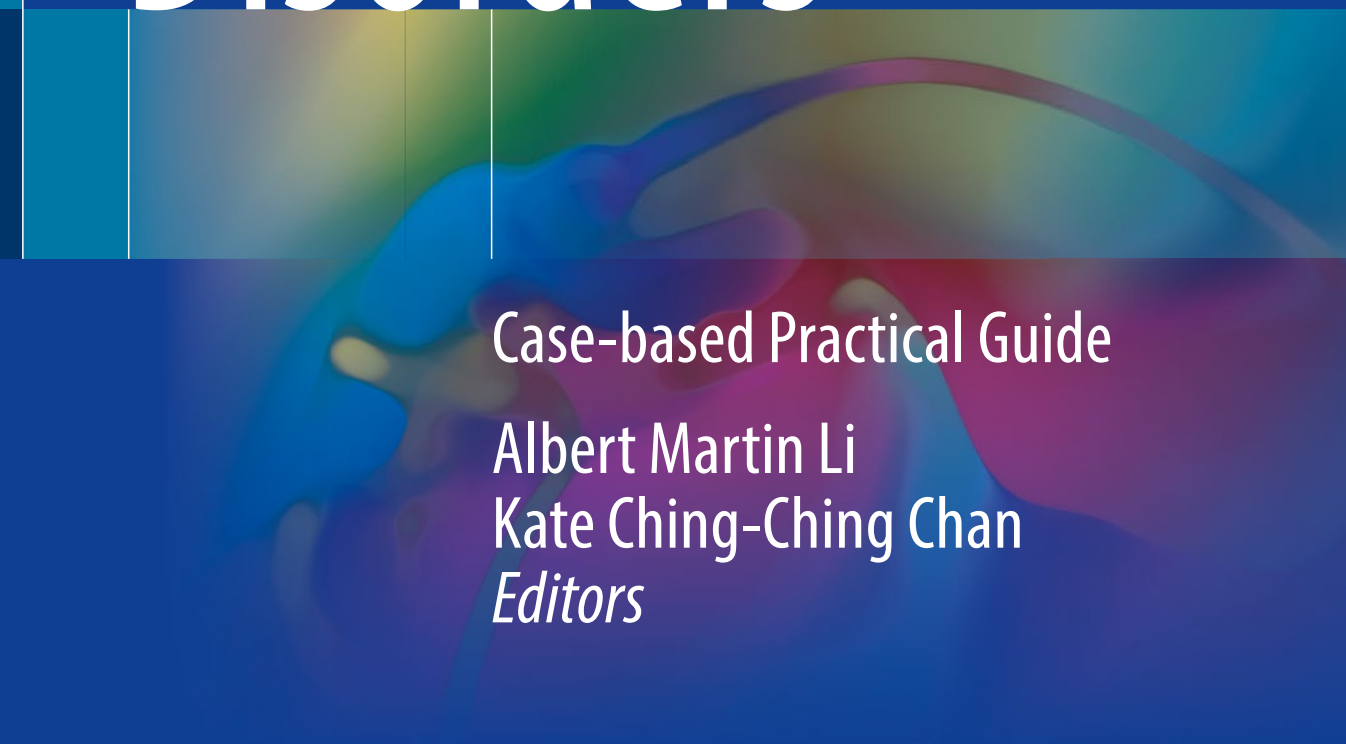
Paediatric Sleep Disorders



Case-based Practical Guide

Albert Martin Li
Kate Ching-Ching Chan
Editors

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Preface

This book aims to use the case discussion format to present the latest information on common sleep problems in children. We think it will be useful for sleep medicine paediatricians as well as for general paediatricians who often encounter patients with challenging sleep problems without the ready availability of a sleep specialist. The case-based format with concise facts together with the current research gaps for each condition is a good way for busy paediatricians to acquire the necessary information easily in small portions. Other readers including trainees, paediatric nurses, allied health care workers, and even parents may also find this book educational and informative. We would like to thank the staff at Springer for endorsing and editing the book. We especially would like to thank our expert authors, many of whom are members of the Asia Pacific Paediatric Sleep Alliance (APPSA), for writing such detailed and outstanding chapters.

Shatin, Hong Kong SAR — Albert Martin Li
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Part I

Introduction

Functions and Control of Sleep

1

Tat-Kong Wong

1.1 The Need to Sleep

Human beings spend about one-third of the life time in sleep. The studies in the past few decades have led us into a deeper understanding of the crucial and complex functions and control of sleep in human beings and other animals. Whether this complex process confers an evolutionary advantage of these higher living organisms in the presence of the day and night cycle on earth, or it simply evolves as a necessity of maintaining the living state in these organisms remains a mystery to us. The observation that a single cell organism can survive for sufficiently long enough without the highly organized process in higher living organisms involving all the neurons, neurotransmitters, and cytokines, has proven that, at least, sleep is not a basic necessity universally required for all living organisms to survive.

Human sleep is classified into NREM Sleep (also called N sleep) and REM sleep (also called R sleep). NREM sleep is further subdivided into stage 1 (N1), stage 2 (N2), stage 3 and 4 (N3). In older children and adults, human sleep cycles between NREM sleep and REM sleep for approximately 90 min for about four to five times during the night in an ultradian cycle. In younger children, the cycles are shorter at approximately 60 min. The first cycle of sleep commences with a brief period of stage 1 and stage 2 NREM sleep, typically lasting for a few minutes, followed by stage 3 and stage 4 NREM sleep ("deep sleep" or "Slow Wave Sleep") that occupy most of the first sleep cycle. At the completion of the first cycle of sleep, there may be a brief period of stage 2 sleep that may or may not be followed by a brief first REM sleep (typically lasting for less than 10 min). Following the first cycle of sleep, sleep cycles for the rest of the night are comprised of NREM-REM cycles with slow wave sleep predominating the second cycle, to later cycles with longer REM periods [1].

1.2 Control of Sleep

Sleep is regulated by interplay of 3 processes [2].

1. Homeostatic process ("Process S")

   Homeostatic process is the main process regulating sleep based on prior level of wakefulness. This is called the "Process S" in the current 2 process model for controlling sleep throughout the course of a day. Process S represents the pressure to fall asleep, building up as the time spent in wakefulness increases, and declining during sleep.
2. Circadian process ("Process C")

   The circadian process ("Process C" in the 2 process model) is a clocklike mechanism,

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that is operating independent of the homeostatic process, governing the day and night tendency to fall asleep, according to the body clock. The two process interacts with each other to control the wake and sleep throughout the day.

3. An ultradian process within sleep, controlling the alternation between non-REM and REM sleep. The exact need of REM sleep, and REM sleep regulation is still not yet clearly understood.

1.2.1 Generation of Circadian Rhythm

The Circadian rhythm "pacemaker" is located at the suprachiasmatic nucleus (SCN). The generation Circadian rhythm cycle is a result of the daily oscillation in the levels of several clock component proteins. These proteins are coded by several genes including CLOCK, BMAL1, PER. The basis for this oscillation lies in the rhythmic feedback regulation of the transcription of the genes encoding these proteins.

1.2.2 Sleep and Arousal

As much as sleep is important for many functions in human and many other higher functioning animals. Sleep is also a very important delicate state that allows all those functions to be achieved, while maintaining a certain level of arousal ability, which is a relatively quick and sudden reversal of the complex process, presumably important for the survival of the animals in the wild, and equally important in the case of internal functional disturbance such as hypoxemia and/or hypercapnia following obstructive sleep apnoea.

Arousal/wakefulness is produced by ascending pathways originating in the brainstem monoaminergic neurons (norepinephrine-producing neurons in locus coeruleus, serotoninergic neurons in dorsal raphe of brain stem, histaminergic neurons in the tuberomammillary nucleus of the hypothalamus) and cholinergic neurons at the mesopontine junction between the pons and the midbrain, a neural circuitry called the "ascending reticular activating system" (Fig. 1.1). Brain areas that produce neurotransmitters in this circuitry, especially acetylcholine and monoamines,

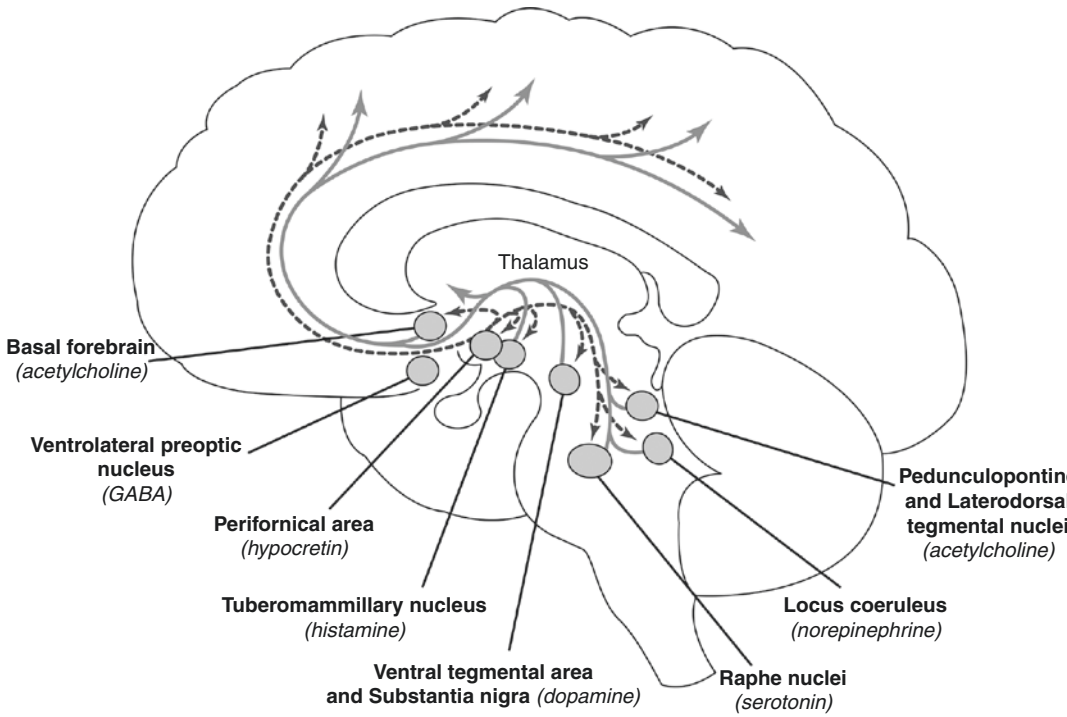

Fig. 1.1 The neurocircuitry of ascending reticular activating system showing the projections from the cholinergic and monoaminergic neurons (solid line arrow); and the widespread projection of the hypocretin neurons (dotted line arrow)

induce arousal rapidly. The redundancies in arousal molecules and networks likely function to rapidly wake and stimulate an animal to avoid potential danger [3].

1.2.3 The NREM and REM Sleep

1.2.3.1 NREM Circuit

Regions in the brain with high concentration of GABAergic neurons are activated during NREM sleep. These include lateral hypothalamus, dorsal raphe nucleus, periaqueductal gray, and locus coeruleus. In particular, GABAergic neurons in the ventrolateral preoptic nucleus (VLPO) of the lateral hypothalamus play a significant role in the promotion of NREM sleep. VLPO neurons innervates the NREM network extensively. They also innervate wake-promoting regions such as dorsal raphe system, locus coeruleus, and also histaminergic cells in the tuberomammillary nucleus (TMN) (Fig. 1.2). VLPO neurons induce NREM sleep by coordinating the NREM promoting regions and inhibiting the wake-promoting regions. VLPO neurons are in turn inhibited during wakefulness by wake-promoting neurotransmitters including acetylcholine, norepinephrine, dopamine, and serotonin.

1.2.3.2 REM Circuit

REM sleep is mainly controlled by the interaction of cholinergic and aminergic brainstem neurons. Cholinergic neurons located near the laterodorsal tegmental/pedunculopontine (LDT/PPT) nuclei at the mesopontine junction are active during REM sleep. During NREM sleep, these REM-active cholinergic neurons are inhibited by the aminergic neurons (norepinephrine, serotonin, histamine). During REM sleep, these aminergic neurons are inactive, thus disinhibiting the REM-generating neurons.

The REM active neurons also produce the muscle atonia of REM sleep through a descending pathway into the brainstem and spinal inhibitory system. Muscle atonia during REM has a crucial role in inhibiting the "acting out the dream" during REM sleep.

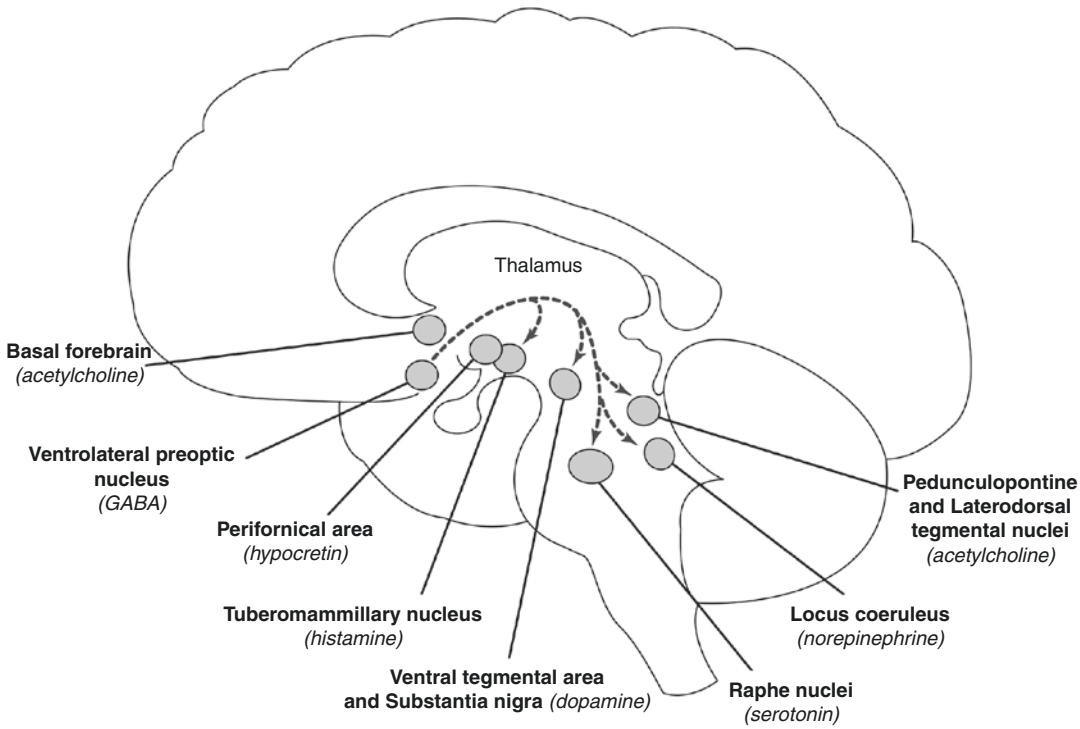

Fig. 1.2 The neurocircuitry of NREM sleep showing the inhibitory projections from the neurons in the ventrolateral preoptic (VLPO) nucleus to the nuclei of the ascending reticular activating system

1.2.3.3 The Role of Hypocretin/Orexin

Hypocretin/orexin is an excitatory neuropeptide produced by a small group of neurons in the lateral and posterior hypothalamus. These neurons project extensively to many areas in the brain, innervating both REM and NREM circuit, and the ascending activating system (Fig. 1.1). These neurons have a critical function in the stabilization of sleep and wakefulness. Lesion in this group of neurons would lead to Narcolepsy. Narcolepsy in human is mostly associated with a marked reduction in the number of these neurons, likely related to an autoimmune process. These neurons are also involved in control of feeding, locomotor activity, body temperature, and autonomic functions.

1.3 Functions of Sleep

1.3.1 Sleep and EEG Recovery

The prolonged wake time leads to increasing propensity for recovery from it. In the two-process model as described above. The homeostatic pressure ("Process S") would increase with increasing duration of wakefulness. This is quantifiable by the intensity of EEG slow wave, which is also evident in the EEG during the "recovery sleep" following prolonged wakefulness. This EEG evidence of the need to "recover" from prolonged wakefulness, however, did not explain why exactly this has to happen in human.

1.3.2 Sleep, Brain Energy Replenishment, Molecular Regeneration

The prolonged wake time leads to increasing energy depletion, as evidenced by reduced intracellular ATPs, which were converted to ADPs and adenosines, thereby releasing the energy presumably required for the wake related activities. Thus, the more prolonged wakefulness is, the lower the ATP level will be, and the higher the level of ADP and adenosine will be. This higher level of adenosine forms the pathway to induce sleepiness and the intensity of the slow wave sleep following the prolonged wakefulness. Caffeine, the adenosine receptor antagonist, is well known to promote wakefulness, supporting the direct role of adenosine in promoting NREM sleep [4].

Glycogen, the primary energy source for the brain, the source of the ATP, has also been the focus of ongoing studies. The synthesis and utilization of glycogen are a continuous process during both wakefulness and sleep. Although glycogen depletion happens during prolonged wakefulness, synthesis of glycogen can actually take place after prolonged period of wakefulness without sleep state, suggesting the non-obligatory role of sleep in the replenishment of brain glycogen storage [4].

1.3.3 Sleep and Toxin Removal Within the Brain

The glymphatic clearance hypothesis states that the effective clearance of metabolites accumulated during wakefulness, were effectively removed by the glymphatic system [5]. This is supported by the observation of significant expansion of the interstitial space in the cortical area. By this hypothesis, the toxic metabolites accumulated during wakefulness are effectively flushed away, with the water and small molecules entering the astrocytes via aquaporin channels, and exiting into the interstitial fluid, that would flow through the perivascular space, into cervical lymphatics and venous blood in the dural sinuses. These metabolites include beta amyloid, soluble proteins, lipids, lactates, etc.

1.3.4 Sleep and Memory

Sleep has a crucial role in memory and learning. The exact mechanisms of memory formation during sleep is still unclear. It is likely that differ-

ent mechanisms exist for multiple types of memory: short-term, long-term, declarative, procedural, etc. Different models have been developed to conceptualize memory formation.

In the "two-stage model", short-term memory was primary stored in the hippocampus during wakefulness, in the form of firing patterns. During NREM sleep, the shutting off of information input that was intense during wakefulness provides a relative clean environment for the replay of the firing sequence that has been stored as short-term memory in the hippocampus. The short-term memory information was transmitted to the cortex by replaying the firing pattern from hippocampus. During the ensuing REM sleep, when neuronal circuits are desynchronized, possibly uncoupling the short term and long term memory systems, circuits associated with specific memory traces are activated in the cortex, resulting in consolidation the memory and integration of the memory with pre-existing long term memory. This consolidation of short term memory involves protein formation, results in a significantly strengthened memory, that forms the basis of long term memory [6].

The exact formation of memory is, however, far more complicated than the "two-stage model". For example, NREM and REM sleep contribute differently to different types of memory. NREM sleep appears to be more important for declarative memory whereas REM sleep is involved more in procedural memory and the emotional components of memory [6].

1.3.5 Sleep and Immunity

Sleep interacts with immunity in a reciprocal way. Cytokine levels are affected by sleep. Cytokines also have important effect on sleep.

Our body immune systems are affected by sleep in both circadian and non-circadian manner. For example, interleukin-6 concentration in the circulation peaks at 19:00 and 05:00 of the circadian clock. Sleep disturbance or deprivation would both shift the peak time as well as reduces the peak concentration of interleukin-6. Serum level of Tumour Necrosis Factor (TNF) declines during sleep, however stimulated production of TNF in response to challenge increased significantly during sleep, independent of the circadian clock.

Prolonged wakefulness is associated with activation of inflammatory pathways. Prolonged wakefulness induces elevated levels of pro-inflammatory cytokines, including interleukin-1, interleukin-2, interleukin-6 activity, and thus the accompanying increase in C-reactive protein. Prolonged wakefulness also induces elevated level of vascular endothelial marker, namely the intercellular adhesion molecule-1 (ICAM-1) [7].

Cytokines are known to affect sleep. Pro-inflammatory cytokines, such as interleukin-1, interleukin-6, and TNF-alpha have NREM sleep promoting effects. Cytokines with anti-inflammatory properties, such as interleukin-10, interleukin-13, and tumour growth factor-beta, have anti-somnogenic properties [7].

1.3.6 Sleep, Mood, and Emotion

Sleep also has important reciprocal relationship with mood and emotion. Numerous studies have shown the effect of sleep deprivation on mood and emotional disturbance. Mood and emotional disturbance during daytime, in turn, significantly affect night sleep architecture.

Sleep loss not only intensified negative emotions, but even diminished positive emotions following a goal achieving event. Both REM and NREM sleep may be involved in the mood regulation function of sleep. Earlier studies focused on the role of REM sleep in mood regulation. This may involve emotional "depotentiation" (the famous theory of "sleep to remember (the emotional memories) and sleep to forget (the emotional tone)"), or "maintenance" of the emotional tone by identification of the optimal outcome of a specific emotional memory, or both. More recent studies have shown the role of

NREM sleep in emotional memory processing, especially in fear extinction [8].

Acute stress and emotional events are known to affect night time sleep in various ways, including sleep duration and sleep efficiency, latency of deep sleep (stage 3 and 4 NREM) and REM sleep, disruption of the normal sleep with increased arousals or awakenings, disruption of NREM and REM sleep proportion, and the content of the dream [8].

1.3.7 Sleep: The Developmental Perspective

Sleep in early infancy period is distinctly different. The very different EEG patterns have been relatively well described. The molecular difference, that is believed to be crucial has been much less studied. In early infancy, sleep commences with REM sleep, as opposed to the NREM sleep later in life. REM sleep also occupies a higher proportion of the sleep duration early in life. The crucial role of REM sleep in the proper neural development in the early life, is described in the ontogenic REM sleep hypothesis. Sleep loss during this developmental period could reduce brain mass, induce neuronal cell death, and increase risk of eventual behavioural problems [9].

Numerous factors contribute to successful development of a normal sleep habit in late infancy and toddlers. Failure to attain a non-pathological sleep routine is associated with issues in sleep onset and sleep maintenance, during both daytime naps and night time sleep, eventually leading to interrupted sleep and sleep insufficiency. Sleep insufficiency in the primary school years also tends to persist into adulthood [10].

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Sleep Physiology and Architecture

2

Chun-Ting Au

2.1 Sleep Architecture

Normal human sleep is a continuous but varying and complex process with two main distinct phases, i.e. rapid eye movement (REM) and non-REM (NREM) sleep. The latter is further classified into three different stages according to the deepness of sleep: NREM 1 (N1), and NREM 2 (N2), and NREM 3 (N3). A healthy human normally goes into sleep stage N1 when sleep starts. Then, he/she goes through stage N2 and reaches a stable and prolonged period of stage N3 sleep, followed by a period of REM sleep to complete the first sleep cycle. In healthy adults, a 7–8 h of sleep consists of 4–6 sleep cycles, each approximately 90–120 min long. In infants and children, the length of sleep cycles increases with age, from 50–60 min in infants to 60–90 min in prepubertal children. Across the night, the proportion of stage N3 of a sleep cycle decreases whereas the proportion of stage R increases (Fig. 2.1).

Sleep architecture can be captured by overnight polysomnography (PSG), which is simultaneous monitoring of multiple physiological signals during sleep including brain waves (electroencephalography, EEG), eye movements (electrooculography, EOG), chin muscle tone (electromyography, EMG), heart rhythm (electrocardiography, ECG), respiratory signals (airflow, effort, and snoring), pulse oximetry and sleep posture. Every epoch of 30-second recording will be scored and staged by a well-trained and qualified technologist based on the pattern of EEG, EOG, and chin-EMG signals [1].

During wakefulness, EEG usually shows an alpha rhythm of 8–13 Hz which will be magnified upon eye closure and attenuated with eye-opening. Various forms of eye movements, such as REMs, reading eye movements and eye blinks, can be present during wakefulness with high chin muscle tone (Fig. 2.2). A normal healthy child normally goes into sleep stage N1 when sleep starts. When one is drowsy, REMs and eye blinks are substituted by slow eye movements. Stage N1 is confirmed when the EEG alpha rhythm is replaced by a low-amplitude pattern with a slower frequency (4–7 Hz) (Fig. 2.3). It is considered to be the lightest form of sleep which usually occurs at sleep onset or resumption of sleep after awakening or arousal from other sleep stages. It is a transient stage that usually lasts less than 2 min each time and accounts for approximately 5% of the total sleep time. Stage N1 quickly progresses to stage N2 which is a more stable sleep stage accounting for a substantial proportion of sleep

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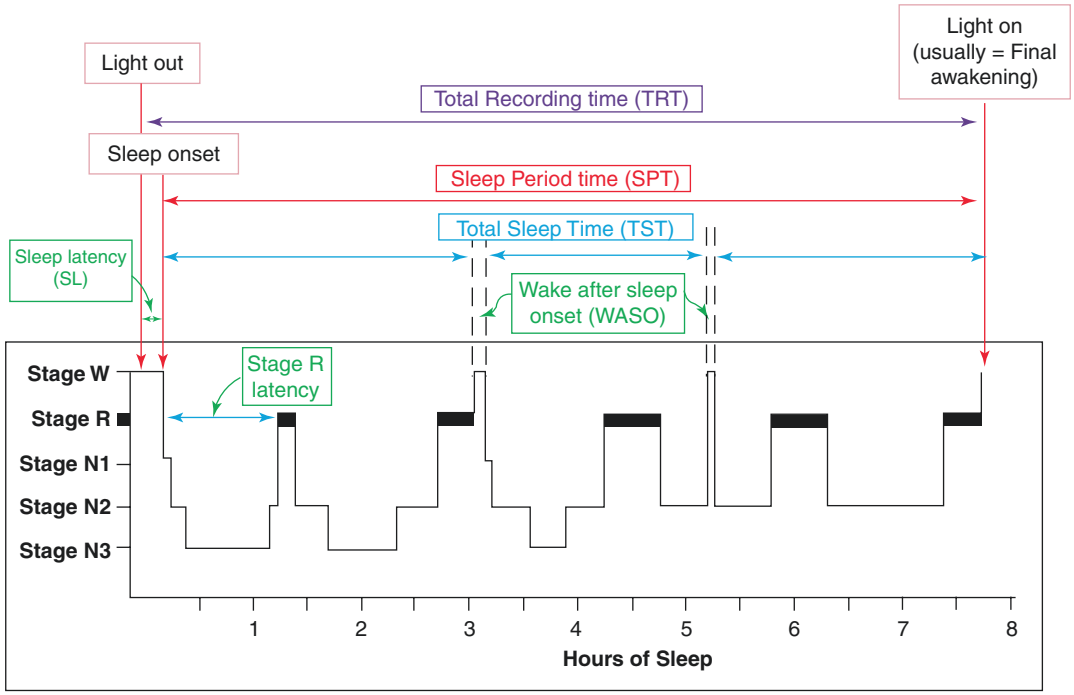

Fig. 2.1 A typical hypnogram of a healthy adolescent captured by a standard sleep study

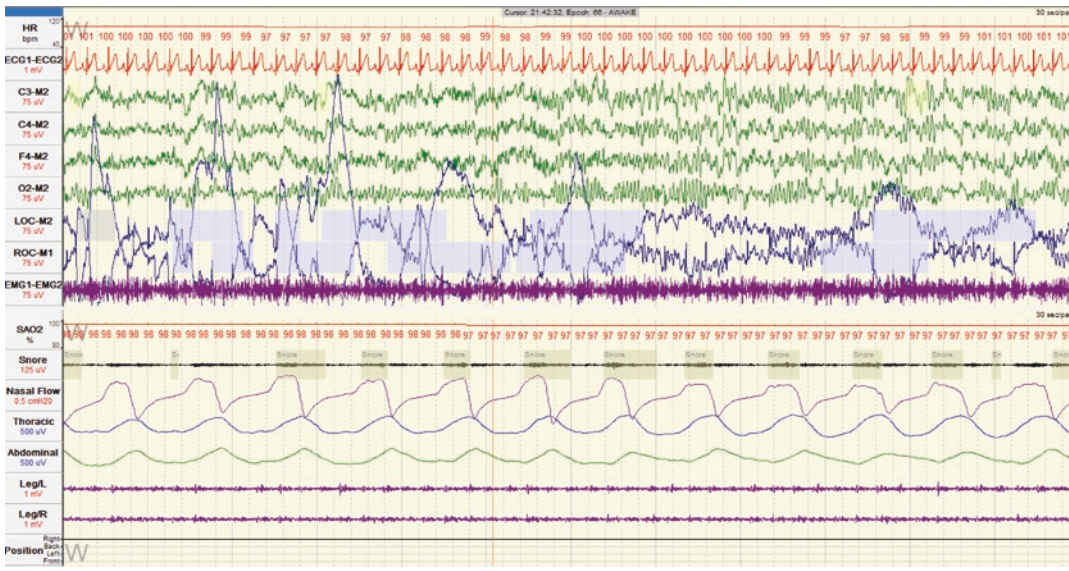

Fig. 2.2 An epoch of stage W of a 10-year old girl. A pattern of alpha (8–13 Hz) rhythm is seen in the EEG channels (C3-M2, C4-M2, F4-M2, and O2-M2). Rapid and slow eye movements can be seen in the EOG channels (LOC-M2 and ROC-M1). The EMG channel displays a high chin muscle tone

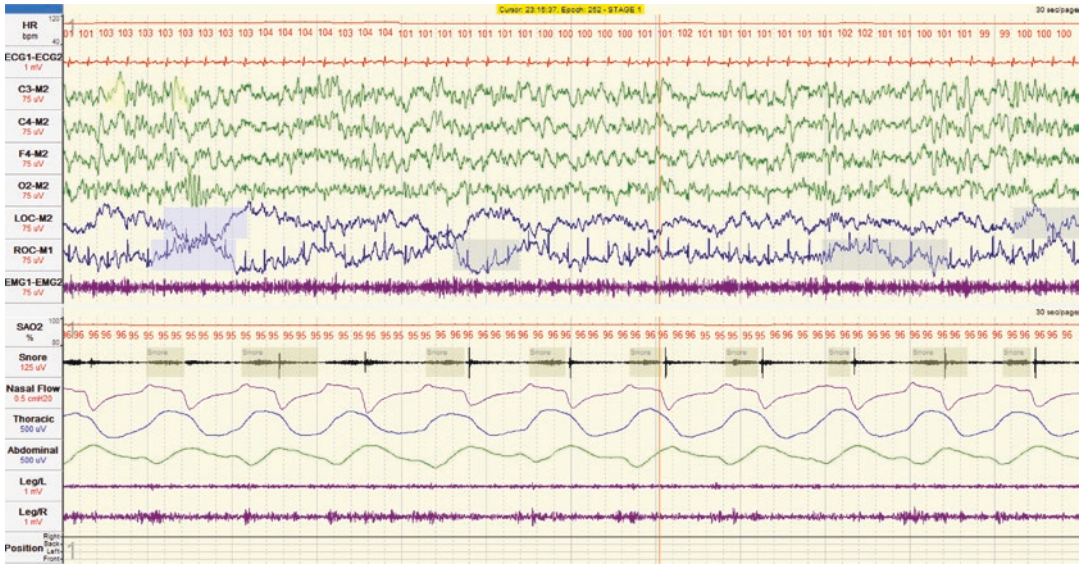

Fig. 2.3 An epoch of stage N1 of a 10-year old girl. A pattern of low amplitude mixed frequency (4–7 Hz) rhythm (C3-M2, C4-M2, F4-M2, and O2-M2) with occasional vertex sharp wave (C3-M2, C4-M2, and F4-M2) can be seen in the EEG channels. No sleep spindles and K complexes can be seen. Slow eye movements can be seen in the EOG channels (LOC-M2 and ROC-M1). The chin muscle tone remains high

time. Stage N2 is characterised by K complexes and sleep spindles in EEG without slow or rapid eye movement (Fig. 2.4). Sleep will then progress to stage N3, which is the deepest form of NREM sleep, characterised by slow frequency (0.5–2 Hz) and high-amplitude (>75 μV) EEG called slow-wave activity (SWA) (Fig. 2.5). Therefore it is also known as slow-wave sleep (SWS) or deep sleep. SWS occurs mostly in the first half of the night when the sleep pressure is the highest. Normally, the first REM sleep (stage R) period will take place after the end of the first NREM sleep period in adults or older adolescents. However, in children, it is common to see no or just a very short period of REM sleep in the first sleep cycle, probably attributed to the high sleep pressure in the first half of the night especially in young children that requires more SWS instead of REM sleep to dissipate. The transition of NREM to REM sleep is highlighted by a dramatic drop of chin muscle tone, accompanied by a low-amplitude mixed frequency EEG pattern without spindles, K-complexes, or slow waves, and followed by episodes of REMs (Fig. 2.6). Other features of stage R include a sawtooth wave of EEG, transient muscle activities from the mostly atonic background EMG, and irregular heart rate and breathing pattern. In contrast to SWS, REM sleep occurs predominately in the second half of the night. The end of a REM sleep period usually indicates the end of a sleep cycle, which will be followed by another one starting with NREM sleep. The whole night of normal sleep comprises of 4–10 cycles depending on age, each lasting 50–60 min for young children and 60–90 min for older children.

The architecture of sleep changes with age. During infancy, it is difficult to assess and monitor sleep architecture. For babies of <46 weeks gestational age when the EEG features of wakefulness and different sleep stages are not yet well developed, it is almost impossible to differentiate

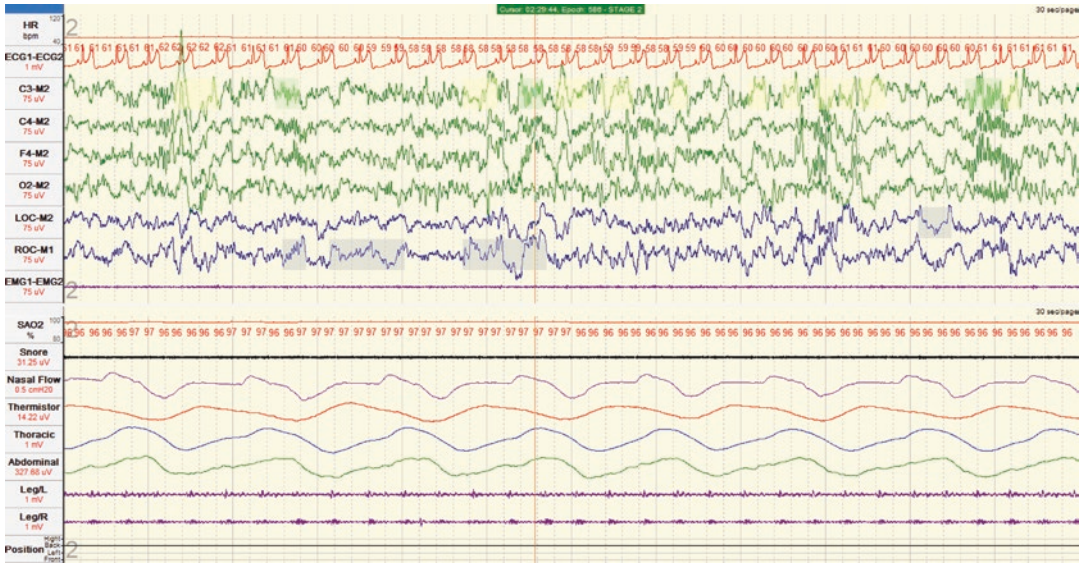

Fig. 2.4 An epoch of stage N2 of a 13-year old girl. Stage N2 features, sleep spindles, and K complexes, are observed mainly in the central and frontal regions (C3-M2, C4-M2, and F4-M2) with a pattern of predominantly theta (4–7 Hz) wave in the background EEG. No eye movements can be seen in the EOG channels (LOC-M2 and ROC-M1). The chin muscle tone is present but low

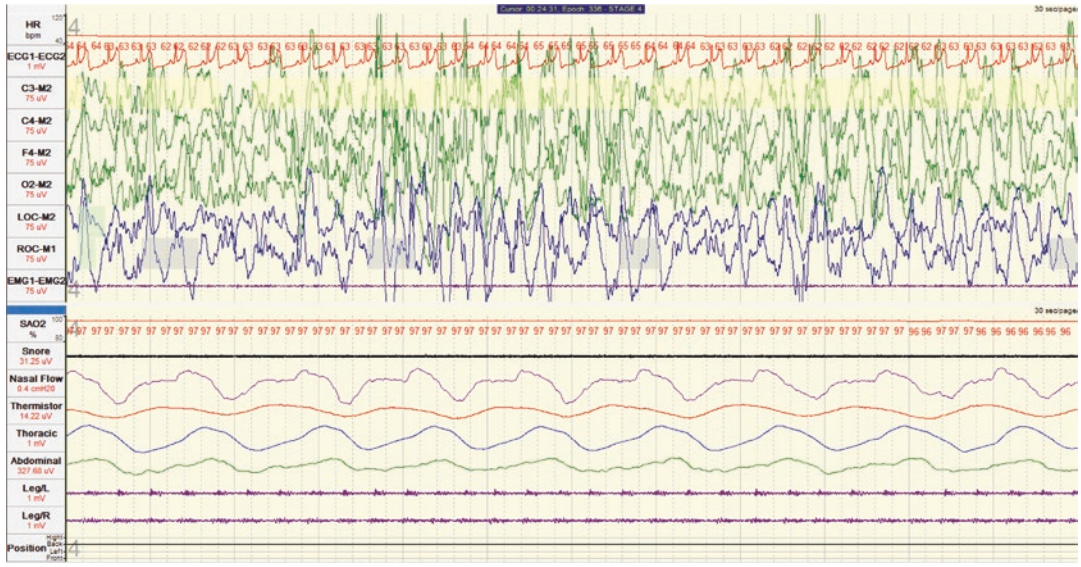

Fig. 2.5 An epoch of stage N3 of a 13-year old girl. A strong slow-wave activity (0.5–2 Hz) can be observed in all the EEG channels (C3-M2, C4-M2, F4-M2 and O2-M2). No eye movements can be seen in the EOG channels (LOC-M2 and ROC-M1). The chin muscle tone is present but low

between wakefulness and sleep of a newborn solely based on EEG pattern. The key EEG feature of wakefulness in adults, alpha rhythm, is not present in infants and young toddlers. Their wakefulness is characterized by posterior dominant rhythm (PDR) which the frequency of PDR in a post-term 3 months old infant is 3.5–4.5 Hz, which gradually increases to 7.5–9.5 Hz at 3 years old. The mean frequencies of PDR will reach 9 and 10 Hz at 9 and 15 years old, respectively. Sleep in early infancy may also be considered unstructured based on the observable EEG

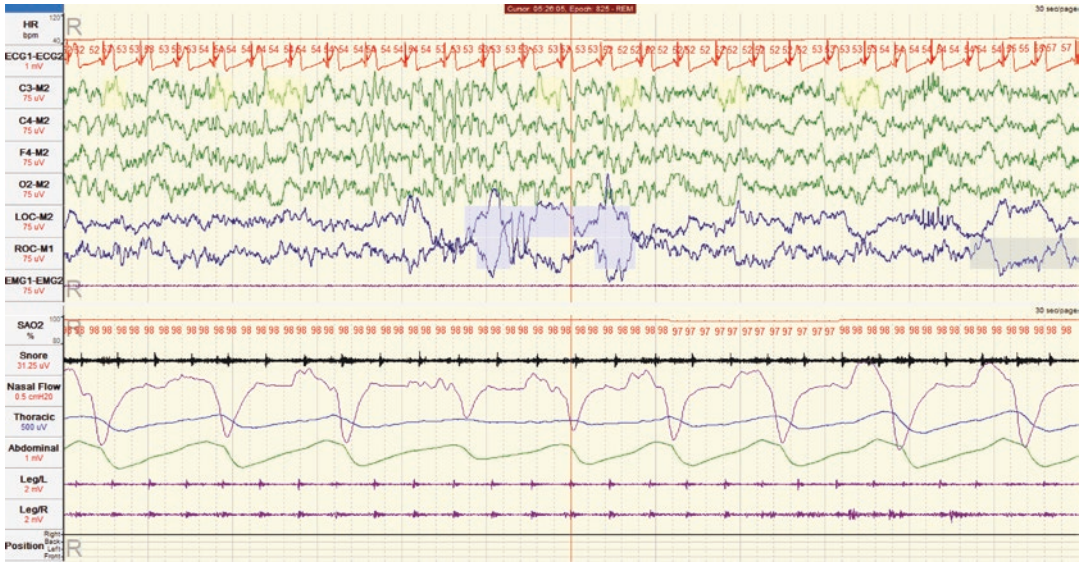

Fig. 2.6 An epoch of stage R of an 11-year old boy. A pattern of low amplitude mixed frequency can be observed in all the EEG channels (C3-M2, C4-M2, F4-M2, and O2-M2). No sleep spindles and K complexes can be seen. Some rapid eye movements can be seen in the middle of the epoch. The chin muscle tone is even lower than what is seen in stages N2 and N3

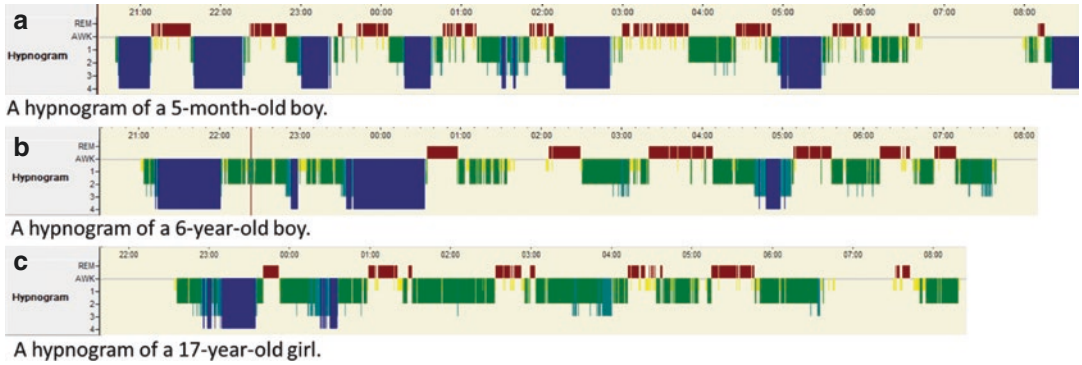

Fig. 2.7 Sleep architecture changes with age

features. NREM sleep of infants less than 6 months of age may not be differentiated into N1, N2, and N3 because NREM-specific EEG features are not yet developed. Therefore, sleep in early infancy is often divided into two main stages only, i.e. stage REM (R) and NREM (N), equivalent to the older nomenclatures of active sleep and quiet sleep, respectively. Stage N during infancy is characterized by regular respiration and discontinuous EEG pattern with high voltage slow waves in infants and develop into different NREM stages of sleep as the infant matures. Sleep spindles usually first appear at 6 weeks to 3 months post-term. K complexes first appear at 3–6 months post-term. SWA first appears at 2–5 months post-term. Therefore by 5–6 months post-term, NREM sleep can be differentiated into stages N1, N2, and N3 sleep. Stage R infancy is characterized by irregular respiration, muscle atonia, continuous EEG pattern mainly with low amplitude, rapid eye movements (REMs), sucking movements, and occasional gross body movements.

Figure 2.7 displays typical sleep periods in infancy, prepubertal childhood, and late adolescence. During infancy, a sleep cycle typically

lasts 50–60 min only. The percentage of REM sleep can be as high as 50%. The percentage of SWS accounts for another 25–40%. During early childhood, each sleep cycle becomes longer at 60–90 min. The percentages of REM sleep and SWS reduce to 25–35% and 20–30%, respectively. In late adolescence, each sleep cycle lengthens to 90–120 min. The percentages of REM sleep and SWS further reduce to 20–25% and 15–20%, respectively [2]. The reductions in percentages of REM sleep and SWS throughout childhood and especially adolescence parallel with the increase in light sleep (mostly stage N2) in adult sleep [3]. Higher amounts of REM sleep and SWS during childhood may be related to the higher rates of growth and brain development during childhood [2]. It was observed that the topographic distribution of SWA during NREM sleep is associated with cortical maturation from childhood through adolescence [4]. Moreover, the maturational cortical thinning measured by structural magnetic resonance imaging (MRI) occurs at the ages when SWA decline at the fastest rate [5], suggesting that SWA may be a marker of brain maturation.

Some studies suggest that there are sex differences in sleep architecture throughout childhood. The current findings in preterm infants and neonates are conflicting and controversial. While one study showed that boys were drowsier and had less active sleep than girls [6], another study found that boys slept less, presented more wakefulness after sleep onset, had more active sleep, and less quiet sleep than girls [7]. In older children and adolescents, a study showed that girls had a higher percentage of SWS and overall SWA power than boys. By regional analysis, girls had higher SWA during the first 60 min of NREM sleep over bilateral cortical areas related to language functions, while boys had higher SWA over the right prefrontal cortex related to spatial abilities [8]. These findings provide a possible explanation of sex-specific brain maturation during development.

2.2 Sleep Physiology

Sleep and wake are controlled and regulated by the balance between two processes- the homeostatic sleep process (Process S) and the circadian process (Process C). When Process C is aligned properly with Process S, the system promotes alertness and facilitates wakefulness during the daytime, and increased propensity for sleep in the late evening, and facilitate continuous sleep at night.

The homeostatic sleep drive, also known as sleep pressure or sleep need, is a physiological need similar to hunger and thirst. It rises with the duration of wakefulness and declines during sleep. When an individual stays up late, the sleep drive continuously increases until he/she falls asleep. When sleep needs are not met (sleep is deprived), sleep debt is developed leading to excessive sleepiness during the daytime. The subsequent recovery sleep usually has a shorter sleep latency and is often longer and deeper to dissipate the sleep debt. SWA during sleep is considered a marker of sleep need. SWA is usually highest at the beginning of a sleep period or the first sleep cycle and then declines gradually across the sleep period, regardless of the timing of sleep onset [9]. SWS rebound is also observed in recovery sleep following sleep deprivation [10].

At the same time, the alternation of sleep and wakefulness is also governed by a circadian rhythm that runs in cycles of approximately 24 h. Similar circadian rhythms are also present in the other biochemical, physiological, and behavioural processes of living entities. These rhythms are governed and synchronised by an internal clock located in the suprachiasmatic nuclei (SCN) in the anterior hypothalamus in humans. The circadian clock consists of positive and negative integrated transcription and translation feedback loops [11]. As the internal clock does not run exactly in 24-h cycles, there are mechanisms that allow the master clock to synchronise with the external time.

This process of synchronisation, also known as entrainment, is triggered by exposure to light, which is the strongest time cue to align the internal clock to the external time. Light exposure induces different changes in the internal clock depending on the timing of light exposure. Light exposure late in the evening results in later bedtime and wake-up time (phase delay) while light exposure in the early morning leads to earlier wake-up time (phase advance). The effect on phase shift is the least when light exposure occurs in the middle of the day. In the case of jet lag, the circadian clock becomes out of sync with the time of day when people fly to a different time zone, creating a mismatch between their internal clock and the actual clock. Light exposure or avoidance at the appropriate time can help adaptation [12].

The circadian wake-promoting signal increases progressively during the day to counteract the increasing sleep drive in order to maintain wakefulness, until melatonin, a sleep-promoting hormone, [13] begins to be secreted by the pineal gland in the brain, that occurs approximately 2 h before the usual bedtime. Therefore, the timing of melatonin onset is considered to be a marker of the circadian phase [14]. Sleep propensity is the highest when sleep drive continues to rise with the increasing melatonin secretion. When sleep begins, sleep drive starts to fall but the continuous secretion of melatonin causes the circadian alertness signal to drop resulting in continuous sleep. Sleep is maintained until the sleep drive becomes sufficiently low, and at the same time, the circadian alertness signal starts to rise with the declined secretion of melatonin, resulting in wakefulness [15].

Adolescents tend to stay awake later in the evening and sleep for longer in the morning [16]. The sleep phase delay may be related to external factors such as social activities and screen time exposure in late hours [17]. However, current findings suggest that these external factors only partially explain the observation. For instance, it was demonstrated that older adolescents had a later dim light melatonin onset (DLMO) than younger adolescents, [18] suggesting the timing of melatonin onset is progressively delayed during puberty. Moreover, circadian phase delay around the onset of puberty was also documented in studies of other mammalian species [19]. These findings suggest the phase delay is at least partially attributed to physiological and/or endocrinal changes related to pubertal maturation. Apart from the phase shift of the circadian rhythm, the delay in sleep timing in adolescents may also be attributed to the changes in sleep homeostasis. A potential mechanism is the slower development or accumulation of sleep drive across the day in teenagers [20]. In other words, adolescents may take longer to accumulate a sleep drive sufficiently high to induce sleep, promoting later bedtimes. Studies showed that SWA declines substantially between the ages of 10 and 20 years [21]. Moreover, female adolescents have an onset of the decline in SWA approximately 1 year earlier than male adolescents [22], suggesting that the decline is related to puberty. However, the rate of dissipation of sleep pressure across the sleep period remains stable across puberty [23]. It means that adolescents need the same amount of sleep and therefore a later get-up time to completely dissipate their sleep need. If they are now allowed to get up late because of social constraints such as school start time, their sleep need cannot be met, and sleep debt will develop. It is supported by current evidence that adolescents function better with a later school start time [24].

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3 Sleep Needs: Cross-Cultural Comparisons and Problems with Sleep Deprivation

Jun Kohyama

3.1 Introduction

In order to assess sleep need, it is necessary to investigate sleep quality and sleep duration [1]. Though quantitative factors of sleep, such as the number of intermittent awakenings at night, sleep latency and sleep duration, could be obtained objectively, sleep quality includes subjective indices of sleep, such as how well rested one feels upon awakening and general satisfaction with sleep [2]. To date, sleep need or sleep insufficiency has mainly been discussed in association with sleep duration. For example, regarding the diagnostic criteria of insufficient sleep syndrome [3], the following description was found: 'The patient's sleep time, established by personal or collateral history, sleep logs, or actigraphy is usually shorter than expected for age'. And in the same section, the following statement is made: 'This condition results in increased daytime sleepiness'. However, the term 'sleep quality' did not appear in this section. In contrast, sleepiness rather than sleep quality might be another important component when discussing insufficient sleep syndrome or sleep need, in addition to sleep duration. If a person has sleepiness, he/she needs more sleep, but if one has no sleepiness, he/she needs no more sleep. To present an overview of sleep need, this manuscript starts by introducing previous reports on sleep duration. Cross-cultural comparisons of sleep duration and problems with sleep deprivation are also examined. Sleepiness is then discussed, and finally, we discuss a novel designated index of a function of both sleep duration and sleepiness, called the Sleep Need Index.

3.2 Sleep Duration

3.2.1 Developmental Alteration of Sleep Duration

Age is considered the single most crucial factor that determines human sleep [4]. Generally, the amount of sleep decreases from about 16 to 18 h/day in the newborn infant to 6 to 7 h in older individuals.

In Fig. 3.1, data from a classic memorandum report by Roffwarg et al. [5] (dashed-and-dotted line) are presented. Iglowstein et al. [6] reported that total sleep duration decreased from an average of 14.2 h (standard deviation: 1.9 h) at 6 months of age to an average of 8.1 h (standard deviation: 0.8 h) at 16 years of age (n = 493, Zurich Longitudinal Studies). Their data are also shown in Fig. 3.1 (dotted line). In contrast to

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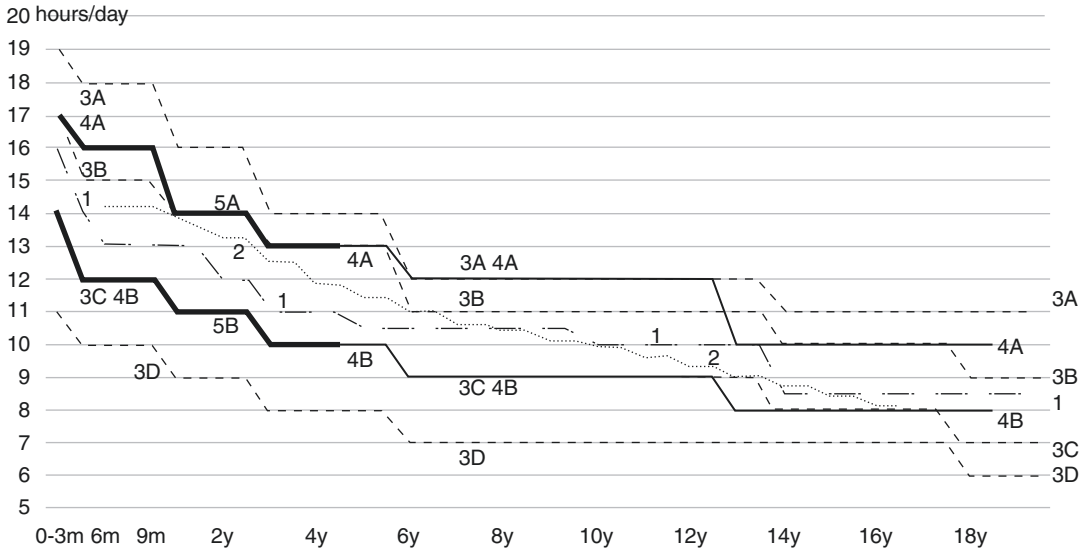

Fig. 3.1 Summary of several reports on recommendation of sleep duration of children and adolescents. Line 1: Roffwarg et al. [5] (dashed-and-dotted line); line 2: Iglowstein et al. [6] (dotted line); lines 3: NSF (dashed lines) [7] (3A: upper sleep duration of "may be appropriate", 3B: upper sleep duration of "recommended", 3C: lower sleep duration of "recommended", 3D: lower sleep duration of "may be appropriate".); lines 4: AASM (thin and thick lines) [8] (4A: upper sleep duration, 4B: lower sleep duration.); lines 5: WHO (thick lines) [9]. (5A: upper sleep duration, 5B: lower sleep duration.); Vertical axis: sleep duration in hours; transverse axis: age in months (m) and years (y)

these real sleep durations, several figures of sleep duration for age have also been recommended. Figure 3.1 includes three of these recommendations [7–9].

Relatively wide ranges have been proposed for the recommended sleep durations of each age group. Another point of caution is that most people in modern society pay attention to the lowest figure in these recommendations because they want to minimise their sleep duration. But there are people who need a sleep duration of the highest figures in these recommendations.

During 1905 to 2008, sleep duration of children aged 5–18 years has been consistently decreasing by approximately 0.75 min nightly per year [10]. These declines were obvious in Europe, the USA, Canada and Asia, while sleep duration was increasing in Australia, the UK and Scandinavia [10]. Sleep durations of preschoolers in Japan obtained in 1935–1936 and 2003 [11] are shown in Table 3.1. Sleep duration, especially nocturnal duration, reduced markedly in these nearly 70 years at least in Japan.

Table 3.1 Sleep duration (hours) of preschoolers in 1935–36 and 2003 in Japan

Age	Total sleep hours (nocturnal sleep hours) in 1935–1936	Total sleep hours (nocturnal sleep hours) in 2003
6–11 months old	13.03 (11.28)	11.70 (10.13)
1-year-old	12.32 (10.88)	12.10 (10.33)
2-year-old	11.67 (10.92)	11.08 (9.68)
3-year-old	11.30 (10.97)	11.05 (9.68)
4-year-old	10.92 (10.87)	10.75 (9.70)
5-year-old	10.92 (10.90)	10.32 (9.73)
6-year-old	10.82 (10.82)	10.18 (9.75)

Made using data in Yatagai and Takahashi [11]

3.2.2 Cross-Cultural Difference of Sleep Duration

Mindell et al. reported sleep duration and sleep onset time among 17 countries/regions (Table 3.2) [13]. Their study included 29,287 baby-data aged from birth to 36 months through net-based expanded version of the Brief Infant Sleep

Questionnaire in both predominantly Asian countries/regions (China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, the Philippines, Singapore, Taiwan, Thailand, Vietnam) and predominantly Caucasian countries (Australia, Canada, New Zealand, the United Kingdom, the United States).

Table 3.2 Sleep duration and night sleep onset time among 17 countries/regions

	Nap hours	Total sleep hours (nap + night sleep)	Night sleep onset time
Australia	2.99	13.16	19:43
Canada	2.90	12.87	20:44
China	3.00	12.49	20:57
Hong Kong	3.14	12.16	22:17
Indonesia	3.36	12.57	20:27
India	3.41	11.83	22:11
Japan	2.19	11.62	21:17
Korea	2.49	11.90	22:06
Malaysia	3.27	12.46	21:47
New Zealand	2.70	13.31	19:28
Philippines	3.53	12.69	20:51
Singapore	3.11	12.36	21:38
Thai	2.81	12.71	20:53
Taiwan	3.34	12.07	22:09
UK	2.61	13.10	19:55
USA	3.18	12.93	20:52
Vietnam	3.67	12.99	21:44

Made using data in Mindell et al. [12]

Total sleep duration ranged from 11.6 (Japan) to 13.3 (New Zealand) hours. This difference was statistically significant. Interestingly, the duration of naps was also the shortest in Japan. A Japanese group emphasized that regular (long) afternoon naps in nursery schools resulted in the bedtime delay in Japan [14]. If this statement is true, countries that showed longer nap duration than Japan might reveal later bedtimes than in Japan. However, according to this survey, Australia, Canada, China, Indonesia, New Zealand, the Philippines, Thailand, the US and the UK had longer nap durations than in Japan and showed earlier bedtimes than in Japan. Recently, this Japanese group mentioned that children's bedtime is determined by diurnal naps as well as by a number of other factors, including family lifestyle [15].

The mean sleep durations (hours) for boys and girls on school days and non-school days in Australia (2010) [16] and Japan (2020) [17] are shown in Table 3.3. Sleep duration tended to decrease with age or grade progression, and girls slept longer than boys on non-school days except for age-14 Australians. Australian children and adolescents slept longer than those in Japan.

Table 3.3 The mean sleep hours for boys and girls on school days and non-school days in Australia (2010) and Japan (2020)

Olds et al. (Australia) [16]					Kohyama et al. (Japan) [17]				
	Boys		Girls			Boys		Girls	
Age	School days	Non-school days	School days	Non-school days	Grade	School days	Non-school days	School days	Non-school days
9	10.40	10.22	10.60	10.38					
10	10.47	10.18	10.33	10.65	5–6	8.60	9.09	8.55	9.58
11	10.00	9.68	9.92	9.73					
12	9.78	9.50	9.92	9.83	7–9	7.55	8.56	7.30	8.70
13	9.70	9.75	9.53	9.98					
14	9.40	9.90	9.45	9.85					
15	9.37	9.75	9.25	9.87	10–12	6.56	7.95	6.50	8.11
16	8.93	9.50	9.03	9.70					
17+	8.90	9.43	9.20	9.55					
All	9.53	9.75	9.57	9.88	All	7.61	8.56	7.58	8.89

Made using data in Olds et al. [16] and Kohyama et al. [17]

3.2.3 Factors Associated with Sleep Duration

Screen time [18] and extracurricular after-school activities [19] are well-known factors that produce sleep loss. Delayed bedtime reduced the total sleep duration of 3-year-old children [20], and a long time waiting for a late meal could decrease nocturnal sleep time in preschoolers [21]. Quante et al. [19] raised two factors that reduce sleep duration; intrinsic factors and extrinsic ones. In addition to the aforementioned factors, intrinsic ones include the reduced sleep pressure accumulated during the day, and early school schedules were included in the latter factors. Family lifestyle [15] may be put into the extrinsic ones. According to Fukuda et al. [15], children's bedtime is also set by delayed awake and meal times. Not only delayed dinner but also irregular dinner time was reported to affect sleep parameters in grades 5–12 pupils [22].

3.2.4 Problems Associated with Decreased Sleep Duration

Insufficient sleep syndrome (ISS) patients are known to reveal irritability, deficits of concentration and attention, reduced vigilance and motivation, and malaise [3]. They also showed increased daytime sleepiness, and may lead to depression, other psychological problems, abuse of stimulants, traffic accidents or injury at work [3]. In addition, prepubertal ISS patients children could complain of behavioral abnormalities due to sleepiness [3].

The highest economic losses due to insufficient sleep across five OECD countries was the US (yearly $411 billion which is 2.28% of its GDP), followed by Japan (yearly $138 billion, which is 2.92% of its GDP) [23]. The percentage of these losses against GDP was the highest in Japan.

On both quantity and quality losses of sleep, every aspects of children's and adolescents' well-being and daytime functioning have been affected; ranging from decreased attention and concentration, to poor academic performance, decreased emotional control, and increased anti-social behaviors and psychological difficulties [12]. Sleep shortage increased the risk of not only the cardiovascular, immune, and various metabolic systems but also accidental and automobile crash injuries [12]. Sleep loss has been known to increase the obesity risk in children, especially in young children [12].

Is it easy to diagnose insufficient sleep syndrome? It should be noted that the correlation among self-reported sleepiness, performance-test decrements, and measured sleepiness through multiple sleep latency test is poor [3]. Additionally, interindividual susceptibility to sleep loss has been widely different among people. Sleep need is not constant, and it alters from person to person and from night to night [24]. Individual variability in sleep need is affected by genetic, behavioural, medical, and environmental factors [8].

It is widely known that sleep shortage is associated with the elevation of body mass index, blood pressure, and of the risk for cardiovascular diseases [12], however, these associations were obtained through comparisons among several sleep duration groups. It is not easy to determine concrete suitable sleep duration value to avoid aforementioned health problems in each individual. It is not an easy process to determine the degree of individual sleep loss or to know personal sleep need to avoid health problems.

3.3 Sleepiness

3.3.1 Sleepiness vs. Sleep Duration

According to Dewald et al. [1], sleep duration, sleep quality, and sleepiness were significantly but modestly associated with school performance. Among these variables, sleepiness showed the strongest association with academic performance ($r = -0.133$), followed by sleep quality ($r = 0.096$) and sleep duration ($r = 0.069$). Among healthy adolescents, Cohen-Zion and Shiloh [25] found that the strongest predictors of poor daily executive capacities are evening chro-

notype and sleepiness, and they concluded that sleep duration was hard to predict executive skills. In comparison with short nocturnal sleep time, daytime sleepiness is known as a better predictor of poor self-regulation in adolescents [26]. Self-regulation among adolescents is associated with potential long-term implications of positive health and functioning. Taking these reports into consideration, it is not unexpected to assume that sleepiness is a better potential candidate to assess sleep need than sleep duration. Although subjective, more attention should be paid to sleepiness for assessing sleep need.

3.3.2 Factors Associated with Sleepiness

There are several standardised scales for assessing sleepiness. The Stanford Sleepiness Scale assesses sleepiness which is assumed to be produced by fatigue [27], and the Epworth Sleepiness Scale evaluates the easiness to fall into sleep [28]. However, test–retest reliability of the Epworth Sleepiness Scale has recently been concerned [29]. The modified School Sleep Habits Survey includes three related scales measuring sleepiness, chronotype and sleep-related problem behaviours [30].

As causes of sleepiness in children, insufficient sleep (insomnia, circadian rhythm sleep disorders), fragmented sleep (obstructive sleep apnea, parasomnias, restless legs syndrome, periodic leg movement syndrome), and increased need for sleep (neurologic disorder, drug-related, narcolepsy) were described [31]. Based on Moore and Meltzer [32], causes of sleepiness in adolescents are summarised, in Table 3.4. It has been recognised that markedly broad factors may affect sleepiness.

Through a simple single question (Do you feel sleepy during class? (never, sometimes, often, always)), sleepy pupils who selected the choice of either 'often' or 'always' were found to be associated with higher school grade, later bedtime before school day, longer non-school day screen time, poorer self-reported academic performance, more breakfast skipping, earlier wake time on school day, higher after-school activity, and more number of days a week performing habitual exercise except for school lessons (physical activity score) [33].

Table 3.4 Causes of sleepiness in adolescents, made using descriptions in Moore and Meltzer [32]

Insufficient sleep
Extrinsic factors
Extracurricular activities (sports, music, drama, and social dubs), employment, academic demands
School start times
Social interaction
Media usage
Environment
Caffeinated beverages, social jet lag
Intrinsic factors
Normative changes
Due to the delay of melatonin release, adolescents feel sleepy later than school-age children
During early adolescence, slow wave sleep stages decline by approximately 40% compared to school-age children
Sleep disorders: delayed sleep–wake phase disorder; insomnia; obstructive sleep apnea; restless legs syndrome; periodic limb movement disorder; narcolepsy

3.4 Sleep Need Index (SNI)

Patients with insufficient sleep syndrome must need more sleep; their daytime sleepiness increase depending on their short sleep duration [3]. Sleep need is hypothesised to be able to be expressed as a function of both sleep quantity and sleepiness. Thus, the SNI was designated as the following formula: sleepiness/sleep time, the larger this index, the larger the sleep need.

The SNI was calculated in the same survey introduced [17, 22, 33, 34]. Of the 4208 questionnaires sent to 28 public schools, 2722 answer sheets were used for the analysis, because these 2722 sheets had documents on the agreement to participate in the study and provided complete answers to the needed questions. Average sleep time was calculated by the following formula: {[(sleep duration before school day) × 5] + [(sleep duration before non-school day) × 2]}/7. Pupils who had an SNI of

less than the mean SNI value were categorised as low sleep-need pupils, and those whose SNI was the mean SNI or more were determined as high sleep-need pupils. SNIs were distributed from 0.0946 to 1.0769, with an averaged value of 0.2642 and a standard deviation of 0.1367. Then, pupils with a SNI of 0.2642 or higher were termed high sleep-need pupils, whereas those with a SNI of less than 0.2642 were named low sleep-need pupils. A logistic regression model was used to calculate the adjusted odds ratio (OR) with a 95% confidence interval (CI) for risks of high sleep-need pupils and to control for the potentially confounding roles of school grade, gender, hours of after-school activity per week, number of days a week performing habitual exercise except for school lessons, dinner irregularity, frequency of skipping breakfast and defecation, screen time of both school day and non-school day, self-rated academic performance, and standardised body mass index. Table 3.5 shows variables obtained for the optimised fitness model for high sleep-need pupils obtained by the stepwise procedure of multivariable logistic regression analysis. Among these coefficients, higher school grade, female gender, poorer self-reported academic performance, higher breakfast skipping, longer after-school activity, and higher physical activity were independently associated with high sleep-need pupils. The Akaike information criterion of this model (2269) was lower than a model obtained by all factors (2672) or that obtained by significant factors (2688). This analysis demonstrated that the SNI increases with age progression, with female dominancy. In contrast to these findings, Kalak et al. [35] reported no gender difference in subjective sleep need and the decrease in subjective sleep need with age progression among university students. However, a worsening of sleep during adolescence has been reported [36], which could support the present result that the sleep need increases with age progression during adolescence. Further studies are

Table 3.5 Variables obtained for the optimised fitness model for high sleep-need pupils obtained by stepwise procedure of multivariable logistic regression analysis

Variables	Partial regression coefficient (B)	SE	Wald χ^2	OR (95% CI)	P value
School grade (5 to 12)	0.57	0.03	453.71	1.78 (1.68–1.87)	<0.001
Gender (male: 1; female: 2)	0.29	0.10	8.44	1.34 (1.10–1.63)	0.004
Dinner irregularity score (regular:1; irregular:2))	0.18	0.11	2.85	1.20 (0.97–1.47)	0.09
School day screen time categories (less than 2 h: 1; 2–4 h: 2; 4–6 h: 3; 6–8 h: 4; 8 h or more: 5)	0.14	0.09	2.51	1.15 (0.97–1.36	0.11
Non-school day screen time categories (less than 2 h 1; 2–4 h: 2; 4–6 h: 3; 6–8 h: 4; 8 h or more: 5)	0.12	0.07	3.66	1.13 (1.00–1.29)	0.056
Self-reported academic performance (very good: 1; good: 2; not good: 3; poor: 4)	0.24	0.06	15.05	1.27 (1.12–1.42)	<0.001
Breakfast frequency (always: 1; often: 2; sometimes: 3; never: 4)	0.17	0.09	3.90	1.19 (1.00–1.41)	0.048
After-school activity (h/week)	0.04	0.01	28.29	1.04 (1.03–1.06)	<0.001
Physical activity (number of days a week performing habitual exercise except for school lessons)	0.08	0.02	19.83	1.08 (1.04–1.12)	<0.001
Constant	−7.67	0.39			

SE standard error, *OR* adjusted odds ratio, *CI* confidence interval

required to conclude on age and gender associations with sleep need during adolescence.

Both screen time and after-school activity were known factors to reduce sleep duration [18, 19], and both factors were associated with sleepiness in our survey [33]. However, a significant association of SNI was obtained not with screen time but with after-school activity. It could be assumed that screen time may stimulate arousal systems to reduce sleep need more strongly than after-school activity, since longer screen time has been reported to alter brain structures [37].

On a significant association between sleepiness/SNI and physical activity score, it should be noted that excessive exercise could result in unfavourable health problems [38]. In fact, pupils with both low and high physical activity levels had significantly higher sleepiness scores than pupils with a medium physical activity level [34]. Although few studies have focused on this association, the current result may shed light on this association between physical activity and SNI. To support adolescents with higher sleep need, although further prospective studies are required, we should instruct pupils to reduce after-school and physical activities in order to promote their physical and mental health.

3.5 Conclusion

Sleep need is hypothesised to be able to be expressed as a function of both sleep time and sleepiness: SNI (=sleepiness/sleep duration). Higher school grade, female gender, poorer self-rated academic performance, higher skipping breakfast frequency, and longer after-school and physical activities were independently associated with pupils whose SNI was the average value or more. To support pupils with sleep need, we should instruct them to lessen after-school and physical activities to improve their daytime functioning. This promotion is expected to contribute to the physical and mental health of youngsters. In this review, I emphasized the need of studies on sleep need or sleepiness. Finally, I would expect further studies on sleep quality [39].

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Part II

Evaluation of Sleep Disorders

Clinical Assessment

4

Jihui Zhang

As with any disease, a thorough clinical assessment is the cornerstone of good clinical management for sleep disorders. The key objectives of this chapter are to introduce clinical assessments to paediatric patients with sleep disorders, with special considerations on history taking, screening tools, and clinical examination. In addition, laboratory test is crucial not only for diagnosis but also for understanding aetiology. In addition to the chief complaint and its associated symptoms, systematic history including medication use, family history, precipitating factor, and development history, also provides important clues for the diagnosis. The clinical assessment procedure shall also consider both diagnosis confirmation and diagnosis differentiation. In addition, it should be noted that there may be significant cultural and ethnic differences in clinical assessments and symptom descriptions.

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4.1 Preparation

The clinical assessments, epically for those younger children, should be taken under the accompany with the primary caregiver(s). The use of direct questions for children and adolescents is helpful. For children younger than 8 years old, the primary caregiver(s) should be the key informant. Older children and adolescents can report on their sleep problems, which their parents may not be aware of. For some situations (e.g., excessive daytime sleepiness and atttention deficit), information from the schoolteacher may be necessary.

4.2 History Taking

4.2.1 Chief Complaint and Associated Symptoms

The chief complaint is the primary reason why the patient seeks help. It is advised to use open-ended questions to obtain the necessary information. The OPQRST, summarizing the initial of some key words describing symptoms, is a useful mnemonic (memory device) approach to assessment pain complaint. The same approach can also be used for sleep disorders. Here we take restless legs syndrome as an example. However, one size does not fit all and this assessment tool may not be applicable to some sleep disorders, such as insomnia.

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OPQRST	Description for restless legs syndrome	Insomnia
Chief complaint	Strange or uncomfortable feeling in the legs/a repeated urge to move legs, while sitting still or lying down	Difficulty initiating/ maintaining sleep or early morning awakening
Onset of the event	When did these uncomfortable sensation/urge to move symptoms start?	When did sleep difficulties start
Provocation or palliation	What kind of factor makes the uncomfortable sensation/urge to move worse or better (movement or rest?)?	What kind of factor makes sleep difficulties worse or better?
Quality	This is the patient's description of the sensory feeling (pain, Itching, or Crawling etc.?). "Can you describe how you feel about it"	How long did it usually take for your to fall asleep (or return to sleep after wakeup)
Region and radiation	Where does the sensation mostly affect the body and whether it radiates (extends) or moves to any other area? Leg, knee, arm?	Not well-applicable
Severity	What are the frequency (times/ week) and distress towards these symptoms	Frequency (times/week) and distress towards these symptoms
Time (history)	When are these symptoms worse (nighttime or daytime)?	Not well-applicable

4.2.2 Sleep Patterns and Sleep-Wake Schedule

To better understand sleep problems, clinicians should not only assess what happens during sleep but also what happens during daytime and nighttime. Therefore, habitual sleep patterns are helpful to understand the usual pattern. For older adolescents, we may also need to separate school days from non-school days to better estimate weekday weekend differences in sleep patterns. Usually, the patients or the parents tend to report the situation in the last few nights or the worse situations. It is helpful to ask about the sleep patterns by following the time order, from dinner to the next day. For example,

1. At what time do(es) you (your child) usually have dinner
2. What kind of activity do(es) you (your child) usually do after dinner
3. At what time do(es) you (your child) usually go to bed
4. How long does it take for you (your child) to fall asleep usually
5. Do(es) you (your child) frequently wake after falling asleep
6. Any abnormal event happens during sleep (snoring, severe sweating, abnormal movements?)
7. At what time do(es) you (your child) usually wake up
8. Do(es) you (your child) feel rest after waking up
9. Do(es) you (your child) take nap and what is the frequency?

4.2.3 Treatment History, Medical History, Developmental History, and Psychiatric History

The treatment history for sleep problems and its effects is helpful to adjust the management strategies. Both significant acute and chronic medical history can affect sleep quality. For example, allergic rhinitis is a risk factor of obstructive sleep apnoea in children. The onset of puberty is closely related to the onset of some sleep disorders, including insomnia, narcolepsy, and delayed sleep phase disorder.

4.2.4 Family History

Some sleep disorders are moderate to highly heritable (e.g., restless legs syndrome, sleep-waking, and insomnia). Therefore, a family history shall be asked for any sleep disorder. In addition, a positive family history for restless legs syndrome is a piece of supportive evidence for the diagnosis.

4.3 Physical Examination

4.3.1 Sleep-Associated Physical Examination

Evaluation of growth parameters: The height and weight of the child should be plotted on the standard growth curve table, and the BMI should be calculated. Obesity is associated with an increased risk for obstructive sleep apnoea (OSA). However, failure to thrive may be a consequence of OSA, or an underlying chronic physical disorder.

Head and neck: Craniofacial malformations may indicate anatomical abnormalities of the upper airway, such as midface dysplasia, maxillary retraction, and maxillary deformity. Children with large neck size or neck deformity, such as torticollis, brevicollis, may experience snoring and obstructive apnoeas, two common manifestations of upper airway obstruction.

Oropharyngeal/airway examination: Adenoid facial, nasal airflow reduction or closed rhinolalia match the symptoms of adenoid hypertrophy, which is associated with OSA. Paediatrician should record the patient's tonsil size and Mallampati classification to describe oropharyngeal crowding and assess the presence of obstructive septal deviation, polyps, or enlarged turbinates. The application of a nasal endoscope allows direct examination of the adenoid and nasal mucosa.

Neurological and mental state examination: Select the appropriate neurological examination according to the developmental age of the child. Children with neuromuscular disease, including scoliosis and amyosthenia, are at risk for OSA (due to oropharyngeal dysfunction) and sleep-associated insufficient ventilation (due to respiratory muscle weakness). The psychological evaluation of a child should include the differential diagnosis of worries and fears suitable for development, other physical problems that may lead to psychological symptoms, and mental illnesses. The use of games, pictures, cartoons, and puppets to communicate, is helpful in diagnostic interviews.

4.4 Questionnaire and Scale

4.4.1 Bedtime Problems, Excessive Daytime Sleepiness, Awakenings, Regularity and Snoring Screener (BEARS)

The BEARS is a user-friendly screening tool for obtaining children's sleeping information and identifying sleep problems in the primary care setting [1]. Parents or older children are asked questions about the five problem domains: Bedtime, Excessive daytime sleepiness, Awakenings at night, Regularity/duration, and Snoring; a "yes" response prompts physicians to solicit further information about the frequency and nature of that certain domain.

4.4.2 Children's Sleep Habit Questionnaire: Preschool and School Ages (CSHQ)

CSHQ is a retrospective, 45-item parent-reported questionnaire for screening both behaviourally based and medically-based sleep problems in school-aged children [2]. It obtains information about the key domains of clinical sleep complaints during this age: bedtime behaviour and sleep onset, sleep duration, anxiety around sleep, behaviour occurring during sleep and night wakings, sleep-disordered

breathing, parasomnias, and morning waking/daytime sleepiness. Parents recall children's sleeping behaviours over a typical recent week, and rate them as "usually", "sometimes" or "rarely". A higher score indicates a higher level of sleep disturbance.

4.4.3 Sleep Disturbance Scale for Children (SDSC)

The SDSC is a parent-rating scale developed according to the diagnostic system proposed by the Association of Sleep Disorders Centres [3] to evaluate children's sleep disturbance [4]. Twenty-six questions assess 6 subdomains of sleep problems during the previous 6 months: Disorders of initiating and maintaining sleep (DIMS), Sleep breathing disorders (SBD), Disorders of arousal/nightmares (DA), Sleep-wake transition disorders (SWTD), Disorders of excessive somnolence (DOES), and Sleep hyperhidrosis (SHY). All questions are scored on a 5-point Likert scale. The original Italian version was developed for children aged 6.5–15.3, while translations have been applied to a wider age range up to 3–18 years old.

4.4.4 Pediatric Daytime Sleepiness Scale (PDSS)

The PDSS is a self-reported scale designed for assessing the relationship between daytime sleepiness and school-related outcomes among 11–15-year-old students, yet is also validated for children aged 5–17. Eight questions concerning sleepiness are scored on a 5-point Likert scale. Higher scores on PDSS are associated with reduced total sleep time, poorer school achievement, poorer anger control, and frequent illness.

4.4.5 Children's Sleep Comic

The Children's Sleep Comic [5] is designed for screening sleep behaviours and sleep problems in children. Thirty-seven items assessed various aspects of children's sleep, including sleep hygiene, quality of sleep, night-time fears, dreaming, awakening in the morning, night-time sweating, night-time bruxism, daytime napping, and chronotype (morning/evening type). Each item comprises a question and cartoons describing the response options. Due to its child-friendly nature, it allows self-rating in younger children (5–11 years old).

4.4.6 Sleep Diary and Sleep Log

It is important to keep a sleep diary or a sleep log of children's sleep behaviours for a prolonged period when assessing sleep problems. Sleep diary (Fig. 4.1) or sleep log (Fig. 4.2) forms are supposed to be completed every day, to record basic features about children's sleep, which usually includes the time when children get in bed, fall asleep, wake up and get out of bed, awakenings during sleep, daily functioning, naps, and other sleep-related events. These records help clinicians to recognize various abnormalities in children's sleep, such as difficulty falling asleep, sleep disruption, and schedule problems, and what may have caused these problems, such as substance use. An electronic platform of sleep diary and sleep log is more user-friendly.

Consensus Sleep Diary-Core ID/Name: ____________

	Sample							
Today's date	4/5/11							
1. What time did you get into bed?	10:15 p.m							
2. What time did you try to go to sleep?	11:30 p.m							
3. How long did it take you to fall asleep?	55 min.							
4. How many times did you wake up, not counting your final awakening?	3 times							
5. In total, how long did these awakenings last?	1 hour 10 min.							
6. What time was your final awakening?	6:35 a.m.							
7. What time did you get out of bed for the day?	7:20 a.m							
8. How would you rate the quality of your sleep?	☐ Very poor ☑ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐ Poor ☐ Fair ☐ Good ☐ Very good
9. Comments (if applicable)	I have a cold							

Fig. 4.1 Example of a sleep diary

4.4.7 Structured Interview

Structured interviews are well-structured sets of diagnostic interviews that systematically investigate sleep patterns, symptoms, and various sleep-related issues. Take Albany Sleep Problems Scale (ASPS) as an example: it is fully designed to depict children's sleep hygiene, bedtime and night waking, sleepiness, medication use, sleep schedule, nightmare, sleep terror, hypersomnia and narcolepsy, breathing-related problems, sleepwalking, and sleeptalking, limb movement and rhythmic movement, bedwetting, teeth grinding, anxiety and depression, daytime behaviour problems, and other causes for sleep problems, to help clinicians to identify children's sleep problems and their potential causes. Questions are presented following a production rule such that different questions will follow when different answers are given to the present question.

Two Week Sleep Log

Name: _____; Sex: _____; Age: _____; Date: _____

Notes: Please indicate your sleep habits using the following icons/letters: Go to bed Sleep /nap period Get up

A: drink alcohol C: havecoffee E: exercise M: take any medicine

Date	Day of the week	Type of Day (Work, School, Day off, Vacation)	Noon	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM	10 PM	11 PM	Midnight	1 AM	2 AM	3 AM	4 AM	5 AM	6 AM	7 AM	8 AM	9 AM	10 AM	11 AM
Sample	Tue.	School								A		M										m C				

Fig. 4.2 Example of a sleep log

4.5 Laboratory Test

4.5.1 Blood Test

Blood tests are helpful to understand the potential aetiology or medical consequences of sleep disorders. For example, iron deficiency defined by a lower serum ferritin level is a potential aetiology of restless legs syndrome, and iron supplements may be effective in treating paediatric restless legs syndrome. As indicated by the International Classification of Sleep Disorders-Third Edition (ICSD-3), mild iron deficiency (characterized by serum ferritin below 50 μg/L) is related to the severity of restless legs syndrome, and repletion of iron stores from below 50–75 μg/L has been found to diminish the symptoms.

4.5.2 Dim Light Melatonin Onset (DLMO)

DLMO, typically assessed via plasma or salivary melatonin levels, is a physiological measure to confirm the endogenous circadian timing [6]. DLMO is helpful for the diagnosis of circadian rhythm sleep-wake disorders like delayed sleep-wake phase disorder and advanced sleep-wake phase disorder [7]. Since melatonin secretion is substantially suppressed by exposure to light, the

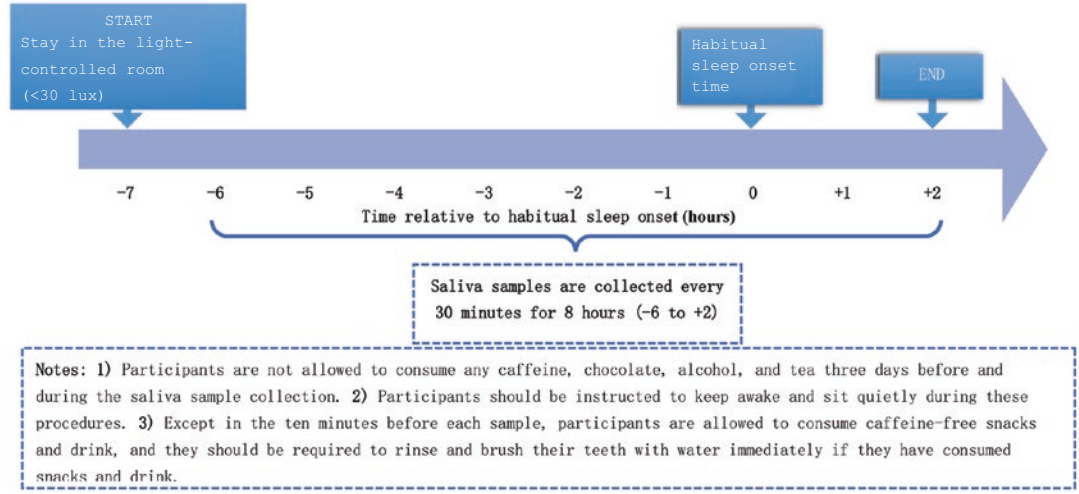

Fig. 4.3 The procedures of saliva sample collection for the dim light melatonin onset test

salivary or plasma sample collection needs to be conducted in dim light (e.g., <30 lux). The typical procedures for sample collection of DLMO are illustrated in Fig. 4.3. In addition, two methods have been commonly used for determining DLMO: (1) when melatonin concentration reaches a threshold of 3.0 pg/mL and remained above this threshold for the next three samples; (2) when melatonin concentration is equal to the mean + 2 standard deviations of 3–5 low daytime values.

4.5.3 Cerebrospinal Fluid (CSF) Hypocretin (Orexin) Level

Hypocretin (orexin) deficiency is a hallmark trait of the diagnostic criteria for narcolepsy type 1 [8]. As outlined by the International Classification of Sleep Disorders-Third Edition (ICSD-3), hypocretin (orexin) testing, a diagnostic procedure requiring a lumbar puncture, can detect narcolepsy type 1 in conjunction with sleep studies like multiple sleep latency tests and polysomnography. One of the diagnostic criteria for narcolepsy type 1 is that CSF hypocretin (orexin)-1 concentration, assessed by immunoreactivity, is either ≤110 pg/mL or <1/3 of mean values of normal subjects with the same standardized assay.

4.6 Imaging Test

4.6.1 Cephalometry

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is recognized as a potentially life-threatening disease, characterized by repeated collapse of the upper airway (UA) with cessation of breathing during sleep [9]. Abnormal cephalometric dentofacial morphologies such as retrognathia, micrognathia, long face, steep mandibular plane, inferior positioning of the hyoid bone, long and large soft palate and large tongue, narrowing of the UA have been reported in patients with OSAHS. The main advantages of cephalometry are its easy access, low cost and minimal radiation exposure. Therefore, cephalometry has gone beyond the boundaries of dentistry, and now it has become an invaluable tool for diagnosing and treatment planning for OSAHS.

4.6.2 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) provides both highly accurate and reliable measurements of UA and surrounding tissues [10]. The adenoid and tonsils as well as the soft palate are signifi-

cantly larger in children with OSAHS concomitant with significantly smaller UA volume. However, a disadvantage of MRI is its long acquisition time (e.g., several minutes for each sequence) and therefore its sensitivity to motion artifact.

4.7 Conclusions

Clinical assessment plays a crucial role in the diagnosis and management of sleep disorders. It includes history taking, clinical interview, screening tools, physical examination, and laboratory tests. For younger patients, the involvement of parents is of importance. While for older patients, the history and complaints shall be mainly obtained from the patients. The clinical assessment shall be conducted not only but only at the beginning but also during the whole management process. Finally, culture differences shall be also considered.

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Sleep Diagnostics

5

Mahesh Babu Ramamurthy

Although sleep is a basic and primordial function of homo sapiens, we have only recently begun to gain an understanding of the underlying physiological processes. This explains why even the science of monitoring and diagnosing sleep related issues is still in its infancy. What complicates this further, is the ever-changing nature of sleep patterns in children; the pressures of current day schooling, increasing long hours of study and increasing reliance on electronic devices all contribute to chronic sleep deprivation. All these have made sleep diagnostics more challenging.

5.1 Diagnosis

Ideally, the best way to diagnose sleep disorders in children will be to longitudinally monitor sleep in their natural environments. The ideal test would be reliable, nonintrusive, cost effective and have the ability to diagnose sleep disorders and its effects on other health parameters. While such a test yet eludes us, great strides have been taken towards achieving this. The following section will aim to consolidate the progress that has been made in sleep diagnostics so far and understand their roles in paediatric sleep.

As with any other field, a good, detailed history and physical examination is the best starting point. However, a good history even when used with validated questionnaires have their limitations. Hence there is need for further investigations to ascertain the diagnosis. Some of the commonly used diagnostic tools are outlined below.

5.2 Home Audio and Video Recording

With the increased reach of smart phones in both developed and developing countries, it has become common for parents to come to a clinical consultation with a recording of their child's snoring or restless sleep habits. While it is intuitively a practical measure of sleep disturbance, it is unfortunately not evidence based. However, it shows great potential for future research in sleep diagnostics.

Goldstein et al. compared the use of audio recordings against polysomnography (PSG) in diagnosing obstructive sleep apnea (OSA) in children. The study showed that audio recordings had a sensitivity of 92% and a specificity of 29%. Though the negative predictive value was 83%, the positive predictive value was 50% [1]. This

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illustrated that audio recordings have the potential to be used as screening tests. Similarly, Sivan et al. analyzed 30-min parent-initiated home video recordings and compared this to the use of PSG in diagnosing OSA in children. Parents, recorded videos during times that they thought their child's breathing was unusual. As compared to PSG, these recordings had a sensitivity of 94%, specificity of 68%, a positive predictive value of 88% and negative predictive value of 83% [2].State of the art advances in smart phones and recording features necessitate need for further research in this field.

5.3 Pulse Oximetry

The intermittent upper airway obstruction that occurs in SDB results in intermittent hypoxia and frequent arousals during sleep. These two underlying pathophysiological events are the causal factors for most of the sequelae that are seen. An overnight polysomnography, which measures both these events and many more, is considered the gold standard in evaluating SDB in children. However, its cost and availability has limited its applicability. Hence, overnight pulse oximetry, which can measure intermittent hypoxia, is considered as an alternative to diagnosis of paediatric SDB.

However, SDB has a wide spectrum in paediatric patients, as shown in Fig. 5.1 above. Intermittent hypoxia is a feature of the extreme entity on the right (OSA). Therefore, measuring hypoxia using pulse oximetry only serves to diagnose the severe form of SDB. Children with less severe forms are likely to be missed by relying solely on pulse oximetry.

5.3.1 Technology Behind Pulse Oximetry

Pulse oximetry measures and estimates the oxygen that is reversibly bound to and carried by haemoglobin. It relies on two basic principles: (1) Pulsatile blood flow. This helps us to measure oxygen saturation in arterial blood. (2) Differing absorption spectra of oxyhaemoglobin and deoxyhaemoglobin. Pulse oximeters have a Light emitting diode (LED) capable of emitting light at 660 nm (red) [deoxyhaemoglobin absorbs more of this wavelength] and 940 nm (infrared) [oxyhaemoglobin absorbs more of this wavelength]. There is also a receiver, which receives this light after it has passed through blood. The amount of light reaching the receiver in both wavelengths are measured. The equipment processor measures the absorption of the two wave lengths and then calculates the ratio of saturated haemoglo-

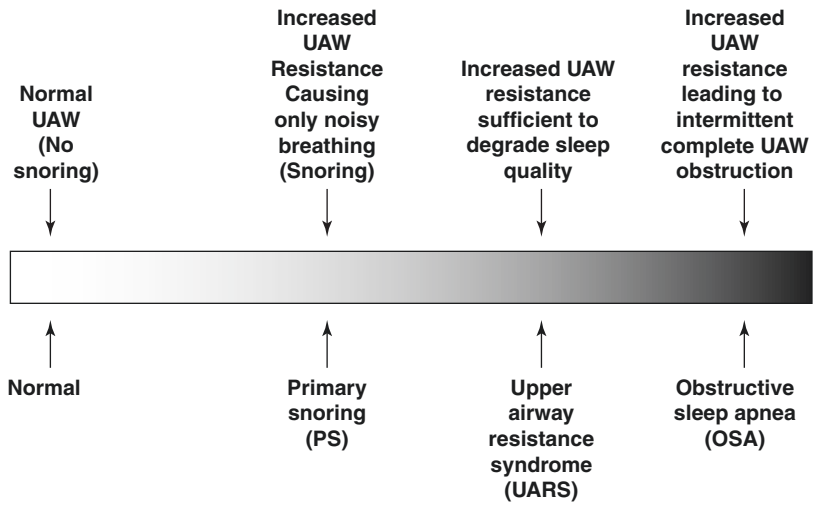

Fig. 5.1 Figure showing spectrum of sleep disordered breathing in paediatric patients [3]

bin (HbO_2) to total haemoglobin concentration in blood ([HbO_2] + [Hb]) and displays it as saturation in arterial blood (SaO_2) [4].

Hypoxic events occurring during upper airway obstruction are not defined as saturation drops below set readings such as 92%. Instead, an obstructive desaturation index (ODI) is calculated and used. This is defined as a saturation drop of 3% (ODI 3) or 4% (ODI 4) from baseline. Hence, if baseline is 99% saturation, a drop to 96% (ODI 3) is considered a desaturation event. These desaturation events are very transient and only last for a few seconds on most occasions. Hence the technology used to measure saturations has to have the resolution to pick up transient drops in saturations. Most widely used pulse oximeters including those in intensive care units display an output which is usually averaged over a long time (12–16 s) [5]. Since this is likely to miss transient desaturations, equipment with short averaging times (2–6 s) are best used for oximetry.

Overnight pulse oximetry is best conducted at home, though in-hospital oximetry study is also possible. A minimum recording of 6 h is recommended. While a few studies have shown that one nights' study suffices [6], more recent studies seem to suggest that recording for multiple nights can increase the number of patients screened positive for OSA [7]. In the author's institution, patients record 2 consecutive nights. If a oximetry study is negative or inconclusive, a polysomnogram is recommended particularly if clinical suspicion is high. . The modern oximetry machines record continuous overnight readings. The inbuilt software analyses data and produces meaningful reports including a saturation versus time graph for the whole night, time spent at various saturation levels, number of desaturations of greater than 3% etc. There are also multiple scoring systems that have been developed to interpret overnight saturation study. One of the commonly used scoring systems is the McGills score [8]. Based on this, a positive study is one with ≥3 clusters with ≥3 desaturations to <90% (desaturation was defined as ≥4% in saturation and a cluster defined as ≥5 desaturations within a 30 min period).

The positive predictive value of a positive study by this definition was 97%, however the negative predictive value was 47%. This meant almost half of patients who had a negative saturation study still had significant OSA.

Further studies have identified possible management decisions based on McGills score. Those with normal or inconclusive oximetry recording will need additional evaluation for OSA, those with mildly abnormal study (≥3 drops on sats <90% and <3 drops of sats <85% and no drop of sats <80%) and moderately abnormal study (>3 drops <85%, ≤3 drops <80%) will need a non-urgent adeno-tonsillectomy, those with severely abnormal study (>3 drops <80% will need an urgent surgery [9]. This approach has been recommended in resource crunched areas and in situations where a full PSG is not possible [10].

5.3.2 Limitations of Pulse Oximetry

As noted earlier, a negative oximetry study does not rule out OSA and hence this cannot be used as a screening tool. Having the right equipment with a short averaging time within the recording software is a pre-requisite.

Motion artefacts are also common even though some of the modern software do have the ability to cancel them. Since the process depends on pulsatile blood flow, significant hypotension and peripheral vasoconstriction can compromise results. Additionally, the presence of abnormal haemoglobin can skew the data (since they have different absorption wavelengths). However, most importantly, the calculations and predictions of saturations are based on values obtained from volunteers. Hence saturations, particularly those below 70% are not validated.

In summary, despite the lure of a cheap and easily available technology that can be used at home, pulse oximetry is far from the perfect test. Children with negative tests still need polysomnography. The current sensors and machines are still not very child friendly. Currently small, cheap, portable and disposable sensors are avail-

able which can wirelessly transmit data. We will soon see real time data from studies being done at home being transmitted to the doctor.

5.4 Actigraphy

Activity based monitoring of sleep is increasingly being used in sleep medicine, particularly in the context of children. It is extensively used in research and as a tool in clinical medicine too. It is an objective way of documenting sleep-wake patterns in the patient's own home environment. It is achieved using a small wristwatch which is worn on the non-dominant hand in older children and on the ankle for infants for a period of a week or more. It consists of an accelerometer which converts movements into numeric data which is easily transferred to a computer software where it can be interpreted. The data is collected every 0.1 s and is therefore quite extensive [11]. The patients also need to complete an activity log for the entire period of recording. Based on activity and the lack of it, it is possible to reliably calculate total time in bed, time of sleep onset, wake time and hence sleep efficiency. When worn for many days, it provides a reliable insight into the sleep rhythm and habits in a child. This objective data is better than parental reports of child's sleep and sleep diaries.

5.4.1 Indications for Actigraphy

A clinical practice guideline of the American Academy of Sleep Medicine endorses the usefulness of actigraphy for the following symptoms/disorders [12].

1. Circadian sleep-wake rhythm disorders
2. Insomnia symptoms
3. Excessive daytime sleepiness
4. Monitoring response to treatment for behavioural sleep problems.

5.4.2 Limitations

Actigraphy cannot replace polysomnography since it is not able to differentiate sleep stages and does not record respiratory events. It is good for picking up periods of sleep but not very accurate in picking up sleep onset (children who are awake in bed without moving are counted as asleep) and wake periods during sleep. While the sensitivity of actigraphy in picking up sleep is more than 90%, the specificity (of picking up wake periods in sleep) is less than 60% in studies [13]. Hence, actigraphy overestimates total sleep time.

In summary, actigraphy is a cost-effective tool to objectively assess sleep in children. By monitoring for prolonged periods (more than five days), it is possible to reduce some of its limitations and improve its reliability. In the past few years, accelerometers have been incorporated in smart phones and smart sensors, which are capable of measuring more parameters like heart rate, heart rate variability, saturations and temperature apart from movement. Many of these smart phone app functions include snoring monitoring, sleep talking and sleep tracking too. There is an explosion of these available apps and electronics. However, lack of standardization is the main drawback. Most of these apps infer sleep from movement like the actigraphy, but there is mystery in algorithms and thresholds used. While it is difficult to compare between various apps, studies have shown that the sleep parameters recorded by these apps do not correlate well with PSG [14]. Hence, while these apps encourage personal empowerment and help people to track their sleep longitudinally, a lot of restraint is advised in using these in clinical decisions as of today.

5.5 Paediatric Polysomnography

Polysomnography (PSG) is considered the gold standard for evaluating sleep disordered breathing (SDB) in children. It is a recording of multi-

ple physiological channels during sleep. Earlier in this chapter, we have seen the limitations of studying single channels such as saturations. Hence, PSG increases the sensitivity and specificity of diagnosing SDB. PSG recordings are usually overnight sleep recordings. Ideally, a minimum of 6 h of recording is required, though 8 h are preferred (Standard polysomnography). Most paediatric PSGs are hospital based and technician monitored. A child friendly sleep technician is a key necessity. This is a challenging role especially with younger children who often displace the leads and pull out the nasal sensors. Home studies increasingly used in adults, but home studies are not included in paediatric guidelines yet. However, quite a few studies have shown that home respiratory polygraphy is acceptable as a diagnostic modality in children [15] and it is sufficient in diagnosing and managing a majority of children with OSA [16].

Table 5.1 Table showing a list of the most commonly used channels in PSG

Channels	Purpose	Sensors
EEG, EOG, Chin EMG	Staging of sleep	Electrodes on scalp, chin and face
Airflow	Recognizing apnea and hypopnea	Thermistor and nasal pressure transducer
Respiratory effort	Recognizing respiratory effort	Chest and abdominal belts (either RIP or piezoelectric)
Peripheral oxygen saturation	Recognizing desaturations	Pulse oximeter
CO_2	Recognizing hypoventilation	Either transcutaneous or endo tracheal CO_2.
ECG	Measuring heart rate	Thoracic electrodes
Audio	Recognizing snoring	Microphone over neck
Video	Recognizing awake state, body position and abnormal movements	Infra-red camera in the room

5.5.1 Mechanics of Polysomnography

PSGs use several channels to record and measure various physiological parameters. Some of the most commonly recorded channels are summarized in Table 5.1 below.

The number of EEG channels recorded for sleep scoring is far less than those recorded for a neurology study. Most labs use two frontal leads (one on each side), two central leads and two occipital leads with mastoids as reference points. Electrodes are positioned using a 10-to-20 montage. The electro-occulogram (EOG) and chin EMG are useful in identifying rapid eye movement (REM) sleep. Two channels are used for monitoring oral and nasal airflow. The thermistor measures the presence or absence of airflow whilst taking advantage of the fact that inspiratory flow is cooler than expiratory flow. The nasal pressure transducer provides a sensitive measure of airflow resistance and subtle changes in inspiratory flow. Hence, pressure transducers are used to recognize drop in airflow (hypopneas) and upper airway resistance syndromes [17]. The two respiratory belts (respiratory and abdominal) provide additional information; They help in identifying asynchronous thoracic and abdominal movements which is an indication of upper airway resistance/obstruction. Carbon dioxide is measured either as end tidal ($ETCO_2$) or transcutaneous (TCO_2).

5.5.2 Interpretation and Scoring

Though polysomnography initially started as a paper recording, it is currently a digital recording. The user can change the channels and the duration of sleep seen on the screen without altering the raw data collected. A monitor screen is calibrated to show a definite period of sleep called the epoch. By convention, sleep staging is scored using a 30 s epoch, i.e., each screen shows

Table 5.2 Description of respiratory events on a PSG

Respiratory event	Description
Obstructive apnea	There is >90% drop in airflow signals that lasts for >2 respiratory breaths
Hypopnea	There is >30% drop in airflow signals that lasts for >2 respiratory breaths and is associated with either an arousal or a drop in saturation of 3%
Central apnea	There is a >90% drop in airflow signal that either lasts for 20 s - associated with absence of respiratory effort, or lasts for >2 respiratory breath time and is associated with either an arousal or a drop in saturations by 3%
Mixed apnea	There is a >90% drop in airflow signal that lasts for >2 respiratory breath time. These events have 2 components—Begins as a central apnea and ends as an obstructive apnea
Respiratory Effort Related Arousals (RERA)	These events last >2 respiratory breaths, associated with increasing respiratory effort and flattening of airflow signal indicative of airflow limitation, associated with arousal

30 s of sleep. Two-minute epochs are used for respiratory scoring. Sleep-wake states and arousal are scored using EEG, EOG and chin EMG channels. Sleep epochs are further classified as non-rapid eye movement (NREM) sleep (Stage1, 2 and 3), REM sleep and movement based on characteristic EEG appearances. In infants, younger than 2 months of age, the sleep stages are not fully developed and hence the stages that are recognized are just wake state (W), non-REM sleep (N), REM sleep (R) and transitional sleep (T) [18].

Some of the respiratory events that are scored in a PSG are shown in Table 5.2 below.

Based on these respiratory events scored and recorded, the following indices are calculated:

1. Apnea Hypopnea Index (AHI): This is calculated by dividing the total number of apneas (both central and obstructive) and hypopneas by the total sleep time.
2. Obstructive Apnea Hypopnea Index (OAHI): This is calculated by dividing the total number of obstructive apneas and hypopneas by the total sleep time. While reporting for SDB, PSGs are reported as [19]:
   (a) Normal study (OAHI < 1)
   (b) Mild OSA (OAHI 1–4.9)
   (c) Moderate OSA (OAHI 5–10)
   (d) Severe (OAHI > 10)

5.5.3 Indications for Paediatric Polysomnography

Indications for paediatric polysomnography are listed below [20]:

1. In diagnosis of OSA particularly if:
   (a) There is a discrepancy between history and clinical findings.
   (b) In high-risk children such as those with obesity, cranio-facial abnormalities, neuromuscular disorders and Trisomy 21.
2. Re-evaluation of children with OSA after adeno-tonsillectomy if:
   (a) OSA was severe before the surgery
   (b) There is recurrence/persistence of symptoms after surgery
   (c) In high-risk children such as obesity, craniofacial syndromes and neuromuscular disorders
3. Titration of Positive airway pressure (CPAP or BiPAP)
4. Evaluation and diagnosis of children with hypersomnia
5. Evaluation of treatment efficacy of oral appliances, weight loss or upper airway surgeries
6. Diagnosis of REM sleep disorders
7. Assessment of selected children with suspected restless legs syndrome
8. Suspected sleep related epilepsy
9. Confirm and treat congenital central alveolar hypoventilation syndromes

5.5.4 Limitations of Polysomnography

Its cost and limited availability globally are important considerations. As it is relatively new, normative values of sleep for various age groups and the global population is as yet evolving. The PSG is also a poor tool to measure the effects of OSA on target organs. Being recorded in a sleep lab, PSG suffers from a phenomenon called "First night effect", with more time supine, less REM sleep and stage 3 sleep. However, this affects the sleep parameters but not the respiratory parameters. Hence, one night PSG is sufficient for diagnosis of OSA but not if one is interested in sleep architecture. Also, level 2 PSG (PSG recorded without an attendant) is associated with risk of loss of channels and data overnight, due to displacement of leads.

5.5.5 Multiple Sleep Latency Test (MSLT)

A daytime MSLT is used in diagnosis of excessive day time sleepiness (narcolepsy, idiopathic hypersomnia and others). Only the neuro channels (EEG, EOG, chin EMG) are used in MSLT. Prior to performing MSLT, the parent is encouraged to record child's sleep log for 14 days. The study starts with an overnight PSG. Then the child is given an opportunity to nap every 2 h through the day for five naps. For example, if the child wakes up at 7 AM, the nap opportunities are offered at 9 AM, 11 AM, 1 PM, 3 PM and 5 PM. Each nap opportunity lasts for 20 min and is terminated if the child does not sleep. If the child sleeps in that period, then 15 min of sleep is allowed. The mean sleep latency (MSL) is calculated from all five naps. The normal MSL in teenage children is 16–18 min [21] and MSL in children with excessive daytime somnolence is <8 min [22]. A sleep onset REM period (SOREMP) is defined as occurrence of REM sleep within the 15 min in each nap. 80% of children with narcolepsy manifest two or more SORMPs [22]. MSLT is considered gold standard in assessment of excessive day time sleepiness in children and adults.

5.6 Drug Induced Sleep Endoscopy (DISE)

Over the past 2 decades, it is clear that there is residual OSA in many children who have had adeno-tonsillectomy [23]. While a repeat PSG will demonstrate residual OAHI, it does not indicate the cause. In those scenarios, an upper airway endoscopy in a child with drug induced sleep, will demonstrate the level of upper airway obstruction. It is performed while the child is sedated under strict protocols. The medications commonly used in paediatrics include IV dexmedetomidine and IV Ketamine [24]. The other medications that have been used include propofol and midazolam. The common findings in these scenarios include a lingular tonsil, regrowth of adenoids, tongue base prolapse and laryngomalacia. While there are studies which have shown that DISE directed surgery is useful in children with OSA [25] [26], this area is still evolving. One of the main impediment is the lack of standardization scoring scheme in children [27]. Further clinical research will help answer questions.

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Part III

Specific Sleep Disorders

Paediatric Insomnia

6

Xiao Li and Shirley Xin Li

6.1 Case Vignettes

Billy is a 5-year-old boy whose parents reported that they often had to have a bedtime battle with him at night. When promoted to bed, Billy always protested and complained of not feeling tired, and was reluctant to follow the bedtime instructions. He often used stalling and various excuses (e.g., wanting to go to the toilet, asking for water) to resist going to bed. Billy's mother eventually had to lie down with Billy in bed until he fell asleep. She complained that this often took more than an hour of struggle. Billy was also reported to have frequent night wakings. When Billy was up at night, he would go to his parent's bedroom and ask his mother to sleep with him.

Kelly, a 15-year-old girl, reported often struggling with difficulty in falling asleep at night. She also presented with a low mood and a loss of interest and energy during the day. She complained of not being able to shut off her mind and has often been tossing and turning in bed all night. She was frustrated by not being able to get enough rest at night and found it difficult to concentrate at school and get the energy to do things during the day.

6.2 Overview

Insomnia is one of the most common sleep problems in children. It affects approximately one-third of the children in the general population [1]. Childhood insomnia, if not addressed properly, may become chronic and persist across a range of developmental stages [2]. It is often linked to a constellation of negative outcomes, including behavioural and emotional problems in young children, as well as impaired cognitive functioning and poor academic performance in school-aged children, and elevated levels of family stress and poor psychological and physical health as well as impaired quality of life in caregivers [3]. In older children (e.g., adolescents), insomnia symptoms have been reported in association with an increased risk for developing anxiety and depression, interpersonal problems, somatic health problems, self-harm, and suicidal ideation [4]. As such, timely identification and intervention for childhood insomnia is essential.

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6.3 Classification and Diagnostic Criteria of Childhood Insomnia

The clinical presentations and definitions of childhood insomnia may vary depending on age, developmental stage, and cultural context. Paediatric insomnia is typically manifested as bedtime refusal or resistance, problems with falling asleep (without parental presence or assistance, e.g., feeding, rocking), frequent or prolonged night wakings, and early morning awakening. Currently, there is no standard definition of childhood insomnia. Different diagnostic criteria and definitions for childhood insomnia have been used in clinical and research settings. A consensus definition of childhood insomnia has recently been proposed by Mindell et al. [5] as: "*a repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite age-appropriate time and opportunity for sleep and results in daytime functional impairment for the child and/or family*." In the ICSD-2 [6], there was a specific category to classify childhood insomnia, i.e. behavioural insomnia of childhood (BIC), which included three main subtypes: *sleep onset association type, limit setting type*, and *combined type*, which have been often used to describe sleep problems in younger children. Table 6.1 shows the characteristics of the three subtypes of behavioural insomnia of childhood.

Childhood insomnia is currently subsumed under the umbrella term "chronic insomnia disorder" in the ICSD-3 [7] and there is no longer any differentiation of subtypes. The diagnostic criteria of insomnia are comparable between the ICSD-3 and DSM-5 (see Table 6.2). According to the ICSD-3 [7] and DSM-5 [8], childhood insomnia is defined as a self-report or parental report of difficulties with night-time sleep (i.e., difficulty falling asleep or problems returning to sleep without a parent or caregiver intervention) that results in some forms of daytime impairment in the child, the parent(s), or the family, and such problems occur at least 3 times per week and the symptoms have been present for at least 3 months. In addition, these symptoms persist despite adequate opportunity and circumstances for sleep, such as sufficient time to sleep, and a safe, comfortable, dark, and quiet sleep environment. To diagnose insomnia disorder, the sleep difficulties should not be explained by other medical conditions, mental disorders, another sleep disorder, or substance use. According to the ICSD-3 [7], insomnia is further classified into *chronic insomnia disorder*, *short-term insomnia disorder,* and *other insomnia disorders*. Depending on the duration of the symptoms, insomnia is classified as either *short-term* (symptoms present for less than 3 months) or *chronic* (symptoms present for more than 3 months).

Table 6.1 Characteristics of the three subtypes of behavioural insomnia of childhood

Subtypes	Common age group	Characteristics
BIC Sleep-Onset Association Type	Infants and toddlers	• Reliance on maladaptive and inappropriate cues for sleep that typically requires parental interventions, such as specific stimulation (e.g., feeding, rocking, watching television), objects (e.g., bottle, toys), or settings (e.g., parents' bed) to fall asleep or get back to sleep after awakening • Difficulty in falling asleep and/or returning to sleep after waking up in the absence of the above conditions
BIC Limit-Setting Type	Pre-school and school-aged children	• Active resistance, verbal protests, and repeated demands at bedtime ("curtain calls") • As a result of insufficient limit setting by the caregiver
BIC Combined Type	Showing the characteristics of both sleep-onset association and limit-setting subtypes	

BIC behavioural insomnia of childhood

Table 6.2 Comparison of ICSD-3 and DSM-5 guidelines for diagnosing insomnia

		ICSD-3	DSM-5
Diagnostic term		"Chronic Insomnia Disorder"	"Insomnia Disorder"
Criterion		Self-report, parent- or caregiver-report of symptoms	Dissatisfaction with sleep quantity or quality reported by individual or complaint made by caregiver or family member
Nocturnal sleep difficulty (at least one of these symptoms)	Difficulty initiating sleep	√	√
	Difficulty maintaining sleep	√	√
	Waking up earlier than desired	√	√
	Resistance to going to bed on appropriate schedule	√	√
	Difficulty sleeping without parent or caregiver intervention	√	√
Related daytime impairments		At least one out of nine domains[a]	At least one out of seven domains
Frequency and duration		Occurring at least 3 times per week and lasting for at least 3 months	
Not explained by inadequate time and opportunity for sleep		√	√
Not better explained by another sleep disorder		√	√
Not better explained by coexisting mental disorders and medical conditions		√	√
Not better explained by the physiological effects of a substance		√	√

[a]As compared to DSM-5, ICSD-3 requires more daytime impairments for the diagnosis of insomnia disorder, including impaired family performance and sleep concerns.

6.4 Prevalence and Consequences of Insomnia

Insomnia is common in the paediatric population, with an estimated prevalence of 20% to 36% in infants and young children (including toddlers and pre-schoolers), 20% to 40% in school-aged children, and 11% to 35% in adolescents. The reported prevalence rates of insomnia in the paediatric population vary across different studies, depending on the sample characteristics (e.g., different age groups and ethnicities), assessment methods (e.g., self-report versus parent/caregiver-report), and defining criteria of insomnia (e.g., symptoms-based versus a clinical diagnosis). The prevalence of insomnia in early childhood is comparable for boys and girls. The gender difference in insomnia often starts to emerge during late and post-puberty where girls are more likely to experience symptoms of insomnia than boys. A previous community-based study showed that the prevalence of insomnia increased from 3.4% to 12.2% (3.6-fold) in girls and from 4.3% to 9.1% (2.1-fold) in boys from pre-puberty to post-puberty [9].

While the assessment of childhood insomnia often relies on parental reports, parents' recall of their child's sleep problem may be subject to recall bias and tend to underestimate their child's insomnia symptoms. For example, a previous study showed that the prevalence of difficulty initiating sleep was 32–40% by child-report vs. 20–25% by parental report [10]. It was found that 23–28% of the children self-reported difficulty in maintaining sleep, whereas such a sleep problem was reported by only 12–14% of the parents of

these children [10]. Previous studies have reported a range of prevalence rates of insomnia in children with different cultural backgrounds, varying from 10% in Vietnam and Thailand, 25% to 30% in the United States and Australia, to as high as 75% in China and Taiwan [11]. A possible explanation for this difference in the prevalence of insomnia might be related to the cultural differences in sleep habits, such as bed-sharing or room sharing. Child-parent bed sharing and room sharing are commonly seen in most Asian countries [12], which make it easier for the caregivers to observe their child's sleep condition during the night. In addition, the activities before bedtime and sleep problems (e.g., snoring, insomnia) of the co-sleepers (caregivers) can potentially cause sleep disturbance for their child who shares the same bed/bedroom [12].

Insomnia is especially prevalent in the paediatric patients with comorbid psychiatric and medical conditions. For example, the prevalence of insomnia was found to be 48–75% in children with depression, and 32% in children with anxiety, 45% in children with cerebral palsy, and 48–56% in children with autism spectrum disorders (ASD) [13, 14]. A previous study showed that the prevalence of bedtime resistance, difficulty falling asleep, and sleep onset delay was 24.6%, 41.3%, and 22.2%, respectively, in children with attention deficit hyperactivity disorder (ADHD), whereas the prevalence of these insomnia symptoms was 9.2%, 17%, and 10.3%, respectively, in typically developing children [15].

Childhood insomnia, if left untreated, is often linked to a constellation of negative health-related and psychosocial outcomes, such as an increased risk for gastroesophageal reflux, and behavioural and emotional problems in young children. In school-aged children, insomnia symptoms have been reported in association with behavioural problems (e.g., hyperactivity, attention deficits, aggression, irritability), impaired cognitive functioning, and poor academic performance. In adolescents, insomnia symptoms have been linked to an increased risk for developing anxiety and depression, interpersonal problems, somatic health problems, substance abuse, self-harm, and suicidal ideation. Not only does childhood insomnia have significant negative impacts on the affected child, but it can also result in detrimental consequences in the family, such as parental psychological and physical health problems and high levels of parental conflict and parent-child conflict. For example, a previous study showed that parents of children with sleep problems have an increased risk of sleep disorders, depressed mood, fatigue, and elevated stress levels as compared to parents of children without sleep problems [3].

6.5 Aetiology of Insomnia

The causes of insomnia are complex and multifactorial. A combination of biological (e.g., genetics, hyperarousal, hypersensitivity, circadian rhythm changes), medical (e.g., asthma, sleep-disordered breathing, ASD, ADHD, anxiety, depression), as well as psychosocial and behavioural factors (e.g., excessive use of electronic media) may contribute to sleep problems in children. Understanding the causes of childhood insomnia, especially those that are potentially modifiable, is critical for the management of insomnia in children.

6.5.1 Biological Factors

Previous research showed that insomnia is linked to multiple genes and environmental factors, as well as complex interactions of gene-gene and gene-environment. A genome-wide association study (GWAS) and a genome-wide gene-based association study (GWGAS) using the UK Biobank sample that included more than 1.3 million adults has identified three loci and seven genes associated with insomnia [16]. A community-based case-control family study conducted in Hong Kong, which involved adolescents with insomnia and their first-degree relatives together with their age- and sex-matched non-insomnia controls and first-degree relatives, showed a significant familial aggregation of insomnia [17]. Previous twin studies have also suggested the role of genetic influences on the

development of childhood insomnia. For example, a study conducted in a sample of 18-month twins (n = 314) showed that heritability was 35.3% for night wakings [18].

Some studies have also suggested that hyperarousal (i.e., heightened arousal systems, hypoactive sleep-inducing pathways, or both) and hypersensitivity might be linked to the development of insomnia in children, especially children with ADHD and ASD. Children with ADHD have been shown to have an increase in cortical activity patterns. Children with ASD often show dysregulation of neurotransmitters (e.g., gamma-aminobutyric acid (GABA), melatonin, serotonin) that can affect sleep by interfering with the normal inhibitory function of GABA and contributing to circadian abnormalities. Children with ASD may also have hypersensitivity to environmental stimulation and difficulties in regulating arousal which may lead to sleep-onset delay.

Changes in endogenous circadian and homeostatic processes (e.g., a delay in the circadian rhythm as reflected by delayed melatonin release, slower accumulation of sleep homeostatic drive) in conjunction with external factors (e.g., increase in academic workload, use of electronic media near bedtime) can lead to an irregularity of sleep schedule and increased sleep difficulty in adolescents [19].

6.5.2 Medical Factors

Several medical conditions could potentially contribute to the development of insomnia in children, such as asthma, upper airway problems (e.g., snoring, obstructive sleep apnea (OSA)), allergies, gastroesophageal reflux, headache, epilepsy, and chronic pain syndromes. Several neurodevelopmental and neuropsychiatric disorders, such as ASD and ADHD, are closely associated with insomnia. Psychiatric disorders, such as anxiety and depression, are often linked to sleep disturbances in children [1].

Some medications may also be linked to increased sleep problems in children. For example, the stimulants (e.g., methylphenidate, amphetamine formulations) that are used to manage ADHD symptoms could potentially prolong sleep onset and increase difficulty in falling asleep, and decrease sleep duration. Medications for asthma (e.g., salbutamol, salmeterol, theophylline) and some antidepressants (e.g., selective serotonin reuptake inhibitors) can potentially disrupt sleep.

6.5.3 Psychosocial and Behavioural Factors

Parental behaviours during bedtime and upon child's nocturnal awakenings, such as night feeding, rocking, and holding the child until he/she falls asleep, may have negative influences on nighttime sleep in young children (e.g., infants) [20]. Co-sleeping (e.g., room-sharing and bed-sharing with siblings or adult caregivers) is another important factor to be considered in the context of paediatric insomnia. Co-sleeping is a culturally diverse practice, with the Eastern societies showing a higher prevalence of co-sleeping as compared with Western societies. A recent systematic review and meta-analysis showed that co-sleeping is associated with bedtime resistance, sleep anxiety, night waking, and parasomnia in children [21]. In particular, co-sleeping is associated with more bedtime resistance and night wakings in children in Western countries, while co-sleeping is related to parasomnia symptoms in children in Eastern countries [21]. In addition, infants and toddlers may experience varying degrees of anxiety and stress after separating from their mother, causing nighttime fears and difficulty in falling asleep.

Social media use and use of electronic devices (e.g., watching TV, using computers and cell phones, playing video games), especially before bedtime, are associated with an increase in pre-sleep arousal and suppressed melatonin secretion, because of excessive light exposure, thereby increasing sleep difficulties in children and adolescents. The consumption of caffeinated drinks (e.g., coffee, black tea, energy drinks) and alcohol intake close to bedtime can negatively affect sleep.

Some children with insomnia may have dysfunctional beliefs that could interfere with their sleep, such as "I can only fall asleep with the teddy bear in my arms," and "If I cannot sleep tonight, I will not be able to concentrate in class tomorrow". A previous study has shown that dysfunctional beliefs and attitudes about sleep, especially pertaining to control and predictability about sleep and causal attributions for insomnia, are associated with sleep difficulties in children [22].

6.6 Assessment

A comprehensive assessment is important for diagnosing insomnia and for developing an individualized treatment plan for the child. This includes taking a thorough sleep and medical history as well as family history, and physical examinations where needed. A comprehensive sleep history provides a detailed background of the child's sleep issues. A variety of subjective (e.g., questionnaires, sleep diaries) and objective measures (e.g., actigraphy) are available and may help to screen and understand the child's sleep problems. Medical and psychiatric history provides important information for understanding the causes or associated factors of insomnia. Family history can also be informative to explore genetic vulnerability and/or learned behaviours within the family context. Caregiver's expectations about the child's sleep should also be considered, as they may not have realistic expectations about their child's sleep or have a lack of adequate sleep knowledge within the child's developmental context.

6.6.1 Sleep History

Unlike in the adult population, where insomnia symptoms are usually reported by patients themselves, the assessment of paediatric insomnia often relies on the report of the parent(s)/caregiver(s). As such, whether a child has a sleep problem or to what extent the child has the sleep problems may be subject to parental recall and caregiver's understanding and interpretation of the child's sleep. In addition, the presenting complaints of paediatric insomnia (e.g., bedtime refusal/resistance, bedtime struggle requiring parental intervention) may be different from those in adults (e.g., subjective complaint of having a difficulty in falling asleep). In addition, the daytime consequences of paediatric insomnia (e.g., hyperactivity, restlessness, academic difficulties) may also appear different from those presented in adults (e.g., fatigue, mood disturbances).

Taking a comprehensive sleep history is important for assessing paediatric insomnia. This should include a detailed assessment of the child's sleep schedule (e.g., when, where, and for how long the child sleeps in a 24-h day, including sleeping in the car, stroller, swing, or at daycare/school), the child's sleep environment (e.g., lighting, noise level, room-sharing with parents or siblings, if any, bed type), sleep habits (e.g., sleep associations, such as parental involvement at bedtime), and bedtime routines (e.g., presence of any routine, types of activities in the evening including use of electronic devices, duration and location of routine).

6.6.2 Medical and Psychiatric History

A thorough medical history should include the evaluation of other possible causes or comorbidities associated with insomnia, including other sleep disorders (e.g., OSA, restless legs syndrome (RLS)/ paediatric limb movement disorder (PLMD), narcolepsy), medical problems (e.g., reflux), neurodevelopmental and psychiatric disorders (e.g., ASD, ADHD, anxiety, depression), and substance use (especially for older children and adolescents). Concurrent medications (e.g., psychostimulants) should also be reviewed.

6.6.3 Subjective Measures

Several questionnaires can be used for assessing sleep problems in children. Table 6.3 lists some of the commonly used measures.

Table 6.3 Questionnaires for the assessment of sleep problems among children

Sleep questionnaire	Acronym	Age group	Self-report or parent/caregiver report	Structure	Period	Measures
Brief Infant Sleep Questionnaire	BISQ	Young children aged 0 to 36 months	Parent/caregiver report	19 items	1 week	Sleep patterns, parent perception, and sleep-related behaviours
BEARS Questionnaire	BEARS	Children and adolescents aged 2 to 18 years	Children (2–12 years): Parent/caregiver report; Adolescent (13–18 years): Self-report	5 items (yes or no)	Not specified	Five sleep domains: bedtime problems, excessive daytime sleepiness, awakenings during the night, regularity and duration of sleep, and snoring
Sleep Disturbance Scale for Children	SDSC	Children and adolescents aged 3 to18 years	Parent/caregiver report	26 items (5-point scale)	6 months	Six sleep problems: sleep-wake transition disorders, disorders of initiating and maintaining sleep, disorders of arousal/ nightmares, sleep hyperhidrosis, disorders of excessive somnolence, and sleep-breathing disorders
Children's Sleep Habits Questionnaire	CSHQ	Children and adolescents aged 4 to 12 years	Parent/caregiver report	45 items (3-point scale)	1 week	Eight sleep problems: bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, sleep-disordered breathing, and daytime sleepiness
Adolescent Sleep-Wake Scale	ASWS	Adolescents aged 12–18 years	Self-report	28 items (6-point scale)	1 month	Five behavioural dimensions: difficulty going to bed, falling asleep, maintaining sleep, reinitiating sleep, and returning to wakefulness

A sleep diary can provide prospective information about a child's sleep-wake pattern over an extended period (typically two weeks). Common sleep parameters collected in the sleep diary include bedtime, sleep onset latency, night awakenings, wake-up time, rise time, self-perceived sleep duration, nap time/duration. A sleep diary is usually completed by the parent(s)/caregiver(s) for younger children, and by self-report for adolescents.

6.6.4 Objective Measures

Actigraphy is an objective non-invasive device that uses accelerometry to measure movement magnitude and velocity during waking and sleeping to estimate one's sleep-wake patterns. An actigraphy is a lightweight, waterproof wristwatch-like device that can be worn on a child's non-dominant wrist (for adolescents and older children) or ankle/calf (for infants and tod-

dlers) or may be placed in the child's shirt pocket (for children with ASD). It can collect movement data continuously for multiple days, weeks, or even longer in a child's natural environment. Although actigraphy is not a routine assessment of insomnia, it can provide a more objective and valid measure of sleep than self-reported or parent-reported sleep diaries and may provide extra information about the child's sleep where needed.

Polysomnography (PSG) is not routinely used for the diagnosis and evaluation of insomnia. However, PSG is only indicated if another underlying sleep disorder is suspected. For example, children with upper airway symptoms during sleep, such as snoring and breathing pauses, should undergo overnight PSG to confirm the diagnosis of OSA. Children with RLS often show symptoms of an irresistible urge to move the legs at rest and limb movements during sleep, which may cause sleep difficulties. Overnight PSG followed by multiple sleep latency test (MLST) on the next day is needed for diagnosing narcolepsy if suspected.

6.7 Interventions for Paediatric Insomnia

6.7.1 Non-pharmacological Treatment of Paediatric Insomnia

Non-pharmacological approaches, such as behavioural interventions, are generally recommended as the first-line treatment for paediatric insomnia [1]. Numerous studies have demonstrated that behavioural interventions could lead to reliable and sustained improvements in nighttime sleep and daytime functioning in young children, as well as a positive impact on the family's wellbeing. Behavioural interventions for insomnia can be applied not only in typically developing children but also those with comorbid disorders [23]. In addition, behavioural sleep interventions have been shown to improve not only sleep but also mood symptoms and daytime functioning in children with mood disorders (e.g., depression, anxiety). Previous studies have found significant improvements in ADHD symptoms and neurocognitive outcomes following the behavioural interventions for insomnia in children with ADHD. It was also found that behavioural sleep intervention could lead to reduced sleep onset latency and improved daytime behaviour (e.g., reduced repetitive behaviors) in children with ASD. Parental involvement and parent education are important for implementing behavioural interventions for insomnia in children. Active participation of the parents in the implementation of the behavioural strategies, especially for young children with insomnia, may help to maximize the effectiveness of the treatment.

Common behavioural strategies in the treatment of paediatric insomnia include implementing a consistent bedtime routine, fading out sleep associations, and using consistent positive reinforcement and rewards. These behavioural strategies aim to help the children to establish good sleep practices and develop their abilities to fall asleep and return to sleep independently following normal nighttime arousals. Table 6.4 provides some examples of non-pharmacological interventions for paediatric insomnia. Whilst these approaches are generally safe and effective in children, it may not be appropriate to use *extinction* (which involves prolonged crying in the child) in certain special paediatric populations, such as infants with developmental issues, children with medical conditions (e.g., severe reflux, seizure disorder) and young children with a history of severe anxiety, trauma or self-injurious behaviors.

Cognitive behavioural therapy for insomnia (CBT-I) is a nonpharmacologic treatment designed to address maladaptive sleep behaviors and distorted beliefs about sleep and insomnia [24]. It may be more suitable for older children and especially adolescents with insomnia. CBT-I typically consists of a collection of behavioural and cognitive strategies, including stimulus control, sleep restriction, relaxation training, cognitive therapy, and sleep hygiene education. It

Table 6.4 Non-pharmacological interventions for paediatric insomnia

Strategies	Aim	Target population	Description
Bedtime routine	Establish a consistent bedtime routine and a regular sleep schedule	All children	Implementing a series of pre-bedtime activities (e.g., taking a bath, diaper change, reading a bedtime story, or singing a song) with the child consistently every night
Bedtime fading	Align a child's bedtime with his/her natural circadian rhythm	Young children, young children with a late bedtime	Gradually delaying the child's bedtime to match his/her natural sleep onset time
Standard extinction	Remove negative sleep-onset associations both at bedtime and during the night	Children >6 months old Not appropriate for children with medical conditions (e.g., reactive airway disease, seizure disorder, severe anxiety)	Parents putting the child to bed and subsequently ignoring the child's behaviours (e.g., not responding to the child's crying and tantrums)
Graduated extinction	Remove negative sleep-onset associations at bedtime	Children >6 months old Not appropriate for children with medical conditions (e.g., reactive airway disease, seizure disorder, severe anxiety)	Parents putting the child to bed and ignoring the child's behaviours (e.g., crying, tantrums) for specific periods before briefly checking on the child
Cognitive behavioural therapy for insomnia	Address maladaptive sleep behaviors and distorted beliefs that perpetuate insomnia	Children aged 8 or above	Sleep hygiene education, stimulus control, sleep restriction, relaxation training, and cognitive therapy

should be noted that implementing sleep restriction in adolescents may be challenging because they are often already sleep-deprived during schooldays, particularly due to early school start time. CBT-I is currently recommended as the first-line treatment for chronic insomnia in adults. Whilst there has been substantial evidence to support the clinical efficacy of CBT-I in the adult population, only a limited number of clinical trials of CBT-I have been conducted in the paediatric population. Nonetheless, the existing data consistently supported the positive and sustained effects of CBT-I on improving sleep, mood symptoms, and daytime functioning in adolescents.

6.7.2 Pharmacological Treatment of Paediatric Insomnia

Pharmacological treatment is usually not suggested as the initial treatment option for children with insomnia. While pharmacological treatment of insomnia may be able to produce rapid short-term effects on relieving sleep symptoms, long-term use may lead to reduced efficacy and adverse effects (e.g., sleepwalking, morning hangover, daytime sleepiness, headaches). As such, pharmacological treatments for insomnia are generally recommended for short-term use, and should only be considered when parents cannot adapt to behavioural interventions due to practical constraints (e.g., time-consuming and interfering with parents' routine work) or when behavioural interventions fail to produce adequate improvements. Additionally, sleep medication is rarely considered as the sole treatment and should ideally be offered in combination with behavioral interventions to achieve sustained therapeutic effect and minimize the side effects.

Despite its known side effects, pharmacotherapy is the most common treatment for behavioural insomnia in children. In a national survey conducted in the United States, approximately 75% of children who presented with a sleep disorder were prescribed over-the-counter sleep

aids, and 50% were prescribed sleep medications [25]. Nonetheless, the data on the efficacy, safety, and tolerability of the medications used to treat paediatric insomnia remained limited. The prescription of the medications for managing insomnia in children is mostly based on the extrapolation of adult data and clinical experiences. It is also important to note that there are currently no medications approved by the US Food and Drug Administration (FDA) for the treatment of insomnia in the paediatric population and no well-defined guidelines for the pharmacological treatment of paediatric insomnia. Therefore, clinicians should always exercise caution when using medications for treating insomnia in the paediatric population. In addition, adolescents should be screened for alcohol, tobacco, and illicit drugs and pregnancy before the initiation of medication for insomnia. Physicians need to communicate closely with the family for choosing the best therapy for the child, and follow-up frequently to monitor side effects, especially during withdrawal, to ensure safe and successful management of paediatric insomnia.

There are a variety of over-the-counter and prescription medications that are commonly used in clinical practice to treat insomnia in children. Antihistamines, alpha-agonists, and melatonin are commonly used for treating paediatric insomnia in clinical practice. A survey of 222 paediatricians in the US found that antihistamines (83%) and melatonin (42%) were the most commonly recommended over-the-counter medications to treat insomnia, and antidepressants (tricyclics 31%, other antidepressants 30%) and benzodiazepines (17%) were the most commonly prescribed sedating medications [26]. Antihistamines (e.g., diphenhydramine, cyproheptadine, hydroxyzine) have been considered as a highly acceptable choice for many families, because of their well-tolerance in children and adolescents as well as their low cost and availability in clinical practice. In a randomized controlled trial, 50 school-aged children (age range: 2–12 years) were given either diphenhydramine or a placebo to treat their insomnia. Children receiving diphenhydramine showed a decrease in sleep onset latency and a reduction in night awakenings [27]. However, another study found that diphenhydramine was no more effective than placebo for improving sleep in infants (aged 6 to 15 months, n = 44) with night awakenings [28]. Clonidine is a noradrenergic alpha-2 agonist that has sedative effects. It is generally used in the treatment of ADHD symptoms (especially impulse control in ADHD) and paediatric insomnia. Two open-label retrospective studies have found an improvement in insomnia symptoms in children with neurodevelopmental disorders following clonidine treatment [29, 30]. Melatonin, a hormone secreted by the pineal gland, plays a pivotal role in the regulation of the circadian rhythms as well as sleep and wakefulness. It also possesses sedative and hypnotic properties. Several studies have shown the efficacy of melatonin in reducing sleep onset latency and the number of awakenings during sleep in children and adolescents with chronic sleep-onset insomnia, as well as improving daytime behaviors in children with special needs (e.g., ASD, ADHD). Antidepressants are commonly used to treat insomnia in both paediatric and adult patients with mood disorders. Trazodone is the most commonly prescribed antidepressant to treat insomnia symptoms in children with mood and anxiety disorders. However, there remained very little data on the efficacy and safety of trazodone for treating sleep difficulties in children and adolescents. Clonazepam, an intermediate-acting benzodiazepines may be considered in children with parasomnias and insomnia. A low dose of clonazepam at 0.25 to 0.5 mg may help improve sleep during the night and decrease the arousal threshold in children. Table 6.5 lists some of the medications commonly used for paediatric insomnia.

Table 6.5 Medications used for paediatric insomnia

Class	Medications	Mechanism of action	Effects on sleep	Potential side effects	Note on the use in the paediatric population
Antihistamines	Diphenhydramine Cyproheptadine Hydroxyzine	Block H1-receptors in the central nervous system	Decrease sleep onset latency	Daytime drowsiness, appetite loss, dry mouth, confusion	Children with insomnia
Alpha Agonists	Clonidine Guanfacine	α-adrenergic receptor agonists	Decrease sleep onset latency, reduce slow-wave sleep	Dry mouth, bradycardia, hypotension, REM suppression	Children with comorbid insomnia and ADHD
Hormone Analog	Melatonin	Action at MT1 and MT2 receptors	Decrease sleep onset latency, effect on circadian rhythms	Suppression of the hypothalamic-gonadal axis, headache, nightmares	Children with comorbid insomnia and ADHD, ASD, or blindness
Melatonin Receptor Agonists	Ramelteon	Selective melatonin type 1 and 2 receptor agonists	Decrease sleep onset latency	No significant side effects noted	Children with ASD and insomnia
Benzodiazepines	Clonazepam	Bind to the GABA receptor	Suppress slow-wave sleep, reduce nocturnal arousals	Residual daytime sedation, respiratory function impairment, impulsivity, and memory impairments	Children with insomnia and parasomnias
Nonbenzodiazepine Benzodiazepine Receptor Agonists	Zolpidem Zaleplon	Bind to GABA-A receptor containing alpha-1 subunits	Decrease sleep onset latency	Sleep-walking, drowsiness, confusion, ataxia, slurred speech	Children with insomnia, especially sleep-onset insomnia
Antidepressants	Trazodone	5-HT, serotonin agonist	Increase sleep efficiency, decrease the number of awakenings	Dizziness, central nervous system depressants, hypotension	Children with comorbid insomnia and mood and anxiety disorders
Antipsychotics	Quetiapine	Antagonizes multiple receptors (5-HT, dopamine)	Decrease sleep-onset latency, increase sleep continuity	Hormonal changes, weight gain	Children with comorbid insomnia and psychiatric disorders (e.g., bipolar disorder, aggression)

6.8 Summary and Take-Home Points

Insomnia is highly prevalent in children of all ages, especially in paediatric patients with comorbid psychiatric and medical conditions. Childhood insomnia may become chronic and persist into adulthood if not properly treated. Paediatric insomnia may be linked to a constellation of negative impacts on both the affected child and their caregivers. A comprehensive assessment is important for understanding factors potentially contributing to paediatric insomnia. Non-pharmacological and pharmacological approaches are available to manage insomnia in children and adolescents. Although the use of pharmacological treatment for insomnia is common in paediatric clinical settings, there is a lack of high-quality, well-designed clinical trials on the efficacy, safety, tolerability, and pharmacodynamics profile of medications conducted in children. Behavioral interventions are recommended as the first-line treatment for paediatric insomnia. Parental psychoeducation and involvement in implementing behavioural interventions are important for the successful management of paediatric insomnia, especially for young children.

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Primary Snoring

7

Zhifei Xu and Yunxiao Wu

7.1 Vignette of Typical Presentation/Real Life Example

A 5-year-old, slightly obese boy presented for evaluation of mild snoring that had occurred on more than three nights per week for the 3 preceding months and had worsened 1 month previously. His parents reported that his sleep was restless and that he sweated a lot, but did not show pauses in his breathing or gasping. He did not experience nocturnal enuresis, sleepwalking, or night terrors. When awake, the child often breathed through his mouth. The child's parents had also noticed a change in his voice, and described it as "muffled, like speaking with cotton balls in his mouth". The child was not irritable, excessively tired or sleepy. In addition, there was no evidence of developmental delay or behavioral problems, such as attention deficit-hyperactivity disorder, depression, aggression, or abnormal social behaviors. There was also no history of recurrent fever, sore throat, dysphagia, otitis media, chest pain, shortness of breath, or stridor. Physical examination confirmed a slight nasal quality to the child's speech. He did not show adenoid facies or mid-face hypoplasia. Oropharyngeal examination revealed enlarged tonsils (grade 3^{+}). The child's height was within the normal range, but his weight was above the 95^{th} percentile for his age (height: 113 cm, weight: 24.7 kg, body mass index 19.3 kg/m^2). The fibro-laryngoscopic examination showed that the adenoid occupied 2/3 of the posterior nostril. The boy's whole night polysomnography reported that the obstructive sleep apnea index was 0.4 episodes·h^{-1} and the minimum oxygen saturation was 94%. The boy was diagnosed as having primary snoring (PS), a consultation was arranged with a nutritionist to facilitate weight control, a nasal spray of glucocorticoid was prescribed and a follow-up visit to the respiratory clinic was scheduled for 3 months later. This flow chart showed our empirical approach to management of children with PS.

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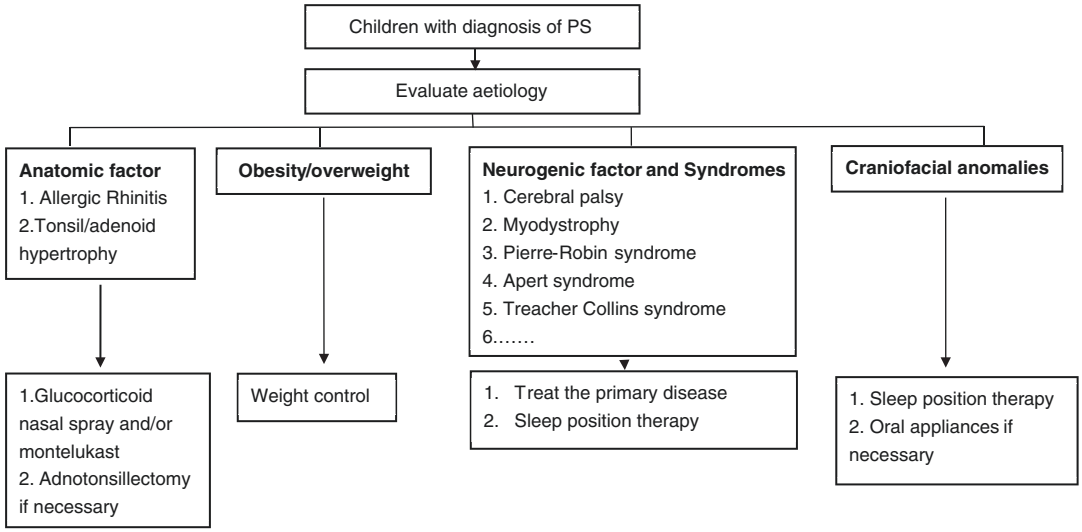

7.2 Epidemiology

Occasional snoring is almost universal. Estimates of the prevalence of snoring vary widely, depending on its definition. Habitual snoring, which is defined as snoring oftenor ≥three nights per week, has been reported to affect 10–15% of children [1]. A cross sectional study of 700 children found that the prevalence of primary snoring (PS) (AHI < 1 and snore) was 15.5% [2]. Its prevalence peaks during the pre-school years.

Population-based cohort studies have provided evidence that approximately one-third of cases of PS will progress to more severe forms of sleep-disordered breathing (SDB). In a 4-year follow-up study of a cohort of children with PS (less than one episode of obstructive apnea hypopnea (OAHI) per hour; age at follow-up 14.7 ± 1.8 years), 37.1% progressed to obstructive sleep apnea (OSA) and 7.1% to moderate-to-severe OSA (OAHI ≥ 5 events per hour) [3]. Persistent overweight/obesity is a predictor of progression from PS to OSA. In the 10-year follow-up of the same cohort, 27% of those who had PS at baseline developed OSA in late adolescence or young adulthood. Male sex, higher baseline body mass index (BMI), increase in BMI, presence of habitual snoring at both baseline and follow-up, or at follow-up alone, were associated with a greater risk of incident OSA [4]. In the Penn State Child Cohort study, the prevalence of persistent PS in adolescence was 30.3%, it resolved in 31.5% of cases, and in 25.8% and 12.4% of cases it evolved into mild and moderate-to-severe OSA, respectively [5].

7.3 Pathophysiology

Snoring results from turbulent air-flow and the vibration of soft tissues. In children, the primary cause of air-flow turbulence is hypertrophy of tonsillar and/or adenoid tissue. This narrows the pharyngeal lumen, and this is further exacerbated by the lower pharyngeal tone during sleep. Vibration of the oropharynx occurs when the oropharyngeal diameter decreases because the negative intrathoracic pressure overcomes the tone of the oropharyngeal dilator muscles. During snoring, vibration of the uvula and soft palate occurs, and the faucial pillars, pharyngeal walls, and lower structures may also be involved [6].

High nasal resistance, secondary to allergic rhinitis and/or septal deviation, can lead to mouth

breathing, which can induce secondary tonsillar hypertrophy when chronic, because of frequent irritation by airborne allergens and pathogens. Dysfunction of the genioglossus and geniohyoid muscles can also be caused by chronic mouth breathing, which may further worsen the airway obstruction [7]. This would in turn result in more posterior mandibular growth. Thus, enlargement of the tonsils and adenoids, enlargement of the nasal turbinates, deviation of the nasal septum, mouth breathing, abnormal tongue position, orthodontic abnormalities, and abnormal craniofacial growth are important risk factors for SDB [7].

Obesity predisposes toward snoring in children, because of the mass loading of the upper airway and respiratory muscles, as well as impaired ventilatory control. Children with Down syndrome are also prone to snoring, because of their small upper airway, which is secondary to their mid-facial hypoplasia, micrognathia, and muscular hypotonia. Individuals with other genetic syndromes, and particularly those associated with craniofacial abnormalities, such as Apert syndrome and Crouzon syndrome, are also prone to develop SDB. Furthermore, many neurological disorders; for example, Duchenne muscular dystrophy and cerebral palsy, predispose children toward SDB, because the already weakened dilator muscles of the upper airway and the respiratory muscles have poor tone during sleep. Finally, exposure to cigarette smoke has been shown to be associated with childhood SDB, which may be because of a reduction in pharyngeal size, secondary to the mucosal edema and inflammation that are induced [8].

Previous studies have shown that African American ethnicity is a significant independent risk factor for SDB, compared with Caucasian ethnicity. The parents of Hispanic children may complain of snoring or apnea more often than the parents of white children, but a significant difference in mean respiratory disturbance index has not been identified between Hispanic and white children. Finally, a study conducted in Singapore showed a higher prevalence of habitual snoring among Malay people than among Chinese or Indian people [9].

7.4 Diagnosis

A diagnosis of PS is made on the basis of the presence of habitual snoring, ≥three nights per week. Polysomnography (PSG) is required to confirm the diagnosis, because clinical history alone is usually insufficient to distinguish a simple snorer from a child with OSA. The most commonly used threshold for PS is less than one obstructive AHI per hour, together with a clinical history of parent-reported habitual snoring [10].

7.4.1 Clinical Features

Careful collection of the history, including daytime symptoms, is the first step in the evaluation of the snoring child. The frequency of snoring, and whether it is daily or seasonal, are of interest. More specifically, poor school performance, hyperactivity, poor appetite, and frequent episodes of rhinorrhea should be noted. Although excessive daytime sleepiness and learning problems are both specific findings, they are not sensitive indicators of SDB in children. Scores derived from parental questionnaires regarding snoring and other sleeping and waking behaviors can be used as surrogate predictors of SDB in children. We recommend that the design and interpretation of questionnaires should consider the age of the child, which risk factors are present, and the purpose of the screening assessment. Questioning the parents about symptoms that they may not attribute to a sleep disorder, and regarding common causes of snoring, such as tonsillar and adenoid enlargement, chronic rhinosinusitis, and allergic rhinitis, is also important [11].

7.4.2 Physical Examination

On physical examination, adenoid facies, mouth breathing, and allergic signs, such as allergic salute, transverse nasal crease, and sneezing, are also of interest. Tonsillar size is usually scored from 0 or 1 (small tonsils within the tonsillar fau-

ces) to 4 (indicating enlarged tonsils that obstruct the oropharyngeal aperture or at least 75% of the lateral airway dimension) [11].

7.4.3 Diagnostic Testing

Clinical examination in combination with endoscopy using a flexible endoscope can be very informative. There are cases like soft tissue masses, small mid-face craniosynostosis, micrognathia, or macroglossia where lateral radiographs are of value for the estimation of upper airway [11]. Finally, PSG is required to rule out OSA. A cut off value for obstructive AHI of less than one episode per hour is currently used for the diagnosis of PS [10].

7.5 Complications

7.5.1 Neurocognitive and Behavioral Impairment

There is increasing evidence suggesting that neurocognitive impairments are more frequent in children with PS than in those who have never snored. In these studies, PS was found to be associated with cognitive abnormalities, memory problems, poor language development, poor visuospatial ability, and poor academic performance. A recent systematic review of 13 studies of the neurocognitive and behavioral impairments associated with PS found that many, but not all studies had demonstrated the presence of cognitive deficits in children with PS. However, although children with PS had lower cognitive function scores and academic ability than non-snoring children, the majority of their scores still fell within the normal ranges [1].

Conclusions were inconsistent for different dimensions of memory in children with PS. Biggs *et al*. found working memory deficits in children with PS compared to controls [12]. Whereas Maski *et al*. revealed that children with PS and controls had comparable memory consolidation across wake and sleep conditions [13].

Previous studies had also consistently shown behavioral impairments in children with PS. Hyperactivity, inattention, and somatic complaints are the most commonly reported deficits, but these are not universal [1]. Jackman AR and his colleagues revealed that children with PS had impaired behavior than controls with poorer scores of Behavior Rating Inventory of Executive Function (BRIEF), Child Behavior Checklist and Adaptive Behavior Assessment System [14]. Another study showed that children with PS were more likely to develop attention-deficit disorder, anxious/depressive symptoms, and social problems [15]. Chervin *et al*. performed a prospective, controlled, cohort study that assessed neurobehavioral and polysomnographic outcomes in 105 school-aged children before and after adenotonsillectomy (AT) [16]. At the 1-year follow-up visit, children with clinically suspected SDB, including those who did not have OSA, showed substantial improvements in all their neurobehavioral outcomes, whereas the controls did not. These datas indirectly suggest that children with PS are at risk of neurobehavioral morbidity, which can improve after AT.

7.5.2 Cardiovascular System

In a cross-sectional study, non-overweight, prepubertal children underwent PSG and ambulatory blood pressure (BP) monitoring. Children with PS had significantly higher daytime systolic and diastolic BP than age-, sex-, weight-, and height-matched healthy controls [17]. There is also evidence that children with PS have lower arterial distensibility, as determined using pulse transit time [18]. In addition, a study of the association between childhood PS and endothelial function was able to demonstrate that children with PS had impaired flow-mediated vasodilation that was independent of their body size [19]. Villa MP demonstrated an alteration

in the late phase of left ventricle diastolic function, characterized by increased A wave amplitude, paralleled by reduced E/A ratio and prolonged isovolumetric relaxation time, in children with PS by means of both conventional echocardiography and Tissue Doppler Imaging analysis [20]. These results suggest that children with PS are at higher cardiovascular risk than non-snoring children. Furthermore, children with PS show signs of parasympathetic impairment, in the form of a delayed heart rate response to fluctuations in BP [21].

The potential mechanisms linking PS to neurobehavioural/cardiovascular complications are not fully understood. The hypotheses involve the upper-airway inflammation and the damage to vascular endothelial cell damage caused by snoring vibration, and the disruption of sleep micro structures. Almendros *et al*. reported that the vibratory mechanical stimulus due to snoring induced upper-airway inflammation in a rat model, which may lead to endothelial dysfunction [22]. Amatoury *et al*. found that during snoring, pressure vibrations occurred in the tissues surrounding the carotid artery wall and were transmitted to the carotid artery lumen itself by using an animal model, providing a potential energy source for carotid arterial wall damage and/or atherosclerotic plaque rupture [23]. Further evidence showed that carotid arteries subjected to 6 h of continuous peri-carotid tissue vibration displayed endothelial dysfunction, suggesting a direct plausible mechanism linking snoring to the development of carotid atherosclerosis [24]. Lee *et al*. suggested that underlying snoring sounds may cause carotid wall thickening [25]. It has been reported that childhood snoring can alter sleep microstructure, which predisposes toward disease. Snoring adolescents have been shown to have a higher arousal index than non-snorers [11]. Lopes and Guilleminault showed that children with chronic snoring often had an abnormal sleep electroencephalogram, with significantly higher cyclic alternating pattern rates and a predominance of abnormalities in their slow-wave sleep [26]. Another study showed that children with PS experience less rapid eye movement (REM) sleep and more frequent arousal than non-snorers. Moreover, the percentage of REM sleep correlated poorly with visuospatial function, which suggested a role for snoring-induced alterations in sleep structure in the neurobehavioral deficits of the patients [15].

7.5.3 Others

Habitual snoring for more than a year is associated with a higher prevalence of sleep abnormalities, such as sleep-onset delay, sleep-wake transition disorders, night awakenings, and nightmares [27]. Deficits in growth hormones, similar to those that are present in OSA, have also been shown in children with PS, although the effect of simple snoring on growth remains unknown [28]. In children with enlarged adenoids, altered craniofacial growth occurs, because of greater nasal resistance and the altered breathing pattern (mouth breathing) [29]. One study showed that children with PS had lower orofacial strength and differences in their breathing and mastication scores, compared with a reference group, which was demonstrated using a validated protocol for orofacial myofunctional evaluation, surface electromyography of masticatory muscles, and measurements of maximal lip and tongue strength [7].

7.6 Treatment

Primary snoring is a type of SDB that principally manifests as snoring, and some academics believe it is an early form of OSA. It should also be noted that children who initially demonstrate simple snoring may be at risk for the development of OSA with age or weight gain. There is a lack of high-quality evidence, published guidelines and consensus statements regarding recommended treatments for PS [8]. In clinical practice, treat-

ment should be initiated in children with PS under some circumstances, and especially when there are significant clinical symptoms present, such as growth delay, poor school performance, enuresis, or behavioral problems. When potential treatments for a child with PS are discussed, the reported likelihood of progression to OSA should also be taken into consideration [3].

7.6.1 Adenotonsillectomy

Although there is evidence for improvements in behavior, cognition, sleepiness, symptoms of sleep-related breathing disorder (SRBD), and quality of life in children with SDB after they undergo AT, relatively few studies have been conducted in children with PS alone. Borovich *et al*. found that children with PS who underwent AT had better pediatric sleep questionnaire-SRBD scores after 5 years than those who did not undergo surgery [30]. In addition, Lee *et al*. studied changes in the OSA-18 score after AT in children with PS, and found that the total score improved post-operatively [31]. The OSA-18 domains that showed the largest changes were on the physical symptoms sub-scale (mouth breathing, frequent colds, nasal discharge, and difficulty in swallowing food) [32]. There is a randomized controlled trial, the Pediatric Adenotonsillectomy Trial for Snoring (PATS), being performed [33]. More evidence-based information regarding the outcomes of AT in children with PS is expected.

7.6.2 Non-Surgical Treatment Options

7.6.2.1 Medication

Anti-inflammatory medication is probably the most common non-surgical treatment that is used in children with PS. Nasal corticosteroids and leukotriene receptor antagonists are of value in children with adenotonsillar hypertrophy [11].

7.6.2.2 Sleep Position Therapy

Sleep in the lateral position is recommended in most cases. For children with Pierre-Robin syndrome or severe micrognathia, the prone position might be preferable, as comparing with supine position, the prone position decreased OAHI in the vast majority of Pierre-Robin syndrome infants and micrognathia [34, 35].

7.6.2.3 Weight Loss

Weight loss or weight control should be recommended for overweight children, because there is a great deal of evidence that obesity is a risk factor for the progression of PS to OSA [2–4].

7.6.2.4 Oral Appliances

For snoring children who may have combined oral and maxillofacial developmental problems, oral evaluation and treatment with an oral appliance are recommended if this is necessary [36].

7.6.3 Follow-Up

Close attention should be paid to the factors that cause snoring, and the development of an appropriate lifestyle is also important. Regular follow-up is important for children with PS, because of the potential for the disease to progress.

7.7 Research Gaps

The mechanisms of development of the neurocognitive and cardiovascular complications in children with PS have been poorly characterized. Children with PS do not, at least according to the current definition, experience intermittent hypoxia. However, questions remain regarding whether the present monitoring techniques and definitions are in fact sensitive enough to identify abnormalities in gas exchange in snoring children.

Although a number of prospective cohort studies have demonstrated spontaneous improve-

ment or resolution of PS in childhood, it is difficult to identify the patients who are likely to improve without treatment. Therefore, studies of the prognostic factors for children with PS should be conducted.

Follow-up studies have shown that impairments in the cardiovascular system in children with PS can gradually worsen. However, the changes in the cognitive impairments of children with PS who undergo different therapies have not been characterized.

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Obstructive Sleep Apnoea

8

Daniel Y. T. Goh

8.1 Vignette of Typical Presentation/Real Life Example

A 7-year-old boy incidentally reports frequent snoring when he presents to the family doctor for a minor superficial injury. He is described to be a healthy child, physically active and not obese. He has no past medical history of note except for childhood asthma, allergic rhinitis and eczema. He has been attending preschool since 3 years of age and has just started primary school. He is described to be snoring regularly and on most nights; not loud, but consistent. This child is also described to be restless in bed; moves about a lot in bed, repositioning himself through the night. He sometimes sleeps with his neck hyperextended over the edge of the mattress. He is an average student and is sometimes described by teachers to be fidgety and hyperactive in class. He doesn't fall asleep in class or in the schoolbus. Incidentally, his father also snores regularly. Mom did raise her concerns about the snoring to the paediatrician previously but was told that it is normal to snore and it will spontaneously get better with time.

Key points in history of significance: Age, habitual snoring, atopic child, restlessness in sleep, abnormal sleeping positions, hyperactivity, no daytime hypersomnolence, positive family history.

Assessment: Tonsils and adenoids are enlarged. No other clinical abnormality noted. Overnight sleep study (polysomnography) shows moderately severe OSAS with an AHI of 6.8/h, no significant desaturation or hypercarbia (measured by end-tidal CO_2 measurement). Snoring is noted throughout the night. Events worst during REM sleep and in the supine position.

Management: Adenotonsillectomy done with significant improvement in snoring and resolution of the restlessness in sleep. The hyperactivity improved partially over time.

Key learning notes: Sleep and snoring need to be actively screened at all healthcare encounters/consultations; parents do not often voluntarily report sleep issues; awareness of snoring and OSA in childhood is still low in many countries in the region.

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8.2 Introduction

8.2.1 What Is OSAS

OSAS is a condition where there is obstruction in the upper airway during sleep resulting in apnoeas or hypopnoeas, which can be associated with gas-exchange abnormalities and sleep fragmentation and result in complications of poor sleep quality, and also developmental and learning impairment.

8.2.2 Spectrum of SDB: Primary Snoring to OSAS

OSAS is part of a group of conditions termed sleep-disordered breathing (SDB) which occurs in a spectrum of severity ranging from mild to severe upper airway obstruction.

On the milder end of the spectrum is Primary Snoring—where there is snoring but there is no apnoea or hypopnoea, no hypoxaemia, hypercarbia or significant arousals. The opposite end of the spectrum is obstructive sleep apnoea syndrome. In between is upper airway resistance syndrome (UARS) where there is evidence of increased respiratory effort and the presence of increased negative intrathoracic pressure during inspiration, associated with arousals and sleep fragmentation despite the absence of airflow or gas exchange abnormalities.

8.3 Epidemiology

This is a common condition in childhood that is often underestimated and under-diagnosed. It occurs in children of all ages but is most common in the pre-school age where it is reported to occur in 1–3% of children, corresponding to the peak age of adenoid and tonsillar hypertrophy. OSAS in childhood occurs equally in boys and in girls although some studies have suggested a higher prevalence in boys.

Apart from upper airway size, OSAS is probably determined by a complex myriad of factors including genetics, craniofacial morphology, neural control of the upper airway as well as respiratory control systems. Up to 40% of its variance can be attributed to genetic factors. There is often a family history of snoring or diagnosed OSAS. Inherited craniofacial structure abnormalities may explain in part the familial clustering of OSAS. Asian children may have a lower prevalence of OSAS compared to western populations, however the severity of OSAS may be greater.

8.4 Risk Factors

Atopy is also described to be a risk factor for habitual snoring, and in turn, OSAS in childhood. Children with multiple allergies including asthma, allergic rhinitis and atopic eczema should be screened for snoring and possible OSAS (Fig. 8.1 and Table 8.1).

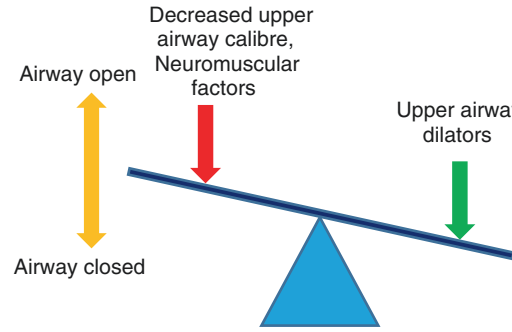

Fig. 8.1 Counterbalancing forces that influence airway patency. (Adapted from Thach, B. Neuromuscular control of the upper airway. In Beckerman, R et al., Respiratory control disorders in infants and children, Baltimore, Williams & Wilkins, 1990, pg 47)

Table 8.1 Factors and mechanisms contributing to the development of OSAS in childhood

Reduced Upper airway calibre—predominantly in the nasal, oropharyngeal, craniofacial areas	
Adenotonsillar hypertrophy	Note that the presence and severity of OSAS does not necessarily correlate with the tissue size
Micrognathia/Retrognathia	E.g. Pierre-Robin sequence
Macroglossia	E.g. Beckwith-Widemann syndrome
Midfacial hypoplasia	With or without craniofacial dysmorphic syndromes e.g., Craniosynostosis
Tissue infiltration	Adipose deposition in obesity, mucopolysaccharides in MPS
Reduced upper airway tone	
Muscle weakness	Muscular dystrophies, myopathies, Prader-Willi syndrome
Neurological disorders	Arnold-chiari malformation, hypotonic cerebral palsy
Reduced central ventilatory drive	
Brainstem lesions	Also contributing to reduced upper airway dilator muscle tone
Combination of multiple factors	
Down syndrome	Hypotonia, glossoptosis, obesity, midfacial hypoplasia, hypothyroidism

Table 8.2 Symptoms of OSAS in childhood

Night symptoms during sleep	
Habitual snoring	Snoring on all or most nights on a regular basis; typically defined as 3 or more nights of week. Note that the loudness of snoring does not necessarily correlate with the severity of OSAS
Pauses in breathing	Observed apnoea. These may also be described as episodes of snorting, gasping and choking during sleep
Paradoxical chest-abdominal movement	See-saw movement of chest and abdomen during breathing
Unusual sleeping positions	Usually hyperextension of neck
Restlessness in bed	Increased movement during sleep due to repeated change in position/posture of sleep
Diaphoresis	Sweatiness during sleep may be present, related to increased work of breathing and activity in bed
Nocturnal enuresis	Children with OSAS have higher risk for secondary enuresis which may resolve when OSAS is adequately treated
Day symptoms	
Mouth breathing and hyponasal speech, dry mouth	Due to adenoidal hypertrophy
Morning headaches	Due to carbon dioxide retention
Hyperactivity	This is a more common feature of poor sleep in children compared to hypersomnolence which is more common in adults
Behavioural changes	Mood swings, irritability, social withdrawal
Decreased school performance	Academic performance may deteriorate with untreated OSAS

8.5 Presenting Features

The most common presenting symptom of OSAS in childhood is regular (Habitual) snoring. Some parents may however not report snoring in their child if they sleep in separate rooms (Table 8.2).

8.5.1 OSAS in Childhood vs. Adulthood

OSAS in childhood is not simply adult OSAS in a smaller scale. They are quite different in many ways; Adult criteria for OSAS when

Table 8.3 Comparing childhood and adult OSAS

	Childhood OSAS	Adult OSAS
Age	Peak in preschool age	Increases with age
Gender	Generally equal in boys and girls. Some studies have described boys >girls	More in men and post-menopausal women
Body weight	Failure to thrive, normal or obese	Usually obese
Associated factors	Craniofacial abnormalities	Obesity
Daytime hypersomnolence	Usually absent	Present
Neurobehavioral	Hyperactivity and developmental delay	Impaired vigilance and cognitive impairment
Adenotonsillar hypertrophy	Often present	Rare
Airway obstruction	Persistent partial	Cyclical almost complete
Arousal	Usually absent. Microarousals may be present	Common, usually occurs at the termination of apnoea episodes
Sleep architecture	Usually normal	Decreased SWS

applied to children would fail to identify serious childhood OSAS and underestimate its severity (Table 8.3).

8.6 Diagnosis

The evaluation of a child with suspected OSAS includes a detailed history, physical examination, and appropriate investigations. A prompt and accurate diagnosis is important to ensure timely treatment is instituted, to prevent or avoid complications.

The history would entail details of medical problems, sleep, development and behaviour, as well as family history. Snoring is an important symptom, in addition to the other presenting features in the table above. Habitual snoring (usually defined as three or more night of snoring per week, on a regular basis) should alert the doctor to proceed with a focused evaluation of OSAS.

Physical examination is often normal. Findings of adenotonsillar hypertrophy, systemic and/or pulmonary hypertension, poor growth (or obesity) and other features that may have causative association e.g. craniofacial dysmorphism, hypotonia, or neuromuscular disorders.

Many attempts have been made to use various combinations of symptoms and signs and clinical scores/criteria, but none has been shown to reliably differentiate primary snoring from OSAS.

Some of the more common modalities used in the diagnosis and assessment of suspected OSAS include (Refer to chapter on sleep diagnostics):

1. *Audio and video recordings*

   Studies using various combinations of audio, video and clinical findings have shown a wide range of sensitivity and specificity. Inconsistent findings in different studies from different centres suggest more work needs to be done before these modalities can be effectively used as diagnostic tools in the evaluation of OSAS in children.
2. *Overnight pulse oximetry recording*

   This is a simple and relatively low cost method to screen for desaturation but does not determine the presence of OSAS. Not all respiratory events are associated with or result in desaturation. It also does not detect events that result in arousals before a desaturation occurs. This by itself would be of limited value in diagnosing OSAS.
3. *Home studies (abbreviated polysomnography)*

   Various modalities have been studied to evaluate their utility in the diagnosis of OSAS; these include pulse transit time (PTT), heart rate variability, inductance plethysmography, in various combinations, with or without pulse oximetry, have not been able to demonstrate good correlation with gold standard

overnight laboratory polysomnography. Some of these may be useful as a screening test to determine who needs to proceed with a full overnight polysomnography.

4. *Overnight polysomnography (Sleep Study)*

   This is the gold standard for the evaluation of OSAS in children. It is the only diagnostic technique that can quantitate the severity of OSA and related gas exchange abnormalities and sleep disturbances. It can also determine the risk of postoperative complications and also enables comparison for post-intervention evaluations should symptoms persist or recur after treatment. It is therefore important that the polysomnography be performed before any intervention is instituted in a child with OSAS. The polysomnography is also useful for the titration of CPAP in children already diagnosed to have OSAS. Data is however still lacking on identifying which polysomnographic parameter is associated with or predicts morbidity in childhood OSAS. The sleep study in children requires appropriate equipment and trained staff. The results also need to be scored and interpreted using age-appropriate criteria. The availability of such facilities especially in the Asian region is still fairly limited, especially facilities and expertise in the evaluation of paediatric OSAS. The role of nap studies and home studies with current conventional equipment is still limited in the assessment of childhood OSAS.

5. *Drug-induced sleep endoscopy (DISE)*

   This is a diagnostic tool to assess the upper airway in conditions that mimic natural sleep. This evaluates the exact area or areas of upper airway collapse during sleep that enables better selection of patients for appropriate surgical intervention. It is performed under sedation to simulate the dynamic state of the upper airway during sleep. Guidelines are being developed on who, where and how to perform DISE, including the modalities for monitoring. It is however important to note that sedation may not induce REM sleep where obstructive events tend to occur, and hence may not be entirely representative of what goes on during a normal night's sleep. As such this modality is unable to provide information for the entire night's sleep. The level of sedation and the technical skill of the endoscopist are essential factors for the success and accuracy of this procedure.

8.7 Severity Grading and AHI Classification

The most commonly used criteria for assessment of severity of OSAS is the Apnoea-Hypopnoea Index (AHI) (Table 8.4).

Unlike in adults, obstructive apnoea episodes are not normally common in children and hence the presence of an AHI of 1 or greater is considered abnormal. In older children above 12 years of age, an AHI of >5 may be taken as the threshold at the discretion of the attending doctor, taking into consideration the risk factors for OSAS, symptom presentation, complications as well as the overall condition of the child. It is also noteworthy that limiting our diagnostic assessment to

Table 8.4 Classification of severity of OSA in childhood

OSAS	Normal	Mild	Moderate	Severe
AHI (/h)	<1	1–5	>5–10	>10
SaO_2 nadir	≥92%	86–91%	76–85%	≤75%
Peak CO_2 (mmHg)	<53	55–59	60–64	≥65
Hypoventilation ($EtCO_2$ > 50) as %TST	<10%	10–24%	25–49%	≥50%

[a]If SaO_2<90% for >10% TST, place in next category

Ref: Carole LM et al., Am Rev. Resp Dis '92;146:1235

a single AHI cut-off would obviously be an oversimplification of this complex condition. It is perhaps necessary to develop a score that depicts the OSAS severity and prognosis, and would likely need to include multiple other parameters and associated comorbidities.

8.8 Complications

Childhood OSAS can result in behavioural and cognitive problems, attention deficit hyperactivity disorder, failure to thrive, enuresis, and even systemic hypertension, pulmonary hypertension and cor pulmonale.

Poor growth and failure to thrive is hypothesized to be related to increased work of breathing with increased baseline caloric expenditure. There is also suggestion that decreased production of growth hormone may be related to sleep fragmentation and also contribute to poor growth. Growth velocity increases after treatment of OSAS.

Enuresis may be a result of increased urine production from hormonal dysregulation associated with increased levels of catecholamines and frequent arousals. Enuresis often resolves with appropriate treatment of OSAS.

Behavioural and cognitive deficits has been described in children with OSAS. Snoring is also described to be associated with poorer academic performance. Sleep deprived children often exhibit hyperactivity and restlessness, more so than daytime hypersomnolence. Intermittent nocturnal hypoxia together with frequent arousals result in sleep fragmentation and these may lead to the development of neurobehavioral consequences. Reports have suggested that these deficits do improve with successful treatment of OSAS, although some may not fully resolve. More recent reports have demonstrated no improvement in cognitive function, through structured testing, in pre-school and primary school aged children after adenotonsillectomy, There is therefore concern that long term residual cognitive deficits may be a consequence of delayed diagnosis and treatment of childhood OSAS.

Cardiovascular complications of systemic hypertension and even pulmonary hypertension and cor pulmonale may result as a consequence of OSAS in childhood. Primary snoring itself has been described to be associated with elevation in systemic hypertension even in the absence of significant OSAS based on current polysomnographic criteria. These complications are fortunately less frequently seen with more awareness and earlier diagnosis and treatment of OSAS.

Sleep is essential to the body's reparative process and maintenance of overall health; untreated OSAS may be associated with poor sleep quality and resultant metabolic sequelae, including glucose metabolism disorders and the risk of developing diabetes. This together with cardiovascular risks may result in higher risks of strokes and heart attacks later in life, contributing to a reduced lifespan in adulthood. There is also demonstrable increase in healthcare utilisation in children with OSAS; particularly so in those younger than 5 years old. The severity of the OSAS also correlates directly with the total annual costs and independent to age. OSAS in childhood has also been associated with decreased health-related quality of life, which improves after adenotonsillectomy.

8.9 Treatment

8.9.1 Adenotonsillectomy (T&A)

Adenotonsillectomy is usually the first-line treatment in childhood OSAS in the presence of adenoid and tonsillar hypertrophy.

In otherwise well and healthy children, OSAS usually resolves in up to 75% to 100% after T&A. Persistent OSAS after T&A has however been reported to occur in up to 13 to 29% of children defined as low-risk patients, while it may persist in up to 75% in higher-risk patients such as obese children.

In the Childhood Adenotonsillectomy Trial (CHAT) study, children with mild to moderate OSAS (AHI ≤5) who underwent early T&A showed normalisation of polysomnography in 79% compared to 46% in the group with watchful waiting with supportive care. There was also significant reduction in symptoms and improvement in behaviour and quality of life in the treatment group.

Adenotonsillectomy for OSAS may present complications in some children; these include pulmonary oedema, hypoxaemia and bronchospasm. These are fortunately uncommon but those who may be at higher risk should undergo close monitoring peri- and post-operatively. The risk factors include:

1. Young age—especially below 3 years old
2. Severe OSA confirmed on polysomnography
3. Presence of cardiac complications e.g. Right ventricular hypertrophy
4. Failure to thrive
5. Significant obesity
6. Presence of craniofacial anomalies
7. Neuromuscular disorders

Source: American Academy of Pediatrics, Clinical Practice Guidelines. Diagnosis and management of childhood OSAS.

It is generally recommended that removal of both the adenoids and tonsils should be performed to avoid recurrence of symptoms even if one appears to be predominant. In addition, tonsillotomy (or partial tonsillectomy) has been shown to be have a much higher risk (more than three-fold) of OSAS recurrence compared to tonsillectomy.

In patients with concomitant enlarged nasal turbinates, the addition of radiofrequency reduction of the inferior turbinates during adenotonsillectomy has been shown to improve the AHI. However, the duration of effectiveness is variable and the therapy may need to be repeated if the turbinate hypertrophy recurs.

Patients with additional risk factors of OSAS such as obesity may still benefit from T&A but the relative risk and benefit should be evaluated by the attending doctor. There may be residual OSAS even after surgery.

OSAS symptoms may take up to 4 to 6 weeks to resolve after a T&A as there may be post-operative oedema. If there are persistent or residual symptoms, especially in the presence of additional risk factors, a follow-up sleep study is indicated, at least 6 weeks post T&A.

8.9.2 Positive Airway Pressure Therapy (CPAP/BiPAP)

Positive airway pressure serves to stent the airway open and overcome dynamic upper airway obstruction. Studies have shown that it improves polysomnographic findings in OSAS and also significantly improves symptoms and neurobehavioral function.

This may be considered for patients who are not surgical candidates for T&A or those with persistent OSAS post-T&A. It may also be a transitory management modality for those with severe OSAS while awaiting surgery, or for stabilisation of condition prior to T&A, with the aim to reduce the post-surgical complication risks.

Two modalities of positive airway pressure therapy can be used. There is no evidence that one is superior to the other and the practice and preference varies between different institutions. The settings should be set through a polysomnographic titration and long-term follow-up is necessary as the pressure settings may change over time as the child grows.

One of the main challenges with positive airway pressure in children is the interface—the size, shape and fit significantly impacts on the comfort, acceptance and hence compliance to use. Most masks are developed in western countries and not primarily designed to fit the Asian facial contours. Also, the range of masks available in some parts of Asia may be limited, contributed by the small market and few distributors as well as relative high cost.

Excessive leaks around the mask can compromise the effectiveness of positive airway pressure and also contribute to patient-ventilator dyssynchrony. Mouth breathing can be alleviated by the use of a chin strap. Dryness in the airway can be reduced with the use of a heated humidifier. Long term adverse effects of the mask include mid-facial hypoplasia and local skin irritation as well as pressure sores. Careful selection and training of caregivers in the appropriate application of the masks are vital in ensuring good outcomes which in turn positively reinforces compliance.

High-flow nasal cannula (HFNC) has been shown to reduce respiratory events, improve oxygenation, reduce heart rate, and may be effective for CPAP-intolerant children with moderate to severe OSA.

8.9.3 Weight Management

Weight loss can be significantly therapeutic in children with obesity and OSAS, in addition to its general health promoting effects. Many studies have demonstrated significant improvement in OSAS symptoms and polysomnographic criteria with weight loss; decreases in BMI z scores are associated with significant corresponding improvements in AHI values. Weight loss should be recommended as part of the management plan if the child is overweight or obese.

Adherence to weight loss programmes is always the biggest challenge in the young; multimodality interventions are often required, including dietary restrictions, physical exercise and psychological support.

8.9.4 Medical Treatment

- Topical intranasal corticosteroids

  Corticosteroids can reduce adenotonsillar tissue inflammation and proliferation in in-vitro models. They may be helpful in mild OSAS in lieu of T&A or in patients with residual mild OSA after T&A. Various topical steroids have been used for 4 to 6 weeks, showing a sustainable effect for up to 8 weeks or even several months. The optimal dosage and duration of treatment are however still unclear.
- Leukotriene receptor antagonists

  Treatment over 16 weeks has been shown to be able to reduce the AHI by a small margin of between 1 to 5/h.

  Combination anti-inflammatory medications with topical nasal steroids and Montelukast has been shown to improve AHI by a margin of over 3.6/h over a 12-week period in post-adenotonsillectomy children with residual mild OSAS.

8.9.5 Others

- Oral appliances

  Mandibular advancing devices and rapid maxillary expansion devices may be useful in selected patients. These are generally used in adults and there have only been limited studies in childhood OSAS. Further studies are needed to determine the clinical indications and patient selection for optimal intervention with these and other oral appliances in childhood OSAS.
- Myofunctional therapy

  Myofunctional therapy aims to train patients to improve labial seal, lip tone and the use of nasal breathing as well as to promote favourable positioning of the tongue within the oral cavity. It involves a structured re-education programme of specific oropharyngeal exercises performed daily. Data suggests some improvement in AHI although there is much heterogeneity in interventions, and the results are marginal. This treatment itself has few complications and is certainly non-invasive, but does require cooperation from the child and compliance to the exercise routine over extended periods of time. Further studies are warranted before a formal recommendation can be made on its use as treatment modality in childhood OSAS (Fig. 8.2).

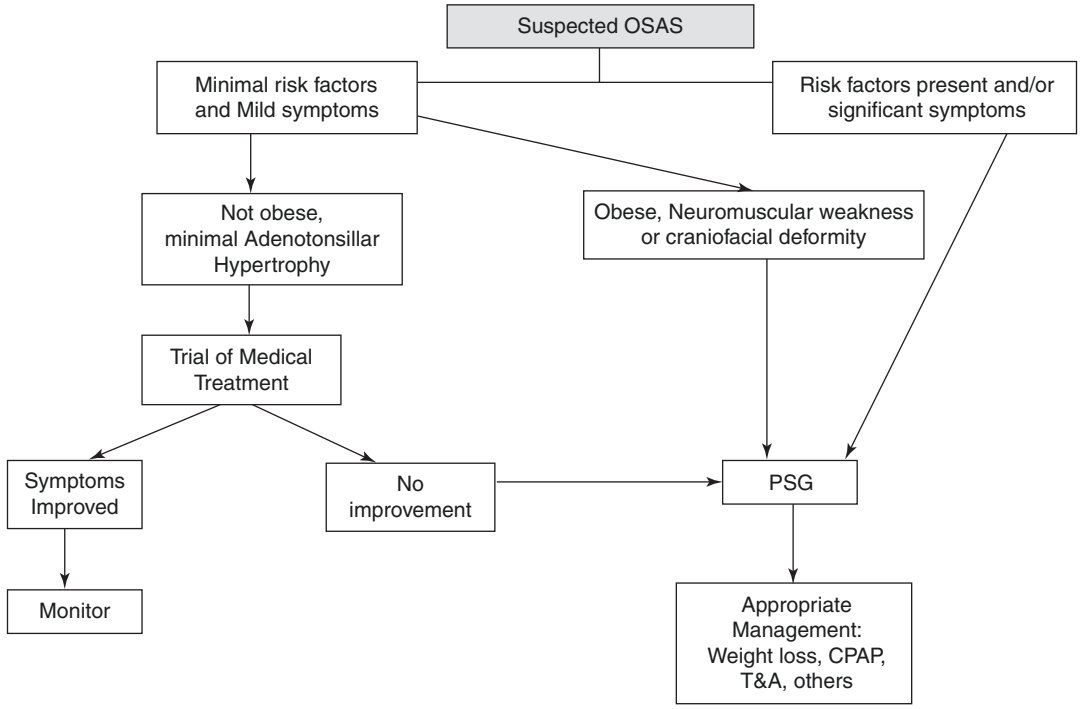

Fig. 8.2 Management Algorithm for Childhood OSA

8.10 Clinical Course and Prognosis

Most children with snoring do improve beyond the peak age of adenotonsillar hypertrophy, after 4 to 8 years old. The persistent of symptoms and that of OSAS may be determined by the chronicity and severity of OSAS as well as the presence of risk factors, such as obesity.

Children with OSAS that is treated, may recur with OSAS later in adulthood if there is development of additional risk factors such as obesity.

Complications of childhood OSAS such as learning and behavioural problems do often improve with treatment, but the course may be determined by the severity and also delay in treatment of the OSAS; some studies have suggested that some of the sequelae may not be totally reversible if treatment is delayed.

OSAS in childhood, especially if severe and untreated, may be a risk factor for the development of chronic diseases later in adulthood; these can include hypertension, diabetes, coronary heart disease and even strokes.

8.11 Some Potential Research Areas

- Development of diagnostic and screening tools for childhood OSAS

  The availability of low-cost, high-sensitivity and high specificity modalities for the diagnosis and assessment of OSAS would be useful especially in developing countries where the current gold-standard overnight polysomnography is not easily available, and where wait-times for a sleep study can be very long. These could also be used as screening

tools to determine who needs to be referred for a formal polysomnography.
- Evaluation of newer imaging techniques in guiding treatment choices, pre- and post-surgery assessment and management.
- Identification of potential biomarkers as correlates of disease severity and morbidity to guide management and follow-up.
- Studies on the prevalence and sequelae of OSAS in different parts of the world, using a common protocol to better compare data across different sites.
- Long term clinical course of childhood OSAS and its relationship with OSAS in adulthood, as well as the chronic diseases in adulthood, such as hypertension, diabetes, coronary heart disease and stroke.

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9 Central Sleep Apnoea Syndromes in Infants

Rosemary S. C. Horne and Flora Y. Wong

9.1 Introduction

Respiratory instability during sleep is common in infancy, especially in those infants born preterm. This respiratory instability, which manifests as periods of apnoea, is thought to be due to immaturity of the central and peripheral mechanisms that control breathing [1, 2]. During an apnoea there is a fall in heart rate and blood pressure and a concomitant surge in these when breathing is resumed. The effects of apnoea are more marked in infants born preterm as these infants also have prolonged immaturity of cardiovascular control, manifest as lower blood pressure, delayed blood pressure recovery following a cardiovascular challenge and impaired control of blood pressure, heart rate and cerebral oxygenation cross the first 6 months after term corrected age, when compared with age matched term infants [3–10].

Apnoeas are characterised as central, obstructive or mixed. *Central* apnoeas are defined as a cessation of nasal and oral airflow in conjunction with an absence of respiratory effort. *Obstructive* apnoeas are defined as the cessation of nasal and oral airflow in the presence of continued respiratory effort against airway obstruction. Central apnoeas (defined as pauses in breathing ≥10 s in duration) are common in infancy and can occur spontaneously, but occur more frequently after a movement [11, 12]. Traditionally, these central apnoeas have been considered benign as they are not associated with significant desaturation and occur in healthy infants [12]. Currently, the American Academy of Sleep Medicine (AASM) recommends a central apnoea be scored if the event is and at least one of the following is met: (1) The event lasts 20 s or longer. (2) The event lasts at least the duration of two breaths during baseline breathing and is associated with an arousal or ≥3% oxygen desaturation. (3) For infants younger than 1 year of age, the event lasts at least the duration of two breaths during baseline breathing and is associated with a decrease in heart rate to less than 50 beats/min for at least 5 s or less than 60 beats/min for 15 s [13, 14]. Using this definition, the frequency of central apnoeas declines with age, with the median number of events per hour declining from 5.5 (minimum 0.9; maximum 44.3) at 1 month of age to 4.1 (minimum 1.2; maximum 27.3) at 3 months [15]. The authors suggested these high rates of central apnoea may be simply due to the fact that the current definitions for central apnoeas used for older children are not appropriate for young infants.

Apnoeas can occur as isolated events or in a repetitive pattern termed periodic breathing.

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9.2 Apnoea of Prematurity

9.2.1 Epidemiology

Apnoea of prematurity is one of the most common diagnoses in the neonatal intensive care unit (NICU) [16]. An apnoea of prematurity episode is usually defined as a cessation of breathing for 20 s or longer, or a shorter pause accompanied by bradycardia (<100 bpm), cyanosis, or pallor. In practice, many apnoeic events in preterm infants are shorter than 20 s, because briefer pauses in airflow may result in bradycardia or hypoxaemia [16].

Apnoea of prematurity is extremely common, occurring in more than 85% of infants born prior to 34 weeks of gestation. The incidence of apnoea of prematurity is inversely related to gestational age occurring in: 3–5% of term-born infants, 7% of infants born at 34–35 weeks of gestational age (GA), 15% of infants born at 32–33 weeks of GA, 54% of infants born at 30–31 weeks of GA and nearly 100% of infants born less than 29 weeks of GA [17, 18]. There are also marked changes in apnoea frequency with postnatal age, with few events in the first week of life, then a progressive increase in weeks 2–3 which plateau in weeks 4–6 and then decrease in weeks 6–8 [19].

9.2.2 Aetiology

Preterm infants have a reduced ventilatory response to CO_2 compared to infants born at term, and respond to increased CO_2 levels with an increase in tidal volume, but little or no increase in respiratory frequency [20]. Furthermore, infants who exhibit apnoea have a reduced response to CO_2 compared to who do not exhibit apnoeic periods. In addition, baseline $PaCO_2$ is only 1 to 1.5 mmHg above the apnoeic threshold and thus only very small changes in $PaCO_2$ can predispose to apnoea. Furthermore, respiratory instability is more marked in active sleep compared to quiet sleep, a sleep state in which preterm infants spend more of their time [21]. Vulnerable respiratory control is exacerbated by a compliant chest wall and reduced lung mechanics which lead to reduced functional residual capacity (FRC) [22]. Reduced FRC is further reduced by the reduced muscle tone which occurs during sleep.

9.2.3 Clinical Significance

Apnoea of prematurity is accompanied by both bradycardia and desaturation. The hypoxia associated with apnoea has detrimental effects on developing tissues and organs and can have long-term or permanent impairments [23–26]. Treatment of apnoea of prematurity, such as respiratory support and caffeine, are only partially successful in reducing bradycardia and desaturation [27] and the effects of apnoea of prematurity [28, 29]. A number of studies that have examined changes in cerebral haemodynamics associated with apnoea of prematurity. These have shown that both cerebral blood volume (CBV) and cerebral blood flow velocity fall [30], and the falls are greater when the apnoea is also associated with bradycardia [30, 31]. Although central apnoeas are more common than obstructive apnoeas in infants, obstructive apnoeas have been reported to be more common in the first days of life [32], when intraventricular haemorrhage usually occurs [17]. Obstructive apnoeas have been associated with greater falls in CBV compared to central and mixed apnoeas [33]. The decreases in both cerebral haemoglobin oxygenation index and CBV were greater during mixed and central apnoeas when infants slept supine compared to prone [34] and apnoea duration is positively associated with the decrease in CBV [35]. In a study which classified events as isolated bradycardias (heart rate <80 bpm), isolated hypoxaemia (oxygen saturation (SpO_2) < 75%), simultaneous (within 4 s) bradycardia and hypoxemia, bradycardia followed by hypoxaemia and hypoxaemia followed by bradycardia, isolated hypoxaemias were the most common events and isolated bradycardias the least common [36]. Falls in cerebral oxygenation were smallest for isolated bradycardias and largest for combined bradycardia and hypoxaemia events.

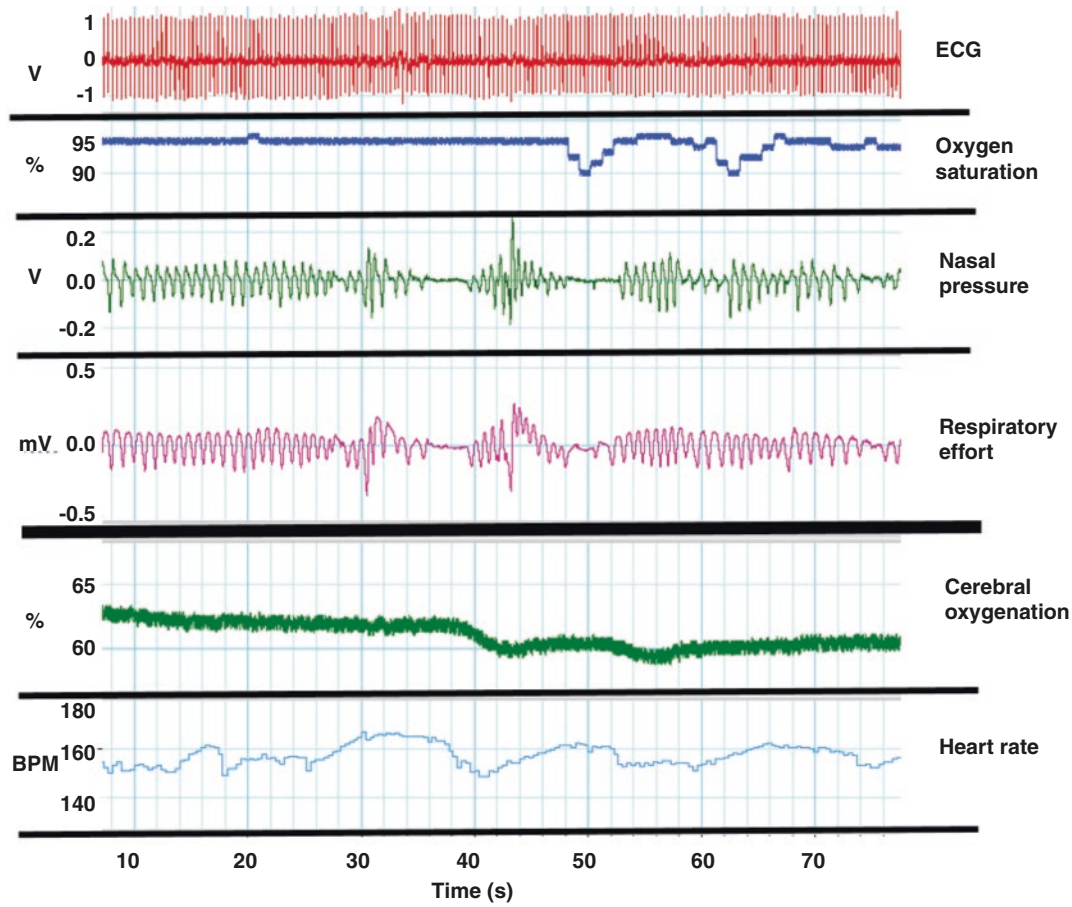


Fig. 9.1 Polysomnographic example of the effects on oxygen saturation, cerebral oxygenation and heart rate of a 3.7 s central apnoea in active sleep in an infant born at 30.2 weeks gestational age and studied at 32.3 weeks

However, the majority of infants were able to maintain their cerebral oxygenation >60% despite severe falls in SpO_2 [36]. Examples of falls in heart rate, SpO_2 and cerebral oxygenation following central apnoeas in preterm infants are illustrated in Figs. 9.1 and 9.2.

Cerebral oxygenation measurements are not routine in most NICUs. Studies have identified that in general falls in cerebral oxygenation index in association with apnoeas >4 s in duration were not well correlated with falls in arterial oxygen saturation (SpO_2) when falls in SpO_2 were small (<3%) [37]. However, when falls in SpO_2 associated with apnoeas >20 s in duration were >85%, SpO_2 and cerebral oxygenation were well correlated, and that falls in SpO_2 >85% could be used as an indication of clinically significant falls in cerebral oxygenation [38]. A more recent study identified that even the most sensitive oximeter setting of a 2 s averaging time underestimated the frequency of bradycardias, missing around 10% of bradycardias and showing significant delays in detecting bradycardias [39]. The study also identified that the falls in cerebral oxygenation during bradycardias were greater in very preterm infants (born ≤31 weeks GA) compared to those in late preterm infants (born >32 weeks GA). Even mild bradycardias (heart rate dropped to 60–80% of baseline) were associated with falls in cerebral oxygenation. The authors suggested that routine NIRS monitoring of cerebral oxygenation in NICUs may increase staff awareness for inter-

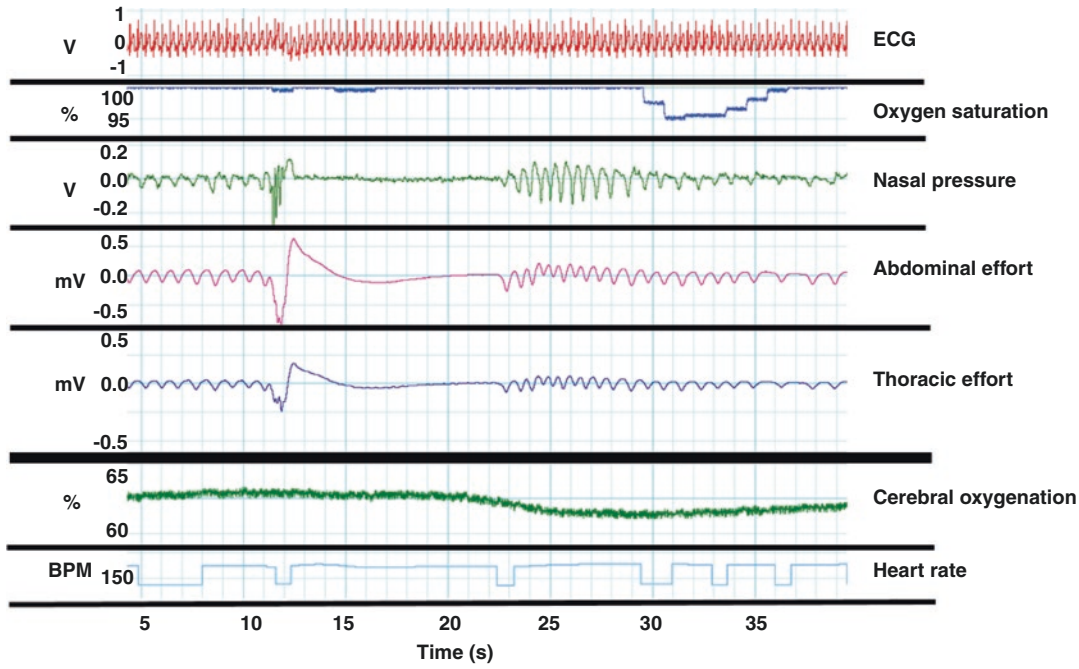


Fig. 9.2 Polysomnographic example of the effects on oxygen saturation, cerebral oxygenation and heart rate of a 10.1 s central apnoea in quiet sleep in an infant born at 31 weeks of gestational age and studied at 38.3 weeks whilst in the Special Care Nursery

ventions to reduce the repetitive falls in cerebral oxygenation in preterm infants [39].

It is important to note that the magnitude and frequency of the apnoeic events are frequently underestimated in the NICU due to the current clinical settings of pulse oximeter monitors, which often are set with long averaging times and to alarm apnoeas of at 8–20 s duration. In one study 1958 apnoeas with desaturation <80% were recorded using an averaging time of 3 s, compared to only 339 when using a more conventional averaging time of 16 s [40]. In a study which used a 2 s averaging time and which counted apnoeas where oxygen saturation fell to ≤80% for between 3–10s, between 50–100 events/day were recorded [23]. Definitions for infant apnoea vary greatly in the literature. In scoring of sleep studies for children over a year of age, respiratory events representing the loss of two respiratory cycles are counted as apnoea with the qualification of an associated oxygen desaturation required if the event is central [13, 14]. The length of two respiratory cycles varies between 3 and 4.8 s in preterm infants and 4.2 and 5.5 s in term infants at birth depending on sleep state and the method of calculation [41]. It has therefore been suggested that a 5-s cut-off for defining central apnoeas in an infant is not unreasonable [41].

9.3 Short Central Apnoeas

Central apnoeas are frequent in infants, particularly in preterm born infants and as highlighted above can be associated with clinically significant falls in oxygen saturation and cerebral oxygenation. There have been limited studies that have examined the effects of short apnoea in preterm born infants after hospital discharge. A study investigating the longitudinal effects of persistent short apnoeas, studied 24 infants born between 27–36 weeks GA who underwent daytime polysomnographic studies at 2–4 weeks corrected age (CA), 2–3 months CA and 5–6 months CA [42]. Changes in heart rate, oxygen saturation and cerebral tissue oxygenation index were assessed for

all apnoeas lasting ≥3 s. The study found that although overall apnoea frequency declined with age, apnoeas occurred in all infants at 2–4 weeks CA, 2–3 months CA and 5–6 months CA. Furthermore, there were no effects of GA at birth on the frequency or duration of apnoeas at any age studied. Interestingly, the effects of apnoeas on the falls in heart rate and cerebral oxygenation were more marked at the older ages than at 2–4 weeks CA. In contrast, apnoea duration had more marked effects on these variables at the younger ages [42]. The study showed that apnoea persists in infants born preterm after discharge home and similar to studies before term-equivalent age, apnoeas are associated with falls in cerebral oxygenation. When the data were compared to age-matched term-born infants, apnoea duration was not different between preterm-born and term-born groups, however the decline in apnoea index with postnatal age observed in the term-born infants was not seen in the preterm-born infants. Importantly, when compared to term infants, falls in cerebral oxygenation associated with apnoeas were greater in the preterm-born infants at all three ages studied [43].

9.3.1 Treatment

There is no consensus as to when to initiate therapy for apnoea of prematurity, however the first line of treatment is usually a methylxanthine [44] Methylxanthines, such as caffeine, aminophylline and theophylline have been used since the 1970's for the treatment of apnoea of prematurity and also to facilitate extubation and weaning off mechanical ventilation [45, 46]. Methylxanthines cross the blood-brain barrier [47] and their primary action is to antagonise the A_1/A_{2a} adenosine receptors in the CNS. Methylxanthines improve apnoea of prematurity by increasing minute ventilation and improving both hypercapnic and hypoxic ventilatory drive [48, 49].

Today caffeine is the most commonly used methylxanthine in neonatal units worldwide [50]. Caffeine's universal acceptance followed the 2006 CAP (Caffeine for Apnoea of Prematurity) randomised control trial, which compared caffeine citrate (20 mg/kg loading dose of caffeine citrate followed by 5 mg/kg/day) with placebo in very low birth weight preterm infants. The study demonstrated both significant short-term benefits of reduced incidence of bronchopulmonary dysplasia, medically and surgically treated ductus arteriosus, and long-term benefits of improved rates of survival without neurodevelopmental delay and significantly reduced incidences of cerebral palsy at 18–21 months [29, 51]. Improved microstructural development of white matter has been demonstrated in a subsample of these children who underwent brain magnetic resonance imaging (MRI) at term equivalent age, a finding which may explain the improved neurodevelopmental outcomes [52]. However, when reassessed at 5 years of age there was no longer any difference in rate of survival without disability between children treated with caffeine and those that were not [53]. A recent study confirmed the safety of maintenance doses up to 10 mg/kg/day in extremely preterm infants for longer durations than recommended on the drug label [54]. Other studies have suggested that higher dose regimens (loading doses up to 80 mg/kg, maintenance doses of 10–20 mg/kg/day) have been shown to be more effective in reducing apnoea and preventing extubation failure compared to conventional doses [55]. Higher average daily doses of caffeine have also been associated with improved neurodevelopmental outcomes [56]. However, there have been some concerns about adverse effects of high-dose caffeine with one study reporting a higher incidence of cerebellar haemorrhage with early high-dose caffeine compared to standard dosing, but there was no difference in developmental outcomes at 2 years [57]. Further randomised controlled trials are necessary to determine the optimal dose of caffeine to treat apnoea of prematurity to optimise neonatal outcomes [44].

In the immediate postnatal period O_2 can trigger apnoea as the peripheral chemoreceptors have not had time to adjust to the higher O_2 levels of extrauterine life. After this initial period, O_2 therapy can be used to reduce the hypoxia associated with apnoea. Nasal continuous positive airway pressure (CPAP) at 4 to 6 cm H_2O improves

FRC and oxygenation [21, 22]. Heated humidified high-flow nasal cannula (HHFNC) at >2 L/kg/min provides similar effects to CPAP, using both O_2 and room air [22]. In preterm infants born at 30.0 ± 3.2 (standard deviation) weeks' gestational age and studied at 38.1 ± 4.4 weeks' postconceptional age, supplemental low flow O_2 delivered via nasal cannula at 0.25 L/min increased the amount of quiet sleep and decreased the amount of active sleep, apnoea index and also the amount of periodic breathing [58].

9.3.2 Research Gaps

As highlighted above studies are still required to elucidate the optimum dose of caffeine to optimise developmental outcomes to treat preterm infants with apnoea of prematurity. Studies are also required to determine if HHFNC is more advantageous than CPAP and if nasal intermittent positive pressure ventilation (NIPPV) is effective in reducing apnoea of prematurity symptoms. Anaemia may exacerbate apnoea by reducing the oxygen-carrying capacity of the blood and thus decreasing oxygen delivery to the brain. There have been limited studies to confirm that blood transfusions reduce apnoea in the short-term and none which have examined the long term effects on reducing apnoea and improving developmental outcomes [44].

While apnoea of prematurity is treated vigilantly in the NICU, it is unknown whether recurrent short apnoeas of 3–10 s, with relatively brief bradycardia and mild hypoxaemia in preterm infants are harmful and if treatment is warranted for the short apnoeas. Limited data suggest that the total number of days with apnoea and resolution of episodes at more than 36 weeks of postmenstrual age (PMA) are associated with worse neurodevelopmental outcome in preterm infants [24, 25]. In addition, levels of cerebral oxygenation of <55% in infants born <32 weeks GA, when measured by adult NIRS probes and <65% when measured with neonatal/paediatric probes, have been associated with adverse cognitive outcomes at 2 years of age [59]. Studies are urgently needed to identify if the short apnoeas experienced while in the NICU and after hospital discharge contribute to the neurodevelopmental deficits which are commonly associated with preterm birth.

9.3.3 Summary

In summary, both apnoea of prematurity and short apnoeas are extremely common in infancy, particularly in infants born preterm. Apnoea of prematurity in the NICU is actively treated, however the majority of apnoeas are short and do not trigger alarms and so go undetected. Even short apnoeas are associated with bradycardia, peripheral desaturation and falls in cerebral oxygenation, however their contribution to developmental outcomes requires further research.

9.4 Periodic Breathing

9.4.1 Epidemiology

Periodic breathing episodes are defined as 3 or more sequential apnoeas lasting >3 s separated by no more than 20 s of normal breathing [13, 14, 60]. Periodic breathing is common in term-born infants in the first 2 weeks of life, however less than 1% of total sleep time is spent in periodic breathing and it usually resolves with increasing postnatal age [61]. In preterm infants after term-equivalent age, periodic breathing is more prevalent, with one early study reporting an increased incidence of periodic breathing at 52 weeks PMA (i.e. 3 months CA) but a similar incidence at 64 weeks PMA (i.e. 6 months CA) compared to term-born infants [62]. At 40 weeks the density of all apnoeas in total sleep time was 2.5 times higher in the preterm group 126/100 min vs. 49/100 min in the term infants [62]. A study of 24 preterm infants born between 27–36 weeks GA, examined the incidence and consequences of periodic breathing in infants studied at 2–4 weeks CA, 2–3 months corrected age (CA) and 5–6 months CA [63]. Although all preterm infants had been discharged home with no clinical concerns of respiratory instability, a total of 261 indi-

vidual episodes of periodic breathing were detected: 164 at Study 1, 62 at Study 2 and 35 at Study 3; 22 of the 24 infants (92%) exhibited periodic breathing during at least one of the three studies: 19 infants (79%) at 2–4 weeks corrected age (CA); 12 (50%) at 2–3 months CA and 10 (42%) at 5–6 months CA. Seven infants (29%) exhibited epochs of periodic breathing at all three studies and 10 infants (42%) at Studies 1 and 2. In term born infants studied at matched ages a total of 95 individual episodes of periodic breathing were detected; 64 at Study 1 at 2–4 weeks (one infant had 35 individual episodes), 24 at Study 2 at 2–3 months and 7 at Study 3 at 5–6 months. Eleven of the 17 infants (59%) exhibited periodic breathing during at least one of the three studies: 10 infants (79%) at 2–4 weeks; 7 (41%) at 2–3 months and 5 (29%) at 5–6 months. Four infants (24%) exhibited epochs of periodic breathing in all three studies and seven infants (41%) at Studies 1 and 2 [43].

9.4.2 Aetiology

Periodic breathing in the preterm infant is likely the result of several interacting mechanisms including chemoreceptor hypersensitivity and impaired gas exchange characteristics of the immature lung [2]. A recent study in preterm infants followed longitudinally from 32–36 weeks postmenstrual age (PMA) to 6 months post-term CA assessed ventilatory instability, using measurements of loop gain. Loop gain represents the sensitivity of the negative feedback loop that controls ventilation and can be defined as the ratio of the ventilatory response to the disturbance that elicited the response. A high loop gain represents a hypersensitive ventilatory control system, where a small disturbance leads to a large corrective response, ultimately causing cyclical oscillations in breathing such as occur in periodic breathing. The study showed that loop gain fell with postnatal age and was correlated with the decline in periodic breathing. Furthermore, those infants who continued to periodic breath at 6 months CA age had higher loop gain at 32–36 weeks PMA [64].

9.4.3 Clinical Significance

Because of its high prevalence, and no strong associations with significant hypoxia or bradycardia, the traditional view of periodic breathing is that it is simply due to immaturity of respiratory control and is benign [2]. However, the small number of studies, which have assessed the impact of periodic breathing, have found that repetitive short apnoeas can be associated with falls in both SpO_2 and cerebral oxygenation. A study of a single preterm infant born at 27 weeks GA and studied at 37 weeks PMA showed significant cyclical changes in cerebral blood volume during episodes of periodic breathing [65]. A study in 10 term born infants studied at 6–8 weeks postnatal age also demonstrated that periodic breathing episodes >1 min in duration were associated with cyclical variations in haemoglobin oxygenation index [66]. These cyclic variations represent changes in CBV, and these occurred in 42% of episodes and were correlated with changes in heart rate [66].

There has been limited investigation of the short- and long-term consequences of periodic breathing after preterm infants are discharged home. The study by Decima et al., found that periodic breathing was associated with repetitive falls in cerebral tissue oxygenation index, heart rate and SpO_2 as illustrated in Fig. 9.3, and these were apparent for up to 6 months CA in some infants [63]. When the data were compared to age matched term-born infants, the time spent in periodic breathing decreased with increasing PNA in both groups, however the falls in cerebral oxygenation associated with periodic breathing were greater at 2–3 months and 5–6 months CA in the preterm-born group [43].

Whilst the clinical significance of the repetitive falls in cerebral oxygenation in these infants remains unknown, it has been shown that a 10% reduction in cerebral oxygenation is of clinical concern for the development of cerebral hypoxic injury in preterm infants in NICU [67]. Cerebral tissue oxygenation index values fell by ≥10% of the baseline values in preterm-born infants at 2–3 and 5–6 months CA, while term-born infants did not experience these large changes at any age studied [43]. These findings, coupled with the

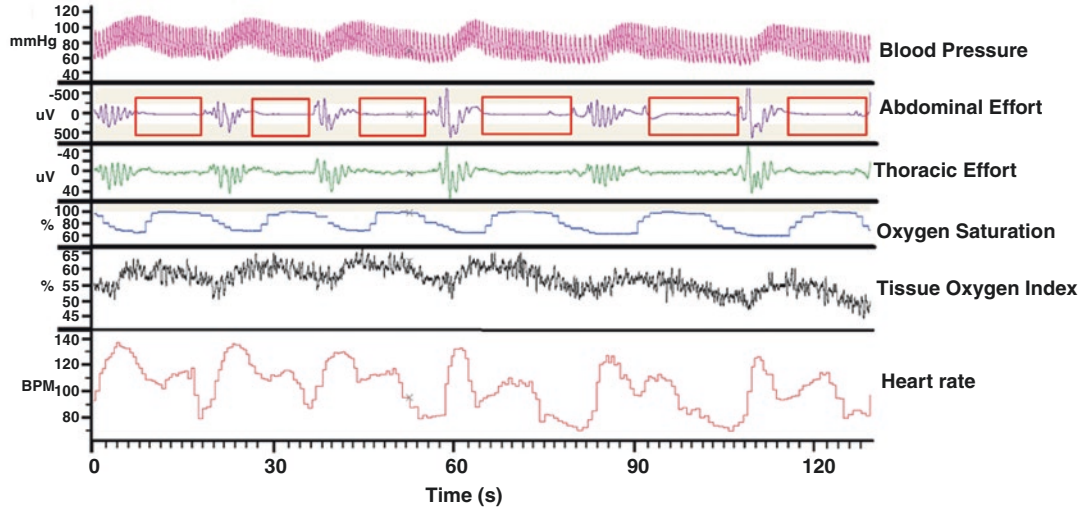


Fig. 9.3 Polysomnographic example of the effects of periodic breathing in an infant studied at 2–4 weeks post-term corrected age after discharge home. The short central apnoeas, indicated by the red boxes, are associated with repetitive oxygen desaturation, falls in cerebral tissue oxygen index to 55% (as measured with Near Infrared Spectroscopy), and repetitive bradycardia which worsens over time. This infant spent 28% of his total sleep time in periodic breathing. Note: lag time of falls in oxygen saturation is due to physiological and signal processing factors

increased frequency of both periodic breathing and apnoea, in the preterm group across the first 6 months CA suggest that even clinically well preterm infants are exposed to significantly greater levels of cerebral hypoxia compared to those born at term. It is well reported that obstructive sleep apnoea in children and adults is associated with neurocognitive deficits and the repetitive hypoxic events associated with this condition have been proposed as the primary mechanism. It is also possible that postnatal intermittent hypoxia can affect cardiovascular control beyond the neonatal period with studies in both rodent models [68] and human infants [69] demonstrating this. Further studies with neurodevelopmental follow-up in this population are required to ascertain if these brief falls in cerebral oxygenation with periodic breathing are associated with the neurocognitive deficits that are more prevalent in infants born preterm.

In addition, population cohort studies show that obstructive sleep disordered breathing is 3 to 6 times more likely in children who were born preterm and whether periodic breathing in infancy is a precursor to sleep disordered breathing later in life is a question requiring further research [70, 71].

9.4.4 Treatment

Periodic breathing is not routinely treated in preterm infants whilst in the NICU, however treatments for apnoea of prematurity (caffeine, CPAP and high-flow O_2) are also effective in reducing the incidence of periodic breathing [50].

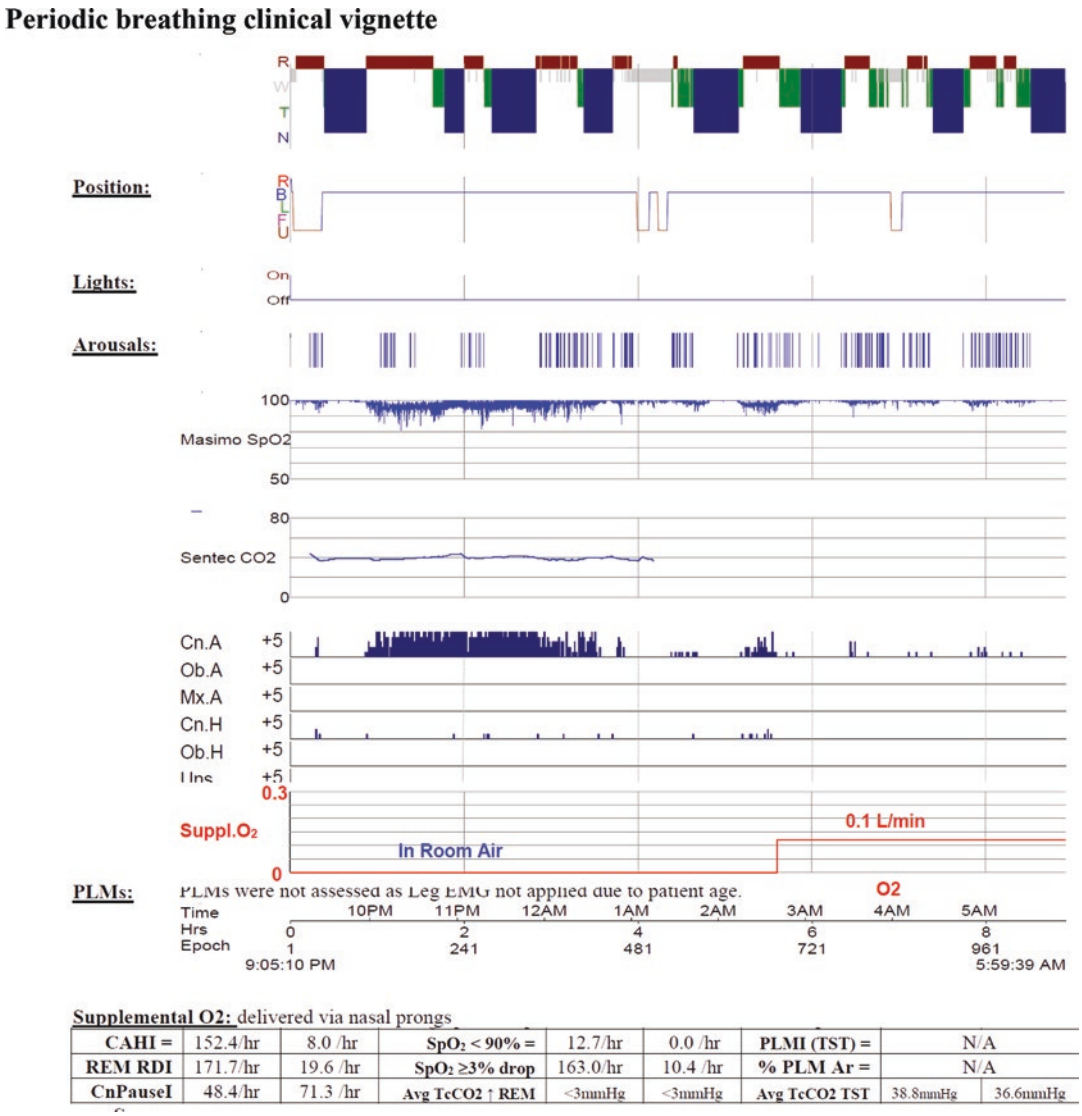
9.4.5 Research Gaps

Unlike apnoea of prematurity there is currently little evidence to associate periodic breathing with adverse developmental outcomes and further research is urgently needed.

9.5 Periodic Breathing Clinical Vignette

Figure 9.4 shows a sleep study report of an infant born at 29 weeks of gestational age and studied at 3 months of age. The infant was referred for assessment of central sleep apnoea.

The parent reported a normal night of sleep with 7.7 h of sleep available for analysis, with a feed at about 1 am. The study showed good sleep



Supplemental O2: delivered via nasal prongs

CAHI =	152.4/hr	8.0 /hr	**SpO_2 < 90% =**	12.7/hr	0.0 /hr	**PLMI (TST) =**	N/A	
REM RDI	171.7/hr	19.6 /hr	**SpO_2 ≥3% drop**	163.0/hr	10.4 /hr	**% PLM Ar =**	N/A	
CnPauseI	48.4/hr	71.3 /hr	**Avg TcCO2 ↑ REM**	<3mmHg	<3mmHg	**Avg TcCO2 TST**	38.8mmHg	36.6mmHg

Fig. 9.4 Periodic breathing clinical vignette

efficiency and normal sleep architecture for age. All sleep was supine. The arousal index was appropriate for age at 14.8/h overall with 57% being spontaneous arousals and 43% due to respiratory events. Nasal airflow was demonstrated. There were quiet breath sounds, no snoring and no increased work of breathing. Heart rate remained within normal limits throughout the study.

There was 4.8 h of sleep in room air. During this time the arousal index was 12.7/h with 61% due to respiratory events. There were no obstructive events. There were very frequent central events and periodic breathing in all sleep states. The central apnoea hypopnoea index (CAHI) was elevated at 152.4/h with central apnoeas associated with mild to moderate desaturation and occasional arousal. Average duration of central apnoeas was 6 s with the longest recorded being 12 s, both of which are within normal limits. There was frequent periodic breathing, which comprised 41% of the diagnostic portion. SpO_2 levels returned to normal between events with a mean SpO_2 of 98% and 1% of the time being spent <90%. The CO_2 was normal.

Supplemental oxygen at a rate of 0.1 L/min was initiated at 02:45 with 2.9 h of sleep on of oxygen. The arousal index was 18.1/h but with 21% now being due to respiratory events. There were no obstructive events. There was a significant reduction in the number of central events on oxygen with the central apnoea hypopnoea index (CAHI) decreasing to 8.0/h. Events mainly occurred in REM sleep, with NREM breathing pattern mostly normalising. The central events were associated with brief and mild desaturation with a nadir of 93%. Periodic breathing comprised 18% of the sleep time when on oxygen. The CO_2 remained normal.

Treatment: The baby was sent home on 0.125 L/min of oxygen with saturation monitoring and follow up with oximetry to track the expected improving course of this condition with time.

9.6 A Note on Obstructive Apnoea in Infants

Obstructive apnoeas are reported to be rare in infancy [15, 72]. However, snoring is reported to be common, with prevalence rates ranging from 5.6% to 26% [73–76]. These wide ranges in prevalence may have been due confounders with some studies including infants with colds and others studying different ethnicities. In a study of healthy predominantly Caucasian children aged 0–3 months a prevalence of 9% has been reported [77]. A significantly greater proportion of 2–3 month old infants were reported to snore habitually than 0–1 month old infants [77]. Cognitive ability at 6 months of age was found to be lower in those infants who began snoring frequently (≥3 nights/week) within the first month of life [78].

9.7 Summary

In summary, periodic breathing is very common in infancy, particularly in infants born preterm. Periodic breathing is considered to be a normal manifestation of immature respiratory control which improves with age. Because the apnoeas are short periodic breathing has been considered benign and is not routinely treated. However, there is growing evidence that periodic breathing persists well past term equivalent age in some infants and is associated with clinically significant falls in cerebral oxygenation and may contribute to neurological deficits.

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10 Sleep-Related Hypoventilation Syndromes

Aroonwan Preutthipan and Teeradej Kuptanon

During sleep, ventilation in a normal man is generally decreased. The tidal volume and respiratory rate are both reduced compared to wakefulness. Minute ventilation is significantly less in all stages of sleep, particularly in rapid-eye-movement (REM) sleep. The tidal volume in REM sleep is reduced to 73% of the level during wakefulness [1]. Moreover, reduction in upper airway muscle tone during sleep results in increasing upper airway resistance and risk of obstructive sleep apnea. Hypoxic and hypercapnic ventilatory drives also decrease during sleep. As a result, normal adults and children when asleep have a reduction in oxygen saturation and increased carbon dioxide levels. These physiologic changes of hypoventilation while sleeping will become more obvious in patients with respiratory compromises. In other words, polysomnography or oxygen saturation and carbon dioxide monitorings during sleep are the most helpful investigation since it allows us to capture hypoxemia and hypercapnia in the earliest stage of disease progression.

According to the third edition of the International Classification of Sleep Disorders (ISCD-3) revised by the American Academy of Sleep Medicine in 2014, the criteria of sleep-related hypoventilation disorders require demonstration of elevated PCO_2 levels, either by direct determination with arterial blood gases or, more commonly, by proxy measures such as end-tidal or transcutaneous CO_2 [2]. ISCD-3 have classified sleep-related hypoventilation disorders into 6 sub-categories including congenital central alveolar hypoventilation syndrome (CCHS), obesity hypoventilation syndrome (OHS), late-onset central hypoventilation with hypothalamic dysfunction, idiopathic central alveolar hypoventilation, sleep-related hypoventilation due to medications or substances and due to medical disorders [2]. In this chapter we will focus on the first two sub-categories, CCHS and OHS, which are more commonly found in children.

10.1 Congenital Central Alveolar Hypoventilation Syndrome (CCHS)

10.1.1 Vignette of Typical Presentation/ Real-Life Example

A Thai baby girl was born by cesarean section at the gestational age of 40 weeks with a birth weight of 4040 g. When she was 5 weeks old, she was noticed to have apnea and cyanosis. As a result, she was intubated and put on mechanical ventilation. Many trials of extubation were

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performed but failed. It was noted that without intubation, she was able to breathe by herself for the first 3–9 days and then decompensated and required respiratory support with mechanical ventilation again and again.

When she was asleep, her respiratory rate was slow at the rate of 18–20/min. She was noted to stop breathing and her body was turning blue. At a previous hospital she was supported with low flow oxygen nasal cannula. Measurements of arterial blood gases were made many times, some of which showed that her pH was 7.18, $PaCO_2$ was increased to 76 mmHg. In one occasion the $PaCO_2$ level was raised to 200 mmHg. Over the first 5 months of life, she had been treated in two provincial hospitals for unknown causes of respiratory failure with intubations and mechanical ventilation followed by extubations as vicious cycles.

To diagnose congenital central hypoventilation syndrome (CCHS), a genetic test using polymerase chain reaction (PCR) followed by direct sequencing of the exon 3 of the PHOX2B gene was performed. The result showed that there were 25 repetitions of polyalanine allele in addition to the normal allele with 20-alanine (GCG) residues or designated as 20/25. Genetic tests on her parents were undetected for such abnormality. Primer sequences are as follows: forward 5′-CCAGGTCCCAATCCCAAC-3′ and reverse 5′-GAGCCCAGCCTTGTCCAG-3′.

Polysomnography was performed. When fully awake, she breathed normally with RR 40/min, end-tidal CO_2 40 mmHg and SpO_2 96–98% in room air. When she slept, she breathed slower and shallower. RR decreased to 28–30/min. Central apnea was demonstrated on polysomnographic monitoring. She was found to have central apnea index of 2.8 events per hour and central hypopnea index of 30.5 events per hour. The maximum level of end-tidal CO_2 was 55 mmHg. Prolonged desaturation with nadir SpO_2 of 78% were noted. The duration of end-tidal CO_2 greater than 50 mmHg was longer duringnon-REM than REM sleep.

A tracheostomy was performed. The mechanical ventilator setting was titrated under polysomnography. Because of the economic problems, a bi-level positive airway pressure ventilator which was manufactured to be used as non-invasive ventilators were tried and used as an invasive ventilator via a tracheostomy [3]. She has been doing well with normal growth and development with long-term nighttime home mechanical ventilation.

10.1.2 Introduction

Congenital central hypoventilation syndrome (CCHS) was first reported in an infant in 1970 and the condition was then known as Ondine's curse [4]. It is a rare genetic disorder characterized by alveolar hypoventilation due to abnormally reduced or absent ventilatory response to hypercapnia and hypoxemia during sleep and/or wakefulness. The disease is the result of a mutation in the paired-like homeobox 2B (PHOX2B) gene, which plays a role in the development of the autonomic nervous system and regulation of neural crest cell migration. Autonomic nervous system dysregulation and disorders of neural crest origin are common associated findings in CCHS.

10.1.3 Epidemiology

The incidence of CCHS has been estimated to be 1 per 200,000 live births in France [5], 1 per 148,000 live births in Japan [6]. In Asia, case series of CCHS were reported from China [7], Hong Kong [8], Iran [9], Japan [10, 11], Korea [12], Taiwan [13–15], and Thailand [3]. Genotypes and phenotypes as well as the nature of the disease in Asia are similar to those reports from Europe and America.

10.1.4 Pathophysiology

The majority of PHOX2B mutations on chromosome 4p12 involve polyalanine repeat expansion mutations (PARMs) producing genotypes of 20/24 to 20/33 whereas the normal genotype is 20/20. The minority (10%) is heterozygous for non-polyalanine repeat mutations (NPARMs) and includes missense, nonsense, or frameshift mutations. Most expansion mutations occur de novo but in 5–10% parents will be mosaic for the PHOX2B mutations, with a 50% chance of transmitting the mutation at all [16]. Studies have demonstrated a relationship between the PHOX2B genotype and the CCHS phenotype. For example, patients with 20/27 to 20/33 genotype and NPARMs typically require 24-h continuous ventilatory support. Hirschsprung disease has been found more common in NPARMs than PARMs genotype [16].

10.1.5 Silent Presenting Features

Most of the patients with CCHS presents with repeated episodes of cyanosis and apnea requiring intubation and mechanical ventilation. The majority manifest in the newborn period, but some are recognized later during childhood or even adulthood. Many patients can breathe spontaneously while awake but have cyanosis and hypoventilation with monotonous respiratory rate and diminished tidal volume while asleep, more apparently during non-REM than REM sleep stages which is unique from other sleep-related hypoventilation syndromes. Since their respiratory centers are not sensitive to hypoxia nor hypercapnia, they do not exhibit any signs of respiratory distress when they are cyanotic or acquired with pneumonia or develop respiratory failure. If they do not receive adequate respiratory support, they may have complications and present with pulmonary hypertension, Cor pulmonale, seizures, and delayed development. Hirschsprung disease, neuroblastoma, ganglioneuroma, and other neural crest tumor have also been described as common associated findings. Autonomic dysfunction including breath-holding spells, diminished pupil response, temperature instability, profuse sweating, esophageal dysmotility, constipation, decreased heart rate beat-to-beat variability, lack of physiologic response to the stressors have been found in children with CCHS [17].

10.1.6 Diagnosis

The first step is to confirm hypoventilation. For children, hypoventilation during sleep is defined as a $PaCO_2$ greater than 50 mmHg for more than 25% of total sleep time [18]. This can be demonstrated by polysomnography or continuous monitoring with transcutaneous or end-tidal CO_2 and pulse oximetry. Figure 10.1 shows an example of an end-tidal CO_2 monitoring graph from a child with CCHS.

Then other possible causes of hypoventilation should be ruled out including upper or lower airway obstruction, diaphragmatic dysfunction, neuromuscular weakness, and medications or substances that can induce hypoventilation. Neurologic abnormalities including brain stem lesion, hypoxic-ischemic encephalopathy, birth asphyxia, infarction, CNS infection, and severe prematurity can also cause hypoventilation. So, they should be listed in the differential diagnosis and should be ruled out before diagnosing CCHS.

To confirm the definite diagnosis as described in the part of pathophysiology above, the patients should undergo a genetic study of PHOX2B.. There have been various types of PHOX2B mutation penetrance and expressivity reported in the literature. Specific genetic abnormalities such as the presence of NPARMs or the higher number of alanine repeated in PARMs are more likely asso-

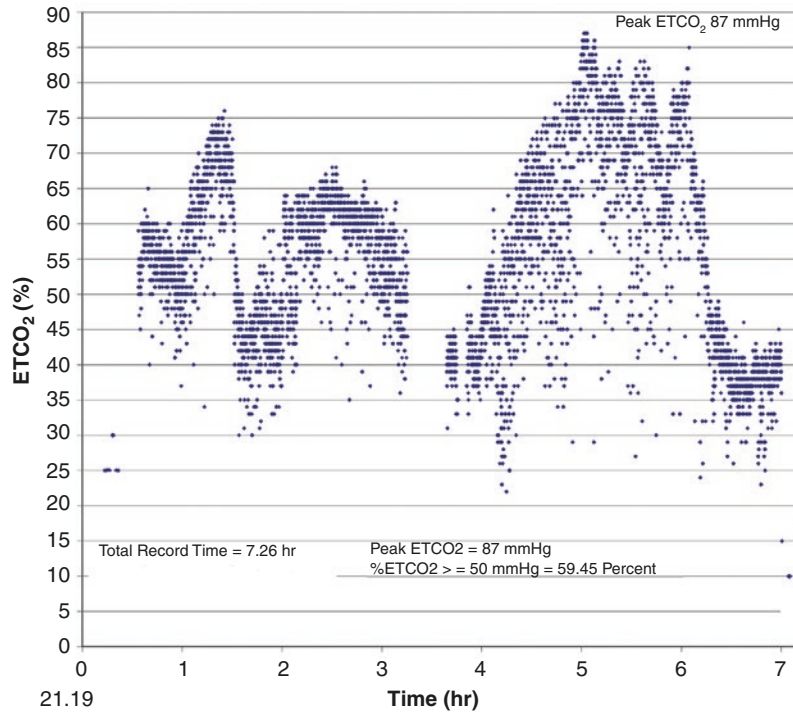


Fig. 10.1 Shows an example of overnight end-tidal CO_2 monitoring trend graph from a child with congenital central alveolar hypoventilation syndrome (CCHS)

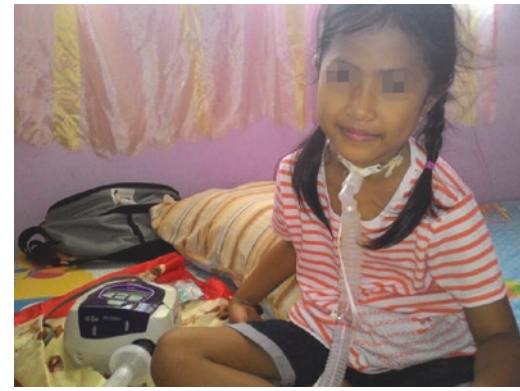
ciated with the severity of CCHS [19]. The parents of the patient with CCHS may not need to inheritany mutation of the PHOX2B gene, since the affected patient may develop a de novo mutation feasibly during the post-zygotic period in either one of the parental gametes [20].

10.1.7 Treatment

The most appropriate management for CCHS is to give life-long respiratory support to achieve normal ventilation and oxygenation during both awake and sleep. Oxygen administration without mechanical ventilatory support is not recommended since it can relieve only hypoxemia but does not treat or may worsen hypoventilation. If respiratory support is delayed or inadequate, the patient may suffer from hypoxic-ischemic encephalopathy, aggravating the degree of hypoventilation.

Before non-invasive ventilation was introduced into pediatric practice, all infants with CCHS required tracheostomy and long-term mechanical ventilation. Tracheostomies were performed to secure the airways. Most of them needed only nighttime ventilatory support and breathed spontaneously during the daytime. After pediatricians acquired more skill and experience in using non-invasive mechanical ventilation, a group from Italy reported success in using non-invasive ventilation initially in infants diagnosed with CCHS [21]. More production of small commercial masks designed for children allows more opportunities to use non-invasive ventilation in small children. The authors also reported an infant with CCHS being non-invasive mechanical ventilated initially since the age of 4 months. We recommended a tracheostomy, but his family disagreed; the parents insisted on using a noninvasive strategy. They hired a layperson to manually keep a full-

face mask on the baby's face all through the night while he was asleep [22]. At 5 years of age, he cooperated to wear a nasal mask with a headgear strap. At present he is 17 years old, doing well. So, the choice of mechanical ventilation, to begin with, should be either non-invasive via masks or invasive ventilation via tracheostomies. Ventilatory parameters should be carried out via polysomnography to confirm the best gas exchange during sleep. If the patient has normal lung parenchyma, the ventilator rate and tidal volume should be adjusted without oxygen supplement until PCO_2 and PO_2 are normal. Targets for ventilatory support are PCO_2 35–45 mmHg and SpO_2 ≥95% [20]. The setting of the ventilator should be periodically checked and adjusted. The ventilator rate should be decreased and tidal volume should be increased by age. Overventilation should be avoided since it may cause chronic respiratory alkalosis and metabolic derangements. For patients who initially are supported with invasive ventilation, they can be switched to non-invasive ventilation when they are old enough to cooperate with the use of non-invasive ventilation. Figures 10.2 and 10.3 shows one of our CCHS patients whom we were able to switch from invasive ventilation to nasal mask non-invasive ventilation when she was 10 years old. Midface hypoplasia from long-term use of nasal masks may be minimized by alternating between different shapes of masks and interfaces. Diaphragmatic pacing by phrenic nerve stimulation is recommended only in some centers that have highly experienced surgeons and specialized teams. Some older children may rely on diaphragmatic pacing when awake and on mask ventilation when asleep.



Figs. 10.2 and 10.3 Show one of our patients with congenital central alveolar hypoventilation syndrome (CCHS), whom we were able to switch from invasive ventilation to nasal mask non-invasive ventilation when she was 10 years old, with written permission to be published from the patient and her family

Other conditions associated with CCHS should be managed according to each patient's symptoms. For example, cardiac pacemaker implantation is needed in a patient with profound bradycardia or life-threatening sinus pauses. A pull-through surgical procedure to remove the diseased section of the intestine that lacks the normal nerve development and to pull the healthy portion of the intestine down to the anus is required in a patient with Hirschsprung disease. A gastrostomy tube is placed in a patient with abnormal swallowing.

10.1.8 Research Gaps

- Conduct an epidemiological survey of CCHS in Asian countries. Collect data of genotype and phenotype.
- Collect polysomnographic findings of CCHS patients. Set up criteria to diagnose CCHS based on polysomnography, oxygen saturation, carbon dioxide monitoring, home sleep testing to diagnose patients as early as possible.
- Establish one excellent center in Asia that can perform complete genetic tests of CCHS. Compare data with Caucasians.
- Improve technology to monitor oxygenation and ventilation and set up home mechanical ventilators via the internet.
- Identify risk factors for poorer outcomes.
- Compare the outcomes between different modes of respiratory support eg. noninvasive VS. invasive ventilation, noninvasive ventilation VS. diaphragmatic pacing
- Assess IQ and academic performance of children with CCHS. Determine factors associated with low IQ or poor academic performance

10.2 Obesity Hypoventilation Syndrome (OHS)

10.2.1 Vignette of Typical Presentation/Real-Life Example

A Thai 12-year-old boy presented with increased fatigue and progressive shortness of breath for 6 months. Excessive weight gain was noted since he was 4 years old. At the age of 8 years, he weighed 100 kg and had adenotonsillectomy due to obstructive sleep apnea. Snoring persisted after the surgery. The mother reported declining school performance and frequent daytime sleepiness. One year ago, his snoring seemed to be louder. He occasionally stopped breathing followed by gasping for air during sleep. Six months ago, his weight increased to 200 kg. He had shortness of breath on exertion and bed-wetting. His breathing difficulty was worsening. One month ago, he had shortness of breath even at rest and needed 6 pillows when sleeping. His development was age-appropriate.

On initial assessment, his height was 165 cm, weight 260 kg, and body mass index (BMI) 95.5 kg/m^2. The pulse rate was 114, respiratory rate 46/min, blood pressure 120/80 mmHg. On room air when he was awake, the oxygen saturation was 92% in the sitting and 80% in the supine positions. When he fell asleep, oxygen saturation dropped down to 60%. Physical examination revealed an alert, markedly obese boy. Acanthosis nigricans of the neck and buffalo hump was seen. Chest auscultation revealed faint heart and breath sounds due to the chest wall thickening.

Laboratory investigations showed hemoglobin 14 g/dL, hematocrit 45% with normal white blood cells and platelets. Electrolytes showed Na 141, K 4.1, Cl 100, HCO_3 36 mEq/L. Arterial blood gases showed pH 7.37, $PaCO_2$ 58, PaO_2 57 mmHg, HCO_3 33.8 mmol/L. Chest X-ray showed cardiomegaly.

Polysomnography performed at the bedside in the PICU revealed an apnea hypopnea index of 153 per hour of total sleep time. The lowest SpO_2 was 22%. Peak end-tidal CO_2 was 56 mmHg. Duration of end-tidal CO_2 $\geq$50 mmHg was 62% of total sleep time. We titrated BPAP gradually under polysomnography until reaching the optimal setting at inspiratory pressure 28 cmH_2O, expiratory pressure 9 cmH_2O, back up rate 30/min. No additional oxygen was administered.

In addition to OSA and OHS, his comorbidities included games addiction, adjustment disorder with depressed mood, allergic rhinitis, vitamin D insufficiency, non-alcoholic steatohepatitis, cellulitis at buttocks, inguinal areas, and abdominal skin folds. His father had schizophrenia and diabetes.

He had been admitted to Ramathibodi Hospital for weight loss intervention for 8 months. During that time, he had been supported with BPAP during sleep. In the daytime, he participated in nutritional management, exercise, and rehabilitation

program. We also consulted child development, psychiatrists, and social workers to prepare psychological and familial support. When his weight was reduced to 195 kg, BPAP was switched to CPAP 18 cmH_2O. He was discharged home at a weight of 167 kg.

10.2.2 Introduction

Obesity hypoventilation syndrome (OHS) was first reported in 1956 as extreme obesity associated with alveolar hypoventilation called a Pickwickian syndrome. Later the term "Pickwickian syndrome" has been used to describe patients presenting with morbid obesity, somnolence, cyanosis, muscular twitching, and periodic breathing. It was noted that all of these symptoms could be reversed following substantial weight loss. After the year 2000, most kinds of literature preferred using OHS to Pickwickian syndrome, perhaps due to OHS implying more directly the pathophysiology of this condition.

OHS should be considered in a patient who is obese and has daytime awake hypercapnia without an alternative neuromuscular, mechanical, or metabolic cause of hypoventilation. If left untreated, OHS is linked to higher rates of death, heart failure, pulmonary hypertension, and frequent hospitalizations [23]. So clinicians should recognize and treat this condition appropriately as soon as possible.

10.2.3 Epidemiology

The exact prevalence of OHS in children is unknown. Even in adults, the reported prevalence varies across studies due to the differences in sample characteristics, the definition of OHS, and investigations to confirm OHS. Since most OHS patients have had obstructive sleep apnea (OSA) as a co-morbidity, many studies tried to estimate the prevalence of OHS from the OSA population. For example, Balachandran et al. aggregated data from 10 studies. They found that the prevalence of OHS among OSA adults ranged from 4% to 50% [24]. In Japan, OHS was identified in 2.3% of OSA patients whereas more than 95% of OHS patients had OSA [25].

At least we know that the prevalence of OHS increases as body mass index (BMI) rises [26]. Among adult patients admitted to an inpatient medical service, the prevalence of OHS increased from 31% to 48% when BMI cut off increased from ≥35 to 50 kg/m^2 respectively [26]. In addition, the prevalence of OHS among ethnic diversity may vary due to cephalometric differences. Among Japanese adults, the prevalence of OHS was 25% when BMI cut off was ≥35 kg/m^2 [25] which is relatively lower than that reported in non-Asian adults.

There have been several OHS studies in adult population conducted in Asia such as China [27–31], Japan [25, 32], India [33], and Thailand [34]. The clinical characteristic and natural course of disease do not differ from non-Asian studies. Unfortunately, there have been very few studies reporting OHS in children. Matsuzawa et al. reported a 5-year-old Japanese boy with severe obesity. He was diagnosed with OHS by polysomnography (PSG) and successfully treated with BiPAP [35]. Some others reported OHS in children with syndromic abnormalities including Prader Willi syndrome [36, 37], and Down syndrome [38].

Since OHS is one of the most detrimental complications of obesity, the prevalence of this condition is expected to increase following a marked surge in the world's obese and overweight population. The burden of overweight and obesity among children and adolescents is also increasingly notable in Asia [39]. Therefore OHS and its complications including Cor pulmonale and congestive heart failure are expected to rise in children as well. A high index of suspicion is needed when clinicians see children with obesity and sleep-disordered breathing. The child may present with serious complications if OHS is not recognized and treated promptly.

10.2.4 Pathophysiology

Adipose tissue surrounding the chest wall impairs respiratory mechanics causing reductions inlung volumes and chest wall compliance, increases in respiratory resistance and work of breathing [40, 41]. Spirometric values from adults with OHS typically reveal a restrictive pattern with a reduction in $FEV_1$and FVC but normal FEV_1/FVC. Functional residual capacity, total lung capacity, and expiratory reserve volume are also reduced [40, 41]. Chest wall compliance is reduced 2.5-fold. Pulmonary resistance is increased, most likely due to the decrease in functional residual capacity [40, 41]. These impairments in respiratory mechanics increase the work of breathing in patients with OHS. When the patients are changing from sitting to the supine position, abdominal contents and adipose tissue are shifting to the cephalad pressing on the diaphragm. Limitation of diaphragmatic movement further impairs respiratory mechanics resulting in further increase in the work of breathing [41].

Theoretically, normal obese individuals need to breathe harder to increase minute ventilation in order to maintain eucapnia or normal carbondioxide level. But central respiratory drive in patients with OHS areblunted to both hypercapnia and hypoxia [40]. Leptin, which is an adipokine produced in adipose tissue that stimulates ventilation, is elevated in OHS patients. So it has been proposed that leptin resistance may be one mechanism of blunted central respiratory drive found in OHS [40].

During sleep, minute ventilation generally reduces as compared to awake. When patients with OHS are sleeping, hypercapnia and hypoxia are aggravating especially in a supine position and REM stage of sleep. Another contributing factor that leads to deteriorating hypercapnia and hypoxia is upper airway obstruction, manifesting as OSA, which is commonly associated with obesity and OHS.

Figure 10.4 illustrates the pathophysiology of OHS caused by obesity.

Compared with OSA alone, OHS is related to higher cardiovascular morbidity including higher rates of congestive heart failure, arrhythmia, and pulmonary hypertension. The underlying mechanisms leading to these problems comprise chronic repetitive hypercapnia and hypoxia, obesity by itself, the severity of obstructive sleep apnea, which pathologically result in pulmonary vaso-

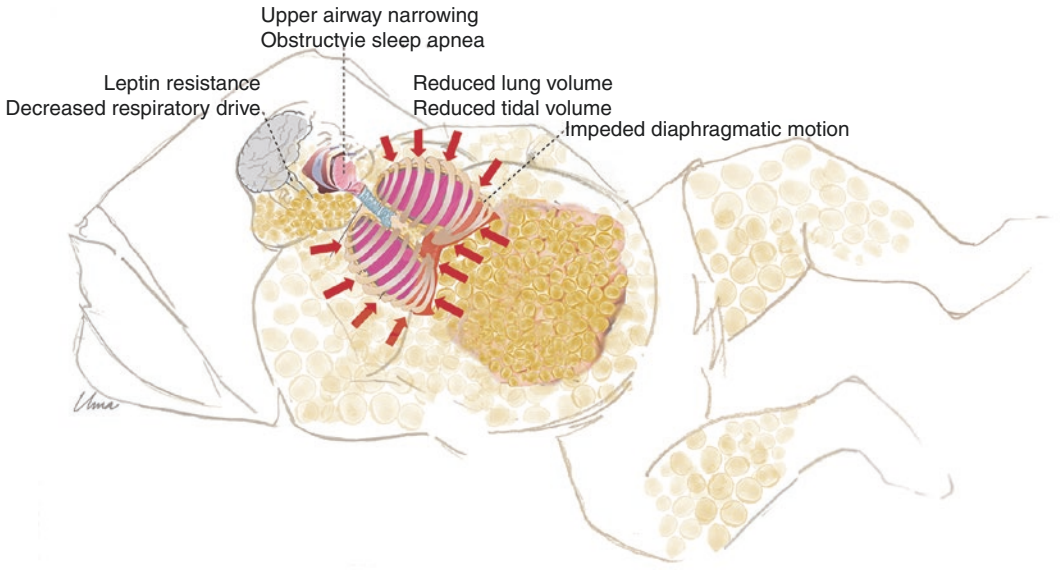


Fig. 10.4 Illustrates the pathophysiology of obesity hypoventilation syndrome (OHS) caused by obesity

constriction, endothelial dysfunction, systemic inflammation, autonomic instability, and impaired myocardial function [42].

10.2.5 Silent Presenting Features

Patients with OHS are severely obese, who present with symptoms and signs of OSA such as daytime hypersomnolence, loud snoring, choking, and witnessed pause of breathing during sleep, fatigue, poor academic performance, impaired concentration, and memory. If the diagnosis is delayed, they likely present with the clinical features of Cor pulmonale with right heart failure consisting of dyspnea on exertion, engorged neck vein, hepatomegaly, pedal edema, facial plethora from polycythemia. From our experience in Thailand, some of them presented with acute pulmonary edema necessitating immediate intubation and mechanical ventilation, in the form of acute-on-chronic hypoventilatory failure. Cardiomegaly was noted on the initial chest radiograph. After weight loss and ventilatory support, the heart was reduced in size.

10.2.6 Diagnosis

American Thoracic Society (ATS) [43] and American Academy of Sleep Medicine(AASM) [44] recommend diagnosing OHS in patients with the following characteristics.

1. Obesity (BMI $\geq$ 30 kg/m^2)
2. Daytime hypercapnia (awake resting $PaCO_2 \geq$ 45 mmHg)
3. Symptoms and signs of sleep-disordered breathing or OSA
4. Absence of other causes of hypoventilation that can explain hypercapnia

The definition of obesity used in children may differ from adults. Some experts define obesity in children as BMI $\geq$ 95th percentile for age and sex [44].

Since arterial blood gases are an invasive procedure and not convenient in clinics, ATS suggests screening for OHS by measuring serum bicarbonate. In patients with serum bicarbonate $\geq$27 mmol/L, measurement of $PaCO_2$ is then required to confirm or rule out the diagnosis of OHS [43].

Unfortunately, there have been no guidelines or statements to diagnose OHS specifically in children. Pediatricians have to use the same guidelines as adults as described above. But in children, it is much more difficult to draw arterial blood. Children frequently cry, hold their breaths or hyperventilate which will result in an error in CO_2 measurement. According to AASM, transcutaneous or end-tidal CO_2 can be used as a surrogate of $PaCO_2$. For pediatric patients, hypoventilation is scored when $PaCO_2$ (or surrogate) is $\geq$50 mmHg for $\geq$25% of total sleep time [45].

In real-life practice, we often screen children by measuring end-tidal CO_2 and SpO_2 in room air in the outpatient setting. Another option is to record overnight transcutaneous or end-tidal CO_2 with respiratory rate by capnometry and SpO_2 with pulse rate by pulse oximetry and display as the trend graphs. Polysomnography with CO_2 monitoring in our opinion is the best option since we can obtain all physiologic parameters during sleep and determine the severity of OSA and OHS. Positive airway pressure (PAP) therapy and titration can also be instituted in the second half of the night.

10.2.7 Treatment

Management of OHS needs a multidisciplinary team consisting of pulmonologists, nutritionists, psychologists, physiatrists, sleep specialists, respiratory therapists, weight trainers, and possibly bariatric surgeons.

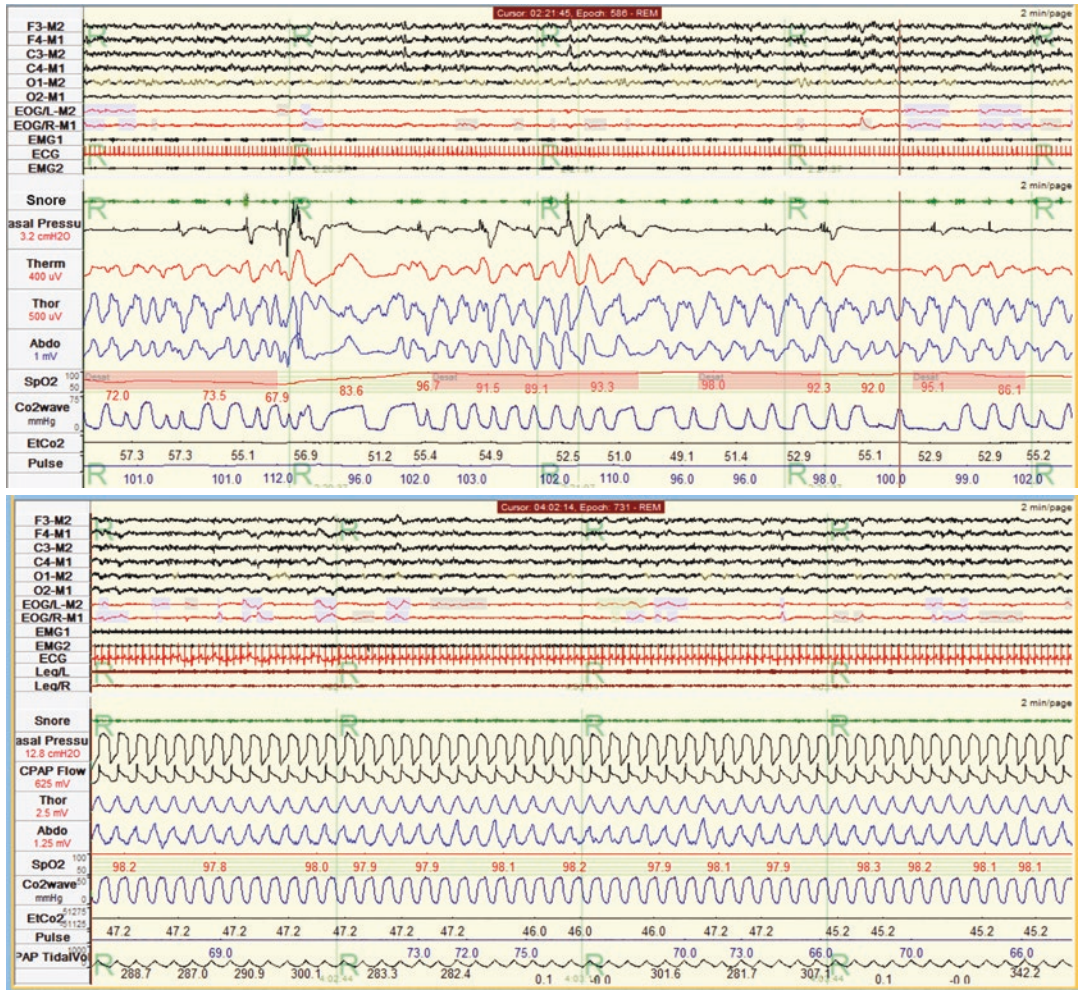
Supplemental oxygen therapy should be avoided since oxygen will suppress hypoxemic drive from peripheral chemoreceptors in patients with chronic hypercapnia, resulting in slower respiratory rate, reduced tidal volume, increased $PaCO_2$, acidemia, and inducing apnea.

PAP therapy during sleep is the mainstay of treatment. PAP can be delivered by continuous PAP (CPAP) or bilevel PAP (BPAP). CPAP dis-

tends the upper airway and acts like an endotracheal tube. Although CPAP does not deliver the tidal volume to the patient, it does relieve the upper airway obstruction and improves respiratory system compliance by increasing the functional residual capacity. Optimal CPAP pressure results in increased tidal volumes and minute ventilation, facilitating CO_2 washout.

BPAP has two levels of pressure set up; inspiratory pressure (IPAP) and expiratory pressure (EPAP). The greater the difference between IPAP and EPAP, the greater the tidal volume being delivered to the patient. BPAP can be set as either spontaneous mode, in which the patient must trigger the ventilator breath, or timed mode, in which a backup respiratory rate is set. Volume-targeted pressure support with a backup rate is another form of advanced BPAP, in which the machine delivers constant tidal volume in almost every breath.

A systematic review compared CPAP and BPAP in OHS patients found that both PAP modalities were similarly effective without significant difference in adherence [46]. Since BPAP is more expensive and requires more expertise and time to implement and monitor, CPAP should be used first. If the patient does not improve or does not tolerate CPAP then BPAP could be another step of the trial. Our division almost always performs polysomnography (PSG) for PAP titration. Figures 10.5 and 10.6 shows an example of PSG tracings in a child with OHS



Figs. 10.5 and 10.6 Show an example of polysomnographic (PSG) tracings in 2-min page from a child with obesity hypoventilation syndrome (OHS) before and after bi-level positive airway pressure (BPAP) support

before and after BPAP support. If PSG is not available, the patient must be admitted and have PAP titration by physicians at the bedside with pulse oximetry and capnometry monitoring to ensure the best setting for an individual patient.

Weight loss interventions should be implemented along with PAP therapy. ATS recommends a long-term sustained weight loss of ≥25% to 30% of actual body weight in adults. This level of weight loss aims to achieve resolution or reduction of hypoventilation [43]. Lifestyle modification although is effective but most of the time not sustainable. Bariatric surgery which is more effective than lifestyle interventions has been found to reduce sleep apnea severity and improve gas exchange [47]. The surgery has also demonstrated improvement in other obesity-associated comorbidities but not OHS in adolescents. American Academy of Pediatrics recently supported bariatric surgery in adolescents with BMI ≥35 kg/m^2 with concurrent comorbid conditions such as OSA, diabetes, hypertension [48]. Data on bariatric surgery in children is limited. It is still doubtful whether or not to perform this kind of surgery in children with OHS or at what age group. Long-term implications of nutrient deficiency including iron, vitamin B12, folate, and others, which may affect children's growth and brain development need further longitudinal studies.

10.2.8 Research Gaps

- Prevalence of OHS in children with OSA and its association with BMI
- Clinical features and long-term outcome of OHS in children
- Polysomnographic parameters to identify OHS in children
- Which screening test is most useful? Serum bicarbonate? End-tidal CO_2? Pulse oximetry? Spirometry?
- Relationship of OHS to adverse neurological and metabolic outcomes
- Comparing treatment strategies between CPAP vs. BPAP vs. weight loss interventions
- Role of bariatric surgery in children with OHS

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Childhood Narcolepsy

11

Wei-Chih Chin and Yu-Shu Huang

11.1 Typical Presentation of Childhood Narcolepsy

Narcolepsy is a chronic sleep-wakefulness disorder. Several differences in presentation have been noted between pediatric and adult narcolepsy patients, and the symptoms of each patient can change between different life stages and whether there is treatment. Besides, racial differences in clinical presentation have been reported. Kawai et al. reported racial differences of African American in lower age of onset, higher sleepiness, and less cataplexy with low hypocretin levels [1]. A study in China reported the mean age of onset is 10.3 years and the most common symptoms included excessive daytime sleepiness, disrupted nocturnal sleep, cataplexy, excessive weight gain, and mood disorder [2], while the study in France and Quebec reported 24.4 years and most symptoms were excessive daytime sleepiness, cataplexy, hypnogogic hallucination, and sleep paralysis [3]. Although it can be contributed to the delay in diagnosis, more pediatric narcoleptic cases may be found in the Asian population. Children with narcolepsy experience constant excessive daytime sleepiness and sudden sleep attacks during activities at any time of the day [4]. Other common symptoms/signs may also occur. We should note that these symptoms may appear gradually during the course of the disease, and not every child experiences all the symptoms [4].

- *Excessive daytime sleepiness (EDS)*: EDS is present in all patients with narcolepsy and often noted as the first symptom/sign in children. Children may complain of mental cloudiness, fatigue, sleepiness, forgetfulness, low energy, and difficulty concentrating, as well as have related behavioral problems, such as irritability, hyperactivity, social withdrawal, depression, or even aggressiveness. EDS impairs children's functions and disturbs daily activities, including school and social life. Sleep attacks last longer in children than adults; preschool children can still experience tiredness soon after afternoon naps for 2–3 h, and the need for napping can persist into childhood after age 5–6.
- *Cataplexy*: Patients with cataplexy experience muscle weakness or a sudden loss of muscle tone, which can be noted in 70% of children with narcolepsy. It is usually triggered by stress or emotion, such as laughter when seeing something funny or being scared. The duration of cataplexy is brief, lasting a few seconds to several minutes, and the severity differs. Cataplexy in children has some unique features, including facial and eyelid weakness,

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sticking out of the tongue, and abnormal facial movements and expressions. It can be wrongly labeled as clumsiness, seizures, or attention-seeking behavior in young children.
- *Sleep paralysis*: When patients have sleep paralysis, they find that they cannot move or speak after they just wake up or before they fall asleep. This symptom usually lasts for seconds to a few minutes.
- *Hallucinations*: Hallucinations in patients with narcolepsy occur before sleep (hypnogogic hallucination) or after waking up (hypnopompic hallucination). Patients have vivid and dream-like events, often involving images or sounds that can be scary.

In addition to the above typical symptoms, other characteristics may include:

- *Disturbed nighttime sleep*: Patients with narcolepsy not only have daytime sleepiness but also disturbed nighttime sleep. Although they do not have problems falling asleep, narcoleptic patients often report difficulty maintaining sleep.
- *Autonomic behaviors*: Patients fall asleep but continue ongoing activities, such as writing or other daily tasks. They are not aware and do not remember what they do during autonomic behaviors.
- *Weight gain*: Obesity is common and can be noted early in childhood during the disease course. Up to 25% of children with narcolepsy are obese.
- *Early onset of puberty:* Previous studies have pointed out that pediatric narcolepsy with cataplexy is associated with precocious puberty, and that children with earlier age of onset have a greater risk of precocious puberty [5].

In children, cataplexy and other sleep phenomena can develop later on, after the onset of EDS. Currently, patients with narcolepsy can be divided into two types based on the presence or absence of cataplexy according to the ICSD-3 [4], and some children who develop cataplexy later may be diagnosed as having narcolepsy without cataplexy initially [6]. The two types of narcolepsy recognized by the ICSD-3 are:

1. **Narcolepsy Type 1 (previously narcolepsy with cataplexy):** In addition to EDS, patients with narcolepsy type 1 also suffer from cataplexy and/or low cerebral hypocretin levels.
2. **Narcolepsy Type 2 (previously narcolepsy without cataplexy):** Patients with narcolepsy type 2 do not have cataplexy, and their hypocretin levels are normal or have not undergone CSF examination.

Researchers have attempted to differentiate the two narcolepsy types by investigating their allergic reaction [7, 8], but data regarding the differences of allergy between these two types are still insufficient. Further investigation of the pathophysiology is still needed for differentiation [9].

11.2 Epidemiology

The reported prevalence of narcolepsy varies in studies from different countries and with different ethnicities. The lowest prevalence is reported in Israel (0.23 per 100,000), while the highest is in Japan (160 per 100,000) [10, 11]. According to previous reports, the global average is between 20 and 50 per 100,000 [12–19], and the variation in prevalence is still unclear, possibly related to gene susceptibility or case definition across studies [12]. Although some studies suggest a higher prevalence in males [20], narcolepsy affects males and females equally. Pediatric narcolepsy is estimated to occur in less than one in every 100,000 children [21], but it can easily be misdiagnosed.

11.3 Etiology and Pathophysiology

One current hypothesis is that narcolepsy is related to the destruction of the specific brain area responsible for sleep and wake function and the loss of hypocretin, a neuropeptide in the

brain. Accumulating evidence has proven that narcolepsy type 1 is caused by the loss of hypocretin-1(orexin) neurons in the lateral hypothalamus [22–24], but patients with narcolepsy type 2 are found to have normal hypocretin levels, and its etiology remains unknown [21].

Tracing back to 1983, Juji et al. found that narcolepsy was associated with the human leukocyte antigen, HLA-DR [25]. Both genetic and environmental factors were assumed to play important roles in the pathogenesis of narcolepsy [26]. Previous studies have shown that most patients with narcolepsy type 1 and half of patients with narcolepsy type 2 carried HLA-DQB1*0602 [9, 18]. The genetic susceptibility of narcolepsy can result from the heterodimer formed by HLA-DQB1*0602 and HLA-DQA1*0102, an antigen presenter to the T cell receptor (TCR). Polymorphism in non-HLA genes affecting immune regulation can also be connected to narcolepsy. Other studies found that narcolepsy is associated with TCR α polymorphisms and anti-TRIB2 antibodies [27, 28]. All these findings support the hypothesis of autoimmune destruction of hypocretin cells in the pathophysiology of narcolepsy.

Other factors may also affect hypocretin neurons. Prenatal nutrition, obesity, stress, and toxins have been factors suggested by some researchers. Early life environmental factors can have a role in the damage of hypocretin neurons, supported by the seasonal predominance of birth (such as May and June) in patients with narcolepsy [29, 30]. Infections have been proposed as a potential trigger for the autoimmune mechanism. Aran et al. reported that streptococcal infections are probably a significant environmental trigger for narcolepsy [31]. Several recent studies have shown increased cases of narcolepsy, especially in children and adolescents, in relation with H1N1 influenza. The increased cases in Europe seem to be related to a specific type of H1N1 influenza vaccination (Pandemrix). A study in Beijing, China found the risk of pediatric narcolepsy was threefold higher in 2010 with only 4% cases receiving the H1N1 vaccines [32]; that finding was in line with findings from Denmark and Germany in spite of a low vaccination coverage population [33, 34]. Although recent global research does not support this association [35], an interesting finding in Taiwan is that narcolepsy can be triggered by the H1N1 infection itself [36]. Streptococcus and H1N1 infections may trigger narcolepsy by activating T-cells and B-cells. The first possible mechanism is molecular mimicry [37, 38]. Antigen from H1N1 or streptococcus is presented by the antigen-presenting cells in major histocompatibility complex (MHC)-DQA1*0102-DQB1*0602, and T-cells are activated after recognizing the antigen through TCR. Subsequently, T-cells may recognize the hypocretin antigen of hypocretin neurons via cross-reactivity and attack these neurons. This molecular mimicry occurs through B-cells, which directly recognizes the antigen, but also requires T-cell activation. Other proposed mechanisms include superantigen activation and by-stander activation [21].

A retrospective chart review study identified 468 pediatric narcolepsy cases, including 193 narcolepsy with cataplexy children and 275 narcolepsy without cataplexy children. An increased shift in the T helper 1 (Th1): T helper 2 (Th2) balance toward Th2 was found. Allergic conditions may modulate the severity of pediatric narcolepsy, reduce the prevalence of cataplexy, and potentially lessen the severity, even among narcoleptic patients with cataplexy [7].

11.4 Presentation and Diagnosis

Pediatric narcolepsy is one of the most commonly underrecognized and underdiagnosed diseases. This fact raises questions about the reasons behind this delay in diagnosis. The onset of narcolepsy symptoms usually occurs between the ages of 10 and 30 years. The peak is at 14 to 15 years, although symptoms can be present in children less than age 10 [39–42]. Levy et al. (2019) reported on 42 children diagnosed with narcolepsy at the Royal Hospital for Children between 1996 and 2016. The time between symp-

tom onset and diagnosis was significantly shorter than that reported in the adult population, but diagnoses were still delayed about 1 year, with the longest delay up to 11 years [43].

Delayed diagnosis may be caused by a variety of reasons. Related behavioral problems of pediatric narcolepsy are often thought to be psychiatric conditions, while cataplexy can be mistaken as normal falls, epilepsy, or other neurological disorder. During school, it is not uncommon to see children slouched over their desks, appear drowsy, or even fall sleep. These conditions make diagnosing narcolepsy in children difficult [6].

Without specific and unique symptoms, young children with narcolepsy may not be diagnosed in preschool or school stages before adolescence or early adulthood. Daytime sleepiness may not be obvious in very young children and is often missed. Other narcoleptic symptoms, such as sleep paralysis and hypnagogic and/or hypnopompic hallucinations, are not always detectable. These symptoms may be atypical and, if present, difficult to recognize. Sleep behavior is often believed by teachers and parents to be apathy, pathological sleepiness, or even normal napping. Prolonged sleep and difficulty waking up are common, but sleepiness can be masked by such abnormal behavior as irritability, aggressiveness, social withdrawal, or shyness [44, 45]. Frequent cataplectic attacks at an early age should lead to detailed clinical, neuroimaging, and other brain examinations to rule out a secondary etiology.

Among all age groups, narcolepsy in infants and toddlers is very rare, and making a diagnosis of infant cases is the most difficult due to atypical features. Infants are incapable of describing their own feelings, and sleep study criteria is lacking. In these cases, professional pediatric sleep studies and further auxiliary examinations, especially the CSF hypocretin level test, are crucial for confirming the diagnosis. HLA haplotype testing (e.g. DQB1*0602 positive) is highly sensitive to narcolepsy type 1 and can also support diagnosis in this early stage [46].

To evaluate and diagnose pediatric narcolepsy, the following procedures and tests can be used:

1. To make the diagnosis and rule out other causes of sleep symptoms, it is important to collect a detailed medical history and have a thorough physical examination. Parents may not detect cataplexy symptoms as well as the children who experience it, but they have better recognition in the circumstances of children's sleepiness. A detailed sleep history should be gathered from the child, their parents, and their teachers. Some questionnaires as "Pediatric Daytime Sleepiness Scale (PDSS)" are helpful in collecting information about sleepiness and treatment responses [47]. Other questionnaires include "Cataplexy Diary" and "Epworth Sleepiness Scale-Child Adolescent (ESS-CHAD)." Cataplexy Diary was modified by using child-friendly terminology and adding a quantitative question for frequency and standardization for evening administration with self-completion. ESS-CHAD was also modified by child-friendly wording and came in two versions: one with a 1-month recall period for general use, and the other for research, with a recall period of "since your last study visit" [48].
2. Actigraphy recordings are useful for ruling out other sleep disorders. Actigraphy measures movement and collects data via a wristwatch type device. It is worn for up to 2 weeks, during which time the child and parents need to fill out a sleep log to document sleep and wake times. Filardi et al. collected the actigraphy data of 22 drug-naïve narcolepsy type 1 children and 21 age- and sex-matched controls for 7 days during the school week. The results showed actigraphic measures have good discriminant capabilities in assessing narcolepsy type 1 nychthemeral disruption in drug-naïve children and indicated its sensibility in the diagnostic work-up of childhood narcolepsy type 1 [49]. Actigraphy also offers the possibility to longitudinally follow up children and has the potential to become a key tool for tailoring treatment [50].
3. Two standard sleep study tests are traditionally performed. The overnight polysomnogram (PSG) and the multiple sleep latency test (MSLT) are still the "gold standards" for diagnosing narcolepsy. PSG and MSLT should be preceded by at least 1 week of actigraphic recording or a sleep log [4]. Most

patients with narcolepsy show disruptions in normal sleep patterns with frequent awakenings. Common findings include rapid sleep onset, rapid REM onset (<15 min), fragmented sleep, frequent awakenings, frequent unexplained arousals, increased stage I sleep, and REM without atonia. Mean sleep onset latency of MSLT in narcoleptic patients is usually less than 8 min, typically less than 5 min, over the course of five naps. More than two sleep onset REM periods (SOREMPS, REM period appears <15 min after sleep onset) are present, or alternatively, one SOREMP on MSLT and one SOREMP on the night preceding PSG.

(a) Children with narcolepsy type 1 have markedly reduced sleep latency and more SOREMPs during the MSLT compared to adult patients [44]. However, strong evidence points to a progressive age-related decrease in the number of SOREMPs and a progressive increase in the mean sleep latency. Dauvilliers et al. (2004) collected 383 narcoleptic patients (aged between 21 and 65 years old) and divided them into five age groups. Their results showed a linear and highly significant decrease in the number of SOREMPs and an age-related progressive increase in mean sleep latency on MSLT. They also found that the severity of cataplexy was at first progressive but declined in frequency in older age [51].

(b) Huang et al. reported a 5-year follow-up study of adolescents and young adults with narcolepsy. They demonstrated that type 1 narcolepsy is a well-defined clinical entity, with very reproducible clinical neurophysiologic findings over time, whereas type 2 narcolepsy had clear clinical and test variability. By the fifth year evaluation, 17.6% of type 2 subjects did not meet the diagnostic criteria, and 23.9% did not show two SOREMPs in MSLT during the 5-year follow-up [52]. If sleep testing is negative and the suspicion of narcolepsy remains, clinicians should consider repeating testing, arranging HLA typing, or checking hypocretin level by lumbar puncture (as discussed below).

4. Another test is measurement of the cerebrospinal fluid hypocretin levels (<110 pg/mL). Kanbayashi et al. (2002) showed that from early infancy to old age, the hypocretin level remains stable, and a low or undetectable hypocretin level is a very valuable diagnostic marker for pediatric narcolepsy [53]. However, it is not commonly performed since it requires lumbar puncture [54], an invasive method that raises many concerns for parents.
5. The blood test of HLA DQB1*0602 haplotype has also been demonstrated to be associated with narcolepsy. Studies by Mignot and colleagues have shown that narcolepsy type 1 is highly associated with HLA DQA1*01:02 and HLA DQB1*0602 [55]. Other studies have also shown that DQB1*0301 is associated with earlier disease onset [56, 57].
6. Neuroimages: Although inconsistent, PET studies of adolescents with narcolepsy type 1 revealed hypo- and hypermetabolism in many cortico-frontal and subcortical brain regions, which had significant correlations with neurocognitive test performance [58–62]. These PET findings parallel those in structural neuroimaging studies, which showed a reduction of cortical gray matter in the frontotemporal areas [62–65]. A recent study reported that the subtle structural brain changes involving attentional and limbic circuits could be detected in children and adolescents with narcolepsy type 1 [66]. Another study using functional magnetic resonance imaging found that adolescent patients with narcolepsy were less likely to spend time in a microstate related to the default mode network than controls, suggesting altered resting state brain dynamics [67].

11.5 Management

Narcolepsy is a chronic neurological disorder that currently has no cure. The goal of treatment is to reduce EDS and other disturbing symptoms and improve daytime function and quality of life.

Treatment plans involve a three-pronged approach: medication, behavioral modification, and education.

1. Medication: Medications are used to treat EDS and other narcoleptic symptoms. Medications approved by the US Food and Drug Administration (FDA) for pediatric narcolepsy include methylphenidate and amphetamine for EDS and sodium oxybate for EDS and cataplexy. However, only sodium oxybate and Pitolisant have been proven effective in pediatric patients through randomized placebo-controlled studies. Long-term use of medication in pediatric narcolepsy may be limited due to such adverse effects as decreased growth (amphetamines or methylphenidate), hypersensitivity reactions (modafinil/armodafinil), and poor tolerability of TCA [68].

   In Taiwan, only Modafinil and Methylphenidate are available to treat narcolepsy. Under current health insurance system, Methylphenidate is the first-line medication. To prescribe Modafinil, sleep medicine doctors first have to apply for permission with the results of work-up including PSG and MSLT. Clinically Methylphenidate is often prescribed in low dose initially, 10–20 mg two to three times per day, if narcolepsy is impressed or if daytime sleepiness is too severe to keep observation. After completing work-up and the application of Modafinil, most patients will shift to Modafinil 100 to 200 mg per day since Methylphenidate is not effective enough for narcoleptic patients or severe side effects can be noted. Below we have reviewed current available medication for pediatric narcolepsy and also medication under development around the word:

   (a) Stimulants: Stimulants can help patients stay awake. For pediatric narcolepsy, amphetamine and methylphenidate (Ritalin®) are options. Alternatively, modafinil (Provigil®) or armodafinil (Nuvigil®) have fewer side effects and are less addictive. In children, the starting dose should be low and increased gradually as needed. High blood pressure, arrhythmia, and drug abuse have been reported [69].

   (b) Pitolisant (Wakix®) and solriamfetol (Sunosi®) have recently been approved by the FDA to improve wakefulness in adults with narcolepsy. Pitolisant is a selective histamine H3-receptor inverse agonist, as effective for EDS as modafinilA multicenter open-label, single-dose study of pitolisant enrolled pediatric patients with narcolepsy aged 6–17 years old, doses up to 17.8 mg/d (body weight <40 kg) or 35.6 mg/d were found to be appropriate [70].

   Solriamfetol (JZP-110) is a selective dopamine and norepinephrine-reuptake inhibitor not yet approved for pediatric patients. Its efficacy on objective and subjective sleepiness was recently demonstrated in an international, double-blind, randomized, placebo-controlled trial, as well its safety [71].

   (c) Antidepressants can be prescribed to treat cataplexy. Two types of antidepressants are often used: tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), but neither have been proven by clinical trials with regard to safety and efficacy in pediatric patients.

   (d) Sodium oxybate: Sodium oxybate (Xyrem®) is the only FDA-approved medication to treat both EDS and cataplexy in patients aged as young as 7 [72]. Filardi et al. conducted a long-term study of sodium oxybate in narcoleptic children evaluated by actigraphy. The symptom severity and anthropometric features were improved as expected [50].

   (e) Mazindol, a non-amphetamine, tricyclic compound, also have proved to be effective in patients presenting with narcolepsy and idiopathic hypersomnia. Current studies support use of mazindol in adult patients, but its safety and efficacy in pediatric patients has not been proved by clinical trials [73].

(f) Immunomodulation strategy: The development of immunomodulation therapy was based on the hypothesis of the autoimmune destruction of hypocretin neurons in narcolepsy, and the treatment may help to prevent such autoimmune reaction. Theoretically, in some patients, the treatment may slow down or decrease the destruction of orexin neurons. Although current studies show limited effects on reducing narcolepsy symptoms, studies have found that after receiving immunomodulation therapy, patients with more severe baseline narcoleptic symptoms achieved symptoms remission faster than controls [74, 75]

2. Behavior modification: Suggestions should be provided to and discussed with children and their caregivers, including:
   (a) Regular sleep/wake schedule: Children should have adequate nighttime sleep with a regular sleep/wake schedule, go to bed and wake up at the same time, and avoid staying up late.
   (b) Good sleep environment: The bedroom should be quiet, dark, and cool, and the matrix should be comfortable. Avoid too much screen time before sleep. Children should avoid caffeine and stimulants before bedtime.
   (c) Short naps: When the child feels most sleepy, a 20- to 30-min nap is recommended. The duration and frequency should be based on each child's needs.
   (d) Exercise: Regular exercise can assist sleep and prevent obesity. Furthermore, children should eat meals at regular times and should not eat heavy meals or too much liquid close to bedtime.
   (e) Relaxation before bed time: Bed-time routines can include a warm bath, meditation, yoga, or music. A wake-up routine can also help to gain alertness in the morning, such as exercise in the sunlight or taking a shower.
   (f) Risk prevention: Children with narcolepsy should avoid dangerous activities like driving, swimming, or cooking, or be supervised carefully.
3. Education: Educating people around children with narcolepsy can be very important, including teachers, parents, family members, and close friends. They need to understand the disorder, how it affects functioning, and how they can assist the patients. Education also protects children from stigmas and from being misjudged as lazy or inattentive. Teachers can also help to screen for narcolepsy if they possess a basic knowledge of the disorder.
4. Mental support: Children with narcolepsy face more difficulties and stress in their daily life. They are more likely to have depression or anxiety and thus support from mental health professionals or support groups can be helpful.

11.6 Prognosis

Comorbidity is frequent in children with narcolepsy, including metabolic, psychiatric, neurological, and other diseases. Jennum et al. evaluated the morbidity and mortality of child and adolescent patients with narcolepsy from the Danish National Patient Registry, comparing 243 patients (128 boys) aged 0–19 years with narcolepsy. Elevated odds ratios of endocrine and metabolic conditions, neurological disorders, psychiatric illnesses, pulmonary diseases, and other diseases were noted both before and after diagnosis. Prior to diagnosis, they had more congenital abnormalities, respiratory and eye diseases, and injuries than after diagnosis [76].

Increased ingestion and reduced activity may be the cause of obesity in narcolepsy. Since hypocretin regulates food intake and glucose and fat metabolism, hypocretin deficiency can lead to rapidly increased BMI in children with narcolepsy type 1. Wang et al. (2016) suggested that decreased basic metabolic rate (BMR) may play a role in the increased BMI. With a prolonged disease course, BMI growth may decrease gradually, along with restoration of BMR, indicating a possible compensatory metabolic mechanism in children with narcolepsy [77].

Vandi et al. (2019) found that pediatric patients with narcolepsy type 1 close to disease

onset had an impaired capability to modulate arterial blood pressure for nocturnal wake-sleep transition. This finding may be related to a direct consequence of hypocretin neuron loss and indicates a possible cardiovascular risk that remains to be determined [78].

Aran et al. found impaired academic performance and fewer social activities in children and adolescents with narcolepsy [41]. A systemic review of cognition of pediatric narcolepsy that included eight studies published between 2005 and 2015 demonstrated that children with narcolepsy had a significant risk of cognitive impairment, as well as such emotional problems as depression, anxiety, and low self-esteem [79]. Witt et al. (2018) found in their adolescent narcoleptic patients that narcolepsy is not just characterized by a deficit in working memory. The cognitive impairment of narcolepsy is rather an imbalance of cognitive resources in monitoring and maintaining attention [80]. Recently, Quaedackers et al. conducted a study exploring social functioning impairments in children with narcolepsy compared to healthy controls. Their results also revealed that impaired social functioning is common in pediatric narcolepsy [81]. A prospective study including narcoleptic patients with onset in childhood or adolescence in Denmark found that narcolepsy significantly influenced educational level, grading, social outcome, and welfare consequences, independent of parental social levels [82]. Adolescents with narcolepsy often report depressive symptoms, which can be associated with poor sleep quality, EDS, and low physical activity levels [83].

Considering the negative impact of narcolepsy and its comorbidities on the development of children and adolescents, early recognition and careful monitoring is essential. Intervention is necessary to control the damage and reduce the impact of both the narcolepsy and its related diseases.

11.7 Summary of the Key Findings and Research Gaps

The diagnosis of narcolepsy in children can be difficult due to insufficient knowledge and underrecognition. The presentation of pediatric narcolepsy may differ from that of adult patients. EDS in children may manifest as irritability, hyperactivity, and poor attention, which may be incorrectly interpreted as misbehavior. Pediatric cataplexy can be subtle, such as unusual facial expressions, which are not observed in adults.

Pediatric narcolepsy is associated with many morbidities, including rapid weight gain, possible cardiovascular risk, cognitive impairment, depression, and anxiety. Children's school performance and social functioning can also be impaired by narcolepsy and its comorbidities. Early diagnosis and intervention are needed to decrease its negative influence on children's development. The use of medication, behavior modification, and education are vital for helping to improve narcolepsy symptoms.

Future research is warranted in several areas. First is the effectiveness of medications in the pediatric population by randomized placebo-controlled studies. Second, the symptomatology of pediatric narcolepsy needs further exploration to assist diagnosis. Last, prospective long-term follow-up is necessary to evaluate the long-term prognosis and outcome for children with narcolepsy.

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12 Circadian Rhythm Sleep Wake Disorders

Joey W. Y. Chan

12.1 Case Vignette

Johnny is a 17 years old boy who was referred to the sleep clinic because of chronic "refractory insomnia" and daytime sleepiness. He was not able to get up in the morning and was often late for school. He missed over 80% of his morning class and school warned him for dismissal. He has very irregular sleep wake schedule. On school days, he struggles to get up at around 9 a.m. He falls asleep only at 3 a.m. despite he went to bed at 12 a.m. Because of the sleep deprivation, he often dozes off in the morning class and has academic deterioration. On the free day, he falls asleep at 3–4 a.m. and gets up at 11–12 a.m., he feels refreshed after waking with adequate sleep duration and quality. He has been prescribed hypnotics and sedative antidepressants for his complaint of persistent difficulty in initiating sleep but had limited improvement. He otherwise enjoys good past health. He has no symptoms of other sleep problems and no prominent mood disturbance.

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12.2 The Molecular Clock

Circadian (circa = about; dies = day) rhythm is the oscillation of bodily functions along the day-night cycle that influences our mood, behavior and biological functions. The endogenous circadian pacemaker lies within the suprachiasmatic nucleus (SCN), which coordinates multiple circadian biological rhythms. The SCN has a self-sustained autonomous rhythm which lasts approximately 24 h and is controlled by the underlying molecular mechanisms: the core circadian genes include *CLOCK and t*he *CLOCK:BMAL1* heterodimer initiates the transcription of *PER* and *CRY* genes. In mammals, it has been shown that the *CLOCK-BMAL1* activates the transcription in the daytime and there is an accumulation of *PER* and *CRY* proteins in the late afternoon or evening. The resulting *PER* and *CRY* protein dimerize and inhibit further *CLOCK:BMAL1* transcription, thus forming a transcriptional translation feedback loop (TTFL). There is a second negative feedback loop as the *CLOCK-BMAL1* complex also activates the nuclear receptors REV-ERBα and REV-ERBβ, the REV-ERB α and REV-ERBβ in turn, lead to the repression of *CLOCK* and *BMAL1*. There are other regulatory elements such as the PAR-bZip (proline and acidic amino acid-rich basic leucine zipper) factors DBP (D-box binding protein), TEF (thyrotroph embryonic factor) and HLF

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(hepatic leukaemia factor), that regulate the TTFL. This molecular clock mechanism is not unique to the SCN, emerging evidence shows that virtually all cells express these genes and have the capacity to generate these oscillations. The circadian clock in mammals is now conceptualized as a hierarchical system in which a clock located in the hypothalamic SCN acts as a master pacemaker to synchronize or entrain peripheral clocks distributed throughout the body (for a review: [1].

12.2.1 Circadian Entrainment

The period of the human intrinsic clock is autonomous, highly precise and stable, and is near 24 h [2]. As the endogenous circadian period (*tau)* is slightly longer than 24 h, it is reset constantly to synchronize with the environment, this process is called *entrainment*. Light is the strongest environmental cue for entrainment, together with exercise, social activity, food intake, they form a constellation of environmental stimuli (*zeitgebers)* that entrain our internal biological clock with the external environment. The SCN receives input from the intrinsically photosensitive retinal ganglion cells (ipRGCs), with which possess a special photopigment, melanopsin, that is most sensitive to short wavelength light ~480 nm (the blue spectrum) [3]. The projections from ipRGCs form the retinohypothalamic tract (RHT) to the SCN, which then signals the pineal gland via the sympathetic fibers of superior cervical ganglion to regulate the production of melatonin. Melatonin has an important role in regulating our sleep-wake cycle. The increase in sleep propensity at night is tightly associated with the onset of melatonin production and its production is suppressed by low intensity of light at night (LAN) [4]. The common phenomenon of electronic device usage in the adolescence was associated with long sleep onset latency, short sleep duration and sleep deficiency.

12.2.2 Human Phase Response Curve

Humans respond to environmental *zeitgebers* differently at different time of the day. In daytime, SCN receives light signal and inhibits melatonin production of the pineal gland. At night, when light is dim, melatonin is secreted to facilitate sleep. A pictorial representation of the circadian phase response to the *zeitgeber* across different times of the day is called a *phase response curve* (PRC) [5]. In a normal person, light exposure in the morning advances the circadian rhythm, while exposure at night delays it. Interestingly, timed-administration of melatonin is about 12 h out of phase with the PRC of light. The PRCs of light and melatonin carry important implications in the treatment of circadian rhythm related disorders, as the timing of exposure to these zeitgebers is of critical importance in phase-shifting the endogenous rhythm in the desired direction. Apart from light and exogenous melatonin, other non-photic stimuli, such as mealtime, exercise and social contacts, may also phase shift the human circadian rhythm For a review: [6].

12.2.3 Circadian Influence on Sleep

It is postulated that sleep is regulated by a two process model, namely the Process S and Process C [7]. Process S refers to the homeostatic sleep drive, which increases with the time of wakefulness and declines during sleep. Process C, on the other hand, refers to the circadian drive, which oscillates rhythmically throughout the day. The circadian drive for arousal is highest during the daytime and lowest during sleep. During the day time, when homeostatic sleep pressure gradually builds up with each hour of wakefulness in the latter half of the day, the circadian drive of arousal consolidates the wakefulness. When sleep propensity is assessed by enforcing an ultra-short sleep cycle (13 min waking/7 min sleep) across different clock times of the day following a night

of sleep deprivation, it was found that circadian drive for wakefulness ceased after the "wake maintenance zone". The "wake maintenance zone" is located approximated 2 h before habitual sleep time, leading to an abrupt onset of sleep period [8]. At night, when sleep pressure quickly dissipates with sleep, the circadian drive for arousal remains at its lowest to consolidate sleep particularly over the second half of the night. The sleep latency is shortest at the minimum of the endogenous circadian rhythm of the core body temperature. The interaction of homeostatic drive and circadian drive regulates our sleep wake cycle in accordance to the external solar environment and sleep need.

12.3 Overview of Circadian Sleep Wake Disorders

Circadian Rhythm Sleep Wake Disorders (CRSWDs) manifest as a chronic or recurrent pattern of sleep-wake rhythm disruption primarily due to alteration of the endogenous circadian timing system or a misalignment between the endogenous circadian rhythm and the sleep-wake schedule desired or required by an individuals' physical environment or social/ work schedules [9]. CRSWDs could be divided into intrinsic and extrinsic disorders. Both types of circadian misalignment could be associated with sleep disruption and impairment in daytime functioning. Intrinsic CRSWDs are thought to be due to chronic alternations in the endogenous biological clock that leads to a persistent misalignment with the external light-dark cycle, these includes delayed sleep-wake phase disorder (DSWPD), non 24-h sleep wake phase disorder (N24SWD)/ free-running disorder, irregular sleep-wake rhythm disorder (ISWRD) and advance sleep wake phase disorder (ASWPD). On the other hand, extrinsic CRSWDs occurs when there is a misalignment due to exogenous factors, for example, jet lag and shift work disorders. This chapter will focus on the discussions of intrinsic CRSWDs (Fig. 12.1).

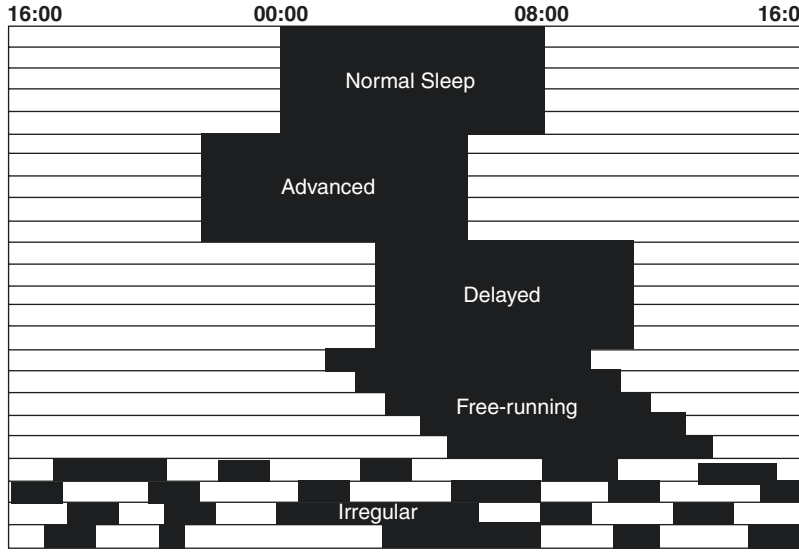

Fig. 12.1 Illustrates the misalignments of the intrinsic CRSWDs in relation to the normal sleep-wake cycle. Time depicted in the figure is the clock time

12.4 Diagnosis

According to the International Classification of Sleep Disorders—third edition (ICSD-3) [9], the general criteria for diagnosing CRSWDs include:

1. A chronic or recurrent pattern of sleep-wake rhythm disruption primarily due to alteration of the endogenous circadian timing system or misalignment between the endogenous circadian rhythm and the sleep-wake schedule desired or required by an individual's physical environmental or social/ work schedules.
2. The circadian rhythm disruption leads to insomnia symptoms, excessive sleepiness, or both
3. The sleep and wake disturbances cause clinically significant distress or impairment in mental, physical, social, occupational, educational, or other important areas of functioning.

Diagnosis is based on clinical findings, it is important to obtain the details of sleep pattern both on free days (supposed the free manifestation of the endogenous rhythm) and on work days (the required sleep-wake schedule). The discrepancy of the week-day and weekend sleep mid-points are termed as "social jetlag". It is worth noting that there is no fixed clock time or temporal cutoffs for defining a circadian rhythm sleep wake disorder in the current diagnostic criteria, and this contributes to difficulty in phenotyping and ascertaining the true prevalence [10]. Biological measurement is not mandatory for the diagnosis but would be valuable in assessing the phase of the endogenous rhythm.

12.5 Delayed Sleep-Wake Phase Disorder (DSWPD)

12.5.1 Epidemiology

DSWPD is the most common CRSWD, the prevalence in the adult general population is 0.2–16% depends on the case definition [5]. Consistent with a gradual change in the sleep-wake cycle along the age: a progressive delay from childhood to early adulthood, then a gradual advance towards increasing age [11], the onset of DSWPD typically occurs in the adolescence, with a higher prevalence ranging from 3.3% to 4% among adolescents and young adults.

12.5.2 Pathophysiology

DSWPD is associated with polymorphisms in the circadian genes (e.g. the PER and CLOCK genes). The proposed mechanisms of DSWPD included a longer circadian period (*tau*) resulting in the difficulty of advancing the rhythm to maintain a proper entrainment, a delay in internal circadian phase and/ or an altered phase relationship of sleep and endogenous markers. Other potential mechanisms included a greater sensitivity to phase-delaying effect to light, a slower dissipation of homeostatic sleep drive, and a later light exposure pattern resulting in less daily advancing light exposure. For a review: [5, 12]. Recently a reduced melanopsin-dependent retinal phototransduction was also being investigated [13].

12.5.3 Presenting Features

12.5.3.1 Poor School Performance

Adolescents with DSPWD struggled to get up early for school and to remain awake in class.

DSWPD is associated with school absenteeism, impaired functioning and poor academic performance. It was found that for those with weekday bedtime after 22:00, the later the bedtime, the lower is the school performance as measured by the grade point average (GPA) in a large cohort of 7798 adolescents aged 16–19 [14].

12.5.3.2 Insomnia

The adolescent typically presents with sleep initiation insomnia at night and difficulty to get up in the morning for school. DSWPD patients typically present with difficult to fall asleep at a desired clock time. It was shown that more than half of the adolescents with DSWPD also met the Quantitative Criteria for Insomnia [15], whereas an estimated 10% of patients with chronic insomnia disorder may be more appropriately diagnosed with DSWPD [12]. However, when allowed to sleep at their own desired time on free days, patients with DSWPD usually go to bed and wake at a later time schedule and are able to achieve the quality and duration for a good sleep. A study compared the sleep variables with healthy controls and found DSWPD patients had normal sleep onset latency, sleep duration and sleep efficiency when they were at the ad libitum sleep-wake schedule [16].

12.5.3.3 Neuropsychiatric Presentations

Apart from sleep complaints, there are increasing evidence suggesting circadian disturbances may play a role in the pathogenesis of mood disorders. Delayed sleep phase is associated with lower average school grades, smoking, alcohol usage, and elevated anxiety and depression scores. Eveningness, a circadian preference towards delayed sleep, was also associated with excessive daytime sleepiness and increased risk of depression in adolescents [17]. As much as 70% of patients with DSPD will fulfil the Diagnostic and Statistical Manual of Mental Disorders—fourth edition (DSM-IV) diagnostic criteria of an Axis I psychiatric disorder, in particular mood, anxiety (most frequently specific phobia) and substance use disorders [18].

On the other hand, patients with autistic spectrum disorder (ASD) have a high incidence of sleep disorders, including circadian rhythm sleep wake disorders, of which DSWPD is the most common phenotype [19]. Similarly, self-reported attention deficit and hyperactivity disorder (ADHD) symptoms increased the odds of insomnia and delayed sleep phase syndrome from a large population study [20]. These suggested that one should look out for delayed sleep-wake problems in young patients with psychiatric co-morbidities. It is also imperative to enquire for mood and other psychological symptoms in patients with DSWPD, for they could be both consequential symptoms or co-morbidities.

12.5.4 Diagnosis

The diagnosis of DSWPD requires a detailed history on the usual sleep wake pattern and sleep habits. The ISCD-3 stipulates that there is a significant delay in the major sleep episodes in relation to the desired sleep and wake time, which last for at least 3 months. When patients are allowed to choose their ad libitum schedule, they will exhibit improved sleep quality and duration appropriate for age and maintain a delayed phase of the 24-h sleep-wake pattern [9].

Sleep log for at least 7 days is essential for diagnosis, ICSD-3 also suggests clinical evaluation to be supplemented by (1) actigraphy, (2) biological measurements demonstrating a delay in the timing of other circadian rhythms, such as melatonin measured by DLMO or urinary 6-sulfatoxymelatonin sampled across 24-h period and (3) standardized chronotype questionnaires (Fig. 12.2).

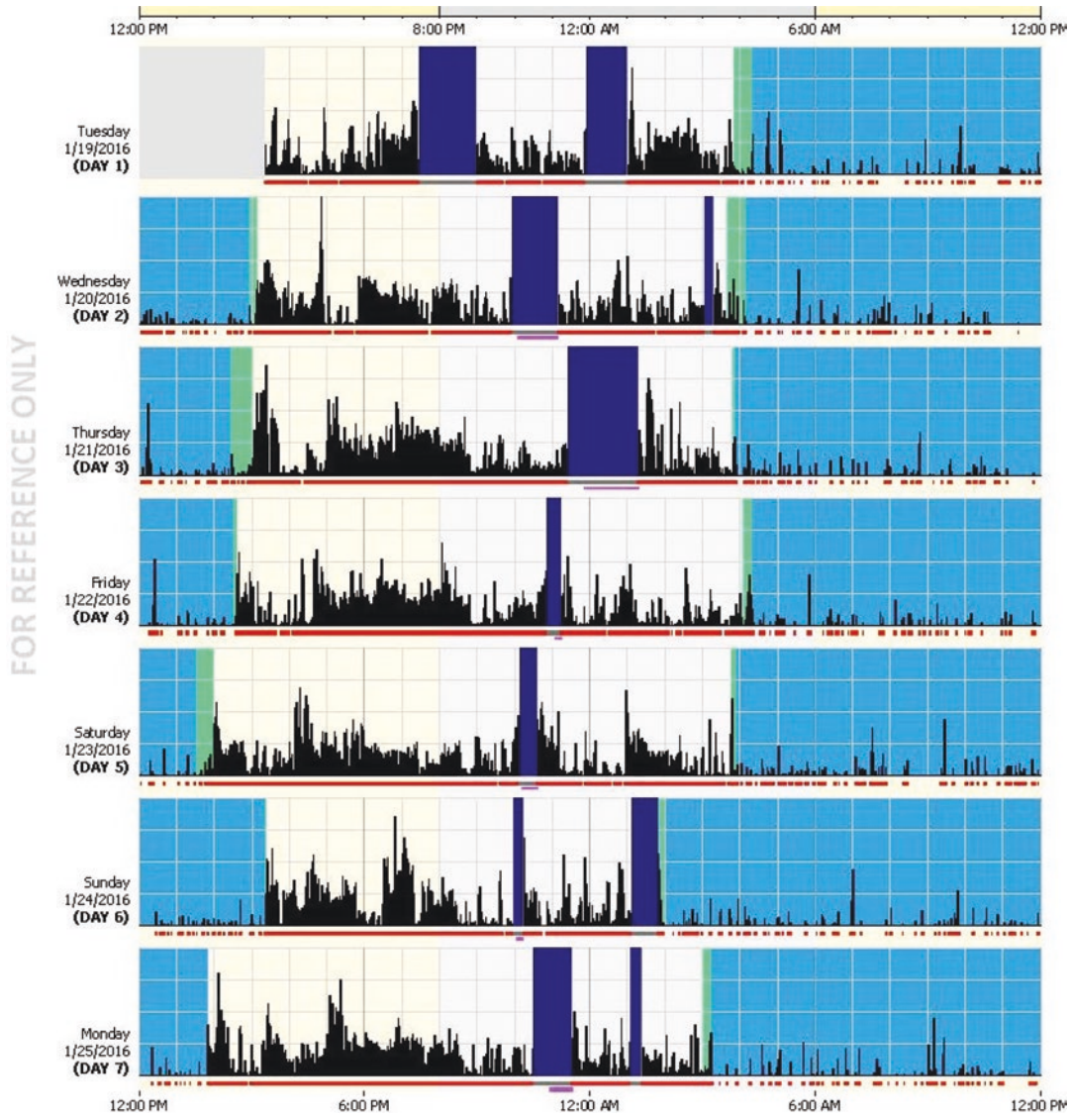

Fig. 12.2 Illustrates a 7-day recording of the actigraphy. The black spikes represent the activity counts. Based on the pre-defined algorithm, blue area represents the rest period. The rest time was delayed at 2–4 a.m.; and the wake time is around 2–3 p.m.

12.5.4.1 Actigraphy

Actigraphy involves the use of a portable device that records movements over an extended period of time. It provides an objective measurement of the sleep-wake activities across days to weeks. It is usually worn on the non-dominant wrist. Subjects would be instructed not to take it off-wrist unless during bathing or water-sports. Collaborated with a sleep diary, which records the bedtime, sleep onset time, wake up time and rise time, actigraphy gives a valuable assessment on the individuals' sleep wake cycle. According to the Clinical Practice Guideline on the use of actigraphy for the evaluation of sleep disorders and CRSWDs published by the American Academy of Sleep Medicine (AASM) in 2018 [21], clinicians are suggested to use actigraphy in the assessment of pediatric

patients with CRSWDs. It has been suggested that sleep log and/or actigraphy should be standardized to 14 days across all the CRSWDs [10], as it captures 2 weekends or non-work days, thus would provide a more complete view of the sleep-wake activity when unconstrainted by work or school.

12.5.4.2 Biological Measurements

Circadian rhythm is demonstrated in many physiological and endocrine functions. There are different ways in measuring the endogenous circadian rhythm. This usually involves continuous or serial periodic samplings of biological markers, e.g. cortisol, melatonin level or the core body temperature.

12.5.4.3 Melatonin

Melatonin is secreted by the pineal gland. It is a preferred circadian marker because it is comparatively less affected by the external environmental factors when compared to the core body temperature, cortisol and heart rate. However, melatonin is very sensitive to light at night and has to be collected under dim light condition. Lewy et al. has proposed to use the onset of melatonin secretion in dim light (i.e. Dim light melatonin onset, DLMO) as a marker of circadian phase [22]. DLMO could be estimated by serial collection of blood, saliva or urine, the latter two are the feasible options for out-patient investigations. The correlation coefficient between plasma and salivary assessment of DLMO is 0.93, and salivary DLMO is proposed to be the most practical and reliable method for assessing circadian phase. Subjects would usually be asked to provide salivary sample at 30 to 60-min intervals, starting from the early evening to 1–2 h after habitual bedtime. DLMO has been validated in the adolescents. In children between 6 and 12 years DLMO is considered to be normal if it occurs between 19:00 and 21:00 h [23] and in a range of 20:32–21:53 for adolescents aged 9–18 [24]. DSPD patients had significantly later timed melatonin profiles that were delayed by approximately 3 h compared to normal sleepers [5]. However, it is worth noting that only about 50% of the clinically diagnosed DSWPD patients had a misalignment between the DLMO and the desired bedtime, suggesting that the reported difficulties in initiating sleep at the desired bedtime could not be explained solely by the mis-timing of the circadian rhythm of sleep propensity [25]. Those who had a delayed in DLMO relative to the desired bedtime were at a higher risk of depressive symptoms and increased DSPD severity [25].

12.5.4.4 Standardized Chronotype Questionnaires

Circadian typology, or chronotype, is the optimal timing for rest and activity of an individual. Some more commonly used self-reporting questionnaires include the Morningness-Eveningness Questionnaire (MEQ), Composite Scale of Morningness (CSM) and Munich ChronoType Questionnaire (MCTQ). The MEQ is a 19-item self-reporting questionnaire enquires about the individual's preferred timing for sleep and activities. Using the MEQ, one could be classified as the morning-type (*i.e. the larks)*, intermediate-type, or the evening-type (*i.e. the night owls).* The score of MEQ ranges from 16–86, and the lower the score indicates a higher tendency of eveningness. Subsequently, a reduced-MEQ (rMEQ), which consisted of five questions extracted from the original 19-item MEQ, was validated for assessing chronotype [26]. A study involving 4849 adolescents in Hong Kong found that 23% of them belonged to the evening-type by the rMEQ. The evening-type adolescents not only had a delayed sleep wake cycle, but they also had more insomnia with predominantly difficulty in initiating sleep, as well as a higher risk of emotional and behavioral problems than the intermediate-type or morning-type counterparts [27]. The CSM has 13 items, among which 9 items were taken from MEQ. It is not surprising that MEQ and CSM had a high degree of correlation of r=0.9 MCTQ measures the sleep-wake behavior on work and free days and uses the midpoint of sleep on free days (MSF), corrected for sleep debt accumulated during the work week as an indicator of chronotype (MSFsc). These questionnaires have the potential in identifying subjects with extreme chronotype, who are at risk of circadian rhythm sleep wake disorders. For a review: [28].

12.5.5 Treatment

The approach we adopt to patients with DSWPD includes a detailed rest-activity pattern, sleep difficulty, and assessments to rule out other comorbid sleep and psychiatric disorders. Sleep hygiene is enforced in every case of CRSWDs. It is important to educate the patient and their carers about the nature of the illness, and the rationale of the treatment. The chronotherapeutic strategies used in DSWPD include timed bright light therapy (BLT), timed melatonin, light avoidance and chronotherapy. Before the initiation of timed BLT or melatonin, subjects should be advised to maintain a regular sleep-wake cycle as an irregular sleep/wake pattern itself is associated with more delayed sleep/wake timing, a more regular sleep-wake timing is also important on appropriately time the chronotherapeutic treatment.

12.5.5.1 Timed Light Therapy

Bright light, if given at appropriate timing, can phase shift the endogenous rhythm. According to the light PRC, bright light therapy should be initiated after the core body temperature minimum (CBTmin) to phase advance the rhythm. As biological measurements are not always available, optimal time of light exposure could be given at 1 to 2 h after the sleep midpoint [29]. An alternative way is to start light treatment at the natural wake time. In both ways, the timing of light therapy could be gradually advanced 15–30 min every other day. Bright light could be delivered via a light box or a light visor. There was a high level of heterogeneity across different trials, in terms of the light intensity, spectrum, duration, timing and the outcome measured. Light intensity ranges from 500 to 10,000lux have been employed.

A meta-analysis of controlled trials in DSPD reported an effect size of 0.32 for morning light interventions in advancing sleep time, which could be translated to 25 min of earlier sleep timing [30]. From the 2015 Clinical Practice Guideline of the American Academy of Sleep Medicine (AASM) for the treatment of intrinsic circadian rhythm sleep-wake disorders, evidence is not sufficient to recommend light therapy as a stand-alone treatment but weak recommendation was given to light treatment given in combination with behavioral interventions for children/ adolescents [31]. More recent trials also showed mixed results. Gradisar et al. evaluated the efficacy of 6 weeks of bright light therapy combined with cognitive behavioral therapy (CBT) in advancing the sleep-wake cycle, and found significant improvement in sleep onset time, total sleep duration and daytime sleepiness [32]. Moreover, many of these improvements were maintained at the 6-month post-treatment follow up, suggesting CBT with a focused on circadian sleep disorder might be a useful treatment modality to consolidate the improvements. However, in a randomized controlled trials that examined the efficacy of green light via a light visor in combination of morning activity, no significant difference was found between green light versus placebo light [33]. Similarly, in another RCT that randomized 40 DSWPD subjects to one of the four treatments: (1) dim light (placebo) + placebo capsule, (2) bright light + placebo capsule, (3) dim light (placebo) + melatonin capsule, and (4) bright light + melatonin capsule for 2 weeks. All of these treatment condition (bright light, melatonin, combination, and placebo) were on a gradual advancement of the rise time schedule, they were almost equally effective in advancing sleep, DLMO [34]. There was a second randomization after 2 weeks to either no treatment or a combination of bright light and melatonin, the treatment group was able to maintain the advanced sleep and the improvements of daytime functions. This study suggested that a gradual advancement of rise times seems to have positive effects on sleep timing and daytime functions, but the effect may wear off and the use of bright light and melatonin is beneficial to maintain the positive effect over time. The relapse rate of DSWPD is high, thus it is important to consider maintenance treatment.

12.5.5.2 Timed Melatonin

Melatonin has both soporific effect and chronobiotic effect (drugs that shift central circadian timing) [35]. The melatonin PRC is 12-h out-of-phase with the PRC of light, such that dosing in the

afternoon/evening shifts the endogenous rhythm earlier, while dosing in the morning shifts rhythms later. Melatonin could be given approximately 5–6 h before habitual bedtime to shift the endogenous rhythm earlier. The time of administration could be advance gradually until a desirable sleep timing is achieved. Melatonin is generally well-tolerated, possible side effects included sleepiness, dizziness, headache, blood pressure changes, gastrointestinal upset. Though there is no major safety concerns but there is a concern about the potential effect of melatonin on sexual maturation, thus melatonin should only be given when the benefits outweigh the risks in prepubertal children [35]. According to the 2015 AASM Clinical Practice Guideline for treatment of intrinsic CRSWDs [31], a weak recommendation was given to timed oral administration of melatonin or agonists for children/ adolescent with or without psychiatric comorbidities.

12.5.5.3 Light Avoidance

Based on the human phase response curve, light at night (LAN) would phase delay the circadian rhythm and suppressed melatonin, a large interindividual variability to light sensitivity has been reported [4]. Some trials have employed avoidance to evening light (e.g. use of an amber glass or avoid exposure to electronic device) as part of the circadian intervention. Though definite superiority of adding evening light avoidance to morning light exposure could not be established in the meta-analysis of DSWPD trials [30], it may also be helpful to reduce engaging/arousing activity before sleep.

12.5.5.4 Chronotherapy

It was postulated that patients with DSWPD had an inadequate capacity to achieve phase advance shifts of the circadian pacemaker, thus chronotherapy was designed to reset the biological clock by the phase delay route [36]. Patients were instructed to delay their sleep time successively over a course of 5–6 days until the sleep-wake cycle synchronized with the desired clock time. Czeisler et al. reported a case series of 5 patients with delayed sleep phase insomnia and found a lasting resolution in all five of them [36]. However, cautious must be taken as chronotherapy may precipitate the development of non 24-h sleep wake pattern in patients with DSWPD.

(Note: The term "chronotherapy" is also being used with another meaning, for example, (1) in a broader sense to include the change of sleep and wake time gradually in a manner that favors the individual's circadian preference, with subsequent strict adherence to the achieved/ desired sleep/wake schedule, or (2) as a acronym for chronomedicine, with which medication is timed according to the circadian rhythm to minimize side effects and/or to achieve the maximal effect)

12.5.5.5 Treatment in Co-Morbid Conditions

For patients with eveningness tendency and comorbid depression, there is evidence suggesting that adjunctive bright light therapy might be useful both in advancing the circadian rhythm and alleviating the depressive symptoms in adults [37]. On the other hand, a randomized controlled trial comparing the efficacy of BLT+melatonin *vs* melatonin *vs* placebo in DSWPD and ADHD found that DLMO was advanced in both treatment groups, but only the melatonin group had an improvement of ADHD symptoms. Of note, these improvement of DLMO and ADHD symptoms returned to baseline 2 weeks after cessation of treatment [38]. Further research is needed on how to augment the treatment efficacy and to consolidate the improvement.

12.6 Non-24 H Sleep-Wake Disorder (N24SWD)

In patients with N24SWD, the endogenous rhythm loses the entrainment with the external environment, and is "*free-running*". Typically, the sleep-wake cycle delays each day, resulting in a constantly drifting rhythm that is out-of-syn with the environment, causing difficulty sleeping, excessive daytime sleepiness or both [9].

N24SWD is observed in up to 50% of blind people but is thought to be rare in sighted individuals. N24SWD is challenging to diagnose,

sleep diary or actigraphy for at least 14 days should be included for diagnosis. It has been suggested to initiate treatment when the sleep-wake time has drifted within 1–2 h of the desired time, with appropriately timed melatonin 2–4 h before sleep onset and bright light after wake [39].

12.7 Irregular Sleep-Wake Rhythm Disorder (ISWRD)

The characteristics of ISWRD is an absence of a well-defined circadian rhythm of sleep and wake. The temporal pattern of sleep and wake is disorganized and variable throughout the 24-h cycle. It is more commonly observed in neurodegenerative disorders, such as dementia; and in children with developmental disorders. The diagnostic features in the ICSD-3 is a recurrent pattern of irregular sleep and wake episodes throughout the 24-h period leading to symptoms of insomnia at night and excessive sleepiness in daytime for at least 3 months [9]. Current data support the use of appropriately timed melatonin to treat ISWRD in children/adolescents with neurological disorders [31]. Timed bright light therapy has been recommended in elderly with dementia but there is insufficient evidence to support the use of combination treatment in children/ adolescents with ISWRD [31].

12.8 Advanced Sleep-Wake Phase Disorder (ASWPD)

In patients with ASWPD, the sleep-wake cycle is advanced typically for two or more hours relative to the desired or required sleep time and wake-up time. Affected individuals complained of early morning awakening or sleep maintenance insomnia, and excessive evening sleepiness [9]. ASWPD is found to be rare in the general population using the strict ICSD criteria. As chronotype advances with age [11], the prevalence of ASPD increased with age and the condition is thought to be more common in the older people. But a familial form of ASWPD has been detected with an autosomal dominant inherited missense mutation at the Period 2 gene [40]. For clinical assessments, sleep log for at least 14 days should be obtained, and actigraphy and chronotype questionnaires should be administered where possible. Treatment is targeted to delay the endogenous rhythm, for example, evening bright light and melatonin 1–2 h after waking. The AASM 2015 Clinical Practice Guideline recommends treating ASWPD adult patients with evening light therapy, but there is not enough evidence to recommend the use of melatonin [31].

12.9 Conclusion

CRWSDs commonly presented as sleep disturbances or excessive daytime sleepiness; in pediatric patients it may masquerade as academic deterioration, poor school performance, or mood problem. Detailed sleep-wake history and assessments with sleep log are essential for ascertaining the diagnosis.

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13 NREM Parasomnias: Disorders of Arousal

Joyce Siu-Ping Lam

13.1 Vignette

An 8-year-old boy was brought in by his parents for consultation of his nocturnal behaviours. The parents reported that he had repeated episodes of nocturnal screaming since the age of 3. Initially, he presented with loud screaming that happened after an hour of sleep. He looked confused, frightened and sweated profoundly during the screaming. The episode mostly lasted for a few minutes or less, then he would fall back to sleep. Since the age of 6, parents reported instead of screaming, sometimes he would leave his bed and walk around at home. He might mumble and mostly looked dazed. At most times, he went back to bed and fell asleep. He had no memory recollection about the screaming or walking upon waking up. As the condition happened rarely, a few times per year, they did not seek medical advice till now when these episodes occurred more frequently. Two weeks ago, he attempted to open the window during the nocturnal wandering and was stopped by his parents. They attempted to wake him but ended up with him fiercely screaming and crying. It took an hour to wake him up fully. Parents reported that he may have such episode if he has febrile illness. The boy had no other medical problems, apart from being overweight. He gained a significant amount of weight in past 1–2 years. Father reported he had similar events in his childhood, but just a few occasions and he no longer had such condition since he grew up.

13.2 Epidemiology

According to the International Classification of Sleep Disorder, third edition (ICSD-3) [1], disorders of arousal (DOAs) are classified under non-rapid eye movement (NREM) parasomnia, suggesting its occurrence at NREM sleep. It is first coined by Broughton in 1968, describing a spectrum of nocturnal behaviours which share common feature of sudden, incomplete awakening during NREM sleep (mostly from stage 3 slow wave sleep) [2]. The classical DOAs include confusional arousals, sleepwalking (somnambulism) and night terror.

These DOAs are usually disorders of children with no gender difference, and commonly occur at the first half of sleep where slow wave sleep is abundant. Instead of a distinct entity, these DOAs may co-exist and appear as a continuum in children [3]. While confusional arousals usually happen in infants and toddlers, night terror is more commonly found among preschoolers. The age of onset of sleepwalking is later compared to confusional arousals and night terror, at around 5

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to 10 years of age [3]. These disorders usually disappear when the children grow up, align with the decrease in slow wave sleep with age. A cohort study of over 1300 children reported that night terror disappears in 67% of children by the age of 10, while sleepwalking resolves in 76% of children by the age of 13 [4].

Varying prevalence rates of DOAs have been reported, ranging from <1% to more than 20%, according to different study methodologies. A meta-analysis looking into 51 published prevalence studies on sleepwalking in children and adult populations reported a great variation of prevalence rates. The study reported a current prevalence of sleepwalking of 5.0% in children and a lifetime prevalence of 6.9% [5]. There is no similar meta-analysis data for confusional arousals or night terror. The high variability of prevalence rates was partially contributed by self-reporting and recall bias. Given the characteristics of impaired consciousness and common occurrence in childhood, the reliability of self-reporting could be hampered, particularly for studies carried out among adult populations. Another contributing factor of the wide range of prevalence rates of DOAs is diagnostic accuracy. Most studies included a single question on DOAs and its interpretation was subjected to individual's understanding. An epidemiological study adopted a sophisticated computer system, the Sleep-EVAL, which had been validated against clinical assessment and polysomnographic data, to conduct the interview. The study reported a relatively low rates of 4.2%, 2.2% and 2.0% for confusional arousals, night terror and sleepwalking, respectively [6].

13.3 Aetiology

The aetiology of DOAs is not fully understood. Given the common features of occurrence in childhood and cessation in adolescence, DOAs are regarded as a developmental condition or a disorder of sleep maturation, with hypothesis of immaturity of neural circuits, synapses and receptors [7]. A study compared 73 children and adolescents with parasomnia, reported more than one third had perinatal risk factors such as premature delivery and asphyxia [8]. Moreover, 40% of the subjects had developmental disorders such as attention deficit hyperactivity disorder, dyslexia and dysgraphia. However, the study findings had to be replicated in further large scale epidemiological studies so as to delineate the association of DOAs and other developmental disorders.

Apart from developmental hypothesis, NREM instability with an interplay between SWS and wakefulness has also been proposed and investigated [9]. Compared to non-sleepwalkers, sleepwalkers showed an unusually elevated number of spontaneous awakenings, abnormal slow wave activity and atypical cyclic alternating pattern during SWS. [9–13] A change in EEG functional brain connectivity prior to the onset of sleepwalking episode had been reported, suggesting a concomitant presence of arousal and deep sleep processes prior to the onset of sleepwalking [14]. Brain imaging studies also reported the dissociation nature of DOAs, particularly in sleepwalking [15, 16]. A study using single-photon emission computed tomography (SPECT) showed a distinct perfusion patterns during a sleepwalking episode. There were simultaneous activation in the posterior cingulate cortex and the anterior cerebellum, and deactivation of the arousal system, namely, the frontoparietal associative cortices [15]. Neuroimaging findings of abnormal coexistence of local sleep and wake brain activities have also been reported in other study, and hence affirming the dissociation of behaviors and varying degree of consciousness during DOAs [16].

This NREM instability serves as an important component in understanding the patho-

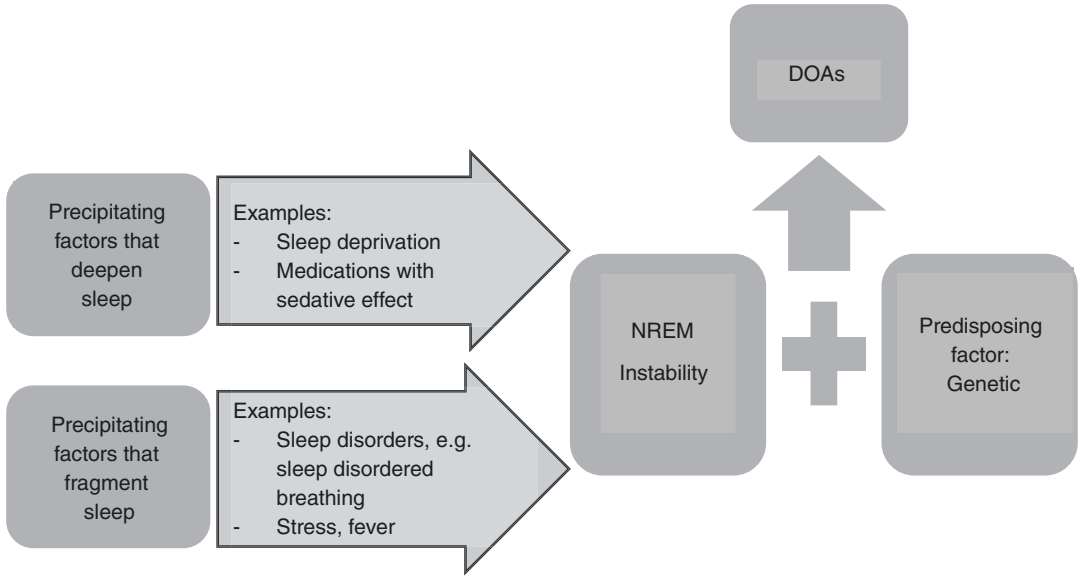

Fig. 13.1 Three Factor Model of Disorder of arousals (DOAs)

physiology of DOAs, by the three-factor model (Fig. 13.1). In DOAs, there is known familial basis serving as predisposing factor, particularly night terror and sleepwalking. Studies revealed that the prevalence of sleep terror and sleepwalking in first degree relatives was at least ten times greater than that of the general population. And there was a 60% risk of sleep terror if both parents were affected [17]. The odds of having sleepwalking also increased with the number of parents affected, rising from 3 times to 7 times when both parents had history of sleepwalking [3]. Despite a known familial association of DOAs, there are limited genetic studies. One study reported a genome-wide investigation of a single family of 22 sleepwalkers and found a significant linkage to chromosome 20q12-q13.12 [18]. Some reported the association between DOAs and *HLA-DQB1*05:01* [19, 20].

While genetic effect serves as predisposing factor, there would be precipitating factors causing the NREM instability and cumulating the DOAs episodes [21]. Factors that deepen sleep or increase slow wave sleep, such as compensation sleep after sleep deprivation, would induce DOAs in predisposed individuals. Conditions that result in sleep fragmentation, such as stress, sleep disorders like sleep apnoea and periodic leg movement, could prime the occurrence of DOAs [21]. A case control study involved 84 prepubertal children with repetitive sleep terrors and sleepwalking and 36 healthy control children, examined the possible triggers of parasomnia by clinical assessment and polysomnography. The study found a high comorbidity (61%) of sleep disorders among children with repetitive parasomnias, particularly sleep disordered breathing (SDB) [22]. Internal events such as febrile illness and a full bladder during sleep could also serve similar effect. Noisy environment is one of the known priming effects. Hence, making a loud noise during slow wave sleep is adopted in sleep laboratory as a maneuver in inducing sleepwalking episodes in predisposed subjects (Fig. 13.2).

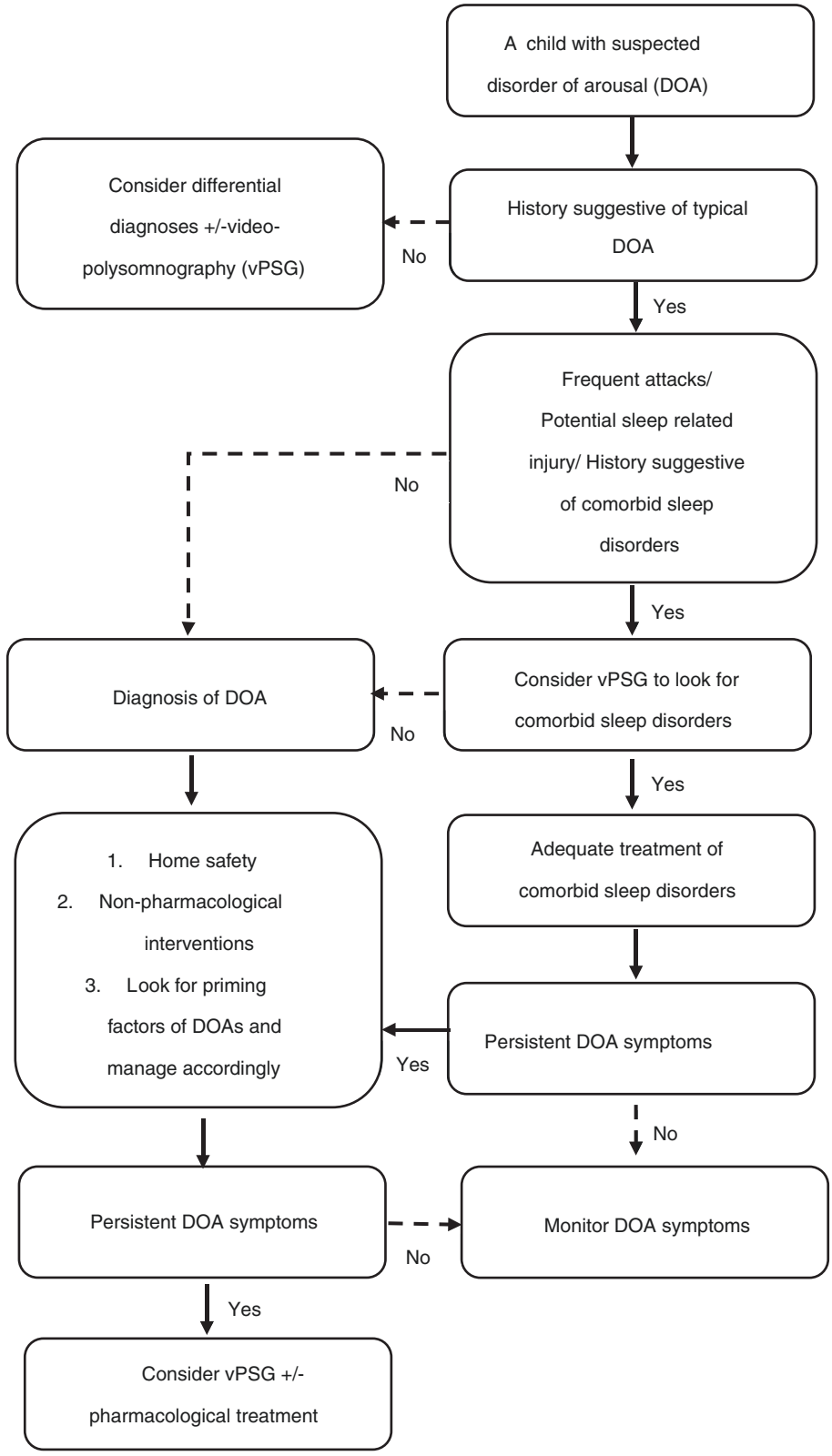

Fig. 13.2 Flowchart of management of disorder of arousal in children

Table 13.1 Comparing the clinical characteristics of confusional arousals, sleepwalking and night terror

	Confusional arousals	Night terror	Sleepwalking
Autonomic arousal such as sweating, tachycardia	Mild	Prominent	Not prominent
Emotions	Yes, crying and agitation	Prominent, frightened and panicky screaming	Not prominent
Movement	Limited to bed, e.g. thrashing around	Mild, mostly simple movement	Simple to complex behaviors
Duration	5–15 min, may up to half an hour	A few minutes	Minutes

13.4 Presentation and Diagnosis

Though the three DOAs share similar features of incomplete arousal from deep sleep, they have different clinical manifestations that distinguish one from the other [1]. Confusional arousals present with predominately mental confusion and agitation, the motor movements are usually simple, such as thrashing around at bed, and mostly limited to the bed. Night terror has the hallmark features of panicky screaming and profound autonomic manifestations such as tachycardia, sweating, and has relatively lack of complex movements. Compared to confusional arousals and night terror, sleepwalking has more prominent movements, ranging from simple to complex motor behaviors, and the child could leave his bed, carrying out purposeful actions. The clinical characteristics of the three DOAs are listed and compared in Table 13.1.

Different from other clinical disorders, patients with parasomnia are often poor historians of their sleep problems as they are usually unaware of the nocturnal manifestations. Hence, it is important to include their family in the assessment. A thorough history covering details of the event and video recording would be helpful in differentiating DOAs from other conditions. Triggering factors, emotional stress, family history, comprehensive sleep and medical history are important information to aid diagnosis and management. Most of the DOAs could be diagnosed by clinical assessment and video-polysomnography (VPSG) is not a mandatory tool for diagnosis [1]. However, VPSG plays an important role in providing supportive features to aid diagnoses when clinical presentations are ambiguous, so as to look for co-morbid sleep disorders or differentials, such as SDB, periodic leg movement and nocturnal frontal lobe epilepsy (NFLE). Among all, NFLE is one of the important differentials of sleepwalking. NFLE refers to seizure presumably of frontal lobe origin and presents with attacks ranging from brief motor manifestations to hyper-motor seizures and sometimes followed by prolonged complex ambulatory behaviours [23]. The two conditions are compared in Table 13.2. For those presenting with clinical symptoms of comorbid sleep disorders, frequent attacks of the parasomnia and those with potentially dangerous symptoms of

Table 13.2 Comparison between sleepwalking and NFLE

	Sleepwalking	NFLE
Age of onset	Children	Children to adulthood
Gender	No gender difference	No gender difference
Clinical characteristics:		
Manifestations	Simple to complex behaviors	Stereotypic
Timing of the event	Usually happens during the first half of the night as SWS predominates	Shortly after sleep and throughout the night as it could happen at any stages of sleep
Duration per event	Minutes	Seconds to minutes
Occurrence per night when there is an event	Usually once	Clustering attacks, could have more than once attack per night

Abbreviations: *NFLE* nocturnal frontal lobe epilepsy, *SWS* slow wave sleep

sleep-related injuries, VPSG is also highly recommended. Apart from clinical interviews and VPSG, screening questionnaires have been adopted at clinical and research settings to aid diagnosis, such as the Paris Arousal Disorder Severity Scale [24], and the Frontal Lobe Epilepsy and Parasomnias (FLEP) scale. The latter was designed to differentiate between parasomnias and NFLE [25].

13.5 Management

Although the frequency and severity may vary, DOAs are usually recurrent conditions. Hence modification of home environment to safeguard the safety of patients and family members are of upmost importance, particularly for patients with sleepwalking. Scrutinisation of the sleeping environment, including the furniture around beds, securing the windows and doors are some of the examples. Alarm system and bells could be installed to alert parents in case the child leaves the bedroom. Advice should also be given to parents in managing the event. Instead of waking the child from sleep, it is advised to provide quiet guidance to lead him back to bed. It is particularly undesirable to wake them up forcefully, as it may result in aggressions [21]. Avoidance of precipitating factors is equally important in the management of DOAs. Stress management, regular sleep wake pattern to avoid sleep deprivation, early intervention of physical illnesses such as febrile illnesses, are effective preventive measures in individuals predisposed to DOAs. Treatment of co-morbid sleep disorders are of equivalent important in children with parasomnia. A study reported the treatment of co-morbid sleep disorders, including SDB and restless leg syndrome in children with repetitive DOAs, results in complete elimination of the episodes [22].

The above treatment modalities are regarded as the mainstay of treatment for DOAs. It is important to reassure and educate the parents about the longitudinal course of DOAs, that most of the episodes subside when the children grow up [1]. In some circumstances, such as frequent attacks, or DOAs with potential dangerous or violent behaviors, pharmacological treatment may have to be considered.. Up till now, there is no controlled trials or evidence-based guidelines in the treatment of DOAs, but only isolated case reports on medications such as clonazepam, melatonin, antidepressants and benzodiazepines. Hence, the use of off-label pharmacological treatment option should be thoroughly discussed with parents. Behavioral and psychological interventions have been suggested, such as relaxation, hypnosis and psychological interventions of cognitive behavioral therapy (CBT) and mindfulness-based stress reduction (MBSR). However, there is no concrete evidence for their efficacy [26]. One of the interventions includes schedule awakening, which is an attempt to wake the child briefly at 0.5–1 h before the usual onset of the DOAs on consecutive nights, ranging from 5 days to a month. Three old case reports stated the substantial resolution of nigh terror or sleepwalking of 5 children up to 6-month post intervention [27–29]. This intervention seems to be a simple one, however, its efficacy and impact on sleep and daytime functioning has not been thoroughly studied. Also, it may only be highly selective to those with frequent and predictable DOAs with occurrence at certain defined timing.

13.6 Summary of Take-home Messages

DOAs are common paediatric sleep conditions. Given the episodic nature and disappearance at adolescence, they are commonly regarded as benign conditions. However, a minority may have consequences of daytime functioning impairment and sleep-related injury. Most studies on DOAs are limited to case series and there is a lack of randomized control trials, particularly on the management aspects. For studies published in recent years, more emphasis has been put on adult DOAs, which may have different aetiology to childhood DOAs, and hence the results could not be generalized to paediatric populations. Effective interventions are needed with evidence-based support for DOAs.

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14 REM-Sleep Parasomnia: Nightmare Disorder

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14.1 Case

Jadon is a 4-year-old boy who has recently experienced frequent nightmares since he started kindergarten. His parents reported that Jadon only presented with occasional nightmare episodes which did not affect his sleep. However, he kept awake at night recently and ran into his parents' room and expressed his fears towards the nightmare content. He dared not to return to sleep and described that he was afraid that the zombies in his dream would come into his bedroom. The nightmares had consistently disturbed his sleep. Both Jadon and his parents denied any recent or past history of traumatic experience and the only significant stress might be the beginning of kindergarten.

14.2 Epidemiology

Occasional nightmare in children is very common as up to 75% of children could recall occasional nightmare experience [1]. Frequent nightmares occur in 5% to 20% of the children [2–4]. The wide variation of the prevalence rate is possibly attributed to the different diagnostic criteria and measurement tools employed in the studies. For example, the prevalence of parent-reported nightmares was often lower than the child-reported data [5]. Different nightmare definitions, terminology (nightmare versus bad dreams), and time frame (once per month versus once per week) might also account for the discrepancy. Despite these considerable differences in the definition of a childhood nightmare, research consistently indicated that nightmare has typical onset at age 3–6 years old, peak between 6 and 10 years of age, and then subsequently decline with increasing age [6–8]. For example, previous evidence suggests that the prevalence of nightmares decreases from 28% in school-aged children to 10% in adolescents [9]. Nonetheless, about 30–40% of frequent nightmares (defined as often or sometimes) would persist into adulthood [10, 11]. Although most childhood nightmare is self-limiting, it is considered as a relatively stable trait in children as revealed by the longitudinal studies [8]. These children tend to be more anxious and have more behavioural difficulties [1].

Gender difference in nightmare prevalence is not evidenced during childhood [12] and the emergence of female predisposition occurs during adolescence. For example, a study conducted on 3433 colleges students found that females were more likely to have frequent

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nightmares than males (12% versus 8%) [13]. Interestingly, the female preponderance became less prominent in late adulthood and the elderly [14]. In a systematic review of more than 100 studies, females are 1.5 times more likely to have frequent nightmares during adolescence and young adults, while there was no gender difference in both young children and older adults [12].

14.3 Aetiology

Dreaming during REM sleep serves important functions including memory consolidation, and fear extinction through a combination of both bad experiences with novel and dissociated contexts, which will offer emotional resolution [15, 16]. A recent review has summarised two core concepts in explaining the aetiology of nightmare: (1) increased hyperarousal and (2) impaired fear extinction [15]. Hyperarousal is a central element in explaining both posttraumatic stress disorder and insomnia, two disorders that are typically related to nightmares [17, 18]. The increased hyperarousal accumulated during daytime and nightmare might further enhance information processing during REM sleep and increased REM sleep instability [19, 20], leading to frequent awakening. In addition, normal sleep, particularly REM sleep which serves as the resolution of emotional and social conflicts, might be impaired in an individual with nightmare disorder. Since nightmares often occur during REM sleep, the occurrence of frequent nightmares might activate arousal memory fragments, which in turn lead to inability to extinct the fear memory [15]. Thus, the enhanced hyperarousal interacted with impaired fear extinction during REM sleep, compounded with the presence of precipitating traumatic events or stressors, resulting in a nightmare experience [15]. Other than traumatic and stressful experiences, trait susceptibility and maladaptive beliefs could disturb fear extinction and increase hyperarousal, further enhance the formation of a nightmare [15, 21]. However, these theories are primarily drawn with reference to the adult population, thus, more evidence in children is needed.

In children, several risk factors are associated with nightmare severity and frequency. These factors include stress, traumatic events, sleep disturbance including insomnia, sleep-disordered breathing and circadian disruption, anxiety problems, and medications that could disrupt REM sleep [1–3, 5]. For example, a large-scale community study including 6359 children indicated that the frequency of nightmares in children is associated with sleep disturbance and family-related factors such as insomnia, sleep-disordered breathing, family economic status, and parental history [2]. Certain personality especially neuroticism trait is also found to be associated with increased nightmare frequency [22, 23]. In addition, children with psychiatric illnesses are more likely to have nightmares than those without. In particular, frequent nightmare is a prominent feature in anxiety disorders including generalized anxiety disorder, separation anxiety and over-anxious disorder symptoms in adolescents [1, 5, 24]. It is also a specific marker for post-traumatic stress disorders (PTSD). Recurrence of traumatic events in a form of a nightmare are cardinal features of PTSD. Not only the stressful life experience leads to the occurrence of nightmares, but the nightmare itself could also become a distressful experience. Young children might be conditioned the fearful nightmare images with bedtime behaviours, leading to physiological hyperarousal and sleep disturbance.

Genetic predisposition of frequent nightmares has been reported in a twin study [10]. Hublin and colleagues quantified the genetic influences affecting the liability to nightmares and found that approximately 44% of phenotypic variance in childhood nightmares was due to genetic effects [10]. A recent genome-wide association study including more than 28,000 individuals has identified the first individual genetic association in nightmares [25]. Li and colleagues also found that children with frequent nightmares were more likely to have parents who also reported frequent nightmares [2]. Nonetheless, shared environmen-

tal risk factors might also play significant roles in the familial aggregation of nightmares such as lower family income and familial stress [2]. Shared traumatic experiences and stress exposure also appear to influence the occurrence of nightmares.

14.4 Presentation and Diagnosis

Nightmares are disturbing mental experiences that resulting in awakening from sleep. Both Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [26] and International Classification of Sleep Disorders, third edition (ICSD-3) [27] share similar diagnostic criteria for nightmare disorder. These criteria include (1) a recurrent episode of awakening from sleep and accompanied with intense feeling of fear, terror, or anxiety, but also anger, sadness, and disgust. (2) dreamers can recall the details of the nightmare content and the alertness is often fully returned after awakening. (3) difficult to return to sleep after the episode and the occurrence of episodes are in the second half of the night. In children, the descriptions of dreams usually include monsters or fantastical imagery and it becomes more detailed in older children. Although dreams can happen in other non-REM sleep stage, nightmares often occur during REM sleep, which explains the high frequency of nightmares in the early hours of the morning. In addition, physical movement is rare during an episode as the presence of REM-sleep-related atonia will normally inhibit the acting out of dreams. In case that the children reported acting out of dreams with frequent sleep shouting, movement, or even sleep-related injuries, one will need to suspect the occurrence of REM sleep behaviour disorder (RBD), which usually occurs in older adults and rarely occur at young age (which are usually secondary to narcolepsy, developmental disabilities and medication usage) [28]. The confirmation of RBD will require further video-polysomnographic investigation to document the REM sleep behavioural events and REM sleep without atonia [29].

Diagnosis of nightmare is relatively straightforward with a good clinician interview. For the occasional nightmare with limited repercussion, it usually does not require further evaluation. While for frequent persistent nightmares that cause significant distress and sleep disturbance to both children and parents, investigation and intervention are needed to alleviate the nightmare intensity and severity. The most common differential diagnosis for nightmares is sleep terrors [30, 31]. Sleep terror is a disorder of arousal from non-REM (NREM) sleep often accompanies with arousal, amnesia for the event, and a range of automatic behaviours [30, 32].

Other than the sleep assessment, it is equally important to evaluate children's emotional and physical illnesses which might increase the occurrence of nightmares. For example, children with psychiatric illnesses are more likely to have nightmares than those without [1, 5].

14.5 Management

An occasional nightmare is considered a benign disorder that requires no special intervention. However, it is important to reassure both parents and children about the benign nature of the occasional nightmare occurrence as it will progressively resolve when they grow up. They should be provided with adequate information and education so that they will not react inappropriately towards these common sleep awakenings. In particular, maintaining healthy sleep hygiene practice and avoidance of precipitating factors such as violence in TV or film content, or events that may trigger their emotion near bedtime are highly recommended to reduce the frequency of nightmares. The use of security objects such as a blanket or the presence of a doll might help to reduce children's bedtime fears. Moreover, identification and management of daily stressors associated with nightmare content are also recommended to reduce nightmare episodes.

However, when nightmare becomes frequent and starts to affect sleep quality and causes day-

time distress, or it becomes persistent even after modification of lifestyle practice, it should be carefully evaluated as frequent nightmares often come with psychopathology. There have been several psychotherapies that have been widely used for treating nightmares. These include relaxation strategies, exposure, positive reinforcement, and systematic desensitisation to reduce nightmare fears, and imagery rehearsal therapy (IRT) to replace children's frightening dreams. Among these strategies, IRT is a cognitive behavioural therapy that has received increasing attention in treating nightmares. In IRT, nightmare content is replaced with less alarming and modified content. It is believed that nightmares are learned behaviours so individuals could learn alternative content to replace it [33]. After rescripting the nightmare content, children are instructed to practice the new dreams by imagery. It is expected that the new script will be more cognitively dominant than the nightmare and eventually replacing the disturbing dream content. However, research into IRT is predominantly conducted in adults. Among a few studies in children and adolescents, Krakow et al., have provided empirical support of IRT on adolescents with comorbid psychiatric illness and traumatic experience [34]. In particular, specific adaptations should be made when conducting IRT in children, especially for those young children. A young child might not be able to describe the dream content in detail. Drawing of nightmares should be added to provide young children an age-appropriate method to express their dreams [35].

For nightmares that are occurring together with other psychiatric illnesses such as anxiety and PTSD, additional treatment approach focusing on mental health issues should be provided. A pharmacological approach might be needed in combination with psychotherapies to maximize the treatment gains. However, pharmacological treatment in children is problematic as there is often no consensus or official approval (such as FDA) regarding the medication use in paediatric population (off-label use) and there is a dearth of data on drug treatment for chronic childhood nightmares. In adults, prazosin has been used in the treatment of nightmares with some empirical efficacy. While in children, there is very limited evidence. A recent review included 9 published studies showed that prazosin may also be a promising drug in treating nightmare associated with PTSD in children. However, the majority of the studies were case reports without any large-scale randomised control trial that evaluated the safety and efficacy of prazosin in children [36]. Thus, caution is needed when prescribing prazosin treatment to paediatric patients. In addition, α2 agonists such as clonidine which is used in treating attention deficit and hyperactive disorder [37] has also demonstrated some efficacy in reducing sleep disturbance and nightmare in children [38]. Nonetheless, the paediatrician should carefully evaluate a child's condition before drug prescription since there is very little evidence to support the use of these agents in childhood nightmare management.

14.5.1 Summary of Key Take-home Messages and Research Gaps

- Nightmare is common at young age and mostly resolves with increasing age.
- About 30–40% of childhood nightmare may persist into adulthood and is associated with an elevated risk of psychopathology including depression, anxiety, and psychotic experience
- Both genetic and environmental risk factors contribute to the occurrence of a nightmare
- Occasional nightmare is considered a benign disorder and does not require specific attention. Parental reassurance and healthy sleep hygiene practice are often recommended to reduce nightmare frequency and severity
- Frequent nightmares that cause distress should be carefully evaluated and provided with adequate psychological (and if needed, together with pharmacological) intervention.

14.5.2 Research Gaps

More research is needed to understand the associated risk factors that contribute to the persistence of nightmares and the comorbid nightmare with psychiatric, physical and sleep disorders.

Although initial evidence supports IRT in treating nightmares in children and adolescents, future studies should incorporate randomised controlled trials to further evaluate its effectiveness in paediatric population. There is also a need to evaluate pharmacological intervention in childhood nightmares.

Summary of main features and characteristics of nightmare in children	
Age of onset	3–6 years
Peak age	6–10 years
Timing during sleep	Second half of sleep
Risk factors	Family history, stress, traumatic events, childhood adversity, neuroticism
Associated consequences	Behavioural problems, daytime impairment, mood problems, psychotic experiences
Management	Relaxation strategies, exposure, positive reinforcement, systematic desensitisation and imagery rehearsal therapy

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Enuresis

15

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15.1 A Vignette of Typical Presentation of the Sleep Disorder

As a paediatrician, you are asked to see a 7-year old boy, Timmy, and his family for his problem of bed-wetting. Timmy enjoyed good past health all along. His parents are worried of his on-going problem of bed-wetting occurring 3–4 times each week. Despite adopting measures for the past 6 months of reducing fluid intake at night and urinating before sleep there has been no improvement.

Timmy usually has 1 episode of bed-wetting every other night and only notices on waking up with his bedsheets being wet. He complained of no urinary frequency, urgency, dysuria or other lower urinary tract symptoms. There were never any urinary incontinence episodes during daytime, and Timmy's bowel openings are normal with no constipation or encopresis. Aside from his night-time urinary incontinence Timmy has no other physical complains.

There were no recent stressors identifiable and Timmy enjoys good relations with his parents and 2 elder siblings. He enjoys school-life and feels no significant stress from his recent examinations. He does not feel any embarrassment from his bedwetting and does not view his bedwetting as a problem, although his parents are obviously concerned. Timmy's physical examination, including a detailed abdominal, genital, and neurological examination, were unremarkable.

On further enquiry, Timmy's father remembered having a similar problem of bedwetting when he was young, which resolved without any treatment in his early childhood. There was no other significant family history identifiable.

15.2 Epidemiology

Enuresis refers to episodes of urinary incontinence during sleep in children aged 5 years or above. A variation of terminologies had been used to describe children with bed-wetting in the past. In 2006, the International Children's Continence Society has developed standardized terminology for lower urinary tract function and malfunction in children [1], with the updated version published in 2016 [2]. To understand the epidemiology of the condition we would first have to understand the terminologies used (Table 15.1).

Enuresis can be classified into monosymptomatic and non-monosymptomatic. For monosymptomatic enuresis, children do not have any other lower urinary tract symptoms. This can be further sub-classified into primary or secondary.

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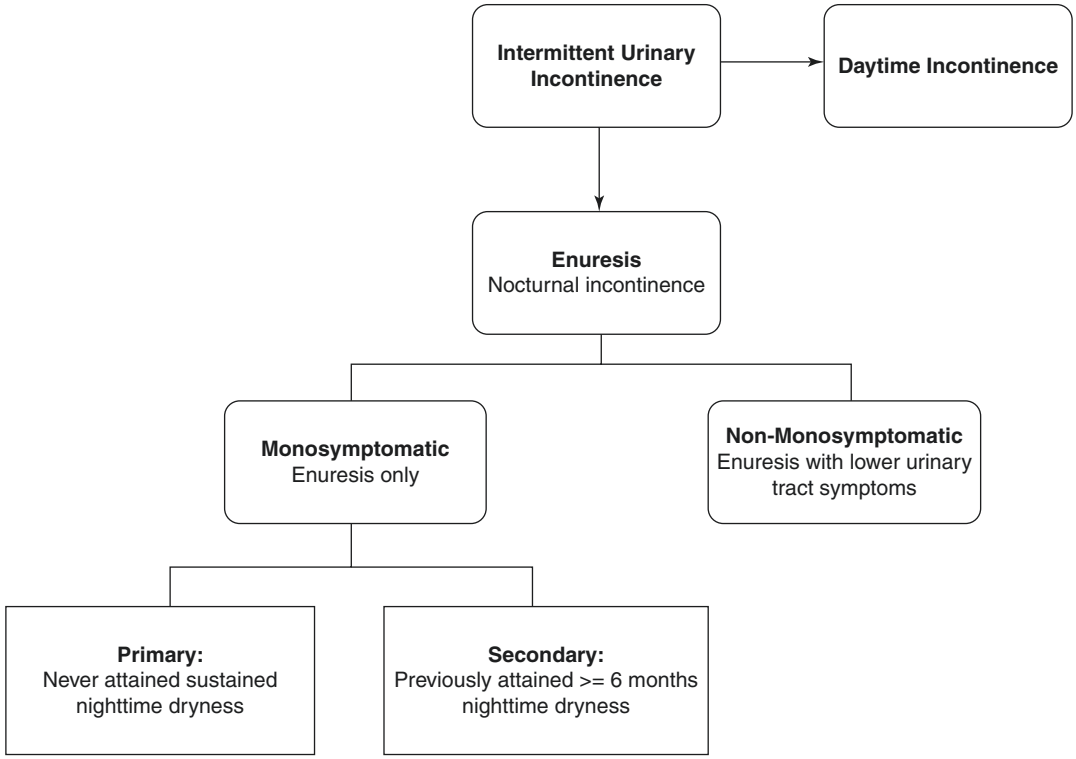
Table 15.1 International Children's Continence Society Classification of enuresis



Primary monosymptomatic enuresis is defined as enuresis in children who have never achieved a satisfactory period of nighttime dryness. This form of enuresis is the most common and around 80% of children with enuresis can be classified as primary.

Secondary monosymptomatic enuresis is used to describe children who had previously attained a period of dryness for at least 6 months but now presents with night-time incontinence without other lower urinary tract symptoms. Secondary monosymptomatic enuresis is often related to stressful life events, such as the death of a family member or the birth of a sibling, but the exact etiology remains unknown.

Non-monosymptomatic enuresis is defined as children who have enuresis and other lower urinary tract symptoms. These symptoms include: increased (≥8 times/day) or decreased (≤3 times/day) urinary frequency, urinary urgency, and hesitancy, the need for straining for urination, weak/intermittent or spraying urinary stream, pain in the lower urinary tract.

For children with daytime incontinence and nocturnal enuresis, they should be classified as having both conditions of daytime incontinence and enuresis. For children with daytime symptoms of urinary urgency, frequency or incontinence, they can be further defined as having bladder dysfunction. Approximately 20% of all children with enuresis can be classified as suffering from bladder dysfunction. In these children, neurological disorders such as spinal dysraphism and urological causes including urinary tract infection and bladder muscle instability need to be excluded.

Finally, for children with daytime symptoms who also have bowel symptoms of constipation or encopresis they are classified as having bowel and bladder dysfunction. Approximately 15% of children with enuresis have bowel and bladder dysfunction.

As most children with enuresis is classified as primary monosymptomatic enuresis (PME) our discussion will focus on this entity alone.

PME affects around 15% of children aged 5 years of age [3]. It has a genetic predisposition and its prevalence is therefore different amongst regions. In western countries, PME is a common problem as identified by epidemiological studies [4–6]. In the United Kingdom it is found to be affecting 15–20% of 5-year-old children and 1–2% of 15-year-old adolescents [7]. In Asia the incidence reported is variable with a male predominance. An epidemiological study performed in mainland China identified the overall incidence to be 11% amongst all 5 year olds [8], whilst another large epidemiological study performed in Hong Kong showed the incidence of PME to be 16.1% amongst 5 year old children with a male predominance (20.7% boys, 10.8% girls) [9]. In India, the overall incidence for children 6–10 year old. was 7.6% with male predominance [10]. Without treatment, most children with PME experience spontaneous symptom resolution at a rate of approximately 15% per year, and 99% of children with PME are dry by the age of 15 years old [3].

Although PME may not be considered a particularly worrisome medical condition by most physicians, data suggest that children who have prolonged enuresis have lower self-esteem [11]. Families often find the condition troublesome and causing a significant impact on the sleep quality of children and their parents. The social consequences of nocturnal enuresis remain a significant reason for children and families to seek medical attention.

15.3 Aetiology

PME is considered a functional type of incontinence rather than secondary to urological, anatomical or psychiatric causes. The pathophysiology of the condition is not well understood but different theories have been postulated. One prominent theory is an abnormal circadian release of antidiuretic hormone (ADH). In normal children, nocturnal urine production is approximately half of the daytime urine production, whilst for children with PME it has been shown that they have decreased nocturnal ADH production [12]. Aside from hormonal differences, anatomical differences with diminished bladder capacities and abnormal urodynamic functions with higher rate of nocturnal bladder instability have also been identified in children with PME [13].

There is definite genetic predisposition to development of PME. Studies have shown that there is a 44% chance of a child to suffer from PME if one of their parent has this condition as a child [14]. The chance is drastically increased to 77% if both parents have the condition [15]. In addition, twin studies support the genetic basis with a high concordance rate of PME in monozygotic twins [16].

Aside from anatomical, physiological differences and a genetic predisposition, psychological factors can also contribute to development of PME. An example is attention-deficit/hyperactivity disorder (ADHD); children with this disorder have a 30% greater chance of PME. Children with PME were also found to have a higher prevalence of motor and speech delay and perceptual dysfunction compared to those without [17]. This supports the another widely accepted hypothesis of neuro-maturational delay as the cause of PME.

In the end, PME is likely the result of an admixture of the aforementioned contributing factors.

Secondary enuresis, on the other-hand, is often related to the occurrence of psychologically stressful life events, such as the birth of a sibling or the death of a close-relative. There are often no organic causes identified to cause secondary enuresis in children.

15.4 Presentation and Diagnosis

15.4.1 History

The key to diagnosis and classification of enuresis is through obtaining a reliable history. History of daytime events and lower urinary tract symptoms can differentiate between monosymptomatic and non-monosymptomatic enuresis. Non-monosymptomatic enuresis requires more

extensive investigations to exclude pathological causes.

For monosymptomatic patients, enquire on whether there had been a history of achieving dryness of at least 6 months in the past to differentiate between primary and secondary enuresis. For children with secondary enuresis, physicians need to further enquire on any recent stressful life events.

For children classified as having PME, a detailed history of the child's urinary, bowel, dietary and sleep habits is crucial to identify any possible lifestyle modifications necessary to help improve the situation. For urinary habits, enquire on the usual voiding pattern and the voiding hygiene of the child, including any straining necessary and any incomplete voiding to suggest non-monosymptomatic enuresis. The stooling habit is also important as enuresis and stooling dysfunction are closely related.

Enquire on the child's eating and drinking habits with details to the content, amount and timing of the fluid intake to identify any potential cause of excessive fluid load for enuresis. Fluid intake shortly before sleep can lead to bladder over-capacity.

A detailed enquiry on sleep habits of the child is necessary. Sleep-disordered breathing such as obstructive sleep apnea can result in impaired arousal causing enuresis. In addition, the child's sleep quality maybe markedly interrupted affecting their daytime social performance, especially when children experience more than one bedwetting episodes per night. On the other hand, children who are deep sleepers are often unaware of their events until the next morning. These children may be more resistant to behavioral modifications therapies which rely on their wakening, such as enuresis alarms.

Finally, the physician needs to review the disorder's emotional impact on the child. PME can be distressing for children and their families. Children are reported with a lower self-esteem. Parents may find the condition challenging to handle especially when there are no obvious improvements with treatment, and there have been reports of a higher chance of physical abuse occurring amongst families with children suffering from PME [11]. Psychological screening and specialist referrals may be necessary.

15.4.2 Physical Examination

Physical examination for children with PME are often normal. However, physicians should still conduct a focused and detailed examination to identify any potential underlying medical conditions resulting in enuresis. Document the growth of the child as obesity is associated with higher incidence of PME and measure blood pressure at rest to identify any features of failure to thrive and hypertension related to chronic renal disease. Perform detailed abdominal examination for any ballotable kidneys, distended urinary bladder and external genitalia abnormalities to indicate an underlying urological abnormality. Hard palpable stool will indicate constipation. Physicians should also perform a detailed lower limb neurological examination and look for abnormalities of the lumbosacral spine to suggest spinal dysraphism/abnormality.

15.4.3 Investigations

In a child with features of non-monosymptomatic nocturnal enuresis, or when the physician is in doubt, investigations should be performed to exclude underlying organic causes. Simple urinalysis can screen for medical conditions of urinary tract infection, diabetes mellitus and diabetes insipidus.

If urinary obstruction is suspected based on history and physical examination, a post-void residual urinary bladder volume measurement and urinary system ultrasound should be obtained. If there is suspicion of spinal anomaly, magnetic resonance imaging of the lumbosacral

spine should be arranged, in addition to urodynamic study to delineate associated neurogenic bladder. In children with recurrent urinary tract infections in addition to enuresis, voiding cystourethrogram and renal isotope testing maybe necessary.

15.5 Management

Treatment of non-monosymptomatic and secondary monosymptomatic nocturnal enuresis is out of the scope of our discussion. We shall focus of management of PME.

Prior to treatment initiation, the necessity and timing for treatment should be discussed as these are dependent on the view of the family and child. Parents with personal history of PME may find it unnecessary to initiate treatment for their child with infrequent episodes. On the-other hand, a 5-year-old-child whose younger sibling had already achieved dryness may find episodes embarrassing with a negative effect on their self-esteem even if they are infrequent. The child's maturity needs also to be taken into consideration, as first-line treatment with behavioral therapy requires the child to be willing to partake responsibility and be highly motivated for change.

Most children with PME will have spontaneous resolution with time. The prevalence decreases from 15% at 5 years to 5% at 10 years, and to 1–2% in ≥15 years. The key is to educate and reassure children and their families of the condition's natural progression. Another key is to set achievable goals. ICCS guidelines categorize response to treatment into initial and long-term response and can act as a reference (Table 15.2). In general, the goals of treatment include: reducing total number of enuretic nights, avoiding enuresis on specific nights, avoidance of event recurrence, and stress reduction for the child and family. Setting goals of treatment should be a joint process and therapeutic goals should match the expectation of the family and child. Some children may not be affected at all by enuretic episodes and hence have little motivation for change. Others may only wish to achieve dryness on special occasions such as during camps with peers to avoid embarrassment.

Table 15.2 Conditions causing enuresis

Conditions	Mechanism
Constipation	Reduced bladder capacity
Urinary tract infection	Reduced bladder capacity Bladder hyperactivity
Diabetes mellitus/ insipidus	Increased urine production
Spinal dysraphism	Neurogenic bladder
Urethral obstruction	Reduced bladder capacity
Stressful life events	Psychological stress

Table 15.3 International Children's Continence Society definition of initial and long term successful response to treatment of enuresis

Initial success	
No response	<50% reduction
Partial response	50–99% reduction
Complete response	100% reduction
Long term success	
Relapse	More than one symptom recurrence per month
Continued success	No relapse in 6 months after interruption of treatment
Complete success	No relapse in 2 years after interruption of treatment

In addition, families should be given the appropriate expectations of treatment. It takes weeks to months before treatment effect is obvious even with medication, and relapse after treatment cessation is common. For some children, a combination of treatment modalities maybe necessary before any significant improvements can be observed (Table 15.3).

15.5.1 Education and General Advice

Education is aimed at normalizing children with PME. The high prevalence of PME and its natural progression and resolution should be emphasized. Neither children nor their families are at

fault, and children should definitely not be punished for bedwetting episodes. This key message should be stressed by the clinician as surveys have identified a high prevalence of punishment, sometimes physical, in children who experience bedwetting [18].

The family is advised to keep track of dry and wet nights with use of a calendar to determine treatment effectiveness. During the day, children are encouraged to regularly and completely empty their bladder around 4–7 times per day, including voiding before sleep. Once asleep, the child should not be awoken intentionally for voiding. Although this method does improve the problem of bed-wetting, it does not condition the child to waking up to the urge sensation of a full bladder.

As simply restricting the total daily fluids may not be effective, families can be advised to set limit to fluid intake after evening to around 20% of the child's total daily intake. Children should especially avoid drinking within 2 h from bedtime. Caffeinated drinks and drinks with high-sugar content should also be avoided. The exact effectiveness of these modifications to fluid intake remains debatable [19, 20] and may not be helpful for all children, they should be discontinued if deemed ineffective after an initial trial.

Identifying, treating and avoiding constipation is also important as it will propagate and worsen enuresis. In the setting of reduced fluid intake, maintaining a high-fiber diet is essential.

15.5.2 Motivational Therapy

Motivational therapies are effective especially for children aged 5–7 years with infrequent bedwetting episodes. They are behavioral interventions based on reward systems such as star charts, and their effectiveness in promoting dryness have been proven in achieving fewer bedwetting episodes per week and greater chance of attaining 14 consecutive dry nights [21]. The rewards can be gradually incremented to maintain adherence and to maintain longer periods of dryness.

In case the enuresis is persistent despite the above measures, active management with either behavioral or pharmacological measures can be considered.

15.5.3 Behavioral

15.5.3.1 Alarm Treatment

Alarm therapy is based on conditioning and teaches children to wake for urination. It is especially effective for children who do not have nocturnal polyuria and in children with adequate family support. Different types of alarms exist but all work on the basis of waking the child when the alarms come into contact with urine, with different intensities of stimulation such as oscillation or sound. There is no evidence favoring one alarm over another, but they should not be used for children who could not be awoken by sound or vibration. All enuresis alarms consist of a sensor and an arousal device, and their use require the child to have comprehension of how to activate, deactivate and reset the alarm.

Enuresis alarms must be used every night. The child is instructed to place the sensor in a dry bed pad or in the undergarments each night before sleep. If the alarm goes off, the child should turn off the alarm, get up from bed and finish voiding in the toilet. They should then replace the sensor in a dry bed pad or undergarment and reset the alarm. Although this process is not complex to adults, some children may find this responsibility challenging to carry out. The child's maturity and comprehension of how to setup the alarm is therefore crucial to treatment success.

Enuresis alarms require motivation and commitment of the child and family as treatment success is not immediately obvious. Their use should be reviewed only after continual use for 12–16 weeks. Effectiveness can be in form of fewer episodes each night, smaller wet patches, and more nights with dryness. If deemed effective, alarms should be used continually for at least achieving 2 weeks of dry nights before discontinuing. Successful treatment with alarm therapy has been reported to be up to 75% [22]. If enuresis recurs after treatment cessation ($\geq$2 wet nights per month), alarm therapy can be reiniti-

ated and usually can result in rapid response. Alternative treatments may be necessary if continual use for more than 12 weeks have shown no response.

15.5.4 Pharmacological

15.5.4.1 Desmopressin

Desmopressin is a synthetic analogue of arginine vasopressin. Based on the observation of abnormal circadian rhythm of vasopressin release in children with PME, especially those with nocturnal polyuria, restoring the hormonal balance can aid in reduction of urine production and promote dry-nights. Desmopressin is available as tablet form or a nasal spray with an effect lasting for up to 12 h. The oral tablet form is recommended as nasal spray is associated with hyponatraemic seizures. Oral medication should be administered 1 h before sleep with dose titrated to best effect. Important side effects to mention include dilutional hyponatraemia, water intoxication, headache, anorexia and visual problems. The effectiveness of desmopressin for treatment of PNE is reported up to 60–70%, although some have shown a relapse rate as high as 50–90% especially with sudden discontinuation [23–25]. Fluid intake should be restricted from 1 h before to 8 h after administration to prevent dilutional hyponatraemia. Routine measurements of plasma sodium or urine osmolarity are unnecessary.

Treatment response is expected within 1–2 weeks. If deemed responsive with fewer bedwetting episodes each night, smaller wet patches and more dry nights, desmopressin should be continued for at least 3 months before discontinuation. Discontinuation should be via gradual tapering rather than abrupt complete cessation to avoid recurrence.

15.5.4.2 Tricyclic Antidepressants

Tricyclic medications inhibit the reuptake of serotonin and noradrenaline from synaptic alpha receptors of the central nervous system. The most commonly used tricyclic antidepressant for control of enuresis is Imipramine. Its specific action in inhibiting enuresis remains unknown but may act through inhibiting the detrusor muscle with its antispasmodic and anticholinergic effect. There have also been reports of an increase in ADH level with Imipramine use thus reducing urine production. Imipramine is administered orally 1 hour before bedtime. The starting dose is 10–25 mg with average effective dose of 25 mg. The maximum dose is 50 mg for children aged 6–12 years old and 75 mg for children ≥12 years old. Its effectiveness is expected after 1 month of treatment. If deemed successful, the dose should be tapered to lowest effective dose.

A wide variation in medication effectiveness has been reported, ranging from 64–80%. However, recurrence of symptoms with discontinuation is common and only 25% of patients remain dry in the long term. Side effects are uncommon but can be serious. Approximately 5% of children develop neurological symptoms including sleep disturbance and nervousness. Serious side effects can result from Imipramine overdose and fatalities from arrhythmias and cardio-toxicities resulting in myocardial depression have been reported. Families should be notified of these significant risks.

15.5.4.3 Anti-Cholinergics

Anticholinergic agents such as Oxybutinin have long been used in the treatment of nocturnal enuresis. They work by relaxation of the urinary bladder's smooth muscle and by increasing bladder capacity. They may not be effective in treating children with PME [26, 27] but may help children with bladder dysfunction who have reduced functional bladder capacity and detrusor instability with symptoms of urgency, frequency or with daytime wetting. They may also improve treatment effectiveness when used in combination with desmopressin. Common side effects include dryness of mouth, headache and blurred vision. Constipation can potentially result and can further precipitate enuresis, families should be advised for adequate fiber intake as preventive measure (Table 15.4).

Table 15.4 Medications for Primary Monosymptomatic Enuresis

Medication	Classification	Starting dose	Maximum dose	Side effects
Desmopressin	Synthetic vasopressin analogue	Tablet: 0.2 mg 1 h before bedtime Gradual titration by 0.2 mg/day every 3 days as needed Sublingual (DDAVP Melt): 120 μg 1 h before bedtime Gradual titration by 120 μg/day every 3 days as needed to a maximum dose of 360 μg/day	Tablet: 0.6 mg/day Sublingual: 360 μg/day	Hyponatraemia, headache, anorexia, visual problems
Imipramine	Tricyclic antidepressant	Oral: 10–25 mg 1 h before bedtime. Gradual titration after 1 week by 25 mg/day to maximum daily dose	6–12 years old: 2.5 mg/kg/day or 50 mg/day (whichever is lesser) ≥12 years old: 75 mg/day	Cardiac: Palpitations, arrhythmia, myocardial depression, cardiac failure, hypertension, myocardial infarction Neurological: Agitation, anxiety, ataxia, confusion, delusions, disorientation, dizziness, hallucination, headache, insomnia, nightmares, restlessness, seizure Haematological:Agranulocytosis, thrombocytopenia Others: Nausea, vomiting Increase risk of suicidal thinking and behavior in children, adolescents and young adults with psychiatric disorders (US Boxed Warning)
Oxybutynin	Anticholinergic	Oral: Immediate release:5 mg twice daily Oral: Extended release: 5 mg once daily Increase dose weekly by 5 mg	Immediate release: 5 mg 4 times daily Extended release: 20 mg/day	Palpitations, tachycardia, Dry mouth, constipation Blurred vision Drowsiness, Dizziness Agitation, Confusion Hallucintations

15.5.5 Choice of Active Treatment

If the trial of general measures and motivational therapy have not resulted in significant improvement, active treatment can be initiated. In general, first-line treatment of PME can either be with an enuresis alarm or with desmopressin.

The choice of therapy would be dependent on the preference of the family and the goals they wish to achieve.

In the setting of a need for short term treatment effectiveness (for overnight camps to prevent embarrassment), when the family requires a more rapid treatment (when the family is expressing great difficulty in coping with the burden of bedwetting), or when the child has nocturnal polyuria (nocturnal urine production more than 130% of expected bladder capacity for age), Desmopressin is more suitable. It is more rapidly effective than enuresis alarms and requires less parental involvement and self-motivation. The child and family should however be aware that Desmopressin has a higher relapse when compared to enuresis alarms when treatment is stopped.

In families where short-term improvement is not a priority, enuresis alarm is the better option. Although its effectiveness is not as apparent initially, it has a more sustained effect with less chance of recurrence compared to Desmopressin. Prior to initiation, the child should be assessed to determine their motivation for change. They should also be ensured to have an adequate understanding of how the alarm works, properly taught the alarm setup and the routine in case of alarm going off in order to ensure effect and adherence.

15.5.6 Refractory Enuresis

Refractory enuresis is defined as less than 50% improvement in baseline frequency of enuresis.

Adequate trial of treatment is defined as a period of at least 3 months of enuresis alarm with good utilization methods and compliance, or an adequate dose Desmopressin at of 0.4 mg regular tablets or 0.24 mg of oral melt tablets.

Physicians should exclude possible reasons leading to a lack of treatment response. History and physical examination should be reviewed to exclude potential underlying medical conditions as trivial as constipation which may result in treatment failure. When in doubt, appropriate investigations such as ultrasonography or urodynamic studies need to be utilized. The child and family needs to describe and demonstrate the correct use of medications or enuresis alarm to identify any inconsistency and misunderstandings. In addition, physicians should pay attention to the social dynamics of the family and the emotional impact the condition has caused the child to review and identify possible psychological contributions to treatment failure.

After comprehensive exclusion of secondary causes, management of refractory monosymptomatic nocturnal enuresis may include switching over from one therapy to another, or additional therapy with combination of alarm treatment and desmopressin.

A trial of tricyclic antidepressant with Imipramine can also be initiated. This option should however be considered only after failure of first-line and combinational therapies given the potentially serious side effect of cardiotoxicity, physicians and parents need to weight the risks and benefits of treatment. Parents should be advised to safely store this medication in order to prevent accidental ingestion and overdose, especially when there are younger siblings in the family. Clinical response of Imipramine should be assessed after 3 months of continual use and should be discontinued if deemed unhelpful. If treatment is effective, the dose should be titrated down to the lowest effect dose. Imipramine should be regularly discontinued every 3 months for at least 2 weeks to reduce risk of medication tolerance.

Anti-cholinergics may not be particularly beneficial for patients with PME. They are, however, proven effective in controlling enuresis in children with urinary urgency and detrusor instability. Conjunctional use of an anti-cholinergic with Desmopressin can be tried in these children with small randomized controlled studies supporting this combinational treatment [28].

15.6 Summary of Key Take-Home Messages and Research Gaps

Nocturnal enuresis is a common sleep related disorder. In dealing with children with enuresis, one should first classify the specific subtype based on presence and absence of lower urinary tract symptoms and whether the child had previously attained night-time urinary continence for at least 6 months.

Although the exact pathophysiology for primary monosymptomatic enuresis remains unknown, it is likely a result of an admixture of underlying hormonal and anatomical factors, genetic predisposition and neuro-psychological maturity.

Most children with enuresis can be classified as PME with expected spontaneous resolution over time. Although considered benign, PME can bring about significant psychological burden on children and their families; active treatment may

be necessary to aid the child's self-esteem and to ease the family's stress.

If PME persists despite general measures of nocturnal fluid restriction, maintaining a good urinary and bowel habit and motivational therapies, active treatment can be initiated after identifying attainable goals of therapy with families. First line active treatment can be either with enuresis alarms or with desmopressin.

An adequate amount of time would need to be given to observe treatment effect. If deemed refractory, combinational therapy can be considered. Tricyclic antidepressants with Imipramine use is one of the treatment options but its use should be carefully discussed with patient and family due to potentially serious side effects.

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16 Restless Legs Syndrome and Periodic Limb Movement Disorder

Arthur Teng

16.1 Vignette

Sami is a 5 year-old otherwise healthy and normally developing boy who presented to the Sleep Clinic with a 2 year history of snoring and restless sleep. On closer questioning the snoring is present on average three nights out of an average week. He never seems to stop breathing but there is some mouth breathing and a mild increase in work of breathing. He also sweats a bit in his sleep. In addition, the parents were worried about his restless sleep: he tosses and turns, much like what the mother described as a "washing machine". In addition, he seems to kick his legs through the night and has in fact fallen out of bed on several occasions. The father reported that no one wanted to share a bed with him during their holidays! Sami has also been complaining of pains and cramps at night. These are often relieved by massage and occasional when they are severe there is some relief with paracetamol or ibuprofen.

Sami has a good sleep routine with bedtime at 7.30 PM; he is usually asleep within 15–20 min and despite his restlessness tends to sleep through the night without disturbing his parents. Sami wakes up at around 7 AM a bit tired and unrefreshed but soon "warms up". By day he is an active boy who has no trouble running around or kicking a ball. His kindergarten teachers report that he seems bright and is graded as average academically. He has a short concentration span and tends to be easily distracted. He fidgets and squirms in his seat. He is generally well-behaved but gets a bit tired after lunch, and sometimes has trouble completing his tasks on time. He is not reported to fall asleep inappropriately at school but he falls asleep often in the short car-trip home from school in the afternoons. There is no scheduled nap. Sami is otherwise well and does not suffer from recurrent tonsillitis or other medical or surgical problems.

16.2 Physical Examination

On examination Sami was afebrile and not in respiratory distress. His blood pressure was 95/50 with normal chest and heart sounds. He was cooperative but was physically busy: he was constantly moving in his chair and tended to get up and pick up things on the desk. His tonsils were grade 2 on 4 bilaterally with a slightly high-

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arched palate. Nasal airflow was demonstrated from both sides with pallor and some swelling and medialisation of his inferior turbinates. Ear drums looked normal. He had a normal gait and neurological examination including deep tendon reflexes. His weight was 18 kg (around 50th percentile) and height 118 cm (just under the 50th percentile).

Summary of clinical presentation and possible diagnoses:

1. Snoring and Sleep disordered breathing/chronic allergic rhinitis.
2. Attention deficit disorder (ADD).
3. Restless legs syndrome (RLS)/periodic limb movement disorder (PLMD)/Growing pains (GP).

16.3 Diagnostic Evaluation

Snoring and Sleep-disordered breathing

Sleep-disordered breathing is best regarded as a spectrum ranging from primary snoring to obstructive sleep apnoea (OSA). Snoring is the main presenting symptom. Restless sleep is also a common symptom. Certainly sleep disruption as well as hypoxia could result in similar daytime symptoms. Unlike adults with obstructive sleep apnoea, in children it is unusual to have excessive daytime symptoms. In fact many children exhibit hyperactive behaviour.

Investigation

An overnight sleep study (polysomnography or PSG) would be regarded as the gold standard for a diagnosis of OSA. However, this is not often available or there is often a long waiting period. Screening oximetry is much more widely available. A strongly positive result has a 98% concordance with a sleep study but a negative result has a negative predictive value of around 50%. This means that with normal oximetry, a full sleep study might still confirm OSA in around 50% of cases. (Can cross reference to OSA diagnostic chapter).

Treatment

A trial of nasal steroids such as fluticasone or mometasone would help sort out the role chronic allergic rhinitis plays in the snoring. Nasal sprays are safe in this age group with the optimal technique (such as pointing away from the nasal septum). The medication with lowest systemic absorption should be chosen. Nasal steroids have also been shown to decrease the size of the adenoids. Together with enlarged tonsils, adenoids are the main cause of snoring in children.

Attention Deficit Disorder (ADD)

At the age of 5 years, the diagnosis of ADD is difficult to confirm. Certainly Sami does exhibit several of the symptoms, including the inattentiveness, fidgeting and physical "busy-ness". Restless sleep is also a common symptom. However, as he seems to be keeping up academically there is no daytime "impairment" as such. The aim is to improve his sleep and see how age and neuro-maturation improves his functioning in the next 12 months [1].

Restless Legs Syndrome (RLS)/Periodic Limb Movement Disorder (PLMD)/Growing Pains (GP)

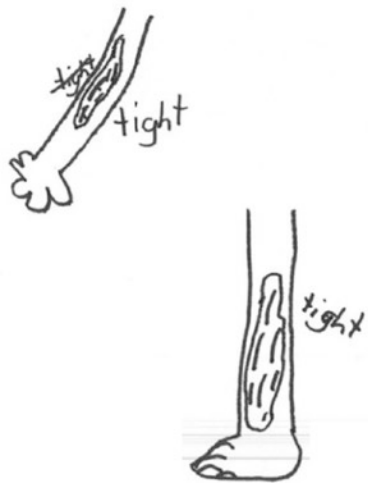
There is often some confusion between RLS and PLMD. The important thing to note is that RLS is diagnosed only on history and clinical features. Therefore it is a difficult diagnosis to make in a preschool child. Most people with RLS (around 80% or more) also have PLMD, however only around 60% of PLMD sufferers have RLS [2]. PLMD on an objective measure such as PSG in children is considered to be supportive of an RLS diagnosis in both children and adults [3] and there is some evidence that PLMD may be an early manifestation of RLS with PLMD [4].

RLS: there are five generally agreed criteria for the diagnosis of RLS in children:

1 An urge to move the legs, usually accompanied by unpleasant sensations
2 The urge to move or the sensations worsen during periods of rest or inactivity
3 The urge to move or the sensations are partially or totally relieved by movement
4 The urge to move or sensations are worse in the evening or during the night
5 The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioural condition

In children who cannot readily voice these symptoms, the occurrence of periodic limb movements on a sleep study and a family history in first degree relatives of RLS are supportive of the diagnosis [5].

Reproduced below are drawings from two school-aged children with RLS produced from my own clinic. This method of eliciting clinical information was first published by Picchietti et al. [6]



Cross Cultural Differences in RLS

Population-based studies using the full standard diagnostic criteria for RLS report a prevalence of 4% to 11% in western industrial countries, but a lower prevalence in Asian populations [7] Prevalence tends to decrease towards the equator [8].

Periodic Limb Movement Disorder (PLMD). Unlike RLS, PLMD is not a clinical diagnosis but is defined by polysomnography (sleep studies). In adults more than 15 PLMs/h and in children more than 5/h is considered abnormal, and must by definition cause clinically significant sleep disturbance or impairment in mental, physical, social, occupational, educational, behavioural, or other important areas of functioning. The PLMs are not better explained by other concurrent disorders [9].

On a PSG, periodic limb movements are defined where:

1. There are more than or equal to 4 limb movements in a series
2. Each movement is separated at intervals of not less than 5 s but not more than 30 s
3. Each movement must last at least 0.5 s but not longer than 10 s [10].

4. The amplitude of the movement must be 8 μV above the resting electromyogram (EMG).

Periodic limb movements must not be confused with sleep starts or hypnic jerks, sleep myoclonus and cannot be part of an arousal from an obstructive breath. PLMs have also been reported in narcolepsy and use of antidepressants.

The prevalence of PLMS could be 4% to 11% [11]. A European study estimated the prevalence to be 3.9% in the general population [12]. In this study, patients were diagnosed with PLMD based on a telephone-based screening questionnaire without any PSG evidence. So, this might not accurately reflect the prevalence. Older age, female gender, shift work, stress, and caffeine intake were thought to be some risk factors in this study. Some studies have found a reduced prevalence of PLMS in African Americans compared to Caucasians [13].

Growing pains are common in children but lack consensus definition, with the diagnosis often made after the exclusion of other diagnoses. Typically the pains are bilateral, and intermittent with some pain-free days and nights. The typical location is the anterior thigh, calf, or posterior knee and with no joint involvement. There is no loss of function by day and the physical examination, laboratory and imaging tests are normal [14]. The overall incidence of GP in children is estimated at around 2%, which is similar to the incidence of GP in people with RLS [15]. There is some association between GP and PLMD though with our own studies suggesting an odds ratio of more than 3.0 [16].

16.4 Sami's Progress

Investigations

1. The overnight sleep study showed no evidence of obstructive sleep apnoea with preservation of oxygen saturation above 95% through the night. However, there were periodic limb movements. There averaged more than 16/h of sleep (Fig. 16.1).
2. Investigations included a full blood count (normal) with iron studies:

   This confirmed low iron stores with a ferritin of 10 μg/L, transferrin saturation of 12%. C-reactive protein was less than 1 mg/L (normal).

Notes

1. It is important to note that normal values of ferritin are under-reported in most pathology labs. In symptomatic children in particular the level should be well above 50 μg/L (ng/ml)
2. As ferritin is an acute phase reactant it is important to request a c-reactive protein (CRP). A so-called "normal" or even high level of ferritin in the context of inflammation and high CRP potentially represents a spurious result [17].
3. Transferrin saturation or iron saturation should be above 20%. A low iron saturation with high ferritin and usually high CRP represents low iron stores [18, 19].

Research Gaps

1. Does iron supplementation lead to improvement in restless legs syndrome? Rosen et al. showed that although the mean ferritin levels improved in children with RLS, the improvement in RLS symptoms was noted but not statistically significant [20].
2. How good is the evidence that ferritin levels should be greater than 50 μg/L?

   One of the first papers linking low iron to PLMS suggested in their dataset that 50 μg/L or less was related to evidence of PLMS [21].

   If one defines normal ferritin as above 50 μg/L then a significant proportion of a normal population of children would fall below this [22].

   In the important paper by Lipschitz [17], the geometric mean ferritin in normal controls, 59 ng per millilitre (59 μg/L) with a 95% con-

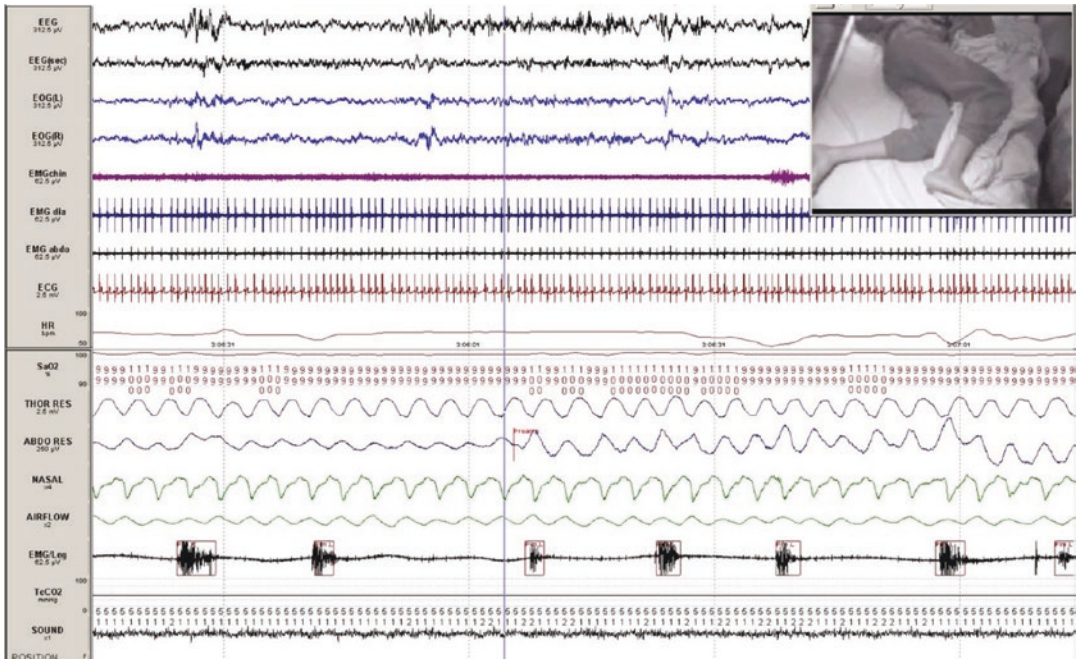


Fig. 16.1 Periodic limb movements showing 7 PLMs is a 1-min epoch of light (N2) sleep. PLMs are most commonly recorded in light sleep

fidence range of 12 to 300 ng/ml). It has been suggested that rather than tell parents that their child is iron deficient, that their ferritin level is sub-optimal for their symptoms [23].

Serum ferritin levels of <50 μg/L should raise suspicion of iron deficiency in children with chronic disease and in high-risk populations such as Indigenous Australians [24].

There is little doubt that significant tissue iron deficiency can exist with ferritin levels less than 30 μg/L in the absence of anaemia [25].

The Australian Blood Authority clearly states that a ferritin level of 20–50 μg/L can be associated with iron deficiency [26].

Serum ferritin levels ≥30 μg/L up to the method-related upper reference limit demonstrates healthy iron stores as long as co-existing inflammatory disease or hepatocellular damage are not present is the recommendation of the Royal Australasian College of Pathologists [27].

3. It is suggested that serum ferritin levels poorly reflect cerebrospinal fluid (CSF) ferritin levels [28, 29]

16.5 Sami's Treatment and Progress

Sami was treated for 3 months on nasal mometasone. The correct technique was demonstrated, including pointing at an angle away from the nasal septum, around 25° laterally, one spray to each nostril nightly, and advised to brush his teeth after. His mother reported better nasal airflow, less mouth breathing and almost no snoring.

In addition, he was commenced on iron in the form 100 mg of elemental iron as 370 mg iron polymaltose. This is equivalent to about just under 5 mg/kg daily for 3 months. The parents were advised in writing to give this after meals

with a small volume of orange juice, and to avoid taking milk, other dairy products and calcium close to the dose. As a general precaution they were advised to keep the medication out of the reach of small children. They were also told to look out for gastric symptoms and constipation. With the newer forms of oral iron, these side effects were less common. This was well tolerated. There was also a good clinical response: the sleep was much less restless, Sami seemed less hyperactive during the day as reported by his teachers and was much more attentive during class. He also had less episodes of night cramps or growing pains. Because he had a good clinical response, a blood test was not repeated.

16.6 Summary

It is important to take a good dietary history, excluding unusual diets in the family. At Sami's age excessive cow's milk ingestion should be avoided and a varied, healthy diet encouraged. A thorough medication history is also important. Paediatricians should also be cautious in avoiding certain antidepressants like mirtazapine, venlafaxine, sertraline, fluoxetine, amitriptyline as they may aggravate periodic limb movements.

Oral iron therapy should last 3 to 6 months. There is some suggestion that there should be slow weaning after that. Ideally the iron tests should be repeated towards the end of treatment [30].

For children poorly tolerant of oral iron, there is some evidence that IV iron sucrose can have a benefit [31].

There is poor evidence at this stage for other treatment of RLS/PLM in children. In adults dopaminergic medications such as pramipexole, ropinirole, rotigotine, and other drugs like gabapentin, pregabalin that are the mainstay of treatment for RLS may also cause a reduction in periodic limb movements in patients with PLMD [32]. Medications such as clonazepam, gabapentin, melatonin, clonidine, magnesium and valproate have been rarely tested in RLS/PLMD, usually without clear results and cannot be applied with certainty to children.

For an excellent review of pharmacotherapy of PLMD/RLs in children see Ref. 33.

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Bruxism

17

Rini Sekartini and Clarissa J. Aditya

A 7-year old male, Brad presented to his dentist with toothache in the left lower mandible area. Nothing was found after thorough examination and the dentist could not identify any particular triggers or relieving factors for Brad's on and off toothache. A course of NSAID was prescribed which did provide temporary relief. Brad usually sleeps alone in his own room but during recent home renovation different sleep arrangement was made. One night when he was co-rooming with his parents, mother could hear "strange" noise coming from Brad's bed, and it turned out Brad was grinding his teeth during sleep. Brad could not recall his teeth grinding. The family represented to the dentist who arranged polysomnography for Brad and his confirmed bruxism was treated accordingly. Parents wondered whether Brad's bruxism would recur!

17.1 Definition and Epidemiology

American Academy of Sleep Medicine (AASM) defined bruxism as: "repetitive jaw muscle activity characterized by the clenching or grinding of teeth and/or bracing or thrusting of the mandible [1]." Bruxism has two separate manifestations according to the circadian rhythm: it can occur during sleep (sleep bruxism) or during wakefulness (awake bruxism) [2]. For the purpose of this topic, we will discuss further the sleep bruxism. The definition of sleep bruxism according to International Classification of Sleep Disorders, second edition (ICSD-2) is "an oral parafunction characterized by grinding or clenching of the teeth during sleep that is associated with an excessive or intense sleep arousal activity" [3]. Sleep bruxism in adults was reported at 13%, while in children the prevalence varied from 6% to 50% [4, 5]. The varying prevalence in children was seen due to different diagnostic tools (self-report, electromyography—EMG, polysomnography—PSG) used in studies [5]. It is also difficult to gather the exact prevalence of sleep bruxism because most studies used self-reported questionnaires and yet most bruxers are unaware of their habit [1]. In a systematic review, no gender difference was reported for sleep bruxism [6]. It was implied that complaints of tooth-grinding during sleep decrease over time, as seen in 14% children to 8% adults to 3% patients over 60 years of age [7]. Specifically in children, it seems that

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with increased age (around 9–10 years old), the prevalence of sleep bruxism tends to decline, possibly as a result of the stabilization of occlusion [6].

17.2 Pathophysiology

Sleep can be divided into two parts, occurring in 3–6 cycles at an interval of 60–90 min: non-REM (Rapid Eye Movement) sleep and REM sleep. Non-REM sleep consists of light sleep (stages 1 and 2) and deep sleep [7]. Most bruxism episodes occur during the light sleep of non-REM and less than 10% during REM sleep. Bruxism during REM sleep is associated with sleep arousals, which is characterized by a brief (3–15 s) cortical brain activity along with or without an increase in heart rate and motor activity. Normally, during REM sleep, muscles are relaxed to the point of paralysis, but the brain activity is similar to when a person is awake. Bruxism during REM sleep can be counted as parasomnia [1].

There is also an involuntary mechanism called rhythmic masticatory muscle activities (RMMA) which occur during sleep. Rhythmic masticatory muscle activities are observed in up to 60% normal subjects and 80% patients with sleep bruxism. RMMA are slow (1 Hz) chewing-like movements in the absence of tooth grinding. When RMMA are frequent or associated with tooth-grinding, sleep bruxism is identified [1].

17.3 Etiology

Sleep bruxism probably is multifactorial, because the exact etiology is still unknown. In the past, morphological (peripheral) factors, like malocclusion and the anatomy of the orofacial bones, have been considered the main causative factors for bruxism [8]. However, Lobbezoo et al. [9] showed that orofacial morphology of sleep bruxers did not differ from non-bruxers. This finding indicates that there is no correlation between anatomical structure of the face and sleep bruxism.

Multiple studies suggest that sleep bruxism is regulated centrally and not peripherally [8, 10]. The central factors can be further divided into pathophysiological and psychosocial factors (Table 17.1). Sleep microarousals have been linked with sleep bruxism based on polysomnographic (PSG) studies. It is known that the bruxers' jaw motor activity is preceded by brain activation and increased heart rate, implying the central/autonomic nervous system involvement in sleep bruxism [7]. Several neurochemicals also play a role in sleep bruxism, namely clonidine (alpha agonist) and L-dopa (dopamine precursor), which both can reduce sleep bruxism [1]. The study of neurochemicals role in bruxism needs to be examined further.

Sleep bruxism was reported in about 50% family members of bruxers. Based on a review of family studies, twin studies, and one DNA analysis, it can be concluded that bruxism appears to be genetically determined [11]. Abe et al. [12] found that the C allele carrier of HTR2A single

Table 17.1 Possible sleep bruxism etiology [1]

	Central factor	
Potential factor	Pathophysiological	Psychosocial
Facial shape & features Condylar asymmetry Dental arch form Malocclusion Centric relation—maximum intercuspation discrepancy Balancing side contacts Occlusal interferences	Sleep problems Brain neurotransmitter imbalance Genetic Lifestyle (e.g., alcohol, caffeine, smoking) Allergies Nutritional deficiencies (e.g. calcium, magnesium) Drug/medicine consumption	Mental stress Emotional problems (e.g. anxiety)

Adapted from: Yap AU, Chua AP. Sleep bruxism: Current knowledge and contemporary management. J Conserv Dent. 2016;19(5):383–9

nucleotide polymorphism rs6313 was associated with an increased risk of sleep bruxism.

In the psychosocial part, stress is known to increase bruxism events during sleep. Karakoulaki et al. [13] showed that bruxers had higher levels of perceived stress than non-bruxers. Moreover, the salivary cortisol was higher in bruxers compared to non-bruxers [13]. This finding was similar to a meta-analysis by Chemelo et al. [14] which suggested that stressed individuals showed a higher chance of presenting bruxism when compared to healthy individuals, although the level of evidence was low due to different evaluation parameters in some studies and lack of established methodological criteria.

Souto-Souza et al. [15] composed a meta-analysis about attention-deficit/hyperactivity disorder (ADHD) and bruxism. They found that children and adolescents with a definitive diagnosis of ADHD are at greater chance of developing sleep and awake bruxism than those without this disorder. It should be stressed that the association between bruxism and ADHD was only significant in cases for which there was a diagnostic confirmation by a physician. These findings were limited by the cross-sectional study design, so the true causal relationship between ADHD and bruxism remained inconclusive [15].

17.4 Presentation and Diagnosis

Sleep bruxism is characterized by clenching and grinding of teeth. This causes heavy load to teeth and mastication muscles. Tooth wear is common in bruxers. Also, pain in the mastication muscles and temporomandibular joint (TMJ) area is frequently observed. Other clinical findings in patients with sleep bruxism are periodontal disease, hypertrophy of the masticatory muscles, and headaches [16].

Diagnosis can be made through clinical presentations according to the international diagnostic criteria proposed by the AASM. Patient history should be taken regarding "Recent patient, parent, or sibling report of tooth-grinding sounds occurring during sleep for at least 3 to 5 nights per week in the last 3 to 6 months". Also, clinical evaluation should be made towards abnormal tooth wear, hypertrophy of the masseter muscles on voluntary forceful clenching, and discomfort, fatigue, or pain in the jaw muscles (and transient, morning jaw-muscle pain and headache). Keep in mind that the jaw-muscle activity cannot be better explained by another current sleep disorder, medical or neurologic disorder, medication use, or substance use disorder [17]. Moreover, bite marks on the buccal mucosa can also serve as a complementary sign for clinical diagnosis of sleep bruxism [18].

Full-night audio-video PSG recording (type I) remains the gold standard for diagnosis of sleep bruxism and the assessment of comorbidity with other sleep disorders (sleep apnea, periodic limb movements, parasomnias) [1, 17]. Objective PSG recordings include brain activity (electroencephalogram), eye movements (electrooculogram), jaw/leg movements (electromyogram), heart rate/rhythm (electrocardiogram), thoracoabdominal movements, oronasal airflow and oxygen saturation [1]. The recordings of the audio-video PSG were checked to see how many RMMA events happened during sleep. The audio and video footages were helpful to distinguish orofacial activities (OFA) and other muscle activities (OMA) that could easily be mistaken for RMMA events [19]. Sleep bruxism was diagnosed if there were: (1) more than 4 episodes per hour, (2) more than 6 bursts per episode and/or 25 bursts per hour of sleep, and (3) at least 2 episodes with grinding sounds [20]. There are also several ambulatory devices for EMG or PSG monitoring (type II, III, and IV) to record RMMA, although the sensitivity and specificity depends on the device used [17].

17.5 Management

To current knowledge, there is no "cure" yet for sleep bruxism. The goal for management of sleep bruxism is directed toward tooth restoration/pro-

tection, reduction of bruxism activity, and pain relief [1]. Management in sleep bruxism can be distinguished in five: pharmacological, psychological, physical therapy, dental strategies, and alternative/homeopathic medicine [21].

In controlled clinical trials for adults, only clonidine and L-dopa managed to reduce sleep bruxism [1]. Clonazepam (a benzodiazepine drug) also showed promising effect to reduce sleep bruxism index in all adult patients included in the study. However, the risk of dependency ceased the drug for long-term use [22]. Botulinum toxin (BTX type A) can be injected locally to masseter muscles in patients with severe bruxism, which are refractory to conventional therapy. Although, this method has its portion of side effects, which can include: difficulty chewing or talking, muscle pain, and asymmetric changes in the facial features [1].

While in children, certain drugs had shown promising result in reducing parent-reported sleep bruxism. Flurazepam (15 mg/day), hydroxyzine (both 25–50 mg/day and 5–25 mg/day), imipramine (25 mg/day) all decreased the occurrence of sleep bruxism when given for 4 weeks. Trazodone (0.5 mg/kg/day) on the other hand, had a significant reduction of bruxism and morning pain after 2 and 4 weeks of intervention. But these drugs had various side effects, such as: drowsiness, nausea, vomiting, irritability, dry mouth, insomnia, confusion, aggression, headache, and diminished appetite. Moreover, it was not known whether the episode of sleep bruxism returned after the therapy had been stopped [21].

Psychological efforts to reduce sleep bruxism include biofeedback, hypnotherapy, cognitive therapy, behavioral therapy, stress, and relaxation management. Even though there is a link between psychological factors (e.g. stress) and sleep bruxism, there is limited evidence pointing out that these therapies have a good efficacy in treating sleep bruxism [1]. Targeted muscle relaxation and reaction competence were proved to be able to reduce parent-reported bruxism in children [21]. Also, it was found that sleep bruxism can decrease the children's quality of life, mainly because of functional limitation and pain. More approaches need to be explored further regarding the quality of life of sleep bruxers [3].

As for physiotherapy, one study of 26 children aged 3 to 6 years showed a 77% reduction of the occurrence of parent-reported tooth-grinding or tooth-clenching during sleep in the intervention group, as opposed to 15% reduction in the control group. The intervention involved 10 sessions of physical therapy done once a week per session [21].

Dental treatment for sleep bruxism consists of occlusal therapy and occlusal splints. There is no association between occlusion and sleep bruxism, although occlusal therapy is recommended if the dentition needs to be rebuilt after being noticeably worn down. Occlusal splints are removable dental devices that fit in between the maxillary and mandibular teeth and are composed of hard acrylic or soft vinyl. Its main function is to shield teeth and restorations from abrasion and harmful traumatic loading. Occlusal splints, depending on how they are made, can also unload, stabilize, and improve TMJ functioning as well as lessen painful muscle activity and aberrant muscle activity [1]. The use of occlusal splint correlate to a reduction in self-reported bruxism in 30 children aged 7 to 10 years old [21].

For alternative medicine, two studies were identified using *Melissa officinalis L* and *Phytolacca decandra* extracts to reduce bruxism in children. It turned out that both extracts could reduce the parent-reported bruxism, with one study showed in 2 years of follow-up, no recurrence of sleep bruxism was identified [21].

Another new therapy method, photobiomodulation, had reportedly successful in treating some muscle disorders [18]. Photobiomodulation and light-emitting diode (LED) therapy are treatment options for reducing pain and inflammatory processes as well as inducing the regeneration of the target tissue. Salgueiro et al. [18] conducted a study to see the effectiveness of photobiomodulation on sleep bruxism. Photobiomodulation over acupuncture points proved to be an alternative treatment for children with sleep bruxism, leading to fewer reports of headache and a reduction in bite strength [18].

Due to various side effects of the treatment, pharmacological therapy must be kept aside for persistent cases of bruxism. The first line inter-

vention should be a psychological therapy. This recommendation was made because the psychological interventions are generally considered not to be harmful, not interfering with maxillofacial growth/development and, therefore, not presenting contraindications. After that, the intervention can be followed by physiotherapy, although no study has investigated if this follow-up improves the results [21].

17.6 Summary

- Sleep bruxism can be regarded as one of the parasomnias, due to motor activities during REM sleep stage.
- Its etiology is multifactorial between peripheral and central mechanism.
- Gold standard for sleep bruxism diagnosis is by using a full-night audio-video polysomnography (PSG) recording, although diagnosis can also be made via clinical judgement or by using ambulatory devices.
- There is no "cure" yet for bruxism. Some studies suggest psychological support as the first line to help children with bruxism.

17.7 Research Gaps

- Difficulty in evaluating the real prevalence of sleep bruxism
- Brain chemistry pathophysiology in causing the bruxism
- Various approaches to reduce or cure bruxism: pharmacological, psychological, physical therapy, dental strategies, alternative medicine
- The association between the bruxers and their quality of life

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Benign Neonatal Sleep Myoclonus

18

Montida Veeravigrom and Tayard Desudchit

A term male newborn GA 38 weeks by date, Birth weight 2800 m. AGA. He was born by vaginal delivery with APGAR score 9 and 10 at 1 and 5 min respectively. No complication was noted during peri or postnatal delivery. At day 10 of life, the baby had brief jerks of arms and legs during sleep for 2–3 s. The cessation of the jerk occurred spontaneously. During the event, there was no changes in vital signs. The patient remained active and alert when he woke up. Physical examination and neurological examination were unremarkable.

18.1 Epidemiology

Three infants with sleep myoclonus were first reported by Coulter and Allen with the term "benign neonatal myoclonus" [1]. Benign neonatal sleep myoclonus (BNSM) is characterized by myoclonic jerks occurred exclusively during sleep at neonatal onset. Myoclonic jerks were abrupt and consistently cessation with arousals. Electroencephalogram is normal during the event with excellent prognosis [2].

The syndrome was underrecognized or unfamiliarity by pediatricians or neonatologists for 25 years and often remain misdiagnosis. This syndrome is a non-epileptic movement disorder that sometime mimic neonatal seizure. After it has been recognized, the syndrome was not a rare disorder. The incidence varies between 0.8 and 3 cases per 1000 birth [3]. This condition is more common in male. The ratio of male to female was 2: 1 in the largest study [4].

18.2 Etiology

Even the syndrome is usually sporadic, genetic factors may contribute to the etiology of BNSM. Some familial cases have been reported [5–9]. Afawi et al. reported that BNSM showed autosomal dominant inheritance and is not allelic with KCNQ2 and KCNQ3 gene [10]. KCNQ2 and KCNQ3 genes were found in benign familial neonatal seizure, one of differential diagnoses of BNSM.

The pathophysiology of BNSM is not fully understood. Two hypotheses were reported. The study of BNSM with combined EEG-polymyography suggested a generator in cervical spinal cord, not in reticular activation system in the brain stem [11]. Another study postulated

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immature or imbalance of serotoninergic system [12]. In neonate, the corticospinal tract is a descending inhibitory pathway and myelination develops in rostro-caudal direction. Immature myelination leads to incomplete control movement which resulted in myoclonic jerks. Myelination increases most at 6–7 months of age coincides with spontaneous resolution of BNSM. The rare presentation of facial involvement is due to the immature myelination of corticobulbar tract. Normally corticobulbar tract is myelinated before the corticospinal tract [11, 13].

18.3 Presentation and Diagnosis

Myoclonus manifested by sudden, brief, shock-like involuntary movement caused by muscle contraction which was called positive myoclonus. It also caused by lapse of contraction which was known as negative myoclonus [14]. BNSM is one of benign self-limiting positive myoclonus that occurred exclusively during sleep. BNSM was observed in term newborn infants during first week of life. From Kaddurah A, et al. eighteen case series, the mean age of onset was 9.6 days ± 8.8 days., with a median onset of 7.5 days (range,1–35 days) [15]. The earliest onset has been reported at 5 h of age [1].

The majority of myoclonus involves bilateral upper and lower extremities. However, unilateral myoclonus has been reported and around one third of the patients had lateralized features. The myoclonus jerks were irregular in frequency with two to three rapid abduction-adduction bilateral jerks followed by short pause. Head and facial myoclonus was rare to be seen in BNMS, however about 11% in the series were reported. Myoclonic jerks typically appear during quiet sleep. They may present in the transition from sleep to wakefulness [15]. Simple maneuvers such as repetitive sound, tactile stimuli or rocking provoke BNSM [16]. Benzodiazepines worsen or exacerbate myoclonic jerks in BNSM [17]. Restraint does not stop myoclonic jerks [18]. The differential diagnosis of BNMS is summarized in Table 18.1.

Table 18.1 Differential diagnosis of benign neonatal sleep myoclonus (BNMS)

Differential diagnosis of BNMS
Neonatal jitteriness
Neonatal drug withdrawal
Physiologic hypnic myoclonus
Benign myoclonus of early infancy
Neonatal seizure • Benign familial neonatal seizure
Neonatal status epilepticus

There are variabilities of case presentation of BNSM. The syndrome appears exclusive during sleep especially quiet sleep. Some cases have been reported during wakefulness at the awakening. The frequency of myoclonic jerks was also variable with median of 1/day (range 0.5–4). This condition was lasted with a mean duration of 11.8 ± 6.2 weeks (median 12 weeks; range 3–24 weeks) [15].

There are several case reports that BNSM was misdiagnosis as neonatal seizure or status epilepticus [19–21]. The misdiagnosis was from variability of the presentation such as focal features, head and face involvement and prolong duration. There is another case series about BNSM evokes somatosensory response. Somatosensory response was seen in EEG as theta band slow waves on vertex and central electrodes concomitant with myoclonic jerks and jerk-locked back-averaging revealed a sequence of deflections following myoclonus [22]. This EEG changes may mimic epileptiform discharges. This resulted in unnecessary diagnostic studies and inappropriate antiepileptic drug therapy (Table 18.2).

Table 18.2 How to differentiate Benign neonatal sleep myoclonus and neonatal seizure

	BNSM	Neonatal seizure
Onset	Commonly in the first 2 weeks of life	Variable depend on causes
Semiology	Myoclonic, majority symmetric, irregular Rare, asymmetric. Head and facial involvement.	Variable; tonic, subtle, clonic, multifocal clonic and myoclonic. Often with facial involvement
Eye characteristic	Persistent eye close	Eye usually open
Provocation	Repetitive sound, tactile stimulus, rocking	Occurs abruptly, spontaneously
Sleep/wake	Appears exclusively during sleep	Occurs in sleep and wakefulness
Terminated by	Arousals, wakefulness	Antiepileptic drug or spontaneously ended.
EEG during the event	Normal	Abnormal
Cause	Healthy term or near-term infant, Normal neurological infant, unknown cause.	Multiple causes; congenital brain malformation, hypoxic ischemic encephalopathy, stroke, metabolic, infection
Outcome	Excellent	Depend on underlying causes.

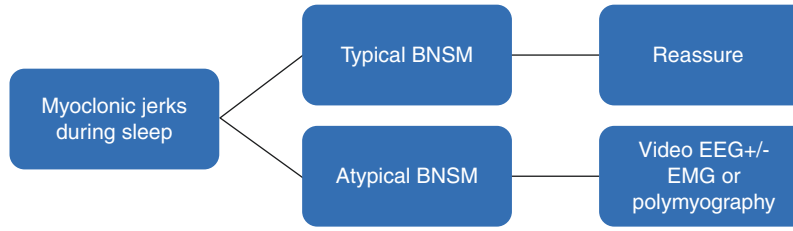

Fig. 18.1 Flow algorithms for management of BNSM

18.4 Management

BNMS is self-limited condition. It is important for pediatrician, neonatologist, and pediatric neurologist to recognize variability of clinical presentation. The correct diagnosis of BNMS will prevent unnecessary diagnostic procedure and unwarranted antiepileptic therapy. Antiepileptic medication does not treat myoclonic jerks and sometimes exacerbate them. The reassurance of this diagnosis will relieve parental anxiety.

There are atypical features of BNMS that sometimes make it is uncertain to diagnose from clinical standpoints. The atypical features were as the followings: prolong duration, head and face involvement, consistent focal features, occurred during wakefulness. These events may need to reconfirm with video EEG with or without EMG/polymyography (Fig. 18.1).

18.5 Cross Cultural Perspective

There are Few researches about BNMS in Asia Pacific region. Case series of 15 patients in Japan showed similar clinical manifestation with previous reported in western countries. BNSM was also misdiagnosed as neonatal seizure. Two patients received antiepileptic drug and three infants underwent lumbar puncture. In this study, there was a link between BNSM and migraine. Long term follow-up, 3 children had migraine

after 5 year of age and 42% of parents in this study had migraine. The link was hypothesized from serotoninergic pathway [23]. Two other papers were from India as a case report and eighteen case series of BNMS that mimics neonatal seizure [21, 24].

18.6 Summary of Key-Take-Home Messages and Research Gaps

1. Benign neonatal sleep myoclonus is a self-limited condition with variability in presentation.
2. The correct diagnosis of BNMS will prevent unnecessary diagnostic procedure and unwarranted antiepileptic therapy.
3. Further research needed regarding of pathophysiology and genetics.

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Part IV

Sleep in Special Populations

19 Sleep and Neuromuscular Diseases: Management and Use of NIV

Kate Ching-Ching Chan

19.1 Vignette of Typical Presentation/Real Life Example

An 11-year-old boy with a diagnosis of Duchenne Muscular Dystrophy (DMD) was referred to you for respiratory and sleep assessment. He initially presented at the age of two with motor clumsiness and later confirmed to have DMD by muscle biopsy. His motor function has been deteriorating and he was started on oral prednisolone at the age of 7 years. He lost ambulation 2 years ago at the age of 9 years. His recent pulmonary function test demonstrated a Forced Vital Capacity (FVC) of 1.21 L (47% of predicted) and a total lung capacity (TLC) 53% of predicted. He did not have major issues with chewing and swallowing. There was no recent hospitalisation for pneumonia or aspiration. His parents reported that he had snoring every night with mouth breathing. He did not have morning headache but complained of daytime fatigue 2–3 days per week. On physical examination, he was obese. He also had scoliosis. Auscultation to the chest was clear. How would you further assess and manage this patient?

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19.2 Epidemiology

Neuromuscular diseases (NMD) are a diverse group of hereditary or acquired conditions involving the anterior horn cells, nerves, neuromuscular junction or muscles [1]. Incidence ranges from 0.05 to 9/100,000 population per year and prevalence ranges from 0.1 to 60/100,000 population among various disorders [1]. The disease spectrum is wide with different ages of onset and varying presentations. Representative NMD in children are dystrophinopathy, in particular Duchenne muscular dystrophy (DMD), and spinal muscular atrophy (SMA). Others include post-polio syndrome, trauma to spinal cord, congenital and metabolic myopathies, myasthenia gravis, hereditary peripheral neuropathies (such as Charcot-Marie-Tooth) and other types of muscular dystrophies (such as limb girdle and facioscapulohumeral muscular dystrophy). The overall prevalence of dystrophinopathy (DMD and Becker muscular dystrophy) in Hong Kong in 2010 was 1.03 per 10,000 males aged 0–24 years, which was lower than other studies [2, 3]. Ethnic differences were reported in previous studies that NMD had a higher prevalence in South Asian ethnic group than in White children in a study performed in Yorkshire, UK [3]. In another study conducted in New Zealand, people of European ancestry had a higher prevalence of genetic muscle disorders when compared with other ethnic groups [4].

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Sleep-disordered breathing (SDB) is common in children and adults with NMD with a prevalence exceeding 40%, which is ten-fold greater than that in general population [5]. Gas-exchange abnormalities and disrupted sleep architecture occur in more than 80% of patients [5, 6]. Aetiologies of development of SDB in patients with NMD will be elaborated in the ***aetiology*** session. Briefly, characteristics of NMD like neuromuscular weakness of respiratory and diaphragmatic muscles, anatomic or neurologic propensity to upper airway obstruction during sleep, and/or cardiomyopathy contribute to the development of SDB [7, 8].

A spectrum of SDB can develop in patients with NMD, including nocturnal hypoventilation, obstructive sleep apnoea (OSA) and central sleep apnoea (CSA). Prevalence, pattern and onset of SDB vary with different types of NMD, depending on the features of the disease and the tempo of progression to respiratory muscle impairment [9]. In patients with DMD, the presence of OSA often precedes the development of nocturnal hypoventilation [7]. The pattern of SDB in DMD is bimodal, with development of OSA earlier in the course of disease during the first decade of life, then transitioning to nocturnal hypoventilation, which usually appears in the second decade [10]. In a study of 21 non-ambulant patients with DMD (aged 13–23 years), 57% had apnoeas associated with desaturation, of which the majority (60%) were obstructive in nature but progressing with advancing age to central/pseudo-central events [11]. Similarly, a retrospective review of patients with DMD reported 31% of children were diagnosed of OSA at a median age of 8 years, whereas 32% had hypoventilation at a median age of 13 years [12]. However, the actual prevalence may be influenced by the diagnostic pitfalls. Obstructive apnoeas may be misclassified as central in NMD due to the inability of weak respiratory muscles to expand the chest or abdomen against an occluded airway, while pseudo-central/diaphragmatic events can be misclassified as obstructive [8]. In fact, a lower prevalence of OSA in NMD is observed in studies which objectively classified obstructive versus non-obstructive events with the use of diaphragmatic EMG or oesophageal monitoring [8]. The diagnosis of the SDB respiratory events and pitfalls will be further discussed in the ***diagnosis*** session.

Respiratory failure is one of the most common causes of death among children and adolescents with NMD [6]. Respiratory failure can present either acutely, as a result of respiratory tract infection, or may develop insidiously with progressive ventilatory decompensation [6]. SDB and nocturnal hypoventilation are often the first signs of progressive respiratory failure, when the reduced capacity of the respiratory system is unable to support a normal respiratory load. This imbalance usually first presents during sleep [13, 14]. SDB very often first develops in rapid-eye-movement (REM) sleep when muscle atonia occurs, followed by continuous nocturnal hypoventilation through the night and eventually by progression into daytime respiratory failure [14, 15]. (Fig. 19.1).

Children with SMA type 1 develop respiratory failure inevitably by 2 years of age unless treated, while respiratory failure in children with DMD usually follows loss of ambulation [13, 14]. Although Nusinersen, the new intrathecal drug, has dramatically improved motor function in children with SMA, its long term effect on respiratory function is not clear. The proportion of patients developing ventilator dependence has not been significantly different in symptomatic infants [14]. The effect of AVXS-101 gene replacement therapy appears to be more promising in symptomatic infants in terms of prognosis for independent breathing [14]. However, many patients will not have access to these expensive novel therapies. Non-invasive respiratory support remains an important part of management of patients with SMA especially type 1 disease [14].

The use of non-invasive ventilation in children with NMD reduces symptoms and hospitalisation, improves survival and quality-of-life [16, 17]. It has favourable long term effect on nocturnal and diurnal gas exchange and sleep [18]. It is associated with stable vital capacity in some patients with NMD as well [18]. Therefore, regular assess-

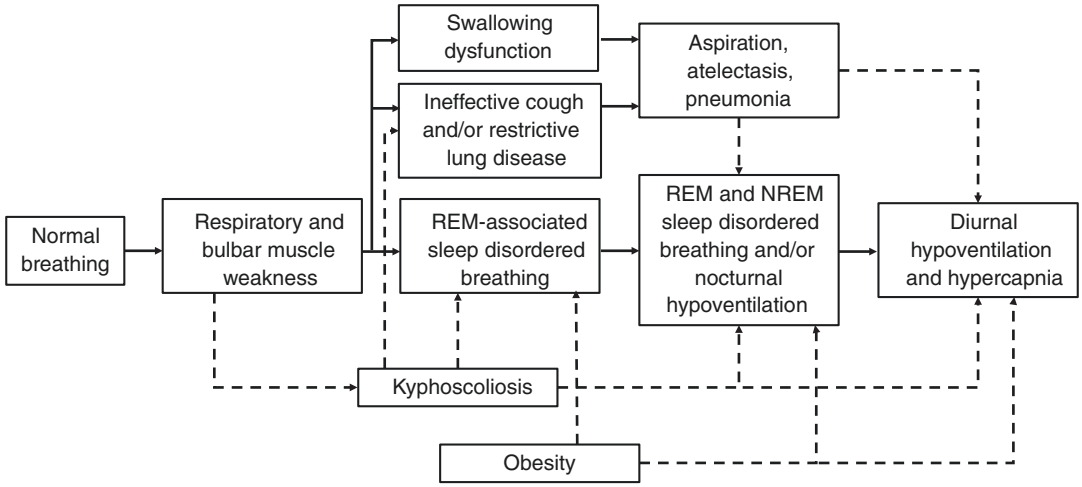

Fig. 19.1 Typical evolution of disease in patients with progressive neuromuscular disease. Dashed lines indicate aggravation

ment of pulmonary function and sleep in children affected by NMD, provision of respiratory care and ventilatory support are essential components of a multi-disciplinary care to improve their quality of life, morbidity and survival.

19.3 Aetiology

Development of SDB in children and adolescents with NMD is multifactorial. Characteristics of NMD like weakness of diaphragmatic and respiratory muscles, anatomic or neurologic propensity to upper airway obstruction during sleep, and/or cardiomyopathy contribute to the development of SDB [7, 8]. Other factors include reduction in lung volumes especially during supine sleep, compromised physiologic adaptation to sleep, reduced chest wall compliance and possible comorbid kyphoscoliosis, chest wall deformities and obesity that further restrict lung capacity [8, 14, 19, 20].

19.3.1 Decrease in Lung Function

Restrictive lung function deficit is common in patients with NMD. Both inspiratory muscle weakness and scoliosis contribute to the restrictive ventilatory defect [13]. The chronic reduction in chest wall expansion in patients with NMD results in reduced chest wall compliance, which also contributes to the restrictive pulmonary function in long-standing NMD [20]. The restrictive pattern in NMD typically consists of a decrease in vital and inspiratory capacities but an increase in residual volume early in the disease course which is inversely related to expiratory muscle strength [20]. The vital capacity and the functional residual capacity (FRC) are reduced in supine position and further compromised during sleep. In normal individuals, the vital capacity and the FRC are reduced by up to 19% and 25% respectively in the supine position. In individuals with diaphragmatic weakness, the erect-to-supine changes in vital capacity become more profound to >25% [20]. During sleep, there is relative hypoventilation that occurs physiologically as a result of reduced muscle tone and reduced ventilatory response to both hypoxia and hypercapnia in all individuals including healthy and diseased ones when compared to wakefulness. In normal individuals, there is an estimated 10–25% reduction in tidal volume, a rise in arterial partial pressure of carbon dioxide of 3–4 mmHg, and a reduction in arterial partial pressure of oxygen of similar magnitude during sleep [7, 8]. In healthy individuals with normal muscle function, activity

of intercostal muscles is augmented during non-rapid eye movement (non-REM) sleep, resulting in a greater contribution of the rib cage to breathing [21]. During REM sleep, atony of skeletal muscles excluding the diaphragm and extraocular muscles occurs, eliminating intercostal and accessory muscle contribution to respiration and accentuating the dependence of gaseous exchange on diaphragm contraction. These changes contribute to a further decrease in tidal volume [15]. A decrease in the activity of the pharyngeal dilator muscles, which is important to maintain upper airway patency, predisposes to upper airway obstruction during sleep. In healthy individuals, an intact diaphragm and accessory respiratory muscles generally compensate for these existing sleep vulnerabilities to the development of SDB. However, in patients with NMD, the gaseous exchange during sleep is impaired by the weakness of the respiratory muscles with the resultant sleep-related hypercapnia and hypoxaemia, which usually first manifests in rapid eye movement (REM) sleep because of muscle atonia [7, 22]. During REM sleep, for instance, when tidal volume is primarily dependent on diaphragmatic contraction, patients with diaphragm weakness will experience hypoventilation and gas exchange abnormalities [15]. Therefore, assessment of vital capacity and supine vital capacity provides important information to identify patients at risk of developing SDB, to diagnose diaphragmatic weakness and to guide initiation of therapy.

Low lung volumes are associated with nocturnal hypoventilation, SDB and oxygen desaturations. They are also risk factor for the development of OSA possibly by reducing the traction and stability of the upper airway [8]. Individuals with NMD may also have weakness of the pharyngeal dilator muscles in the upper airway, which contribute to increased upper airway resistance during sleep. Risk of developing OSA is further aggravated by the presence of obesity or upper airway abnormalities such as macroglossia and retrognathia [7].

Central sleep-disordered breathing can also occur in some patients with NMD. It can be caused by Cheyne-Stokes breathing in association with cardiomyopathy as seen in DMD, or from instability in the control of breathing due to diaphragm weakness as seen in myotonic dystrophy or post-polio syndrome [8].

19.3.2 Increase in Respiratory Loads

Increase in respiratory loads in patients with NMD further aggravates the respiratory insufficiency caused by the imbalance between inadequate muscle strength and the ventilation demands during both wakefulness and sleep [14]. Micro-atelectasis secondary to shallow breathing, impaired secretion clearance, reduced elastic recoil of the lungs, chest deformities, scoliosis, obesity as well as chronic parenchymal changes due to atelectasis and recurrent chest infections all contribute to the increase in the respiratory loads [6]. Although an increased respiratory drive can initially compensate the imbalance between increased respiratory load and decreased respiratory muscle function, hypoventilation and respiratory failure will eventually set in particularly with progressive muscle weakness in many NMD. (Fig. 19.1) Therefore, respiratory care plays an important role in reducing the respiratory loads and reduce the progression of hypoventilation, SDB and respiratory failure in patients with NMD [14].

19.3.3 Reduced Chemoreceptors Sensitivity

During sleep, there is a physiological reduction in the ventilatory response to both hypoxia and hypercapnia in all individuals when compared to wakefulness. In patients with uncorrected nocturnal hypoventilation, hypoxaemia and hypercapnia, further development of reduced sensitivity of chemoreceptors to carbon dioxide is anticipated and will worsen hypoventilation and reduce respiratory drive. NIV use to maintain normal gas exchange is crucial to maintain chemoreceptors' function in this regard [14].

19.4 Presentation

The characteristics of SDB at presentation in NMD is variable. Many present insidiously with the disease progression. Symptoms and signs of SDB are summarised in Table 19.1. Night time symptoms include snoring, nocturnal sweating, frequent nocturnal awakenings, sleep disturbance, poor sleep quality, awakenings with dyspnoea and tachycardia, while daytime symptoms include morning headaches, daytime lethargy, hypersomnolence, anorexia for breakfast, poor growth and difficulty concentrating [7, 13, 15, 23]. Both OSA and nocturnal hypoventilation are associated with significant morbidity and mortality. The neurobehavioural consequences of SDB are well documented, including a profound impact on cognitive function [7]. Physical examination may reveal some clues to the presence of SDB, although it is most often non-contributory. The presence of adenotonsillar hypertrophy, mouth breathing, nasal obstruction, and hyponasal speech may suggest the presence of OSA. Cor pulmonale and digital clubbing may be present in severe disease [7]. Paradoxical breathing is classically seen in patients with SMA type 1, whose weakness affects all respiratory muscles with initial sparing of the diaphragm [14]. Thoraco-abdominal asynchrony is thus caused by the imbalance between the intercostal muscles and the diaphragm with indrawing of the upper rib-cage during inspiration by the negative pressure generated by the diaphragm instead of being elevated [14]. Chest deformity such as bell-shaped chest and pectus excavatum is a common feature in young children with SMA secondary to chronic thoraco-abdominal asynchrony [14]. However, symptoms and signs can be vague and may be attributable to other facets of NMD, clinical presentation may not be predictive of the presence of SDB [7]. Therefore, a high index of suspicion for SDB is required by those caring for children with NMD and risk of SDB.

Table 19.1 Symptoms and signs of sleep-disordered breathing

Symptoms	Signs
Night time	Adenotonsillar hypertrophy
Snoring	Mouth breathing
Nocturnal sweating	Nasal obstruction
Mouth breathing	Hyponasal speech
Frequent nocturnal awakenings	Macrogloassia
Sleep disturbance	Facial and lingual myopathy
Insomnia	Cor pulmonale, heart failure
Poor sleep quality	Hypertension
Aakenings with dyspnoea and tachycardia	Digital clubbing
Orthopnoea	
Restless legs	
Hypoxic seizures	
Daytime	
Morning lethargy	
Daytime hypersomnolence	
Morning headache	
Anorexia	
Poor growth, failure to thrive	
Poor school performance	
Attention deficits	
Mood changes	

19.5 Diagnosis and Assessment

An anticipatory approach to the assessment and management should be adopted. Monitoring of respiratory muscle function and diagnosis of SDB are important in patients with NMD given their significant impact on morbidity and mortality, and respective core therapies can reduce respiratory complications, improve quality of life and prolong survival [23].

19.5.1 Symptoms Evaluation

Symptoms of SDB should be actively sought at each consultation, such as snoring, nocturnal sweating, frequent nocturnal awakenings, sleep disturbance, poor sleep quality, awakenings with dyspnoea and tachycardia, morning headaches, daytime lethargy, hypersomnolence, and difficulty concentrating [7, 13, 23]. Prompt evaluation with respiratory muscle function assessment and polysomnography should be provided to symptomatic patients. However, it is important to be aware that the presence or absence of symptoms do not adequately predict SDB nor the

Table 19.2 Recommendations for pulmonary evaluation in patients with DMD

Disease stage	Assessments
Evaluation every visit	History, physical examination, anthropometric measurements
Baseline evaluation	Pulmonary function test with MIP and MEP starting from age 5–6 years, and then at least annually; Supine vital capacity can be considered
	Cough peak flow
	Oxygen saturation, end-tidal or transcutaneous CO2, or arterial blood gas
	Polysomnography with capnography if symptomatic of SDB, or when VC <60% predicted, or when $PaCO_2$ ≥45 mmHg, particularly if the base excess is ≥4 mmol/L.
	Swallowing assessment if clinical suspicion of dysphagia and aspiration
Early non-ambulatory stage	Pulmonary function test with MIP and MEP every 6 months; Supine vital capacity can be considered
	Cough peak flow every 6 months
	Oxygen saturation, end-tidal or transcutaneous CO_2, or arterial blood gas every 6 months
	Polysomnography with capnography at least annually
When VC <60% and/or MIP/MEP <60 cm H_2O	Pulmonary function test with MIP and MEP every 4–6 months; Supine vital capacity can be considered
	Oxygen saturation, end-tidal or transcutaneous CO_2, or arterial blood gas every 6 months
	Polysomnography with capnography every 6–12 months
Diaphragmatic weakness ≥25% fall in FVC from seated to supine position	Polysomnography with capnography should be considered

severity of SDB [7]. Symptoms are even more difficult to predict hypoventilation given they are often variable and vague [7]. Therefore, objective assessment is vital to enable early identification of respiratory insufficiency and SDB in patients with NMD, particularly with the recent recommendations to initiate respiratory care earlier with a higher pulmonary function thresholds (milder levels of respiratory impairment) as part of a more anticipatory management approach in patients with DMD [23]. The recommendations for pulmonary evaluation for patients with DMD is summarized in Table 19.2.

19.6 Pulmonary Function Tests

Pulmonary function tests are likely the best clinical predictors of SDB and nocturnal hypoventilation in patients with NMD [7]. Although total lung capacity (TLC) is the recommended volume to detect restrictive lung function deficit, the vital capacity may be reduced ahead of the TLC in restrictive pulmonary impairment from NMD [8]. The early decline in vital capacity is accompanied by the increase in residual volume (RV) with decreasing expiratory muscle strength, while the TLC can remain initially preserved despite declining respiratory muscle strength. Therefore, the decline in vital capacity is often the earliest marker showing pulmonary restriction in patients with NMD.

Vital capacity should be measured in all those capable of spirometry [13]. In patients whose true height is difficult to establish such as non-ambulatory patients or those with scoliosis, arm span or ulnar length can be used to predict normal values. In patients with DMD, it is recommended to initiate spirometry at the age of 5–6 years, followed by at least annual monitoring of pulmonary function [23]. Deterioration in forced vital capacity (FVC) can remain asymptomatic and unrecognised unless pulmonary function is measured regularly [23]. In patients with DMD not treated with corticosteroids, earlier loss of ambulation, when compared to later loss of ambulation, is predictive of an earlier and lower peak FVC, and a more rapid subsequent decline [23]. In patients with DMD reaching early non-ambulatory stage, twice yearly mea-

surements of spirometry (seated FVC) with maximal inspiratory and expiratory muscle pressures (MIP and MEP), peak cough flow, oxygen saturation, and end-tidal or transcutaneous CO_2 are recommended [23].

Ragette et al. demonstrated that progressive ventilatory restriction in NMD correlates with respiratory muscle weakness, development and progression of SDB. Inspiratory vital capacity (IVC) and maximal inspiratory muscle pressure (MIP) show high predictive value for SDB onset (hypoventilation confined to REM sleep) (IVC <60%, MIP <45 cmH_2O), SDB with continuous hypoventilation through the night regardless of sleep stage (IVC <40%, MIP <40 cmH_2O), and SDB with diurnal respiratory failure (IVC <25%, MIP <35 cmH_2O) [24]. IVC is a surrogate measure of FVC. In a small prospective series of children with congenital and limb girdle muscular dystrophies, similar observation was reported that IVC <40% predicted was predictive for nocturnal hypoventilation with a high sensitivity and specificity [25]. In another study in adolescents with DMD, it was found that a forced expiratory volume in 1 s (FEV_1) below 40% predicted was sensitive for the presence of SDB (91%) but not specific, while a FEV_1 below 20% predicted was associated with daytime carbon dioxide retention [26].

A ≥25% fall in FVC from seated (erect) to supine position is a good indicator of diaphragmatic weakness [15]. Previous studies show that it has 90% sensitivity and 79% specificity for diaphragm weakness, while bilateral diaphragm paralysis is associated with 40–50% drop in vital capacity [8]. Comparison between seated to supine FVC is commonly performed in patients with NMD to assess diaphragmatic weakness, which is a risk factor of nocturnal hypoventilation particularly during REM sleep. However, previous study did not demonstrate correlation between a fall in the supine FVC and the presence of SDB in patients with DMD [15]. Further studies are needed to evaluate the diagnostic and prognostic utility of supine FVC for SDB or nocturnal hypoventilation in patients with NMD [23].

19.6.1 Cough Peak Flow

Cough peak flow (CPF) can be used to establish cough efficiency and can be readily measured in the clinic using a standard peak flow meter. It is also an important part to monitor as secretion clearance often becomes problematic before the development of respiratory failure, and is particularly representative of expiratory muscle weakness. CPF measurements derived from adult population are often used to recommend initiation of assisted cough therapies. Healthy adults have CPF ≥400 L/min. A CPF of <270 L/min in an adult or adolescent (over 12 years of age) suggest problems with secretion clearance will occur during a chest infection and values <160 L/min suggest profoundly weak cough [13, 27]. However, studies showed that children had lower baseline CPF than adolescents and adults [28, 29]. Reference levels for CPF in Caucasian paediatric population were published before [28]. Further studies are required to derive paediatric and preferably ethnic specific reference values for CPF in children with NMD.

19.6.2 Spot Oxygen Saturation

Spot check of oxygen saturation (SpO_2) can be easily performed with a pulse oximetry but a low SpO_2 is a late feature of respiratory failure. Values ≤93% prompts swift investigation with chest radiography and measurement of arterial carbon dioxide and oxygen tension [13].

19.6.3 Blood Tests

Measurement of daytime capillary or arterial blood gases can reliably predict nocturnal hypoventilation if arterial carbon dioxide ($PaCO_2$) is at >45 mmHg (6 kPa) on a daytime sample [26]. It is recommended that in patients with DMD, arterial blood gases should be performed once the FEV1 falls below 40% of the predicted value, and polysomnography should be considered when the $PaCO_2$ is ≥ 45 mmHg, particularly

if the base excess is ≥4 mmol/L. [26] However, we should not rely on daytime blood gas monitoring to detect nocturnal hypoventilation as it is almost certainly present when there is evidence of daytime hypercapnia. Otherwise, opportunity to intervene at an earlier point when hypoventilation is limited to nocturnal events would be missed.

19.6.4 Polysomnography

Polysomnography (PSG) remains the gold standard for assessment of SDB. A normal saturation level may occur despite nocturnal hypoventilation, especially with supplemental oxygen. Therefore, capnography with transcutaneous or end-tidal CO_2 monitoring is necessary to assess for hypoventilation [8]. Besides the diagnosis of SDB, PSG plays an important role in identifying SDB triggered by non-invasive ventilation, and optimizing non-invasive ventilation settings [8].

In patients with DMD, PSG with capnography may be necessary during the ambulatory stage, especially for individuals with weight gain due to glucocorticoid therapy and for individuals with symptoms of SDB [23]. The British Thoracic Society guidelines for respiratory management of children with neuromuscular weakness suggest PSG should be performed in patients with symptoms of nocturnal hypoventilation or OSA, and should be undertaken at least once a year in patients with a VC <60% predicted or if patients have lost ambulation in DMD [27]. However, a lower threshold for PSG should be considered in patients with rigid spine syndrome and diaphragmatic weakness.

In young children who cannot perform conventional spirometry but with an earlier respiratory decline as seen for example in SMA, PSG may be a screening tool to detect early respiratory failure which usually first develops during sleep, as non-volitional lung function in infants or young children is technically difficult and often not available in clinical practice.

19.6.4.1 Polysomnographic Characteristics of SDB in NMD

In NMD, hypoventilation very often first starts during REM sleep, and then progresses into non-REM sleep with continuous desaturation and hypercapnia [8]. Saw-tooth oxygen desaturation possibly represents the earliest manifestation of respiratory muscle weakness, secondary to the normal decrease in the rib cage contribution to the tidal volume during phasic REM sleep [8]. It can also be nocturnal desaturations secondary to OSA especially REM-related [8]. To differentiate from central events, obstructive events are usually ascertained by the persistence of effort and by the presence of thoracoabdominal paradox in the absence or reduction of airflow during sleep [7, 8].

However, there are several important pitfalls to note in the diagnosis of SDB in NMD and scoring of respiratory events in patients with NMD requires experience and interpretation together with the clinical context to reach conclusive results [14]. Diaphragmatic and respiratory muscle involvement in NMD may hinder the identification of the precise aetiology of SDB, particularly in the absence of direct or indirect measurement of inspiratory effort, such as diaphragm EMG, oesophageal or supraglottic pressure monitoring [8]. For instance, hypopnoeas, secondary to inadequate muscle activity with concomitant reduction in nasal flow, thoracic and abdominal effort, may be mistaken as central in origin [14]. In an apparent central apnoea, continued submental EMG activity noted during inspiration may indicate otherwise. In contrast, paradoxical movement of the chest and abdomen even in the absence of airway narrowing, as seen in patients with SMA, may be mistaken as obstructive events [8, 14].

19.6.4.2 Diagnosis of Nocturnal Hypoventilation

In children, the definition of nocturnal hypoventilation is complicated and there has been no clear consensus. A number of definitions of nocturnal hypoventilation exist. The most recent American Academy of Sleep Medicine scoring rules for

respiratory events define hypoventilation during sleep as: (1) arterial carbon dioxide (or transcutaneous or end-tidal carbon dioxide as surrogates) >55 mmHg for ≥10 min; or (2) there is an increase in PCO_2 of >10 mmHg from the awake supine value to a value exceeding 50 mmHg for ≥10 min. For those in the paediatric age range, hypoventilation is scored when PCO_2 is >50 mmHg for more than 25% of the total sleep time [13]. When using another more liberal definition, nocturnal hypoventilation with an arterial Pa_{CO2} >50 mmHg for ≥5% of monitoring in adults or ≥2% of monitoring time in children is seen in more than 40% of subjects with NMD not using non-invasive ventilation and with no daytime hypercapnia [8].

19.6.4.3 Changes in Sleep Architecture

In NMD, changes in sleep architecture have been reported. Compensation for hypoventilation occurs initially with an arousal response that prevents prolonged oxygen desaturation or hypercapnia [7]. REM sleep may be reduced or even completely absent with diaphragm dysfunction, thereby reducing the vulnerable period during which SDB is more likely to occur [8]. Such compensatory responses are at the expense of quality sleep, with sleep fragmentation leading to daytime fatigue and hypersomnolence. However, with time and progression of disease, the ventilatory chemo-sensitivity would be reset with blunting of the arousal response, allowing longer periods of REM sleep, during which hypoventilation occurs. Eventually, with the depression of respiratory drive, severe hypoventilation develops during both day and night.

19.6.4.4 Alternatives to PSG

In settings where full PSG is not available, multichannel respiratory studies can be considered [13]. Overnight oximetry is a more widely available test that can be performed overnight in a patient's home. Patterns of desaturation on oximetry may be suggestive of SDB. Repetitive clusters of "saw-tooth" desaturation may occur in REM sleep in the presence of OSA, whereas prolonged periods of desaturation may be evident with hypoventilation [7]. However, oximetry does not distinguish between OSA and hypoventilation. A normal pulse oximetry could not exclude SDB, because respiratory events that result in arousals rather than desaturation could not be detected. Moreover, technical problems such as a long built-in averaging time of the device can result in overestimation or underestimation of respiratory events [7]. Addition of capnography to oximetry has been proposed as a tool to aid in the diagnosis of SDB, but it has not been evaluated rigorously [7]. Ambulatory level III study with end tidal CO_2 ($etCO_2$) was compared to a level I sleep study for the diagnosis of SDB in children with NMD [30]. The sensitivity of the level III study to detect SDB at AHI cut-offs of >1 event/h and ≥5 events/h was at 68.2% and 61.5% respectively. The positive predictive value was 80.0% and the negative predictive value was 72.0%. Fifty percent of the cohort were either missing or had incomplete or falsely low ambulatory $etCO_2$ data. The results suggested that level III device with capnography is not ready for clinical practice as a diagnostic tool for SDB in paediatric NMD [30]. Nap studies, especially when conducted in an unfamiliar environment, unlikely contain representative REM sleep. Therefore, they generally carry low sensitivity and run the risk of underestimating the severity of SDB [7].

19.7 Management

Respiratory complications are a major cause of morbidity and mortality in individuals with NMD. Therefore, an anticipatory approach to management including timely implementation of chest physiotherapy, assisted coughing and assisted ventilation is critical to decrease respiratory complications, improve quality of life and prolong survival in this population. Summary of recommendations and common practice of respiratory care in patients with NMD is shown in Table 19.3.

Table 19.3 General recommendations for respiratory care in patients with NMD and recommendations for patients with DMD and SMA type 1

General recommendations for patients with NMD—basic interventions and training	
• Nutritional consultation and guidance • Regular chest physiotherapy and respiratory muscle exercises • Intensification of chest physiotherapy during respiratory tract infection • Immunisations including annual influenza vaccine and pneumococcal vaccine	
Recommendations for patients with DMD	
When FVC <60% predicted	Lung volume recruitment
When FVC <50% predicted and/or PCF <270 L/min and/or MEP <60 cm H_2O	Assisted coughing
Symptoms or signs of nocturnal hypoventilation or SDB and/or abnormal sleep study[a] and/or FVC <50% and/or MIP <60 cm H_2O and/or awake baseline SpO_2 <95% and/or awake baseline pCO_2 >45 mmHg	Initiation of nocturnal NIV with back-up rate close to breathing; early escalation of NIV with increased inspiratory pressures and extension of ventilation should be considered during respiratory tract infection
When awake SpO_2 <95% and/or pCO_2 >45 mmHg and/or symptoms of awake dyspnoea despite use of nocturnal ventilation	Addition of assisted daytime ventilation; early escalation of NIV with increased inspiratory pressures and extension of ventilation should be considered during respiratory tract infection
Recommendations for patients with SMA type 1	
SMA type 1	NIV is often initiated for signs of respiratory distress and thoraco-abdominal asynchrony

[a]Polysomnographic indications for nocturnal NIV include transcutaneous ($TcCO_2$) or end-tidal carbon dioxide ($ETCO_2$) of > 50 mmHg for ≥2% of sleep time, a sleep-related increase in $TcCO_2$ or $ETCO_2$ of 10 mmHg above the awake baseline for ≥2% of sleep time, an SpO_2 of ≤88% for at least 2% of sleep time or for at least 5 min continuously, or an apnoea–hypopnoea index (AHI) of ≥5 events/h

19.7.1 Respiratory Care: Physiotherapy and Cough Assist Devices

Airway clearance and physiotherapy are important parts of the management of children with respiratory muscle weakness. Physiotherapy can be performed during NIV which will augment inspiration and reduce tiring. In patients with DMD, lung volume recruitment is indicated when FVC is <60% predicted to preserve lung compliance. It can be achieved with a self-inflating manual ventilation bag or mechanical insufflation–exsufflation device to provide deep lung inflation once or twice daily [23]. Besides standard manual physiotherapy, insufflation–exsufflation device provides a large insufflation and then cycles to negative pressure to mimic expiration. A variety of these devices are available which can be used manually or automatically. Compared to manual physiotherapy and NIV, insufflation–exsufflation device was shown to be more effective in increasing cough peak flow in both adults and children [31]. In patients with DMD, cough assist devices are indicated when FVC is <50% predicted, when peak cough flow is <270 L/min, or when the MEP is <60 cm H_2O [23].

Children with NMD are prone to rapid deterioration during respiratory tract infections due to impaired cough, mucus plugging and aspiration of secretions. Secretion clearance and use of cough assist device should be intensified during respiratory infections to reduce hospitalisations. Early escalation of NIV with increased inspiratory pressures and extension of ventilation up to 24-h use during respiratory tract infection has been suggested to reduce the need of intubation [14]. Intubation during respiratory decompensation poses the risk of failure to wean from invasive ventilation and therefore will put the family into a position to decide between tracheostomy or palliative care. Family should be prepared for such situations and advanced management directives should be made covering these issues such as intubation, resuscitation and tracheostomy before the first severe decompensation occurs [14].

19.7.2 Non-invasive Ventilation

Non-invasive ventilation (NIV) refers to the provision of positive pressure ventilation via a non-invasive interface such as a nasal mask, in patients with NMD, to support the weak respiratory muscle, to alleviate airway obstruction if there is any, to normalise gaseous exchange and improve sleep architecture.

NIV is generally indicated in patients with daytime hypercapnia, with symptomatic nocturnal hypoventilation, or with symptoms or signs of SDB, even in the absence of raised daytime PCO_2 and irrespective of the level of pulmonary function [13, 23]. The time to initiate NIV therapy varies among different NMD. In patients with SMA type 1, NIV is often initiated once the children show signs of respiratory distress even while the gas exchange is still normal, aiming to improve functional residual capacity, reduce the work of breathing and ameliorate thoraco-abdominal asynchrony [14]. In patients with DMD, recent recommendations suggest to initiate nocturnal NIV with back-up rate of breathing when there are symptoms or signs of nocturnal hypoventilation or SDB, abnormal sleep study, FVC <50% predicted, MIP <60 cm H_2O, or awake baseline SpO_2 <95% or pCO_2 >45 mmHg [23]. Polysomnographic indications for nocturnal NIV include transcutaneous ($TcCO_2$) or end-tidal carbon dioxide ($ETCO_2$) of > 50 mmHg for ≥2% of sleep time, a sleep-related increase in $TcCO_2$ or $ETCO_2$ of 10 mmHg above the awake baseline for ≥2% of sleep time, an SpO_2 of ≤88% for at least 2% of sleep time or for at least 5 min continuously, or an apnoea–hypopnoea index (AHI) of ≥5 events/h [23].

In light of respiratory muscle weakness in patients with NMD, respiratory support should be in the form of bilevel positive airway pressure (BIPAP) support with a back-up rate [9]. Although continuous positive airway pressure (CPAP) can be considered in patients with predominant OSA, in many patients with NMD, progression to nocturnal hypoventilation is inevitable when inspiratory and expiratory muscle strength decline, hence progression to BIPAP will be required [13]. Moreover, with CPAP that little inspiratory support is given, expiration against a positive end-expiratory pressure (PEEP) could be uncomfortable and difficult for patients with NMD. Therefore, in individuals with DMD, nocturnal NIV with BIPAP ventilation mode is the first-line therapy even for OSA, and a back-up rate of breathing should be incorporated in the ventilation device to avoid apnoeas in late non-ambulatory stage [23]. In children with SMA, BIPAP therapy is also the treatment of choice [14]. Low flow long-term oxygen therapy alone (LTOT) is not recommended in patients with nocturnal hypoventilation as it abolishes hypoxic ventilatory drive and may worsen hypercapnia [13]. In conjunction with assisted ventilation, oxygen therapy can be safe especially when blood CO_2 levels are monitored [23].

To initiate NIV use in patients with NMD, mask fit and careful acclimatisation are always crucial for successful therapy [14]. Nasal mask is often preferred, especially in the presence of bulbar dysfunction and risk of aspiration of oral secretions or gastric content [14]. For NIV in young children, ventilator device should be able to safely deliver low tidal volumes and has a sensitive flow trigger to facilitate patient synchrony with the ventilator [14]. NIV can be provided in pressure or volume cycled modes [9]. A back-up rate close to spontaneous breathing rate (2–3 breaths below and usually not higher than 30–35 breaths/min) and a fixed inspiratory time are recommended in weak children as they are often not able to trigger inspiration, hold a sufficient duration of inspiratory time, or cycle into expiration [9, 14]. NIV therapy should ideally be set up in hospital with thorough training of the parents or the caregivers. In elective situations, children should be initiated on low pressure settings, followed by titration following clinical or polysomnographic criteria [14]. Humidification is recommended to improve respiratory comfort and reduce drying of bronchial secretions [32].

NIV has markedly changed the natural history of NMD. It improves quality of life and prolongs survival of patients with DMD and SMA [13, 14]. It can also palliate symptoms related to chronic hypoventilation and facilitate discharge from hospitalisation [33]. Patients with symp-

tomatic nocturnal hypoventilation should be initiated on NIV as symptoms can be successfully reversed with NIV treatment [18]. In a randomised controlled trial, patients with nocturnal hypoventilation but normal daytime arterial blood gas tensions were randomised to NIV or control group, health related quality of life was improved in those randomised to NIV [34]. It was also observed that 70% and 90% of patients in the control group required NIV treatment within 12 months and 24 months respectively [34]. Moreover, initiating NIV at the time nocturnal hypoventilation is diagnosed has the advantage that time is allowed to prepare both patient and their family for the intervention rather than unexpected initiation at the time of acute ventilatory failure [13].

With declining pulmonary function, patients will develop symptoms of hypoventilation such as dyspnoea, fatigue and difficulty concentrating despite the use of nocturnal NIV [23]. Extension of assisted ventilation into the daytime should be initiated if the patients have symptoms or evidence of daytime hypoventilation, including arterial, venous or capillary carbon dioxide (or transcutaneous or end-tidal carbon dioxide as surrogates) is >45 mmHg, or baseline SpO_2 is <95% on room air [23]. Mouthpiece ventilation with a portable volume ventilator can be considered for continuous NIV during the day, while continuous nasal ventilation with a bi-level ventilation device is also effective and well tolerated [23]. When a patient requires continuous ventilation to support life, a back-up ventilator and a manual resuscitator should be available in case the primary ventilation malfunctions. Moreover, external batteries or a generator should be available for use during a power outage [23]. Caregivers should be provided with adequate training and support to operate the devices and handle potentially catastrophic medical events.

NIV titration with attended PSG is the recommended method to determine an effective level of nocturnal ventilatory support in patients with NMD. Regular review of ventilator settings is also best achieved with a PSG. If not available, clinical observation together with oxycapnography is an alternative option although it is less precise when compared to PSG [14]. Guidelines to address obstructive SDB, hypoventilation, and asynchrony on polysomnography have been published [35]. Suggested recommendations from those guidelines are to use a back-up rate on a bilevel device, correct obstructive sleep events first then hypoventilation, and improve synchrony by adjusting the inspiratory time to between 30% and 40% of the total cycle time. Generally, a longer inspiratory time within this range is preferred by patients with NMD, as it may be more comfortable and tolerable with a slower rise time to the set pressure [35]. In conditions where OSA and hypoventilation coexist, such as in DMD, there may be competition between the optimal expiratory positive airway pressure necessary to alleviate OSA and the higher pressure support required to correct hypoventilation. The strategy to resolve these issues will require careful balance between maintaining or increasing the pressure support, and maintaining adequate expiratory positive airway pressure, with monitoring of capnographic readings and avoiding central apnoeas from overventilation. Moreover, particular attention should be paid to minimise the work of muscle required to effect respiration when titrating NIV in this population. A decrease in achieved tidal volume in pressure modes of ventilation, or an increase in pressure to achieve adequate tidal volume in volume ventilation should be an alert of changing respiratory mechanics with the disease progression [9].

Although NIV is a standard-of-care management option for SDB, it can itself trigger specific SDB events including air leaks, patient–ventilator asynchrony, central sleep apnoea and glottic closure [20, 36]. These events results in arousals, treatment non-adherence and disruption of sleep architecture [8, 20]. Therefore, it is important to identify, score and manage such respiratory events occurring in the context of NIV [36–38]. Other typical problems with NIV are pressure sore caused by the interface and midface hypoplasia when it is used from early age. Using alternate masks with different pressure points can be

considered [14]. Aerophagia with NIV use can usually be managed by releasing gastric air via the gastrostomy or nasogastric tube [14]. In patients with bulbar palsy, NIV may exacerbate pooling of oral secretions and aspiration, use of nasal mask, regular suctioning of oral secretions, use of anticholinergic medications and lateral position can be considered [14].

In the era of evolving novel therapies and changing natural history of NMD, protocols to wean individuals from ventilatory support have been published [9]. Future studies are need to characterize breathing patterns during sleep to assess possible readiness to wean respiratory support and hence the respiratory outcomes of new treatments [9].

19.7.3 Invasive Ventilation

Whether to initiate invasive ventilation via tracheostomy is controversial, especially in children with life-limiting NMD which can lead to complete paralysis and considerably poor quality of life. However, quality of life is often difficult to measure and should not solely focus on physical abilities. Joint decision making with the parents or the caregivers is crucial with careful consideration of different aspects including clinical status, disease progression and prognosis, quality of life of the child and the family, and also the resources (physical, social support and financial) of the family. There are huge variations in practice among countries and centres [14]. In some countries, such as Scandinavia and some European countries, a sequential approach of NIV and then tracheostomy ventilation is used when there is failure of NIV [13]. Comparisons in outcome between NIV and invasive ventilation are difficult as tracheostomy ventilation is usually applied later in the natural course of the disease [13]. Time on the ventilator (such as ≥16 h/day) is used in some centres as an indication for tracheostomy. However, use of continuous NIV 24 h/day has been shown to be effective and well tolerated [14, 23]. Therefore, in most circumstances, NIV would be preferred than tracheostomy ventilation [14]. On the other hand, novel therapies have significantly altered the natural course of some of the NMD, such as Nusinersen and gene therapy in SMA [39, 40]. The dramatic improvement in the prognosis may influence the individual perception and decision making about tracheostomy and invasive ventilation in this group of patients [14].

19.8 Summary of Key Take-Home Messages and Directions for Future Research

SDB is common in children with NMD. Importantly, it is often the first signs of respiratory muscle weakness in patients with NMD. Untreated SDB and hypoventilation in NMD carries high respiratory morbidity and mortality. Therefore, screening for SDB and nocturnal hypoventilation is a vital part of long-term management of NMD and to detect patients at risk for respiratory failure. Anticipatory and multidisciplinary approach with regular evaluation of symptoms, pulmonary function and sleep in children affected by NMD can aid early diagnosis and management of SDB. Timely provision of respiratory care and non-invasive ventilation are essential components of a multi-disciplinary care to improve quality of life and survival of individuals with NMD.

Diagnostic tools such as cough peak flow, maximum insufflation capacity, the difference between maximum insufflation capacity and FVC, supine FVC have high clinical relevance but require further studies to define their role in identifying patients with NMD at risk of SDB [23]. Paediatric and preferably ethnic specific reference values are needed for CPF in children with NMD. While improving quality of life remains the main focus of care for patients with NMD, further development of measures to assess quality of life in this group of patients with special focus on respiratory morbidity and ventilator dependence is needed [14]. More studies are needed to evaluate the impact of novel therapies on respiratory function in patients with NMD,

such as the characterization of breathing patterns during sleep to assess possible readiness to wean respiratory support. Multicentre or multinational studies to enable larger sample size and studies of more robust design with a focus on the impact of long-term NIV use on patients with NMD and their families are needed.

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20 Sleep in Children with Neurodevelopmental Disorders

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In general, poor sleep is common in children with a neurodevelopmental disorder [1, 2] and is related to additional difficulties for these children, such as increased daytime behaviour problems, poorer adaptive behaviour, and worsened academic functioning. Furthermore, sleep problems in children with neurodevelopmental disorders have a negative impact on families, particularly parents including increased parenting stress and poorer parent mental health [3–5]. This chapter examines sleep problems in the two most common neurodevelopmental disorders, Autism Spectrum Disorder (autism) and Attention-Deficit/Hyperactivity Disorder (ADHD). Additionally, as examples of sleep difficulties that commonly co-occur in a range of genetically determined neurodevelopmental disorders associated with developmental delay and intellectual disability (ID), we describe sleep in the X-linked disorders (Fragile X syndrome [FXS] and Rett syndrome), and the chromosome 15 imprinting disorders (Prader-Willi syndrome [PWS] and Angelman syndrome [AS]).

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20.1 Autism Spectrum Disorder

Autism Spectrum Disorder is characterised by social-communicative difficulties and repetitive and stereotyped behaviours and sensory sensitivities; more boys than girls are diagnosed [6]. Reported prevalence varies according to country, site, and ascertainment methods but, autism affects around 2% of the population [7]. Poor sleep in autism begins in early childhood [8]. Research over the last three decades has established that significant and often severe sleep difficulties, associated with a range of behavioural difficulties, are common in autism [9, 10], with reported prevalence as high as 86% for autistic children [10]. Sleep problems are likely to be chronic in autism and other developmental disorders [11] and occur at all levels of intellectual ability [12], though cognitive functioning or IQ can have some impact on reported sleep issues [13]; poor sleep quality continues to be reported in adulthood [14].

Long sleep onset latency, increased wake after sleep onset, reduced total sleep time and poor

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sleep efficiency are the most often reported sleep difficulties [2] in autistic children. Other sleep issues include sleep fragmentation [15]; bedtime struggles, which are common in younger children; and sluggishness, difficulty waking and daytime sleepiness or fatigue particularly in older children or adolescents [16, 17]. Epilepsy is also more common in autism than in the general population and may be a consideration when sleeping problems are present [18, 19], while gastrointestinal symptoms, which are very common in autism, are associated with increased risk for sleep difficulties [20].

Based on reported sleep symptoms many autistic children are likely to meet criteria for an Insomnia Disorder, while in adolescents Delayed Sleep-Wake Phase Disorder (DSWPD) [21] should also be considered. Restless legs syndrome [18], and sleep apnoea [22, 23] are also reported (Table 20.1). While little attention is generally paid to classifying sleep symptoms into specific sleep disorders in autistic children at least two relatively comprehensive sleep studies have done so with a Behavioral Insomnia of Childhood being the most common diagnosis [24, 25], though these authors also reported that some children's sleep could not be classified and was due to the autism itself. Thus, there are a range of diagnostic possibilities that may explain a child's presentation. The cause of high rates of sleep problems in autism remains unknown and may be multi-factorial, including circadian rhythm dysfunction and melatonin abnormalities, and hyperarousal. Core autistic traits, behavioural difficulties and other co-occurring conditions such as anxiety and ADHD are also associated with sleep difficulties, as are alterations in the sleep EEG [9, 12, 26, 27].

Table 20.1 Sleep symptoms in autism and their relationship with ICSD-3 sleep disorders

ICSD-3 sleep disorder category	Reported symptoms/behaviours or sleep disorder
Insomnia	Settling difficulties, co-sleeping, night waking, sleep efficiency <85%, long sleep onset latency, early waking, problematic bedtime routines, daytime sleepiness, short sleep
Sleep related movement disorders	Restless sleep; restless legs syndrome, periodic limb movements disorder
Sleep related breathing disorders	Sleep apnoea, sleep disordered breathing
Central disorders of hypersomnolence	Kleine-Levin syndrome, hypersomnia, daytime sleepiness
Circadian rhythm sleep-wake disorders	Delayed sleep-wake phase syndrome, late sleep onset, irregular sleep-wake patterns, free-running sleep patterns
Parasomnias	Nightmares, wakes screaming, enuresis
Sleep related epilepsy	Increased risk for epilepsy in autism

Melatonin is a photosensitive neurohormone, produced in the pineal gland, and acts as a marker synchronising circadian rhythms, including the sleep-wake rhythm. It is light sensitive, particularly to blue light; levels are very low during the day and begin to rise at night prior to sleep onset peaking in the first half of sleep [28, 29]. It has been hypothesised that an abnormality in melatonin production may underly sleep difficulties in autism (e.g., [12]). Some studies have shown reduced plasma melatonin or its urinary metabolite, 6-sulphatoxy-melatonin in autism (see [30] for a review). In contrast, a study examining the melatonin circadian rhythm in a small sample of nine autistic children aged 3- to 8-years found it was similar to non-autistic children [31]. Examining dim light melatonin onset (DLMO) in autistic adolescents and young adults the same group also found no difference from non-autistic individuals [32], while in young autistic adults DLMO was consistent with individuals' sleep-wake patterns and increased melatonin prior to sleep was associated with better sleep efficiency [28].

There is some evidence for altered melatonin synthesis in autism. Increased NAS (N-acetylserotonin; [33]) and decreased ASMT (converts NAS to melatonin) gene expression are reported in autistic children [34, 35] and ASMT genotypes have been related to sleep in autistic individuals [35, 36]. Investigation of the heritability of the melatonin synthesis pathway showed that (NAS) and the enzyme ASMT were highly heritable but autistic children tended to have lower heritability

for ASMT than unaffected family members; heritability for serotonin and melatonin was not significant in the autistic group [37]. Relatedly, clock genes, which control circadian rhythms, may be impaired or different in autism, resulting in disruption of the sleep-wake rhythm [36, 38]. Much remains to be understood about the role of melatonin and clock genes in sleep in autism and altered melatonin synthesis likely does not apply to all autistic individuals.

Poor sleep is generally associated with increased overall autism trait severity [39]. However, directionality remains speculative as poor sleep may exacerbate these behaviours or vice versa. One longitudinal study examining sleep and autistic traits from 1.5- to 9-years found that while autistic traits and poor sleep were associated at all ages, sleep problems did not worsen autistic traits, but autistic traits were associated with poorer sleep over time [40]. Social and/or communication difficulties [13], repetitive and stereotyped behaviours [39] and sensory sensitivities [41, 42] are also associated with poor sleep. Sensory sensitivities and repetitive behaviours may be indicators of increased anxiety and arousal. Path analysis has shown that sensory over-responsivity and anxiety predict sleep difficulties in autistic children supporting an association between hyperarousal, anxiety, and poor sleep [41]. Hyperarousal is thought to play a prominent role in insomnia and may underpin the development of anxiety [43], and there is evidence that hyperarousal is related to insomnia in autistic adults [44].

About 70% of autistic individuals have a co-occurring psychiatric disorder, including anxiety and ADHD [6]. Autistic children are at higher risk for an anxiety disorder compared to children in general [45]; anxiety in the general population is associated with poor sleep quality or insomnia [46]. Anxiety in autistic children is associated with poor sleep [47, 48], while examination of sleep and anxiety from 2- and 8-years and autistic traits at 2-years in a large, general population sample showed that autistic traits, anxiety and sleep were related at age 2, but at 8-years the best predictor of anxiety was sleep at 8-years and vice versa [49]. There are also consistent reports of an association between poor sleep and behavioural difficulties, particularly aggression, and neurodevelopmental disorders such as ADHD [2]. For example, aggressive behaviour significantly increased the odds of having poor sleep over time in autistic children [50]. Children with ADHD and co-occurring autism have similar levels of sleep problems as children with ADHD alone, with both internalising and externalising behaviours being associated with their poor sleep [51].

20.2 Attention Deficit Hyperactivity Disorder

Attention-Deficit/Hyperactivity Disorder (ADHD) affects approximately 5% of children and adolescents worldwide [6]. The core symptoms of ADHD are inattention, hyperactivity and/or impulsivity and to meet criteria for a diagnosis, symptoms need to be frequent, commence before the age of 12 years, occur across settings (e.g., home and school), and contribute to significant impairment in daily life [6]. ADHD is more prevalent in males compared to females [52] and is on average, associated with poorer outcomes across the lifespan [53]. It is understood that ADHD results from a combination of genetic and environmental risk factors, each having a small effect [52]. Co-occurring conditions are the rule rather than the exception in ADHD [52], with sleep problems being amongst the most common co-occurring conditions experienced by children with ADHD [54]. Given the similarity in behaviours that can result from sleep deprivation and the symptoms and consequences of ADHD, there is increasing interest in whether better assessment and treatment of sleep problems in children with ADHD can lead to improved functional outcomes [55].

The last decade has seen a surge in research publications on the topic of ADHD and sleep [54]. Up to 70% of children and adolescents with ADHD experience sleep problems according to parent report, comprising difficulties with both initiating and maintaining sleep [56]. Studies using objective measures (e.g., actigraphy, polysomnography (PSG)) to assess sleep problems in

children with ADHD also point to increased evidence for sleep disturbances in children with ADHD, although this evidence is less consistent than studies using subjective measures of sleep [57].

There is a great deal of variation in the types of sleep problems experienced by children with ADHD. Insomnia, circadian rhythm disorders (e.g., Delayed Sleep Phase Disorder) and parasomnias are all more common in children with ADHD compared to children without ADHD [58]. Additionally, more biological or medically-based sleep problems are also seen at increased rates in children with ADHD including narcolepsy, sleep breathing disorders and restless legs syndrome [59]. There is increased interest in whether variability in sleep parameters are increased in children with ADHD relative to controls with some studies supporting this notion [60], while others do not [61]. Furthermore, daytime sleepiness also appears to be more common in children with ADHD irrespective of night-time sleep problems [62].

The cause of sleep problems in children with ADHD is likely to be multi-factorial. For example, research suggests that higher levels of unhealthy sleep habits (e.g., screen time before bed, caffeine use etc.) in children and adolescents with ADHD is associated with increased sleep problems [63, 64]. Parenting factors such as increased parenting consistency have also been found to be associated with better sleep in children with ADHD [64]. Evening circadian preference is also associated with elevated sleep problems in this population [65]. There is some evidence that individuals with ADHD may experience a delay in DLMO [66], which may also explain the elevation of sleep problems in individuals with ADHD. Additionally, there is evidence of an association between circadian gene single nucleotide polymorphisms and ADHD symptoms [67].

A recent study points to the biological overlap between ADHD and sleep problems. This study found that there were three overlapping areas of association between sleep problems and grey matter volume, and ADHD symptoms and grey matter volume, largely in areas of the brain important for cognitive control and attention [68]. This study also found evidence that ADHD symptoms mediated the association between sleep problems and grey matter volume, and that areas where there were a higher proportion of the association between sleep and grey matter volume mediated by ADHD symptoms had higher gene expression including those important for dopamine [68]. The authors concluded that these complex findings support the notion that changes in grey matter volume and gene expression increase ADHD risk and that ADHD in turn, increases risk for sleep problems [68].

ADHD often co-occurs with other conditions such as internalising disorders (e.g., anxiety and depression) and externalising disorders (e.g., oppositional defiant disorder, conduct disorder [69]), with these additional co-occurring conditions conferring risk for sleep problems. For example, one study of 392 children with ADHD found that children with co-occurring internalising and externalising disorders had the highest risk for sleep problems [70]. In terms of other clinical factors that may be contributing to sleep problems in children with ADHD, the main treatment for ADHD, stimulant medication, has been associated with increases in insomnia [71]. However, research in this area is conflicting [72].

A number of studies now point to the increased burden that sleep problems have on children with ADHD. A recent study by Craig and colleagues found sleep problems in children with ADHD were associated with poorer quality of life and social functioning [73]. Additionally, sleep difficulties in children with ADHD have been associated with poorer cognitive functioning (e.g., executive function, delay aversion and working memory), although the strength of associations is generally small [74, 75]. Most of the research examining the connection between sleep problems and broader functioning in children with ADHD has been cross-sectional with few published longitudinal studies.

Of the small body of longitudinal research in this area, one study found that sleep problems were associated with greater behavioural and emotional problems in children with ADHD over a 12-month period [76]. Similar findings have been reported in young adolescents with ADHD, with one study finding that sleep problems were

predictive of greater behavioural difficulties and depression symptoms 1 year later even when accounting for initial ADHD severity and co-occurring conditions [77]. One recent large-scale study found some evidence to support bi-directional relationships between sleep problems and ADHD symptoms over time, however, there was evidence of a stronger association in the direction of ADHD symptoms predicting later sleep problems compared to vice versa [68].

The strongest evidence to date demonstrating the impact of sleep problems on the daily functioning of children with ADHD comes from sleep restriction studies, where researchers experimentally manipulate sleep times and then assess impact on functioning during normal or extended versus reduced sleep conditions. For example, a large study by Becker and colleagues found that sleep restriction in adolescents with ADHD was associated with increased inattention, oppositional symptoms and greater daytime sleepiness [78] and poorer affective functioning [79].

20.3 Neurodevelopmental Disorders with a Known Genetic Origin

In comparison to autism and ADHD, much less is known about the types of sleep problems and their causes in individuals with X-linked and chromosome 15 imprinting disorders.

20.3.1 X Linked Disorders

Fragile X syndrome (FXS) affects 1 in 4000 males and 1 in 6000 females [80] and is the most common inherited cause of ID and autism. FXS is caused by hypermethylation of the *FMR1* gene, resulting in silencing of *FMR1* mRNA and its protein (FMRP), which is essential for normal neurodevelopment [81]. The behavioural phenotype comprises speech delay, motor and language perseveration, abnormal sensory reactivity, sleep problems, aggression, anxiety, and hyperactivity and short attention [82]. Shyness and social anxiety interfere with social interaction and predispose to autistic features. In fact, ~75% of males and 25% of female patients with FXS also meet criteria for autism [83]). In a large survey study, 32% of children with FXS were reported to have sleep problems with 84% having ≥2 current sleep problems [84].

Most studies examining sleep in FXS have been by parent report. These studies have indicated insomnia symptoms are the most frequently reported problems [84]. Tolerability to objective measures of sleep in FXS and other neurodevelopmental disorders associated with ID can be poor, making objective assessment of sleep difficult. Nonetheless, a study [85] found good adherence to actigraphy and PSG in a small sample of children with FXS (n = 9). This study also demonstrated instability of circadian rhythms and variability in sleep patterns. While there has been a growing amount of work on circadian rhythm dysregulation in autistic adults, there is limited research examining circadian rhythmicity in autistic children and individuals with FXS. Nonetheless, *FMR1* knockout animal studies have demonstrated that both FMRP and FXR2P (a protein family member of FMRP with similar function), play a role in the regulation of sleep physiology [86]. In experimental studies, mice lacking *FMR1* exhibit abnormal circadian behavioural rhythms including loss of rhythmic activity in a 12:12 light-dark cycle and a free running period (<24 h) in constant darkness [86, 87]. Additionally, altered expression of the clock component of circadian rhythm genetic control has been observed in FXS animal models. The overexpression of FMRP via transfection assays increases the transcriptional activity of several key clock genes [86], suggesting that FMRP is essential for the regulation of rhythmic circadian behaviours. Moreover, Drosophila lacking FMRP exhibit altered circadian rhythmicity [87]. Together, these results indicate that FXS-related proteins might be associated with abnormal sleep patterns in FXS, due to alterations in circadian genes.

Rett syndrome (RTT) is a severe neurodevelopmental disorder associated with ID. RTT occurs predominantly in females with a prevalence of 1 in 9000 [88]. The disorder is associated with a mutation within the *MECP2* gene which is located on the long arm of the X chromosome

[89]. Individuals with RTT have an apparent early period of typical development, followed by a regression in communication skills. Co-occurring conditions experienced by individuals with RTT include epilepsy, sleep problems, and scoliosis. In a large questionnaire study of children and adults (median age 14 years, 4 months) with a *MECP2* mutation, 93.4% were reported to have either difficulties falling asleep or night waking [90]. In the same study, 38% of parents reported that the sleep problem had a moderate or major impact on the child, and 44% reported a moderate or major impact on the family unit.

The cause of sleep problems in RTT is not well understood. Nonetheless, research has shown that the severity of the sleep problem is dependent on the type of genetic change that has caused RTT [91]. Specifically, those with large deletions in the *MECP2* gene have the most severe sleep problems. The differences in severity of sleep problems based on the genetic subtypes of RTT, is suggestive of genetic factors contributing to sleep problems in this condition.

20.3.2 Chromosome 15 Imprinting Disorders

Chromosome 15 imprinting disorders including Angelman syndrome (AS) and Prader-Willi syndrome (PWS) are associated with varying degrees of ID and social communication deficits [92]. The chromosome 15 imprinting disorders arise from different deletions or duplications at the 15q11-q13 imprinted region, located on chromosome 15 [93]. These deletions or duplications affect expression of genes located in this region. PWS results from the loss of function of paternal genes from chromosome 15q11.2-q13, while AS from the absence of function of the maternal genes in the same region [93]. Chromosome 15 imprinting disorders affect approximately 1:15,000 individuals [94], with no sex bias.

The most common sleep problems for persons with PWS are excessive daytime sleepiness, sleep disordered breathing (SDB), reduced sleep quality, and early morning waking [95]. Cataplexy and narcolepsy are also commonly experienced by individuals with PWS [96]. PWS is the most common genetic cause of life-threatening obesity, due to an increased appetite and hyperphagia. Thus, obesity is thought to contribute towards the presence of SDB and hypersomnolence in those with PWS; however, oxygen desaturation has been shown to occur during rapid eye movement (REM) sleep even in the absence of obesity [97]. SDB in PWS includes central sleep apnoea (CSA), obstructive sleep apnoea (OSA), and sleep-related hypoventilation disorder [95]. SDB (including OSA and CSA) is reported to affect 53% of children with PWS, while up to 80% of children are reported to have OSA [98].

In AS the most common sleep problems reported are insomnia symptoms, including increased sleep onset latency, frequent and prolonged night wakings, and reduced total sleep time [99]. Interestingly, the diagnostic criteria for AS reports abnormal sleep-wake cycles and a diminished need for sleep as associated features of the disorder [100]. The latter feature was included as individuals with AS do not appear to experience negative consequences of sleep deprivation. However, this may be attributed to an inability to accurately measure the negative consequences of poor sleep in AS, given nearly all individuals with AS have no verbal communication and moderate to severe ID. Using PSG individuals with AS have been shown to have an increased number of transitions between sleep states, increased frequency of awakenings indicating fragmented sleep, and a reduction in the time spent in REM sleep—all suggestive of reduced sleep [101, 102]. The sleep problems have been shown to emerge during infancy in both AS and PWS [103]. Using the Brief Infant Sleep Questionnaire (BSIQ) children with AS had atypical sleep patterns including shorter and more variable sleep duration and longer and more variable periods of night waking. Infants and toddlers with PWS had significantly longer sleep duration over 24 h than those with other neurodevelopmental disorders, suggesting an early emergence of hypersomnolence.

UBE3A is the imprinted gene most likely responsible for maternal-specific effects of

15q11.2-q13 in PWS and AS [104]. In most peripheral tissues, *UBE3A* is biallelically expressed; however, in mature neurons in some areas of the brain, *UBE3A* is expressed off the maternal allele only. Thus, in those with AS there is a loss of *UBE3A,* while in those with PWS there is overexpression of *UBE3A*. In addition to having a critical role in the normal development and regulation of the nervous system, *UBE3A* also plays a significant role in the regulation of sleep homeostasis in animal models [105, 106]. More specifically, in a mouse model of AS with a maternal deficit of *UBE3A*, significant sleep-wake disturbances were observed [105] indicative of circadian dysregulation. Thus, one hypothesis for the cause of the sleep problems in AS is an inability to synchronize the sleep-wake cycle with the light-dark cycle, resulting in atypical melatonin secretion and consequently CRSWDs [107]. Few studies have examined the melatonin profile in AS. However, from the limited number of studies, AS individuals have a tendency towards reduced night-time levels of melatonin and/or altered timing of melatonin secretion [107].

Epilepsy is one of the most common medical co-occurring conditions in AS with approximately 70% of those with AS experiencing seizures which may also contribute towards sleep problems. Specifically, seizures may interfere with night-time sleep structure. Moreover, antiepileptic drugs may also influence sleep. Behavioural symptoms such as anxiety, hyperactivity, and autism traits may also contribute towards the presence of sleep problems in AS.

20.4 Assessment and Treatment of Sleep Difficulties in Children with Neurodevelopmental Disorders

Given the high prevalence and impact of sleep problems in children with neurodevelopmental disorders, it is important that consideration of sleep is given during clinical consultations. Recent research points to the under-identification of sleep difficulties in children with ADHD and autism [108], and both sleep itself and treatment approaches in PWS, AS, FXS and RTT are under researched, with sleep problems remaining ineffectively managed. Little has changed since earlier overviews of approaches to assessment and treatment in autism and other developmental disabilities [109], and ADHD [110].

Clinicians are advised to enquire in more detail about children's sleep patterns and behaviours and not to rely on parents spontaneously reporting poor sleep. While single questions such as such as "Does your child have a sleep problem?" may have good correspondence with sleep diaries and lengthier sleep measures [111], and have been shown to be associated with greater levels of functional impairment in children [56], parents may lack knowledge about normal sleep development in childhood or childhood sleep problems [112, 113]. Parents of children with and without an ID or developmental disorder (DD) scored well below chance on knowledge about childhood sleep and sleep problems [113], and while 63% of parents of children with an ID or DD reported one or more child sleep problems only 27% checked "yes" when asked if their child had a sleep problem [11].

In assessing children's sleep problems screening questionnaires are useful and there are many to choose from [114], though they are not generally developed with children with a neurodevelopmental disorder in mind. Sleep diaries and actigraphy will provide additional information if a sleep problem is indicated and of course PSG will be indicated in some circumstances, for example when sleep apnoea is suspected (e.g., in PWS). A range of factors including co-occurring medical conditions, behavioural difficulties, co-occurring anxiety or other mental health diagnoses, the presence and/or severity of autistic or ADHD traits, and the presence and degree of ID also need to be considered. Furthermore, broader family factors such as organisation and structure in the family environment and parent stress and mental health should be ascertained. These factors can all impact on treatment choice and treatment effectiveness. Behavioural approaches are recommended as the first line of treatment [115,

116]. A useful practice pathway to guide assessment and intervention for poor sleep in autistic children is provided by Malow et al. [116] and these guidelines may be usefully adapted to other developmental conditions.

20.5 Behavioural Interventions

One of the first considerations in treating children's sleep problems is implementing healthy sleep habits, particularly bedtime routines and the elimination of screens from the bedroom [117–119]. For example, in RTT healthy sleep practices were associated with reduced impact of the sleep problem on the family [90]. There is a growing body of research supporting the usefulness of behavioural treatments, generally implemented by parents for insomnia symptoms in autism and other neurodevelopmental disorders [120–122]. Behavioural approaches, including implementing healthy sleep habits, are recommended as part of a treatment plan, even when a pharmacological intervention is used [115] and can also improve child behaviour [121, 123].

There is a range of behavioural interventions for sleep problems in children with neurodevelopmental disorders including education about healthy sleep habits [124], extinction [125], bedtime fading with response cost [126], and graduated extinction procedures [127]. A functional assessment should be conducted prior to implementing a behavioural sleep intervention to determine antecedent and maintenance factors of the presenting sleep problem [128]. For example: (1) functional assessment of the child's sleep problems together with a behavioural sleep training program educating parents about children's sleep development, healthy sleep practices, and extinction procedures to address sleep onset, co-sleeping and night waking in five autistic children and six children with FXS was both successful and acceptable to parents [125]; and (2) individualised behavioural treatments based on functional assessment of each child's sleep difficulties in six boys with neurodevelopmental disorders, including one with PWS and one with ADHD, were reported to lead to significant sleep improvements [129]. While individualised behavioural sleep interventions are often necessary and can take many weeks to be successful, brief behavioural interventions, conducted in small groups or individually have also been reported to be efficacious in treating sleep problems in children with developmental disorders [121, 130].

There is a lack of studies examining the usefulness of cognitive behavioural therapy for insomnia (CBT-I) and acceptance and commitment therapy (ACT) approaches for helping with sleep in the context of children with neurodevelopmental disorders. CBT-I is considered the recommended approach to sleep intervention [131] and ACT is also an effective sleep intervention [132]; both approaches may have utility in addressing insomnia in older children with neurodevelopmental disorders, particularly adolescents. For example, following CBT for anxiety, sleep was reported to improve in autistic children [48]. However, adaptations may be needed to suit these intervention approaches to adolescents with neurodevelopmental disorders [133].

20.6 Pharmacological Interventions

While research on pharmacological intervention is lacking, there are recent reviews on these approaches to treating sleep problems in autism [36] and children with neurodevelopmental disorders [115], with a growing number of studies supporting pharmacological approaches to managing sleep problems in children with ADHD [134]. Nevertheless, with the exception perhaps of melatonin clinical data on management are lacking as is approval by agencies such as the FDA (USA) [115, 135].

Melatonin is the most prescribed pharmacological treatment for paediatric sleep problems and is reported to be an efficacious short-term treatment for sleep onset insomnia [136] and DSWPD in children [137]. Nevertheless, the action of melatonin in sleep in children with neurodevelopmental disorders remains unclear as it

has circadian, soporific [138] and anxiolytic effects [139] and is often prescribed without obtaining clear evidence that a circadian rhythm sleep disorder is present or that there is any abnormality in the child's melatonin rhythm. Melatonin's long-term safety in children requires further investigation [136, 137, 140] and it is recommended that behavioural treatments be tried first [135, 137]. One study demonstrated that a combination of controlled release melatonin with behavioural treatment was superior to melatonin alone in a group of autistic children [141].

Randomised placebo-controlled trials have demonstrated that immediate release [142] and controlled release melatonin [143] can improve sleep latency and total sleep in children with a neurodevelopmental disorder. Using a randomised double-blind, placebo-controlled, multi-national trial the Gringras group later showed that autistic children with and without ADHD, or Smith-Magenis Syndrome (3.2% of group) who had not responded to behavioural treatment had decreased sleep latency, improved total sleep and improvement in parent-reported sleep following prolonged release melatonin treatment [144]. Follow-up, open label trials provided evidence of melatonin efficacy and safety for children from Gringras et al. [144] for up to 2-years with no significant adverse, long-term effects of melatonin and continued improvement in sleep latency, night waking and total sleep, as well as parent-reports of sleep problems [145, 146]. In ADHD, a naturalistic trial of melatonin was largely successful in treating sleep onset delay that developed in 74 children following methylphenidate treatment [147].

Treatment options for sleep problems in AS are usually pharmacological. In a systematic review of 10 studies that investigated interventions to improve sleep in AS, weak evidence for the effectiveness of behavioural interventions and mixed outcomes for the effectiveness of pharmacological treatments were shown [148]. Although one study demonstrated treatment fidelity for a behavioural intervention there was no direct measurement of sleep with all treatment outcomes being subjectively reported by parents [149]. Most studies examining pharmacological interventions included mixed samples of individuals with various neurodevelopmental disorders and results were not reported separately for AS individuals. Nonetheless, in one randomised placebo-controlled efficacy study in eight children with AS and chronic insomnia [150], melatonin significantly advanced sleep onset time, reduced sleep onset latency and the number of nights with wakes per week, and increased total sleep time. However, of the four children who received melatonin, three were reported to have a return of increased night waking at the cessation of the open label period or at the 1-month follow-up. For RTT, pharmacological treatments, including melatonin, have not been shown to improve the sleep problem. In a study of 364 individuals with RTT, those taking medication remained more likely to have more difficulty falling and staying asleep, with greater impacts from the sleep problem still reported [90]. Thus, while melatonin remains one of the most prescribed pharmacological treatments, with some promising results for those with autism, ADHD and FXS, treatment effects in RTT and AS are less promising.

Other common pharmaceuticals that may be efficacious for various neurodevelopmental disorders include gabapentin, clonidine, trazodone, and mirtazapine [115]. Gabapentin, an anticonvulsant, has been shown to have beneficial effects on sleep in a variety of clinical conditions [115]. Moreover, in a case series in 23 children (87% with a neurodevelopmental disorder), gabapentin was shown to be safe and well-tolerated, with 78% of children showing parent-reported improvements in sleep [151]. Clonidine, an α_2-adrenergic agonist, has sedative effects and is commonly prescribed as a sleep aid in paediatric samples [152]. There is also research indicating efficacy of clonidine for sleep problems in ADHD [153, 154], autism [155], and children with neurodevelopmental disorders [156]. There is some support for mirtazapine and trazadone, antidepressant medications with hypnotic effects, for the treatment of sleep disorders in autism and other neurodevelopmental disorders, respectively. However, the evidence for these pharmaceuticals

is preliminary with further research needed. Moreover, trazadone is not recommended for RTT. Clinicians should always consider the severity and type of sleep problem, the associated neurological pathology, and polypharmacy, when considering pharmaceutical intervention.

20.7 Other Treatments

Children with a neurodevelopmental disorder diagnosed with SDB problems are usually treated with oxygen or continuous positive airway pressure (CPAP) [157] and a behavioural intervention may assist compliance to CPAP. Adenotonsillectomy is also used to treat OSA in neurodevelopmental disorders [157, 158]; in an autistic girl both sleep and behaviour improved after adenotonsillectomy for obstructive OSA [22]. A meta-analysis of six studies with 41 PWS patients, showed OSA symptoms significantly improved after surgery. Nonetheless, residual OSA was still frequently observed postoperatively [159], suggesting other factors contribute towards SDB in PWS. Readers should refer to relevant chapters in this textbook on OSA and central sleep apnoea syndromes for further information.

20.7.1 Summary and Research Gaps

While there is a vast amount of research exploring sleep problems, their causes and correlates in autism and ADHD, research in the genetically determined neurodevelopmental disorders is more limited. This is likely due to the rare nature of these conditions inhibiting researchers' ability to examine large samples of affected individuals and reach conclusive findings. Nonetheless, it is evident that sleep is disrupted with impacts on daytime functioning of both parents and children [101, 160, 161]. Further research is needed to delineate the type of sleep problems and their causes in these rarer conditions. Determining the nature of specific sleep problems and correctly diagnosing a sleep disorder has significant implications for the management and treatment of sleep problems in rarer neurodevelopmental disorders. Moreover, for all neurodevelopmental disorders, treatment options remain limited. Further research is needed to explore both behavioural interventions and pharmacological treatments. Individualised treatment plans based on the nature and cause of the sleep problem, as well as other co-occurring conditions experienced by these individuals is required.

20.8 Vignette

Jessica is a 12-year-old child who has been diagnosed with ADHD and autism. She takes long-acting stimulant medication to manage her ADHD symptoms. Jessica has a bedtime of 8 pm and generally needs to be out of bed at 7 am to get ready for school. She has a television in her bedroom and watches television in bed from 8 to 9 pm each night. After lights out at 9 pm she lies in bed awake for many hours and often doesn't fall asleep until 11 pm each night. Her parents then find it hard to wake her in the morning. She generally sleeps well overnight once she falls asleep. On weekends Jessica doesn't follow a set bedtime or waketime and generally falls asleep at 11 pm–12 am and sleeps until about 9 am. A diagnosis of Delayed Sleep Phase Disorder was made.

A number of strategies were suggested to improve her sleep including increased alignment between weeknight and weekend bedtimes and waketimes, removing the television from the bedroom and replacing TV time before bed with reading (in an area of interest). Bedtime fading was also used whereby Jessica's bedtime was temporarily set closer to her approximate sleep time and then the bedtime was brought forward by 15 min once she was able to fall asleep within about 20 min of getting into bed. This fading approach was coupled with a set wake time and early morning light exposure e.g., eating her breakfast in a sunny part of the house. This plan was developed with Jessica in collaboration with her parents. Overall, Jessica's sleep improved with her shifting to fall asleep by 9.30 pm and waking more easily at 7 am.

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