunting of the HCVR, particularly in the context of obesity, may facilitate not only the emergence of obstructive sleep apnea but may also facilitate the appearance of obesity-hypoventilation. In this context, we reported a case whereby tracheostomy and mechanical ventilatory support during sleep resulted in progressive improvements in HCVR over time [26]. Interestingly, treatment with growth hormone (GH) for 6–9 months improved ventilation at rest, and enhanced HCVR responses independently from the underlying BMI improvements in BMI [27, 28].

The presence of hypotonia and obesity can obviously impose adverse effects on chest and pulmonary mechanics, thereby further increasing the risk of compromised ventilation during sleep. The presence of restrictive lung patterns is frequently detected among children and young adults with PWS in both obese and non-obese individuals and will be further exacerbated by coexisting kyphoscoliosis [29].

The prevalence of obstructive sleep apnea (OSA) is exceedingly high in both obese and non-obese children with PWS (around 75–80%), and its prevalence seems to increase with age [30–33]. As with other children, adenoidal and tonsillar hypertrophy are common contributors to OSA in PWS children, in addition to the underlying hypotonia, obesity, and hypothyroidism, and therefore, initial treatment is not different from any other child, except for the necessary precautions related to anesthesia and postoperative cardiorespiratory monitoring [34]. Of note, and similar to other children, REM sleep predominance of respiratory events seems to be present in PWS children with OSA [35], while a tendency toward excessive alveolar hypoventilation is frequently present [36]. Residual OSA after surgery may be frequently present and therefore repeat sleep study after adenotonsillectomy is routinely recommended [37–39]. If residual OSA is detected, orthognathic approaches may be attempted since behavioral issues may impose very low adherence to CPAP [40, 41]. In younger children with PWS (<2 years of age), central sleep apnea appears to be more prevalent [42], likely reflecting underlying hypothalamic dismaturation and deficits [43] with the concern that the aforementioned alterations in control of breathing may lead to maladaptive arousal responses [44]. Supplemental oxygen therapy carefully monitored for the emergence of alveolar hypoventilation may be considered when central apnea is present [45].

In subjects with PWS, untreated OSA may promote the emergence of excessive daytime sleepiness (EDS) similar to any other child suffering from OSA. However, PWS may also manifest severe EDS that is unrelated to OSA, since EDS may persist even after OSA has been effectively treated [46–50]. Notably, EDS has been linked to significantly worsened behaviors including aggressiveness and impulsiveness [51, 52]. Some patients with PWS may present with features of narcolepsy including cataplexy [53–55], which may be related to reduced levels of orexin in the cerebrospinal fluid, and such EDS may favorably respond to drugs routinely used in the treatment of narcolepsy such as modafinil or pitolisant [33, 56, 57]. Irrespective of the aforementioned sleep issues, restless sleep with frequent nighttime awakenings and disruption of sleep continuity is also likely to be present in children with PWS and may lead to substantial stress among caretakers [58, 59].

Growth Hormone Therapy and PWS

In light of the extensive use of GH in the treatment of children with PWS, some insights into this problem and potential risks are needed. The aims of growth hormone (GH) treatment in PWS are distinct from the use of GH in other clinical pediatric problems [60]. Indeed, the aims are not specifically to enhance height, although treated PWS patients will achieve increased final height in PWS. The major benefits of GH therapy are to ameliorate body composition, enhance exercise capacity, and hopefully prevent accelerated weight gain and morbid obesity. Impaired GH responsiveness to a variety of GH secretagogues and decreased 24-hour spontaneous GH secretion with reduced IGF-I levels have been reported in 40–80% of patients [61–66]. According to the perturbations in GH secretory patterns, subnormal IGF-I levels are frequently found in PWS children, such that a true GH/IGF-I axis dysfunction is detectable in the vast majority of children with PWS. These findings have led to the premise in which GH testing is not routinely required before initiating GH treatment. GH trials in PWS have demonstrated improved muscle mass and strength, reduced adipose tissue mass and increased levels of daily physical activity. Furthermore, GH treatment also leads to improved developmental and cognitive functions in children with PWS. The ideal age for starting GH is unclear, but a clear trend toward initiation of GH therapy at younger ages has been documented worldwide [67].

GH replacement treatment is generally well tolerated by most patients. Nevertheless, fatal events in young patients with PWS have been reported during the first months of GH administration, with respiratory infections being the most likely common cause of death, rather than a specific role for GH itself [68, 69]. Of note, a high incidence of silent aspiration is present in many infants and younger patients with PWS suggestive of significant swallow dysfunction, which may add to the risk of respiratory infection and other adverse consequences [70]. However, the debate on the potential contribution of GH to fatalities has prompted a more conservative surveillance approach that includes polysomnography, otolaryngological evaluation, and assessment of thyroid function [69]. In case of lymphoid tissue hyperplasia, adenoidectomy/tonsillectomy should be taken into consideration either before or during GH treatment, while assessing its impact of underlying sleep-disordered breathing [71]. At this stage, there is inconclusive evidence supporting an adverse effect of GH per se on respiratory functioning, and as a trigger or facilitator of respiratory issues during sleep [27, 49, 72–76]. However, the concern for the potentially accelerated growth of lymphoid tissues and the degree of hypertrophy, which may be related to GH-induced increases in IGF-1 levels, would justify periodic polysomnographic assessments. While the American Academy of Pediatrics recommends that polysomnography be repeated 6–10 weeks after starting GH therapy in children [77], others have recommended less frequent evaluations [60].

Summary

In summary, PWS children are a high risk of manifesting sleep problems including sleep maintenance insomnia, EDS resembling narcolepsy, and sleep-disordered breathing. In light of the high prevalence of such conditions and the conglomerate of many additional organ system dysfunctions, it is highly recommended that the multidisciplinary teams involved in the care of these complex patients will include a pediatric sleep physician.

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Craniofacial Syndromes

54

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Abbreviations

AT	Adenotonsillectomy
CFM	Craniofacial microsomia
ICP	Intracranial pressure
MDO	Mandibular distraction osteogenesis
OAHI	Obstructive apnea hypopnea index
OSA	Obstructive sleep apnea
PRS	Pierre Robin sequence
TCS	Treacher–Collins syndrome
TLA	Tongue lip adhesion
VCFS	Velocardiofacial syndrome
VPD	Velopharyngeal dysfunction

Historical Perspective and General Considerations

Infants and children with craniofacial conditions are a high-risk group for OSA. Upper airway obstruction has long been recognized in children with craniofacial abnormalities, from the time of the original description by Pierre Robin in the 1920s [1]. Compared with otherwise healthy children, both the diagnosis and treatment of OSA in children with craniofacial conditions are more challenging and have evolved from descriptive diagnosis in the historical literature to include more objective evaluation and testing in recent years.

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Similar to patients without craniofacial conditions, polysomnography has allowed for the diagnosis of OSA in less severe cases and provides an objective measure of successful treatment with either surgical or nonsurgical therapy. Identifying which children with craniofacial conditions to evaluate for OSA remains a challenge, as validated screening tools have been shown to be less useful in children with these conditions [2, 3]. The management of OSA in children with craniofacial conditions has also evolved. Unlike many otherwise healthy children, the anatomic location of obstruction in children with craniofacial conditions could be highly variable, including at the level of the tongue base, midface hypoplasia, or multilevel areas of obstruction, depending on the underlying condition and anatomic features, and treatment must be individualized. Multidisciplinary team management of these patients allows for comprehensive evaluation and treatment of OSA, as well as other nonrespiratory consequences of the craniofacial syndrome, including speech, feeding, orthodontics, audiology, pulmonary, otolaryngology, craniofacial surgeon, physical and occupational therapy, and genetic counseling. Once identified, OSA can be managed in a stepwise pattern that involves noninvasive and nonsurgical treatments, as well as surgical management, that can improve obstructive anatomy as well as facial/skeletal harmony.

Specific Craniofacial Conditions

Cleft Lip/Palate Without Micrognathia

With a prevalence of at least 12.4 per 10,000 births, cleft lip and/or palate (CLP) is one of the most common congenital malformations [4]. Craniofacial clefts may include cleft lip, cleft palate, or both. Although most (approximately 85%) of clefts occur in isolation, over 200 syndromes CLP as a feature [5, 6]. Cleft palate without associated cleft lip has been reported to be associated with a syndrome in as many as 50% of cases, while cleft lip and palate together have an incidence

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of syndromes of about 30% [6]. Cleft palate may be unilateral or bilateral, affecting either the soft palate alone or both the hard and soft palate. There are many genetic mutations that cause cleft palate and although some clefts occur as a result of familial inheritance, most are somatic mutations with an unknown cause. Clefts can occur as a constellation of congenital anomalies that form a syndrome. The syndromes that commonly include cleft palate include Stickler syndrome, Treacher Collins syndrome, Goldenhar syndrome, and Nager syndrome. In addition, cleft palates can occur due to an error during embryological development, such as Pierre Robin sequence.

Diagnosis/Treatment

Children born with CLP may have an increased risk of developing OSA [7]. The craniofacial morphologic findings of children with cleft palate have demonstrated a tendency to have a shorter anterior skull base, maxillomandibular retrusion, and a more vertically oriented mandibular plane [8, 9]. These skeletal growth issues can compound soft tissue structures such as the tonsils and adenoids that can lead to obstructive patterns. The oropharyngeal musculature is disrupted by the cleft palate, which impacts speech development as well as airway patency especially during sleep. Unlike otherwise healthy children, snoring may not be a reliable symptom of OSA presence, especially in infants with CLP [10]. There is some evidence that children with isolated cleft palate may be at increased risk for OSA. In a prospective study by MacLean and colleagues that included 35 infants with isolated CLP, all had an obstructive apnea hypopnea index (OAHI) greater than 1/hr and 69% had an OAHI greater than 3/hr [10]. However, another prospective study including 15 infants with isolated cleft palate found that these patients did not have significantly more obstructive apnea compared to an infant control group [11].

Children with CLP who have adenotonsillar hypertrophy may be candidates for adenotonsillectomy (AT). Because of the risk of velopharyngeal insufficiency following removal of the adenoids, many surgeons will opt for partial adenoidectomy to treat OSA in children with cleft palate, although removal of the tonsils should not worsen velopharyngeal dysfunction [12].

Children with cleft palate are also at risk of upper airway obstruction from the palate repair itself. In developed countries, children with cleft palate are treated with primary palatoplasty before or around the child's first birthday, which creates an airtight seal between the nasal and oral cavities and alters airflow. Following primary palatoplasty, as many as 13% of children suffer from velopharyngeal dysfunction (VPD) due to discoordination between the velum and the posterior pharyngeal wall [13]. Surgical correction of nasal emissions and VPD often involves decreasing the circumference of the posterior pharynx. Procedures such as posterior pharyngeal flap or sphincter pharyngoplasty can improve nasal emissions, but the risk of developing OSA following these procedures can range from 9% to 27% [14, 15]. It is the practice of many multidisciplinary craniofacial centers to evaluate for OSA prior to committing them to an airway procedure that could worsen OSA. In some cases, pharyngeal flap takedown may be needed to relieve OSA.

Micrognathia with or Without Cleft Palate

Pierre Robin Sequence (PRS) is a triad consisting of glossoptosis, retrognathia, and airway obstruction. Fifty percent of cases involve clefting of the secondary palate in a U-shaped or V-shaped pattern [16]. The term "glossoptosis" refers to displacement of the tongue posteriorly to obstruct the airway. PRS can exist in isolation or as part of a syndrome. There is a higher incidence of isolated PRS in twins versus the general population, but the etiology of isolated PRS is still unclear, as the condition represents an embryological sequence of symptoms and phenotypes resultant from a single pathological insult rather than a single genetic syndrome. Although there are many syndromes that are associated with PRS, the majority of cases are isolated and not part of a genetically identified syndrome with other systems involved [17].

However, in some children with PRS, the findings are part of an identifiable syndrome. The most common syndrome associated with PRS is Stickler syndrome, which affects approximately 11–18% of patients with PRS [18] and is caused by a mutation in the COL2A1 gene, leading to dysfunction in the production of type 2 collagen. Stickler syndrome is characterized by a flat midface, long philtrum, prominent eyes, retinal detachments, cataracts, joint hypermobility, and a retrognathic and hypoplastic mandible. Molecular genetic testing is available for COL2A1; however, the clinical features are often characteristic for Sticker syndrome. Shprintzen syndrome, also known as velocardiofacial syndrome (VCFS), is another syndrome associated with PRS. The etiopathogenesis is felt to be secondary to a deletion in the 22q11 gene. VCFS is found in up to 11% of patients with PRS. The craniofacial characteristics of VCFS can include cleft palate, retrognathic mandible, and an elongated face. In addition, the cardiothoracic anomalies include pulmonary atresia, ventricular septal defects, and hypoplastic arteries. Other less common syndromes include unique multisystem features in addition to the tongue-based obstruction common to all patients with PRS. There are a number of less common syndromes which include micrognathia (Fig. 54.1) and have unique features that should be considered in the evaluation of a patient with PRS.

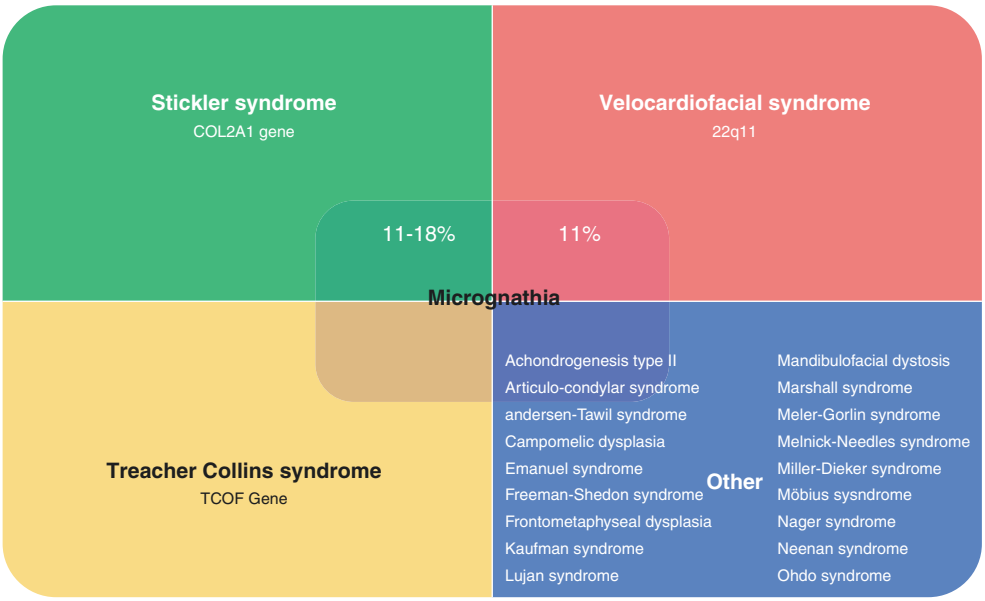

Fig. 54.1 Syndromes associated with Pierre Robin Sequence. Genetic loci have been identified for several of the most common conditions, but many of the less common syndromes are identified based on clinical criteria

Presentation/Evaluation

The severity of both the craniofacial abnormality and associated sleep-disordered breathing in infants born with isolated or syndromic PRS is highly variable. In the most severe cases, airway obstruction in the delivery suite will require endotracheal intubation immediately following delivery. More commonly, infants present with either respiratory and/or feeding symptoms in the hours to weeks after birth. These symptoms may vary in severity and include poor feeding, long feeding times, hypoxia during feeding, gagging, vomiting/gastroesophageal reflux, aspiration, chest retractions, and difficulty gaining weight. Older infants may present with symptoms of upper airway obstruction that become apparent with upper respiratory tract infections. As with other infants with severe OSA, failure to thrive may be attributed not only to their poor caloric intake but also to the excessive metabolic demand due to their increased work of breathing and prolonged feeding times.

As with other syndromic/multisystem anomalies, the ideal clinical scenario for a child with a suspicion for PRS is within a multidisciplinary pediatric airway team [19]. This team should include craniofacial surgery, pediatric pulmonology/sleep medicine, otolaryngology, genetics, nutrition/speech, neonatology, developmental pediatrics, physical and occupational therapists, and social work, among others. A thorough history should include assessment of the prenatal course as well any family history of craniofacial syndromes or disorders. While many infants with PRS who have OSA do snore or have noisy breathing, these symptoms may not correlate with the presence of OSA or its severity [10]. History should also include a detailed account of feeding, including increased work of breathing, gagging, and length of time per feed.

A careful examination can be helpful in diagnosing the underlying syndrome as well as anticipating possible treatment options for OSA. It is important to evaluate the craniofacial features and intraoral pathology of a patient with suspected PRS. The ideal positioning is for the examiner to be seated with the head of the infant on their lap. A tongue blade and light are useful tools to access the oral cavity and maintain visibility. As with other infants with OSA, the respiratory assessment of an infant who is suspected to have PRS can be highly variable, even in those with moderate or severe OSA. If possible, infants should be examined in different positions, while awake and asleep, and during feeding. Careful attention should be paid to suprasternal retractions, stridor/stertor, chest rise/fall, and lack of breath sounds with obstructive events. Continuous pulse oximetry during different scenarios (sleeping, feeding, and varied positioning) can also provide supporting evidence for OSA, although none of these modalities has been shown to be adequately sensitive or specific for detecting OSA. For infants with PRS, various algorithms have been published, but there should be a low threshold to proceed with polysomnography to identify the presence and severity of OSA [20, 21].

When the diagnosis of OSA is made, patients with PRS may benefit from an evaluation of the entire airway to assess for the level of obstruction. Based on this evaluation, there could be a variety of scenarios: no level of obstruction identified, tongue-based obstruction, infraglottic obstruction, or a combination of the two obstructions. In addition, a jaw thrust anteriorly with a well-positioned endoscope can simulate the potential improvement of the tongue-based obstruction with a surgical intervention. This exam is often repeated in the operating room if the patient is planned for a surgical intervention. Additional levels of airway involvement can exist,

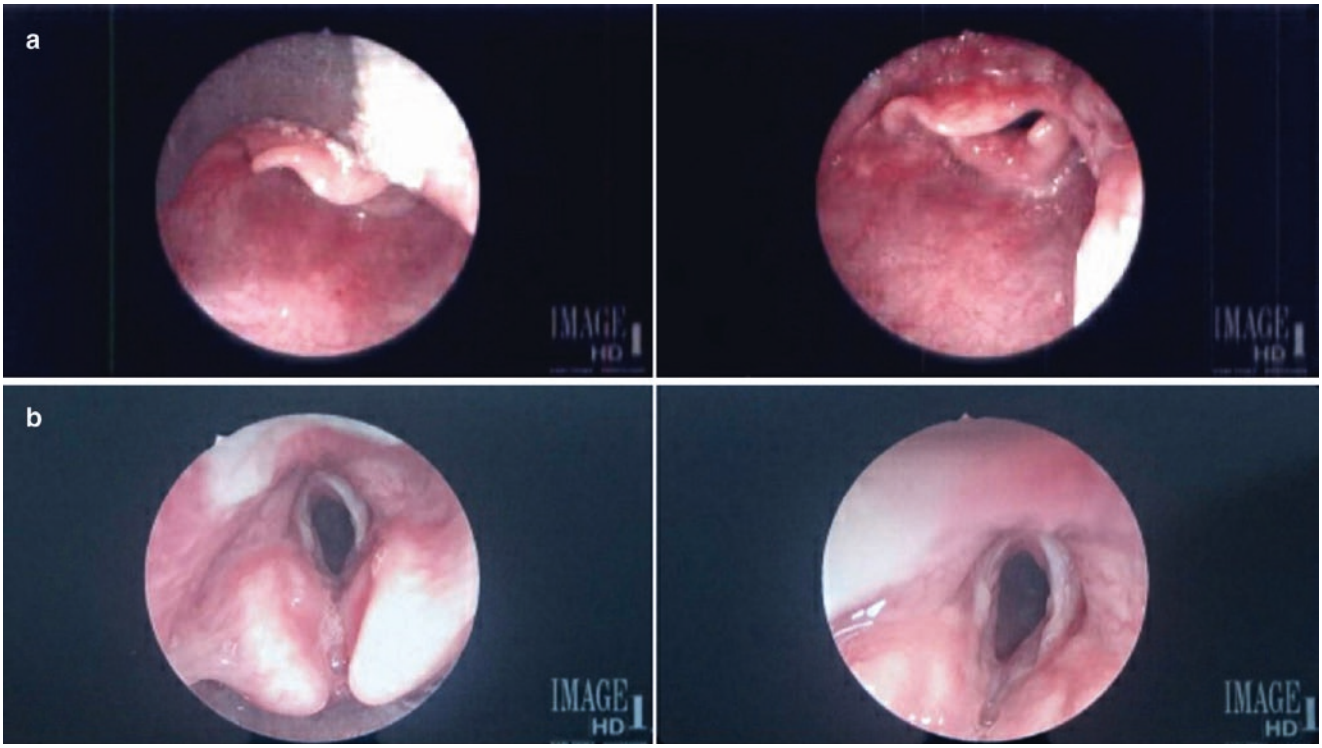

Fig. 54.2 Airway evaluation of a young child with Pierre Robin sequence with severe obstructive sleep apnea requiring tracheostomy, before and after mandibular distraction. (**a**) Before mandibular distraction. Note the glossoptosis and significant retroflexion of the epiglottis. (**b**) Following distraction. Note the widely patent airway at the level of the epiglottis. Tolerated capping of tracheostomy and planning for decannulation

and 10–15% of infants with PRS have been found to have laryngomalacia, which is significantly greater than the likely incidence in the general population of 1 in 2100 newborns [22]. At our center, infants undergo a bedside nasoendoscopic exam as part of the standard clinical evaluation (Fig. 54.2).

Nonsurgical Management

A host of surgical and nonsurgical options are available for OSA in infants with PRS, depending on the severity and anatomy [23]. A stepwise treatment algorithm should be used, and the child should be treated with the least invasive method that effectively treats OSA. Prone positioning during sleep may be attempted as a first-line approach. This treatment, which simply uses gravity to displace the mandible and tongue base forward, was first described by Robin in 1934 and may be effective in a significant percentage of infants even with severe OSA [1, 24]. The benefit of prone positioning should be considered against the potential increased risk of sudden infant death syndrome. Additional nonsurgical treatment options include the use of supplemental oxygen during sleep and nasopharyngeal airway placement or intraoral devices [25]. Continuous positive airway pressure is highly effective in treating severe OSA in children and should be considered in more severe cases. In infants with severe OSA awaiting more definitive management, endotracheal intubation may be required. OSA will improve in subset of infants with PRS with growth, and watchful waiting with close follow-up is appropriate in some patients [26]. Failure of a less invasive approach may warrant more invasive nonsurgical or more definitive surgical treatment options.

Surgical Airway Management

Tracheostomy, by bypassing the site of the obstruction, is highly effective at alleviating OSA and is still appropriate in severe cases when less invasive option is not available, such as a child with infraglottic obstruction or if other methods were employed and the child is still failing to thrive. A tongue lip adhesion (TLA) is a surgical procedure that can aid in the resolution of airway obstruction due to micrognathia and glossoptosis originally described by Shukowsky in 1911 and modified by Douglas in 1943 [27]. This technique involved simply suturing the tongue to the anterior positioned lower lip. The modern version of the TLA involves creation of a mucosal flap on the ventral surface of the tongue and a corresponding mucosal flap from the labial surface of the lower lip. A large suture is then used to secure the tongue to the lip

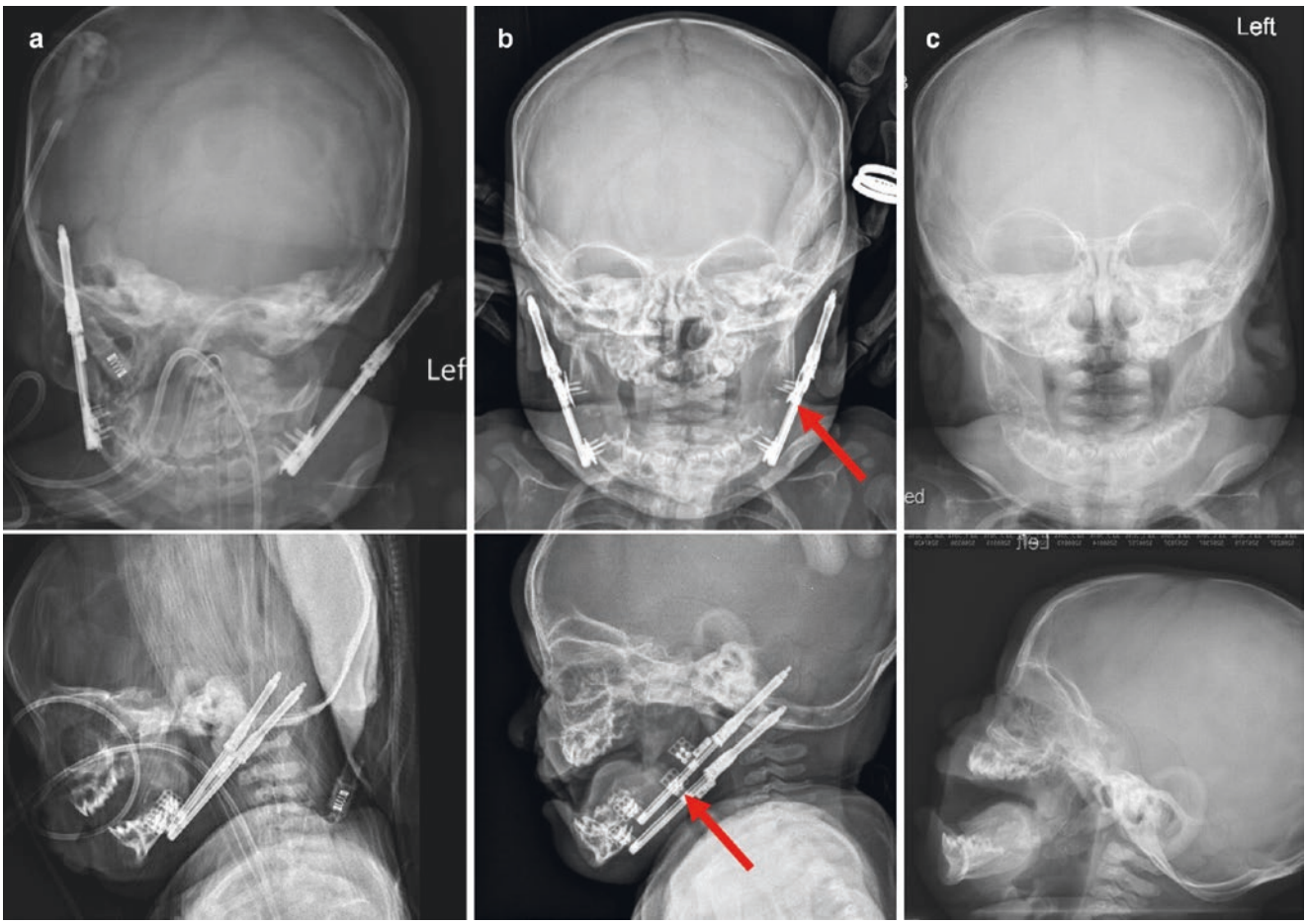

Fig. 54.3 Pre- and postoperative X-rays of a patient with Pierre Robin sequence who underwent mandibular distraction osteogenesis. (**a**) Prior to distraction with placement of the devices. The mandibular dentition is retruded (dental and skeletal class 2 relationship) compared to the maxillary dentition. (**b**) Following mandibular distraction of 22 mm. Note the distance between screws, corresponding to distraction (*arrow*). (**c**) Post distraction after the devices have been removed. The mandibular dentition is now anterior to the maxillary dentition (class 3 dental and skeletal relationship). The surgeon will often determine when to stop distraction with the maxillary and mandibular skeletal/dental relationship

and the mandible. The tongue suture is typically secured with some form of button to prevent the migration of the suture and can be taken down at time of palatoplasty. Rodgers et al. retrospectively reviewed their experience with TLA in infants with PRS, formulating an acronym to correlate with airway failures after a TLA: GILLS (gastroesophageal reflux, intubation preoperatively, late operation (2 weeks of older), low birth weight (< 1872 g), and syndromic diagnosis). In their cohort of 53 infants with PRS who had undergone TLA, 6 failed treatment and underwent a tracheostomy, all of whom had a GILLS score of 3 or greater [28]. The drawbacks to TLA include wound issues related to lack of lip adherence to the tongue and protentional speech developmental disturbances [29]. There are limited studies assessing improvements in OSA following TLA that involve objective testing with polysomnography.

Infants refractory to conservative management may be candidates for mandibular distraction osteogenesis (MDO). MDO is a surgical procedure that involves an osteotomy of the mandible and placement of a device that will incrementally advance the mandible anteriorly (Fig. 54.3). In addition to the bony movement of the mandible, the soft tissue structures such as the base of tongue and musculature will advance as well. Once sufficient mandibular advancement is achieved, the distraction device is left in place for several weeks to allow consolidation of the new bone regenerate that is formed between the two osteotomy sites. There is generally minimal scarring visible following MDO and continued mandibular growth is typically proportional (Fig. 54.4). Multiple studies including objective testing like polysomnography have shown that MDO can be highly effective in treating even very severe OSA in infants with PRS [30]. Complications

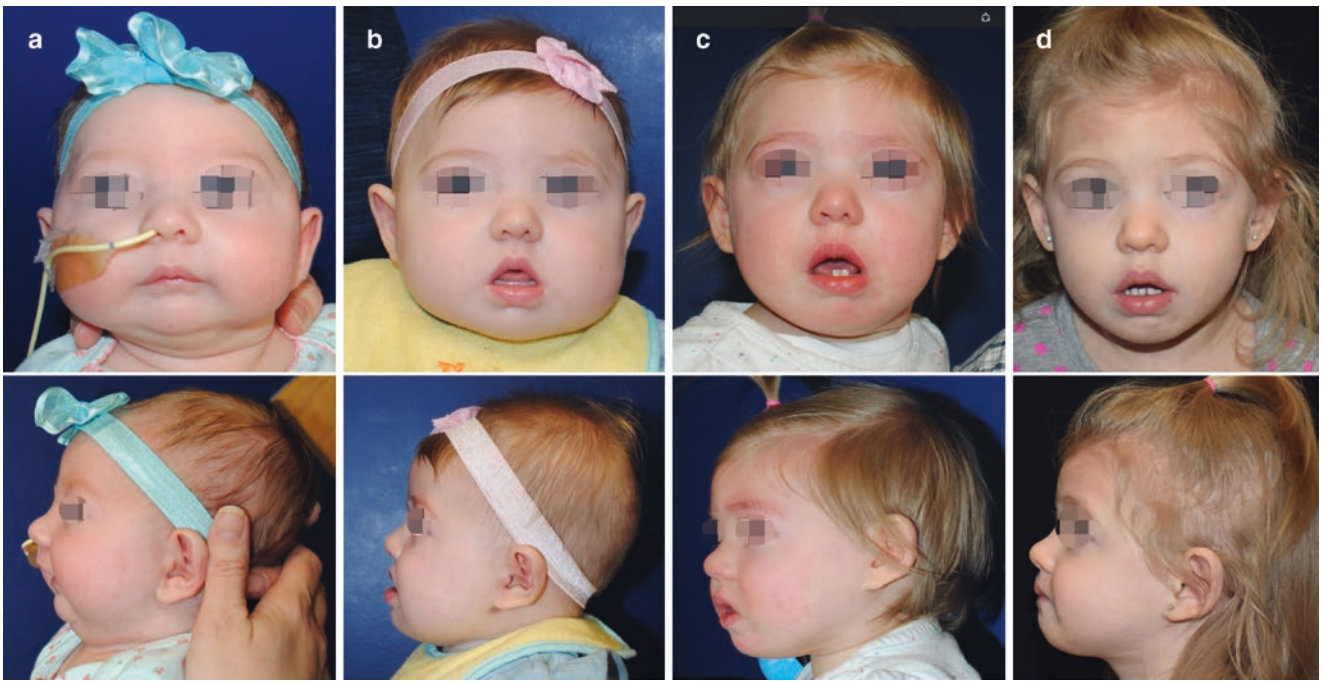

Fig. 54.4 Photographs of a patient with Pierre Robin sequence who underwent mandibular distraction osteogenesis (MDO). (**a**) 3 months of age prior to MDO. Notice the severe micrognathia. (**b**) 1 month after MDO. Notice the anterior position of the mandible. (**c**) 1 year after MDO. (**d**) 2 years after MDO. Long-term mandibular advancement

from MDO include infection, malocclusion of the jaws, dental damage, nerve injury, and scarring [31].

There have been no prospective trials comparing MDO and TLA. Flores et al. reported their clinical experience over a 15-year span utilizing both TLA and MDO for nonsyndromic neonates with PRS. Following surgery, patients who underwent MDO had significantly better oxyhemoglobin saturation and lower apnea hypopnea index compared to those who had TLA, despite that fact that baseline OSA was more severe in those who had MDO [32]. The decision to undergo either mandibular distraction osteogenesis or tongue-lip adhesion is influenced greatly by the surgeon's specialty and experience [33, 34]. A number of studies have proposed algorithms and patient-selection guidelines, but these rely largely on expert opinion or results from small studies [35, 36]. There is a paucity of primary literature directly comparing outcomes of tongue-lip adhesion versus mandibular distraction osteogenesis. In a literature review that included 67 studies, Zhang et al. found that both TLA and MDO were effective techniques to avoid tracheostomy and improve oral feeds, but concluded that MDO may provide a superior long-term resolution of the airway obstruction when compared to TLA, but may have a more complex complication profile [37].

Syndromes with Other Mandibular Anomalies

Craniofacial microsomia (CFM) is a condition that involves a range of underdevelopment of the mandible. Disruption of the first branchial arch during embryogenesis can result in malformations of the maxilla, mandible, temporomandibular joint, muscles of mastication, ear, and the facial nerve. Unilateral and bilateral cases of CFM have been described to be associated with OSA. Much like micrognathia, the cause of OSA is multifactorial, involving adenotonsillar hyperplasia, retrognathia, and glossoptosis [38]. Patients with CFM should be investigated for signs and symptoms of OSA, including nasoendoscopy, polysomnography, and craniofacial CT scan. Management of the mandibular deformity can range from mandibular distraction, mandibular reconstruction with autografts, and/or orthognathic surgery.

Treacher Collins syndrome (TCS) is another condition that results in micrognathia and obstructive sleep apnea. It is an autosomal dominant that has an incidence of 1 in 50,000 live births. The loss-of-function mutations are found in the TCOF1 gene [39]. Cephalometric studies correlate skeletal deformities such as mandibular retrognathia, decreased posterior facial height, obtuse mandibular plane with increased airway severity in the TCS patient [40]. The multilevel areas

of airway obstruction in TCS make treatment in this patient population very difficult. The incidence of tracheostomy dependence is reported to be 23–41% [41]. Patients with TCS and mandibular anomalies should be managed in a multidisciplinary setting much like those with PRS and micrognathia. Traditional methods of mandibular surgery utilized in PRS may not adequately address all the levels of skeletal obstruction [42]. Hopper et al. examined the effectiveness of utilizing subcranial Le Fort III bilateral osteotomies, and external distractors to create a counterclockwise rotation of the craniofacial skeleton. The authors demonstrated successful decannulation of 4 out of 5 patients who underwent this treatment. Although a small sample size, this treatment provides a promising surgical method to tackle the complexities unique to TCS [43].

Syndromic Craniosynostosis

Craniosynostosis is a congenital disorder affecting 1 in 2500 live births and is characterized by the premature fusion of cranial sutures. This abnormal fusion restricts the normal growth of the skull, brain, and face. Forty percent of the time, craniosynostosis is seen in syndromes such as Apert, Crouzon, Pfeiffer, or Saethre-Chotzen. The most common syndromes include those that are caused by mutations of the fibroblastic growth factor receptor gene (FGFR) [44]. These include Apert, Crouzon, and Pfeiffer syndromes. The genotype–phenotype interactions for all these conditions remain poorly understood. The same gene mutation in 2 different individuals can cause a different penetrance, phenotype, and even syndrome [45]. As many as 68% of patients with syndromic craniofacial disorders (Apert, Crouzon, or Pfeiffer syndrome) have OSA, often in the neonatal period [46]. In children with syndromic craniosynostosis, the primary craniofacial abnormality felt to contribute to OSA is midface hypoplasia, which may be severe in some cases. In recent years, the role of cranial base development impacting midface hypoplasia has been investigated. Taylor et al. performed a retrospective radiographic study of their syndromic craniofacial patients and found that earlier fusion of the spheno-occipital synchondrosis was positively correlated with severity of midface hypoplasia development of the midface [47]. Early fusion of the cranial base is seen in patients with Apert syndrome when compared to those with Muenke syndrome, the latter having variable rates of midface hypoplasia, while it is seen in almost 100 percent of children with Apert syndrome [48]. In addition, other factors such as adenotonsillar hypertrophy and retrognathia can compound the upper midface and cranial base hypoplasia to contribute to OSA.

Evaluation

Like patients with cleft palate and PRS, patients with syndromic craniosynostosis are managed in a multidisciplinary team. In addition to the craniofacial surgery, these patients should be closely followed by a pediatric neurosurgeon due to high risk for increased intracranial pressure (ICP). There are several factors that can account for the increased ICP in children with syndromic craniosynostosis, including abnormal venous drainage, hydrocephalus, and restricted cranial growth. In addition, OSA may exacerbate these factors due to intermittent hypercapnia and its effects on arterial and cerebral perfusion pressure [49]. Multiple studies have shown a significant correlation between the severity of OSA and increased ICP measurements in children with syndromic craniosynostosis [50, 51]. In addition to OSA, children with syndromic craniosynostosis are also at risk for central apnea. The incidence of Chiari 1 malformation in these children is between 50% and 70%, as the premature fusion of the cranial sutures can result in an abnormally small posterior fossa [52]. This can cause local compression of the medullary respiratory centers of the hindbrain resulting in central apnea. It is important to rule this out, as a neurosurgical intervention could be warranted [53].

As part of their multidisciplinary care, patients with syndromic craniosynostosis should undergo polysomnography to evaluate for both central and obstructive sleep apnea. Additional diagnostic workup may include nasoendoscopy and bronchoscopy to rule out multilevel obstruction. In addition, craniofacial CT is often performed to evaluate for signs of increased intracranial pressure and Chiari malformation, and to better assess midface retrusion that would contribute to airway obstruction. The neurosurgical evaluation also involves brain MRI to determine the amount of hind brain compression before and after a possible posterior fossa decompressive procedure [54].

Management

If patients with syndromic craniosynostosis are found to have significant OSA in the neonatal period, there are usually limited surgical treatment options. In many cases, patients are be treated with nonsurgical management of their OSA. CPAP has been shown to be effective, and success has been demonstrated with the use of a palatal plate [55]. Nasopharyngeal airway has been shown to improve OSA severity in young children with syndromic craniosynostosis [56]. In more severe cases that are refractory to noninvasive management, tracheostomy may be required at least until more definitive surgical treatment is available.

The surgical management for patients with syndromic craniosynostosis involves multiple operations, beginning with cranial remodeling and expansion at some time in the

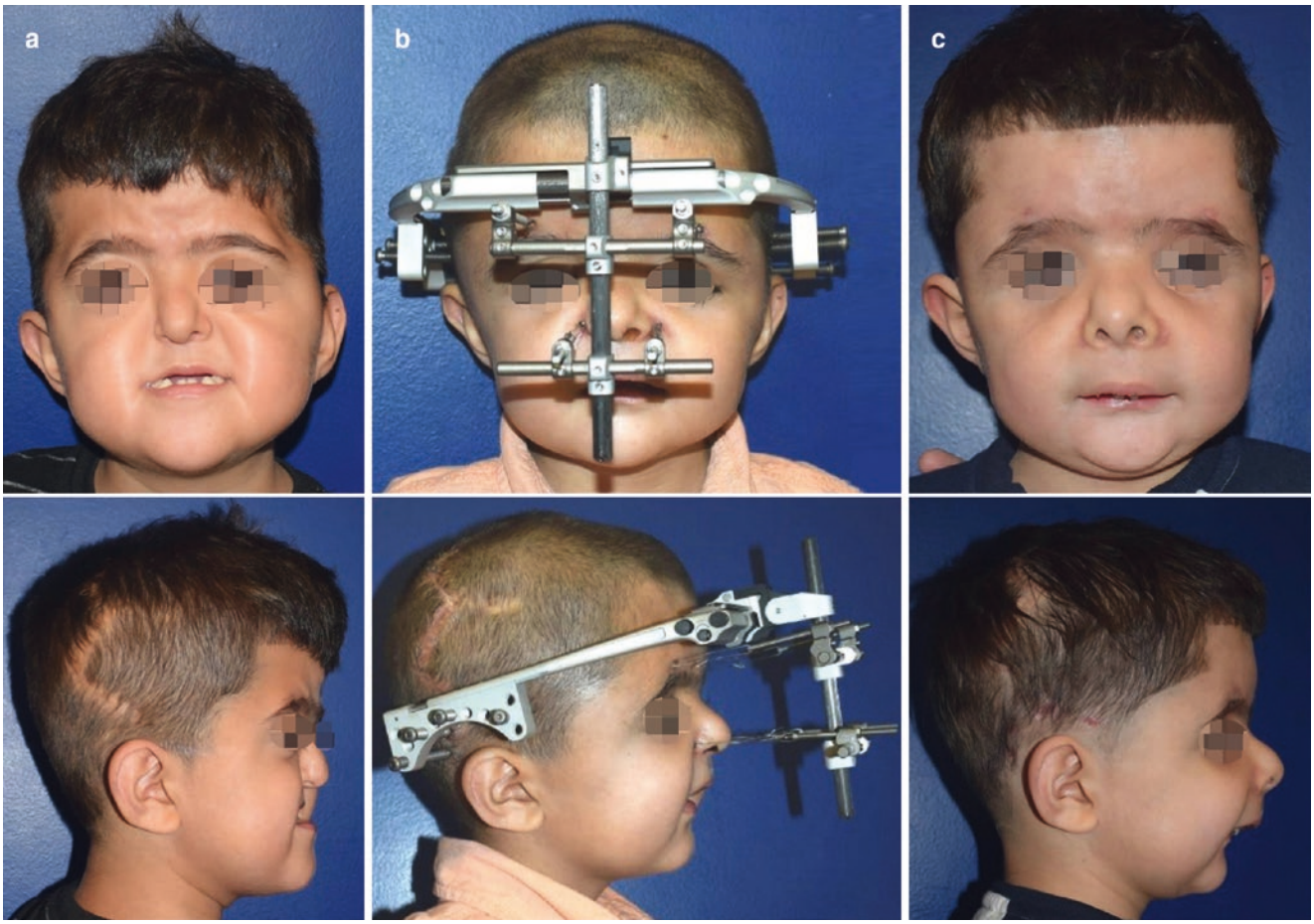

Fig. 54.5 5-year-old male with Apert syndrome undergoing midface distraction. (**a**) Before advancement; (**b**) during advancement; (**c**) after advancement complete and after midface distraction. The advancement of the midface results in an overbite relationship of the maxillary and mandibular dentition

first year of life followed by midface advancement. The midface procedures can involve multilevel craniofacial approaches. Recent development of external and internal distraction devices has enabled more advancement than the historical procedures, which were previously limited by soft tissue (Figs. 54.5 and 54.6). The range of reported improvement of OSA after a midface distraction procedure is between 43% and 73% [57, 58]. One study of 11 children with syndromic craniosynostosis found improvement in OSA in the short term after a monobloc or Le Fort III distraction procedure [59]. The utilization of pre- and postoperative nasoendoscopy can be a vital examination tool to determine the optimal surgical treatment. This can help determine the role of the dynamic pharyngeal airway collapse in this patient population [48]. In addition, the vector of midface distraction may be as important as the linear distance of distraction in the treatment of OSA in this population. In a study assessing children with syndromic craniosynostosis undergoing Le Fort III distraction, patients who had a more obtuse angle of distraction of the midface from the cranial base (sella-nasion-subspinale) resulted in a greater improvement of OSA [60, 61]. While some studies have shown that adenotonsillectomy may improve OSA in some children with syndromic craniosynostosis who have adenotonsillar hypertrophy [62], others have shown little improvement following AT [63]. In addition to improving OSA, midface advancement may help to improve facial harmony, dental occlusal relationships, and exorbitism.

Conclusion

Patients with a variety of craniofacial conditions are at increased risk for OSA due to a variety of structural abnormalities, including mandibular hypoplasia and midface hypoplasia, among others. There are a variety of syndromes that can result in craniofacial abnormalities, many of which are uncommon or rare, and there is a wide range in the severity of sleep-disordered breathing even within specific syndromes. In children with syndromic craniosynostosis, central

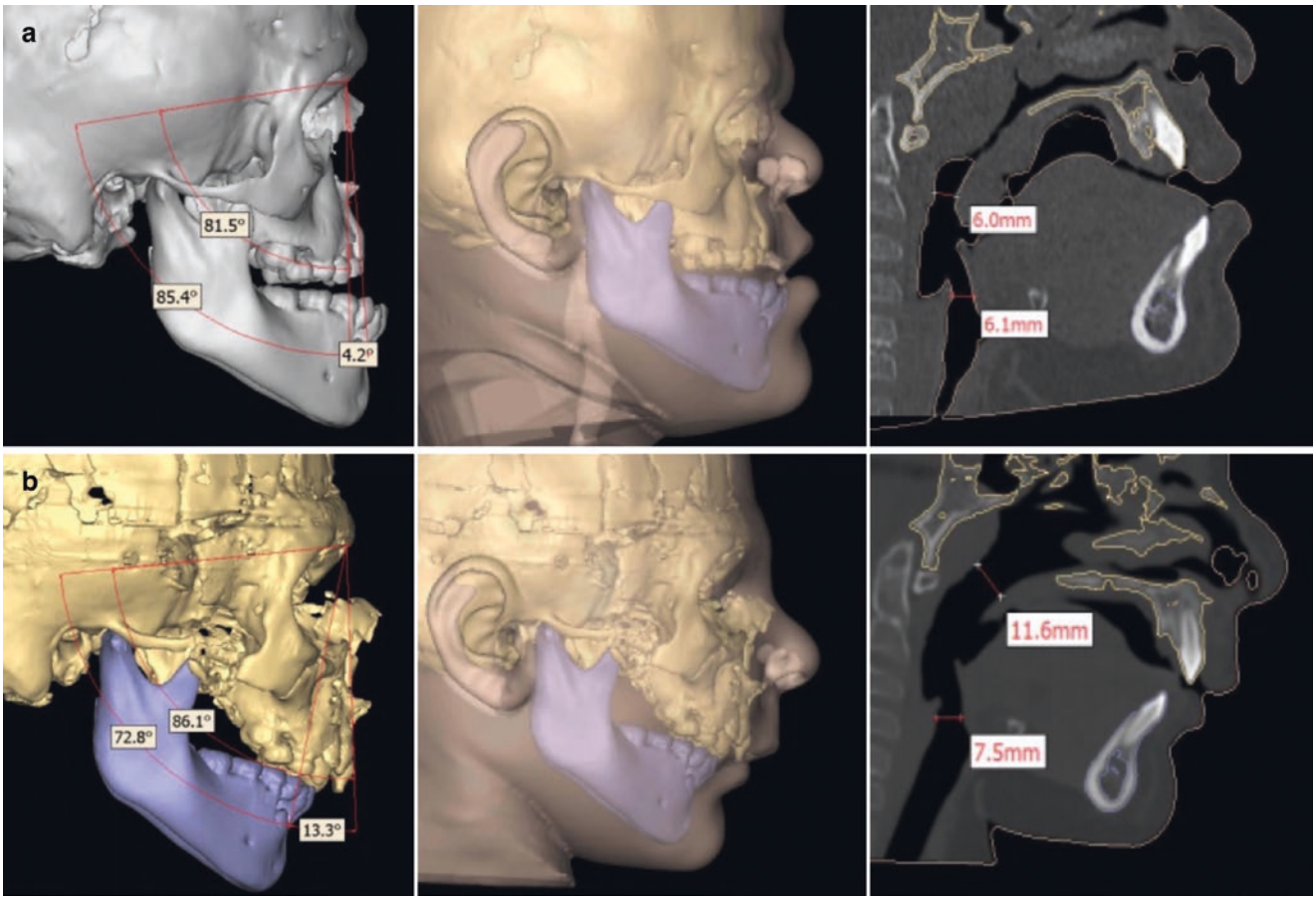

Fig. 54.6 (**a, b**) Pre- and postoperative 3D reconstruction CT for the 5-year-old child with Apert syndrome who underwent midface distraction. The skeletal relationship shows a dramatic advancement of the midface and overbite of the dentition and airway diameter increased at the level of the epiglottis and tongue base

sleep apnea should be considered in addition to OSA. A careful history and physical exam should be performed to evaluate for OSA in all patients with craniofacial conditions, ideally in the context of a multidisciplinary care team. There should be a low threshold for polysomnography as there are not good OSA screening tools available for these patients. Treatment should be individualized; there are a variety of options, including both conservative/nonsurgical and surgical treatments. Larger and longitudinal studies with objective testing for OSA are needed to provide better guidelines for the evaluation and management of OSA in these patients.

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Sleep Problems and Developmental Delay

55

Stacey Bissell, Ashley Liew, Caroline Richards, and Andrew Surtees

Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
CPAP	Continuous Positive Airways Pressure
CSHQ	Children's Sleep Habits Questionnaire
EEG	Electroencephalogram
GDD	Global developmental delay
ICSD-3	International Classification of Sleep Disorders – third edition
ID	Intellectual disability
SEN	Special Educational Needs
SQ-SP	Sleep Questionnaire – Simonds and Parraga
TD	Typically developing

Introduction

Sleep plays an important role in memory, attention, cognitive functioning, cell repair and health maintenance. When sleep problems occur in children with developmental delay, their impact may be particularly pronounced, as these areas of development are likely to already be compromised in the absence of sleep difficulties. Children with global developmental delay (GDD) experience a significant lag in reaching developmental milestones (e.g. gross motor skills, speech, and language) [1]. When such difficulties continue beyond the age of 5 years, intellectual disability (ID) is diagnosed according to intellectual ability impairment (e.g. academic learning, abstract reasoning), adaptive functioning deficits (e.g. daily living skills, communication) and the need for additional service provision [2]. Here, the term developmental delay is used to refer to both GDD and ID populations. In this chapter, the three subsequent sections will:

1. Profile the biomedical, psychological and contextual comorbid factors that may underlie poor sleep associated with developmental delay and consider the behavioural model of sleep from a psychosocial perspective.
2. Provide an overview of current measures and methodologies used to assess sleep quality in populations with developmental delay and outline how such tools can be used in clinical formulation.
3. Present current behavioural and medical sleep interventions suitable for such populations.

There is good evidence that behavioural and physical sleep difficulties are more prevalent in children with developmental delay compared to their typically developing (TD) peers [3, 4]. Overall, rates of poor sleep in ID populations range from 34–86% [5, 6], compared to 25–43% in TD children [7, 8]. However, the prevalence of 'sleep disorders' likely underestimates broader difficulties often associated with developmental delay. The International Classification of Sleep Disorders – third edition (ICSD-3 [9]) defines sleep disorders according to seven categories: insomnia, sleep-related breathing disorders (e.g. obstructive sleep apnoea), central disorders of hypersomnolence (e.g. narcolepsy), circadian rhythm sleep–wake disorders (e.g. advanced sleep-wake phase), parasomnias (e.g. nocturnal enuresis), sleep-related movement disorders (e.g. restless legs syndrome) and other sleep disorders (e.g. environmental sleep disorder). Like other diagnostic manuals, diagnosed sleep disorders and their descriptors primarily reflect the experience of TD populations and as such, the application of such diagnoses may be challenging to populations of children with developmental delay. It is therefore preferable to adopt the term 'sleep problem' in the current chapter to encompass broader sleep disturbances and behavioural issues that do not necessarily adhere to TD models of sleep (e.g. insomnia occurring in the absence of daytime symptoms, bedtime

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Table 55.1 Results from meta-analysis by Surtees et al. [12] reporting poorer sleep quality in heterogeneous ID and genetic syndrome/developmental disorder cohort studies (highlighted in bold) compared to TD control groups

Analysis	Number of studies	Model	Number of experimental groups	Weighted mean difference, [95% CI]	Heterogeneity statistics	
					Cochran's Q (p)	Higgins I^2
All studies	18	REM	27	−4.56[a] [−7.86, −1.26]	21934.67 (< 0.01)	100%
	18	QEM	27	−2.46 [−12.48, 7.57]	21934.67 (< 0.01)	100%
Objective measures only	14	REM	20	−3.81[a] [−5.75, −1.86]	352.69 (< 0.01)	95%
	14	QEM	20	−1.73 [−6.84, 3.37]	352.69 (< 0.01)	95%
Heterogeneous intellectual disability	7	REM	8	*−0.44[a] [−0.86, −0.03]*	13.39 (0.06)	48%
	7	QEM	8	*−0.59[a] [−1.18, 0]*	13.39 (0.06)	48%
Genetic syndromes/developmental disorders	15	REM	19	*−5.98[a] [−9.54, −2.43]*	951.34 (< 0.01)	98%
	15	QEM	19	*−8.98[a] [−17.89, −1.84]*	951.34 (< 0.01)	98%
Only 1 intellectual disability group per study	18	REM	18	−4.76[a] [−8.91, −0.61]	21725.16 (< 0.01)	100%
	18	QEM	18	−2.47[a] [−13.18, −8.23]	21725.16 (< 0.01)	100%

Notes. Results of the meta-analysis of sleep quality: *REM* random-effects model, *QEM* quality effects model
[a]Indicates a significant difference between intellectual disability and control groups
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resistance, evidence for REM-related parasomnias in the absence of verbal report).

Variable prevalence rates for sleep problems associated with developmental delay can be attributed: (1) methodological differences between studies, (2) multiple comorbid disabilities associated with the severity of ID and (3) the inclusion of known genetic syndrome groups (e.g. fragile X syndrome, Down syndrome) in reported samples [10, 11]. One recent meta-analysis reported poorer sleep quality associated with both heterogeneous developmental delay and syndrome-specific ID compared to TD peers [12], as highlighted in Table 55.1. However, shorter sleep duration was specific to comorbid developmental delay associated with neurodevelopmental and genetic conditions. Therefore, it is important to adopt a person-focused approach when considering assessment and treatment options for children presenting with both developmental delay and sleep problems.

Comorbid Factors

As outlined previously, there are a number of co-occurring physical and cognitive characteristics associated with developmental delay that may contribute to the prevalence of specific sleep problems and poor sleep more generally [12]. These factors may be biomedical, psychological or environmentally mediated and should be considered when identifying appropriate treatment choices.

Biomedical Factors

A number of secondary health conditions associated with developmental delay are also found to be associated with poor sleep quality (e.g. constipation, gastro-oesophageal reflux, respiratory tract infections, otitis media and dental caries [13–15]). When health conditions/physical discomfort occurs, pain may be the mediating variable that triggers and/or exacerbates poor sleep [16, 17]. Research specifically exploring the relationship between pain and sleep problems in children with developmental delay by Breau and Camfield [18] found that children experiencing pain had shorter sleep duration and more sleep problems (night waking, parasomnias and sleep-disordered breathing) than children not experiencing pain.

In known neurodevelopmental disorder and syndrome groups associated with developmental delay, there may be syndrome-specific physiological characteristics that exacerbate poor sleep. For example, the inverted circadian release of melatonin in Smith–Magenis syndrome [19, 20] is a strong causal mechanism for the frequency and severity of night wakings, early morning wakings, daytime sleepiness and reduced sleep duration phenotypic of this syndrome [21–23]. In Angelman syndrome, the disrupted sleep architecture characterised by distinctive electroencephalogram (EEG) patterns and dysregulated GABAergic neurotransmission may underlie night-time arousal, parasomnias and daytime sleepiness [24, 25].

Prevalence rates of epilepsy associated with ID are approximately 30 times higher than in TD community populations [26]. Sleep-disordered breathing, obstructive sleep apnoea and daytime sleepiness are commonly reported when epilepsy comorbidity occurs [27, 28], which may be attributed to: which may be attributed to: (1) fragmented sleep architecture, (2) abnormal EEG activity, (3) the presence of nocturnal seizures, or (4) the prescription of anti-epileptic medication fragmented sleep architecture, abnormal EEG activity, the presence of nocturnal seizures, or the prescrip-

tion of anti-epileptic medication [29–31]. Several studies have shown that anti-epileptic drugs can disrupt sleep either as a result of sedative adverse effects inducing daytime sleepiness [32], or by disrupting sleep architecture and time spent in slow wave and rapid eye movement stages of sleep, reducing overall sleep efficiency and quality [33].

Psychological Factors

Higher rates of psychiatric disorders are reported in individuals with developmental delay and ID compared to typical development, most notably anxiety [34] and depression [35]. Anxiety is associated with increased night-time arousal, decreased slow wave sleep, insomnia, parasomnias and sleep-related anxiety in children and adults without developmental delay or ID [36, 37], and high rates of insomnia and hypersomnia are described in children with depression [38]. Few studies have noted a significant relationship between anxiety and sleep problems [39, 40] and depression and sleep problems [41, 42] specifically in children with developmental delay or adults with ID. This may reflect a larger clinical difficulty in identifying mental health concerns in adolescents and adults with an ID. Clinicians need to be mindful that children with developmental delay or adolescents and adults with ID may present with symptoms of anxiety and depression that evade diagnosis [43] but converge with the profile of poor sleep (e.g. frequent night waking, parasomnias and daytime sleepiness). If comorbid psychiatric disorders are diagnosed in children with developmental delay or adults with ID, clinicians must also consider the adverse effects of benzodiazepines (e.g. daytime sleepiness [44]) and selective serotonin reuptake inhibitors (e.g. treatment-induced insomnia [45]) when used to treat anxiety and depression, respectively.

Prevalence rates for autism amongst children with developmental delay vary between 18%–69% [46, 47]. Poor sleep associated with developmental delay and comorbid autism has been specifically explored in relation to heightened autonomic activity that may underlie purported relationships between sleep difficulties, anxiety and sensory over-responsivity [48]. Cotton and Richdale [49] found that children with autism were more likely to experience settling problems than other known syndrome groups associated with ID. Giannotti et al. [50] found that autistic children with ID, compared to children without ID, were more likely to evidence delayed sleep phase disorder, irregular sleep/wake disorder, later sleep onset, shorter sleep duration, and more frequent bedtime resistance and night wakings. More information about the profile of sleep problems in autism is presented in Chap. 50.

The prevalence of attention deficit hyperactivity disorder (ADHD) in children with developmental delay is approximately 39% [51], but varies depending on: the measure of ADHD used, severity of ID reported and diagnostic classification of ADHD (e.g. hyperactive-impulsive, inattentive and combined subtypes [2]). The prevalence of diagnosed sleep disorders in children with ADHD is estimated at 25–50% [52], with children and adolescents presenting most often with insomnia [53], periodic limb movements [54] and increased bedtime resistance [55]. Children with a combined ADHD subtype present with more night-time arousals, whereas children with inattentive ADHD are more likely to evidence daytime sleepiness [56]. Given the diagnostic overshadowing of ADHD in known neurological conditions [57], there is limited research exploring sleep problems specifically in people with ID and comorbid ADHD, or the influence of methylphenidate- and amphetamine-based stimulants on the presentation of sleep problems, particularly insomnia and delayed sleep phase disorder [58]. A model depicting the association of biomedical and psychological factors with sleep problems in developmental delay is presented in Fig. 55.1.

Contextual Factors

Sleep problems associated with developmental delay do not occur in isolation. For effective treatment, environmental and familial factors should also be considered. There is well-delineated evidence that sleep problems in children with developmental delay predict the frequency and severity of daytime externalising behaviours [59–61], with a likely bi-directional relationship between sleep problems and daytime behaviour. Wiggs and Stores [61] state that the nocturnal responsibility placed on caregivers is compounded by increased daytime behaviour demands. These challenges must be acknowledged when behavioural interventions are proposed by professionals. Similarly, impaired communication abilities can present significant barriers when implementing behavioural or medical interventions [12]. Limited expressive communication skills make it difficult for children with developmental delay to communicate their experiences of poor sleep or responses to medication. Limited receptive communication skills impede the ability to acquire sleep hygiene practices and establish bedtime routines.

Caregivers also experience reduced sleep duration when managing their child's sleep problems [61–63]. In particular, settling difficulties, night-time restlessness and night waking induce feelings of stress, and the association between caregiver stress and night waking is strongest in children with severe ID compared to mild ID [64]. This may be because children with severe ID: (1) experience more health-related difficulties associated with nocturnal medical technologies that require parental monitoring (e.g. assisted

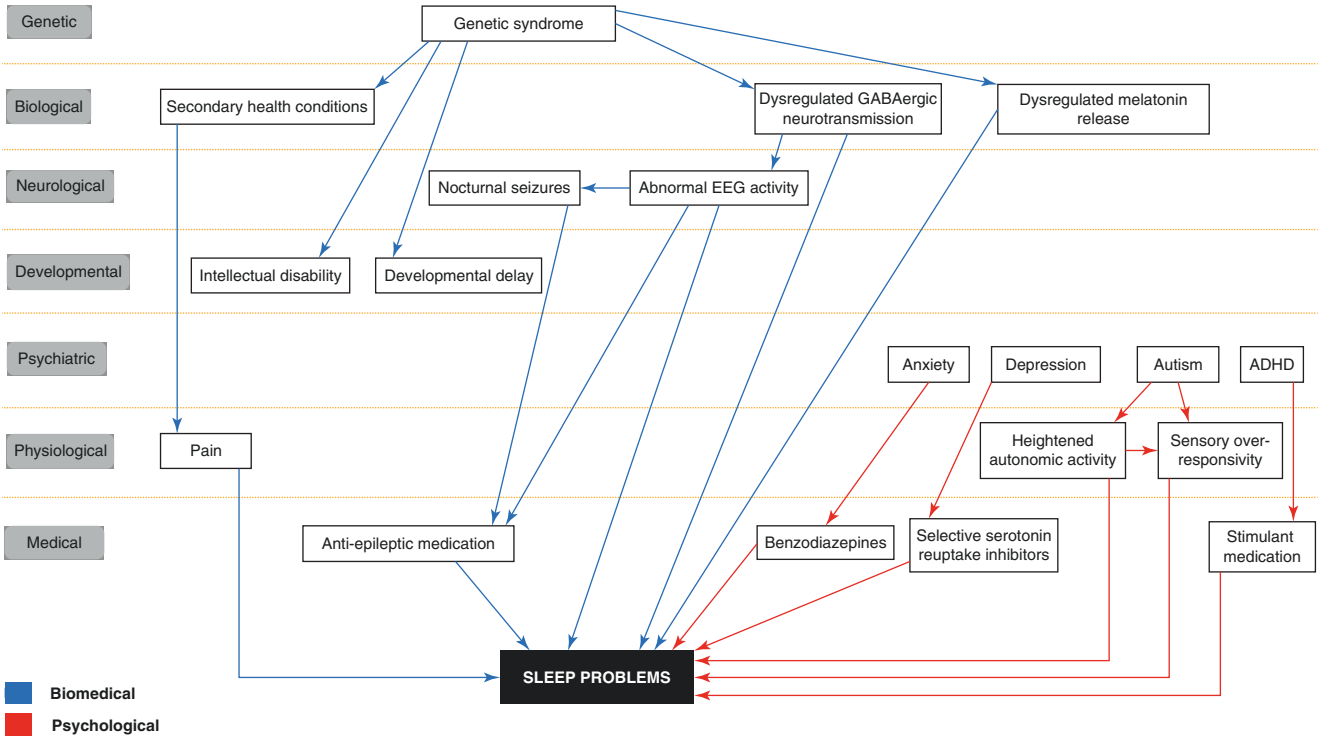

Fig. 55.1 Biomedical and psychological factors that may be associated with sleep problems in children with developmental delay

ventilation and artificial nutrition) [65], (2) experience more pain-related health conditions that evoke disturbed sleep and require a caregiver nocturnal response (e.g. nocturnal seizures) [66], (3) have mobility or adaptive functioning limitations that require caregiver assistance (e.g. toileting, feeding or changing at night) [66] or (4) have less well-developed self-soothing strategies than TD peers [67], leading to challenging night-time behaviours (e.g. self-injurious behaviours and proximity-seeking behaviours). Although these factors are not causative, their influence can exacerbate or prolong sleep problems in children with developmental delay.

Assessment of Sleep Problems Associated with Developmental Delay

It is often difficult to determine the specific profile of a sleep disorder (e.g. sleep onset insomnia, sleep-related anxiety, periodic limb movements and obstructive sleep apnoea) and identify potential underlying causes of presenting sleep problems in children with developmental delay. People with impaired intellectual functioning may struggle to accurately label and communicate their experiences of sleep problems, pain and seizure severity. Therefore, the assessment of sleep problems is often restricted to the use of informant-report questionnaires and direct objective measures as described in the autism literature (Table 55.2 [68]).

Informant-Report Measures

Spruyt and Gozal [69] provide a comprehensive overview of measures in the literature that are currently used to assess sleep. However, many of these measures are not validated in populations of children with developmental delay, with the exception of the Sleep Questionnaire – Simonds and Parraga (SQ-SP) [70], which has been modified for use [61] and directly validated in populations with ID [71, 72]).[1] Although the Children's Sleep Habits Questionnaire (CSHQ) is perhaps more widely used in recent studies [73–75], professionals should still exercise caution when it is used in clinical practice until psychometric properties in populations of children with developmental delay have been established.

Professionals should also consider the specific information they wish to gather from informant-report questionnaires. For example, informant-report measures cannot capture the more biologically intrinsic precursors to some sleep behaviours (e.g. whether abnormal EEG activity preceded night waking). Subscale structures also differ slightly between measures, and factors relating to sleep onset and duration may not be measured if the focus is on sleep behaviours as opposed to sleep routines. If this information is

[1]Psychometric properties were only established for part four of the SQ-SP, which explores the frequency of 45 sleep behaviours within the last 3 months (e.g. reluctant to go to bed, heavy or loud breathing).

Table 55.2 Outline of measures used to identify sleep problems in individuals with autism, as presented by Moore et al. [68]

Subjective sleep measures				
	Age range	*Population characteristics*	*Items (No.)*	*Subscales/content*
The Children's Sleep Habit Questionnaire (CSHQ)	4–10 years	Typically developing ASD (modified)	Total: 45 Subscale: 33	Bedtime resistance Sleep onset delay Sleep duration Sleep anxiety Night wakings Parasomnias Sleep disordered breathing Daytime sleeping
The Modified Simonds & Parraga Sleep Questionnaire (MSPSQ)	5–18 years	ASD, other developmental delays (modified)	Total: 51 Likert: 36	*Part 1:* sleep quantity and quality *Part 2:* sleep disorders *Likert-item subscales:* Bedtime resistance/struggles Sleep onset delay Parasomnias Sleep-disordered breathing Sleep anxiety Daytime sleepiness
The Family Inventory of Sleep Habits (FISH)	3–10 years	ASD	Total (V1): 12 Total (V2): 22	Daytime habits Pre-bedtime habits Bedtime routine Sleep environment Parental behaviours around bedtime
Sleep Diaries	N/A	Typically-developing ASD	N/A	Time at which child goes to bed Time at which child falls asleep Night waking information Morning waking time Daytime nap information Antecedents, behaviours, and consequences
Objective sleep measures				
	Setting	*Procedures*		*Sleep variables/disorders*
Actigraphy	Portable	Watch-like device placed on wrist (or leg) to detect limb movement as proxy for sleep; data collected from device using computer software with age-adjusted algorithms		Total sleep time Sleep onset time Morning waking time Frequency of night wakings Longest sleep period Sleep efficiency
Polysomnography	Laboratory Portable	Electrodes placed on scalp and face throughout sleep duration		Sleep latency Total sleep Sleep paralysis Sleep disordered breathing Narcolepsy
Videosomnography	Portable	Time-lapse video recording equipment used to provide visual and auditory data on participant sleeping behaviours		Sleep–wake states Frequency and duration of night wakings Parent–child bedtime interactions

Notes. ASD Autism Spectrum Disorder, *N/A* Not Applicable, *V1* Version 1, *V2* Version 2

important to clinicians, the use of sleep diaries may be preferred. An example sleep diary is presented in Fig. 55.2.

Sleep diaries are useful in capturing night-to-night variability in daytime behaviours as well as night-time behaviours (e.g. externalising behaviours and daytime naps), more specific information relating to sleep efficiency and sleep duration, and antecedents and consequences of particular sleep-related behaviours. Although a richer level of detail may be acquired from sleep diaries, they rely heavily on caregiver input, availability and objectiveness of interpretation (e.g. exact timings, caregiver observing night wakings) and require a minimum of 14 diary entries to ensure validity [68]. To reduce caregiver burden, a more objective short-term method of sleep assessment may be appropriate.

Sleep Diary

Child's Name: Parent/carer's Name:

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Date							
Time of waking in morning							
Mood upon waking							
Times of naps during the day							
Times started preparing for bed							
What time did the child go to bed?							
What time did the child got to sleep?							
Time(s) of waking during the night (e.g. 2:30am, 4am etc.,)							
What did you (parent/corer) do?							
Length of time(s) taken to fall asleep again							
Total no. of hours sleep							

Fig. 55.2 An example sleep diary. (Reprinted with permission from Agar et al. [120]. Copyright 2017 by the authors http://www.findresources.co.uk/uploads/Guides%20for%20parents/sleep-guide-june17-web.pdf)

Direct Objective Measures

The use of direct objective sleep measures needs to be person-focused and will greatly depend on how well sleep equipment is tolerated. As previously outlined [48], children with developmental delay and comorbid autism may present with heightened physiological arousal and sensory over-responsivity that not only predispose sleep difficulties (e.g. sleep onset insomnia), but also an aversion to sensory aspects of the sleep environment (e.g. noise, temperature). This is especially pertinent in relation to the three direct measures of sleep most widely used in ID research (actigraphy, polysomnography and videosomnography) [68], as the level of sensory tolerance required increases with the complexity of the methodology used.

Actigraphy uses an accelerometer worn on the wrist or ankle to measure movement, as a proxy measure of sleep parameters (e.g. sleep onset). Although actiwatches may not be well tolerated in some cases (e.g. child cohorts diagnosed with autism [76]), they are fairly well tolerated in a number of studies involving syndrome group populations, such as Down syndrome, Williams syndrome [77], Prader–Willi syndrome [78] and Angelman syndrome [63, 79]. Therefore, the utility of actigraphy may to some extent depend on factors that are person-specific (e.g. sensory over-responsivity). Best practice guidelines have been developed by Fawkes et al. [80] outlining the use of actigraphy in children with developmental delay, which advocate the use of event markers, comprehensive parent training, and a practice night of data collection to increase actiwatch tolerance. As a proxy measure of sleep, a key limitation of actigraphy is its capacity to overestimate sleep and underestimate wakefulness in paediatric and neurodevelopmental disorder populations [81, 82]. However, one study [83] recently reported that actigraphy identified more wakefulness than informant-report sleep diaries in a group of autistic children.

The use of actigraphy with people diagnosed with autism and/or ADHD is sometimes supported by videosomnography, in an effort to minimise caregiver burden [84, 85]. In particular, the use of portable time-lapse video recording is beneficial in identifying certain aspects relating to diagnosed sleep disorders (e.g. wake after sleep onset) that are difficult to infer using actigraphy alone [84]. Ipsoriglu et al. [85] developed a

comprehensive home videosomnography protocol to record bedtime behaviours and observable sleep problems in individuals with neurodevelopmental disorders, with recommendations relating to: suitable software options, confidentiality, obtaining consent, and practical considerations regarding bedroom environment, clothing and shared sleeping arrangements. Videosomnography also has particular merit in identifying child–caregiver interactions and models of behaviour that may be maintaining poor sleep, with a view towards intervention and behavioural sleep management [68].

Polysomnography is considered a standalone 'gold standard' sleep assessment [85], as it adopts a multifaceted approach (e.g. electroencephalogram, electrooculogram, electromyogram, electrocardiogram, phasic muscle activity and pulse oximetry [68, 86]). Polysomnography can confirm aspects relating to a disrupted sleep architecture that are more nuanced than actigraphy (e.g. slow wave sleep activity [86]) and has been used effectively to uncover sleep phenotypes in a number of specific groups, particularly autism [87], Down syndrome [88] and fragile X syndrome [89]. However, its widespread utility is limited by: (1) level of tolerance in individuals with sensory over-responsivity, (2) overestimation of sleep problems due to the unfamiliarity of the laboratory setting [90, 91] and (3) participant burden from spending multiple nights within the unfamiliar laboratory setting [92].

Assessment of impact is often as important as assessment of the sleep problem itself. In the context of developmental delay, biological factors may sometimes be less amenable to treatment, and behavioural patterns often reflect a functional need of the person or their family. Assessment of sleep should not occur in isolation. Consideration of challenging behaviours, interpersonal conflict, family sleep loss and stress to the person and their family is crucial. Thorough clinical interview is always recommended. Similarly, clinicians primarily focused on these additional difficulties should consider the role of sleep in their formation and maintenance.

Clinical Considerations

Formulation: Biological and Behavioural Models of Sleep

A clinical case formulation aims to explain the development and maintenance of particular difficulties and the complex interplay with other co-occurring contextual and individual factors based on psychological theories and processes with a view towards intervention [93]. Sleep problems associated with developmental delay are often underpinned by a complex array of biological, psychological and behavioural factors [94]. In the real world, these factors often interact and should be considered in combination. Although a sleep problem in itself may be governed by biological or psychological origins (e.g. inverted circadian release of melatonin, abnormal EEG activity, restless legs syndrome, sleep-related anxiety and nocturnal seizures), problems with settling at night or high levels of arousal during night waking may be maintained and exacerbated by behavioural reinforcement cycles. Using autism as an example, both biological and behavioural models can facilitate our understanding of the individual and environmental factors that contribute to the complex presentation of sleep problems in a known neurodevelopmental disorder (Fig. 55.3).

Thomas is a 14-year-old male diagnosed with autism and severe ID. Thomas is non-verbal, incontinent during the night and suffers from tonic-clonic seizures. Thomas frequently wakes during the night from 11pm onwards. Upon waking at 11pm, Thomas does not appear sleepy and will cry out for his mother. These cries are difficult to ignore, as Thomas will often need to have his incontinence pad changed at this time, and his mother is becoming increasingly concerned about night-time seizures. He often comes downstairs to play with his toys and watch television but will then refuse to go back upstairs to sleep. Trying to encourage a bedtime routine for Thomas to stay in his bedroom when he wakes at 11pm has been difficult. If Thomas is discouraged from leaving his bedroom, this results in tearful outbursts, banging furniture, slamming doors and disturbed sleep for Thomas's older brother. Thomas's parents no longer encourage a bedtime routine after waking and will allow Thomas to stay downstairs with them until he falls asleep. At this point, Thomas is carried upstairs to bed by one of his parents, which is becoming increasingly difficult to manage as Thomas is getting bigger and older. Remaining downstairs after waking is reinforcing for Thomas as he enjoys this additional time playing downstairs. Positive reinforcement has increased the likelihood of Thomas showing bedtime resistance whenever his parents initiated a bedtime routine after waking. By allowing Thomas to fall asleep downstairs, his parents may have unintentionally reinforced bedtime resistance. This reinforcement cycle is also mutually reinforcing for them, as Thomas does not destroy his bedroom every night, and his older brother can sleep relatively undisturbed upstairs. Via means of negative reinforcement, Thomas's bedtime resistance removes the demands of a bedtime routine and in turn, leads to a reduction in externalising behaviours. A learned association has been established that it is rewarding for Thomas and his parents but will become increasingly difficult to maintain into his adult years.

Formulation: Priorities for Intervention

Case formulations are particularly useful when the relationship between diagnosis and intervention is not necessarily apparent. For children with developmental delay experienc-

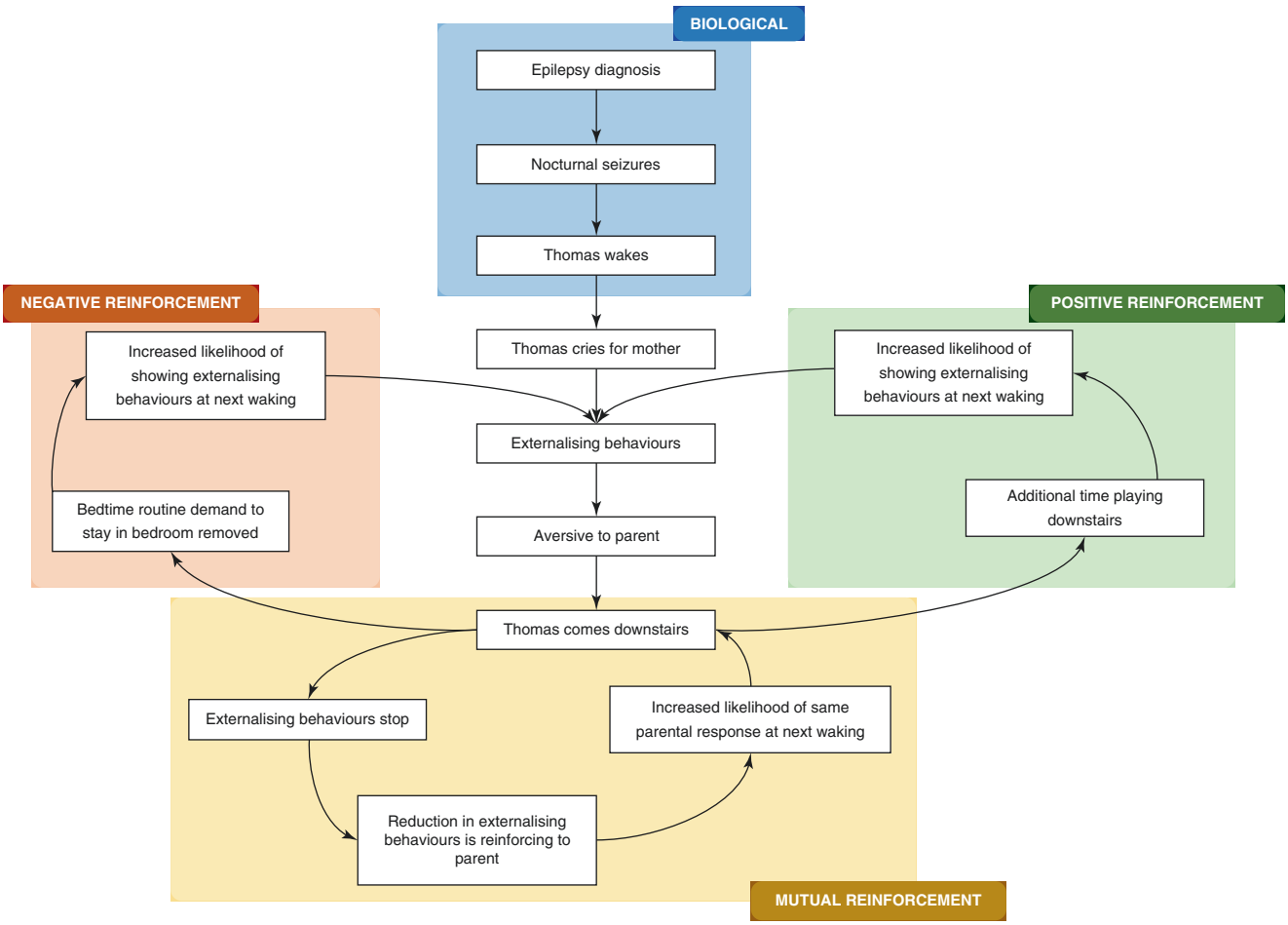

Fig. 55.3 Potential biological and behavioural models for Thomas's presenting sleep problems

ing sleep problems, a case formulation links probable causes, contextual factors and intervention pathways. Clinicians should consider which perpetuating factors are present and absent in an individual case when determining priorities for treatment, and equally which protective factors could be successfully implemented into an effective treatment programme for sleep. There are a number of important aspects that will influence the therapeutic benefit to both the individual and their caregivers in a sleep formulation. Clinicians should aim to:

1. Establish realistic goal setting and treatment aims with families to manage the overall complexity of the sleep problem and intervention programme (e.g. reducing wake after sleep onset as opposed to increasing overall sleep duration).
2. Determine capacities in the system to implement a suggested intervention (e.g. caregiver availability, service provision and educational support) and potential barriers to treatment in relation to both access to services and demands within the family setting (e.g. prescription of melatonin, sleeping arrangements within the family home).
3. Consider which factors are exacerbating or maintaining poor sleep (e.g. early morning waking, settling difficulties and self-injurious behaviours) as an initial focus for treatment interventions.
4. Assess and treat comorbid health conditions as a matter of priority, to alleviate the potential underlying role pain and respiratory factors may be having in relation to poor sleep.

Additional information for Thomas is presented below, which may be important when formulating treatment objectives. Some goal-setting targets and treatment priorities are presented in Fig. 55.4, as a guide for researchers and clinicians to use when initially confronted with a complex presentation of sleep problems and adaptive functioning deficits.

In addition to bedtime resistance, Thomas wakes very early each morning around 4am. He is often unable to return to sleep upon waking, and will damage furniture, climb fur-

1. Realistic goal-setting and treatment aims

- Need to take into account severe ID and level of verbal ability when introducing behavioural interventions
- Feasibilty of prolonging sleep until 6am as a treatment objective
- Suitability of proposed intervention for initial waking at 11pm (Thomas does not appear sleepy)
- Specificity of caregiver attention directed towards the mother at initial waking needs to be taken into account
- Interventions need to be appropriate for an older male transitioning through adolescence

2. System capacities and potential barriers to treatment

- Additional support from behavioural services has not targeted all aspects of waking behaviour (Thomas's vocal outbursts)
- Family do not currently have access to overnight respite
- Treatment objectives need to take into account the sleep needs of Thomas's older brother
- Treatment objectives need to take into account Thomas's safety (risk of overnight seizures) and level of caregiver burden (family work full-time)

3. Factors exacerbating or maintaining poor sleep

- Some aspects of bedtime resistance may be maintained by behavioural reinforcement cycles
- Suitability of prescribed melation use and dose
- Incontinence at night may be considered atreatment priority
- Possibility of sleep-related abxiety at initial waking underlying self-injurous behaviours and vocal outbursts

4. Treatment of comorbid health conditions

- Consult Thomas's neurologist to explore changes in epilepsy profile and current suitability of anti-epileptic medication and dose
- Need to rule out the possibility of comorbid painful health conditions with paediatrician or general practitioner, such as reflux, constipation, or ear infections
- Explore possibility that discomfort associated with incontinence rash may be linked to initial waking

Fig. 55.4 Priorities for intervention in a treatment formulation for Thomas's presenting sleep problems

niture, hit his head against the walls and floor and cry out for his mother. The family has been advised to remove all furniture and toys to reduce levels of behaviour and self-injury. However, Thomas's vocal outbursts and crying upon final waking are difficult to ignore. Thomas's mother uses video recording to monitor his night-time activity, and will wake with him at 4am, to limit waking of other family members. This arrangement is becoming increasingly difficult to manage, as his mother works full-time, and the family does not currently have access to overnight respite. Although Thomas is on a 3mg prescription of melatonin, this has not improved Thomas's early morning waking time. The family has been referred to social services for additional support, given the complexity of Thomas's night-time behaviours and daytime aggressive outbursts both at home and at school. Thomas's SEN school have a good relationship with the family and incorporate a daytime nap into his school routine at 11am. The family is keen to establish a routine that would allow the family to sleep until 6am, although it is unlikely that Thomas's sleep cycle will stretch to this.

Intervention

Sleep Hygiene

Promotion of good sleep hygiene practices facilitates the onset of sleep, specifically in relation to increasing predictability of bedtime routines and decreasing external environmental stimulation, outlined in more detail by Jan et al. [95]. It is important to note that a specific sleep disorder that is biological in nature (e.g. inverted circadian release of melatonin) may not in itself be adequately treated with behavioural sleep hygiene practices [95]. A meta-analysis of cohort and case studies pre- and post-intervention found structured bedtime routine practices to be most successful in relation to managing co-sleeping arrangements and improving sleep onset latency as opposed to improving total sleep duration or reducing the frequency of night-time wakings [96]. However, pharmacological interventions and psychological strategies may prove to be less effective if poor sleep habits are not first addressed [97, 98].

Sleep positioning (e.g. elevation of the head in a propped position to alleviate gastro-oesophageal reflux), breathable absorbent bedding, enclosed safety beds, limited access to electronic devices before bed, a sleep-conducive environment and bedtime routine, increased daytime physical exercise, reduced caffeine intake, and a consistent sleep/wake routine should be thoroughly considered as coherent sleep hygiene practices [95, 99]. However, clinicians need to be aware of the importance of modifying such behavioural techniques in children with developmental delay when they are based on TD sleep parameters and expectations. For example, the inverted melatonin secretion in Smith–Magenis syndrome evokes a significant need for daytime napping around mid-afternoon [100]. However, late afternoon naps are strongly discouraged in the TD sleep literature [99]. Therefore, some sleep hygiene strategies may not be successfully implemented without some degree of flexibility or adaptation. Individualised sleep programmes are preferred [101], and on a case-by-case basis, the potential benefits of accompanying behavioural programmes and medical interventions should be comprehensively explored.

Behavioural Interventions

Bedtime Fading

This is particularly useful when addressing problems relating to sleep onset latency and bedtime resistance and works by formulating an establishing operation for sleep by setting bedtime later in the evening when the individual is naturally tired, and gradually initiating bedtime earlier over time [101]. An establishing operation is formulated whereby tiredness increases the motivation to initiate the bedtime routine (e.g. being taken to the bedroom, being settled into bed), utilising sleep as the reinforcer with some efficacy in children with developmental delay [101].

Extinction and Graduated Extinction

Ignoring all nocturnal caregiver-seeking behaviours (extinction) and ignoring caregiver-seeking behaviours after a delayed interval that gradually increases over time (graduated extinction) are effective in response to settling and night-waking difficulties [101], and have been used with moderate success (see reviews by Lancioni, O'Reilly, & Basili [102] and Priday, Byrne, & Totsika [103]). However, practitioners need to be aware of the difficulties with implementing extinction-based approaches (e.g. caregiver distress in response to endured crying, caregiver availability and additional risks implementing a nocturnal behavioural intervention [104]). These are even more pertinent in children with developmental delay where additional health-related and physical considerations need to be taken into account (e.g. nocturnal seizures, monitoring night-time feeding equipment, toileting needs), as well as the increased risk of an extinction burst associated with severe self-injurious behaviours [105]. Under such circumstances, the combination of bedtime fading and extinction-based approaches may be beneficial to both increase the homeostatic drive for sleep and decrease the presentation of severe challenging behaviours.

Medical Interventions

As discussed previously, pain and discomfort may underlie the presentation of poor sleep [18] and, thus, the use of appropriate interventions should be considered early in the treatment process (e.g. the use of analgesics such as paracetamol to treat pain and a proton pump inhibitor to treat gastro-oesophageal reflux). However, practitioners should be aware that medication to treat some comorbid health conditions have side effects relating to sleep disturbance, such as the use of anti-epileptic medications [106]. If certain medications are known to exacerbate sleep problems, practitioners should also consider regularly reviewing medication use and doses in concordance with measures of sleep quality (e.g. actigraphy). In certain situations where sleep difficulties may be related to a physical disorder, such as obstructive sleep apnoea in Down syndrome [107], other medical interventions like Continuous Positive Airways Pressure (CPAP) or an adenotonsillectomy may be indicated [108]. Likewise, restless legs syndrome that may cause sleep disturbance can be treated with oral iron supplementation [109].

Although over-the-counter non-prescribed antihistamines are commonly used in the treatment of paediatric insomnia [110], there is limited literature exploring their utility in known syndrome groups. The long-term administration of antihistamines as a sleep aid is strongly discouraged [111], as common adverse side effects of antihistamines include: blurred vision, constipation, urinary retention, headaches and nausea [112]. These may be particularly difficult to monitor and treat in children with developmental delay. Other medications used to treat insomnia in children with developmental delay, such as clonidine and benzodiazepines, have been rated as having moderate effectiveness and very weak effects, respectively [96]. Additionally, children with developmental disabilities are at higher risk for paradoxical disinhibition when taking benzodiazepines [113].

Much of the recent literature has focused on the potential benefits of melatonin as a pharmacotherapy to aid sleep. A number of clinical reviews, meta-analyses and randomised controlled trials have explored its effectiveness (see [114] for a review of the literature), with significant reductions in sleep onset latency reported, but minimal improvements to overall sleep duration when using the immediate-release form of melatonin [115]. General consensus appears to suggest that the use of melatonin in children with developmental delay and adults with ID: (1) is more effective in cohorts experiencing severe sleep problems [116], (2) does not appear to cause severe adverse side effects, but should be closely monitored when co-administered with other medications [117] and (3) is particularly effective when targeting settling problems and delayed sleep phase disorders, but demonstrates little efficacy for night waking or early morning waking when using the immediate-release form of melatonin [115]. More recently, a clinical trial investigating the efficacy and safety of a specific paediatric prolonged-release form of melatonin demonstrated improvements in sleep latency and total sleep time without inducing early morning waking [118]. Importantly, almost half of caregivers reported a significant improvement in their quality of life.

In the UK, this paediatric prolonged-release formulation of melatonin has recently been licensed to treat insomnia in children and adolescents aged 2–17 with autism and/or Smith–Magenis syndrome, where sleep hygiene measures have been insufficient [118]. In the USA, there are concerns that over-the-counter formulations vary markedly in their

melatonin content and bioavailability [119]. Therefore, there is currently limited available literature on the effective dose or recommended longevity of treatment for melatonin as a sleep aid for children and adolescents. Clinicians should consider its use on an individual basis, taking into account co-existing health problems and medication use, and its potential usefulness in combination with behavioural interventions where possible.

Conclusions

The presentation of sleep problems associated with developmental delay is complex and depends on a multitude of comorbid and contextual factors, in addition to known biological mechanisms. Although some diagnosed sleep disorders are more prevalent in certain syndrome groups, comorbid and contextual factors increase the heterogeneity of sleep disorder symptomatology. Clinicians should therefore be mindful of the contribution of clinical and psychological diagnoses, but also consider the relative contribution of individual factors that may influence sleep architecture and associated behaviours. Both biological and behavioural models are important when formulating treatment options, and a particular emphasis should be given to the needs, expectations and capacities of caregivers and families when treatment plans are introduced. It is often the case that the child with developmental delay may not themselves perceive their sleep to be problematic (e.g. caregiver-seeking behaviours during night-time waking), but it is recognised as particularly detrimental to caregivers and families. With this in mind, the importance of realistic goal setting and collaborative treatment objectives with families should not be underestimated.

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Sleep in Children Following Brain Concussion

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Introduction

Sleep has only recently become a focus of research in the context of pediatric concussion. This surge of interest has been stimulated by the development of pediatric sleep medicine, the growing realization that sleep disturbances are common in this patient population, and the recognition that sleep is potentially one of the modifiable factors that could enhance outcome.

Defining Concussion

According to the American Academy of Neurology, concussion is a term often used interchangeably with "mild traumatic brain injury" (mTBI [1]). The 2012 Zurich Consensus Statement on Concussion in Sport, however, purported that mild TBI and concussion are separate entities [2]. The universal consensus has not been reached regarding the definition of concussion [3]. This manuscript will not differentiate between mild TBI and concussion. For simplicity, we shall refer to mild TBI and concussion as "concussion" for the rest of this manuscript.

In children and adolescents, concussions are common and represent a significant public health issue [4]. In the United States, over 100,000 children present to Emergency Departments (EDs) with concussion [1], and worldwide it is estimated that four million children present to EDs with concussion each year [2]. In addition, it has been estimated that only about 12% of children who sustain concussion present to EDs [5]. Hence, the overall number of children who sustain concussion worldwide is enormous, at approximately 33 million per year.

It is universally agreed that concussion is caused by an external biomechanical force that induces alteration of brain function, which may, but does not have to, involve loss of consciousness. The core symptoms of concussion encompass one (or more) of the following: (i) loss of consciousness up to 30 min, or (ii) Glasgow Coma Scale [6] score of 13–15 after 30 min, or (iii) post-traumatic amnesia of less than 24 hours [5, 6].

Post-concussion symptoms can involve one or more clinical domains, namely, somatic, physical, behavioral, cognitive, or sleep [2]. These symptoms are typically short-lived and resolve spontaneously, but not instantaneously, in most children within 1-month post-injury [7]. However, longitudinal studies have indicated the presence of post-concussion symptoms in up to 30% of children at 1 month post-injury and in 10% of children 3 months post-injury [8, 9], with some showing evidence of even longer-term symptoms [10–12].

Overview of Sleep Outcomes Following Pediatric Concussion

Disturbed sleep is one of the most commonly reported symptoms following pediatric concussion [13]. Yet, sleep has been largely neglected in pediatric TBI literature relative to other outcomes and relative to adult research [14].

In children, sleep has been found to be important for cognitive functioning, academic performance, and behavior [15]. Sleep is also vital for brain development, especially for building and strengthening connections in response to early experiences [16]. Childhood sleep disturbances impact not only the child but also the sleep of other family members [17]. Children with concussion are known to be at risk of cognitive, behavioral, emotional, and academic difficulties [18, 19]. It seems likely that sleep disturbances contribute to these negative outcomes and possibly prolong recovery in this vulnerable population [20]. Early detection and treatment of sleep disturbances post-concussion is thus crucial, as it might facilitate recovery and improve quality of life for

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the entire family. In this manuscript, we will review evidence for:

1. Prevalence of sleep disturbances in pediatric concussion
2. Nature of sleep disturbances in pediatric concussion
3. Factors contributing to sleep disturbances in pediatric concussion
4. The impact of sleep disturbances on daily functioning and quality of life
5. Assessment of sleep disturbances in pediatric concussion
6. Treatment of sleep disturbances in pediatric concussion

Prevalence of Sleep Disturbances Following Pediatric Concussion

The reported prevalence of sleep disturbances in children and adolescents with concussion varies considerably. A very high rate of sleep disturbances (50%) was found in a study that investigated post-concussive symptoms soon after injury (mean = 2 days post) [21]. In that study, 38% of the adolescents were still reporting difficulties falling asleep 2–3 weeks post-injury. In a separate study, caregivers of children who had sustained a mTBI (of whom only 39.9% had been hospitalized) reported a 14.7% prevalence rate of sleep disturbance at 1 month post-injury, 10.7% at 4 months, but none at all by 10 months post-injury [13].Taken together, these two studies suggest that the prevalence of sleep disturbances following pediatric concussion drops and may even completely resolve within a year of injury.

Other studies that examined sleep outcomes following pediatric concussion, however, suggest that sleep disturbances subside but may not completely resolve in a proportion of injured children and adolescents. In a cross-sectional study, adolescents who presented to hospital with concussion reported significantly reduced sleep quality 5–12 months (mean = 8.7 months) post-injury compared to healthy controls [11]. In a second cross-sectional study, adolescents who were admitted to the hospital with concussion reported significantly higher rates of sleep disturbance (28%) compared to healthy controls (11%) 6 months to 6 years post-injury [10].

Studies examined thus far included children who presented to EDs or were admitted to hospitals. As mentioned above, it is estimated that only 12% of children and adolescents with concussion present to hospitals [22], so findings of the studies reviewed thus far may not be generalizable to children and adolescents with concussion who do not present to EDs. Hence, of particular interest is a population-based longitudinal study that used multiple ascertainment sources. The study assessed sleep in 109 children and adolescents, aged 8–16 years, who sustained concussion during a 1-year period in the Hamilton and Waikato Districts of New Zealand [12]. Parents completed a standardized sleep questionnaire at baseline (within 2 weeks of injury), 1 month, 6 months, and 12 months post-injury. At baseline, parents were also asked to report on their child's pre-injury sleep. A marked increase in sleep difficulties was noticed from pre- (4.1%) to post-injury at 1 month (39%), 6 months (30%), and 12 months (28%) assessments. Moreover, at 12 months post-injury, the odds of sleep disturbances were 3.09 higher compared to the healthy controls.

In a longitudinal study that examined sleep outcomes in a large number of children and adolescents, aged 2–17 years, with concussion (n = 616), moderate/severe TBI (n = 113), or an arm fracture, but no head injury (n = 197) [23], parents reported an increase in sleep disturbances relative to the pre-injury baseline at 3 and 12 months post-injury for all groups (including the clinical control group). By 24 months post-injury, only children who sustained moderate/severe TBI (but not children who sustained concussion or children with a broken arm) showed a significant increase in frequency of sleep problems relative to the pre-injury baseline. To our knowledge, only one longitudinal study has examined very long-term (i.e., 20 years) sleep outcomes post-pediatric TBI. The study included 14 participants with mTBI, 40 participants with moderate/severe TBI, and 13 healthy controls [24]. Rates of clinically significant poor sleep quality were higher in the participants with concussion (42.9%) and moderate TBI (48.1%) relative to severe TBI (7.7%), but the difference was not statistically significant, possibly due to the limited statistical power. The concussion group did not differ from controls on measures of insomnia or excessive daytime sleepiness.

Traditionally, it has been assumed that concussion is relatively harmless and free of long-term sequelae [3]. While the research has shown that the rate of sleep disturbances drops considerably from over 50% in the early stages of recovery, the rates at which symptoms of sleep disturbances subside are variable in duration, with a significant proportion (up to a third) of children and adolescents with concussion reporting symptoms of sleep disturbances for months if not years after injury. Taken together, the high rates of pediatric concussion and high rates of sleep disturbances post-pediatric concussion alerts us to the urgent need for studies into sleep recovery and treatment following pediatric concussion.

The Nature of Sleep Disturbances in Pediatric Concussion

Few of the studies that addressed the issue of sleep following pediatric concussion have attempted to discern the *nature* of the disturbances detected. Instead, they have tended to report either on the overall frequency of sleep disturbances

post-concussion [13, 23, 25, 26] or on the change in the rate of sleep disturbances pre- to post-concussion [23]. However, in studies that have examined a range of sleep disturbance symptoms, insomnia symptoms have been frequently reported.

The *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition [27], defines insomnia as difficulty initiating sleep, trouble maintaining sleep, or early morning awakening with inability to return to sleep. Blinman et al. [21] reported as many as half of child participants had difficulties falling and slept less than usual at 2 days post-concussion. Difficulties falling asleep and fatigue were reported to be the most severe post-concussive symptoms at 2–3 weeks post-concussion. Furthermore, in a separate study, adolescents with concussion were found to have more trouble maintaining sleep and poorer sleep quality on both objective (actigraphy data) and subjective (sleep questionnaires) measures of sleep at 5–12 months (mean 8.7 months) post-injury compared to healthy controls [11].

Other types of sleep symptoms are also reported. Drowsiness was reported in one study; it was very common in the first 72 hours post-concussion but had completely resolved by 2 months post-injury [28]. Symptoms of hypersomnia, such as sleeping more than usual, have also been reported post-concussion; 38% of adolescents reported hypersomnia in the first few days after injury, and 33% reported it weeks after injury [21].

One of the rare studies that examined in detail the types of sleep disturbances experienced by children with concussion was conducted by Kaufman and colleagues [29]. The study involved 19 adolescents who sustained concussion and complained of sleep disturbance 3 years post-injury as well as a healthy control group. On a questionnaire specifically designed for this study, the patients reported higher rates of various sleep difficulties relative to healthy controls, including difficulties waking up in the morning (79% vs 69%), daytime sleepiness (68% vs 31%), restless sleep (63% vs 44%), and parasomnias (42% vs 19% [sleep enuresis, 21% vs 0%; bruxism 42% vs 6%]). In addition, participants with concussion and longstanding sleep issues moved to another person's bed more often (44%) than control participants (6%). What's more, fears of going to sleep (42%), fearful awakenings from sleep (63%), and frightening dreams on a weekly basis were only observed in children with concussion. Such symptoms are typically reported among children who have experienced psychological trauma [30]. While this study found a range of sleep difficulties in adolescents with concussion, one must be careful in attributing sleep disturbance to the brain injury, given that it is unknown whether the control groups were matched on psychosocial variables to the concussion group, and the concussion group included a select group of adolescents who complained of sleep difficulties several years post-injury.

Factors Contributing to Sleep Disturbances in Pediatric Concussion

Sleep disturbances in children with concussion are likely to be multifactorial. First, sleep disturbances may be related to disruption of brain networks implicated in sleep regulation. While structural neuroimaging studies routinely employed in clinical work, such as computed tomography scans, typically show no evidence of structural intracranial abnormalities in cases of concussion, more advanced imaging techniques, such as diffusion tensor imaging (DTI), often reveal evidence of widespread damage to connective, white matter tracts. A recent systematic review of neuroimaging following pediatric concussion identified 22 studies [31]. The studies used a variety of neuroimaging methods including DTI, functional magnetic resonance imaging (MRI), susceptibility-weighted imaging, anatomic MRI, resting-state functional MRI, and magnetic resonance spectroscopy. While all but one study that used DTI showed significantly higher functional anisotropy (FA) in patients with concussion relative to controls, the brain regions and tracts where these group differences were found varied considerably. Most consistently, between-group differences in FA were found in the corpus callosum, corticospinal tracts, and/or frontal lobe white mater. Significant correlations were found between DTI findings and behavioral/cognitive outcomes in five out of seven studies, including correlations with emotional distress [32, 33], concussion symptoms/outcome scores [32–35], and arithmetic problem-solving [36]. Several (but not all) studies using other imaging techniques also found correlations with either concussion symptoms [5, 37] or cognitive assessments [38]. Taken together, these findings provide preliminary evidence of post-concussion symptoms being related to changes in underlying brain substrates. Unfortunately, none of these studies examined correlations between imaging findings and sleep outcomes in pediatric concussion.

Second, psychological difficulties that follow pediatric TBI [10–12, 23] may be contributing to sleep disturbances. Greater sleep disturbance was found to be associated with greater anxiety [10], higher depressive symptoms [11], and presence of psychosocial problems (internalizing, externalizing, and attention symptoms) [23]. Of interest is a population-based longitudinal study that found poorer sleep quality at 1 month post-concussion was correlated with higher internalizing and externalizing behavioral difficulties at 12 months post-injury [12]. In this study, children at risk of ongoing difficulties with sleep had higher levels of post-concussion symptoms at 1 month post-injury but did not differ on any other variables from those who did not experience ongoing difficulties with sleep post-concussion. However, from these child concussion studies, it is difficult to ascertain the order of appearance in the relationship between sleep

disturbances and psychological difficulties. In the general population, it is well known that acute stress can be a cause of transient sleep disturbances [39]. In children, a review of the literature showed that "the sleep/wake system is the most prominent, nonspecific vulnerable system to succumb to a significant stressor" (p. 694; [40]). Thus, sleep disturbances in children with concussion may be secondary to stress of being injured in an accident. In those with more severe and persistent stress reaction, sleep disturbances may be one of the symptoms of post-traumatic stress disorder (PTSD), which in children may include difficulty falling asleep, difficulty maintaining sleep, and parasomnias (i.e., nightmares and bedwetting) [41]. Studies conducted in the general pediatric population have also shown that sleep problems in childhood were a risk for anxiety, depression, and behavioral difficulties in later life (i.e., [42–44]). Hence, it is also possible that, at least in some children, sleep disturbances precede or exacerbate psychological difficulties following concussion. The relationship between sleep and psychological difficulties post-child concussion requires further examination.

Third, pain, especially chronic headache, is associated with difficulties initiating and maintaining sleep in adults with TBI [45]. Similarly, in one study of children with concussion, headaches have been found to be related to a higher frequency of sleep disturbances 6 month to 6 years post-injury, but this was an incidental finding [10]. It has been purported that pain may account for sleep disturbances in children with concussion [23]. To investigate this hypothesis, two studies compared sleep outcomes of children with concussion and children who sustained orthopedic injuries, but no head injuries [26, 46]. Both studies found no differences between groups in sleep outcomes on actigraphy. Parents of children with concussion (but not children themselves) reported greater sleep disturbances compared to orthopedically injured control children in one study [46]. Parental ratings of sleep disturbances were comparable in two groups in another study [26]. Neither of these two studies, however, assessed pain. A separate study examined sleep outcomes and assessed pain in adolescents with concussion and healthy controls [11]. Pain intensity was not a significant predictor of either sleep quality on a self-report questionnaire or sleep efficacy on actigraphy 5–12 months after injury [11]. The authors pointed out that the lack of relations between pain and sleep outcomes may be due to the level of pain intensity (mild to moderate) being lower in adolescents with concussion than in an earlier study that included adolescents with more severe TBI and found that frequent pain was a significant predictor of sleep disturbances 24 months post-injury [23]. Nevertheless, as different methods were used to measure pain, it is difficult to ascertain whether or not pain intensity did differ or not.

Fourth, Milroy and colleagues [46] proposed that higher rates of sleep disturbances found in children who sustained concussion relative to non-injured controls may simply be a continuation of pre-injury tendencies and furthermore that these pre-injury sleep disturbances might have contributed to the injury being sustained in the first place. Hence, Tham and colleagues [23] asked parents of children who sustained concussion to complete questionnaires about pre-injury functioning as soon as possible after the injury. Pre-injury, children with concussion had significantly higher parental ratings of sleep disturbances relative to children with more severe TBI and orthopedically injured children. At 3 and 12 months post-injury, children with concussion (as well as children with more severe TBI and children with orthopedic injuries) showed significantly more sleep disturbances relative to pre-injury. At 24 months post-injury, while children with concussion and moderate to severe TBI continued to present with more sleep disturbances compared to pre-injury, children with orthopedic injuries did not. When several covariates, however, were included in a subsequent analysis, only children with moderate to severe TBI, but not children with concussion, had significantly more sleep disturbances 24 months post-injury. In another study, parental ratings of pre-existing sleep disturbances were a significant predictor of sleep disturbances 6 months post-injury [26].

Fifth, environmental factors are known to impact sleep in children in the general population. Wickwire and colleagues [47] suggested that for patients admitted to hospital, greater sound and light levels and higher treatment/caregiving activities might disrupt patients' sleep and contribute to the development of sleep difficulties. Indeed, this has been observed among children admitted to hospital [48], children treated in pediatric intensive care units [49–52], and children treated for cancer [53]. As only a small proportion of children and adolescents with concussion are admitted to hospitals, investigation of environmental factors that impact sleep at home and parent-based sleep education on management of sleep environment post-concussion may be important for this patient population.

Sixth, in the general pediatric population, parenting factors such as poor limit setting and lack of routines have been found to increase the risk of sleep disturbances [54–56]. Higher levels of mothers' psychological distress [57] and parental discord [58] have also been noted to be more frequent in preschool children with sleep problems. Little research has examined the role of parenting on sleep outcomes post-concussion, though at least one study has failed to find correlations between sleep and parental stress and mood or family functioning in preschool children with concussion [26]. Although parental concerns about their child having sustained brain damage have been shown to be related to the presence of sleep disturbances after concussion [59],

the direction of this relationship is not clear. This is an area that merits further investigation, as it might yield a number of modifiable factors.

Seventh, there are good reasons to believe that age at injury could also impact sleep outcomes following concussion. Sleep changes markedly during infancy and early childhood and continues to change into adulthood. The major developmental changes in sleep over childhood years involve "… (1) decrease in total sleep time, (2) consolidation of periods of sleep at night and wakefulness during the day, (3) decrease in the intensity of (EEG power) of NREM 3 slow-wave activity (SWA); and (4) a steady decline in the percentage of sleep time spent in REM sleep" [60, 61]. In addition, major physical, cognitive, emotional, and behavioral changes also occur from infancy to adulthood. The child's stage of development at the time of injury could influence how the concussion is experienced, how the concussion impacts the body, and whether particular types of sleep disturbance are experienced. To illustrate this, excessive daytime sleepiness, a cardinal symptom of obstructive sleep apnea (OSA) in adults, is rare in young children with OSA [62]. Instead, children with OSA typically present with hyperactivity, difficulties in concentration, and academic and emotional difficulties [63, 64]. Our review of the literature revealed that several studies involved exclusively or predominantly adolescents [10, 11, 21, 29]. Studies that included a wide range of ages [13, 23, 25, 59] have not examined whether age relates to sleep outcomes either by stratifying samples by age or by correlating outcomes with age. Thus, the impact of age at injury on sleep outcomes post-concussion remains unknown. Establishing how changes in sleep vary in response to concussion across infancy, childhood, and adolescence with respect to presentation, recovery, and functional impact may increase diagnostic accuracy of sleep disturbances arising from concussion and assist in formulation of developmentally appropriate clinical guidelines.

The Impact of Sleep Disturbance on Daily Functioning and Quality of Life

While emotional and behavioral difficulties may lead to the onset of sleep disturbances, the opposite can also be the case. For instance, lower sleep quality at 1 month post-concussion was a significant predictor of internalizing and externalizing behavioral difficulties at 12 months post-concussion [12]. Vassilyadi et al. [65] examined the relationship between post-concussive symptoms and quality of life in children aged 10–18 years who had been sequentially referred to the specialized concussion neurosurgical clinic. The study was limited to those whose post-concussion symptoms persisted for more than 3 months. Severity of difficulties falling asleep was found to be negatively related to quality of life, and in regression analysis, difficulties falling asleep (i) were a significant independent predictor of quality of life and (ii) combined with memory problems explained 62% of variance in quality of life. Hence there may well be widespread consequences to post-concussion sleep disturbances for the child with concussion. In addition, as it is known that childhood sleep disturbances impact not only the child but also the sleep of other family members and their functioning [17], disturbed sleep of children with concussion could have a similar effect on their families.

Assessment of Sleep Disturbances in Pediatric Concussion

When sleep has been examined after pediatric concussion, studies have used a wide variety of tools, including structured interviews, in-house non-validated post-concussion questionnaires, and norm-referenced post-concussion questionnaires. Given the limited scope, sleep disturbances are likely to remain overlooked in studies that rely on post-concussion symptom questionnaires. Particularly concerning is that the recently developed standardized tools for assessment of concussion in children aged 5–12 years (Sport Concussion Assessment Tool; SCAT 3) contains items assessing somatic, physical, behavioral, and cognitive domains, but not sleep. It goes without saying that applying the SCAT 3 will provide no information on sleep disturbances following a concussive injury in children. Another commonly used instrument for assessment of post-concussion symptoms, the Post-Concussion Symptom Inventory [66], involves only one item assessing a specific aspect of sleep, hypersomnia. Thus, administration of this instrument will miss all other types of sleep disturbances, including insomnia, which is a commonly reported type of sleep disturbance following concussion.

Subjective assessments (as opposed to objective, physiological measures) of sleep outcomes have often been employed in pediatric concussion studies. Given that symptoms of sleep disturbances change over the course of development, one of the difficulties in assessing sleep in pediatric populations is having a scale with adequate sensitivity to identify and classify symptoms of different sleep disorders across ages. Only three studies that examined sleep in children with concussion [46, 67] have used well-established norm-referenced multidimensional questionnaires that screened for a wide range of sleep problems and were deemed well established [68] against the criteria of the American Psychological Association Division 54 Evidence-Based Assessment [69]. These three studies used one of the two questionnaires, namely, the Sleep Disturbance Scale for Children (SDSC) [70] and the Children's Sleep Habits Questionnaire (CSHQ) [71]. The SDSC has an advantage

over the CSHQ in covering a wider age range, 5–15 years, as opposed to 4–10 years for the CSHQ. The two studies that used multidimensional questionnaires, however, reported on overall scores obtained on these questionnaires rather than on scores obtained on subscales assessing different types of sleep problems, such as sleep initiation and maintenance (insomnia), sleep-related breathing, sleep arousal/ nightmares, sleep-wake transition, excessive somnolence (daytime sleepiness or fatigue), and hyperhidrosis (bed sweating) on the SDSC. Other studies have used questionnaires that focus on a particular aspect of sleep, such as sleepiness (Parent Report Sleepiness Scale [72] and Epworth Sleepiness Scale [73] used by Osorio et al. [74]) or sleep initiation/ maintenance (Adolescent Sleep-Wake Scale [75], used by Tham et al. [11]). Both studies found significant problems within the area assessed, but we were left to wonder about other aspects of sleep.

Objective tools have been employed for assessment of sleep following pediatric concussion in a few studies, but only one study has used polysomnography, the gold standard to assess sleep [29]. The study involved a small convenience sample of adolescents (n = 19) who reported sleep disturbances on average 3 years post-concussion and a healthy control group (n = 16) and revealed lower sleep efficacy, increased wake time, and more frequent prolonged awakening in the concussed group compared to the healthy control group. Correlational analysis uncovered multiple significant correlations between polysomnography findings and questionnaire items; specifically, (i) longer sleep latency on polysomnography was associated with questionnaire reports of "frightening dreams, difficulty awakening in the morning, daytime sleepiness and fears before the head injury" (p. 132); (ii) lower polysomnography sleep efficacy was related to questionnaire reports of higher complaints of restless sleep, more frightening dreams, and more headaches before the head injury; (iii) short awakenings (1–3 min) on polysomnography were correlated with questionnaire reports of daytime sleepiness; and (iv) longer awakening (>3 min) on polysomnography was related to greater fear of going to sleep, more restless sleep, moving to another person's bed, and early awakening.

Actigraphy has also been used alongside questionnaires in several studies [11, 26, 46]. Similar to the polysomnography findings, in at least one study, actigraphy indicated more trouble maintaining sleep (i.e., more wake time after onset of sleep and reduced sleep efficacy) in previously concussed adolescents compared to healthy controls. In two studies where actigraphy revealed no significant differences between concussed and control groups [23, 27], the children were younger (7–12 and preschool-age, respectively) and many months post-injury. Nevertheless, the between-study differences in findings may also be related to methodological limitations of actigraphy, especially differences in equipment/ software, measurement issues (i.e., placement, algorithms, epoch lengths) and scoring and poor specificity for recording wake after sleep onset [76].

While polysomnography provides a unique insight into sleep architecture and actigraphy offers objective data on sleep and wakefulness patterns, they both have limitations. Polysomnography is costly and demanding on resources. It usually requires an overnight admission to a specialized hospital facility, which may be confronting for a child who has recently presented to hospital with TBI. In addition, due to the unfamiliar sleep environment, a polysomnography study may not capture a typical night of sleep [77]. It has been suggested that sleep is better assessed in a home environment [78] and home-based polysomnography may be a more viable option for capturing typical sleep patterns in younger children [78–80]. In actigraphy, the high cost of actigraphy watches makes it difficult to use in large studies. Furthermore, studies involving adolescents with concussion have noted reluctance to wear actigraphy watches, non-compliance, early discontinuation of monitoring, and failure to return the devices [11].

Treatment of Sleep Disturbances Post-pediatric Concussion

Research into the treatment of sleep disturbances following pediatric concussion is lacking. No evidence-based guidelines exist for management of sleep disturbances in this population. This is likely to be due to sleep having become an outcome of interest in the pediatric concussion literature only recently and the very limited characterization of sleep disturbances available in children and adolescents post-concussion.

Given that a range of factors are likely to contribute to sleep disturbances post-pediatric concussion and that different children present with different types of sleep disturbances, a suite of treatments may need to be developed and/ or validated for use. An individual stepped-care approach may be suitable, where interventions are offered in stages from the least to the most intensive, as per an individual's needs. For example, given that environmental factors (e.g., noise, lighting, or changes in daily routines) may interfere with established sleep habits and instigate or promote sleep disturbances post-concussion, provision of sleep hygiene education at the time of the concussion might reduce the risk of developing sleep disturbances post-concussion. In those who experience difficulties with sleep in longer-term follow-up, detailed investigations of sleep would need to be conducted to determine the precise type of sleep disturbance and establish its potential underpinnings. This is critical for development of adequate, targeted treatments. It is yet to be seen whether sleep treatments employed in the general

pediatric population are effective for the treatment of sleep disturbances in children and adolescents with concussion.

One study reported on the use of melatonin for treatment of sleep disturbance post-concussion. Bramley and colleagues [20] prescribed melatonin to adolescents who presented with persistent symptoms involving difficulties falling or staying asleep 4–6 weeks post-injury. Improved sleep was reported by 67% of participants who were placed on melatonin. However, in this trial, participants were not randomized to treatment groups, and improvement in sleep was based solely on self-report. While this finding is encouraging, further randomized controlled studies are needed to determine the efficacy of melatonin (and potentially other pharmacological agents) for sleep disturbances following pediatric concussion.

In a recent review of non-pharmacological interventions for sleep disturbances post-TBI (of any severity), we found ten adult but no pediatric studies [81]. Improvements in sleep were found following cognitive behavioral therapy for insomnia (CBT-I), blue light therapy, problem-solving treatment, and combined sleep hygiene and prazosin treatment. Behavioral and psychological treatments, including CBT-I, are recommended first lines of treatment for insomnia in children by the American Academy of Sleep Medicine [82] and Australasian Sleep Association [83], and several of the studies mentioned above reported that pediatric concussion is frequently followed by symptoms of insomnia. Given that improvements in sleep have been found following treatment with (i) CBT-I in adults with TBI [84–86], non-injured adolescents [87, 88], and adolescents with physical and psychological comorbid [89] and (ii) behavioral therapy in children and in children with comorbid neurodevelopmental disorders [90], such as attention deficit hyperactivity disorder (i.e., [91]) and autism spectrum disorder (i.e., [92]), their usefulness in children with longer-lasting sleep issues post-concussion merits investigation. It is likely that children and adolescents with concussion will require individually tailored interventions. A good deal of support and repetition might also be needed to help them learn and implement strategies supplied through behavioral therapies, given that sleep difficulties may co-exist with other post-concussion symptoms, such as headache and problems with attention.

Summary and Conclusions

Pediatric concussion happens frequently, and our review shows that it is associated with a high rate of sleep disturbances, especially in the early stages of recovery. The rate of sleep disturbances drops over the course of recovery, but some children experience sleep disturbances months or even years after injury, with insomnia being the most commonly reported type of sleep disturbance. In some studies, children with concussion are found to have more sleep disturbances than healthy control children, but not compared to control children who sustained other injuries, such as orthopedic injuries but no head injuries. These findings raise the likelihood that several factors other than brain injury (e.g., patient or parental stress, pain, environmental changes) play a role in sleep disturbances post-concussion. The effect of physiological changes that affect the brain post-concussion, however, cannot be discarded as a potential contributing factor to sleep disturbances following concussion.

Many of the studies on sleep in pediatric concussion conducted to date have methodological limitations, including the infrequent use of objective measures, the use of non-validated subjective measures, and/or questionnaires that are limited in their assessment of types of sleep disturbances. Furthermore, the studies are largely cross-sectional and are largely limited to adolescents and school-aged children, so that extremely little is known about the effects of concussion in pre-schoolers. There are no studies of cognitive/behavioral treatment interventions, and the one pharmacological treatment study that was conducted in adolescents with post-concussion sleep disorders was not a randomized control trial. Hence, much more research into sleep post-pediatric concussion is required. There is an urgent need for prospective, longitudinal studies that will (i) characterize sleep in this population using a combination of norm-referenced subjective and objective instruments, (ii) examine sleep outcomes across ages (from infancy to late teenage years) and recovery stages, and (iii) identify factors that place children at risk of prolonged recovery. It is critical to develop treatments and evidence-based care pathways for sleep disturbances following pediatric concussion, as sleep disturbances, if left untreated, can prolong recovery and exacerbate other comorbidities [93].

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Diabetes

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Alexandra D. Monzon, Arwen M. Marker, and Susana R. Patton

Type 1 Diabetes

Epidemiology

Type 1 diabetes mellitus (T1D) is a chronic disease characterized by loss of function of pancreatic beta cells that produce insulin, a hormone necessary for regulating blood glucose. While many individuals develop T1D through an autoimmune response that destroys pancreatic beta cells (Type 1a), the cause of beta cell destruction in a minority of individuals is idiopathic, or unknown (Type 1b). T1D is the most common type of diabetes in children and adolescents [1] affecting 1.94 per 1000 youth worldwide [2] and approximately 167,000 youth in the United States [3]. Around the globe, approximately 78,000 children and adolescents are newly diagnosed with T1D annually [3]. T1D affects slightly more males than females, with recent increases in the incidence rate for males [4]. The highest incidence of T1D occurs between the ages of 10–14 years, but epidemiological data suggest that the rate of T1D diagnoses has significantly increased for all children older than age 5 since the early 2000s [4]. The incidence of T1D also varies by country and ethnicity, with the highest incidence reported in Northern Europe (e.g., Finland, Sweden, Norway), Sardinia, Portugal, the United Kingdom, Canada, and New Zealand, and the lowest incidence reported in China and South America [1]. In the United States, the incidence of T1D is highest in non-Hispanic white youth, followed by African American and then Hispanic youth, although rates of T1D have significantly increased for Hispanic and biracial youth since the early 2000s [4, 5]. While non-Hispanic white youth are most likely to develop T1D, racial and ethnic minority background (e.g., African American, Hispanic) and lower socioeconomic status are associated with poorer glycemic control, reduced access to T1D-related technology (e.g., pump therapy), poorer psychosocial functioning, and a greater number of acute T1D-related health complications [6–8].

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Treatment Guidelines

Although there is no cure, youth with T1D can lead full, healthy lives through engagement in a complex treatment regimen focused on managing blood glucose levels. Glucose is the basic substrate of carbohydrates and one of the primary energy sources for the human body. When a child eats food that contains carbohydrates, blood glucose levels rise, and insulin acts as a key to "unlock" body cells, thus allowing glucose to enter cells and be converted into energy or stored for later use (e.g., liver glycogen stores). Without natural insulin production, children and adolescents with T1D rely on exogenous insulin to process glucose and maintain near-normal glycemic control (e.g., 72–142 mg/dL). Exogenous insulin is typically administered via multiple daily injections or continuous subcutaneous insulin infusion (i.e., insulin pump therapy) and includes two types: long-acting insulin that provides a baseline to manage natural glycogen release from the liver (i.e., basal) and fast-acting insulin that is administered in coordination with carbohydrate intake, as well as to make necessary treatment corrections (i.e., bolus). Recent technological advances to T1D management include the development of closed loop systems, in which continuous subcutaneous insulin infusion and continuous glucose monitoring technology are coupled with computer-generated algorithms to make automatic adjustments to basal insulin. The process of regulating insulin exogenously is complex, including steps to self-monitor blood glucose, count carbohydrates, and administer insulin in coordination with many factors that can influence blood glucose levels, such as diet,

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exercise, and stress level. Current treatment guidelines established by the International Society for Pediatric and Adolescent Diabetes (ISPAD) and the American Diabetes Association (ADA) recommend that youth maintain blood glucose levels between 70 and 180 mg/dL and hemoglobin A1c (HbA1c), a proxy measure of glycemic control over 3 months, below 7.0% (53 mmol/mol) or 7.5% (58 mmol/mol), respectively [9, 10]. These guidelines aim to maintain blood glucose, through intensive insulin therapy, within levels that reduce the risk for long-term health complications, as demonstrated by the landmark Diabetes Control and Complications Trial [11].

T1D Challenges and Complications

Unfortunately, T1D is associated with life-threatening acute and long-term health complications. Hyperglycemia (i.e., very high blood glucose) can lead to acute diabetic ketoacidosis, brain edema or death, and severe hypoglycemia (i.e., very low blood glucose) can lead to loss of consciousness, seizure, coma, or death [3]. At lower levels of severity, hyperglycemia and hypoglycemia can cause uncomfortable physiological symptoms like hunger, thirst, fatigue, irritability, blurry vision, difficulty concentrating, shakiness, sweating, dizziness, lack of coordination, frequent urination, and headaches [9]. Long-term T1D is associated with microvascular damage that increases the risk of cardiovascular disease, retinopathy, neuropathy, and nephropathy [3]. T1D is also associated with increased risk for cognitive dysfunction and academic underperformance [12, 13]. Perhaps related to the stress of managing T1D and the risk of health complications, youth with T1D experience higher rates of depression, anxiety, distress, family conflict, and lower quality of life than youth without a chronic illness [14–18]. Youth with T1D are also at increased risk for developing eating disorders [19], as well as autoimmune conditions like Celiac disease and thyroid disease [20–22]. Finally, T1D is associated with an increased risk of sleep disturbance disorders [23] (Fig. 57.1).

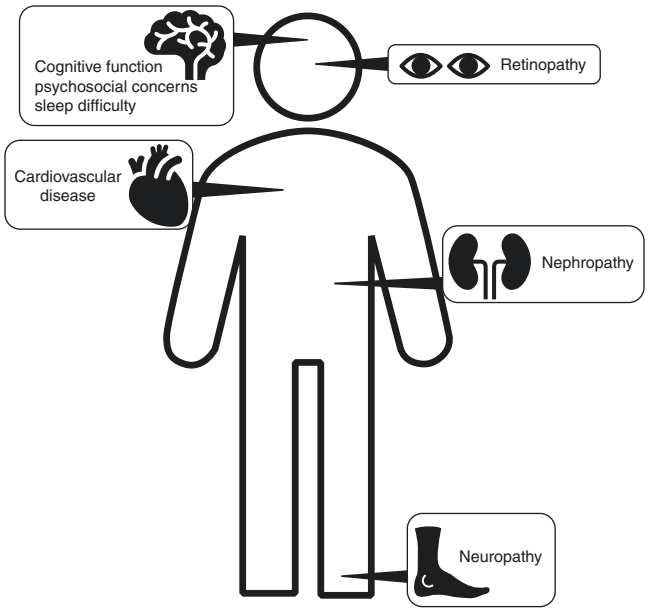

Fig. 57.1 Illustration depicting long-term health complications associated with T1D

Type 1 Diabetes and Sleep Behaviors

Like same-age peers without diabetes, the majority of children and adolescents with T1D do not meet current recommendations regarding sleep duration [24, 25]. Subjective data suggest that adolescents with T1D report longer sleep durations than adolescents without T1D, indicating possible deficits in sleep quality [26]. However, objective research demonstrates significantly shorter sleep durations and more periods of wakefulness for youth with T1D compared to youth without T1D [27, 28]. Indeed, when measured via polysomnography, youth with T1D spend significantly more time in stage N2 (i.e., second stage of non-rapid eye movement sleep) and less time in stage N3 sleep (i.e., slow wave sleep, or third stage of non-rapid eye movement sleep) than their same-age peers without T1D [29]. Moreover, compared to adults with T1D, children with T1D are 2.98 times more likely to experience insufficient sleep duration, while adolescents with T1D are 5.85 times more likely to experience insufficient sleep [30]. Unfortunately, some research suggests that sleep difficulties in youth with T1D strongly predict parent-reported impairments in adolescents' daytime functioning (i.e., working memory, ability to plan and organize, aggression, difficulties with attention, anxiety, and depression), resulting in important implications and challenges for diabetes management and treatment monitoring [31].

Sleep and Glycemia

Research suggests there may be associations between sleep and glycemia. Specifically, when children and adolescents with T1D spend less time in stage N3 sleep, they are more likely to have higher HbA1c values [29]. More time spent in stage N2 sleep is also related to higher HbA1c values, higher average blood glucose values measured with continuous glucose monitoring (CGM), and more time spent in hyperglycemia [29]. In one study in adults with T1D, researchers also demonstrated that a single night of partial sleep deprivation induced peripheral insulin resistance and higher glycemic levels [32]. While this study has yet to be replicated in youth, children and adolescents are particularly prone to restricted sleep schedules and

sleep deprivation. Thus, it is possible that youth with T1D could also be at higher risk for chronic peripheral insulin resistance and hyperglycemia, suggesting sleep duration may be an important target to improve glucoregulation [32].

Polysomnography shows that youth with T1D spend less time in slow-wave sleep during the first half the night, and they also report less restorative sleep then their peers [33]. Related, there is research showing that rapid changes in glucose concentrations associate with more nighttime awakenings from sleep [34]. However, to date, much of the research examining the relationship between sleep and glycemic outcomes in pediatric diabetes has relied on self-report measures and/or used mean-level versus day-level data for analysis. To advance this area of research, a recent conceptual model highlights the need for future research to examine sleep behaviors over a 24-hour period and analyze outcomes both between and within person, as both of these methodologies would enable a deeper understanding of the relationships between glycemia and sleep behaviors [35] (Fig. 57.2).

Nocturnal Hypoglycemia

Nocturnal hypoglycemia is often asymptomatic and may be difficult to detect without the use of CGM. Adult studies demonstrate that 55% of severe hypoglycemic episodes occur while asleep, between the hours of midnight and 8:00 am [36]. In youth, studies using polysomnography demonstrate that periods of hypoglycemia may not affect sleep architecture or cause youth to wake [27, 37]. Thus, youth with T1D are at increased risk for experiencing undetected and prolonged periods of nighttime hypoglycemia [38–40]. In fact, periods of hypoglycemia have been associated with increased sleep efficiency, fewer arousals, no increases in sympathetic activation, and an increased percentage of time in slow-wave sleep in both youth and adults with T1D [34, 41]. This may be because of reduced or impaired counterregulatory hormone responses during nocturnal hypoglycemia, thus reducing the likelihood for arousal [37, 42]. In persons without diabetes, the body can typically detect falling glucose concentrations and prevent

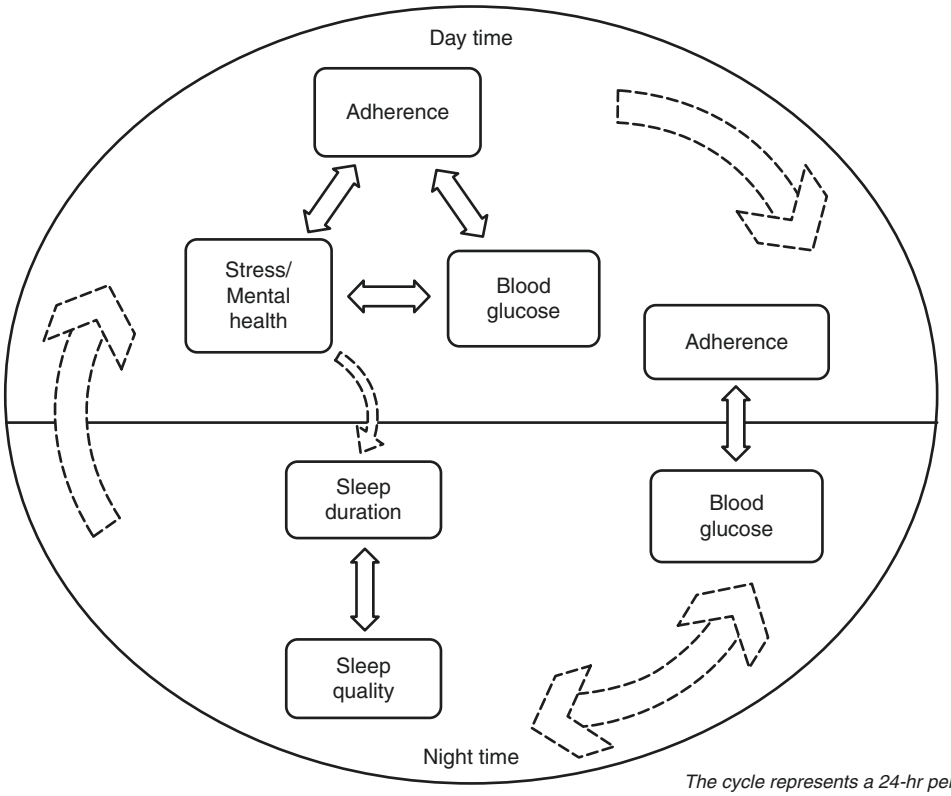

Fig. 57.2 24-hour recursive cycle in T1D. For youth with T1D, stress levels and symptoms of depression/anxiety impact their daytime adherence and blood glucose levels, and then later, these interactions impact youth's nighttime adherence and glucose levels. Youth sleep behaviors can be affected by stress during the day, blood glucose fluctuations, and adherence to their nighttime treatment plan (e.g., checking blood glucose levels, administering treatment). Following the recursive nature of the cycle, sleep quality and sleep duration then affect their stress, adherence, and glucose levels the following day. Note: The majority of research supporting this model is cross-sectional, indicating particular areas in need of longitudinal research. The solid arrows indicate relationships examined both cross-sectionally and longitudinally, and the dashed lines indicate relationships that require more longitudinal research. (From Monzon A, et al. [35]. Reprinted with permission from John Wiley and Sons)

hypoglycemia through pancreatic, neuroendocrine, and autonomic nervous system responses. However, in patients with T1D, it is the sympathetic nervous system that should launch a response to hypoglycemia, although the threshold to release epinephrine or other counterregulatory hormones is often set at far lower glucose concentrations than persons without T1D [43, 44]. This results in a delayed metabolic reaction and a lack of awareness of hypoglycemia, which could be very dangerous. In the absence of a predictable counterregulatory response to nocturnal hypoglycemia, many persons with T1D and their family members engage in constant vigilance of overnight blood glucose concentrations, which also may disrupt sleep [45]. Nocturnal hypoglycemia is a particular concern for parents, and some research suggests that parent's fear of hypoglycemia is related to more frequent nighttime glucose checks, thus introducing additional child sleep disturbances [25]. More research is needed, however, to better understand how youth's fear of hypoglycemia relates to their objective sleep behaviors.

Sleep and Treatment Monitoring

As described previously, treatment for T1D is difficult and time-consuming and involves multiple self-care behaviors. Some research suggests that sleep can be disrupted by nocturnal T1D self-care [46]. For example, checking blood glucose via finger pricks and administering insulin via injections can increase sleep disturbances and lead to longer and more frequent periods of wakefulness. Interestingly, at least one study has found that adolescents who use insulin pumps (i.e., automated insulin delivery systems) report fewer sleep disturbances and longer sleep durations than adolescents using injections, suggesting this treatment modality may be less disruptive to sleep [24].

In addition to evidence showing an association between nighttime self-care and sleep, there is strong evidence of a bidirectional association between sleep and T1D self-care. Notably, adolescents who report longer sleep durations are more likely to engage in increased T1D self-care including more frequent daytime glucose monitoring and more appropriate insulin use [24, 47]. It is possible this association occurs because adolescents who obtain sleep durations closer to the recommended amount feel less fatigue during the day and have more cognitive resources to self-monitor blood glucose and calculate insulin doses. Providing some additional evidence that longer sleep durations could associate with better daytime T1D management, one study found that greater variability in sleep duration was associated with poorer glycemic control and less frequent blood glucose monitoring in adolescents with T1D [48]. This suggests that a consistent sleep schedule may help adolescents to increase their blood glucose monitoring and maintain glucose levels within the target range.

Closed-Loop Systems

Closed-loop insulin delivery systems may help persons with T1D to better approximate normal glycemic control by combining continuous glucose monitoring technology with an insulin delivery system that relies on computer-generated algorithms to adjust basal insulin. While still an emerging technology and having limited uptake in daily management, some youth report improved sleep and better daytime glucose control when using a closed-loop system, while parents reported less anxiety about their child's nocturnal diabetes management [49, 50]. In the future, research is needed to see if these self-report data also translate into objective improvements in sleep for persons with T1D.

Prevalence of Sleep Disorders in T1D

In addition to published associations between sleep and aspects of T1D management, some studies indicate a higher prevalence of sleep disorders in youth with T1D. Limited studies utilizing objective measures of sleep-disordered breathing have found higher rates of sleep apnea in children with T1D [51] and older patients with and without higher BMI [52, 53]. Children with T1D who have higher HbA1c values exhibit more episodes of respiratory apnea than children with lower HbA1c values [51]. Related, there is evidence that youth with T1D who experience sleep-disordered breathing display higher CGM glucose levels and experience longer periods of hyperglycemia during the night [29]. In contrast, self-report sleep studies suggest the prevalence of sleep disorders (e.g., obstructive sleep apnea, restless leg syndrome) does not differ between children and adolescents with T1D and non-diabetic populations, on average [23, 54]. However, variation exists within sub-populations of pediatric T1D, with greater sleep disturbances reported by children using CGM, more frequent disorders of sleep initiation and maintenance reported by children using subcutaneous insulin infusion (i.e., pump therapy), and both lower sleep duration and increased disturbances of sleep initiation reported by children with higher HbA1c values [23, 54]. Thus, methodological variation appears to impact current prevalence estimates of sleep disorders in children and adolescents with T1D, indicating a need for additional studies with a focus on objective sleep measures and sleep disorder diagnoses.

Type 2 Diabetes

Epidemiology

Type 2 diabetes mellitus (T2D) is a disease characterized by insulin insensitivity/resistance and pancreatic beta-cell dysfunction that affects 0.48 per 1000 youth between the ages of

10–19 years [2]. T2D develops when beta cells no longer secrete enough insulin to overcome insulin resistance leading to impaired glucose tolerance [55]. T2D accounts for a minority of pediatric diabetes cases (e.g., estimates range from 8% to 45% in adolescents [56]) but increases to account for 90–95% of all diabetes cases in adulthood [57]. Approximately 5000 new children and adolescents are diagnosed with T2D annually in the United States, with incidence rates in youth demonstrating dramatic increases from 2002 to 2012 [4, 9]. T2D disproportionately affects racial and ethnic minorities (e.g., Native American/Canadian First Nations people, African American, Hispanic/Latino, Asian, and Pacific Islander), females, and those with low socioeconomic status [9, 58, 59]. Additional risk factors for the development of T2D include a family history of T2D, history of maternal gestational diabetes, small-for-gestational age birth weight, overweight/obesity (i.e., body mass index >85th percentile) [60], excess abdominal adiposity, and lifestyle factors (e.g., poor diet, inadequate physical activity, sedentary lifestyle) [9]. The average age of onset for T2D is older than the age of onset for T1D, with the majority of epidemiological research in T2D focusing on children 10 years and older, as diagnoses of T2D before age 10 are rare [61].

Treatment Guidelines

Multicomponent family-based interventions are currently recommended for youth with T2D to reduce excess weight, decrease sedentary behavior, increase daily exercise (e.g., 60 minutes of moderate-to-vigorous physical activity per day plus 3 days of strength training per week), reduce consumption of "junk foods" and sugar-added beverages, and encourage adoption of a nutrient-dense diet [9]. In addition, guidelines recommend that interventions address family, cultural, psychosocial, and environmental factors that can influence the development and maintenance of healthy lifestyle behaviors long term. Pharmacologically, metformin is recommended to stabilize blood glucose levels in youth with moderate glycemic control (HbA1c ≤8.0% or 64 mmol/mol [62]). However, the addition of basal insulin is recommended for youth with chronic hyperglycemia (e.g., blood glucose >250 mg/dL or 13.9 mmol/L), poor glycemic control (HbA1c ≥8.5% or 69 mmol/mol), or acute episodes of ketosis or ketoacidosis [63].

T2D Challenges and Complications

Complications of T2D and insulin resistance include hypertension, dyslipidemia, microalbuminuria, retinopathy, polycystic ovary syndrome, sleep apnea, hepatic steatosis (i.e., fatty liver disease), and orthopedic concerns (e.g., spinal complications, fractures, slipped capital femoral epiphysis, and Blount disease [9, 64]). Adolescents with T2D are significantly more likely to experience microalbuminuria, hypertension, and obesity than youth with T1D and just as likely to develop neuropathy as youth with T1D [65]. Similar to T1D, individuals with T2D are at increased risk for psychosocial comorbidities, including depression, social rejection, and low health-related quality of life [66]. Although mainly studied in adults to date, sleep-disordered breathing, poor sleep quality, and excessive daytime sleepiness correlate with the prevalence of T2D [67, 68].

Type 2 Diabetes and Sleep Behaviors

In comparison to the literature in youth with T1D, there is limited research regarding sleep behaviors in youth with T2D. Moreover, the few existing sleep studies in youth with T2D are limited by a lack of objective measures to assess youth sleep patterns. Therefore, the following sections summarize the current literature describing the link between sleep and risk of developing pediatric T2D, with some references to adult studies when necessary to identify areas in need of further research in youth.

Sleep and Insulin Resistance

With respect to biomarkers of T2D, most of the current research has examined the relationship between sleep behaviors and insulin resistance. Reduced insulin sensitivity, or insulin resistance, occurs when the body requires increasing levels of insulin to achieve normal blood glucose levels. Nocturnal sleep involves a prolonged period of fasting, which requires several active mechanisms to maintain stable blood glucose levels at night. Specifically, to achieve glucose homeostasis, the body must balance glucose production in the liver with glucose utilization by insulin-dependent (i.e., muscle and fat) and non-insulin-dependent (i.e., the brain) tissues. Supporting this balance, beta cells in the pancreas release insulin in a sustained response to modulate small fluctuations in glucose levels. Experimental studies with adults have demonstrated a link between restricted sleep and insufficient beta cell secretion, impairment of glucose utilization in cells, and increased insulin resistance [69, 70]. Although most of the pediatric literature base is cross-sectional versus experimental, one experimental study in youth demonstrated an association between short-term sleep restriction and increased insulin resistance in healthy adolescent boys [71], essentially replicating the results previously seen in adults. Unfortunately, children and adolescents are particularly vulnerable to shortened sleep durations due to lifestyles involving multiple activities (e.g., school and extracurricular activities) and increased electronic use. Indeed, as further evidence of the potential negative effects of sleep

restriction, at least one study using youth-reported sleep suggested a pattern between insulin resistance and shorter sleep durations, in addition to other lifestyle behaviors [72].

Studies that have utilized objective measures of sleep (i.e., actigraphy, polysomnography) suggest a direct association between insulin resistance, shorter sleep durations, and more nighttime awakenings in racially diverse healthy adolescents [73, 74]. Polysomnography, specifically, offers the opportunity to examine the relationship between sleep architecture and insulin resistance. For example, one study demonstrated that adolescents who are insulin resistant do not display shorter sleep durations, but they do spend more time in stage N1 sleep (i.e., first stage of non-rapid eye movement sleep) and less time in stage N2 and N3 sleep (i.e., slow-wave sleep [75]). Similarly, Zhu and colleagues [76] demonstrated that longer sleep durations, higher sleep efficiency, and more time in stage N3 sleep were associated with lower insulin resistance and better beta cell function in healthy children and adolescents. Overall, the literature suggests that long-term sleep restriction and less time in stage N2 and N3 increase insulin resistance, which is particularly problematic for humans. In the presence of increasing insulin resistance, the body is unable to maintain normal glycemic levels, thus eventually leading to the development of T2D. Insufficient sleep is a modifiable health behavior and one that should be included as a point of intervention for youth at risk for developing T2D.

Sleep and Inflammatory Pathways

While there is evidence suggesting a link between sleep restriction and insulin resistance, researchers have hypothesized that the underlying pathways of this association include sympathetic nervous system activation, pro-inflammatory cytokines, increased corticosteroids, and alterations in adipokines that impair glucose homeostasis in adults [77]. For example, one potential pathway is the impact of inflammatory cytokines and epinephrine. It is known that insufficient sleep (i.e., shorted sleep durations) can increase levels of inflammatory cytokines and counterregulatory epinephrine. Thus, according to this pathway, higher levels of inflammatory cytokines and counterregulatory epinephrine may lead to reduced insulin secretion, greater glycogen breakdown, and higher glucose concentrations in youth. However, according to a second model, youth experience insulin resistance because sleep impairment causes the sympathetic nervous system (SNS) to activate and stimulate the hypothalamic-pituitary-adrenal axis (HPA) to release cortisol into the body [78]. In this model, release of cortisol into the body is also responsible for increased glucose production in addition to the insulin resistance, thereby leading to weight gain and metabolic syndrome [79]. No studies to date have determined whether improving sleep leads to positive changes in glucose homeostasis in youth with a predisposition to T2D. However, given the available literature, it will be important for future studies to assess the role of inflammatory cytokines and SNS activation to better understand the influence of these potential pathways.

Sleep and Appetite

Several adult studies support the association between sleep disturbances and biological pathways to increase hunger. Numerous metabolic processes, including glucose intolerance, change throughout a 24-hour period. When the circadian rhythm is disrupted, neuroendocrine physiology can be altered and ultimately lead to negative metabolic consequences, such as comorbid obesity and T2D. Significant disruptions to sleep can negatively impact appetite regulation such that satiety is decreased, and caloric intake is increased, which significantly contributes to the development of obesity and T2D. Sleep loss is associated with increases in the peptide ghrelin and decreases in the hormone leptin [80]. Leptin is secreted by adipose tissue and promotes satiety, while ghrelin is released from the stomach and increases appetite and food intake [81, 82]. Adolescence is a time typically marked by irregular sleep-wake cycles, which may introduce risk of insulin resistance and poor glycemic control early in development. Sleep restriction may also affect appetite regulation by altering eating times and by reducing energy expenditure across the day. As evidence of an association between sleep restriction and appetite regulation, the Wisconsin sleep cohort study demonstrated a significant reduction in leptin levels, as well as elevations in ghrelin, in partially sleep-deprived adult subjects [83]. Since these hormones both aid in appetite regulation, findings suggest that individuals with short sleep durations may also experience disruptions in eating behavior that could result in increased body mass index and ultimately greater risk of T2D. It will be important for future studies to examine interactions between sleep and appetite in youth.

Prevalence of Sleep Disorders in T2D

Sleep-disordered breathing and T2D are highly comorbid disorders in adults; however, the pediatric literature is sparse regarding the prevalence of sleep disorders in T2D. Adiposity is one of the strongest risk factors for the development of obstructive sleep apnea (OSA), and there is also an association between abdominal obesity and the development of T2D [84]. Interestingly, several systematic reviews and meta-analyses have determined the relative risk (RR) of developing T2D based on the presence of a sleep disorder. Specifically in adults, these studies suggest a RR of 2.02 for developing T2D given a diagnosis of OSA [85], a RR of 1.28 for devel-

oping T2D given the presence of short sleep duration, a RR of 1.48 for developing T2D given the presence of long sleep durations, and a RR of 1.84 for developing T2D given any difficulty maintaining sleep [86]. Additional studies are needed to understand the RR of developing T2D in children and adolescents.

Some research suggests that OSA negatively impacts glucose metabolism, insulin sensitivity, and pancreatic beta-cell functioning, via sleep fragmentation and intermittent hypoxemia (i.e., low levels of oxygen in the blood), thereby further increasing the risk for individuals to develop obesity and T2D [87–90]. For example, Barone and colleagues [91] suggest an interactive cycle between OSA, sleep impairment, T2D, and obesity. They hypothesize that sleep impairments relate to fatigue, sedentary behavior, and increased hunger. Further, they predict that OSA increases impairment of glucose utilization in cells and increases insulin resistance, leading to greater impairments in glycemic control for individuals with T2D. Unfortunately, the relationship between OSA and insulin resistance requires additional research to gain a greater understanding of its underlying pathways. Moreover, while it is clear that there is an association between T2D and OSA among adults, additional research is needed to determine whether the presence of T2D also increases the risk of developing OSA in youth (Fig. 57.3).

Conclusion

Pediatric T1D and T2D are chronic illnesses associated with altered sleep duration, maintenance, and quality. Both T1D and T2D are associated with an increased prevalence of sleep apnea but through different pathways. In T1D, the most common type of diabetes in childhood, youth report increased risk for insufficient sleep related to their complex treatment regimen (e.g., monitoring nocturnal blood glucose and exogenously administering insulin) and glucose variability. Importantly, hyperglycemia appears to be related to poor sleep quality, whereas hypoglycemia appears to be related to potentially dangerous impaired counterregulatory responses. Inadequate sleep has also been linked to insulin resistance and increased appetite in adults, two risk factors for the development of T2D and obesity. Thus, it is important to consider youth with T1D and T2D separately, as differential pathways appear to link sleep and diabetes-related outcomes. Future research is needed to better understand how sleep patterns impact glycemia and treatment monitoring in T1D, such as assessments of CGM data linked with polysomnography to examine immediate and delayed effects of sleep disturbances on blood glucose levels. In T2D, assessments of pathways between sleep disturbance and insulin resistance need replicated in youth. Finally, research on effective inter-

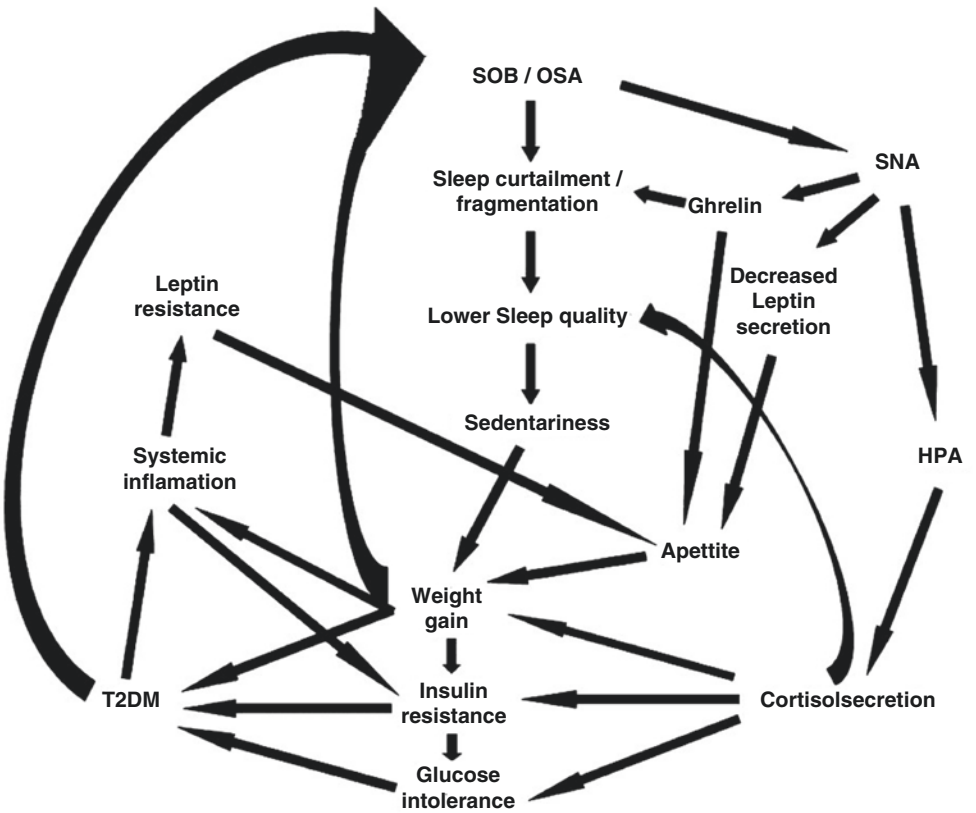

Fig. 57.3 Interactive cycle depicting the pathways between OSA, sleep impairment, T2D, and obesity. (From Barone MTU, Menna-Barreto L [91]. Reprinted with permission from Elsevier)

ventions to improve sleep quality are indicated, and researchers may consider interventions that target fear of hypoglycemia, adherence behaviors, and/or targeting sleep in multicomponent lifestyle interventions.

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Cerebral Palsy

58

Evelyn Constantin

Sleep problems affect 30–55% of typically developing children [1–4] and up to 95% of children with neurodevelopmental disorder (NDD) [5–7]. Children with NDD such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), fetal alcohol spectrum disorder (FASD), and cerebral palsy (CP) have sleep disturbances similar to children without NDD, with the most frequent cause of sleep disturbance in children with and without NDD being behavioral insomnia (behaviors that impact on sleep, including difficulties in initiating or maintaining sleep) [8]. There are, however, several factors particularly associated with NDD that can disturb sleep, such as pain, reflux, seizures, disordered breathing, and restless leg syndrome [9].

This chapter will highlight the characteristics of CP in children, sleep disturbances that are particularly prevalent in children with CP, diagnostic measures, and treatment/interventions, as well as impact of sleep problems on children with CP and their families.

Cerebral Palsy: The Most Common Cause of Physical Disability Among Children Worldwide

One of the NDDs that is associated with sleep problems is cerebral palsy (CP), the most common cause of physical disability among children worldwide [10, 11] with a prevalence of 1.5–2.5 per 1000 live births in developed countries [12–14]. CP is a group of disorders of movement, motor development, and posture attributed to nonprogressive central nervous system abnormalities that occur in the developing fetal or infant brain [15, 16]. These motor delays cause limitations in activity, are often associated with abnormal muscle tone, contractures, and deformities [17], and are often accompanied by disturbances of sensation, cognition, communication, perception, behavior, and by epilepsy [11, 15].

CP is classified using the Gross Motor Function Classification System (GMFCS), differentiating severity of mobility and ambulation: GMFCS I, ambulatory; II, walks without aids; III, walks with aids; IV, mobility requires wheelchair or assistance; and V, dependent for mobility [18] (Fig. 58.1). Children with GMFCS IV and V often have the most severe form of CP. There are also several subtypes of CP, namely, spastic diplegia, hemiplegia, and quadriplegia (depending on number and type of limb involvement) as well as dyskinesia, hypotonia, ataxic, and mixed subtypes [16] (Fig. 58.2). Children with spastic quadriplegia are often children with severe motor abnormalities and comorbidities.

Associated medical conditions in children with CP are quite common and can hinder sleep in children with CP. The main comorbidities are sleep-disordered breathing (SDB), seizure disorders, visual impairments, circadian rhythm abnormalities, motor impairments leading to pain and other disturbances, and gastrointestinal abnormalities (related to pain, gastroesophageal reflux, disturbances from gastric tube feedings), drooling and uncoordinated swallowing, intellectual disabilities, and psychological factors [17, 19–22]. In the next section, the prevalence of sleep disorders in children with CP will be described, and the association of these comorbidities and risk of sleep problems will be elaborated.

Prevalence of Sleep Disorders in Children with CP

The prevalence of sleep disorders in children in CP is quite variable and depends on several factors, including GMFCS, CP subtype, age (e.g., preschool vs school aged), and comor-

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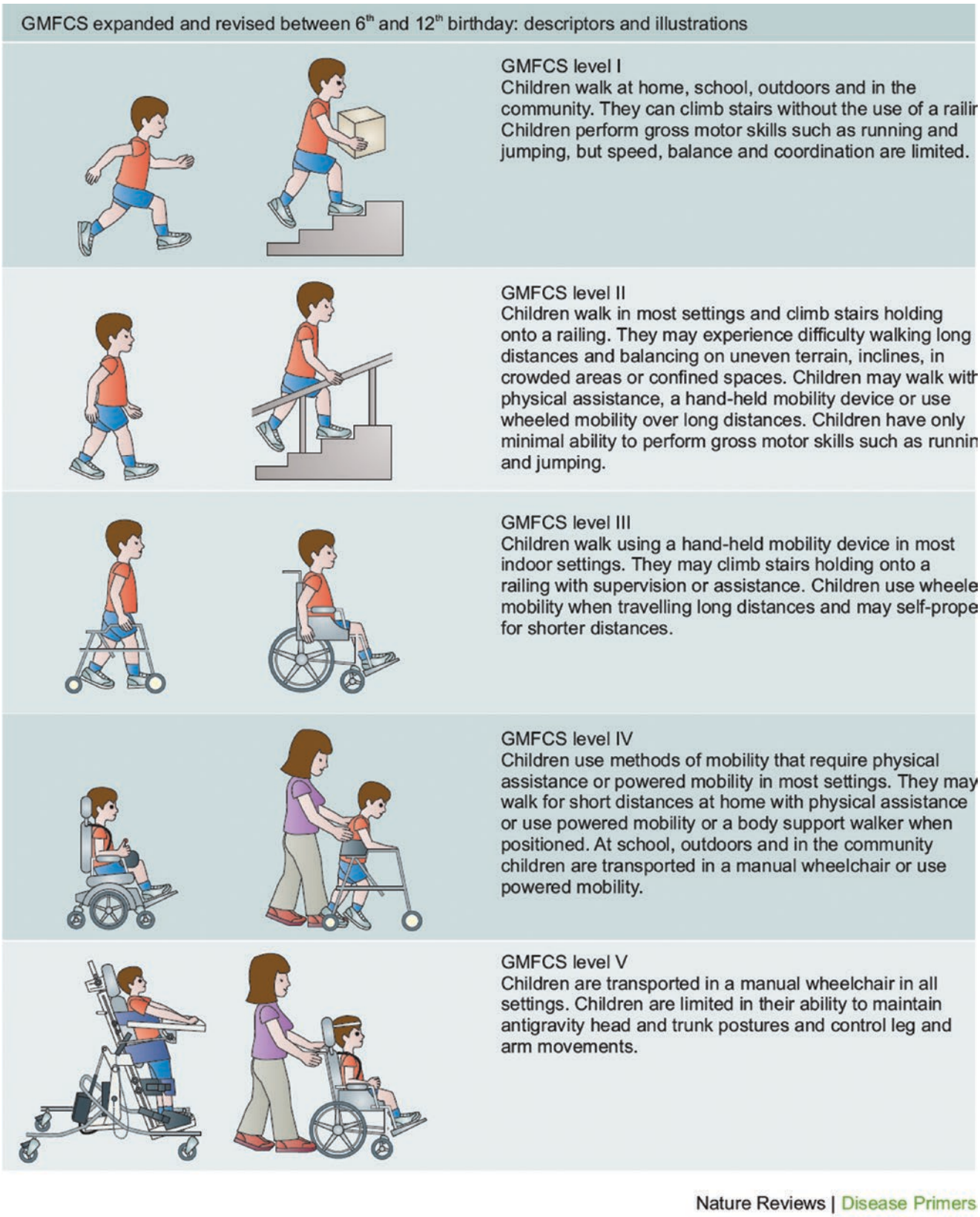

Fig. 58.1 The Gross Motor Function Classification System (GMFCS expanded and revised) for children with cerebral palsy, 6–12 years of age. This figure depicts GMFCS levels I-V, classifying severity based on mobility and ambulation. Children with GMFCS IV and V often have the most severe form of CP. (From Graham et al. [70]. Published 2016 Jan 7. Reprinted with permission from Springer Nature)

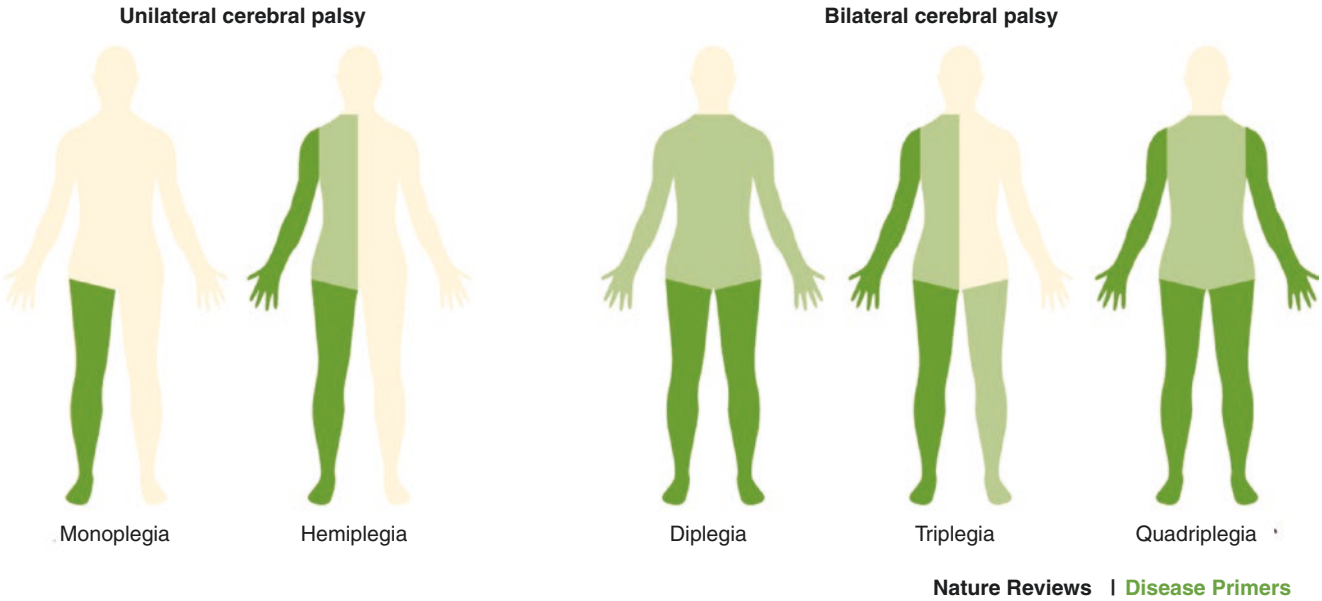

Fig. 58.2 Topographical representation of cerebral palsy. This picture shows the different subtypes of CP: unilateral (monoplegia, hemiplegia) and bilateral (diplegia, triplegia, quadriplegia). (From Graham et al. [70]. Published 2016 Jan 7. Reprinted with permission from Springer Nature)

bidities. Prevalence rates of sleep problems in children with CP have been reported to be as low as 13% to as high as 46% [17, 21–23].

In a recent systematic review and meta-analysis assessing prevalence of sleep disorders in children with CP, we found that the prevalence of sleep disorders as measured by an abnormal total score on the Sleep Disturbance Scale for Children, SDSC, ranges from 13% to 36%, with a pooled prevalence of 23.4% (95% CI 18.8–28.4%). We also found that behavioral insomnia and disorders of initiation and maintenance of sleep (DIMS) were most prevalent of all sleep disorders reported by parents and caregivers. Notably, several studies also showed high prevalence of other sleep disturbances, including sleep breathing disorders, parasomnias (such as bruxism, nightmares), and restless legs. Daytime symptoms such as excessive daytime sleepiness were also highly prevalent (ranging from 12.8% to 63.5%).

A few studies have shown that school-aged children have a higher prevalence of sleep problems as compared to preschool-aged children [22, 24, 25]. Moreover, children with more severe CP (by GMFCS or by CP subtype) have higher prevalence of sleep disturbances [24–26].

Types of Sleep Disorders in Children with CP

Children with CP are at risk of several types of sleep disorders. Not surprisingly, many sleep disorders in children with CP are similar to those present in children with other NDDs and in typically developing children. Children with CP are at risk of sleep disturbances, including behavioral insomnia, DIMS, sleep-disordered breathing, and sleep disruption secondary to pain and problems with sensory processing and/or associated medical conditions (motor impairment/muscle spasms, seizures, gastroesophageal reflux [GERD], and feeding issues) [17, 21–23, 24, 25]. One study showed that ~80–90% of children with severe CP have a chronic gastrointestinal condition, with GERD being most common [17]. Children with CP taking medications for comorbid medical conditions may also have side effects affecting sleep.

Notably, some children with CP also have multiple and concurrent sleep disorders. Romeo and colleagues found that 42% of their study population of children with CP had at least one sleep disorder (with an abnormal score on at least one SDSC factor) [24]. Similarly, in our study of Canadian children with CP, a high percentage (44%) of children in our cohort had one or more sleep disorder [22]. Interestingly, we also found that school-aged children had a higher prevalence of multiple sleep disorders than preschool-aged children (59.5% vs 24.2%, respectively).

Behavioral Insomnia

The most common sleep disorder in children with CP is behavioral insomnia. The prevalence of behavioral insomnia in children with CP ranges from 36% to 89% [27–29]. The findings from our systematic review and metanalysis on sleep problems in children with CP demonstrated that as per the SDSC, the most common sleep disorder in children with CP was DIMS (12–50%) [27, 30, 31], followed by sleep-

wake transition disorders, sleep breathing disorders, disorders of arousal, disorders of excessive somnolence, and lastly, sleep hyperhidrosis.

Sleep-Disordered Breathing

Compared to typically developing children, children with CP are at higher risk of SDB (from snoring to the most severe form on the SDB spectrum, obstructive sleep apnea) [19, 21, 32–34]. The prevalence of SDB among children with CP ranges from 12% to 79% [19, 24, 25, 27, 28, 30, 35]. Snoring is common in children with CP (37–78%) with higher rates compared to controls [27, 35]. CP places children at higher risk of SDB due to a number of factors, including craniofacial abnormalities specific to children with CP (including maxillary hypoplasia, palatal hypotonia, glossoptosis, retrognathia, laryngomalacia, and laryngeal dystonia), abnormal tone of upper airway muscles, and primary central control of breathing abnormalities [23, 36–38]. However, it is important to note that children with CP may also have SDB secondary to the common causes similar to typically developing children, such as adenotonsillar hypertrophy, nasal/allergic rhinitis and inflamed/enlarged turbinates, and obesity. Often the etiology of SDB in children with CP is multi-factorial.

Other Sleep Disorders

Similar to children without CP, children with CP can have parasomnias, such as nightmares, sleep talking, and sleepwalking [21, 22]. Of particular note, a few studies showed a high prevalence of bruxism in children with CP, ranging from 23% to 38% [28, 39]. Higher rates of bruxism are reported in preschool-aged children with CP compared to school-aged children [28]. Restless legs and restless leg syndrome are also prevalent in children with CP [27, 28].

Medical conditions are common in children with CP and can be associated with or lead to sleep problems. These medical conditions include motor impairment and muscle spasms, seizure disorder/epilepsy, gastrointestinal issues, auditory and visual problems, pain, and consequences of treatment of medical conditions related to CP, such as medications or orthotic devices.

Impact of Sleep Problems on Children with CP and Their Families

Negative effects of sleep disorders on children with CP may include both daytime and sleep symptoms, including daytime sleepiness, napping or falling asleep during the day, and poor daytime functioning, which may lead to decreased participation in daytime activities, behavior issues (irritability, hyperactivity, impulsivity) and poor quality of life [40–42]. One study found that this interplay of poor quality of life, sleep issues, and pain also is prevalent in young adults with CP [43].

Children with CP have neurodevelopmental and behavioral issues. One study in school-aged children with CP showed a moderate correlation between having a sleep disorder (as measured by the total SDSC score) and the child's behavior (as measured by the Child Behavior Checklist (CBCL)) [24]. A knowledge gap in the CP literature was the association between sleep problems and behavior issues in younger children and the interplay between sleep problems, behavior issues, and pain. We conducted a study to help fill this knowledge gap and showed for the first time the association between *specific* sleep problems and behavioral difficulties in children with CP, finding that several sleep problems (including sleep anxiety, difficulty getting to sleep, and frequent awakenings) were associated with behavioral difficulties [44]. We found that peer problems were the most common behavioral difficulty, while emotional symptoms and hyperactivity were also highly prevalent. There were differences between preschool-aged and school-aged children, with the prevalence of behavioral issues being 17.6% and 29.1% of preschool- and school-aged children, respectively; specifically, the prevalence of peer problems was 23.5% and 30.4%, respectively [44].

As sleep problems lead to negative effects on children with CP, sleep problems also can negatively impact the families/caregivers [45]. In particular, sleep problems in children with CP may lead to sleep deprivation and sleep loss in the family/caregivers due to sleep disturbances from frequent nighttime awakenings from observing/monitoring their child's sleep or feedings. The combination of these issues may lead to parental/caregiver sleep disturbances that, in turn, may impact quality of life of family. Compared to typically developing children, children with CP have poorer health-related quality of life (HRQoL) with lower physical, social, school, and emotional functioning [40, 41]. In our cohort of Canadian children with CP, we found that 33% of children have poor overall HRQoL (more than two standard deviations below normative values) and that children with poor HRQoL were more likely to be non-ambulatory, to have sleep problems, and to have significant comorbidity (controlled for age and pain) [42].

Physical Exam and Diagnostic Measures for Sleep Disorders in Children with CP

Physical exam findings for sleep-disordered breathing (SDB)/obstructive sleep apnea (OSA) in children with CP are similar to that of children without CP and involve the fol-

lowing: examination of upper airway, specifically assessment of tonsillar size, nasal turbinates for inflammation, polyps or nasal septal deviation, midfacial hypoplasia, "adenoidal facies" (from chronic mouth breathing secondary to adenoidal hypertrophy), and maxillary and/or mandibular hypoplasia. Children with CP also have risk of palatal hypotonia, glossoptosis, retrognathia, laryngomalacia and laryngeal dystonia, and abnormal tone of upper airway muscles [23, 36–38].

Diagnostic measures for sleep disorders include polysomnography in a sleep laboratory, nocturnal home oximetry, and actigraphy. Laboratory polysomnography is the gold standard diagnostic tool for SDB as well as for periodic leg movement disorder. Nocturnal home oximetry has been used as a screening test for OSA in children [46, 47]; though not specifically validated for children with CP, nocturnal oximetry can be useful in detecting desaturations in children with CP and can potentially help with screening and prioritization for laboratory polysomnography. Actigraphy, a wristband worn to assess movement (proxy for wake) vs non-movement (proxy for sleep) is used to determine sleep patterns, sleep fragmentation, and sleep duration in children; actigraphy has been used to assess sleep in children with NDD such as CP [48–51], though it is likely more challenging in children with CP who are less mobile during sleep (e.g., children with CP with severe impairments, quadriplegia).

Subjective tools such as sleep logs/diaries and sleep questionnaires have been used to assess parental report of sleep problems in children. Specifically, in children with CP, we found that the most common parental questionnaire is the SDSC (sleep disturbance scale for children) [21], a validated questionnaire for children 3–18 years consisting of 26 sleep-related behaviors [52]. In addition to a total SDSC score, there are also four SDSC subscale scores: (1) disorders of initiation and maintenance of sleep, (2) sleep breathing disorders, (3) disorders of excessive somnolence, and (4) sleep hyperhidrosis [52]. Another tool used to assess sleep in children with CP is the Pediatric Sleep Questionnaire (PSQ) [53], a validated tool for children 2–18 years old comprised of items including snoring, sleep-disordered breathing, sleepiness, and behavioral problems.

Sleep Interventions for Children with CP and Sleep Disorders

As in typically developing children and children with NDDs, the main intervention for children with CP and sleep disorders is behavioral sleep interventions [54–56]. These strategies include optimization of sleep habits/sleep "hygiene" and the sleep environment, ensuring a regular and consistent sleep routine, and avoidance or minimization of external stimuli prior to bedtime (e.g., light, noise, screen time). We are currently in the recruitment phase of our Canadian-wide randomized controlled trial to assess the impact of our online behavioral sleep intervention tool (BetterNightsBetterDays-NDD), which we tailored for families of children with NDD (including CP) [57, 58].

Another strategy that may be helpful is incorporating relaxation techniques or activities (such as reading, music, light touch with soft/dim lighting) as part of the wind-down period prior to bedtime and as part of the bedtime routine. Massage therapy by a qualified massage therapist for children with CP may also help with sleep and relaxation in some children, with one before-after study showing improvements in child's mobility, eating, and sleep quality, as well as improved parental well-being [59]. Massage therapy may be contraindicated in some children with CP; thus, the decision for massage therapy should be made in conjunction with the child's medical team.

Treating underlying medical conditions related to CP is important, as many of these comorbid conditions can impact sleep: conditions related to motor impairment of CP, including muscle spasms, spasticity, and inability to move independently in bed. Changing body position during sleep may lead to sleep disruption; however, change in position may also help with discomfort and in prevention of pressure sores, thus decreasing nocturnal pain and potentially improving sleep quality. Similarly, wearing splints or orthotic devices for motor impairments can lead to sleep disturbance from discomfort from these devices; however, often these devices can also help with muscle spasms and spasticity which can lead to improved sleep quality. Pharmacology treatment, such as Baclofen, can alleviate symptoms of hypertonia and spasticity. Studies found that in children taking Baclofen, there was parental report of improvement of the child's spasticity during sleep and reduction of nighttime awakenings [60, 61]. Children with CP have a high prevalence of seizure disorder which may lead to sleep disturbance and nighttime awakenings and ultimately daytime sleepiness. Treating the underlying seizure disorder and ensuring good seizure control can help with overall sleep and thus daytime functioning.

In children with CP and SDB/OSA, treatment of the underlying cause can help with sleep quality and symptoms of OSA [62–64]. If nasal obstruction secondary to allergic rhinitis and/or adenoidal hypertrophy are present, then medical treatment with nasal steroids (if no contraindications) may help decrease inflammation and may help reduce adenoidal size. Referral to specialists may help for management if child is a surgical candidate for adenoidectomy and/or tonsillectomy or a candidate for noninvasive ventilation. Treating the upper airway obstruction with medical or surgical treatment may help with quality of sleep with improvement of restless sleep/awakenings from these breathing disturbances during sleep.

Children with CP may also have difficulty swallowing, and/or pain from gastrointestinal reflux, and some children may have gastric feeding. Reflux and nighttime feedings can disturb sleep. Treatment of underlying reflux can help improve sleep symptoms; moreover, timing of feeds can sometimes be scheduled to minimize sleep disruption.

Sleep positioning systems are sometimes used in children with CP during sleep to help prevent hip migration, especially those children with CP who are non-ambulatory. A recent Cochrane review assessed the effectiveness of these sleep positioning systems on reduction or prevention of hip migration as well as the impact on pain reduction during sleep and on sleep quality [65]. There were very few studies in the literature, and the review did not show significant differences on hip migration, pain, and sleep quality in children using and not using these sleep positioning systems [65].

In children with NDDs, limited research has shown effectiveness of melatonin in treating sleep problems in children [66, 67]. Specifically, studies have shown improvement in sleep latency and awakenings; however, the impact on sleep duration and sleep quality remains unclear. Of note, no studies have been done specifically assessing the effectiveness of melatonin on children with CP [56, 68]. Moreover, the long-term safety and efficacy/effectiveness of melatonin in children with and without NDDs have not been determined. Despite these facts, melatonin is commonly used in children with NDDs; in our Canadian cohort of children with CP, we found that 21% of children had used melatonin for sleep [22]. As suggested in a national review on melatonin and sleep disorders in children (Canadian Paediatric Society), more robust studies in children, in particular randomized controlled trials, are required to determine the clinical effectiveness on sleep outcomes and safety of melatonin in children [69]. Notably, in light of the high prevalence of sleep disorders in children with CP and other NDDs, effectiveness studies are critically needed for this at-risk population.

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Sleep in Children with Myelomeningocele

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Medical and Surgical Care of the Child with Spina Bifida

Spina bifida is often diagnosed early in pregnancy through alpha-fetoprotein (AFP) screening and fetal ultrasonography [1]. This grants time to families and providers to weigh the pros and cons of various management options, since caring for the child with spina bifida will be a lifelong commitment for providers and caregivers alike. Currently, there is no cure for spina bifida, but there are a number of treatments available to help manage the disease and prevent complications. In the most severe cases, when the fetus has myelomeningocele and evidence of hydrocephalus, fetal surgery can be an option. Prenatal myelomeningocele repair can reduce hindbrain herniation and risk for hydrocephalus requiring ventriculoperitoneal shunt and increase the chances of independent ambulation but does not necessarily improve cognitive outcomes [2, 3]. Treatment after birth may include surgery to close a spinal defect and/or to place a VP shunt, medications, urinary catheterization, and physical, occupational, and behavioral therapy. Since this patient population usually requires intensive multidisciplinary care, the AAP has released a statement in favor of primary care management of spina bifida in the medical home [1]. The primary care provider thus becomes responsible for delivering care that is cost-effective, family centered, and efficiently coordinated.

The specific therapies and treatments needed by a person with spina bifida depend on several factors, unique to each patient, as follows. The effects of spina bifida relate to the location and size of the defect and the presence of hydrocephalus, brain abnormalities such as the Chiari II malformation (Figs. 59.1 and 59.2), and other neurologic, urologic, and orthopedic conditions. Compared to lower lumbar or sacral defects, myelomeningocele lesions in thoracic and higher lumbar levels are more likely to be associated with significant motor and sensory deficits and structural abnormalities in the lower extremities [4]. Functional defects of the urogenital and lower intestinal tract are likely regardless of the spinal level [5].

Children with the mildest form of the disease, spina bifida occulta, usually do not need treatment, but only when this term is used to describe an isolated defect in the closure of the lamina only. In most other types of spina bifida occulta, the term refers to skin-covered lesions with underlying spinal lipomas, split spinal cords, or simple tethered spinal cord. These lesions can cause symptomatic tethered cord syndrome, and surgery to release the tether is sometimes recommended. Children with spina bifida meningocele, involving the meninges but not neuronal components, typically can be treated without surgery. However, they may develop complications, such as hydrocephalus, which would then require placement of a ventriculoperitoneal shunt. Myelomeningocele, the most severe form of spina bifida, involves the meninges as well as spinal cord elements. Surgery is generally required to correct the myelomeningocele spinal defect and prevent infections, further injury or trauma to the exposed spinal cord and nerves [6].

In addition to the primary deficits in motor and sensory function, patients with spina bifida experience a range of comorbid conditions including learning disabilities, prob-

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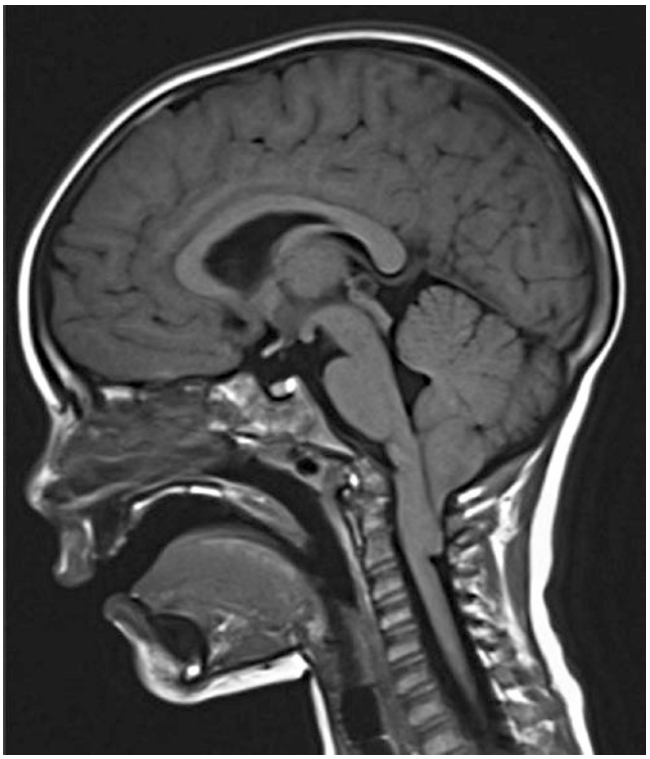

Fig. 59.1 This figure depicts a typical Chiari I malformation, which is almost never seen in patients with myelomeningocele. Key features are that the cerebellar tonsils are low, seen in the upper cervical spine, but the remaining anatomy is entirely normal. (From Tubbs and Oakes [52]. Reprinted with permission)

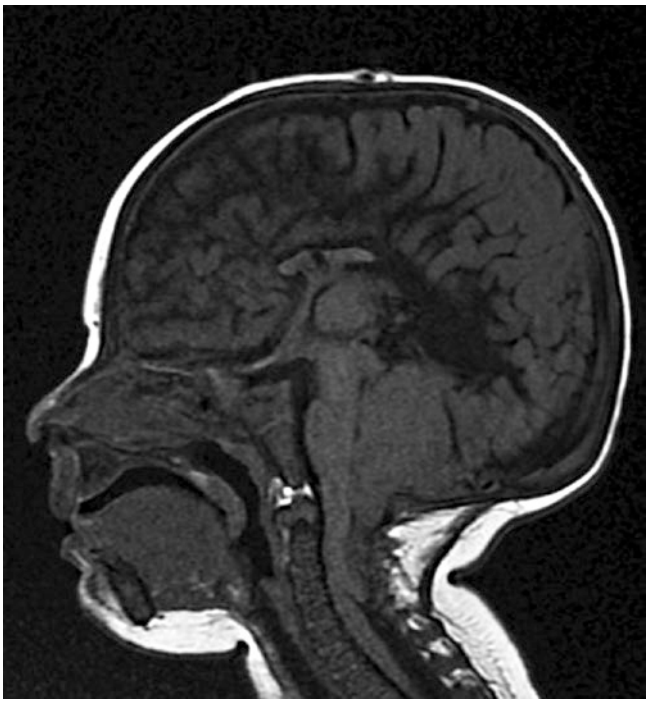

Fig. 59.2 Chiari II is commonly seen in patients with myelomeningocele. The features in this image are typical, with a small posterior fossa and low torcular, which results in crowding of its contents. The midline of the cerebellum (the vermis) is just outside the skull behind the brain stem. The soft tissue seen just below the vermis is the cervicomedullary kink and represents the level of the junction of the medulla and the upper spinal cord. The fourth ventricle is distorted and flattened. The cerebrum itself is also abnormal, with partial absence of the corpus callosum and abnormal cortex (polymicrogyria). (From Tubbs and Oakes [52]. Reprinted with permission)

lems with attention and executive function, dysfunction of upper extremities, strabismus, and seizures. These comorbidities often require coordination of care among a large team of subspecialists. These children are also at risk for functional complications such as limitations of movement and ambulation, scoliosis, joint instability, fractures, bowel and bladder dysfunction, altered growth including precocious puberty, and obesity, which require involvement of multiple therapists in their care (physical, occupational, nutrition, etc.).

Many children with spina bifida experience partial or complete lower extremity paralysis and need assistive devices such as braces, crutches, or wheelchairs. These children work with specialists in orthopedics and physical therapy to learn specific muscle-strengthening exercises. Some children may also require orthopedic surgery on the hips, legs, and feet.

It is also common for children with spina bifida to develop an allergy to latex, which may be caused by early exposure during surgeries and medical procedures. Latex allergy in spina bifida children is multifactorial. Prophylactic measures initiated immediately to avoid latex exposure can prevent potentially serious allergic reactions [7].

More than 160,000 Americans younger than 18 years are affected by spina bifida, and the 30-year survival rate has improved to nearly 90% [8]. In a report published by the CDC, spanning 10 years (1980–1990), it was found that for a person with typical severe spina bifida, estimated lifetime costs are approximately $250,000 [9]. These include direct costs such as medical and surgical care, long-term care, disability, and education. Indirect costs include survivor productivity effects and loss of parental income. Another study done a decade later showed that the medical care per case estimate in the United States was $635,763 in 2002. Most of the increase was due to price/compensation increases between 1988 and 2002 [10]. This increasing trend is anticipated to continue over the coming years.

Neurosurgical Considerations

Individuals with myelomeningocele, or open spina bifida, are followed by neurosurgeons over the entire life span. It is rare to elect not to actively manage the infant with myelome-

ningocele, unless the neonate is found to have another major anomaly or process (such as extreme prematurity) which is non-survivable. The neurosurgical interventions are therefore centered around closing the open spinal defect, treating hydrocephalus, treating post-repair tethered spinal cord syndrome, and managing the Chiari II malformation.

The open spinal defect is routinely closed surgically. This is done not to improve the function of the absent elements of the spinal cord but to prevent further deterioration of function and to prevent meningitis. All closure procedures are essentially intended to disconnect the exposed neural elements (the placode) from the skin and return them to the spinal canal. Repair of the dura, the myofascial planes, and the skin are then accomplished with varying degrees of success, depending on the tissue available. Classically, this procedure has been performed within the first few days of life, once the infant is clinically stable. Since the publication of the results of the Management of Myelomeningocele Study (MoMS) in 2011, fetal repair has become increasingly common and is also an option offered to appropriate women who are carrying a fetus with an open defect. The benefits of prenatal repair primarily consist of a lower frequency of needing to treat hydrocephalus (largely due to apparent improvement of the severity of the Chiari II malformation) and a trend toward better motor function at follow-up [3].

Most children with myelomeningocele will develop hydrocephalus, most often in the neonatal period. The frequency is as high as 80% of children with post-natal repair and approximately 40% of those repaired prenatally. The mainstay of treatment is the insertion of a ventriculoperitoneal shunt. Other locations for the distal terminus may also be considered, but all such systems have a common design of a catheter in one of the lateral ventricles, attached to a subcutaneous flow-controlling valve and a distal tube. Although shunts are very effective at treating hydrocephalus, they are associated with a variety of forms of burden. Shunts can become infected, nearly always as a consequence of recent surgery. The majority of shunt infections occur within 6 months of surgery. Management of shunt infection is nearly always surgical and may involve shunt removal and use of a temporary ventricular drain, followed by replacement of the shunt. In general shunt infection rates are less than 10%.

An alternative treatment of hydrocephalus involves the use of endoscopy in an attempt to avoid implanted hardware. Using this method, an endoscope is used to create an opening in the floor of the third ventricle, bypassing the obstructed posterior fossa directly. This is often combined with cauterization of choroid plexus, which reduces the rate of cerebrospinal fluid production. Endoscopic third ventriculostomy (ETV) combined with choroid plexus cauterization (CPC) has a higher early failure rate that shunting, but ETV/CPC can be successful in infants with myelomeningocele. Higher success rates are associated with smaller initial ventricle size, older age at surgery and absence of prior infection [11].

It is important to understand that any new neurologic symptom, including any form of brainstem dysfunction, can be a presenting sign of shunt malfunction or failure of endoscopic treatment of hydrocephalus. Although enlargement of the ventricular system on imaging is the mainstay of the diagnosis of shunt malfunction, it is recognized that ventricular volume can be stable at the onset of shunt malfunction or ETV/CPC failure [12].

The tethered spinal cord syndrome refers to development of signs and symptoms of distal spinal cord dysfunction whenever the terminus of the spinal cord is restricted in its normal movement. This syndrome commonly presents during growth spurts or after relatively minor trauma. The most frequent presenting features are back and/or leg pain, increasing weakness and bladder disturbances. Management is surgical, but confirmation of shunt function is always required prior to release. Isolated tethered spinal cord syndrome does not present with cerebral, brainstem or upper spinal cord syndromes. If these are present, it is more likely that underlying shunt malfunction is evolving, in patients with hydrocephalus.

The Chiari malformation, type II, is the most enigmatic and controversial area of neurosurgical management in patients with myelomeningocele. This hindbrain malformation is seen almost exclusively in myelomeningocele, and only rarely in other forms of spinal dysraphism. It bears no relationship to other lesions with the same eponym. It is now generally accepted that the malformation is a direct consequence of the presence of the open neural tube defect. Loss of spinal fluid from the spinal neural tube results in decompression of the future fourth ventricle (the rhombencephalic vesicle) at a time when the surrounding mesoderm is induced to form the dura and skeletal elements of the posterior fossa. The posterior fossa is too small for its contents, resulting in displacement of the normal-sized brainstem and cerebellum. The vermis medulla descends, kinking the junction with the spinal cord and blocking the flow of spinal fluid. The upper cerebellum ascends and blocks the tentorial incisura, also contributing to the blockage of spinal fluid flow. This disturbance of normal distension of the ventricles at this point results in abnormal migration of neurons in the cerebrum (resulting in polymicrogyria) but also results in the abnormal development of nuclei in the pons and medulla [13, 14].

It is likely that the similar naming of these eponymic lesions has resulted in the conflation of management of the Chiari type I with that of the Chiari type II. The cerebellar compression in the former entity, with its associated disturbance of spinal fluid flow across the craniovertebral junction, is the sole cause of any symptoms, which are greatly helped by surgical decompression. In Chiari II however, compres-

sion of neural tissue at the foramen magnum is not a consistent feature. More compression occurs in the upper cervical canal. More importantly, transmitted pressure from above is the more common reversible source of dysfunction. This transmitted pressure is from hydrocephalus, either before it is treated or with failure of a previous treatment. Once hydrocephalus is treated, the other major source of signs and symptoms of the Chiari II are the intrinsic brainstem abnormalities. Clearly, abnormal or absent brainstem nuclei will not be improved by decompressive surgery.

In an aggressively managed group of infants with symptomatic Chiari II, Pollack et al. identified improvement in 10 of 13 infants who had previously undergone management of their hydrocephalus. However, they noted that no child with bilateral vocal cord dysfunction avoided tracheostomy. This cohort had been managed in the pre-MRI era and without polysomnography. More recently, the trend has been toward fewer Chiari decompressions and more aggressive management of hydrocephalus. In a large registry study, Kim et al. identified that the frequency of Chiari decompression in patients with myelomeningocele has decreased since 2005. This study also noted that the frequency of Chiari decompressions was greater in children who also required tracheostomy and was also associated with a higher spinal lesion [15, 16].

It is known that fetal repair of myelomeningocele is associated with improvement of the apparent severity of the Chiari II (i.e., in terms of appearance). The improvement of appearance was confirmed in a recent study in radiologic literature by Nagaraj et al., but this could also be inferred from the observation of decreased need for shunting in the prenatal group in the MoMS trial. However, it seems unlikely that the reversal of the position of the cerebellar tissue would result in better function of lower brainstem nuclei. Moreover, in the report by Shellhaas et al. on sleep-disordered breathing in infants with myelomeningocele, the frequency of disordered breathing during sleep was significantly worse in infants with myelomeningocele when compared with controls. This report included 5 infants with prenatal repair and 15 with postnatal repair. There was no difference in apnea-hypopnea index between the two groups. Although the numbers are small, the significant finding is that both groups were worse than controls, and by inference the brainstem is still abnormal even after fetal surgery [17, 18].

Pathophysiology of Sleep-Disordered Breathing in Children with Spina Bifida

The majority of children with myelomeningocele have some degree of sleep-disordered breathing, which may include central apnea, obstructive apnea, hypoxemia, and/or hypoventilation [19–21]. Even asymptomatic infants with myelomeningocele have a high incidence to abnormal breathing during sleep, up to 72% in one series [22]. Sleep-disordered breathing was identified by gold standard polysomnography in every neonate with myelomeningocele in a more recent case-control study [18].

The sleep-disordered breathing in this population is likely multifactorial. Brainstem dysfunction, including the respiratory control centers of the medulla and cranial nerve abnormalities (cranial nerves IX and X), may lead to abnormal control of respiratory drive and to anomalous vocal cord movement or abnormal bulbar muscle function that mediate airway patency, respectively [23]. In addition, children with myelomeningocele and apnea may have deficient arousal mechanisms to respiratory stimuli, with decreased arousal to hypoxia or hypercapnia, likely due to anatomic disruption of the neurologic centers controlling arousal and ventilation secondary to Chiari malformation [24]. These children may also have altered peripheral chemoreceptor responsiveness to hypoxia, hyperoxia, and hypercapnia [25]. Finally, they may have restrictive lung disease due to scoliosis or ventilator muscle weakness and are at high risk for aspiration pneumonia and atelectasis, which can exacerbate the hypoxemic events [23].

The cumulative effects of sleep-disordered breathing can adversely affect growth, cognitive function, and cardiac function in children [20]. Even among apparently normal infants and toddlers, parent-reported snoring that resolves within 1 year is associated with measureable neurobehavioral consequences at school age [26, 27], and there appears to be a dose-response impact of sleep-disordered breathing on childhood cognitive outcomes [28]. Thus, prompt diagnosis and effective management of sleep-disordered breathing have the potential to provide wide-ranging benefits to children with myelomeningocele. That said, a recent study of infants with myelomeningocele and sleep apnea found no difference in disease severity, operationalized via apnea-hypopnea index, between those with or without developmental delay at age 6 months [18]. Similarly, studies of neurodevelopmental outcome in infants with sleep apnea but without myelomeningocele have found no association between the apnea-hypopnea index and neurodevelopmental outcome [29, 30].

In addition to chronic sleep-related breathing disorders, children with myelomeningocele and Chiari 2 malformation are also at risk for episodes of cyanotic expiratory apnea of central origin (PEAC), which may result in sudden death [23, 31, 32]. Indeed, among young adults with myelomeningocele, a history of sleep apnea is associated with sudden death (relative risk 5.4, 95% confidence interval 2.5–11.8, $p = 0.005$ of sudden death for patients with versus without sleep apnea) [33]. The episodes are thought to be due to central neural dysfunction [32]. In generally healthy children who may have PEAC (blue breathe-holding spells), the epi-

sodes are generally benign and spontaneous resolve in later childhood; in contrast, children with myelomeningocele typically develop severe cyanosis and bradycardia associated with episodes, and in one series five out of six patients with PEAC and myelomeningocele died during a spell [31]. Likewise, a more recent analysis found that death is more likely in patients with myelomeningocele and Chiari 2 malformation if they experienced early central apnea [34]. Treatment of PEAC episodes using bag-tracheostomy ventilation has been described [32]. Another cause for acute respiratory decompensation may be obstruction from bilateral abductor vocal cord paralysis [32]. These two mechanisms are not mutually exclusive, as children may also progress from stridor and obstruction to PEAC, and both represent a spectrum of underlying brain stem dysfunction [31]. Chronic central sleep apnea itself has been described in association with respiratory failure in a single child with myelomeningocele, but in that case, there were persistent apneas with desaturations to 60% noted consistently, resolved with awakening from sleep, and the child was successfully treated with neurosurgical decompression; this is in contrast to the episodic nature of acute respiratory failure or severe apnea described above [35].

Overview of Treatment Options for Sleep-Disordered Breathing

There are several potential treatment options for sleep-disordered breathing in this population, and a stepwise approach has been suggested from some authors [20, 21]. For obstructive sleep apnea, consideration should be given to evaluating for surgical sites of obstruction such as adenotonsillar hypertrophy. In addition to possible adenotonsillectomy, evaluation for micrognathia and/or vocal cord dysfunction is important. Noninvasive positive pressure or supplemental oxygen may be effective for some patients; if supplemental oxygen is utilized, care should be taken to ensure that hypoventilation is not induced or worsened with its application. For central apnea, options include supplemental oxygen or noninvasive positive pressure ventilation. For hypoventilation, supplemental oxygen or noninvasive positive pressure has been found effective. Restrictive lung disease may also contribute to sleep-disordered breathing. Posterior fossa decompression and/or shunt placement has been utilized as a treatment for both central and obstructive sleep apnea [21, 35, 36]. Patients for whom less invasive treatment modalities fail, whose sleep-disordered breathing progressively worsens, or who have irreversible brainstem damage, may require tracheostomy with mechanical ventilation [32].

A multidisciplinary evaluation for chronic sleep apnea in these patients may be able to address several important components of their disease. Neurosurgical evaluation may identify opportunities for surgical remediation, such as VP shunt dysfunction or need for Chiari II decompression. Evaluation by an otolaryngologist may help to assess for potential sites of airway obstruction (i.e., adenotonsillar hypertrophy), assess for vocal cord dysfunction (which can result in stridor and airway obstruction), and assess for airway anomalies that can predispose to aspiration and exacerbate hypoxemia. A pulmonologist may evaluate for control of breathing abnormalities as well as pulmonary function, especially restrictive lung disease. Once these aspects of evaluation have taken place, a treatment plan may be individualized to a particular patient's underlying pathophysiology, and options include supplemental oxygen, noninvasive positive airway pressure, or surgery (otolaryngology or neurosurgery as above). If these measures are ineffective, then tracheostomy with mechanical ventilation may be the next step.

Considerations for Treatment of Sleep-Related Breathing Disorders in Children with Myelomeningocele

Important aspects of treatment for chronic sleep apnea include multidisciplinary evaluations:

- Neurosurgical evaluation to identify opportunities for surgical remediation (i.e., VP shunt dysfunction or need for Chiari II decompression).
- Otolaryngology evaluation to identify potential sites of airway obstruction (i.e., adenotonsillar hypertrophy), assess for vocal cord dysfunction (which can result in stridor and airway obstruction), and assess for airway anomalies that can predispose to aspiration and exacerbate hypoxemia.
- Pulmonary evaluation for evaluation of control of breathing as well as pulmonary function, especially restrictive lung disease.
- Treat any chronic sleep-disordered breathing with one of several options, including supplemental oxygen, noninvasive positive airway pressure, or surgery (otolaryngology or neurosurgery as above). If these measures are ineffective, then tracheostomy with mechanical ventilation may be the next step.

Important aspects of treatment for acute respiratory failure or acute severe apnea include:

- Differentiate obstructive apnea from prolonged expiratory apnea with cyanosis (PEAC). Acute apneic spells can occur due to airway obstruction (i.e., from vocal cord dysfunction) and are characterized by continued respiratory effort and stridor,

followed by complete apnea and cyanosis; these episodes are terminated with intubation and can be treated with tracheostomy.
- PEAC episodes may be precipitated by the child being surprised; the child will cry, then during expiration apnea occurs and cyanosis develops quickly, followed by bradycardia and loss of consciousness.
- In generally healthy children with PEAC (blue breathe-holding spells), the episodes are typically benign and spontaneous resolve in later childhood; in contrast, children with myelomeningocele typically develop severe cyanosis and bradycardia associated with episodes and are at risk for death during spells.
- Acute apnea due to obstruction (i.e., from vocal cord dysfunction) can increase in frequency with respiratory tract infection, reflux, and aspiration. These episodes are prevented with placement of tracheostomy.
- Obstruction and PEAC are not mutually exclusive and may exist in the same child.
- PEAC can increase in frequency with intercurrent illness, aspiration, and shunt dysfunction. PEAC episodes can end spontaneously, by talking the child out of the spell; with active resuscitation, with the loss of all respiratory drive; or with death.
- Placement of tracheostomy may provide a secure airway for bag-tracheostomy ventilation during acute episodes but does not always prevent death.

As described in the above section, children with myelomeningocele may also experience episodes of acute respiratory failure or acute severe apnea. In such cases, it may be helpful to differentiate obstructive apnea from prolonged expiratory apnea with cyanosis (PEAC). Acute apneic spells can occur due to airway obstruction (i.e., from vocal cord dysfunction) and are characterized by continued respiratory effort and stridor, followed by complete apnea and cyanosis; these episodes are terminated with intubation. In contrast, PEAC episodes may be precipitated by the child being surprised; the child will cry, then during expiration, apnea occurs and cyanosis develops quickly, followed by bradycardia and loss of consciousness. Acute apnea due to obstruction (i.e., from vocal cord dysfunction) can increase in frequency with respiratory tract infection, reflux, and aspiration. These episodes may be treated with placement of tracheostomy. PEAC can increase in frequency with intercurrent illness, aspiration, and shunt dysfunction, and an individual episode may end in one of several potential ways: spontaneously, by talking the child out of the spell; with active resuscitation, with the loss of all respiratory drive; or with death. Continued severe episodes may require placement of tracheostomy for bag-tracheostomy ventilation during episodes. As noted above, these two mechanisms are not mutually exclusive and represent an underlying brainstem dysfunction.

People with spina bifida remain at increased risk of sleep-disordered breathing throughout their lifetime [37]. Sleep-disordered breathing may be ubiquitous as early as the neonatal period for infants with myelomeningocele [18] and cross-sectional studies of older children demonstrate that most have sleep apnea (~20% moderate to severe, ~40% mild) [19, 23]. Given the risk for systemic complications, cognitive consequences, and even sudden death, these children should be systematically screened for signs of sleep-disordered breathing and polysomnography obtained when clinically indicated. Yet, screening is not commonplace for this patient population [38, 39]. This is a clear area for potential improvement with optimally coordinated clinical care pathways.

Special Considerations for Noninvasive Support

The management of sleep-disordered breathing in young infants and children is challenging and traditionally included supplemental oxygen unless the severity warranted tracheostomy placement with initiation of invasive ventilatory support. Traditional bilevel positive airway pressure (BPAP) machines are constructed with flow triggers that require pressure changes that are not realistically achieved by smaller airways. The FDA has not approved the use of BPAP or continuous positive airway pressure (CPAP) machines for children less than 30 kg [40]. Over the last decade, newer technology has allowed for successful initiation of noninvasive bilevel positive airway pressure support in infants weighing 5 kg or more using home ventilator units [41, 42]. This is now considered a potential treatment option and could help some children avoid the traditional tracheostomy with invasive ventilatory support. Tracheostomy placement in young children poses intrinsic risks over time from infection, decannulation, airway scarring, and malacia [43].

In the spinal muscular atrophy (SMA) population, invasive ventilatory support with a tracheostomy has increased risk for hospitalizations over time compared to SMA patients managed with NIV in infancy [43, 44]. The use of noninvasive ventilatory support with a home ventilator and nasal mask is becoming more common in younger children and infants [45, 46]. There are also risks associated with this noninvasive ventilatory support which include development of midface hypoplasia, pressure ulcers, mask dislodgement, and the risk of aspiration of oral or gastric contents [47, 48]. Due to the risk of aspiration for infants on noninvasive venti-

latory support, a nasal mask is recommended as a first-line option and a full-face mask should only be used if a nasal mask trial fails. The infants who are most successful in initiating this therapy are usually between 6 and 12 months of age. In infants and very young children, noninvasive ventilatory support must be delivered through a home ventilator since conventional adult bilevel positive airway pressure machines have flow trigger algorithms that do not properly function in smaller airway dynamics with smaller flow volumes [49]. It is also important to make sure an appropriate backup rate has been set since hypotonia and components of central sleep apnea can worsen with illness, and the infants may not be able to trigger the ventilator on their own. Appropriate modes for ventilating young infants include pressure control or pressure support/timed modes. Noninvasive ventilatory (NIV) support can also be used to help support chest wall growth over time for hypotonic infants and prevent chest wall deformities from developing [45, 46]. Therefore, if severely weak patients with spina bifida have normal oxygen and carbon dioxide levels but are moving less than 8–10 cc/kg with each exhaled tidal volume, they may still benefit from NIV to help promote chest wall development, prevent atelectasis with sleep, maximize mucociliary airway clearance with sleep and prevent hospitalizations with acute respiratory tract infections.

For patients with mild obstructive sleep apnea, surgery or supplemental oxygen therapy can be considered. If NIV is being considered for older individuals, the decision between CPAP vs BPAP must be based on the degree of hypotonia present. If the patient has any significant degree of hypotonia, then it is possible their respiratory muscles could tire over time on the CPAP, especially in times of acute illness. Therefore, low pressure bilevel positive airway pressure with a backup rate should be initiated. It could be argued that any patient with myelomeningocele who needs nocturnal support should be on bilevel positive airway pressure with a backup rate if they tolerate this modality, since they are at risk for central events due to the differences in their underlying brain structures that control sleep (see discussion of pathophysiology of sleep-disordered breathing in previous section).

In older children, the average volume-assured pressure support (AVAPs) modality can be trialed. AVAPs allows for auto-adjusting inspiratory pressures to assure a goal exhaled tidal volume. In times of illness, when lung compliance is altered, this mode can adjust to assure the patient is receiving appropriate volumes of air. A newer AVAPs mode, called AVAPs AE (average volume assured pressure support auto EPAP), allows for both the EPAP and IPAP pressures to be adjusted which helps better address changing components of upper airway resistance and alveolar hypoventilation over the entire night when patients are shifting through different sleep stages. When using the AVAPs mode, it is important to realize that both a respiratory rate (the breath rate per minute for the patient) and an AVAPs rate (how fast the IPAP pressures will adjust to meet the goal exhaled tidal volume) can be set. There is an additional rate consideration in the trilogy AVAPs AE mode called auto which allows the machine to adjust the backup rate to the patient's spontaneous respiratory rate; however, in very weak patients or patients with a component of central sleep apnea, this would not be an appropriate mode since their spontaneous rate may not be adequately perceived by the machine. AVAPs AE mode has been reported to reduce rehospitalizations by 68% and improve quality of life by 80% in patients (trilogy anonymous reporting link), but further prospective studies need to be done to further validate this; however, the rapid improvement in technology is extremely promising for ongoing improved compliance, comfort, and quality of life for patients who require NIV.

Sleep Disorders Beyond Sleep-Disordered Breathing

Sleep problems are common among children with neurodevelopmental disorders like spina bifida. In 2012, Edelstein and colleagues published their study results revealing that children and adults with spina bifida endorsed sleep problems more often than healthy controls [50]. Adolescents with spina bifida have been reported to be at risk for sleep disturbances and daytime fatigue [37]. This is likely secondary to poorer sleep quality, sleep apnea, decreased sleep duration, and greater sleep maintenance difficulties that have been documented in spina bifida patients.

Researchers have also measured the chronotypes of patients with spina bifida compared with controls. Chronotype is the behavioral manifestation of underlying circadian rhythms. A person's chronotype is the propensity for the individual to sleep at a particular time during a 24-hour period. In their study, Edelstein and colleagues found that chronotype was correlated with early morning awakening in adult controls, reflecting the typical developmental shift in sleep timing. In contrast, for adults with spina bifida, chronotype was related to reported severe sleep problems including daytime sleepiness/fatigue and trouble falling asleep, raising the possibility that disturbances in circadian timing contribute to sleep difficulties in this population [50]. Murray and colleagues recently shared their study results, revealing that adolescents with spina bifida reported worse sleep quality, shorter sleep duration, greater sleep maintenance difficulties, and higher levels of fatigue, with females being particularly vulnerable [37].

In the spina bifida population, biological factors may also affect sleep quality and duration. Risk factors include the use of medications, risk for obesity, and presence of neurological abnormalities (e.g., Chiari II). These patients are also at risk

of pain resulting from shunt malfunction, orthopedic problems (e.g., scoliosis), and tethered spinal cord [51]. Establishing a regular bedtime routine may also be difficult for this population due to certain environmental factors, such as frequent hospitalizations and intensive medical management (e.g., nighttime catheterization).

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Inborn Errors of Metabolism: Mucopolysaccharidoses and Others

60

Zheng Fan, Joseph Muenzer, Laura Dosier, and Bradley V. Vaughn

Introduction

Inborn errors of metabolism (IEM), also called inherited metabolic diseases, represent a diverse group of genetic disorders usually resulting from deficient enzymatic activity in critical metabolic pathways [1]. In patients with an IEM, the chronic accumulation of toxic metabolites can lead to irreversible impairment in the function of multiple organ systems, including the central nervous system, neuromuscular system, and airway. Though individual IEM often are rare, collectively the incidence is estimated 1 in 800–2500 births [2, 3].

Sleep, as a function of the brain, offers an opportunity to see the impact of these disorders on alternative neuronal networks and functions that are not commonly witnessed during wake. The assorted stages of sleep utilize different circuitry and processes of the brain and thus create a window into understanding the dysfunction related to these disorders. Similarly, these disorders also can create change in other physiological systems that impacts sleep. Sleep disruption can cause impairment of brain function, and the treatments of some sleep disorders are noted to improve some neurological dysfunction. Therefore, the dynamic interaction of the metabolic disorder and the complex function of sleep offer an excellent potential opportunity for diagnosis and therapeutic intervention.

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Due to the advances of newborn screening for early detection and advances in management, such as enzyme replacement therapy, many patients with IEM are often surviving longer. Managing sleep disorders becomes important part of multidisciplinary care for patients with IEM.

We have conducted a comprehensive literature search. The majority of references were related to mucopolysaccharidosis (MPS) that often involves multiple systems including airway, pulmonary function, and central respiratory controls [4]. We will cover the MPS disorders in one section and other IEMs in another section.

MPS Disorders and Sleep

Overview

Mucopolysaccharidoses (MPS) are a group of rare progressive genetic disorders of glycosaminoglycan (GAG) catabolism. Each MPS disorder is caused by a specific lysosomal enzyme deficiency required for GAG degradation. MPS disorders are progressive disorders due to the accumulation of partially degraded GAG within the lysosome resulting in cellular and tissue damage and reduced lifespan in most individuals with MPS [5–7]. MPS disorders are inherited in an autosomal recessive pattern, except for MPS II (Hunter syndrome), which is an X-linked recessive disorder that primary affects males [5]. Collectively, the country-specific incidence ranges from 1 in 22,000 to 65,000 live births [8–10]. Typically, MPS disorders are suspected based on clinical feature, but because of the heterogeneous presentations, most MPS patients have significant clinical involvement by the time the diagnosis is made. Diagnosis of MPS disorders is made based on clinical features, elevated urinary GAG levels, deficient enzyme activity, and genetic analysis [11]. Common sleep disorders in MPS subtypes are summarized in Table 60.1.

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Table 60.1 MPS subtypes and sleep disorders

Disease	Enzyme deficiency	Sleep complaints		SDB		Circadian rhythm
		Insomnia	EDS	Obst	Central	
MPS I (Hurler)	Alpha-L-iduronidase	+		++		+
MPS II (Hunter)	Iduronate sulfatase	+		+++		+
MPS III A (Sanfilippo A)	Sulfamidase	+++		+	+	++
MPS III B (Sanfilippo B)	Alpha-N-acetyglucosaminidase					
MPS IV A (Morquio)	N-acetyggalactosamne-6-sulfatase			+		
MPS VI (Maroteaux-Lamy)	N-acetylglucosamine-4 -sulfatase	++		+++	+	

EDS excessive daytime sleepiness, *Obst* obstructive, *SDB* sleep-disordered breathing

Clinical Characteristics

The organ system involvement for each MPS is dependent on specific enzyme deficiency but may involve the nervous, musculoskeletal, circulatory, and respiratory systems. Typical clinical features are characterized by coarse facial features (with protruding or depressed frontal bone, depressed base of the nose, and/or hypoplastic mandible), macroglossia, restricted temporomandibular joint mobility (TMJ), adenotonsillar hypertrophy, frequent sinusitis and respiratory infections, obstructive airway disease, sleep apnea, cognitive impairment with speech and language delays, communicating hydrocephalus, spinal cord compression, seizures, decreased joint range of motion, scoliosis, hepatosplenomegaly, cardiac valvular dysfunction, short stature, gait disturbance, and premature death in the second or third decade of life in the severe forms [6, 11–16]. Clinical evaluations can be challenging secondary to having decreased hearing and vision, speech and language delays, and behavioral problems. Behavioral problems may manifest as temper tantrums, hyperactivity, and aggressiveness, which may be exacerbated by poor sleep quality [14, 17].

Sleep Disorders

Sleep Complaints

Due to diverse clinical features of MPS, sleep-related complaints in MPS are varied and heterogeneous. Sleep disturbances that are reported in MPS include bedtime resistance, difficulty falling asleep, frequent awakenings often with disruptive behavior, parasomnias, excessive daytime sleepiness, snoring, and sleep-disordered breathing [6, 12, 14, 17]. Sleep disturbances have been associated with increased behavioral problems, depression, and reduced quality of life [14].

Sleep-Disordered Breathing

One of the most commonly reported sleep disturbances in patients with MPS is sleep-disordered breathing. Most patients with MPS reportedly snore, and many suffer from obstructive sleep apnea [5, 6, 13, 18–21]. MPS patients with significant somatic disease (MPS I, II, IVA, VI, and VII) can develop moderate-to-severe obstructive sleep apnea (OSA) [5, 7, 18, 19]. Typical anatomic features of MPS that contribute to increased upper and lower airway obstruction include turbinate hypertrophy, adenotonsillar hypertrophy, decreased motion of the TMJ, macroglossia, increased deposition of GAG products throughout the upper and lower airway, laryngomalacia, tracheomalacia, and restrictive lung disease [11, 13]. It has been suggested that there is poor correlation between symptoms of sleep apnea and the presence of obstructive sleep apnea on polysomnography (PSG). Therefore, patients with MPS should undergo PSG early in life [13]. Restrictive lung disease in patients with MPS may also put them at increased risk for hypopneas and sleep-related hypoventilation with hypoxemia and hypercapnia [7, 11]. The sleep-related breathing problems in MPS patients typically progress with age.

Mucolipidosis II (inclusion cell or I-cell disease) is an autosomal recessive lysosomal storage disorder clinically comparable to the MPS. Wooten et al. reported a child with mucolipidosis II who had worsening sleep-related hypoventilation, OSA, and sleep state fragmentation despite advancing PAP therapy. Background slowing and reduction in spindle activity on limited EEG may reflect progressive CNS disease affecting thalamic neurons [22].

Sleep Architecture

Sleep architecture is variable in patients with MPS, and most of the studies investigating polysomnography in MPS have a small sample size and limit the study population to one or a few MPS types; however, collectively, sleep architecture disturbances that have been reported in MPS include prolonged sleep-onset latency, which increased with age, decreased nighttime sleep, inefficient sleep, increased time in stage 1 sleep, decreased REM, and slow-wave sleep, and increased daytime sleep [7, 14, 19]. Sleep architecture disturbances may progress and worsen with age [14].

Circadian Rhythm

It is unclear what contribution circadian rhythm disturbances may contribute to the disruption of sleep architec-

ture, but this has been most extensively studied in Sanfilippo syndrome (MPS III) [14, 15, 17]. Patients with MPS III may have elevation in daytime melatonin release, depression of nighttime melatonin, and reduced circadian variability which has also been demonstrated in mouse models of MPS III [14, 15, 17]. Although the mean periodicity of the circadian rhythm did not significantly differ between patients with MPS and typically developing controls, there was a greater variance and fragmentation of the circadian rhythm as measured by actigraphy in patients with MPS [15]. Some MPS patients exhibited phase advancement, and some patients exhibited phase delay with phase delay being more common [15]. Descriptive activity analysis revealed increased activity in MPS III patients from 12 am to 6 am and decreased activity level from 6 am to 12 pm [15]. Disruption in the circadian rhythm can have significant impact on cognitive functioning, behavioral disturbances, and quality of life for patients and their caregivers [14]. In a preclinical murine study by Canal et al., they suggest that altered circadian responses in MPS III are a result of an alteration in the photo-retinal signaling to light rather than altered central nervous system (CNS) responses in the suprachiasmatic nucleus of the brain [17].

Others: Movements and Nocturnal Events

Although not consistently reported in the literature of polysomnographic findings of patients with MPS, Lin et al. did record a higher periodic limb movement score in patients with MPS as compared with controls [19].

Management

The focus of treatment for sleep disorders in MPS is centered on behavioral modification, regulation of the circadian rhythm, and treatment of sleep-disordered breathing [23]. As sleep apnea can worsen excessive daytime sleepiness and circadian rhythm disturbances, patients should undergo evaluation for sleep apnea using polysomnography, if able, upon diagnosis. Overnight polysomnography, upper airway computed tomography, and nasal endoscopy are useful tools for diagnosing obstructive sleep apnea syndrome in MPS and identifying the site and severity of airway obstruction [21]. If behavioral problem or cognitive impairment prohibits evaluation using in-lab polysomnography, home sleep study and overnight oximetry may be alternatives; however they need to be reviewed with caution. Patients with mild-to-moderate sleep apnea should undergo evaluation for airway obstruction and be referred to ENT for possible adenotonsillectomy (T & A) [11]. Transnasal coblation and microdebrider adenoidectomy is a safe and effective surgical treatment for OSA in patients with MPS and adenoidal hypertrophy [24].

MPS patients have a significant increased anesthesia risk. Increased risk of cervical instability due to odontoid hypoplasia, limited TMJ mobility, and upper airway obstruction all could lead to difficult intubation or preclude a successful procedure. Preparations should be made for fiberoptic intubation and tracheotomy if needed [11, 13]. Increased postoperative complications, such as airway edema and failure to extubate, should be considered along with the risk for postoperative hemorrhage in MPS patients being considered for adenotonsillectomy. Adenotonsillectomy is often successful in reducing the severity of obstructive sleep apnea, but often insufficient to eliminate OSA completely. A postoperative sleep study should be obtained to assess the need for continued treatment of OSA with positive airway pressure (CPAP or BiPAP), or possibly tracheotomy placement. Although there is evidence of recurrence of adenoid hypertrophy following T & A in patients with MPS, the size of recurrent post-op adenoids is likely less than the pre-op adenoid size [13]. The current treatment options for MPS patients, intravenous enzyme replacement therapy or hematopoietic stem cell transplantation, appear to impact the progressive airway complications, yet the effects of these treatments on many of the MPS sleep-related issues are unknown.

Other IEMs and Sleep Disorders

Sleep disorders in IEMs are summarized in Table 60.2.

IEM Predominantly Involves Central Nervous System

Aspartylglucosaminuria

Aspartylglucosaminuria (AGU) (OMIM #258406) is a rare autosomal recessive lysosomal storage disorder due to deficiency of the enzyme glycosylasparaginase with a high prevalence in the Finnish population. The accumulating glycoconjugates result in progressing encephalopathy, cognitive impairment, speech delay, weakness joint, hypermobility, and loose skin. Lindblom surveyed 81 patients with AGU (3–55 years with a mean age of 22 years) using a modified Basic Nordic Sleep Questionnaire and found that over 60% of children and over half of adults with aspartylglucosaminuria were affected daily from sleep-related issues [25]. Most of the issues in children were related to difficulty settling at night and more snoring. Adults were more likely to note fragmentation of sleep and long sleep periods with more disturbing movements at night. It was also found that adults with AGU had longer night sleep duration of 9.5 hours compared to controls with 7.2 hours [25].

Cystinuria

Cystinuria (OMIM # 220100) patients are also noted to have frequent sleep disturbance, reported as early as 1942 by

Table 60.2 Summary of sleep disorders in IEM

Diseases		NT	Sleep complaints		SDB		Circadian rhythm	Others
			Insomnia	EDS	Obst	Central		
CNS	AGU		+					Movements
	Cystinuria		+					
	MCAD							movements
	NCL		+++				++[a]	Epileptic form in SWS
	NKH	Glycine				++		EEG burst-suppression and epileptic forms
	NPC							Myoclonus cataplexy
	PKU	Dopa, NE	++	++			+	
	SSADH	GABA	++	+				Seizure Reduced REM
	Wilson D	Dopa	+	++				Cataplexy REM behavior
Peripheral or multi-systems	Fabry			++	++	+		PLMD
	Pompe			++	++			hypoventilation
	PHP1A				++			
	SLOS		++	++	++			

AGU aspartylglucosaminuria, *EDS* excessive daytime sleepiness, *MCAD* medium chain acyl-CoA dehydrogenase deficiency, *NCL* neuronal ceroid lipofuscinoses, *NE* non-epinephrine, *NKH* nonketotic hyperglycinemia, *NPC* Niemann-Pick disease type C, *NT* neurotransmitter, *Obst* obstructive, *PHP* pseudohypoparathyroidism, *PKU* phenylketonuria, *SLO* Smith-Lemli-Opitz syndrome, *SSADH* succinic semialdehyde dehydrogenase, *SWS* slow-wave sleep

[a]Ovine model

Crevald. Jouvet et al. also described sleep disturbances in patients with intellectual disability in 1966 [26].

Medium Chain Acyl-CoA Dehydrogenase Deficiency

Medium chain acyl-CoA dehydrogenase deficiency (MCAD) (OMIM *607008) is an autosomal recessive disorder of fatty acid oxidation. Patients with abnormalities in fatty acid oxidation are typically thought to have normal sleep. One case report of an adolescent with MCAD deficiency demonstrated paroxysmal vermicular movements in sleep lasting up to 40 minutes. These movements were not responsive to anticonvulsant therapy. The sleep-induced paroxysmal motor behaviors during non-REM sleep improved with diet therapy (low fat diet, high glucose, and high-protein diet), oral carnitine, vitamin B2 and B12 supplementation, and intravenous glucose and coenzyme complex infusion [27].

Neuronal Ceroid Lipofuscinoses

Neuronal ceroid lipofuscinoses (NCL) are a group of rare inherited progressive neurodegenerative lysosomal storage disorders [28]. The most prevalent NCL are CLN3 disease (also called Batten disease) (OMIM *607042) and classic juvenile and CLN2 disease (OMIM *607998). NCL are characterized by the accumulation of lysosome-derived storage bodies occurring in nearly every tissue. Neurodegeneration of the cortex is marked, and the clinical symptoms include visual impairment, motor deficits, epileptic seizures, cognitive, and sleep abnormalities, which increase in severity until the premature death of the patients [29].

Caregivers of these patients report that the children have a high frequency of sleep disturbances and breathing difficulties and that these abnormalities present significant challenges to their daily care [30]. Using the results of a sleep disturbance screening tool, Lehwald found 52 of 54 subjects had at least one abnormal sleep subscale [31]. In this group, the onset of sleep disturbance heralded worsening symptoms with the onset of seizures and the loss of vision. Restless leg syndrome symptoms were also reported. On polysomnography of ten patients with juvenile forms of NCL, Lauronen reported nearly every patient had abnormal sleep, finding frequent epileptiform activity in slow-wave sleep [32]. Studies in sheep with an NCL showed a loss of the increase in slow-wave sleep following sleep deprivation suggesting that there is a block in the expression of the sleep homeostatic drive that could contribute to early disease symptoms, such as behavioral disorder and cognitive decline [33].

Nonketotic Hyperglycinemia

Nonketotic hyperglycinemia (NKH), also called glycine encephalopathy (OMIM #605899), is an autosomal recessive disorder caused by defect in the glycine cleavage pathway. Glycine functions as a neurotransmitter and acts in an inhibitory fashion in the brainstem and spinal cord, but in an excitatory manner in the cerebral cortex. Excess glycine causes apnea by its effect in the brainstem and seizures through its

action on the cortex [34]. In a natural history of 65 patients with NKH, one-third of the patients died, 8 females died during the neonatal period, and 14 patients died thereafter (2 females and 12 males). This study revealed unexpected gender differences – female patients with NKH were susceptible for severe complications and had a higher mortality rate during the neonatal period [34]. Severe central apnea and epilepsy are among the suspected causes of death.

Niemann-Pick Disease Type C

Niemann-Pick disease type C (NPC) (OMIM # 257220) is an autosomal recessively inherited lipid storage disease that leads to progressive and disabling encephalopathy and premature death. One of the first descriptions of cataplexy in NPC was from Kandt et al. in 1982 [35]. Cataplexy has been reported in patients with Niemann-Pick type C disease (5 out of 22 patients had cataplexy); sleep disturbances are described only rarely [36]. Vankova et al. performed overnight in-lab polysomnogram and next day multiple sleep latency study and measured CSF hypocretin level in a case series of five patients with Niemann-Pick type C (one had clinical cataplexy). Overnight polysomnography showed fragmentary myoclonus [37]. Hypocretin levels in CSF were significantly reduced in two patients (one with cataplexy). This study suggests that lysosomal storage abnormalities in NPC patients may impact the hypothalamus and, more specifically, hypocretin-containing cells. These changes might be partially responsible for sleep abnormalities and cataplexy in patients with NPC [37].

Phenylketonuria

Phenylketonuria (PKU) (OMIM *612349) is an autosomal recessive disorder caused by deficiency of the enzyme phenylalanine hydroxylase (PAH). PAH deficiency results in elevated phenylalanine and decreased production of tyrosine, a precursor of the neurotransmitters dopamine and norepinephrine. In a sleep disturbances study in PKU patients, Bruinenberg et al. analyzed questionnaires from 25 treated PKU adult patients and 23 healthy first-degree relatives. They found that nearly half of their cohort had a global score greater than 2.02 on a Holland Sleep Disorders Questionnaire indicating a sleep disorder. Most of the issues were related to insomnia and circadian rhythm issues. Similarly, this cohort indicated more disturbed sleep on the Pittsburgh Sleep Quality Index and more daytime sleepiness on the Epworth Sleepiness Scale [38].

Succinic Semialdehyde Dehydrogenase Deficiency

Succinic semialdehyde dehydrogenase (SSADH) deficiency (OMIM *610045) is a rare autosomal recessive disorder in the catabolism of the neurotransmitter GABA, in which developmental delays are prominent, accompanied by hypotonia, ataxia, behavior problem with aggression, seizures, and sleep disturbances either as excessive daytime somnolence or as disorders of initiating or maintaining sleep [39, 40]. About 45% of patients with SSADH deficiency have difficulty with sleep, most predominantly with difficulty initiating or maintaining sleep or having disturbed sleep [41]. In ten individuals with SSADH deficiency, polysomnograms showed prolongation of REM stage latency (mean 272 ± 89 minutes) and decreased percent stage REM (mean 8.9%, range 0.3–13.8%). Decreased mean sleep latency was present in 6 of 11 studied using daytime multiple sleep latency testing [42]. In two patients, Gibson showed temporary benefit of sleep in two patients with the use of benzodiazepines [42]. They went on to hypothesize that this defect results in disruption of the glial-neuronal glutamine/GABA/glutamate shuttle which might explain the constellation of neurological findings.

Wilson Disease

Wilson disease (OMIM # 277900) is a rare autosomal recessive genetic disorder related to a defect in ATP7B gene characterized by excess copper stored in various body tissues, particularly the liver, brain, and corneas of the eyes. Nevsimalova et al. conducted a case-control study of 55 patients with Wilson disease (22 hepatic, 28 neurological, 5 asymptomatic form) and 55 age- and sex-matched control subjects. Patients with Wilson disease were more prone to daytime napping accompanied by tiredness and excessive daytime sleepiness, cataplexy-like episodes and poor nocturnal sleep, and REM sleep disturbances [43]. REM sleep behavior disorder can be the presenting symptoms in Wilson disease. REM sleep behavior disorder in Wilson disease offers a possible theoretical model for potential early treatment [44]. Using the Uppsala Sleep Inventory Questionnaire, Portala et al. found sleep disturbances in 42% of the patients as well as likely an altered REM sleep function in patients with Wilson disease [45].

IEM Predominately Involved in Peripheral Nervous System and/or Non-neurological Systems

Fabry Disease

Fabry disease (OMIM # 301500) is an X-linked lysosomal storage disorder due to the deficiency of the enzyme alpha-galactosidase with both males and females having clinical disease. The accumulation of globotriaosylceramide (Gb3) results in acroparesthesias, angiokeratomas, cardiomyopathy, renal failure, and strokes. In patients with Fabry disease, a prospective clinical trial of 62 patients showed that sleep-disordered breathing, especially obstructive sleep apnea, is highly prevalent (25%). Excessive daytime sleepiness in

Fabry is also common (14%); however, it seems to be correlated with depression rather than sleep-disordered breathing [46]. In addition to obstructive sleep apnea, periodic limb movements of sleep are highly prevalent in patents with Fabry disease [47].

Pompe Disease

Pompe disease (glycogen storage disorder type II; GSD II; OMIM # 232300) is an autosomal recessive lysosomal storage disorder due to deficiency of the enzyme acid alpha-glucosidase (acid maltase). GSD II primary affects the heart and skeletal muscles, including diaphragm muscle. The degree of clinical severity depends upon the amount of residual maltase activity. In all three forms, infantile, childhood onset, and adult onset, patients are at significant risk for sleep apnea, hypoventilation and, in particular, REM sleep-related breathing disorders. Kansagra found 7 of the 17 patients had obstructive sleep apnea and 6 in their cohort had hypoventilation based upon end-tidal CO_2 measurements being above 50 torr for greater than 25% of the night. The hypercarbia was more likely in patients on oxygen therapy [48]. Nabatame et al. reported on four patients with childhood onset of Pompe disease, all had sleep-disordered breathing with AHI ranging from 6.7 to 25.9 events per hour and all worse in REM sleep. One patient had sleep apnea despite no daytime symptoms. In the three more severe patients, noninvasive ventilation (NIV) improved their daytime symptoms [49]. In a study of 22 adult patients with late-onset Pompe disease, sleep-disordered breathing, including both OSA and hypoventilation, were common. Fifty percent of patients in this study had either OSA and/or hypercapnia [50]. Noninvasive ventilation was initiated in 15 individuals and led to significant improvement of ventilation and oxygenation in the first night of treatment. In follow-up for up to 40 months, these patients were found to have normal oxygen and carbon dioxide levels without deterioration of sleep outcomes [50]. In adult patients with Pompe disease, sleep disturbances and sleep-disordered breathing are a common cause of excessive daytime sleepiness and fatigue [51]. In many of these cases, REM sleep appears to be a more vulnerable time for respiratory failure, most likely due to the muscle atonia and sole reliance on the diaphragm for airflow.

Pseudohypoparathyroidism Type 1A

Pseudohypoparathyroidism (PHP) type 1A (PHP 1a) (OMIM # 103580) is an autosomal dominant disease caused by mutations in the GNAS gene effecting dysfunction of the Gs-alpha isoform and resulting in end-organ resistance to parathyroid hormone. PHP 1a clinical features (Albright hereditary osteodystrophy) include short stature, obesity, subcutaneous ossifications, skeletal anomalies, and, in some, cognitive impairment. Children with PHP type 1A are at an increased risk (4.4 fold greater relative risk) for OSA compared with similarly obese peers [52]. They also have higher rates of otitis media and adenotonsillar hypertrophy. Screening for OSA should be considered in all patients with PHP1a and possibly PHP1b [53].

Smith-Lemli-Opitz Syndrome

Smith-Lemli-Opitz syndrome (SLOS) (OMIM # 270400) is a rare autosomal recessive disorder with multiple congenital anomaly and cognitive impairment caused by a deficiency of the enzyme 7-dehydrocholesterol-delta 7-reductase, the final step in cholesterol synthesis resulting in low cholesterol and elevated 7-dehydrocholesterol. In a case series of 28 patients (2–31 years of age), Zarowski et al. found that sleep-disordered breathing, sleep-related anxiety and sleep associations, disturbed sleep patterns at night, and excessive daytime sleepiness are frequent in children with SLO syndrome [54]. Biochemical severity of SLO syndrome was also associated with specific sleep problems (e.g., decreased sleep duration and increased sleep-onset delay) and was identified as a significant predictor of these factors [55]. In patients with SLO syndrome, most markers of cholesterol synthesis disruption were associated with overall sleep disturbance [55].

Conclusion

Sleep disorders are common in children and adults with IEM. Though individual IEM are typically rare, collectively, IEM are common. In addition to the risk of sleep-disordered breathing, patients with IEM are often at risk for other sleep disorders, such as disrupted intrinsic sleep architecture in patients with NCL, and hypoventilation related to diaphragm and neuromuscular weakness in patients with myopathy, such as Pompe disease. Disruption of sleep architecture, onset, maintenance, and quality in any form can significantly impact patient and caregiver quality of life. If identified, sleep disruptors are often treatable. Untreated sleep disruptions may lead to worsening of neurocognitive or behavioral manifestations that make the care of patients with IEM very challenging. Identifying, diagnosing, and treating these sleep disorders may significantly improve patient and caregiver quality of life. It may also prolong survival or prevent development of sequelae or comorbidities of untreated sleep disorders, such as in obstructive sleep apnea or chronic hypoventilation. Development of comorbid conditions can make chronic disease management challenging for patients, providers, and families. Optimal quality sleep is important in neurocognitive and psychological functioning and development. It is important to screen patients with IEM for sleep disturbances, poor sleep quality, and REM behavior disorders during routine health maintenance examinations.

Treatment of sleep-related disorders in patients with these complex and often multisystem diseases is often best managed in a multidisciplinary setting with expertise in primary care, sleep medicine, genetics, pulmonary, neurology, ENT, respiratory therapy, psychology and nursing as needed.

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