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Editor

Sleep in Children with Neurodevelopmental Disabilities

An Evidence-Based Guide

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Editor
Jennifer A. Accardo
Departments of Pediatrics and Neurology
Virginia Commonwealth University School of Medicine
Richmond, VA
USA

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To my husband Dwight, our children Fei and Joseph, and my parents

In memory of Carole Marcus, MBBCh

Preface

While I was in training to work with children with neurodevelopmental disabilities, three girls changed the course of my career. One girl, with profound microcephaly, would not fall asleep despite her young mother's best efforts. She literally ran tracks in her home's carpet before settling for the night. Another girl had Angelman syndrome, and stayed up all night raising a ruckus. Her younger brother, who had attention-deficit/hyperactivity disorder (ADHD), was equally lively during the day, and their mother was at her wit's end and exhausted. A third girl had ADHD herself and snored, and her mother was concerned about her sleep quality. Her overnight sleep study did not show obstructive sleep apnea, yet I did not understand the terminology of the study well enough to discern whether it revealed something else. I met these patients and their families with the knowledge that I did not yet understand how to help them, but the conviction that their lives would be better if their sleep could be improved.

This book is for those engaged in the care of children with neurodevelopmental disabilities and sleep problems, whether by choice or chance. I am hopeful this may include both those who work in the world of pediatrics and the subspecialties that treat children with developmental disabilities more specifically, and also practitioners of sleep medicine. The book is divided into four parts, with overlap among chapters, and perspectives that differ from author to author.

To begin, in the first part, chapters on the impact of sleep problems in children with disabilities and the evaluation of sleep complaints set the stage. Major tools of the trade, polysomnography and actigraphy, each merit their own chapters. These detail the information which can be gleaned from and the limitations of these respective methods and provide special considerations for their use in children with neurodevelopmental disabilities as well.

The International Classification of Sleep Disorders, Third Edition, lists 74 sleep disorders, isolated symptoms, and normal variants [1]. Yet sleep problems can be lumped into sleeping too little, sleeping too much, sleeping at the wrong time, or doing something abnormal during sleep (or some combination thereof). The second part of this book covers the major categories of sleep disorders as they apply in children with disabilities. Sleeping too little, manifested by falling asleep too late, waking inappropriately during sleep, waking too early for the day, or experiencing poor quality sleep, is treated in the chapter on insomnia—but is also a theme that runs throughout the book as a whole, as highlighted in chapters including, but not limited to, those on autism and behavioral interventions. Sleeping too much is ably covered in the chapter on hypersomnia. Sleeping at the wrong time is addressed in the circadian rhythm sleep disorders chapter. Abnormal activities during sleep could be considered to include parasomnias, sleep-related movement disorders, and even sleep-related breathing disorders.

The third part highlights specific neurodevelopmental disabilities that reflect a variety of sleep disorders and treatment approaches. The autism chapter not only focuses on insomnia but introduces the ecological approach. Attention deficit hyperactivity disorder and sleep problems tend to be entwined, such that symptoms of one can be interpreted as symptoms of the other. The chapter on cerebral palsy explores the overlap of physical, neurological, and behavioral in terms of impact on sleep. Chapters on spina bifida and prematurity present the applied neurophysiology of control of breathing. Specific genetic disorders with sleep manifestations are represented herein: Prader-Willi syndrome, Down syndrome, Rett syndrome, Williams syndrome, tuberous sclerosis, Fragile X syndrome, and 22q11 deletion syndrome, each with

somewhat different sleep phenotypes. The chapter on Down syndrome in particular revisits sleep disordered breathing and its long-term impact. Likewise, Prader-Willi syndrome has distinctive hypersomnia, a risk of sleep disordered breathing, and risk of sudden death potentially related to a common treatment. Some conditions that arise in the developmental period have the potential to derail both sleep and neurodevelopment: concussions and cancer. Other frequent comorbidities, namely intellectual disability, comorbid psychiatric disorders, and epilepsy, affect sleep across many disabilities.

The fourth part details options for treatment. There are few easy answers for treatment, and certainly inadequate evidence, so the clinical knowledge and review of existing research shared here yields helpful guidance. Approaches to treatment include the behavioral and environmental, as well as medications—and melatonin has its own well-deserved chapter. Occupational therapy approaches and exercise as a moderator of sleep are intriguing directions. Behavioral desensitization techniques both for diagnostic procedures (polysomnography) and treatments (continuous positive airway pressure) are addressed in detail.

My quest for training in sleep medicine led me to Children's Hospital of Philadelphia to learn from the indefatigable Carole Marcus via a sleep medicine fellowship. Carole had, in fact, pioneered the translation of sleep medicine into neurodevelopmental disabilities, with the publication of one of the first articles documenting the high risk of sleep disordered breathing in children and adults with Down syndrome [2]. Although she was a pediatric pulmonologist, she hypothesized and explored neurologic factors contributing to OSA via respiratory-related evoked potentials, in addition to the more recognized anatomic factors of adenotonsillar hypertrophy and obesity [3]. Even as OSA dominated people's impressions of sleep medicine, its effects on learning and behavior provoked more research on the implications of disrupted sleep for children. Carole and her colleagues also published the seminal Childhood Adenotonsillectomy Trial, to rigorously test the effects of surgical treatment of OSA on outcomes including measures of attention and executive function [4]. She died November 19, 2017. She was an extraordinary scholar and teacher who is terribly missed.

Thank you to all the clinicians and researchers who have contributed reflections and recommendations here based on review of the medical literature and their shared experience. Your generosity is humbling. I have learned a tremendous amount from you as role models and colleagues, and hope readers will as well. I acknowledge with gratitude and respect the many families with children who struggled to sleep, who shared their experiences and from whom I have continually learned. I thank Suresh Kotagal and Christopher Earley for introducing me to the world of sleep medicine and for invaluable encouragement at pivotal times, and to Beth Malow for unfailingly sharing her expertise and kindness. I salute my friends and colleagues at the Kennedy Krieger Institute in Baltimore, at which I had the priceless opportunity to develop a program for children with neurodevelopmental disabilities and sleep problems, in particular Valerie Paasch, my long-time psychology collaborator. Finally, to my father, Pasquale Accardo, who introduced me to the world of developmental pediatrics, and with whom I have had the privilege to work over the past 2 years at Virginia Commonwealth University: thank you and love always.

Richmond, VA, USA Jennifer A. Accardo

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Contributors

Jennifer A. Accardo, MD, MSCE Departments of Pediatrics and Neurology, Virginia Commonwealth University School of Medicine, Richmond, VA, USA

Adetayo Adeleye, BSc, MSc, MD, RCPC Department of Paediatrics, Alberta Children's Hospital/University of Calgary, Calgary, AB, Canada

Nicole Ali, BA, BScH, Bed, PhD (student) Department of Psychology and Neuroscience, Dalhousie University, Halifax, NS, Canada

Emma K. Baker, BPsySc (Hons), PhD Diagnosis and Development, Murdoch Children's Research Institute, Parkville, VIC, Australia

Amanda E. Bennett, MD, MPH Developmental and Behavioral Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, PA, USA

Sundeep Singh Bola, BSc, MD Department of Paediatrics, Markham Stouffville Hospital, Markham, ON, Canada

Lawrence W. Brown, MD Neurology and Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, PA, USA

George T. Capone, MD Down Syndrome Clinic and Research Center, Neurodevelopmental Medicine, Kennedy Krieger Institute, Baltimore, MD, USA

Mary E. Cataletto, MD, MMM Clinical Pediatrics, Stony Brook University School of Medicine, Stony Brook, NY, USA

Pediatric Pulmonology and Sleep Medicine, NYU – Winthrop Hospital, Mineola, NY, USA

Aliza P. Cohen, MA Division of Pediatric Otolaryngology – Head and Neck Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Penny Corkum, PhD Department of Psychology and Neuroscience, Dalhousie University, Halifax, NS, Canada

Susan C. M. Crane, PsyD, MS, BA Pulmonary, Children's Hospital Colorado, Aurora, CO, USA

Fiona Davidson, MASP, PhD (student) Department of Psychology and Neuroscience, Dalhousie University, Halifax, NS, Canada

Michael A. DeMarcantonio, MD Division of Pediatric Otolaryngology – Head and Neck Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Whitney T. Eriksen, PhD, MS, BNS, BA School of Nursing, University of Pennsylvania, Philadelphia, PA, USA

Robyn A. Filipink, MD Fragile X Clinic, Movement Disorders Clinic, Tourette Syndrome Clinic, Division of Child Neurology, Children's Hospital of Pittsburgh, Pittsburgh, PA, USA

Ximena Celedon Flanders, PsyD Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Department of Behavioral Psychology, Kennedy Krieger Institute, Baltimore, MD, USA

Tanjala T. Gipson, MD Tuberous Sclerosis Center of Excellence, LeBonheur Children's Hospital, Memphis, TN, USA

Daniel G. Glaze, MD, FAASM Pediatrics and Neurology, The Children's Sleep Center, The Blue Bird Circle Rett Center, Bioethics Committee, Texas Children's Hospital/Baylor College of Medicine, Houston, TX, USA

Paula Goldenberg, MD, MSW, MSCE Medical Genetics, Massachusetts General Hospital, Boston, MA, USA

Ann C. Halbower, MD Pediatrics, University of Colorado School of Medicine, Aurora, CO, USA

Andrea Heyman, MS, RD, LDN Nutrition, Kennedy Krieger Institute, Baltimore, MD, USA

Aaron Hockley, MD Clinical Neurosciences, University of Calgary, Calgary, AB, Canada

David G. Ingram, MD Pulmonary and Sleep Medicine, Children's Mercy Hospital, Kansas City, MO, USA

Stacey L. Ishman, MD, MPH Upper Airway Center, Division of Pediatric Otolaryngology – Head and Neck Surgery, and Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Department of Otolaryngology-Head and Neck Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Aditi Kantipuly, MHS, BS Department of Psychiatry, Kennedy Krieger Institute, Baltimore, MD, USA

Paige Kaplan, MBBCh, FRCP(P), FCCMG, FACMG Genetics Division, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Valerie Kirk, MD, FRCPC Department of Paediatrics, Alberta Children's Hospital/ University of Calgary, Calgary, AB, Canada

Fiona Elize Kritzinger, MBChB, FC, Masters in Medicine Christiaan Barnard Memorial Hospital, Cape Town, South Africa

Rebecca Kronk, PhD, MSN, CRNP Nursing, Duquesne University, Pittsburgh, PA, USA

Janet C. Lam, MD, MHS Neurology and Developmental Medicine, Kennedy Krieger Institute, Baltimore, MD, USA

Neurology and Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Mary Lashno, MS, OTR/L Occupational Therapy, Kennedy Krieger Institute, Baltimore, MD, USA

Lucy R. Leibowitz, PhD Department of Behavioral Psychology, Kennedy Krieger Institute, Baltimore, MD, USA

Roberta M. Leu, MD Pulmonary, Allergy/Immunology, Cystic Fibrosis and Sleep Division, Emory University/Children's Healthcare of Atlanta, Atlanta, GA, USA

Carmen López-Arvizu, MD Department of Psychiatry, Kennedy Krieger Institute, Baltimore, MD, USA

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Marilyn MacPherson, BScNCS, MD Pediatrics, Colchester East Hants Health Center, Truro, NS, Canada

Kiran Maski, MD Department of Neurology, Boston Children's Hospital, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

Thornton B. A. Mason II, MD, PhD, MSCE Departments of Neurology and Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Maria Cecilia Melendres, MD Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Lisa J. Meltzer, PhD, CBSM Department of Pediatrics, National Jewish Health, Denver, CO, USA

Eugenio Mercuri, MD, PhD Pediatric Neurology Unit, Policlinico Gemelli, Catholic University, Rome, Italy

Indra Narang, BMedSci, MBBCH, MD Division of Respiratory Medicine, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

Dragos A. Nita, MD, PhD, FRCPC Department of Pediatrics, Division of Neurology, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

Judith Anne Owens, MD, MPH Sleep Medicine, Neurology, Boston Children's Hospital, Boston, MA, USA

Valerie Paasch, PhD Department of Behavioral Psychology, Kennedy Krieger Institute, Baltimore, MD, USA

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Amee A. Patel, DO Pediatrics, Children's Sleep Center and Pediatric Pulmonary Medicine, Texas Children's Hospital/Baylor College of Medicine, Houston, TX, USA

Raghuram Prasad, MD Clinical Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Department of Child and Adolescent Psychiatry and Behavioral Sciences, Autism Integrated Care Program, The Children's Hospital of Philadelphia, Philadelphia, PA, USA

Jennifer Linton Reesman, PhD, ABPP Neuropsychology, Kennedy Krieger Institute, Baltimore, MD, USA

Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Ann Reynolds, MD Pediatrics, University of Colorado Denver, Children's Hospital Colorado, Aurora, CO, USA

Amanda L. Richdale, PhD Olga Tennison Autism Research Centre, La Trobe University, Melbourne, VIC, Australia

Domenico M. Romeo, MD, PhD Pediatric Neurology Unit, Policlinico Gemelli, Catholic University, Rome, Italy

Kathy J. Ruble, MSN, PhD Pediatric Oncology Survivorship Program, Johns Hopkins University, Baltimore, MD, USA

Samata Singhi, MD Department of Neurology, Boston Children's Hospital, Boston, MA, USA

Keith J. Slifer, PhD Department of Behavioral Psychology, Kennedy Krieger Institute, Baltimore, MD, USA

Department of Psychiatry and Behavioral Sciences and the Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Margaret C. Souders, PhD, CRNP Biobehavioral and Health Sciences Department, University of Pennsylvania, Philadelphia, PA, USA

Child and Adolescent Psychiatry, The Children's Hospital of Philadelphia, Philadelphia, PA, USA

Karen Spruyt, PhD Lyon Neuroscience Research Center, INSERM U1028-CNRS UMR 5292 – Waking Team, University Claude Bernard, School of Medicine, Lyon, France

Erin Steinhart, BA, MA Clinical Research Operations, Department of Neurology, Boston Children's Hospital, Boston, MA, USA

Gregory Stores, MD, MA, DPM, FRCPsych, FRCP Department of Psychiatry, University of Oxford, Oxfordshire, UK

Elaine Tierney, MD Department of Psychiatry, Kennedy Krieger Institute, Baltimore, MD, USA

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Margaret A. Tunney, PsyD Department of Behavioral Psychology, Kennedy Krieger Institute, Baltimore, MD, USA

Allison L. Wainer, PhD Department of Psychiatry, Rush University Medical Center, Chicago, IL, USA

Miriam Rachel Weiss, MSN, CPNP, RN Pulmonary and Sleep Medicine, Children's National Health System, Washington, DC, USA

Shelly K. Weiss, MD Department of Pediatrics, Division of Neurology, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

Barbara Y. Whitman, PhD Department of Pediatrics, Saint Louis University School of Medicine, St. Louis, MO, USA

Ariel A. Williamson, MA Sleep Center, Divison of Pulmonary Medicine, Department of Child and Adolescent Psychiatry and Behavioral Sciences, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Theresa Zakorchemny, MS, OTR Occupational Therapy, Kennedy Krieger Institute, Baltimore, MD, USA

Stefanie Zavodny, MS, BSN, RN School of Nursing, University of Pennsylvania, Philadelphia, PA, USA

Part I

Introduction

Impact of Sleep in Children

1

Karen Spruyt

Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
CAP	Cyclic alternating pattern
NREM	Non-rapid eye movement
REM	Rapid eye movement
SDB	Sleep-disordered breathing
SWA	Slow-wave activity

Introduction

We are far from full understanding of the neurophysiology of the sleep state and the transition between sleeping and waking states. The convolutedness of this interplay is increasingly shown in studies of sleep-wake state organization. Alternatively, the universally reported phenomenological age-related differences in presentation, evaluation, and treatment of pediatric sleep problems have become the subject of progressively more research. In fact, studies consistently indicate that how we (re)act, think, feel, and perceive is affected by poor sleep. Specific hallmarks of sleep and its stages such as sleep spindles, slow-wave activity, or cyclic alternating patterns appear particularly germane to these questions. Sleep impacts wakefulness, and subsequent sleep, and so forth, in a potentially cyclic relationship which may eventually impair a child's overall development. Therefore, an important question in understanding the impact of sleep might be whether dysfunction is related to sleepiness and/or sleeplessness? Investigating several sleep parameters (e.g., sleep offset latency) and hallmarks of sleep across the life span may aid our understanding, but thus far scientific findings are scant. That is, in children with developmental disabilities, poor sleep is often accompanied by a plethora of other problems which can cause, coexist with, or proceed from poor sleep in both subjective (e.g., perception of drowsiness) and objective (e.g., changes in sleep structure) manners. In general, poor sleep may generate more diverse types of poor performance and may result in poor performance of a greater severity than in those subjects without sleep problems. In summary, considering this sleep-wake interplay may foster a growing understanding of the relationship between aberrant brain networks and phenotypes of neurodevelopmental disability.

K. Spruyt, PhD
Lyon Neuroscience Research Center, INSERM U1028-CNRS UMR 5292 – Waking Team, University Claude Bernard, School of Medicine, Lyon, France
e-mail: karen.spruyt@inserm.fr, karen.spruyt@univ-lyon1.fr

The Coexisting Complaint: Sleeplessness and Sleepiness?!

Neurons that fire together, wire together. Donald Hebb 1949

The Interplay

The vital role of sleep in brain maturation is widely acknowledged [1–4], even though its exact function remains elusive. We are similarly far from full understanding of the neurophysiologic mechanisms of the sleep-wake cycle and the sleep state in particular. Intense research over the years on the neurophysiological processes involved in sleep has established that sleep is a dynamic and complicated behavioral state during which the brain is quite active [5, 6]. This neural activity consists of complex series of non-rapid eye movement (NREM) and rapid eye movement (REM) sleep stages repeating themselves in a characteristic pattern [6, 7]. In fact, the waking state is the last to mature [6]. Namely, evolutionary conserved activating systems build a neurophysiological network in the brain orchestrating the different behavioral states. Ascending activation of the cerebral cortex generates wakefulness and REM sleep, whereas inhibition allows NREM sleep. The synchronization of this network through local field potential oscillations seems like the cortex talking

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to itself. In other words, the cerebral cortex is active nonstop yet consciousness is dependent on external perturbation. Although the pathways through which these behavioral states are reached are still a mystery, most of the maturation of the sleep-wake cycle and sleep structure takes place during early development. But despite research pointing to the importance of sleep, more scientific attention is needed to the impact of sleep specifically on development in childhood, either in the short or long term. For instance, although preliminary, it has been suggested that difficulties with sleep/wake transitions might be useful for identifying risk and resilience indicators in infant behavior to predict trajectories of neurodevelopment [8, 9]. Thus, equally important in this developmental quest regarding the impact of sleep should be the waking brain, since waking systems are activated to stop sleep [10].

To determine the timing and quality of sleep, both homeostatic processes (process S) (i.e., a self-maintaining process involving a "biochemical" pressure to sleep, which depends not only on how long we are awake but on how active we are while awake) and circadian processes (process C) (i.e., a process involving the internal biological or circadian clock governing a "circa" (approximately) "diem" (day) rhythm), modulated by hypothalamic areas, are believed to interact [7, 11–13]. A marker of our circadian phase, endogenous melatonin, also called the "sleep" hormone, is released by the pineal gland during darkness (dim light melatonin onset; see sleep parameters) [14–16]. In individuals with developmental disabilities, exogenously administered melatonin is frequently given to treat sleep problems [17, 18]. Noteworthily, the role of endogenous and exogenous melatonin in individuals with developmental disabilities as well as in neurogenesis is a growing field of scientific interest.

As a third process determining the timing and quality of sleep, the ultradian (referring to cycles shorter than a day) alternation between NREM and REM sleep further organizes the sleep-wake state. Although the mechanisms for this ultradian rhythm are not yet fully elucidated, this cyclic sequence of NREM and REM sleep is very characteristic of sleep. Namely, the REM sleep rhythm is defined as the intervals between the onset of one REM period and the beginning of the next. Studies investigating this reciprocal interaction of sleep stages acknowledge that, for instance, around the first year of life, the NREM sleep becomes classifiable into substages (i.e., N1, N2, and N3; see Fig. 1.1) and that the length of the ultradian REM-NREM cycle slowly increases across childhood.

Several theories and pathways have been put forward in literature to document the interplay of the sleep state and its structure, as well as the transition to and from the waking state [7, 11–13, 19]. In summary, sleep is more than the absence of wakefulness. Moreover, there are many examples of the complexity of the interplay between the states. Some studies [12, 13] show that, for instance, periods of forced waking lead to increased sleep drive, manifesting as sleepiness, with compensatory increases in the amount of certain sleep states in subsequent sleep, also known as sleep rebound [11]. The literature further highlights that this interplay is even more complex as during early development, internal biological clocks become increasingly organized around environmental cues, such as the light-dark cycle, temperature, noise, and social interaction, further fine-tuning the sleep-wake interplay. Altogether these factors are potential diagnostic and therapeutic venues across the 24-h sleep-wake cycle.

The Care

Due to the interplay between states, clinical care needs to involve all 24 h. Despite the paucity of scientific studies of *normal* sleep in children, there is a host of data describing the consequences of "poor" sleep (e.g., sleep-disordered breathing) in rather general terms. One way to

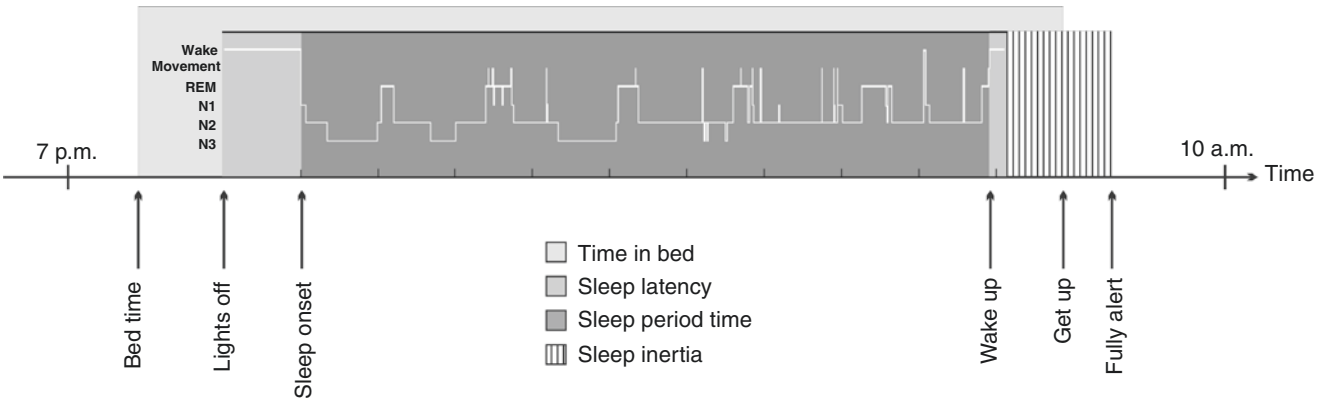

Fig. 1.1 Sleep parameters. The hypnogram shows the sleep structure and parameters of interest that can be assessed through questionnaires, actigraphic recording, and polysomnography

Table 1.1 Sleep parameters (Fig. 1.1)

1. Bedtime (e.g., lights out time, how long it takes to fall asleep)
2. Sleep duration, from sleep onset to awaking or get-up time/ waking for the day
3. Wake time (e.g., spontaneous awakening, how long it takes to wake up, sleep inertia, or impaired alertness following awakening)
4. The timing(s) of sleep within the 24-h rhythm (don't forget naptime or daytime sleep)
5. The variability of the sleep phase within the circadian rhythm (don't forget special circumstances: e.g., weekday vs. weekend, seasonal variation, school year vs. summer)
6. Sleepiness and sleeplessness and their degree, timing, and duration
7. When applicable, establish dim light melatonin onset, which refers to the start of the endogenous melatonin production during dim light conditions

understand the benefits of sleep is indeed to investigate the consequences of its deprivation, disruption, or disturbance. Although much of the work on the adverse effects of poor sleep on development remains speculative to date, increasingly more studies show that neurons begin to malfunction or that brain activity is altered following inadequate sleep [7, 20].

Given the enormous neurophysiologic evolution of the child over time, phenomenological age-related differences in presentation of sleep behavior are commonly reported. Therefore, it makes sense that evaluation and treatment of pediatric sleep complaints vary progressively with age as well. Pending additional progress in translational research, from a clinical care perspective, we might start with routinely asking about the following sleep parameters or anchor points when investigating the sleep-wake cycle. Each of these anchor points can be questioned in more detail (Table 1.1).

The Impact

When discussing the impact of sleep, the scope needs to extend beyond nighttime sleep. That is, how sleepiness, or increased sleep propensity, affects waking performance should also be considered. Remember, the stability of the wake state is ascribed to similar neurophysiological networks that determine the timing of sleep onset and offset [21]. An increased sleep propensity both affects waking performances and also involves changes in sleep, for example, by reducing latency to sleep onset and shortening the latencies from lighter stages of NREM sleep to deeper slow-wave sleep [22, 23]. Sleep latency is therefore considered a physiological indicator of sleep propensity, which can be assessed in two ways. The multiple sleep latency test (a protocol of structured nap opportunities) assesses excessive daytime sleepiness or how quickly you fall asleep in a quiet environment during the day. The maintenance of wakefulness test (a protocol in which you are commanded to stay awake) assesses how alert you are during the day or how alert you remain in quiet times of inactivity [24, 25]. How fast you fall asleep and how well you stay awake is very informative with respect to your sleep-wake cycle. When sleep remains poor, eventually "microsleeps" or "sleep attacks" intrude into wakefulness, further impairing function.

Thus, sleep impacts wakefulness, and subsequent sleep, and so forth. This potential predictive ability of sleep toward subsequent wakefulness and sleep, and hence its potential usefulness in phenotyping during human development, has been chronically overlooked. Childhood specifically is characterized by a great capacity to learn and to memorize, coinciding with the period during which humans sleep the most: both longer in duration and more deeply in terms of sleep architecture. As a result, childhood becomes an ideal period during the life span to investigate the impact of sleep. Unfortunately, the scientific interest in this concurrence of overall development and sleep has often been overshadowed by a bias toward waking behaviors. Nonetheless it is worth mentioning that, and as previously highlighted, the absence of objective documentation of the preceding night's/nights' sleep in assessing general abilities (e.g., cognitive performances, behavior) could jeopardize validity of findings from research conducted during normal waking hours. Additionally, although the impact of sleep might not be straightforward, more findings across development could highlight (dis)similarities in outcomes, for example, some aspects of performance might be more susceptible to poor sleep and this throughout the life span.

Currently generalizations from findings are limited; that is, the impact might depend on the performance or behavior investigated, the design of the experiment (e.g., partial sleep deprivation associated with sleep deficits in nightly sleep versus total sleep deprivation which comprises complete lack of sleep or continuous wakefulness), timing of assessments (e.g., before or after sleep), the population under investigation, and so forth.

Summarizing, and unmistakably, the predictive role of sleep should be of interest to many researchers, not only to sleep researchers and clinicians. It remains that the impact of sleeplessness and sleepiness is an underrecognized problem in children and more so in children with developmental disabilities. In this chapter, each of the following sections will embed the discussion of findings in children with developmental disabilities within an overview on sleeplessness, sleepiness, or poor sleep in typically developing children.

The Quest for Phenotypes: Sleeping and Cognition

In a Nutshell

In the past, it has been suggested that performance in abstract and complex tasks (e.g., the Wisconsin Card Sorting Task, where cards need to be classified according to different criteria) involving higher brain functions (e.g., prefrontal cortex) declined more strongly after sleep deprivation than performance on simple memory tasks [26]. In adolescents, for instance, experimental manipulation of one night's sleep deprivation revealed reduced performance [27]. More importantly, though, their sleepiness during assessment decreased performance depending on the task and the daytime activity across the study design [27]. Another group [28] highlighted the discrepancies in impact of total sleep deprivation versus partial deprivation. In sleep-restricted children, empiric evidence of impaired academic performance, as illustrated both by difficulties in the classroom and also school-related attention problems characterized by "sluggish cognitive tempo," have been reported [29]. These examples illustrate that the impact of sleep is not straightforward across developmental age, function, and type of sleep problem. In general, most authors have proposed that poor sleep impairs executive function, causing problems with cognitive control.

Specific Hallmarks of Sleep

Researchers have started investigating the role of specific hallmarks of sleep in typically developing children, in whom slow-wave sleep and sleep spindles appear particularly relevant in the consolidation of memory and maintenance of cognitive function [30–32]. That is, slow-wave sleep and sleep spindles have been associated with full-scale intelligence and fluid intelligence (i.e., the ability to think and reason abstractly and solve problems independent from education or experience), in the processing and learning of new material in both humans and animals and in a variety of indices of cognitive performance measured on several well-validated instruments [31, 33–36]. In other words, higher sleep spindle activity related to higher cognitive abilities. Also slow-wave activity, which is maximally expressed during NREM sleep and relates to prior wake duration, hence reflecting the depth of sleep, may play a crucial role in the synaptic plasticity that operationalizes our learning capacity [37, 38].

REM stage sleep has similarly been the object of cognitive research. Many research findings have strengthened the hypothesis that REM sleep is involved in learning and cognitive functioning (e.g., memory) and might even serve as an indicator of brain plasticity. For instance, animal models have demonstrated that intensive learning sessions are followed by consistent increases in REM sleep. Also, individuals with intellectual disabilities have reportedly shown sleep patterns characterized by reduced REM sleep percentages, increased undifferentiated sleep (i.e., no clear sleep stage scorable), and prolonged latency to first REM periods [39–42]. Yet even today, the specific role of REM sleep in cognitive functioning remains controversial.

While slow-wave sleep is an acknowledged marker of the homeostatic drive for sleep [12], and REM sleep expression is modulated by circadian rhythmicity [43], their reciprocal interaction in the sleep-wake cycle plays out in the evolution of napping over time [23, 44, 45]. More specifically, in the early years of life, children's total 24-h sleep time declines primarily due to a gradual reduction in napping frequency and duration, at the same time as consolidation of sleep at nighttime. Previous studies also demonstrated that napping alters sleep structure and that in young adults, frequent napping appears to be associated with lighter daytime sleep and their increased sleepiness during the day [46]. Despite its known restorative value and pervasiveness during early childhood, napping has gained scarce research attention until more recently. For instance, findings such as the association between the acquisition [47] and ability to generalize word meanings [48] and napping in young children, or the influence of napping on individual variability of dim light melatonin onset, are all intriguing. In other words, napping may warrant more research, especially in children with atypical development.

Disturbances of Sleep

Among the few studies investigating the concurrent relationship of sleep and cognition in childhood, the majority have focused on sequelae of sleep-disordered breathing (SDB). SDB is characterized by repeated events of partial or complete upper airway obstruction during sleep, resulting in disruption of normal ventilation, hypoxemia, arousal, and sleep fragmentation [49], providing one clinical model of poor sleep and its outcomes (see also next sections). Impairments of memory have been suggested in pediatric SDB, along with attention, executive function, language, visuospatial functions [50–53], and scholastic achievement [54]. Children with SDB have been characterized by a "sluggish cognitive tempo" and executive dysfunction.

Children with developmental disabilities can be at higher risk for difficulties with breathing during sleep [55], as well as epilepsy [56, 57], pain [58], or other medical conditions [59]. SDB, epilepsy, or other medical conditions correspondingly may impact sleeplessness and sleepiness, such that in

addition to the impact predicted by experiments involving partial sleep deprivation or by disturbed sleep (e.g., SDB), a more complex phenotype might be expected in those with an atypical development.

In Children with Developmental Disabilities

Much of the information about the relationship between sleep on cognitive performance in children with developmental disabilities is contained in studies addressing specific hypotheses or populations. Earlier reports investigated dreaming and REM sleep primarily in adults with intellectual disabilities [41, 42, 60], and findings suggested a positive covariation of REM sleep state rate with severity of intellectual disability. A mean peak-to-peak interval of stereotyped activity at daytime (i.e., hand waving) corresponded with the mean REM-to-REM period of consecutive nights in a young girl with intellectual disability, which was considered to be suggestive of sleep-wake cyclic behavior [61]. Studies in individuals with Down syndrome pointed out that their high prevalence of sleep disorders, particularly SDB (with onset as early as in infancy), and thus high ratings of sleep disruption or fragmentation were accompanied by greater difficulties with executive function [62, 63] and verbal intelligence (about nine intelligence quotient (IQ) points) [63]. Comorbid SDB was also found to increase their light transitional stages of sleep at the expense of deeper slow-wave sleep [63].

Yet again, problems in the wake state as well as in the sleep state appear to be associated with poor sleep, potentially fostering a double effect across neurodevelopment in children with developmental disabilities. For example, Fernandez et al. [64] already postulated that the acknowledged link between sleep disruption with Alzheimer disease and cognitive decline in general might converge in individuals with Down syndrome, given that virtually all suffer poor sleep from infancy onwards. In other words, could poor sleep be a precursor to (additional) cognitive decline? Along the same lines, sleep measures were found to explain 78% of the variance of a developmental quotient (DQ) measured by a questionnaire on behavioral development for infants with developmental disabilities of unknown etiology [65]. In particular, cumulative awakening time during nocturnal sleep time, duration of REM stage sleep, and percentage of REM comprising total sleep time were significantly associated with the DQ [65]. Given that obstructive respiratory events are predominantly present in REM sleep in typically developing school-aged children [66] and that sleep is an important mediator in the relationship between general abilities and health [52], the presence of disturbed breathing and REM sleep deficits might generate increased cognitive difficulties in children with developmental disabilities. But controversies in findings exist. That is, sleep quality, duration, and respiratory variables were not related to sustained attention in children with Down syndrome and Williams syndrome [67]. In individuals with Prader-Willi syndrome, hypoxemia during sleep appeared to be predictive of increased performance IQ [68] and unrelated to psychomotor development; however, for those identified as having SDB, mental development was more severely affected [69].

Much less attention has been given to children with milder developmental disabilities in contrast to those with specific genetic syndromes. Borderline intellectual functioning represents alterations in sleep architecture, with an interesting significant correlation with IQ [70]. Sleep in those individuals has shown the following characteristics: shorter sleep duration; increased rate of stage shifts, awakenings, and wakefulness after sleep onset; lower percentages of total sleep time for stage N2 and REM sleep; and slightly higher slow-wave sleep percentage [71]. In children with specific learning disabilities (i.e., school-related difficulties) in comparison to controls, more hypnagogic hypersynchrony characteristic of drowsiness and more stage N1 sleep was found [72]. Similarly, children with reading disabilities have altered sleep architecture with more slow-wave sleep, less REM sleep, and longer REM onset latency leading the authors to associate these differences with chronic sleep deprivation and maturational delay [73]. Such sleep architecture findings alone or in relation to other factors could contribute to the outcome of impaired information processing and cognitive dysfunction [74].

Microstructure of Sleep

Since there is mounting evidence that sleep impacts neural plasticity and promotes cognitive function, more studies have investigated the microstructure of sleep. The cyclic alternating pattern (CAP) (Fig. 1.2) is one way to look at this microstructure. It can be considered an expression of arousal (in) stability [75–77]. It is composed mostly of slow waves with an intermittent temporal pattern during NREM sleep and maps over the frontal and prefrontal regions of the scalp. Therefore it may play a role in sleep-related cognitive processes. Slow EEG oscillations in slow-wave sleep characterize the A1 subtypes, in which the brain is trying to maintain sleep, and the fast-wave contain the subtypes A2 and A3 of CAP, which occur due to central nervous system arousal. When children with developmental disabilities with intellectual disability are compared with those without intellectual disability, studies suggest that CAP differences may be related to their degree of intellectual disability and therefore cognitive dysfunction [78]. We could summarize CAP findings in children with developmental disabilities as a condition of "suboptimal" activity, where during sleep, arousal and/or deep sleep are blunted (i.e., neither of them is fully expressed).

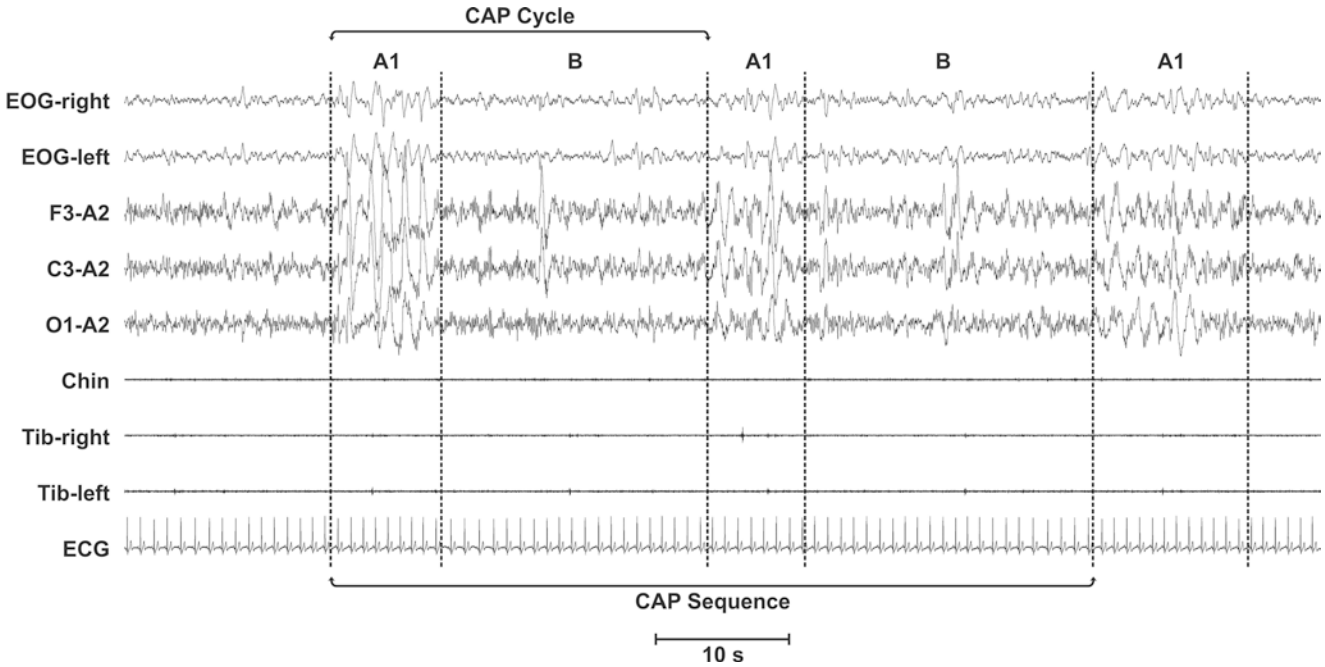

Fig. 1.2 Example of cyclic alternating pattern. EOG = electrooculogram, International 10–20 system EEG recording F3-A2, C3-A2, and O1-A2 channels, Chin = chin muscle tone, Tib = tibial electromyography, ECG = electrocardiogram

Final Remarks

Interestingly enough in most studies of "poor sleep" in children with developmental disabilities, difficulties initiating and maintaining sleep, either in relation to other sleep parameters (e.g., total sleep time), are not discussed in association with cognitive functioning despite how extremely common these complaints are. To our knowledge, associations with a multiple sleep latency test or sleep maintenance test, or other similar assessments, have not yet been reported in literature. Also, in order to understand the impact of sleep, an important question might be whether sleep-related cognitive dysfunction is due to sleepiness or sleeplessness. In this context, it is also important to recognize that cognitive function is not a unitary process and should be understood also in the context of emotions and behaviors.

The Quest for Phenotypes: Sleeping and Emotion

In a Nutshell

Goldstein et al. [79] recently reviewed the role of sleep in emotional brain function. REM sleep in particular has been the object of much research since the neuroanatomical and neurochemical pathways mimic waking brain mechanisms of emotion processing. For example, increased activity during REM sleep in emotion-related regions both subcortically, in the amygdala, striatum, and hippocampus, and cortically, in the insula and medial prefrontal cortex, was recorded. Besides imaging, studies demonstrated not only objective impairments (e.g., in attention and alertness) but also subjective reports of irritability and emotionality. Additionally, poor sleep was found to impact emotion recognition and expression [79, 80], and as a consequence how we (re)act, think, feel, and perceive could be affected.

In typically developing children, special interest has been directed toward child temperament and sleep and to studies exploring the synergy between sleep, maternal well-being, and parenting. For example, early sleep patterns (e.g., night wakings) have been associated with temperamental differences and especially associated with temperaments subjectively considered to be "difficult" [81]. Alternately, increased sleep duration has been correlated with an "easy" temperament characterized by increased approachability, rhythmicity, adaptability, and low distractibility [9]. The most commonly discussed association with poor sleep is probably inattentiveness. This is based on the consistent observation that increased homeostatic sleep drive in the child can manifest as behaviors resembling in attention-deficit/hyperactivity disorder (ADHD) or affective symptomatology (e.g., mood behaviors).

The impact of sleep on emotion is therefore complex but intriguing, given the additional putative role of sleep in psychopathology and the possibility of spurious associations between psychiatric diagnosis and sleep behaviors. Alfano et al. [82] reviewed the literature on the role of sleep in

childhood psychiatric disorders and concluded that the relationship is reciprocal and therefore may impair a child's functioning throughout development. Indeed, in the long term, sleep problems were found to both predict and be predicted by generalized anxiety disorder and depressive symptoms [83]. Alternatively, experimental manipulation of bedtime in adolescence showed increases in inattention, oppositional behavior, irritability, behavioral dysregulation, and mood difficulties (i.e., signs of depression, anxiety) as expressed via self-report [84]. Although certain caveats exist in studies, shortened total sleep time, erratic sleep/wake schedules, late bed and rise times, and poor sleep quality were key players in this relationship. In school-aged children with restricted sleep, more frequent and more severe behavioral problems were found [29]. Survey results in youth further suggest correlations between poor sleep and increased overall behavioral problems, delinquent behavior, thought problems, and negative mood [84, 85]. In toddlers, acute nap restriction adversely affected self-regulation or the ability to control behavior, emotions, and attention [86]. Of peculiar interest, in adolescents, analogous to infants, substantial links were found between their and their parents' subjective sleep disturbances, depressive symptoms, and perceived family climate [87]; e.g., the sleep continuity and architecture of adolescents and their mothers were strongly related. Thus in short, across childhood findings have been inconclusive regarding the "direction" of impact.

Specific Hallmarks of Sleep and Disturbances of Sleep

Experimental findings on the impact of sleep deprivation or restriction on emotional processing in children as regards hallmarks of sleep are scant, apart from those associated with sleep disrupted by underlying SDB. Here again, the cause and effect in the relationship of SDB and emotional symptoms in children is often debated in studies. Examples of problematic emotional functioning described in children with SDB include the following: aggression [88], ADHD [89], depression [90, 91], externalizing disorders [92], and a plethora of others [50, 93]. Conversely, children with conduct problems, in comparison with nonaggressive peers, more often have SDB symptoms [88]. In fact, empathetic processing was found to be influenced by SDB, i.e., poorer conflict monitoring and attention allocation [94]. Although REM sleep is better known as being associated with emotional problems, high NREM stage 2 spindle density has been associated with less internalizing behavior, more prosocial behavior, and fewer overall behavior problems [95]. Overall, primarily survey studies have been used to investigate the impact of sleep on emotional processing in children.

In Children with Developmental Disabilities

Before considering the impact of sleep on emotional processing in children with developmental disabilities, some findings from the adult literature regarding the impact of sleep on emotional processing are relevant. Specifically, pupil diameter responses (i.e., increased reaction to negative stimuli) [96] and heart rate variability changes (i.e., vascular dysfunction before the increase in sympathetic activity and systolic blood pressure) [97] have been related to sleep deprivation. Both are physiological parameters that might provide objective correlates in addition to psychological tests or survey data. In fact, in 1975, Kales et al. [98] linked nocturnal psychophysiological correlates of somatic conditions with sleep disorders, such as in duodenal ulcer patients, gastric acid secretion is experienced during REM sleep. Later, in 1988, Dollinger et al. [98] imputed that sleep problems reflect underlying emotional concerns.

To date, although several studies [99, 100] assessed behavioral and pharmacological strategies for "reducing" sleep problems, they primarily intended to address the emotional behavior problems in individuals with severe intellectual disabilities or multiple handicaps. Unfortunately, daytime behavioral as well as emotional problems are still major targets of pharmacological treatment rather than the underlying sleep problems [101]. Given the problematic self-regulation findings in toddlers, as previously discussed, the role of sleep (including napping) [102] in responding to the challenges of daily life shouldn't be discounted, especially in children with developmental disabilities. An example of such dysregulation might be seen in individuals with Smith-Magenis syndrome, where their disrupted melatonin pattern with concomitant complaints of early sleep onset, repeated and prolonged waking at night, and early sleep offset is surrounded by their daytime behavioral repertoire of tantrums, self-injury or self-aggressiveness, and compulsive lick and flip behavior. In fact, prescribing them melatonin should be done cautiously [103].

In terms of sleep phenotyping of emotional disturbances, autism-like symptomatology has certainly received substantial interest. For instance, an autism-like social impairment has been associated with SDB in Prader-Willi syndrome [104]. Whereas reports about the inability of children with autism to use social cues to entrain their sleep-wake cycles are common [105–110], in fact, a distinct impact of sleep on emotional functioning was demonstrated in a study showing that neither the degree of cognitive impairment nor autism spectrum disorder subtype was correlated with the prevalence of sleep problems. On the contrary, sleep disturbances in these children correlated with aggressive behavior, developmental regression, and internalizing problems [110]. On the other hand, deficiency of REM sleep [111], circadian

rhythm dysfunction, and abnormal melatonin levels [112] are similarly reported in relation to social difficulties in children with autism. In addition, in line with the previous temperament studies, maternal cognitions and bedtime interactions were significantly associated with sleep problems in children with autism [113]. Nevertheless, exogenous melatonin is commonly administered [17, 114]. Its effectiveness was suggested to be influenced by the type of sleep disturbances, environmental factors, and the intellectual disability [99]. Once again, given the convoluted interplay of the sleep and wake states within the sleep-wake cycle, establishing directionality of such associations certainly challenges the field.

Alternatively, sleep phenotyping of individuals with autism, Down syndrome, and fragile X syndrome has used behavioral and electrophysiological measures to detect differences in sleep architecture. Overall, the greater the level of intellectual disability, the less time spent in REM sleep; yet differences in sleep structure across syndromes (e.g., greater levels of undifferentiated sleep in autism) were certainly observed [115]. Yet, findings with respect to sleep architecture are too preliminary as the need for polysomnography data beyond clinical description, between and within disabilities, is abundant. In fact, to date a vast amount of research has focused on surveys or clinical reports and investigating sleep behavior treatments (e.g., [17, 116]).

Lastly, the night-to-night sleep-wake variability reported in children with ADHD is equally relevant in diagnosing and treating children with developmental disabilities, especially in the long term [117, 118]. As an example, in very preterm children, restorative sleep is associated with better behavioral and emotional outcomes during middle childhood [119]. Namely, in preterm infants, non-restorative sleep involves more nocturnal awakenings, more stage N2 sleep, and less slow-wave sleep. As a consequence, the next sleep period may involve an important restorative factor (i.e., the rebound of sleep). Therefore, monitoring the sleep parameters, and hence their variability, as stipulated in Fig. 1.1 should aid in sleep phenotyping of emotional disturbances across the life span of children with developmental disabilities. Yet when inquiring about and monitoring those sleep parameters, disorders such as SDB and epilepsy are likewise influential factors and add to the complexity of an already potentially adverse impact on a night-to-night basis. This train of thought is also valid for other sleep disturbances. In other words, similar to cognition, for instance, more individuals with Down syndrome and comorbid SDB were found to experience major depression [120]. In the context of the convoluted interplay of the sleep and wake states within the sleep-wake cycle, good sleep on a daily basis is imperative for both states across the life span.

Final Remarks

Regarding sleep phenotyping of emotional and also behavioral problems, sleep disruption is mainly reported as insomnia and surprisingly less frequently reported as hypersomnia and parasomnia (e.g., sleep talking, sleepwalking, or sleep terrors) [121]. Interestingly as regards parasomnias, indirect evidence suggests parallel patterns of development between neural maturation and dreaming [122]. Children's dreaming enlightens us not only on the nature and role of dreaming but also adds to our knowledge of consciousness and cognitive and emotional development. As a consequence, emotions and behaviors during daytime and nighttime should be monitored, such as in the previously mentioned case in which hand waving during the daytime corresponded with the mean REM-to-REM period of consecutive nights [61]. Yet up till today the directionality of impact remains challenging. Once again, more studies are needed to understand especially emotional (dys)regulation and hence social behavior in the case of sleeplessness and sleepiness.

The Quest for Phenotypes: Sleeping and Behavior

In a Nutshell

Behavior continues after the day is over. In children, developmental inconsistency in state organization (i.e., behavioral states such as active waking, quiet alert, fuss or cry, drowse or transition, active sleep, and quiet sleep) during the neonatal period is predictive of risks for later development [123]. Emerging motor skills, for instance, were found to involve periods of disrupted sleep [124]. But patterns of early motor development might also be affected by sleep position [125]. Overall, improved motor performance was recently found to relate to sleep [126]. Additionally, sleep disrupted by frequent awakening was similarly associated with lower sensory thresholds [81]. These studies are furthermore in line with earlier studies on temperament (see sleeping and emotion). Overall, quality sensory input and appropriate motor responses are crucial throughout development, as through them we understand, explore, and organize our world. Nonetheless the impact of sleep on sensorimotor behavioral development has been somewhat ignored [127].

In Children with Developmental Disabilities

In brief, primarily survey, case, and treatment studies have related poor sleep with challenging behavior of children with developmental disabilities, for example, intellectual disability [128], Angelman syndrome [129], fragile X [130], Rett

syndrome [131], tuberous sclerosis [132], multiple disabilities [133], and others. Their characteristic nighttime behaviors (or sleep problems) might moreover interfere with family life. As a result, sleep-hygiene practices or habits may need to be modified and adapted specifically for children with developmental disabilities. Behavioral problems characteristic of different disabilities may emerge as involving specific sleep problems. In general, children with co-occurring sleep problems might demonstrate more types of challenging behavior and challenging behaviors of greater frequency and severity than presented by those children without sleep problems. Increased maladaptive behavior can be expected, and specifically, chronic poor sleep has been linked to behavioral problems [134].

In children with intellectual disability, investigation of the first phase of sleep (i.e., NREM-REM cycle) showed that in several subjects, REM sleep onset was observed at the first wakefulness-sleep transition of the night, though in the majority of subjects, NREM sleep onset was found [135]. Although the sleep-wake cycles of children with intellectual disability have seemed to develop normally with age [136], some exceptions have been illustrated, such as Rett syndrome [137]. More detailed investigations of sleep hallmarks within and between types of developmental disabilities might be relevant to increase better understanding of the role of the behaviors in the sleep-wake state organization [6, 39, 40, 138].

In addition to the emotional problems as described previously, some examples of sleep-behavior relationships include the following: motor phenomena (e.g., rhythmic movement disorder, hypnic jerks) linked to sleep-wake transition periods; more low intensity activity in terms of leg activity measured with an accelerometer and also to have more fragmented sleep in infants with Down syndrome, which may impact achievement of functional motor behavior [139]; and increased muscle tone and improved motor performance as long-lasting results when infants with Down syndrome were treated with 5-hydroxytryptophan (i.e., a precursor as well as a metabolic intermediate in the biosynthesis of the neurotransmitters serotonin and melatonin) [140]. In children with fetal alcohol spectrum disorder, their characteristic sensory processing deficits have been associated with multiple sleep problems [145, 146]. Several other studies are suggestive of the relationship between emotions, behavior, and sleep. For instance, psychomotor agitation and disturbed sleep were significant predictors of a diagnosis of mania in individuals with severe/profound intellectual disability [141]. Self-mutilation even during sleep was frequently observed in stages N1, N2, and REM in individuals with Lesch-Nyhan syndrome [142]. Children with Williams syndrome demonstrated difficulties falling asleep, with greater restlessness and more arousals from sleep than controls, and many showed features of ADHD [143]. Restless sleep is well-described in children with ADHD. In fact, it was once part of the diagnostic criteria. Recently Miano et al. [144] underscored the need for full sleep assessments to more accurately identify cases of ADHD in terms of sleep phenotypes. In children with Prader-Willi syndrome, increasing severity of SDB or sleep disturbance was associated with daytime inactivity, sleepiness, and autistic-relating behavior and impulsiveness [68].

Thus non-specific examples exist, yet more research is needed. Of note, movement patterns related to discomfort may challenge sleep transitions [147] and further complicate the sleep phenotype. Indeed, some are making efforts to better describe "discomfort-related behavioral" [147] movement patterns in individuals with developmental disabilities via home-videosomnography.

The Quest for Phenotypes: Sleeping and Health

Sleep is "of the brain, by the brain, and for the brain" [148], and the health consequences ascribed to the lack of sleep are epic, e.g., obesity, cancer, diabetes, cardiovascular disease, and even early mortality. Thus, it would lead us too far afield to discuss in detail the health benefits related to sleep. Instead, our recent model of the moderating relationship of sleep in the case of two health problems may serve to provoke thought [52]. Modeling the interrelations between cognitive performance, obesity, and SDB showed that each moderated the relationship with the other. More specifically, the risk for an even more adverse impact was the highest when cognitive (dis)abilities mediated the relationship.

In summary, there is emerging evidence that neurodevelopmental processes and health are affected by poor sleep. The importance of this relationship is especially acute in individuals with intellectual disabilities such as in Prader-Willi syndrome or Williams syndrome [149, 150] where eating and sleeping problems have a high prevalence. Alternatively, a case report of the effect of sleep disruption on the mealtime behavior of a young boy with developmental disabilities illustrates the potential role of sleep in health treatment [151]. Given the obesity epidemic, a multitude of studies have focused on the role of sleep in the metabolic syndrome. Growing evidence further suggests that sleep loss triggers maladaptive responses in challenging situations; in particular, more primary reward-motivated behaviors such as appetitive food desire were found. The related neural changes were further found to be accompanied by an increased preference for higher-calorie foods [152] and greater tendencies to overeat [153]. Moreover, sleep loss may represent a common and reliable predictor of relapse in numerous addiction disorders [154]. In other words, the role of sleep in neural plasticity may exert a widespread impact on overall development.

Sleep as an Aid to Phenotyping

Study the past if you would define the future. Confucius

Are we ignoring the impact of poor sleep in children with developmental disabilities? While sleep problems are common and chronic in children with developmental disabilities, the types of complaints and outcomes reported remain vastly generic and based on clinical observation. That is, the developmental trends of sleep ontogeny in children with developmental disabilities remain mysterious and this even though inter-individual differences in NREM sleep, specifically slow wave activity and sleep spindles have been reported in the literature. In addition, although both REM sleep and wakefulness share ascending activation of the cerebral cortex, their specific role in phenotyping among individuals with developmental disabilities remains unclear. In other words, the early findings of REM sleep and dreaming in people with intellectual disabilities [41], rapid transition from wakefulness to sleep [155], and quantification of eye movements related to sleep [156], for example, have likely been overridden by a more "modern" sleep research in which the aim to treat dominates. This jump in focus from "cause/observation" to "solution" has unfortunately not evolved into more answers. To the contrary, to date, data obtained from both day and nighttime EEG recordings or other measurements (e.g., videos) are still very much needed. They may furthermore provide us with useful and innovative information regarding presentation, evaluation, and treatment of sleep complaints in children with developmental disabilities. Such data may in fact reflect underlying brain circuit malfunction and could play a direct role in the understanding of the progression of those disabilities across the life span. Ultimately, the directionality of the impact of inadequate sleep on the sleep-wake cycle might become clearer.

Since particular phenotypes of sleep in childhood have yet to be well characterized, data on developmental differences, severity, duration, and impact as well as responses to intervention or environmental factors will be extremely important information. This information is relevant for evaluating the impact of transient or persistent poor sleep throughout the life span. Resolving sleep difficulties as they arise may benefit the child with a disability not only in the short term but likely also long term. Certainly the caregiver, who is usually also the historian, will benefit as well [157].

Overall, understanding the complaint and actual sleep problem is customarily a process of trial and error, in which investigating the sleep parameters (Fig. 1.1) may aid the process. Hence in our quest for the "cause of" and "solution to" poor sleep, each state within the sleep-wake cycle should be monitored and eventually interrelated.

To enhance this optimal data-collection endeavor, child-friendly sleep measurements should be advocated; that is, improving and/or adapting sleep monitoring, sleep measurement, and sleep-treatment technology to the needs of children with developmental disabilities should be a priority. Finally, given that poor sleep is often accompanied by a plethora of other problems which can cause, coexist with, or follow poor sleep in a subjective (e.g., somnolence) and objective (e.g., changes to sleep architecture) manner, sleep awareness [158] should be increased. After all, the consideration of the sleep-wake cycle by clinicians, researchers, and caregivers may foster a growing understanding about relationships between aberrant brain networks and phenotypes across 24 h.

Research Agenda

With respect to the impact of sleepiness and sleeplessness among children with developmental disabilities, many questions are still unanswered. Firstly, from a neurodevelopmental perspective, we are just embarking on this journey toward understanding how to improve sleep and how sleep improves development. As is the case in typically developing children, findings from one developmental period often cannot be readily generalized to other developmental periods or even clinical populations. Secondly, throughout this chapter, a clear need for studies of the (micro)organization of sleep states as being a potential marker of optimal versus high-risk development is obvious. That is, special attention should be given to the different developmental periods as well as gender differences given the population under investigation. Studies should moreover make auxiliary report of descriptives of sleepiness/sleeplessness and its impact on development during both day and night (e.g., dysregulation). For instance, approaches such as a multiple sleep latency test or a sleep maintenance test, or other comparable assessments, may bring new insights within a population of individuals with developmental disabilities. Similarly, the field would greatly benefit from detailed descriptions of poor sleep between and within developmental disabilities, apart from clinical diagnostics. Lastly, an increased awareness of the sleep-wake cycle, and its interrelatedness, should be fostered across disciplines involved in the care of children with developmental disabilities.

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Evaluation of Sleep Problems in Children

2

Judith Anne Owens and Miriam Rachel Weiss

Introduction

The prevalence of sleep disturbances in typically developing children ranges from 9% to 50% [1]. The range of sleep disturbances in children with neurodevelopmental disorders (NDDs), such as autism, may be as high as 75–80% [2]. Neurodevelopmental disabilities are defined as a collection of a large number of neurologic disorders that start in childhood and have different etiologies [2]. The *Diagnostic and Statistical Manual of Mental Disorders V* (DSM-V) categorizes these disorders as intellectual disabilities, communication disorders, autism spectrum disorders, attention-deficit/hyperactivity disorder, learning disorders, motor disorders, and other neurodevelopmental disorders [3]. This wide range of disorders includes intellectual disability, epilepsy, cerebral palsy, Rett syndrome, and Down syndrome, to name a few [2]. The various types of sleep disorders are not unique to this population. However, sleep problems in these children can be more severe, chronic, and difficult to treat and more likely to relapse [4]. More than one sleep disturbance in a given child is common. Impaired sleep in general often has an impact on their physical health and predisposes children to mood, behavioral, and cognitive impairments; these consequences may be more pronounced in children with underlying neurodevelopmental disorders [2, 4]. In addition, the burden of sleep problems in caregivers of children with NDDs is often substantial and may add significantly to family stress [5].

The etiology of sleep disorders[1] in these children is often the consequence of underlying disease-related factors, which include the extent and location of brain abnormalities; severity of developmental delay; communication challenges; associated sensory loss such as visual impairments, concomitant health problems, and limited mobility; and pain. In addition, medications such as anticonvulsants and antidepressants prescribed for medical or psychological conditions can contribute to sleep problems in these children; for example, antidepressants can exacerbate restless legs syndrome symptoms and may contribute to sleep onset and maintenance insomnia [6, 7]. Children with neurodevelopmental disabilities often have comorbid mental health impairments such as mood or anxiety disorders, which can be exacerbated by sleep disorders and vice versa. Similarly, strong associations have been found between disruptive behaviors such as hyperactivity, aggression, and oppositionality and sleep disruption [4].

Biological factors can play a role in sleep disorders in children with NDDs. An example of this is the high prevalence of sleep disturbances in children with autism spectrum disorder. Circadian rhythm abnormalities have been postulated, and a number of studies have shown that a large portion of the studied children with autism spectrum disorder (ASD) had low plasma melatonin concentration. Melatonin is a hormone secreted by the pineal gland in response to decreased light, mediated through the suprachiasmatic nucleus, thus regulating sleep and wake cycles. Supplementing these children with exogenous melatonin has been shown to be beneficial in regulating sleep [7, 8]. Finally, environmental factors and issues related to caregivers also play important roles in these sleep disturbances. Environmental factors can include the child's sleeping space,

J. A. Owens (✉)
Sleep Medicine, Neurology, Boston Children's Hospital, Boston, MA, USA
e-mail: judith.owens@childrens.harvard.edu

M. R. Weiss
Pulmonary and Sleep Medicine, Children's National Health System, Washington, DC, USA
e-mail: MiWeiss@childrensnational.org

[1]While this term is used interchangeably for the purposes of this review with sleep disturbances, problems, issues, etc., it should be noted that sleep disorders are typically defined by specific diagnostic criteria as found in the American Academy of Sleep Medicine International Classification of Sleep Disorders (ICSD), 3rd edition, or the *Diagnostic and Statistical Manual (DSM) V*.

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noise, room, bed sharing, family composition, as well as lifestyle issues such as parental work status, household rules, and socioeconomic status. Caregiver variables include discipline styles, parental mental health issues, family stress, and parental education level [2, 5].

Conceptual Framework of Sleep Disturbances in Children

The majority of sleep problems in children can be categorized by one or more of the following disturbances of sleep. These include insufficient sleep (inadequate sleep quantity), fragmented sleep (poor sleep quality), circadian rhythm disorders (disrupted regulation of sleep timing), and primary sleep disorders of excessive daytime sleepiness (EDS). Insufficient sleep results from a mismatch between the child's sleep needs and the amount of sleep actually obtained; however, this calculation is often based on recommended sleep duration ranges for typically developing children in different age ranges, which may not necessarily always be applicable to children with neurodevelopmental disabilities. Insufficient sleep can be the result of suboptimal time in bed (opportunity to sleep) but usually stems from difficulty initiating and/or maintaining sleep. Sleep fragmentation impacting sleep quality usually results from frequent and repetitive nighttime arousals, such as those associated with obstructive sleep apnea. Circadian rhythm disorders are characterized by inappropriately timed sleep periods that often interfere with daytime functioning (e.g., a child sleeps during the day and is awake all night), but the sleep quality and quantity is typically normal if the child is allowed to sleep on his or her preferred schedule. Primary disorders of EDS such as narcolepsy and idiopathic hypersomnia are relatively rare in children in general but may be more common in children with neurodevelopmental disorders such as Prader-Willi syndrome and Niemann-Pick disease [4].

Screening for Sleep Problems

While a broad range of sleep disorders including obstructive sleep apnea (OSA) and restless leg syndrome (RLS) are discussed in this chapter, the focus will be on the most common presenting sleep complaints in children with neurodevelopmental disorders including insufficient sleep, irregular sleeping patterns, bedtime resistance, delayed sleep onset, frequent and/or prolonged night wakings usually requiring caregiver intervention, and early morning wakings [4]. It should be noted that while often related, bedtime resistance and delayed sleep onset are not necessarily equivalent; i.e., a child may exhibit a prolonged struggle at bedtime but then fall asleep immediately after lights out or may go to bed willingly but remain awake for hours. Due to the high prevalence of sleep disturbances in these children, it is essential that clinicians both have a systematic approach to screen them at regular intervals for sleep problems and maintain a high index of suspicion.

The BEARS sleep screening tool is a brief five-item instrument that is easy for the provider to remember and user-friendly for families. The parent (and child, if developmentally appropriate) should be asked if the child experiences possible problems in each of the five items below based on the BEARS acronym.

B – Bedtime issues. This should include difficulty falling asleep and bedtime resistance.
E – Excessive daytime sleepiness. Specifically issues related to morning waking, napping during the day, and involuntary daytime sleepiness.
A – Night awakenings. Particularly if parental intervention is required.
R – Regularity and duration of sleep. This includes inquiring as to the specifics of bedtime and wake time and variability night-to-night and variability on weekend/weekdays.
S – Snoring. Questioning about nocturnal behaviors such as snoring, sleep disordered breathing sleepwalking/sleep terrors/confusional arousals, enuresis, bruxism and nocturnal seizure activity [9].

Components of the Pediatric Sleep Evaluation

The assessment should include a very detailed sleep history, medical history, developmental/school history, family history, psychosocial history, behavioral assessment, and physical examination [4].

Sleep History

A thorough sleep history is essential when assessing a child for a sleep disturbance and should include details of the presenting complaint(s), sleep-wake schedules, bedtime, nighttime behaviors, and daytime behaviors. It is helpful to obtain information about the presenting complaint from the caregiver, the child when possible, and if applicable/possible the individual who shares a room/bed with the child. The sleep complaint should include a detailed account of the onset, duration, severity, and night-to-night variability. Any events that preceded and possibly triggered the sleep problem should be elicited (e.g., new sibling, move, illness or death in family, changes in medication). It is also helpful to understand why the caregivers are requesting help at this particular time (e.g., school year starting, expecting new baby). It is important to inquire as to what methods the family has tried and to describe in detail (e.g., tried a "cry it out" approach for

2 days or inconsistent response to night wakings by each parent) and how they trialed those methods. Lastly, parental expectations regarding treatment goals must be discussed and understood to guide treatment recommendations [7].

It is important to understand the sleep schedules and sleep habits for any child presenting with a sleep problem. This can help the provider better understand the sleep problem in order to formulate etiologic hypotheses and thus generate potential interventions and to identify other coexisting sleep issues [7]. While clearly overlapping, for the sake of completeness and clarity, we have divided these various sleep components into (1) sleep schedule (bedtime and wake time, night-to-night and weekday/weekend variability), (2) evening behaviors, (3) bedtime routine, (4) the process of falling asleep (how and where the child falls asleep, including problematic sleep onset associations), (5) night wakings (including required parental interventions), (6) other episodic nocturnal behaviors (e.g., snoring and respiratory symptoms (choking, gasping, mouth breathing, etc.), sleepwalking/sleep terrors/confusional arousals, enuresis, bruxism, nocturnal seizure activity), (7) sleep environment (noise, temperature, light), and (8) morning waking and daytime sleepiness, including scheduled napping and involuntary daytime sleepiness.

Sleep Schedules

The caregiver should be asked if the child has a set bedtime. Many children are allowed to fall asleep when they choose. It is important to evaluate the timing of bedtime for age and developmental level of appropriateness. The variability of bedtime should be elicited by asking for night-to-night variability as well as weekday, weekend, and vacation discrepancies. Some children will have a strict bedtime on weekdays but are allowed to stay up late and wake up late, thus contributing to difficulty falling asleep on their regular schedule. Since children with NDDs are more vulnerable to sleep and circadian rhythm disruptions, it is particularly important that they have regular and appropriate bedtimes and wake times [2]. It is also important to understand what parental involvement consists of at bedtime. For example, some children will only go to bed with one parent, suggesting possible limit-setting issues. Other parents go to bed before their child falls asleep, which can often be the case with teenagers, and thus are unaware of the child's activities after their own bedtime.

Evening Behaviors (Including Bedtime Resistance)

It is helpful to ask the caregiver to describe activities from dinnertime until bedtime to best understand evening and bedtime behaviors. For example, engaging in vigorous exercise with several hours of bedtime may not only be energizing but may increase core body temperature, making it more difficult to fall asleep. Similarly, eating a heavy meal just before lights out may prolong sleep onset. In particular, children with NDDs can become easily over stimulated, as they may have difficulty processing large amounts of information resulting in an overload state [2]. Overstimulation may occur when children with NDDs are exposed to new or unexpected events, anxiety, excessive noise, cold or heat, vigorous exercise, hunger, large meals, pain, seizures, and certain drugs [2]. Other factors that can affect bedtime should be questioned, such as evening activities of the child/parent/family and family schedules. Some families schedule family-centered activities later in the evening, potentially further delaying bedtime to an inappropriate hour.

The provider should thoroughly review with the caregiver all refusal behaviors of the child at bedtime. The details can be obtained by asking about the characteristics of the refusals (coming out of room/bed, crying), the intensity of the behavior (calling out to parent or crying and screaming), how often the behavior occurs (daily or once a week), and how long the behaviors last at bedtime. A critical factor is whether the child behaves differently with various caregivers or family members, and the caregivers' response to the behavior, because a key element to reducing these behaviors is consistency, not only on the part of the caregiver with each interaction but also among all of the family members who are involved with bedtime [7].

Multiple studies have noted delayed sleep onset particularly in children with Asperger syndrome (AS). One hypothesis is that the anxiety that is often found in children with AS can contribute to difficulty falling asleep at bedtime. The study by Paavonen et al. [10] noted a high prevalence of sleep fears and negative attitudes toward sleeping in children with AS. Some other stimulating examples could include playing with siblings, watching a TV show, or participating in a physical activity close to bedtime. Certain textures can be difficult for children with autism spectrum disorder (ASD) to tolerate (such as pajamas or blankets), contributing to difficulty settling at bedtime; a weighted blanket may be beneficial [1].

The child's level of sleepiness at bedtime should be evaluated, sleep location (bed, couch) and variability of location as well as the transfer of a child from one bed to another once the child falls asleep [7]. Children with delayed sleep phase disorder, often seen in adolescence due to circadian preference, are not sleepy until later in the evening. Delayed sleep phase disorder is a circadian rhythm disorder, which involves a significant, persistent, and intractable phase shift in sleep-wake schedule (later sleep onset and wake time) that interferes with environmental demands. This can often result in significant daytime sleepiness and academic and behavior problems if the child cannot adhere to their preferred sleep schedule [7].

Bedtime Routine

Caregivers should be questioned about the presence of a regular bedtime routine and what activities are included. Electronic media use such as television viewing, playing video games, or even using an e-reader as part of the bedtime routine should be elicited (especially the presence of electronic media in the bedroom) as this has been clearly shown to be associated with sleep problems such as difficulty initiating sleep and shorter sleep times in both typically developing children and those with NDDs [7]. In a study published by *Pediatrics* in 2013, for example, results indicated that having bedroom media decreased total sleep time at night. Access to a computer or television in the bedroom showed a stronger association to less nighttime sleep in boys with ASD as compared to boys with ADHD and typically developing children. This study also demonstrated the amount of time playing video games was associated with less nighttime sleep in boys with ASD [11]. This study confirms the importance of evaluating for media use in the bedroom within a sleep evaluation. Some households have televisions in each bedroom and are not aware of the consequences of bright light on their child's sleep. Exposure to light, including light-emitting devices (television, tablets, cellular phones), suppresses the release of the sleep-facilitating hormone melatonin. In turn this shifts the circadian clock to a later time, which contributes to difficulty falling asleep at bedtime [12, 13]. The provider may have to be creative and compromise with the family to allow for realistic expectations in such households.

An extended bedtime routine may point to limit-setting difficulties, e.g., a child demanding to be read five or more books at bedtime. However, the lack of a bedtime routine does not allow the child to transition as easily from wake to bedtime. Sleep routines in children with ASD may involve stereotypic and repetitive behaviors, and these children can have difficulty adapting to changes in their routines [4].

Some characteristics of children with ASD can contribute to delayed sleep onset and include difficulty with self-regulation, hypersensitivity to environmental stimuli, and repetitive thoughts or behaviors that interfere with settling [1]. For example, some children with ASD may find pacing calming at bedtime. However, this activity can be stimulating in itself and can contribute to difficulty with sleep onset. Calming activities can include a well-structured routine of quiet baths, listening to stories, prayers, or small snacks. The sleeping environment should be comfortable and cool with minimal light and sound [1, 7].

Falling Asleep

The provider should ask when lights are turned out and what time the child actually falls asleep. A child who has difficulty falling asleep should be assessed for possible causes such as restless leg syndrome (RLS), anxiety, or delayed sleep phase syndrome. Children with ASD commonly exhibit symptoms of sleep onset insomnia [1]. Children with ASD are also susceptible to RLS, and some medications used by children with ASD (risperidone, selective serotonin reuptake inhibitors) can exacerbate RLS. Specifically the child with RLS would describe the urge to move the legs and leg discomfort that may include verbal descriptors such as "ants crawling on my legs" or terms such as squeezing, tingling, wiggling, itching, or "funny" feeling. Nonverbal children may be observed to move, shake, or rub their legs. These symptoms usually occur exclusively or are worse at rest such as in a lying or sitting position and in the evening. This uncomfortable leg sensation is accompanied by the urge to move the legs. The leg sensation diminishes with movement but returns when movement is stopped [7].

Sleep onset associations are behaviors that are required by the child in order to fall asleep at bedtime and return to sleep after night wakings. Examples of sleep associations, which are needed to help the child fall asleep, can include rocking, nursing, cuddling, or parental presence. This can be problematic as these can cause prolonged bedtimes and night wakings as well as disrupting other family members' sleep. However, some children with profound brain damage may require sleep-promoting cues such as gentle rhythmic movements, light massaging, or tightly tucked bedsheets [2, 7].

Night Wakings

A thorough evaluation of nighttime activity should be discussed. Night wakings should be evaluated by discussing when the night wakings started occurring, the frequency per week and per night, and the timing and duration. Possible triggers (getting up to void, external noise) should be reviewed as well as the child's behavior upon awakening (calling out, leaving room) and the parental response (ignoring, responding inconsistently). It should be noted whether the child needs help returning to sleep (rocking to sleep, television, bottle) [7]. Two studies, one by Schreck et al. [14] and one by Mayes and Calhoun [15], suggest that more severe autism symptoms predict more frequent night wakings and sleep disturbances [6].

Episodic Nocturnal Behaviors

The evaluation should include questioning whether the child experiences partial arousal parasomnias, including sleepwalking, sleep terrors, and confusional arousals. Sleepwalking commonly occurs at the beginning of the night during slow-wave sleep and is not remembered by the child.

The child may appear dazed and occasionally agitated and may perform bizarre actions. Sleep terrors are a sudden arousal from slow-wave sleep and include autonomic and behavioral manifestations of intense fear. Confusional arousals are nocturnal episodes characterized by confusion, disorientation, grogginess, and at times significant agitation upon awakening from slow-wave sleep or following forced awakenings [7].

Other nocturnal events are sleep-related rhythmic movements (SRRMs) which include head banging, body rocking, and head rolling which are common among young children and often function as self-soothing behaviors. These episodes usually occur at sleep onset following normal nighttime arousals and can occur during night wakings. While most typically developing children outgrow SRRMs by elementary school, it is not uncommon in children with NDDs to have these behaviors persist, and they may require more aggressive management (including pharmacologic interventions in some cases) than "tincture of time." Bruxism is the repetitive grinding or clenching of teeth during sleep. Sleep enuresis involves involuntary voiding during sleep, at least twice a week beyond the age of 5 years [7]. Night screaming and laughing are particularly common in younger children with Rett syndrome, whereas night wakings are found among all age groups in girls with Rett syndrome [16]. Some studies have reported an increase in sleepwalking, bruxism, and other partial arousal parasomnias in children with ASD. There is also an increase in REM behavior disorder in children with ASD; this behavior is characterized as acting out their dreams due to the absence of muscle atonia normally present during REM sleep [4].

Nocturnal symptoms of sleep-disordered breathing include snoring, snorting, pauses in breathing, mouth breathing, restless sleep, sweating during sleep, and abnormal sleep positioning (i.e., neck extension or requiring multiple pillows). Daytime symptoms can include excessive daytime sleepiness, irritability, emotional dysregulation, internalizing behaviors, aggression, hyperactivity, inattention, and learning problems and academic problems. Some additional features that can be associated with sleep-disordered breathing include enuresis, growth failure, increase in partial arousal parasomnias, increase in seizure activity in predisposed children, and other comorbid sleep problems such as periodic limb movement disorder or RLS [7].

Sleep Environment

Bedroom space and location should be ascertained. This includes bed sharing or room sharing and with whom. The questions should include with whom the child co-sleeps, how long at night, when at night, how often per week, and reason for co-sleeping (i.e., "lifestyle" or "family bed" by choice versus "reactive co-sleeping" in which the parent brings the child into bed in an attempt to solve a sleep problem such as prolonged night wakings) [7]. If the child sleeps in a separate room from the parent, the distance between their rooms should be determined. Some parents may place an alarm on the child's door if they are prone to sleepwalking or exiting their bedroom in the middle of the night. If the child sleeps in multiple sleep locations, such as with divorced parents or grandparents, the bedtime routine and sleeping arrangements at these alternate locations should be discussed. The caregiver or child should describe light exposure at bedtime, which includes a main light, small lamp, or night-light on, as well as exposure to outside light, including streetlights and use of blackout shades. Some children may be afraid of the dark and may require a small light source such as a night-light. Noise exposure from outside or from other family members as well as the time of day of the noise should be ascertained by the provider. Some children will benefit from a "white noise" machine if they are sensitive to noise. The ability to adjust room temperature and comfort in the room is important to review as well. The provider should ask what type of bed the child is using, crib versus bed, and what type of bedding [7]. Children with gastroesophageal reflux may benefit from an elevated head of bed. Immobile patients such as children with cerebral palsy may require frequent repositioning due to risk of bedsores. Some infants feel comforted by swaddling, whereas other children with ASD may prefer a weighted blanket [2].

Morning Waking and Daytime Sleepiness

The time of awakening for the day should be evaluated on weekdays and weekends and during vacation periods. In particular, the failure to awaken spontaneously at the desired time and the need for alarm clocks and especially repeated reminders and prompts from caregivers to get up suggest that a child is not meeting his or her sleep needs with the current schedule. Sleeping longer on the weekends also suggests that a child may be getting insufficient sleep during the week. Alternatively, children with a circadian phase delay will also tend to awaken later in the morning because their sleep-wake schedule is shifted later; they may revert to their preferred sleep schedule of going to bed and waking up later on weekends and on vacation/school break. Furthermore, if a child awakens sleepy and groggy despite apparently sufficient sleep, this may indicate a sleep disruptor such as obstructive sleep apnea or periodic limb movement disorder. Finally, some children and adolescents display extreme difficulty in waking on school days that appears out of proportion to their sleep schedule but rise without difficulty on nonschool days, suggesting that school avoidance may be a potential confounding factor [7].

The timing, frequency, location, and duration of both planned/scheduled and developmentally appropriate naps and involuntary sleep periods (i.e., "dozing off") should be assessed. For example, a planned nap in a preschool child in the late afternoon may interfere with falling asleep at bedtime. Since the majority of children over 5 years have stopped napping, planned or unplanned naps in an elementary-aged child suggest insufficient sleep or the presence of sleep disruptors [7]. Nocturnal events such as partial arousal parasomnias, nightmares, symptoms of sleep-disordered breathing, and symptoms of periodic limb movement disorder should be elicited as these sleep disruptors can contribute to daytime sleepiness [7].

Caregiver reports of a child falling asleep riding in a car and during passive activities or especially during stimulating activities such as being in school or during a conversation could be due to inadequate sleep, a sleep disruptor, or primary hypersomnia disorder such as narcolepsy. Younger children often exhibit behavioral manifestations of sleepiness such as irritability, aggressiveness, hyperactivity, or impulsivity rather than "classic" symptoms such as yawning or dozing off [7]. It is important to explain to parents that a mismatch between sleep needs and sleep obtained can be a major contributor to daytime sleepiness. Children with a sleep disruptor such as OSA or periodic limb movement disorder (PLMD) may display symptoms of overtiredness or sleepiness depending on the severity and their age. Once their sleep disruptor is diagnosed and adequately treated, their sleepiness should be reevaluated.

As noted above, some children may have daytime sleepiness due to a primary hypersomnia disorder such as narcolepsy. These symptoms include falling asleep during the day during passive or more importantly active activities despite adequate sleep at night or other sleep disruptors. The child may describe an intense sudden need to sleep or "sleep attack." The child with narcolepsy may also experience the intrusion of REM sleep, phenomena such as muscle atonia or dream mentation into wakefulness. The primary example is cataplexy, which is the abrupt, bilateral, partial, or complete loss of muscle tone in the face of retained consciousness, classically triggered by positive emotion. Cataplectic episodes last seconds to minutes, and the child recovers completely afterward without any residual effects. Other REM-related symptoms include hypnagogic (falling asleep) or hypnopompic (waking up) hallucinations. These hallucinations can be auditory, visual, or tactile and can be very frightening. Another example of REM intrusion into wakefulness is sleep paralysis, which is the inability to move or speak for a few seconds also when falling asleep or waking up. While it should be noted that hypnic hallucinations and sleep paralysis could occur in otherwise normal individuals who are sleep deprived, cataplexy is unique to patients with narcolepsy. Furthermore, children with narcolepsy often have difficulty sleeping at night with frequent and lengthy night wakings. The definitive diagnostic tests for narcolepsy include an overnight polysomnogram in conjunction with a multiple sleep latency test the following day and/or a CSF measure of hypocretin levels; HLA testing for DQB1*06:02 may be helpful but lacks specificity as a substantial percentage (25–35%) of controls are positive [4].

It is just as important to elicit daytime behaviors while evaluating for sleep issues. Insufficient sleep can have negative consequences on many functional domains including mood, behavior, attention, learning, school performance, school relationships, and overall health [7]. The parent should provide information pertaining to the child's mood such as grumpiness in the morning or at bedtime. The provider should ask about the child's behaviors, as to whether they demonstrate hyperactivity, impulsivity, inattention, or disrespect to parents or others. It is also important to ask about the child's school experience and any learning difficulties. If the child has been diagnosed with a learning disability, ask if an evaluation has been performed to provide the services the child needs. It is vital to understand school performance when diagnosing sleep issues. If a child is not getting adequate sleep, often their grades suffer, although some children are able to continue to perform well in school despite their tiredness. The child should be able to discuss how they relate to their peers. It is important to obtain information such as negative relationships at school that can be classified as bullying. Some children try to avoid school due to bullying, difficulty making friendships, or disliking school. This avoidance may be exhibited by a child who goes to bed quite late at night, is unable to wake up in the morning for school, or, if they do attend school, sleeps through their classes. The provider must evaluate how interested the child truly is in fixing a sleep pattern to return to school.

Some children with NDDs have health problems that can cause multiple hospitalizations or may require extended time away from school. It is important to understand how this has impacted the child as well as their education.

Of note, fatigue is typically defined as lethargy (i.e., without sleepiness) and is often described as subjective feelings of low energy and low motivation without an increased sleep propensity. Fatigue tends to be associated with medical or psychiatric disorders. It is important to investigate the child's medical and psychiatric history as well as medications that may contribute to fatigue or sleepiness. On the other hand, sleepiness is described as the tendency to fall asleep usually in inappropriate settings. However, this can be difficult to distinguish when first interviewing a child and family members [7].

Medical History

A medical history and review of systems should be elicited with an emphasis on past and current medical conditions,

prior hospitalizations, surgeries, and medications [7]. The infant should be screened for conditions such as gastroesophageal reflux, colic, and milk allergies as these can be associated with sleep problems. Likewise the child should be screened for asthma, upper respiratory infections, and headaches which may contribute to sleep-disordered breathing [6]. The child should be screened for past history of concussion particularly if daytime sleepiness is a complaint. Surgical procedures should be recorded, particularly adenoidectomy or tonsillectomy in the child with symptoms of sleep-disordered breathing. A comprehensive medication list should be obtained as certain medications can worsen RLS/PLMD and contribute to daytime sleepiness or insomnia.

Risk factors for sleep-disordered breathing include asthma, allergies, gastroesophageal reflux, adenotonsillar hypertrophy, obesity, prematurity, craniofacial abnormalities, nasal septal deviation, neuromuscular disease, hypothyroidism, hypotonia, and family history of sleep-disordered breathing [7]. A number of congenital syndromes are also associated with an increased risk of sleep-disordered breathing. For example, children with Down syndrome have multiple risk factors for OSA including generalized hypotonia, midface and maxillary hypoplasia, glossoptosis, hypothyroidism, adenotonsillar hypertrophy, obesity with central adiposity, and gastroesophageal reflux [4, 17]. The AAP recommends that children with Down syndrome should be screened for sleep-disordered breathing at least once in their first 6 months of life and then yearly thereafter with a recommended overnight polysomnogram before their fourth birthday [18]. Children with Prader-Willi syndrome are also at high risk for sleep-disordered breathing including obstructive sleep apnea, hypoventilation, and central sleep apnea due to obesity, hypotonia, and adenotonsillar hypertrophy [4, 19]. A study in 2011 by Hagebeuk et al. noted that 50% of a small cohort of girls with Rett syndrome showed obstructive sleep apnea and more frequently displayed central sleep apnea on overnight polysomnogram [20]. Thus it is important to screen these girls for sleep-disordered breathing and perform an overnight polysomnogram if warranted. Children with cerebral palsy have a higher risk for sleep-disordered breathing not only due to adenotonsillar hypertrophy but also due to disproportionate midface anatomy, mandibular alterations, abnormality of upper airway tone, abnormal central control of respiration, obesity, and medications that increase the collapsibility of upper airway musculature and reduce the patency of the airway [21].

Symptoms of PLMD include non-restorative sleep, clinically significant sleep disruption, and/or daytime sequelae [7]. Children with ASD may be at higher risk for PLMD possibly due to limited dietary choices which can contribute to limited iron in their diet; low ferritin is a risk factor for PLMD [4]. Parents of children with Williams syndrome have noted increased leg movements when sleeping; these children may have a higher prevalence of PLMD [22].

Developmental/School History

A developmental history should include prematurity and/or birth complications, developmental delays, and impaired neurological functioning. A developmental history is necessary to provide the most developmentally appropriate sleep advice. Academic problems can occur with inadequate sleep [7]. Therefore a school history including grade, academic performance, extracurricular activities, and behavior with students and teachers is important to elicit. At times, a concern for daytime sleepiness stems from a teacher reporting a child falling asleep frequently in class.

Family History

It is helpful to obtain a family history as some sleep disorders have a genetic component including partial arousal parasomnias, restless leg syndrome, obstructive sleep apnea, and narcolepsy. Even if a family member has not been diagnosed, it is helpful to discuss whether family members have symptoms of a sleep disorder such as snoring [7].

Psychosocial History

A complete psychosocial history should be elicited and should include overall family functioning, effectiveness of parenting skills, family structure, parental psychological functioning, and family discord. If the parents are divorced, the provider should elicit how much time has lapsed since the divorce, visitation schedules, level of parental involvement, consistency of sleep patterns and habits, discrepancies in parenting styles, and level of stress on the child. The provider should elicit significant life events such as a death of a family member, change in school, or a recent move. Cultural influences on sleep behaviors should be evaluated as well as family values regarding health priorities and family beliefs about sleep and importance of sleep. The effect of the child's sleep problem on the family should be understood, such as the effect on the parent's sleep, impact on parent's daytime functioning, and impact on marital and family satisfaction [7].

Behavioral Assessment

A behavioral assessment is important as sleep disturbances can result in psychiatric symptoms such as mood changes and oppositional behaviors. Conversely psychiatric disorders can result

in sleep disturbances. It is important to evaluate for symptoms of depression, anxiety, and other psychiatric disorders [7]. It is helpful to understand the temperament of the child, as children who have higher levels of physiological arousal and feel their lives are more stressful may have increased rates of insomnia due to increased vigilance, anxiety, and hyper-responsiveness to threatening environmental stimuli [6].

Physical Examination

A physical exam should be performed on all children presenting with sleep concerns. The exam, while comprehensive, should be targeted toward the presenting complaints and potential etiologies of the sleep problems, for example, focusing on the otolaryngologic exam in children who have concerns for snoring or other symptoms of sleep-disordered breathing, including signs of atopy such as allergic shiners or mouth breathing. A neurologic examination should be done if there is concern for daytime sleepiness or seizure activity. The child's general appearance should be taken into account. Growth parameters should be evaluated as both growth failure and BMI/overweight/obesity can be associated with sleep-disordered breathing. Additionally, as circadian delayed sleep phase disorder often develops at the onset of puberty, the child's pubertal status should be evaluated as well [7].

Diagnostic Tools

A sleep diary is a helpful tool when evaluating many sleep problems, particularly if the child or parent is uncertain regarding the amount of sleep a child is getting and the variability in the sleep-wake schedule. A daily sleep diary collects information including bedtime, latency to sleep onset, number and duration of nighttime wakings, time of morning waking, total sleep time, sleep efficiency, and duration and timing of naps, over a 1–2-week period, and can be filled out by the parent or by the older child/adolescent [7]. Documenting sleep-wake patterns on a sleep diary can provide helpful feedback for the child and parent, given that there may be a discrepancy between self-report or parent-report of "typical" sleep schedules and the actual day-to-day reporting.

An overnight polysomnogram (PSG) is indicated to diagnose and delineate sleep-disordered breathing, determine optimal treatment options for sleep-disordered breathing, document periodic limb movement disorder, and investigate potential etiologies for sleep-related daytime sleepiness as well as to delineate etiology [23–25]. Some children with NDDs may have difficulty tolerating the PSG due to the multiple leads that are applied and must stay on throughout the night. Some children benefit from a desensitization period of being exposed to the equipment used prior to coming in for the PSG. All children should be tested in an AASM-accredited pediatric sleep lab that has the expertise and experience to study children who may pose significant behavioral challenges. This is necessary to ensure the PSG is scored according to pediatric criteria but also to ensure this population of children are tested in a laboratory that is familiar with children and those with NDDs and meet their needs.

The multiple sleep latency test (MSLT) provides an objective quantification of daytime sleepiness as well as REM onset sleep periods, which is highly characteristic of children with narcolepsy. This test consists of five 20-min nap opportunities every 2 h. The data that are collected include the number of naps during which the child slept, the length of sleep time during each nap, and whether the child had a period of REM sleep during each 20-min nap opportunity. It is essential to perform a PSG the night before the MSLT to insure that the patient had sufficient sleep the night before and to determine whether there is another underlying explanation for daytime sleepiness such as obstructive sleep apnea. Medications that affect the central nervous system could skew the results of the MSLT as some suppress REM sleep (e.g., selective serotonin reuptake inhibitors). If possible, the child should be weaned off such medications prior to the test, with adequate time to avoid REM sleep rebound [7].

Actigraphy utilizes a wristwatch-like device called an actigraph that records and stores data regarding body movements over a period of time (usually 2 weeks) that is downloaded and then transformed using a software program into an approximation of sleep-wake patterns. In conjunction with a sleep diary, the data will show the approximate sleep duration, sleep latency, and the length of time during the night that the child is asleep and is awake. Actigraphy is particularly helpful in quantifying sleep amounts more objectively when subjective sleep duration seems implausible (e.g., 4 h of sleep for a 5-year-old) or determining whether a child has a circadian rhythm disorder [7].

Summary

Sleep problems, ranging from insomnia to circadian rhythm disruption to sleep-disordered breathing, are extremely common in children with NDDs. Therefore, the clinician needs to maintain a high index of suspicion and institute a systematic screening and evaluation process in clinical practice settings. While often more challenging to manage, successful identification and treatment of sleep problems in these children often improve the health and quality of life of the entire family.

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Polysomnography

3

David G. Ingram, Susan C. M. Crane, and Ann C. Halbower

Case Vignette

Roberto, a 13-year-old child with a history of epilepsy, underwent a diagnostic polysomnogram (PSG) because of abnormal respirations observed during sleep by the parents. In addition, he had a history of difficulty awakening in the morning and was falling asleep in school during the day. His PSG demonstrated numerous respiratory events, with a representative event depicted in Fig. 3.1. His overall obstructive apnea-hypopnea index was 12 events per hour. Working with the child's neurologist, following the sleep study, the patient's vagus nerve stimulator settings were adjusted by lowering the frequency and increasing the cycle time. These adjustments decreased the frequency of respiratory events and improved his clinical symptoms.

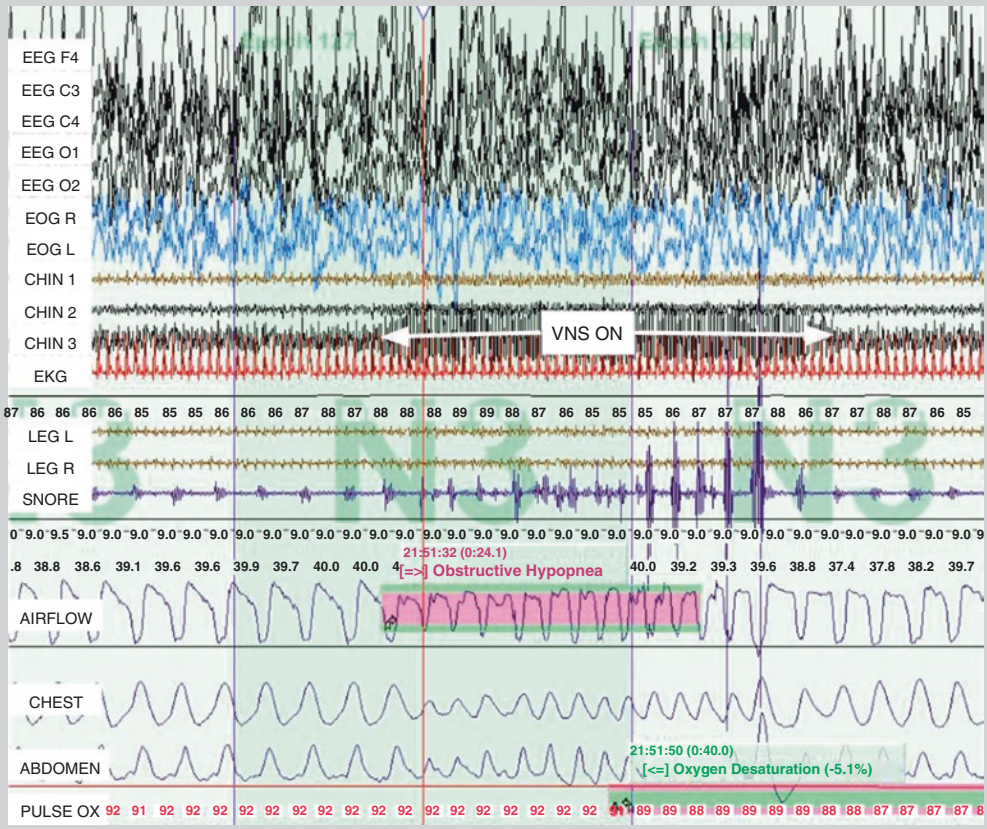

Fig. 3.1 Example respiratory event from case presentation. Note the increased chin tone during vagus nerve stimulator activity and associated obstructive hypopnea

D. G. Ingram
Pulmonary and Sleep Medicine, Children's Mercy Hospital, Kansas City, MO, USA

S. C. M. Crane
Pulmonary, Children's Hospital Colorado, Aurora, CO, USA

A. C. Halbower (✉)
Pediatrics, University of Colorado School of Medicine, Aurora, CO, USA
e-mail: ann.halbower@childrenscolorado.org

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Introduction

The polysomnogram, which is often referred to as an overnight sleep study, represents one diagnostic tool available to the sleep clinician and serves an important purpose in the clinical evaluation of many patients evaluated in the sleep clinic. However, like any diagnostic test, its results need to be interpreted with the particular patient and clinical context in mind. The case presented above is a good example of this. Although this patient does have frequent respiratory events such that he could have been diagnosed with obstructive sleep apnea (OSA), the knowledge that the patient has a seizure disorder clues the practitioner into the fact that the etiology of these respiratory events is primarily the patient's vagus nerve stimulator. This clinical context aids in interpretation of the PSG and therefore subsequent clinical management of the patient.

In this chapter, we will review some basics of polysomnography, including selected technical aspects, scoring of important parameters, and interpretation of derived metrics in a clinical context. We will also discuss preparing a child to undergo a sleep study, which is of special importance for children with neurodevelopmental disorders. The current guidelines for indications for performing a PSG will be reviewed, and we will discuss other modes of sleep diagnostic testing, including multiple sleep latency test (MSLT). Finally, we will discuss selected sleep metrics and modalities that are currently experimental but hold some promise for future clinical application.

Indications for Polysomnography

Standard Practice Parameters

Practice parameters for indications for PSG in children, both respiratory and non-respiratory, were recently published by the American Academy of Sleep Medicine (AASM) [1, 2]. These practice parameters were developed by the AASM Standards of Practice Committee, who combined the best scientific evidence available at the time with expert opinion within a framework of an evidence grading system. Indications are outlined in Tables 3.1 and 3.2. For reference, standard recommendations are felt to be based on a high

Table 3.1 American Academy of Sleep Medicine practice parameters for the respiratory indications for polysomnography in children

Recommendations for use (level of evidence)
1. Polysomnography in children should be performed and interpreted in accordance with the recommendations of the AASM Manual for the Scoring of Sleep and Associated Events (Standard)
2. Polysomnography is indicated when the clinical assessment suggests the diagnosis of obstructive sleep apnea syndrome (OSAS) in children (Standard)
3. Children with mild OSAS preoperatively should have clinical evaluation following adenotonsillectomy to assess for residual symptoms. If there are residual symptoms of OSAS, polysomnography should be performed (Standard)
4. Polysomnography is indicated following adenotonsillectomy to assess for residual OSAS in children with preoperative evidence for moderate to severe OSAS, obesity, craniofacial anomalies that obstruct the upper airway, and neurologic disorders (e.g., Down syndrome, Prader-Willi syndrome, and myelomeningocele) (Standard)
5. Polysomnography is indicated for positive airway pressure (PAP) titration in children with obstructive sleep apnea syndrome (Standard)
6. Polysomnography is indicated when the clinical assessment suggests the diagnosis of congenital central alveolar hypoventilation syndrome or sleep-related hypoventilation due to neuromuscular disorders or chest wall deformities. It is indicated in selected cases of primary sleep apnea of infancy (Guideline)
7. Polysomnography is indicated when there is clinical evidence of a sleep-related breathing disorder in infants who have experienced an apparent life-threatening event (ALTE) (Guideline)
8. Polysomnography is indicated in children being considered for adenotonsillectomy to treat obstructive sleep apnea syndrome (Guideline)
9. Follow-up PSG in children on chronic PAP support is indicated to determine whether pressure requirements have changed as a result of the child's growth and development, if symptoms recur while on PAP, or if additional or alternate treatment is instituted (Guideline)
10. Polysomnography is indicated after treatment of children for OSAS with rapid maxillary expansion to assess for the level of residual disease and to determine whether additional treatment is necessary (Option)
11. Children with OSAS treated with an oral appliance should have clinical follow-up and polysomnography to assess response to treatment (Option)
12. Polysomnography is indicated for noninvasive positive pressure ventilation (NIPPV) titration in children with other sleep-related breathing disorders (Option)
13. Children treated with mechanical ventilation may benefit from periodic evaluation with polysomnography to adjust ventilator settings (Option)
14. Children treated with tracheostomy for sleep-related breathing disorders benefit from polysomnography as part of the evaluation prior to decannulation. These children should be followed clinically after decannulation to assess for recurrence of symptoms of sleep-related breathing disorders (Option)
15. Polysomnography is indicated in the following respiratory disorders only if there is a clinical suspicion for an accompanying sleep-related breathing disorder: chronic asthma, cystic fibrosis, pulmonary hypertension, bronchopulmonary dysplasia, or chest wall abnormality such as kyphoscoliosis (Option)
Recommendations against use
1. Nap (abbreviated) polysomnography is not recommended for the evaluation of obstructive sleep apnea syndrome in children (Option)
2. Children considered for treatment with supplemental oxygen do not routinely require polysomnography for management of oxygen therapy (Option)

Table 3.2 American Academy of Sleep Medicine practice parameters for the non-respiratory indications for polysomnography and multiple sleep latency testing in children

Recommendations for PSG and MSLT (level of evidence)
1. PSG is indicated for children suspected of having periodic limb movement disorder (PLMD) for diagnosing PLMD (Standard)
2. The MSLT, preceded by nocturnal PSG, is indicated in children as part of the evaluation for suspected narcolepsy (Standard)
3. Children with frequent NREM parasomnias, epilepsy, or nocturnal enuresis should be clinically screened for the presence of comorbid sleep disorders, and polysomnography should be performed if there is a suspicion for sleep-disordered breathing or periodic limb movement disorder (Guideline)
4. The MSLT, preceded by nocturnal PSG, is indicated in children suspected of having hypersomnia from causes other than narcolepsy to assess excessive sleepiness and to aid in differentiation from narcolepsy (Option)
5. The polysomnogram using an expanded EEG montage is indicated in children to confirm the diagnosis of an atypical or potentially injurious parasomnia or differentiate a parasomnia from sleep-related epilepsy (Option)
6. Polysomnography is indicated in children suspected of having restless leg syndrome (RLS) who require supportive data for diagnosing RLS (Option)
Recommendations against use
1. Polysomnography is not routinely indicated for evaluation of children with sleep-related bruxism (Standard)

level of evidence, guideline recommendations have a moderate evidence base, and option recommendations reflect areas of uncertainty with conflicting evidence or expert opinion. While Tables 3.1 and 3.2 outline the standard indications for the use of PSG in children, a more focused discussion on the use of PSG in selected special populations follows below.

Down Syndrome

Obstructive sleep apnea is substantially more prevalent in children with Down syndrome as compared to the general population, with estimates in the 50% range [3]. This increased prevalence is likely related to several factors associated with Down syndrome, including craniofacial features, macroglossia, hypotonia, and obesity. Sleep apnea in this population may result in worsening neurocognitive impairment as well as cardiovascular disease.

Due to its high prevalence and potential associated morbidity, sleep apnea in children with Down syndrome has received special attention. Guidelines published by the American Academy of Pediatrics (AAP) recommend that starting at 6 months of life, providers should discuss symptoms of OSA with parents and that all children with Down syndrome should undergo PSG to evaluate for OSA by age 4 years [4]. Formal assessment for OSA with PSG is important especially in this population given the poor correlation between reported symptoms and sleep study abnormalities [5]. A recent study suggests that PSG should perhaps be considered earlier than 4 years, especially in children with Down syndrome living at altitudes >1500 m [6].

Furthermore, while its lower cost and decreased need for manpower are attractive, overnight nocturnal oximetry as a screening tool has not been shown to be sufficiently sensitive to detect OSA in children, either healthy or with Down syndrome, compared to formal PSG [7, 8]. Finally, PSG assessment for residual OSA in children with Down syndrome following adenotonsillectomy or other sleep surgery is important given the observed lower rate of surgical cure compared to typically developing children [9, 10].

Prader-Willi Syndrome

Children with Prader-Willi syndrome (PWS), which has a prevalence of approximately 1 in 10,000 to 1 in 25,000 live births, have a high prevalence of OSA, estimated to be about 80% [11–14]. This increased risk for OSA is likely related to several features of the disorder including craniofacial abnormalities, hypotonia, and increased prevalence of obesity. Similar to children with Down syndrome, children with Prader-Willi syndrome also have a lower cure rate with adenotonsillectomy for OSA [11], so a postoperative PSG to evaluate for residual disease should be considered. Drug-induced sleep endoscopy may play a role in identifying additional surgical sites of obstruction, such as the tongue base [15].

Of special significance is the role for PSG prior to initiation of growth hormone therapy in this population. The impetus for this testing prior to initiation of therapy came about in the early 2000s when several fatalities were noted worldwide that appeared to coincide with the use of growth hormone treatment in children with Prader-Willi syndrome [16, 17]. Therefore, although it is unknown what exact role growth hormone may have played in those deaths, one hypothesis is that growth hormone may have caused or worsened existing OSA by stimulating adenotonsillar hypertrophy; therefore, current guidelines recommend evaluation with PSG prior to, as well as 6–10 weeks after, initiation of growth hormone therapy, regardless of age [18]. In children who are found to have OSA on their study, treatment of OSA should be initiated, and the provider should consider delaying or stopping growth hormone therapy until adequate control is achieved [18, 19]. Besides growth hormone initiation, increasing body mass index (BMI) percentile also confers additional risk of OSA among children with PWS [11].

Achondroplasia

Achondroplasia is a disorder related to a mutation in fibroblast growth factor receptor 3 that results in short-limb dwarfism and affects more than 250,000 individuals

worldwide [20]. Children with achondroplasia are at risk for several different sleep-related breathing disorders (SRBD): craniofacial changes including midface hypoplasia may predispose to OSA; a restrictive lung physiology may lead to hypoventilation and nocturnal hypoxemia without sleep apnea; and increased risk for compression of the medulla from foramen magnum stenosis may lead to central sleep apnea [21]. In fact, compression of the foramen magnum resulting in central apneas is postulated to contribute to the 2–5% rate of unexpected infant deaths in this population [22]. Current AAP guidelines recommend that infants who are not diagnosed in the newborn period should undergo PSG at the time of diagnosis [23].

Epilepsy

Epilepsy occurs in approximately 1% of the population and has recently been explored in relation to OSA and children. The prevalence of sleep-disordered breathing, estimated with a questionnaire, was found to be higher in children with epilepsy compared to those without [24] and even higher in the subset of children with severe epilepsy compared to those with mild epilepsy [25]. Subsequent research has revealed that poorly controlled epilepsy is a risk factor for OSA and that more severe sleep apnea is associated with use of multiple antiepileptic drugs [26]. It has been hypothesized that the increased prevalence of OSA in children with epilepsy may be related to altered neuronal control of breathing resulting in respiratory events, or, conversely, OSA may exacerbate pre-existing epilepsy by causing increased sleep fragmentation and time in stages N1 and N2 when seizures most commonly occur [26]. Importantly, treatment of OSA in children with epilepsy has been found to be associated with decreased seizure frequency [27]. Taken together, the above evidence suggests that clinicians should strongly consider assessing for OSA with PSG in children with poorly controlled epilepsy.

Chiari 1 Malformation

Chiari malformations, abnormalities affecting the anatomy of the brainstem, come in several different forms. People with Chiari type 1 malformations are typically asymptomatic until adulthood, at which time they most commonly develop headaches [28]. That said, Chiari 1 malformations can cause headaches, neck pain, behavioral difficulties, and cognitive impairment in children [28]. Other symptoms may include abnormal eye movements, hoarse voice, stridor, and cyanotic breath holding spells. Children with Chiari 1 malformations are at increased risk for both obstructive and central respiratory events, with the hypothesized mechanisms being compression of cranial nerves innervating pharyngeal/laryngeal muscles and compression of the medullary respiratory centers, respectively [28]. Among children with Chiari 1 malformation, having a SRBD may be an indication for decompression [28]. That said, at this time there are no guidelines for when children with Chiari 1 malformation should undergo PSG. Because studies have found that relying on symptoms alone to detect SRBD among patients with Chiari 1 malformation will miss a substantial portion of those with a sleep related breathing disorder (SRBD), providers caring for these patients should consider routine evaluation with PSG [28]. While symptoms of Chiari 1 malformation in children may include headaches, neck pain, hypersomnia, and developmental delay, this condition may also be asymptomatic.

Preparing Children for Polysomnography

Once it had been determined that a PSG is indicated for a patient, it is important to prepare for a successful study. Simply ordering a PSG does not guarantee clinically useful study results. While technical limitations, such as unreliable equipment or poor electrode placement, can contribute to diminished PSG results, common reasons that pediatric PSG studies "fail" also include insufficient hours of sleep due to the patient being too upset to sleep and/or intolerance of essential data collection equipment. Failed PSG studies result in increased family frustration and a significant revenue reduction. Therefore, preparation for a successful study is well worth pre-PSG resource allocation.

The first step to prepare for a successful PSG is to assess the likelihood that the child will cooperate with the study procedures and adequately tolerate the study's physical sensations. This assessment utilizes clinical judgment based on communication with the child's caregivers, history gathering, and direct observation. After hearing an adequate description of the PSG, the caregiver may indicate that the child will probably struggle with the study. Clinical history review may reveal that the child has not done well with previous medical procedures or has poor adherence with past medical interventions. Perhaps the child is observed reacting negatively to descriptions of the PSG or not responding appropriately to typical expectations and limits in the medical setting. General groups of children who often benefit from PSG preparation include children with the following conditions: mental health concerns (autism spectrum disorder, anxiety disorders, attention-deficit/hyperactivity disorder, trauma histories, oppositional and aggressive behaviors), negative experiences with past medical procedures and hospitals, developmental delays, overwhelmed caregivers, and "sensory issues." These can all be indications that additional preparation for a PSG is warranted.

If it appears that a child may require minimal training for a PSG, a "tour" of the sleep lab can be scheduled to see how the child reacts to the setting and the placement of some of the PSG sensory items. If the child does well, they can be given instructions regarding home practice and a sleep study training kit (described below). If the child responds poorly to the sleep lab tour, or if it is clear from the clinic appointment that more extensive training is likely necessary, they are scheduled for a "desensitization" appointment. One working model for desensitization for a diagnostic PSG is a 1 h clinic visit with two trained staff members followed by one to three follow-up phone calls. A two-staff member model decreases the chaos in the room and increases the probability of a successful appointment by allowing one staff member to focus on managing the child, while the other staff member teaches the caregiver(s) the key training points. These roles can be exchanged as needed throughout the appointment. A second set of trained hands is often advantageous when it is time to place items on the child. It is ideal if one staff member has behavioral expertise (e.g., psychologist, social worker, licensed counselor, child life specialist), while the other has specific medical training with the sleep equipment (e.g., sleep technician, respiratory therapist, sleep-trained nurse, nurse practitioner, physician).

The first task in the desensitization clinic visit is to build rapport with the caregiver(s) and child. The potential benefits of the PSG are discussed to help increase the family's motivation to prepare for the study. When skepticism is observed, families may be reminded that with consistent practice, virtually all children, even with special needs, have been successfully prepared to complete PSG studies. An overview of what to expect during the PSG study can be provided by showing a short video demonstration of a pediatric sleep study. A number of these videos are available on YouTube, such as this video (under 5 min), "What to Expect from Your Sleep Test at Children's Colorado" (https://www.youtube.com/watch?v=rrUr4cyEHEc). A color step-by-step photograph book is typically reviewed and given to the family to continue to use at home for cognitive training and normalization. Caregivers are then taught to use some key behavioral interventions (i.e., positive reinforcement (a reward is chosen which can be earned by following directions during the appointment); graduated exposure (PSG sensations are gradually introduced); counter conditioning (PSG sensations are paired with enjoyable distractions such as movies, video games, tactile toys, and music); selective attention/differential positive reinforcement (the child is given attention and praised when exhibiting calm, cooperative behaviors, and negative or oppositional behaviors are ignored); and escape/response prevention (negative vocalizations are ignored, the child's hands are redirected when attempting to remove the PSG practice sensations, if the items are removed they are quickly replaced, the items are only removed by the caregivers and staff and are only removed when the child is being calm and cooperative).

Oftentimes it is important to also discuss limit management issues with caregivers. By observation and/or by family report, it may become clear that the caregivers have not experienced success in setting and enforcing developmentally appropriate limits with the child. Simply stated, the child "runs the show." To be successful in preparing for a PSG, this dynamic will need to shift, at least in this one area. It may be necessary to explore what prevents the caregiver from successfully setting and enforcing limits. A "reframe" can be provided by suggesting that good parenting results in children being angry and upset with their caregivers at times. Learning to tolerate not getting their way and having to do things they don't want to do actually help children be more successful in life. Caregivers may need to be given suggestions on how they can tolerate their emotions when their child is upset with them (e.g., rather than giving in, remain calm in the moment, and then scream into a towel, or debrief with another adult later). Caregivers need to be prepared that their child will likely escalate their resistance to limits, especially when historically they are used to controlling the situation and getting their way. Caregivers should know that "it will get worse before it gets better," but if they consistently follow through, their child can learn to comply.

During the appointment initially, one provider demonstrates the skills, while the other provider narrates or explains to the caregiver what is being done and what it accomplishes. Eventually the parent is coached to perform the hands-on training so that it can be replicated in the home setting prior to the PSG. The parent's progress in using the skills is pointed out and praised throughout the meeting. Goals for in-home practice are to gradually work up to the point that all of the sleep study sensors are placed on the child, and the child can fall asleep with the sensors on several nights in a row. The family is given a home practice "kit," which includes paper tape to imitate the pulse oximeter, thermistor/flow sensor, and PSG "stickers" (leads on the legs, chest, neck, and face), rolls of gauze to serve as the abdominal and chest effort belts, net mask or gauze to wrap the head, nasal cannula, and detailed written practice instructions and tips. After the family's appointment, the desensitization staff initiates telephone calls to the family every 2–3 weeks to make sure they are progressing on their goals. If needed, another face-to-face meeting can be scheduled to provide greater encouragement and troubleshooting. The staff also helps to ensure that a PSG is scheduled to occur around the time when it is anticipated the child will be prepared for a successful study.

Increasing the likelihood of a successful PSG can better utilize health-care expenditures, increase family satisfaction with services, and, ultimately, optimize treatment efficacy. This topic has also been reviewed elsewhere [29].

Polysomnogram Setup and Measurements

The typical PSG montage utilizes several sensors and measures. A limited electroencephalogram (EEG) montage, electrooculogram (EOG), and submental electromyogram (EMG) are recorded in order to accurately detect and stage sleep. Respiratory inductance plethysmography belts (RIP) are one of several possible techniques to measure chest and abdominal wall motion. Pulse oximeter and end-tidal capnography sensors detect oxygen saturation and expired carbon dioxide levels, respectively. Oral and nasal airflow are measured with thermistor and nasal pressure transducer. Limb muscle activity is recorded with surface EMG leads. Cardiac rhythm is monitored with limited electrocardiogram (ECG).

The EEG setup utilizes a smaller number of electrodes compared to standard EEG recording, which follows the International 10–20 system [30]. In this system, an imaginary line is drawn from the bridge of the nose to the prominence at the base of the occiput from anterior to posterior and then from the preauricular points on the left and right in the lateral dimension. The 10 and 20 numbers refer to fractions of distance of head circumference from those landmarks to the placement of individual EEG electrodes. Individual electrodes are abbreviated either F, C, or O depending on the region of the brain that they cover, corresponding to frontal, central, and occipital regions. A subscript is assigned as well in order to describe the lateral position of the electrode with Z referring to midline, odd numbers referring to the left side, and even numbers referring to the right side. Right and left mastoid electrodes are also applied.

Eye movements and chin tone are monitored. Specific eye movement patterns can be recognized, including blinking, reading eye movements, slow eye movements, and rapid eye movements. Slow eye movements are important for identifying the onset of sleep, and rapid eye movements are important for identifying rapid eye movement (REM) stage sleep. Measuring chin tone is of particular importance as reduction of muscle tone is characteristic of REM sleep. Abnormally maintained or increased chin tone during REM sleep may be seen in REM behavior disorder.

Given that the majority of sleep studies are performed in order to evaluate for SRBD, measurement of airflow and breathing effort is of paramount importance. The use of an oronasal thermistor is recommended for scoring apneic respiratory events [31]. The advantage of thermal sensors is that they can detect both nasal and oral airflow based on temperature change from exhaled air [30]. In contrast, measurement of nasal pressure provides an approximation of nasal airflow and is recommended for scoring of hypopneas (partial decreases in airflow associated with oxygen desaturation or arousal) [31]. Importantly, the nasal pressure signal can underestimate airflow at low flow rates and overestimate at high flow rates [30]. The thermistor is used to score apneas rather than the nasal pressure sensor because in some patients with mouth breathing, a hypopnea might be misclassified as an apnea if the nasal pressure signal is used alone, as any oral airflow might not be captured [30]. One important characteristic to note on the nasal pressure signal is the shape of the waveform; a drop in amplitude of the signal with flattening of the waveform may indicate an obstructive etiology, while a drop in amplitude with preserved waveform shape suggests a reduced inspiratory effort [30]. Finally, determination of respiratory effort by measuring abdominal and chest wall movement is required in order to classify respiratory events properly: obstructive events are characterized by preserved (albeit sometimes altered) attempts at movements, while these are absent in central events. Most commonly, chest and abdominal movements are sensed with respiratory impedance plethysmography. Other modalities include esophageal manometry (gold standard but uncomfortable), respiratory muscle EMG, and piezoelectric sensors.

Measurement of oxygenation and ventilation is essential for characterizing respiration during sleep. During a sleep study, a pulse oximeter is used in order to estimate oxygen saturation. It is important to note that this measurement can be influenced by factors including abnormal hemoglobin and acid base abnormalities. It is also important to be cognizant of your particular pulse oximeter sampling rate, which may be faster and more sensitive to intermittent desaturations than those used on the typical inpatient ward unit; clinically, this may become important when explaining to parents why a sleep study performed on their child has detected frequent oxygen desaturations when continuous overnight oximetry performed as a part of routine care during previous hospitalizations did not reveal the same finding. Hypoventilation is assessed with measurement of carbon dioxide, either estimated from end-tidal carbon dioxide ($ETCO_2$) or transcutaneously ($TcpCO_2$). Values from both of these tools need to be interpreted with caution. Transcutaneous CO_2 sensors need to be calibrated, the temperature of the probes should be sufficient, and values obtained from this device during the study may lag behind actual changes and arterial PCO_2 by a short time [31]. Similarly, $ETCO_2$ values may be falsely low in patients with nasal obstruction or in mouth breathers; ensuring that a good end-tidal CO_2 waveform is obtained is essential to ensure accurate values [31].

Limb muscle activity is recorded with EMG in order to assess for leg movements and is part of the standard PSG montage. Sensors are typically placed over the right and left anterior tibialis muscles, and, in patients with suspected REM behavior disorder, arm muscle EMG is also monitored [30]. The limb movements and periodic limb movements of sleep derived from these measures are discussed later in this chapter.

A single-channel recording of ECG is useful for characterizing cardiac rhythms and arrhythmias. Normal sinus rhythm is characterized by an upright P wave, R wave, and T wave in lead II [30]. For children 6 years and older, bradycardia

during sleep is defined as sustained (>30 s) heart rate less than 40 bpm [31]. Clinically, children who have congenital heart disease and have previously undergone cardiac surgery are at increased risk for heart block. The ECG can sometimes cause an artifact in the EEG channel, which can mimic spikes.

The snore channel is customarily a part of the pediatric PSG montage. Clinically, this can be helpful, as snoring is a sign of upper airway resistance and work of breathing. In addition, the presence or absence of snoring often helps to distinguish central from obstructive respiratory events in ambiguous cases.

Finally, body position is a standard part of PSG. While this is a simple measurement, it is clinically important as many times obstructive respiratory events are more common in the supine position. If this is the case, positional therapy may play a role in the overall management of an individual child.

Information Derived from the Polysomnogram

Sleep Staging and Architecture

Of course, at its most basic level, a sleep study measures sleep. This is readily apparent in clinic, as many times the first question that parents will ask a sleep provider after their child has had a PSG is, "so, how did my child sleep?" Parents are often interested in exactly how much "light sleep," "deep sleep," or "dream sleep" the child had the night of the study and have attitudes and beliefs regarding the meaning of those measures for their child's health and well-being. Therefore, it is imperative that sleep providers have an expert understanding of how these measures are derived, what normal and abnormal is, and what the implications for those findings are for their individual patient.

Sleep staging is achieved through the use of EEG, EOG, and EMG measures. The AASM has published detailed rules for the scoring of sleep and its associated events for infants as well as children [31], and the following discussion is meant to highlight important differences from adult rules and is based on the AASM scoring manual unless otherwise specified.

Unlike in adults and older children, sleep in infants is staged into wakefulness, non-REM, REM, and transitional [32]. Using previous terminology, REM sleep may also be referred to as active sleep, and non-REM sleep may be referred to as quiet sleep [33]. In addition, a major difference in infants compared to older children and adults is that sleep is scored based not only on EEG/EOG/EMG but also on behavioral and respiratory characteristics. Wake is associated with the infant having their eyes open, crying, or feeding; irregular respirations; low-voltage irregular or mixed EEG; rapid eye movements, blinks, or scanning eye movements; and chin tone on EMG. During non-REM sleep, body movements are reduced compared to wake; respirations are regular; the EEG may demonstrate tracé alternant (three or more alternating runs of symmetrical synchronous high-voltage bursts of delta activity and low-amplitude theta activity), high-voltage slow frequency, sleep spindles, or mixed; the eyes are closed; and the chin EMG may be present or low. REM sleep is characterized by having the eyes closed with small body movements, irregular respirations, low-voltage irregular or mixed EEG, rapid eye movements on EOG, and low or transient muscle activity on chin EMG. If there are characteristics of both non-REM and REM sleep stages in a single epoch, it should be scored as transitional sleep. Periodic breathing is common during REM sleep in infants, and the regularity of respirations may be one of the most reliable characteristics differentiating REM and non-REM sleep in infants, with non-REM sleep being characterized by a more regular respiratory pattern. In terms of overall sleep architecture, newborns typically have sleep periods lasting 3–4 h, with awakenings for feeding; they typically begin their sleep going right into REM sleep; and REM sleep comprises approximately 50% of the total sleep time, which begins to decrease at approximately 3 months of age and reaches adult levels by adolescence [30].

After about 2 months of age, sleep may be able to be staged according to the pediatric, rather than infant, rules. This is made possible by the fact that sleep spindles characteristic of stage N2 sleep appear around 2–3 months of age, K complexes (also characteristic of N2) around 4–6 months, and slow wave activity (frequent during stage N3 sleep) by 4–5 months. Because of the variable appearance of these characteristics, which allow one to differentiate stages of non-REM sleep, there will be inter-individual differences in the exact age when N1, N2, and N3 can be scored, but this is usually possible by age 6 months. Examples of sleep stages are presented in Fig. 3.2. A posterior dominant rhythm, which is observed in the occipital region during wakefulness and eyes closed, first appears in infants around 3–4 months of age and is slower in frequency. Hypnagogic hypersynchrony, consisting of bursts of high-amplitude low-frequency (3–4 Hz) sinusoidal waves in the frontal and central regions, usually begins around 3 months of age, disappears by age 12 years, and is associated with stages N1 and N2. Hypnagogic hypersynchrony is important for identifying the onset of sleep in those children who do not generate a posterior dominant rhythm. The scoring of stages N2, N3, and REM sleep is the same for children as they are for adults.

As noted above, sleep architecture changes with age, so when discussing this with parents, one must have an understanding of what is normal for that child in the context of their development. In infants less than 3 months of age, sleep onset is usually characterized by rapid entry into REM stage sleep, which constitutes approximately 50% of total sleep time, and sleep cycles that last for 45–60 min. Typically starting around 3 months of age, the percentage of REM sleep decreases, children start to enter sleep via non-REM rather than REM sleep, and sleep cycles began to increase in

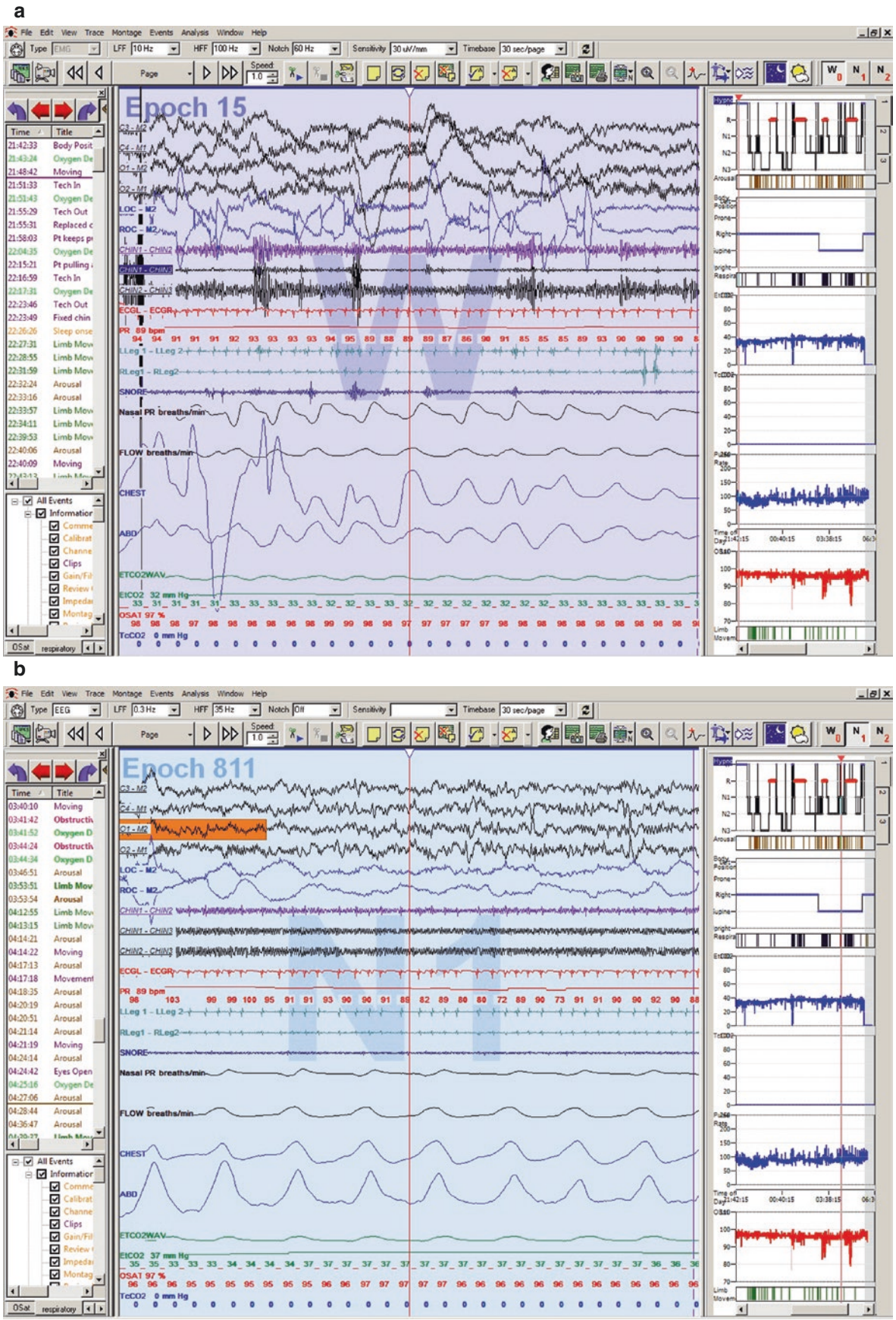

Fig. 3.2 (**a**) Rapid eye movements, increased chin tone, and posterior dominant rhythm denote wake. (**b**) Slow eye movements and vertex sharp waves signal the onset of N1 sleep. (**c**) K complexes are associated with N2 sleep. (**d**) Delta waves are characteristic of N3 sleep. (**e**) Rapid eye movements in association with low chin tone identify REM sleep

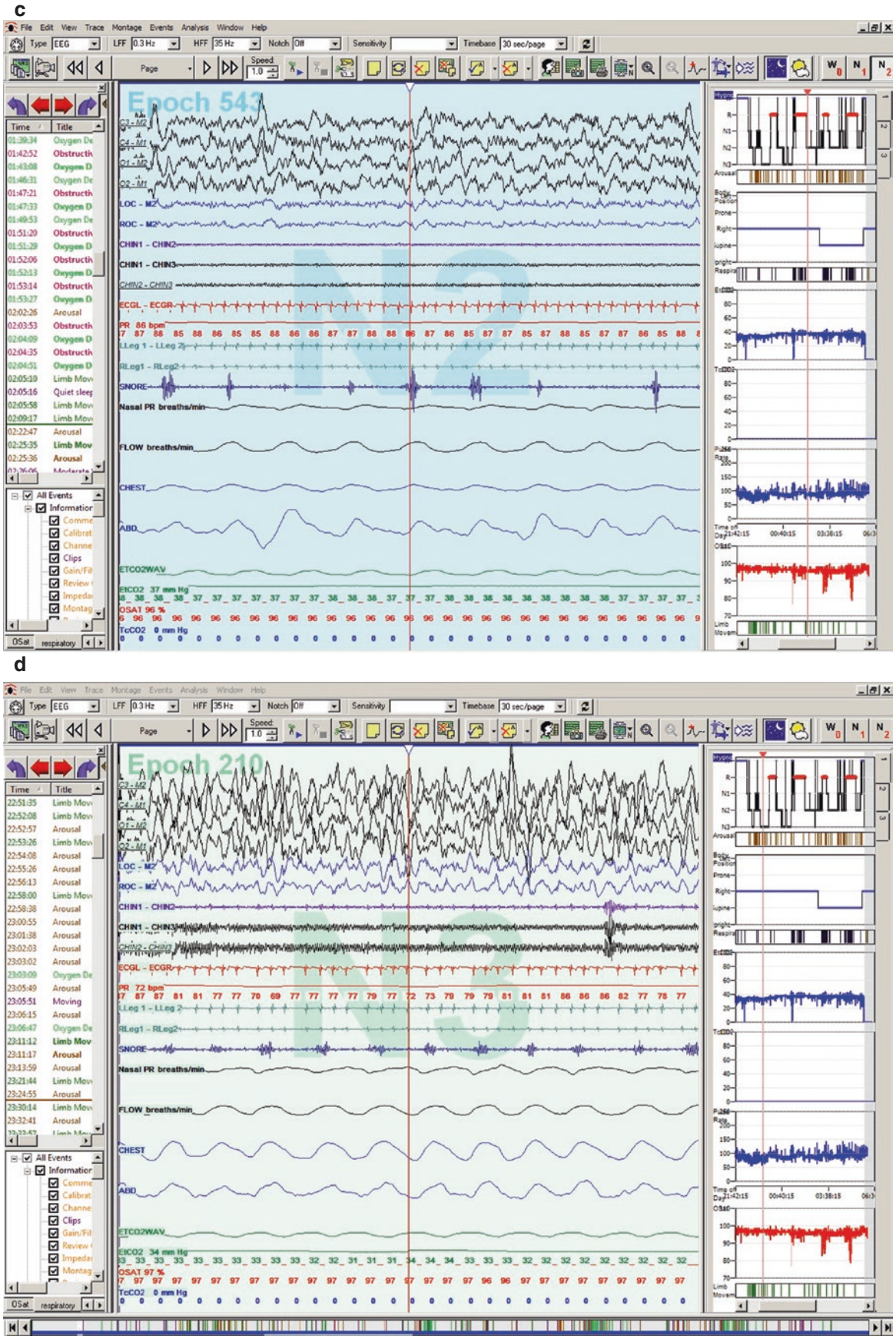

Fig. 3.2 (continued)

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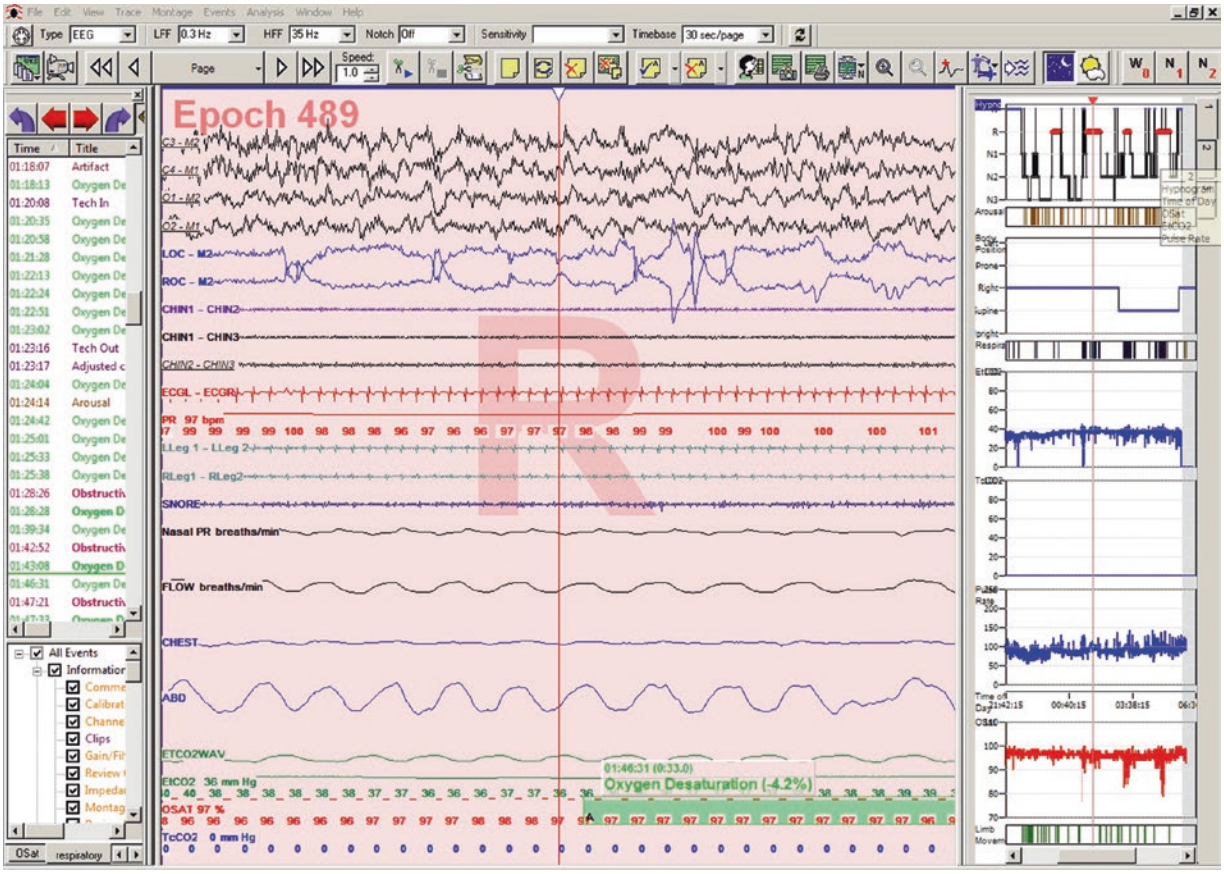

Fig. 3.2 (continued)

Table 3.3 Sleep architecture in healthy children without clinical sleep problems by age [34]

Age	1.4±0.3	2.9±0.5	5.1±0.5	8.1±1.4	11.5±1.2	12.8±1.6	15.2±1.4	16.9±0.9
TST (min)	488.7±87.1	489.7±92.2	541.7±67.3	512.2±61.7	478.6±53.7	477.5±68.0	481.5±46.2	452.1±80.2
WASO (%)	12.1±8.1	7.7±7.3	4.1±3.2	5.1±5.2	5.2±4.9	6.7±5.9	4.2±3.7	5.1±3.0
Sleep latency (min)	24.4±29.7	33.1±25.9	32.0±30.5	21.8±23.5	20.4±19.6	34.3±33.8	22.0±21.7	22.6±29.8
R latency (min)	83.9±36.6	100.2±38.3	140.0±57.5	155.1±44.1	161.8±42.3	125.2±40.3	138.2±54.5	132.7±36.4
Sleep efficiency (%)	83.5±7.9	86.0±9.0	90.0±6.5	89.6±6.4	89.8±5.6	85.7±7.6	90.7±6.0	88.9±6.9
N1 (%)	7.0±3.3	7.3±2.9	6.4±4.1	6.7±2.8	6.9±4.1	7.6±4.0	7.9±5.1	7.7±3.1
N2 (%)	31.1±7.6	29.6±6.2	36.5±7.4	38.6±6.8	42.6±5.0	42.2±8.3	45.6±7.9	49.4±7.0
N3 (%)	34.9±8.6	38.4±8.3	32.9±7.1	31.9±6.7	28.9±5.2	28.6±7.5	25.5±4.7	22.9±7.3
REM (%)	25.6±4.0	23.2±4.8	22.6±3.8	21.1±3.7	20.3±4.5	20.3±5.1	19.4±3.9	19.0±5.4
Stage shifts (#)	8.5±3.0	8.5±1.5	9.3±1.7	9.8±1.6	9.7±2.0	9.4±1.8	10.7±3.1	11.1±1.9

Data are presented as mean ± standard deviation

duration. Normative data regarding sleep architecture for children aged 1–18 years have been previously published [34] and are presented in Table 3.3. These ranges for sleep architecture should be viewed as possible typical values for reference rather than strict cut points for normal versus abnormal, and the authors of this chapter strongly urge sleep providers to interpret any one individual patient's sleep architecture within the clinical context rather than as a standalone metric on which diagnoses or treatment decisions are based. In addition, it should be noted that sleep architecture may be different in the sleep laboratory than in the home environment, as a "first night effect" has been observed in non-infant children who are naïve to the laboratory environment, characterized by an increased sleep latency and decreased sleep efficiency on the first night of study [35]. With those caveats in mind, alterations in sleep architecture may provide clues to individual sleep disorders. For example, a shortened REM latency (<15 min) and/or substantial sleep fragmentation would provide supportive evidence for the diagnosis of narcolepsy in the appropriate context.

Breathing

The scoring of respiratory events forms the basis upon which SRBD are diagnosed. The cutoff age for which pediatric, rather than adult, respiratory rules are used is anywhere from 13 to 18 years, at the discretion of the sleep practitioner; note that this distinction is not as critical as it used to be, because hypopneas in adults may now include events associated with arousal rather than only desaturation. Apnea refers to a drop in amplitude of thermistor signal by at least 90% for at least two breaths. If there is continued respiratory effort for the duration of the event, it is scored as obstructive. In contrast, if there is no respiratory effort, it is scored as central; of importance, if the central apnea is not associated with arousal or desaturation in a child, it must be either 20 s in duration or be associated with bradycardia. Hypopnea refers to a decrease in nasal pressure signal by at least 30% associated with desaturation or arousal, as demonstrated in Fig. 3.3. While differentiating obstructive from central hypopneas can be challenging and is optional by AASM standards, it may be

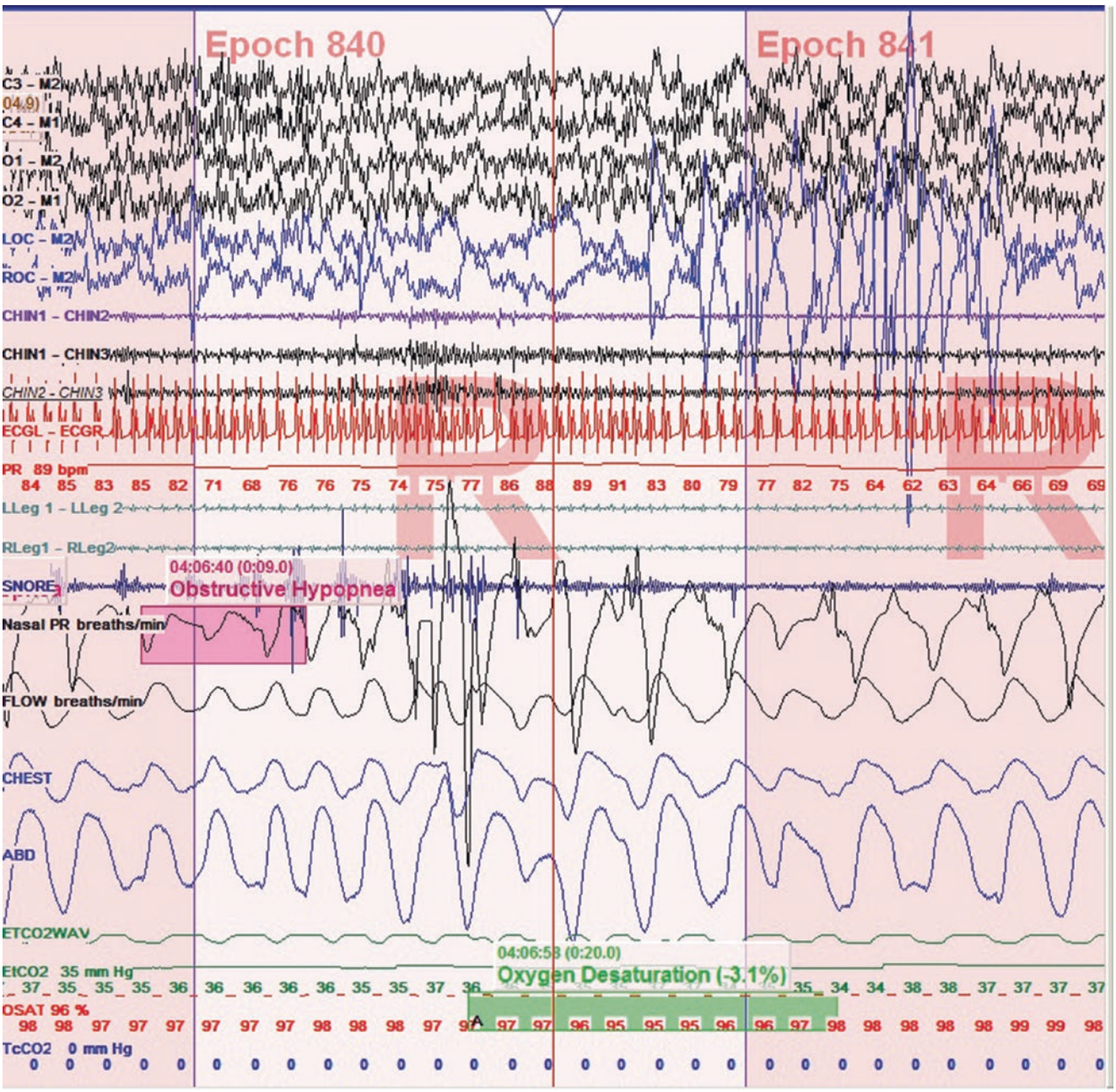

Fig. 3.3 A decrease of 30% in the nasal pressure signal accompanied by oxygen desaturation defines this respiratory event as a hypopnea. Note that the desaturation occurs following, rather than concomitant with, the decrease in airflow and that snoring identifies this as obstructive rather than central in nature

of clinical utility, especially in infants and children with neurodevelopmental disorders and at high altitude. A hypopnea is likely of central origin if there is no associated snoring, flattening of the nasal pressure waveform, or paradoxical breathing. Scoring respiratory effort-related arousals (RERAs) is optional; these events represent increasing respiratory effort or flattening of nasal pressure waveform that does not meet criteria for hypopnea but is associated with the consequence of arousal. If >25% of the total sleep time is spent with carbon dioxide as measured by $ETCO_2$ or $TcpCO_2$ above 50 mmHg, then hypoventilation is said to be present. Periodic breathing may be scored if there are three or more episodes of absent airflow and respiratory effort lasting at least 3 s and separated by less than 20 s of normal breathing; note that individual central apneas nested within periodic breathing sequences should also be individually scored.

Once individual respiratory events are scored, they must be combined into summary indices that are clinically useful and carry diagnostic significance. It is useful to combine obstructive and mixed respiratory events into a single obstructive apnea-hypopnea index (OAHI). There exists controversy regarding the appropriate cutoff for OAHI, but in the most recent ICSD-3, an OAHI ≥ 1 event per hour is considered as part of the diagnostic criteria for pediatric OSA. In contrast, values of 1.5 events per hour or greater have been proposed elsewhere [35], and values of 2 events per hour or greater for OAHI were used in the only randomized controlled trial of adenotonsillectomy in children with OSA [36]. It should be noted that many of the original studies establishing normative data for the OAHI used varying definitions of hypopnea and utilized nasal thermistor rather than the now standard nasal pressure transducer (Table 3.4). Some practitioners view an OAHI from 1 to 5 events per hour as a diagnostic gray zone in children, with management directed by the presence or absence of clinical symptoms (e.g., daytime sleepiness or neurobehavioral symptoms) and OSA-associated morbidity (e.g., pulmonary hypertension). Central respiratory events may be combined into a central AHI (CAHI), with a threshold of ≥5 events per hour (plus CAHI > OAHI) as consistent with central sleep apnea. This number is much higher in infants living at high altitude [37]. Furthermore, periodic breathing that composes 5% or more of the total sleep time is considered abnormal and supportive of central sleep apnea of infancy/prematurity (again, altered by altitude). If significant periodic breathing is present in the older child, consider neurologic, medication, and cardiac etiologies. Hypoventilation may be associated with OSA or neuromuscular disease, but one should also be aware of its association with a condition known as congenital central hypoventilation syndrome; worsening respiratory status during NREM sleep, compared to REM sleep, may help clue one into this diagnosis as opposed to other SRBD. The oxygen saturation does not typically decrease below 91% in normal children at sea level, and when there are 5 min or greater of saturations ≤90% during sleep without hypoventilation or OSA, one may diagnose sleep-related hypoxemia.

Limb Movements

The scoring of single-limb movements and combining them to score periodic limb movements of sleep (PLMS) are detailed and covered thoroughly in the AASM scoring manual [31]. Having five or more PLMS per hour is considered abnormal [43] and may be a sign of periodic limb movement disorder, restless leg syndrome, REM behavior disorder, or narcolepsy. Elevated PLMS have also been associated with iron deficiency, OSA, ADHD, migraines, seizures, and autism spectrum disorders in children [44, 45]. The clinical significance of PLMS, with or without arousals, remains controversial, with some studies in children demonstrating no substantial clinical impact at all [46]. Normative data for periodic and single-limb movements and their associations with arousals have also been reported for children aged 1–18 years [47].

Given a previously observed relationship between PLMS and autism as well as PLMS and iron deficiency, many practitioners screen for and treat ferritin levels <50 mcg/L in children with autism spectrum disorders and elevated PLMS. Indeed, in an open-label trial in children with ASD, subjective sleep disturbance and restless sleep improved, and ferritin levels increased with supplemental oral iron therapy [48].

Table 3.4 Previous studies reporting normal obstructive AHI (OAHI)

Study	Hypopnea definition	*N*	OAHI mean (SD)	OAHI ULN
Traeger et al. [38]	Thermistor. ≥50% reduction in flow associated with ≥3% desat or arousal	66	0.23 (0.31)	0.9
Wong et al. [39]	Thermistor. >50% reduction in flow associated with ≥3% desat or arousal	16	0.0 (0.1)	0.2
Verhulst et al. [40]	Thermistor. ≥50% reduction in flow associated with ≥3% desat or arousal	60	0.08 (0.17)	0.4
Witmans et al. [41]	Thermistor. <50% reduction in flow (associated arousal or desat not required)	41	0.2 (0.6)	1.4
Montgomery-Downs et al. [42]	Thermistor or $ETCO_2$ cannula. ≥50% reduction in flow associated with ≥4% desat and/or arousal	153	0.08 (0.16)	0.4
		388	0.14 (0.22)	0.6

Upper limit of normal (ULN) was calculated as the reported mean plus two standard deviations

That being said, studies that have examined the relationship between PLMS and iron deficiency within ASD have not found a significant association [45, 49]. Therefore, the relationship between iron status, PLMS, and autism remains to be fully elucidated.

Artifacts

There are several artifacts that clinicians will encounter on a frequent basis while interpreting PSGs, so familiarity with them is imperative to avoid misinterpretation. Popping refers to an electrode pulling away from the skin, usually associated with breathing, and results in high-amplitude deflections [30]. When there is electrical contamination from power lines during the sleep study, this can cause a 60-cycle artifact, characterized by 60 Hz contamination in the channels as well as a "rope-like" artifact in the chin EMG; this can sometimes be alleviated by the use of a 60 Hz notch filter [30]. As discussed above with respect to the ECG, this can sometimes contaminate the EEG channel and mimic spikes [30]. In addition, vagus nerve stimulator activity can distort multiple channels and was illustrated in the introductory case. When patients sweat during a study, this can sometimes result in slow-frequency artifact and can mimic stage N3. Sweat artifact is thought to be due to sweat changing the electrode potential [30] and is more frequently seen during NREM sleep, when sweating is more common. Excellent illustrations of these and other common artifacts are available elsewhere [30].

Experimental Measures of Sleep Disturbance and Respiratory Effort

The current gold standard metric to diagnose and grade the severity of OSA is the obstructive apnea-hypopnea index (OAHI) [50]. While this does provide a standardized measure for classification purposes, it is an imperfect measure. For example, a similar degree of neurocognitive deficits has been observed in children with primary snoring compared to those who meet formal diagnostic criteria for OSA [43, 44]. In addition, adenotonsillectomy in children with primary snoring results in significant improvement in symptoms compared to observation alone [51]. Finally, data from the Childhood Adenotonsillectomy Trial (CHAT), which was the first large randomized controlled trial of adenotonsillectomy for OSA in children, demonstrate minimal, if any, relationship between OSA severity as assessed by the OAHI and either baseline morbidity or response to adenotonsillectomy [52, 53]. As a result, alternative metrics to characterize sleep disturbance and respiratory effort are actively being developed.

Cyclic Alternating Patterns

Cyclic alternating pattern (CAP) is a finding on EEG that is characterized by transient electrocortical events during non-REM sleep and is a measure of sleep microstructure [54]. CAP is thought to reflect the brain's effort to preserve the normal structure of sleep and is therefore taken as a metric of sleep instability and quality [54]. Altered CAP measures have been associated with selected sleep disorders in children, as reviewed by Parrino and colleagues [55]. Namely, abnormal CAP has been associated with sleepwalking, sleep terrors, and narcolepsy. There have been contradictory results with respect to OSA. In addition, CAP has been shown to be altered in several neurodevelopmental disorders, including fragile X syndrome, Down syndrome, autism spectrum disorders, Prader-Willi syndrome, ADHD, and dyslexia [55]. Therefore, studies to date suggest that the CAP represents a clinically important metric related to sleep disturbance and daytime functioning, but more research into appropriate reference ranges and scoring is needed.

Duty Cycle

Duty cycle refers to the inspiratory time relative to the duration of the respiratory cycle (length of time required to breathe in divided by length of entire respiratory cycle, including both inspiration and expiration) [56]. Experimental manipulations of the inspiratory resistance of upper airways, by abruptly lowering applied nasal pressure, have demonstrated that duty cycle increases substantially compared to unobstructed breathing [57]. It is hypothesized that an increase in duty cycle represents a compensatory response to upper airway obstruction. It has also been demonstrated that children with OSA treated with a high-flow nasal cannula system have decreases in duty cycle [56]. However, a more recent analysis comparing children with and without sleep-disordered breathing did not find any between-group difference in duty cycle [58].

Pulse Transit Time

Pulse transit time (PTT) is calculated as the time between ECG peak and the photoplethysmography waveform measured by the finger pulse oximeter (illustration is available at [59]) and is thought to be related to arterial stiffness, blood pressure, and autonomic state. An acute decrease in PTT is thought to represent an autonomic, or subcortical, arousal. Indeed, changes in PTT have been shown to be correlated with changes in systolic blood pressure during PSG [60]. During acute respiratory events (apneas and hypopneas), the heart rate increases and the PTT decreases, which may

represent changes associated with the development of hypertension [61]. Interestingly, PTT may help identify more respiratory events and microarousals compared to standard EEG [62, 63]. The PTT arousal index may be able to distinguish between primary snoring and upper airway resistance syndrome, as assessed with esophageal manometry [63]. Finally, changes in PTT may help differentiate obstructive and central respiratory events (large PTT oscillations with obstructive versus reduced oscillations with central events), which can sometimes be challenging without the use of esophageal manometry [64].

Biomarkers

An alternative approach to identifying individual patients at risk for end-organ disease associated with OSA who should be targeted for therapy involves the use of biomarkers. A vast array of biomarkers has been examined over the last decade, and a recent review and synthesis of the literature have been published [65]. In all, the reviewers found 31 biomarkers that were evaluated in the literature, both blood and urine. One potential biomarker identified was high-sensitivity C-reactive protein (hsCRP), which was found to be elevated in children with neurocognitive deficits associated with either OSA or primary snoring [66]. Other potential biomarkers with positive results in children included IL-6, MRP 8/14, and urinary neurotransmitters [65].

Other Modes of Sleep Testing

Home Sleep Testing

To date, in-lab PSG remains the lone validated and standardized method for diagnosing OSA in children. However, the high cost and limited access to laboratory-based PSG can cause large financial and travel burdens on patients and families as well as delays in diagnosis and treatment. Additionally, environmental differences between the sleep laboratory and home may reduce the applicability of laboratory findings to the home setting. These limitations make home sleep testing (HST) an attractive alternative, and this method has already been adopted and is mainstream in the adult population.

In contrast to the adult literature, there are a limited number of studies examining HST in children. In a 1995 Canadian study, Jacob and colleagues [67] compared in-laboratory PSG to a limited home setup consisting of cardiorespiratory monitor, video, and inductive plethysmography in diagnosing OSA in pediatric subjects with adenotonsillar hypertrophy. The authors observed higher sleep efficiency and fewer environment-related arousals during the home studies and no differences in other measured sleep indices. Similarly, Brockmann and colleagues performed a feasibility study and found that 95% of children who underwent HST had technically acceptable recordings [68]. A more recent feasibility study performed by Marcus and colleagues demonstrated technically satisfactory HST in 91% of cases in school-aged children [69]. This is an area of active development and with recent progress and future directions elucidated by Tan and colleagues [70].

Actigraphy

Actigraphy is covered separately in detail elsewhere in this book. It should be noted, however, that this is still a developing area and may hold potential beyond the simple measurement of total sleep time and circadian phase shifts, such as being able to identify and differentiate disorders of hypersomnia [71].

Multiple Sleep Latency Test

The multiple sleep latency test (MSLT) is a daytime test intended to measure an individual's propensity for sleep. It typically immediately follows overnight PSG in patients being evaluated for hypersomnia, consists of five nap opportunities, and is validated in children 5 years and older [1]. While the MSLT is considered the gold standard for measuring sleep propensity and is part of the diagnostic criteria for idiopathic hypersomnia and narcolepsy, it is not without substantial limitations. For example, a mean sleep latency of ≤8 min is taken as the cut point for hypersomnia diagnoses. However, in patients with a clear-cut clinical diagnosis of idiopathic hypersomnia but sleep latency >8 min, there are no clinical or PSG differences compared to those with sleep latency less than 8 min; furthermore, a normal MSLT does not predict less severe symptoms or response to treatment [72]. The MSLT has a poor test-retest reliability among patients with narcolepsy without cataplexy and those with idiopathic hypersomnia, with a change in diagnosis in over half of patients on retest [73].

Maintenance of Wakefulness Test

While the MSLT is designed to measure an individual's propensity to fall asleep, the maintenance of wakefulness test (MWT) is meant to measure one's ability to stay awake. Specifically, during the MSLT, patients are instructed to "try to fall asleep," while at the start of each nap opportunity during MWT, patients are instructed to "sit still and remain awake for as long as possible." Results of the MWT may be clinically useful to assess wakefulness when public safety is

a concern or to evaluate response to treatment [74]. There are currently no normative data available for the pediatric population. The use of MSLT and MWT is covered elsewhere in this book in greater detail.

Extended Polysomnography

Due to the significant limitations of MSLT outlined above, the development of extended PSG protocols has been pursued in the research arena. Vernet and Arnulf had patients with idiopathic hypersomnia undergo a habituation night, next day MSLT, and then 24 h spontaneous sleep monitoring; 71% of those with hypersomnia with long sleep time (>10 h total sleep time) had MSLT sleep latency >8 min [75]. In a separate protocol by Fabio Pizza and colleagues, patients underwent 48 h of continuous PSG (first 24 h adaptation) with spontaneous sleep followed by MSLT [76]. Certainly, while these procedures are still in the research phase, they may hold promise to better diagnose and characterize sleep in patients with hypersomnia.

Areas of Uncertainty and Future Directions

In terms of its overall development, sleep testing in its current form is likely in its toddler years. While the AASM has made great strides by formally codifying PSG scoring in its manual [31] and defining the role of derived metrics in the diagnosis of specific sleep disorders in its recent ICSD-3 [50], many areas of uncertainty remain. For instance, the role of preoperative PSG in the context of adenotonsillectomy for OSA in the otherwise generally healthy child remains controversial. While the AAP guidelines recommend routine preoperative PSG for proper diagnosis of OSA when available (leaving open an option for referral to an otolaryngologist or sleep specialist) [50, 77], the American Academy of Otolaryngology-Head and Neck Surgery recommends that preoperative PSG should be reserved for patients with selected conditions or those with discrepancy between tonsil size on examination and reported history [78]. Other important areas of uncertainty have already been discussed above in context and include improved measures of respiratory effort and sleep disturbance, reliability, and validity of the MSLT in hypersomnias, the meaning of the OAHI in terms of measuring the presence of sleep apnea, the use of MWT for driving clearance, and home sleep testing.

Conclusions

Polysomnography is an integral part of pediatric sleep medicine. In this chapter we have reviewed common indications, scoring procedures, and interpretation of results with a focus on selected neurodevelopmental disorders. From a practical standpoint, we also discussed how to prepare children for their sleep study, identified common artifacts, and highlighted areas of uncertainly along the way. To reiterate an important theme, PSG should be viewed similarly to any other diagnostic test, in that the results always need to be interpreted in the clinical context, and testing should only be performed when the results will change patient management.

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Actigraphy

4

Allison L. Wainer and Lisa J. Meltzer

Case Vignette

Emma was a 4-year-old girl with WAGR syndrome, a genetic condition characterized by intellectual disability, visual impairments, and tumors of the kidneys and gonads and commonly associated with anxiety, attention-deficit/hyperactivity disorder (ADHD), and autism. She has been blind from birth. Her family had used melatonin at bedtime to help her sleep. However, Emma had never learned to sleep independently. At bedtime she would scream and cling to her parents as they tried to place her in the crib. Most nights her mother would remain in the room holding Emma until she was asleep. Emma then had prolonged night wakings that would last 1–3 h. Her parents stated that some nights she would play and other nights she would scream but then return to sleep around 6:00 a.m. Because she was nonverbal and developmentally delayed, her parents had not been comfortable using the same behavioral interventions that they had used for her older brother. Instead she had been tried on a number of different medications. When they presented to the sleep clinic, Emma's parents were ready to try behavioral interventions with guidance.

In addition to adjusting the timing of her melatonin (smaller dose given at 5:00 p.m.), her parents initiated a gradual extinction approach at bedtime only, teaching Emma to fall asleep independently. One month after their initial appointment, her parents reported significant improvements, with Emma falling asleep quickly, easily, and independently. However, they were concerned about an increase in daytime sleepiness, as indicated by teacher reports that she was falling asleep during school. Emma's parents reported that if she woke during the night, they only heard her crying or playing for brief periods. However, they were unsure if she was truly sleeping through the night. Thus, an actigraphy study was ordered to monitor her sleep-wake patterns, as well as to determine whether she was having prolonged nocturnal wakings.

Introduction

Behavioral sleep problems are common among children, with prevalence rates estimated to be around 30% in typically developing children [1]. Rates of behavioral sleep disorders have been found to be even higher in children with neurodevelopmental disorders, with prevalence estimates for children with autism spectrum disorder (ASD), intellectual disability (ID), and attention-deficit/hyperactivity disorder (ADHD) ranging from 25% to 80% [2].

Appropriate and valid evaluation of sleep duration and quality in children is critical, as it can offer important information related to diagnosis and treatment response. The "gold standard" method for the diagnosis of sleep disorders, including obstructive sleep apnea (OSA) and periodic limb movements in sleep (PLMS), is the use of polysomnography (PSG) or overnight monitoring in a laboratory using physiologic recording sensors. This allows for the measurement of sleep stages and the physiological activities that occur during sleep such as eye movements, oxygen saturation levels, and muscle movements. However, there are a number of limitations with PSG in terms of sleep measurement. First, PSG captures only a single night of sleep measurement in a sleep

A. L. Wainer (✉)
Department of Psychiatry, Rush University Medical Center, Chicago, IL, USA

L. J. Meltzer
Department of Pediatrics, National Jewish Health, Denver, CO, USA

J. A. Accardo (ed.), *Sleep in Children with Neurodevelopmental Disabilities*, https://doi.org/10.1007/978-3-319-98414-8_4

laboratory, which can be costly, so that repeated administrations (e.g., to track treatment response) may not be feasible. Second, children with neurodevelopmental disorders may have a particularly difficult time tolerating the PSG sensors and adjusting to the unfamiliar sleep laboratory environment. Third, while PSG captures physiological measures needed to diagnose sleep disorders, it does not provide information about sleep-wake patterns in a child's natural sleep environment. As such, it is not indicated for the diagnosis or treatment of insomnia.

So while PSG remains the "gold standard" for the diagnosis of OSA or PLMS, alternative approaches must be utilized to measure sleep patterns in children with neurodevelopmental disabilities in a way that is both feasible and cost-effective. One of the most common strategies for collecting sleep data in this population has been the sleep diary. The use of a sleep diary involves a parent (or older child) maintaining a record of the time the child first attempted sleep, the time the child actually fell asleep, the number of times the child woke in the night, the time the child awakened in the morning, and the number and duration of nap periods throughout the day. Sleep diaries are low-cost and easy to use and can provide valuable information about sleep patterns and sleep duration. However, limitations to this approach include the subjective nature of the diary, lack of data due to nonadherence with daily diary completion, and as was highlighted in Emma's case example above, the potential inability for a parent to accurately report on a child's sleep onset latency and/or night-waking frequency or duration. Thus the use of actigraphy may be indicated to provide an objective estimate of sleep-wake patterns.

An actigraph is a wristwatch-sized device that can be worn for multiple nights in the child's natural sleep environment. Actigraphs contain accelerometers that record movement data, with the premise that when we are awake, we are moving, and when we are asleep, we are not moving. These movement counts are captured in epochs (e.g., 30 s or 1 min), and data are transferred to a device-specific software. Epochs are then scored as sleep or wake based on device-specific algorithms.

Although the use of actigraphy in pediatric sleep research has gained significant popularity in recent years [3], there remain a limited number of validation studies in pediatrics. Those that have been done have consistently shown that compared to overnight polysomnography, actigraphy provides a valid estimate of sleep periods, although it is less accurate in measuring wake after sleep onset [3]. That said, actigraphy remains a clinically useful tool, with the use of actigraphy recommended for the diagnosis of multiple sleep disorders in the *International Classification of Sleep Disorders*, 3rd edition [4]. For children with neurodevelopmental disorders, the utility of this approach has started to be explored within the literature.

Guidelines for Actigraphy in Practice

As with any testing procedure, there are a number of factors for clinicians to consider. We will briefly review some of the most common factors; however, the reader is referred to the Society of Behavioral Sleep Medicine's (SBSM) Guide to Actigraphy Monitoring [5], which provides more detailed information on the use of actigraphy.

Actigraphy testing is a billable procedure with CPT code 95803, defined as actigraphy testing, recording, analysis, interpretation, and report (minimum of 72 h, up to 14 consecutive days of recording). However, almost all private insurances still consider actigraphy to be experimental, while reimbursement by Medicaid/Medicare varies by state. There is no standard approach on how to manage billing for actigraphy; however, some clinics will simply charge a flat fee for the actigraphy study rather than billing insurance.

For clinicians and researchers who want to start using actigraphy, one of the first considerations is what type of device to purchase. There are a number of different devices on the market. That said, very few actigraphs have been validated against overnight PSG [3], with even fewer validated in children with neurodevelopmental disabilities (see following section). Thus it is important to examine the literature when determining which device to use.

When purchasing an actigraphy system, it is important to consider the costs, which include not only the device but also the interface, software, batteries, and warranty. For example, some devices require the purchase of a software license for each computer that may use the program, while others only require the software to be purchased once, with use across multiple computers. Similarly, some devices have rechargeable batteries, while others require a new battery be inserted prior to each use. It is also important to ensure appropriate customer service for your needs. Device size and extra functions (light meter, off-wrist detection) can also play a role in decision-making, especially when working with children with neurodevelopmental disabilities.

Once a system is purchased, the devices should be given to families only after in-depth training is provided in terms of how to use the watch (including when to press an event marker, if available) and when to remove the device (i.e., showering, bathing, or any time the watch could get lost or damaged; see section "Special Considerations" for more details). In addition, the scoring of actigraphy data is most accurate with an accompanying sleep diary. The sleep diary helps the clinician to identify reported bedtimes and wake times, information that can also be obtained by reliably pushing the event marker at the time the child attempts to fall asleep and wakes up. Without this data, it is not possible to calculate sleep onset latency or sleep efficiency. In addition, the sleep diary is needed to identify artifact, such as a child sleeping in a moving vehicle (which will be scored as wake

by the device), as well as days that are not typical for reasons such as illness, vacation, or sleepovers. Finally, the sleep diary is useful in determining differences between parental report and actual sleep patterns. For example, a parent may believe their child is awake for multiple hours during the night, yet actigraphy consistently shows the child is only awake for brief periods during the night. Thus, parents, and children, if appropriate, need to learn how to monitor sleep patterns with the sleep diary (example provided in the Appendix A). However, if a family is unable to complete the sleep diary, there is still useful information that can be collected from the actigraphy study, including the child's average sleep onset time and sleep offset time, average sleep duration, and variability in sleep patterns.

Actigraphy studies should be a minimum of 72 h according to the CPT code; however, it is typically most useful for clinicians to have at least 1 week and preferably 2 weeks of data collection. This allows for the consideration of differences between weekday and weekend differences in sleep patterns, as well as a more likely representation of the child's typical sleep patterns. While the CPT code specifies that the device should be worn 24 h a day, for children with neurodevelopmental disorders, it may be important to remove the device at breakfast time and place it on the child again at dinnertime. While this will prevent the detection of daytime sleep, it will also prevent the device from becoming lost or damaged at school.

Actigraphy devices are typically worn on the non-dominant wrist, but alternate placements can be considered for children with neurodevelopmental disorders (e.g., sewn into a pocket on a sleeve, see Special Considerations section for more details). For some children who may not tolerate wearing the device, having them wear a wristwatch for a week or 2 prior to the actigraphy study can help acclimate them. Another solution for children who may be sensitive to the device on the wrist is to place it over a sleeve or cotton wristband.

While most devices provide automatic scoring, clinicians should manually score actigraphy to prevent errors in outcome variables. Manual scoring includes setting the reported bedtime and wake time based on the sleep diary and/or event markers, as well as selecting the appropriate scoring algorithm or sensitivity level appropriate for the age of the child [6]. Again, for clinicians interested in learning the many details on how to use actigraphy, the SBSM Guide [5] provides complete information on all aspects of actigraphy.

Evidence Base: Actigraphy in Children with Neurodevelopmental Disabilities

A growing number of studies have utilized actigraphy to measure sleep patterns and behaviors in children with neurodevelopmental disorders. In general, these studies have indicated good agreement between parent report of certain sleep variables, such as sleep onset latency and sleep length, and actigraphy data [7]. Additionally, actigraphy has been found to provide additional information about sleep patterns, above and beyond parent report. For example, one study found that children with ASD demonstrated compromised sleep quality on actigraphy, even in the absence of a parent-reported sleep problem [8]. Similarly, results from a recent meta-analysis suggest that actigraphy may detect altered or disturbed sleep patterns (e.g., greater sleep activity) in children with ADHD who do not necessarily present with a diagnosed sleep disorder or parent report of a sleep problem [9].

Actigraphy has also been found to be more sensitive to sleep onset latency, wake after sleep onset, and the number of night wakings after sleep onset relative to parent report via sleep diaries for children with ASD, developmental delay, and typically developing children [10]. In an effort to compare actigraphy with the "gold standard" PSG, Goldman [11] utilized both approaches simultaneously to measure sleep patterns in children with ASD. Results indicated strong concordance between actigraphy and PSG. However, this study also reported greater wake after sleep onset (WASO) as recorded by actigraphy. This study provided preliminary evidence that actigraphy provides a feasible and valid assessment of sleep in children with ASD.

However, the utility of actigraphy for capturing the frequency and duration of nighttime wakefulness in children, particularly those with neurodevelopmental disorders, remains unclear. While the Goldman [11] study found more actigraphic WASO, another study that compared actigraphy to video coding of sleep behavior (videosomnography) in children with ASD, developmental delay, and typically developing children found much different results [12]. In particular, actigraphy recorded an overall greater number of nighttime wakings than were observed via video recording. For example, actigraphy only recognized night wakings characterized by the child sitting up and looking around 27% of the time while recording the remainder of such awakenings as sleep [12]. Another study found that actigraphy may underreport the frequency and duration of motionless wakefulness (awake, but not moving) in children with ASD [13]. This is of particular concern given that children with neurodevelopmental disorders have been found to frequently lie awake quietly [8, 14]. As such, actigraphy may both over- and underestimate sleep and wakefulness in pediatric samples, including those children with neurodevelopmental disorders.

Although additional work is necessary to better enhance the specificity of actigraphy, particularly for identifying wakefulness, the above studies support the use of actigraphy as a viable and valid alternative for assessing certain sleep behaviors and patterns (e.g., sleep onset, sleep movements) in populations of children with neurodevelopmental disabilities.

Special Considerations

Importantly, children with neurodevelopmental disabilities often experience sensory sensitivities and discomfort. Indeed, prior research has indicated that as many as 33% of children with neurodevelopmental disorders have a difficult time tolerating actigraphy when administered via the standardized wrist placement [13]. Thus, efforts have been made to explore alternative actigraph placements in order to increase the feasibility and acceptability of such an approach with children with special needs. The standard placement of actigraphy is on the ankle for children under the age of 3 years, and on the non-dominant wrist for children over the age of 3 years [5]. However, Adkins [14] conducted a pilot study to examine the placement of the actigraphy device on the shoulder of children with ASD, as the shoulder and wrist move in the same plane of motion. The shoulder placement was well-tolerated by all of the children. Results also indicated good agreement between the wrist and shoulder placement, primarily for sleep onset latency. However, the concordance rates for total sleep time, sleep efficiency, and wake after sleep onset were lower. These researchers have continued to use shoulder placement for those children unable to tolerate the traditional actigraphy approach and have found high acceptance rates and scorable data associated with the use of the shoulder placement [14]. Although additional research validating the shoulder placement is needed, this is a promising alternative for those individuals sensitive to the standard wrist placement.

Another important consideration when using actigraphy with pediatric populations, particularly those children with neurodevelopmental disorders, is the role of the parent in helping to use the actigraphy device to produce valid and usable data. Indeed, Fawkes [15] noted the lack of empirical data examining optimal ways to work with and support parents in using actigraphy with their children. These researchers examined the utility of a manualized training to help parents of children with neurodevelopmental disabilities engage effectively with their child and the actigraphy device via discussions, demonstrations, quizzes, practice, and feedback. The importance of the child wearing the device every night was emphasized, as was the importance of accurate event marking. Results indicated greater adherence (for wearing the actigraphy device and completing concurrent sleep diaries) and higher concordance between actigraphy and sleep diaries for those families who received the structured actigraphy training [15].

Future Directions

The research described above suggests a growing evidence base for the use of actigraphy to measure sleep behaviors in children with neurodevelopmental disabilities, along with important considerations for implementation with special populations. However, science utilizing actigraphy with these pediatric populations is still in its infancy. Indeed, direct comparisons of actigraphy to PSG are needed to develop a more nuanced understanding of the validity and utility of this measurement approach with children with neurodevelopmental disorders. Furthermore, additional research is needed to validate alternative actigraph placements (e.g., shoulder) in this population. Although these alternative placements are often better tolerated than the standard non-dominant wrist placement, the extent to which the placement can be altered while still providing valid information about sleep patterns remains largely unknown.

Clinically, more work is needed in determining normative values for actigraphy in children with and without neurodevelopmental disorders. In addition, as new consumer wearable devices are flooding the market, their value for clinical practice remains to be determined. Initial research on the validity of these devices for differentiating sleep from wake has found mixed results [16, 17]. Another issue is the difficulty extracting data from most of the commercially available devices. However, if accurate sleep duration values are not necessary, it may be that commercially available devices provide useful information about sleep-wake patterns over multiple nights, at a lower cost to both the clinician and the family (i.e., if the device is lost). Finally, more work examining strategies for ensuring the appropriate use of actigraphy, such as manualized training about procedures for using actigraphs and corresponding sleep diaries, is necessary to support the use of actigraphy in real-world clinical settings.

Conclusions and Recommendations

The research summarized in this chapter supports the potential of actigraphy to provide critical information about sleep-wake patterns and behaviors for children with neurodevelopmental disabilities. Although this approach is not without limitations, actigraphy can often provide more detailed and clinically relevant information than can parent report alone, as highlighted in Emma's case example above. Actigraphy can provide supplemental information for

Case Vignette, Continued (See Appendix B for Full Report and Fig. 4.1 for Actigram)

Emma wore the actigraph for 14 nights, and the results showed that she had a somewhat prolonged sleep onset latency of 42 min, but with notable variability. She also had early sleep termination on four mornings. Despite an appropriate sleep opportunity of 10.9 h per night, she slept an average of only 8.4 h per night, with her sleep efficiency low at 77%. Parents reported brief nighttime wakings on most, but not all nights. Actigraphy found an average of almost 2 prolonged wakings (>10 min) per night, with a waking lasting more than 2.5 h on 4 of the 14 nights.

The results of this actigraphy study were discussed with her parents, highlighting the pattern of several short nights of sleep followed by two to three nights of long sleep. While asleep her sleep quality was good, but the delayed sleep onset and long night wakings resulted in the low sleep efficiency. The actigraphy study provided the foundation for discussing treatment options with the parents, including behavioral and pharmacological options to consolidate her sleep and address this refractory insomnia.

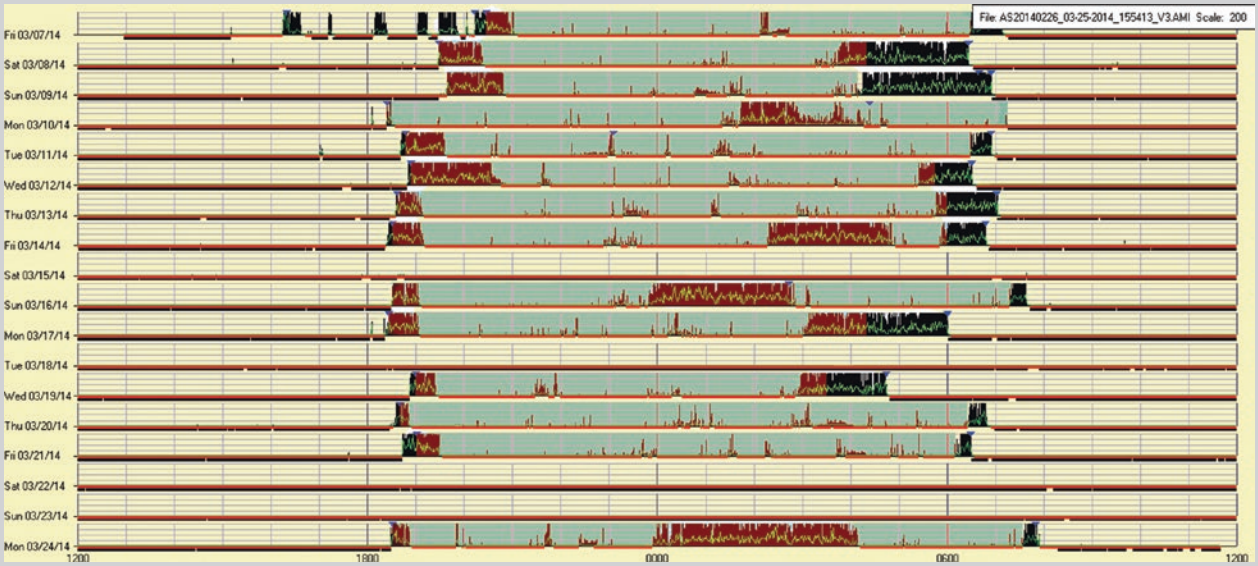

Fig. 4.1 Sample actigram. This graph represents the patient's sleep during the study. The dates are on the left, and the time is across the bottom, starting at noon, with midnight in the middle. The black sections are when the watch thought the patient was awake. The underlined sections are when the watch thought the patient was asleep. Shaded is the sleep period per sleep diary

parents who have difficulties reporting on child sleep behaviors and/or for children with limited verbal abilities. Importantly, actigraphy may offer a more feasible and affordable way to diagnose certain sleep disorders (e.g., insomnia) and track treatment response in both clinical and research settings. Actigraphy may also be a useful tool for comparing sleep data among individuals and populations in order to understand the specific sleep-wake patterns in children with neurodevelopmental disabilities. As such, actigraphy appears to be well-suited for examining sleep-wake patterns in children with neurodevelopmental disabilities in both research and real-world practice settings.

Appendix A (Table 4.1)

Table 4.1 Sample actigraphy sleep diary

Today's date	**Tuesday 3/6/12**							
Did you/your child remove the actigraphy today? If yes, what time?	Yes 7:30 p.m.							
Did you/your child nap today? If yes, what time?	Yes 3:15 p.m.							
Did you/your child sit quietly for a long time? If yes, what time?	No							
What time did you/your child get into bed last night?	8:00 p.m.							
What time did you/your child try to fall asleep?	8:15 p.m.							
How long did it take you/your child to fall asleep?	15 min							
How many times did you/your child wake up during the night?	2							
How long (total) were you/your child awake during the night?	1 hour 10 min							
What time did you/your child wake up this morning?	7:00 a.m.							
What time did you/your child get out of bed this morning?	7:15 a.m.							
Comments	I had a cold							

Please complete the shaded part before bed and the white part in the morning after waking up

Appendix B

Sample Actigraphy Report

Emma Jones is a 4-year-old girl with WAGR syndrome, a genetic condition characterized by intellectual disability, visual impairments, and tumors of the kidneys and gonads and commonly associated with anxiety, attention-deficit/hyperactivity disorder (ADHD), and ASD. Emma has a history of difficulties initiating sleep, prolonged nocturnal awakenings, and/or early sleep termination. An actigraphy study was ordered to evaluate Emma's sleep patterns, including sleep onset time, sleep onset latency, night-waking frequency and duration, sleep offset time, and sleep efficiency.

Emma was asked to wear an Ambulatory-Monitoring Sleepwatch actigraph for 17 days (although she only wore the device 14/17 days), and her parents kept a concurrent sleep diary. This report contains an overall summary. Attached is the actigram, giving a picture of the full actigraphy study.

Summary of Overall Sleep Patterns

Per her parents, Emma's average bedtime (time when she attempted to fall asleep) was 7:52 pm. Actigraphy found a sleep onset time of 8:35 pm. Emma's parents reported an average wake time of 6:46 am, with actigraphy showing her average wake time to be 6:30 am. Notably on four mornings, Emma had early sleep termination (waking between 3:51 am and 5:09 am).

Emma's average sleep onset latency was somewhat prolonged at 42.4 min, with a sleep onset latency above 30 min on 10 of the 14 nights. There was notable variability in her sleep onset latency, with six nights between 30 and 50 min, and four nights greater than 50 min.

Overall Emma had an average sleep opportunity of 10.9 hours, with her sleeping an average of only 8.4 h. Emma's sleep efficiency (actigraphy time sleeping divided by reported time in bed) was low at 77% (normal above 80%). Again, significant variability was found with her sleep efficiency, with three nights below 70% and five nights 85% or higher.

Parents reported an average of 0.3 night wakings, estimating these wakings were approximately 1 h each. However, by actigraphy Emma averaged 1.9 wakings per night (>10 min), with a range of 0–3 wakings per night. Notably, on 4 of the 14 nights Emma had a prolonged waking greater than 150 min (or 2.5 h). These prolonged night awakenings are highly abnormal.

Summary and Recommendations

Emma is a 4-year-old girl with WAGR syndrome and a history of difficulties initiating and maintaining sleep. Prior to this study, Emma began taking small doses of melatonin both at dinnertime and bedtime, which her parents reported has been helpful with sleep initiation. Parents also reported that in general Emma seems to be sleeping better than before. However, this actigraphy study shows that Emma continues to experience prolonged nighttime awakenings approximately twice a week, in addition to early sleep termination approximately twice a week. Subsequently, Emma will have about two to three nights per week where she sleeps 9.5–10.5 h

At this point it is not clear whether Emma or her family would benefit from additional pharmacological treatment for her sleep issues. Behaviorally the parents have worked on sleep training, and now Emma is able to fall asleep at bedtime independently and return to sleep independently following nighttime awakenings. Parents were not aware of all of Emma's nighttime awakenings as she no longer cries every time she wakes but instead plays quietly, sometimes even singing or laughing.

I discussed with Emma's parents the importance of monitoring Emma's sleep and daytime functioning, and if one or both should significantly change, then a repeat actigraphy study may be indicated to help determine the need for additional treatment.

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Part II

Sleep Disorders

Insomnia

5

Jennifer A. Accardo

Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
CBT-I	Cognitive behavioral therapy for insomnia
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, 5th edition*
DSM-IV-TR	*Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision*
EEG	Electroencephalography
ICSD-3	*International Classification of Sleep Disorders-3rd edition*
IEP	Individualized Education Program
NDD	Neurodevelopmental disabilities
OSA	Obstructive sleep apnea
REM	Rapid eye movement

Case Vignette

Jeremiah is a 5-year-old boy who is in Early Childhood Special Education and has an Individualized Education Program (IEP) on the basis of developmental delay. His mother estimates he thinks more like a 3-year-old. She brings him to clinic for evaluation of his chronic sleep problems. He started waking early in the morning at 2 years of age, and sleep has gotten progressively worse since then. He has a set bedtime routine which unfolds starting at 6:30 PM, such that he is in his bed by 7:15–7:30 PM. He usually falls asleep after an hour or more. Sleep onset takes 3–4 h once a week, though occasionally he dozes off within 5 min. He tosses, turns, and whispers to himself, falling asleep with his mother seated in a chair nearby. One to 4 h later, he migrates to his mother's bed, fully awake and cheerful. He is in constant motion in the bed both before and during sleep, and she traded her queen size mattress for a king size to give him more space. He has nightly noisy breathing and occasional gasping during sleep. He is not yet toilet trained. Jeremiah wakes for the day 4–5 AM, in a good mood, and wakes his mother. His schedule is the same on weekends as on weekdays. He sleeps on the lengthy bus ride home from school, and she sees him as being tired all the time. He has dark circles under his eyes, rubs his eyes, and is "droopy." He gets overwhelmed and frustrated easily. His mother would like him to get more restful sleep and maybe sleep in a little later.

Defining the Problem

The problem of insomnia, although discussed in specific here, permeates the field of sleep in children with neurodevelopmental disabilities. The reader must forgive the frequent cross-referencing of other chapters in an effort not to rewrite the entire book in microcosm.

The prevalence of insomnia is 10–30% in children, higher among children with neurodevelopmental disabilities, with estimates varying based on how insomnia is defined [1]. Families may believe that the term has a highly technical definition and shy away from using it. In fact, insomnia refers to difficulty falling asleep, difficulty staying asleep, waking too early, getting poor quality sleep, or any combination of the above. However, the term denotes more than simply inadequate sleep:

J. A. Accardo
Departments of Pediatrics and Neurology, Virginia Commonwealth University School of Medicine, Richmond, VA, USA
e-mail: jennifer.accardo@vcuhealth.org

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ICSD-3 Diagnostic Criteria for Insomnia [1]

Chronic Insomnia Disorder

Criteria A–F must be met

(A) The patient reports, or the patient's parent or caregiver observes, one or more of the following:
1. Difficulty initiating sleep
2. Difficulty maintaining sleep
3. Waking up earlier than desired
4. Resistance to going to bed on appropriate schedule
5. Difficulty sleeping without parent or caregiver intervention

(B) The patient reports, or the patient's parent or caregiver observes, one or more of the following related to the nighttime sleep difficulty:
1. Fatigue/malaise
2. Attention, concentration, or memory impairment
3. Impaired social, family, occupational, or academic performance
4. Mood disturbance/irritability
5. Daytime sleepiness
6. Behavioral problems (e.g., hyperactivity, impulsivity, aggression)
7. Reduced motivation/energy/initiative
8. Proneness for errors/accidents
9. Concerns about or dissatisfaction with sleep

(C) The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (i.e., enough time is allotted for sleep) or inadequate circumstances (i.e., the environment is safe, dark, quiet, and comfortable) for sleep.

(D) The sleep disturbance and associated daytime symptoms occur at least three times a week.

(E) The sleep disturbance and associated daytime symptoms have been present for at least 3 months.

(F) The sleep/wake difficulty is not better explained by another sleep disorder.

Short-Term Insomnia Disorder

Criteria are the same as for chronic insomnia disorder, with a single exception: instead of meeting criteria D and E, above, the sleep disturbance and associated symptoms have been present for less than 3 months.

Other Insomnia Disorder

This diagnosis is reserved for individuals who complain of difficulty initiating and maintaining sleep and yet do not meet the full criteria for either chronic insomnia disorder or short-term insomnia disorder. In some cases, the diagnosis may be assigned on a provisional basis when more information is needed to establish a diagnosis of one of the two. It is expected that this diagnosis will be used sparingly, given its nonspecific nature.

Both the International Classification of Sleep Disorders, 3rd edition (ICSD-3) and the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) emphasize dissatisfaction with sleep quantity or quality as the defining criterion [2]. The DSM-5 elaborates that in children, insomnia "may manifest as difficulty returning to sleep without caregiver intervention." [2] The ICSD-3 further notes tactfully, "Parents….may develop negative feelings towards the child who disrupts their sleep and demands attention overnight" [1]. In pediatrics, insomnia often implies impairment not only to the child himself but sleep disruption and resulting problems for parents and siblings. When a child wakes during the night, frequently a parent does, too. Yet many parents, such as Jeremiah's mother, have modest goals for their children's sleep.

Types of Insomnia

Although both the DSM-5 and ICSD-3 discuss insomnia's manifestation in children, at least briefly, there are no specific criteria for pediatric insomnia published in either nosology but, rather, diagnostic criteria for insomnia affecting both adults and children [1, 2]. In a triumph of lumping over splitting, nomenclature of primary and secondary insomnia from previous editions of the ICSD was abandoned, with the

idea that although an insomnia may arise "secondary" to some other condition, in becoming chronic, it often takes on a life of its own with more similarities to "primary" insomnias than differences [1]. Past primary insomnia subtypes (e.g., psychophysiologic insomnia, paradoxical insomnia, etc.) were also jettisoned, again due to concerns about overlap with each other within the larger category of primary insomnia [1]. As per the DSM-5, "The weight of available evidence supports the superior performance characteristics (interrater reliability, as well as convergent, discriminant, and face validity) of simpler, less-differentiated approaches to diagnosis of sleep-wake disorders," and further, "The field of sleep disorders medicine has progressed in this direction since the publication of DSM-IV" [2].

Behavioral Insomnias of Childhood

Discussion of what have been called the behavioral insomnias of childhood falls under the category of chronic insomnia [3]. Their identification under this more specific heading has implications for treatment [4]. They are common and can be quite satisfying to address. Limit-setting type will sound familiar to any parent who hears a bedtime request for just one more drink of water, one more story, or one more hug. These are the children who come for "curtain calls" and push the limits to see what they can get away with. Sleep-onset association disorder type may be less obvious. A key question here is, who is in the room with the child when he falls asleep (and who subsequently exits, stage left)? A broader question, though, is what changes in the child's environment between the time when he falls asleep and when he wakes up during the night. Parents may need to hear that everyone wakes briefly during the night, multiple times an hour, and children expect that they will wake up with the same conditions present as when they fell asleep—whether that is with another person present, or with a light or television on, and so forth. When the original conditions under which children fall asleep are no longer met when they wake, disorientation may prolong the waking. Further, the child may become what one parent described as "a mommy and daddy-seeking missile," rocketing down the hall to find an absent parent. A child will usually come to attention on the basis of persistent night wakings rather than on the basis of how he falls asleep. Sleep-onset associations are so common that the ICSD-3 cautions against identifying their presence as a disorder unless they reach a threshold of being "highly problematic or demanding" to deliver, require frequent adult intervention to enact, or result in significantly delaying sleep in their absence [1]. Jeremiah, above, has a sleep-onset association disorder as evidenced by his nightly migrations, made more intense by his difficulties falling asleep in the first place. Turnbull et al. state that "Children with conditions that involve behavior problems and difficulty with self-regulation, notably attention-deficit/hyperactivity disorder (ADHD) and autistic spectrum disorder (ASD), present with behavioral sleep problems more frequently than children within the general population, particularly daytime sleepiness (ADHD) and shorter overall sleep duration, reflecting difficulty settling to sleep, night waking, and early morning waking (ASD)" [5].

A Digression on Co-sleeping

Closely related to the topic of sleep-onset associations, co-sleeping requires a tactful approach. This involves children sleeping in close proximity to parents, with a subset sharing their beds. Although there are "lifestyle" co-sleepers, parents who are adherents of attachment parenting and who choose a family bed, and cultures in which co-sleeping is normative, many families of children with NDD adopt co-sleeping of perceived necessity or desperation [6, 7]. Often parents in this situation are present when their child falls asleep but leave the room afterward. Parents may not be forthcoming about this or admit with embarrassment that they "know they shouldn't." This is a situation to be handled compassionately. Clinicians may guide parents to acknowledge that there are things they have done in order to survive their child's sleepless nights, and now that they find those strategies are creating other problems (the child who depends on the parent not only to fall asleep but also back to sleep), they can use this knowledge to direct change. Interventions for sleep-onset associations are discussed in detail in Chap. 28 but have the advantage of focusing on behavior changes at bedtime, when most parents are still conscious, rather than at the late hours during which children often wake and migrate, when parents are not at their most motivated or alert.

There are special circumstances surrounding co-sleeping which deserve further comment. One is epilepsy, a condition reviewed in detail in Chap. 20. Some parents of children with epilepsy prefer to co-sleep with them in the event that they seize overnight and require immediate medical attention [8]. This is an under-recognized situation. Parents should address this with the doctor treating their child's epilepsy, to determine whether the seizures are severe or brittle enough to be a credible threat, requiring parental presence, in which case co-sleeping throughout the night may be indicated. Even if parental presence is not deemed medically necessary, families may be difficult to dissuade from some degree of co-sleeping. They can be made aware that the inconsistent message of presence at bedtime rather than throughout the night can contribute to sleep disruption. A variant on this is behavioral necessity: the parent who stays in the room with a child who could otherwise be expected to engage in unsafe or destructive behavior while unsupervised. Flooding bathrooms, playing with knives, and smearing feces are all

behaviors which have inspired some degree of co-sleeping or, at least, the development of sleep-onset associations produced by parents staying in the room to monitor. Another powerful circumstance is parental guilt. A parent might feel guilt over her son having an NDD and then oblige him in his preference to stay with an adult at bedtime. Although parents may understand the idea of gradually moving out of their child's bedroom at night in order that he learns to fall asleep independently and hence back to sleep more independently, they may not be able to accept setting a limit of any sort, thus dooming typical behavioral treatments. Further, parents who feel this way are not always forthcoming about these feelings.

Other Types of Insomnia

Other types of insomnia described in past diagnostic schemes still have traits that can be seen in some children with disabilities. Psychophysiologic insomnia, discussed as common among adults, implies a kind of "performance anxiety" insomnia. People "strive hard" to sleep and fail, experiencing distress in being unable to fall asleep, which they come to associate with being in their beds, and setting up a vicious cycle of placing greater pressure on themselves to fall asleep [9]. This sort of scenario can be identified in older, verbal children with the ability to communicate this anxiety. What was called idiopathic insomnia was most typically diagnosed in adults, with the notation that it often had its onset in childhood but was less well described in children, as it was a diagnosis of exclusion [9].

Some researchers have asked, "Is insomnia a symptom or a disorder?" [10]. In terms of subtyping, insomnia related to other medical or psychiatric conditions, a form of "secondary" insomnia, seems somewhat self-explanatory. Even if the diagnostic category has become moot, one could still ask the question of whether it is sufficient to explain insomnia as being due to a diagnosis of, say, attention-deficit/hyperactivity disorder (ADHD) or autism when sleep problems are not universal among these conditions [11]. Some of the features of autism cited as diagnostic criteria in the DSM-5 include failure to respond to social interactions, hyperreactivity to sensory input, insistence on sameness, inflexible adherence to routines, and ritualized patterns of verbal or nonverbal behavior [2]. As omnipresent as autism is, these features may be present to greater or lesser extents in many other disabilities as well, if less pathognomonic—and similarly disruptive to sleep. Likewise, depression and anxiety are common, yet can present atypically in children with all kinds of neurodevelopmental disabilities, and are strongly associated with sleep disruption, as treated in more detail in Chap. 24, on psychiatric conditions and sleep. When these comorbid conditions go unrecognized, insomnia may persist.

Bruni et al. hypothesize that "The absence of a specific symptom-based classification of insomnia for children may explain the inadequacy of the screening for sleep problems, as well as the underdiagnosis of insomnia in childhood" [12]. They undertook structured parent interviews for 338 boys aged 6–48 months who presented with insomnia symptoms and then used latent class analysis of this group to identify three pediatric insomnia phenotypes: difficulty falling asleep, restless sleep, and night wakings (17%); early morning wakings (21%); and a combination of difficulty falling asleep and night wakings (62%). It is hoped that developing more specific classifications such as these will aid in understanding the pathophysiology of insomnia particular to children and, ultimately, tailored treatments.

Evidence Base

Children with neurodevelopmental disabilities (NDD) have sleep problems more frequently than their typically developing peers. This is the case almost across the board for different types of NDD, including ADHD and autism. Sleep disruption is common enough in children with ADHD that it used to be part of the diagnostic criteria, until it was dropped as not especially specific to the diagnosis [13]. It is far and away the most frequent sleep disorder in children with autism [11]. One study carefully characterized sleep in a group of 59 children with autism, of whom 39 were assigned the ICSD-2 insomnia diagnoses [14]. These percentages totaled >100%, as participants often met criteria for more than one type of insomnia: behavioral insomnia of childhood sleep-onset association type, 31%; behavioral insomnia of childhood limit-setting type, 15% (of whom 1/3 also had inadequate sleep hygiene); other sleep disorders (sleep-disordered breathing and night terrors) potentially related to insomnia symptoms, 10%; other medical conditions (asthma and gastroesophageal reflux—all with behavioral insomnias of childhood) potentially related to insomnia symptoms, 15%; and medications with potential sleep-disrupting side effects, 23%. An additional 28% had "adequate sleep hygiene, strong bedtime routines, fell asleep by themselves, and had no identifiable medical condition that might cause sleep disturbances," such that they were assigned the diagnosis of insomnia due to a mental disorder: pervasive developmental disorder (a category used in prior editions of the DSM encompassing autistic disorder, Asperger disorder, and Rett syndrome). Yet even among children with autism, it is still underdiagnosed [15]. There is research evidence for a higher than typical prevalence among children with intellectual disability, learning and language disorders, epilepsy, and anxiety, as discussed throughout this book—but frequently, studies of various NDD describe sleep *problems* rather than

sleep disorder *diagnoses*, making the actual prevalence of insomnia often elusive.

Spielman et al. propose a 3-P model of how insomnia develops in adults, discussed in detail in Chap. 11, on autism [16]. People have baseline *predisposing* factors for insomnia and may be pushed over their thresholds by *precipitating* stressors, such as illness, grief, or other stress. For some people, sleeplessness resolves with the resolution of this acute stressor, but for others, *perpetuating* factors then maintain the sleepless state as habitual. Whether predisposing or perpetuating, a hyperarousal state has been connected with insomnia, and hyperarousal has been investigated specifically in children with autism as contributory [17]. It has been defined as "heightened physiologic, affective, or cognitive ability, which interferes with the natural 'disengagement from […] the environment' and decreases the likelihood of sleep" [18]. Levels of arousal can be documented using EEG, heart rate variability, cortisol levels, skin conductance, or questionnaires, and the distinction between arousal and hyperarousal is not clearly drawn [18]. Intriguingly, there is the suggestion of some physiologic underpinning even in children with behavioral insomnias in terms of sensory profile [19].

In terms of physiology of sleep, there is no specific area of the brain which lesioned destroys sleep, and no single responsible neurotransmitter yet identified, such that sleep "is better understood as a broad system-wide phenomenon" [20]. A variety of genetic risk factors for insomnia have been identified or are emerging. A study of 8- to16-year-old twins indicated moderate heritability for insomnia and suggested "genetic factors related to the etiology of insomnia overlap with those related to depression and anxiety" [21]. Genome-wide association studies have begun to unearth the genetics of this condition, revealing significant heritability, potential gene loci, and unsurprising associations with major depressive disorder and diabetes mellitus type 2 [22]. Morningness chronotype (circadian preference) and subjective well-being were negatively correlated with insomnia [22].

Trials of experimental sleep restriction, and conversely, sleep extension, may represent our best hope of looking more stringently at consequences of pediatric insomnia. It is hard to replicate the chronic experience of insomnia experimentally and, indeed, frowned upon by Institutional Review Boards for research in children. Sadeh et al. used "modest" changes in sleep in grade school children (setting bedtime temporarily 1 h later to restrict sleep or earlier, to extend it, for three nights at a time) to assess effects of sleep on neurobehavioral function [23]. These manipulations resulted in 35 min more and 41 min less on average, respectively, of sleep, with the recognition that for some subjects, there was no significant change in sleep duration. Those who did successfully extend their sleep showed improvement on a continuous performance task, reaction times, and memory tests. A study using similar methods of sleep extension and restriction found significant improvements in alertness and emotional regulation with the extension condition and corresponding decrements with restriction [24]. When a child with typical development is sleep deprived, she may have some cognitive and emotional reserves to draw on with which to temporarily compensate; a child with NDD may function with fewer reserves such that the impairment of sleep deprivation has more obvious effects. He may be running on all cylinders during an intense school and therapy schedule such that any additional demand (continued function on inadequate sleep) creates an unacceptable drain on his system.

The implications of having a child who doesn't sleep can be significant for families. Parents caring for children and adolescents with chronic medical illnesses, including those who are technology dependent, endorse frequent sleep disruption, although studies have often lacked control groups [25]. In a study specifically comparing parents of children with autism to parents of typically developing children, mothers of children with autism woke an average of 37 min earlier and recorded 51 min less sleep nightly [26]. Anecdotally, consequences for parents can include not only frustration but motor vehicle collisions due to parental sleep deprivation, concerns about eviction due to rambunctious behavior in the family apartment late at night, and departure from a job due to chronic daytime drowsiness. Yet a short behavioral sleep intervention for children with ADHD succeeded in improving subjects' sleep, quality of life, behavior, and daily function along with showing modest benefits to ADHD symptoms failed to significantly affect scores of parental anxiety, depression, and stress [27].

Differential Diagnosis

A barrage of questions comes to mind in evaluating a child for insomnia. Is this a child who can't sleep—or won't sleep? Is this a sleep problem, or does it rise to the level of a diagnosable sleep disorder? Does this child simply need less sleep than his peers? Is the challenge environmental or one of inappropriate expectations? Does this problem originate from some other sleep disorder? Does it originate from some other medical or psychiatric condition? Finally, is this a sleep disorder that affects the child's life or a more pervasive life disorder that also manifests in sleep symptoms?

The challenge of competing priorities is perhaps a variant on poor sleep hygiene. To an extent, sleep is voluntarily suppressible. Children whose parents work very late shifts, for example, may stay awake in order to see them and spend time with them. Some older children and adolescents may preferentially stay awake during the night in order to enjoy time on their own without interference from families (and subsequently avoid school by sleeping through it).

More specifically, some children effectively sleep deprived themselves to gain electronic access. Bedroom media access is associated with shorter sleep, specifically due to prolonged sleep latency when electronics are part of the bedtime routine [28, 29]. Anecdotally, a common scenario is for children to appear to prolong their wakings in order to engage in obsessive pursuits, often involving electronics. A poorly rested school-aged child with ADHD might insist on waking earlier than needed for school in order to spend a block of time online before getting his bus. The pernicious influence of electronics on sleep cannot be overstated. There was a time when clinicians could remind parents that they grew up just fine without TVs (and DVD players, and game systems) in their bedrooms, and their children could, too; that time seems to be gone. Parents often feel helpless about setting limits on screens in the face of child resistance. Alternatively, they may appear blasé as they themselves endorse "needing" to fall asleep to television. It used to seem like children with disabilities were disproportionately fascinated by electronics compared with typically developing peers; this too seems no longer the case given how incredibly pervasive screens are in our society.

Voluntary, and involuntary, sleep deprivation may be achieved via caffeine, "the most widely consumed psychoactive substance in the world," which lengthens time to sleep onset and reduces total sleep, as well as interfering with subjective sleep quality and slow-wave activity [30]. Families do not consistently connect the dots between a child's habit of drinking iced tea throughout the day and late bedtime, and it is incumbent on the practitioner to request that this be addressed. Anecdotally, many adults do not recognize that caffeine is present in green tea and sodas such as certain root beers or ginger ales, and we cannot assume that children are not drinking coffee [31]. Of course, other non-prescription substances can affect sleep as well and should be asked about more frequently, especially in adolescents, whether or not they have disabilities. Likewise, prescription medications such as stimulants prescribed for inattention and hyperactivity can prolong sleep latency and shorten sleep duration [32]. Some clinicians have questioned whether stimulants' interference with sleep results more from rebound after these medications wear off rather than directly from drug effects; the use of a late dose of short-acting stimulant to help children organize themselves sufficiently for bedtime is sometimes proposed clinically and has not been extensively studied.

Many children have sleep problems, broadly and variably defined. Much published literature on sleep in children with disabilities is questionnaire-based; often using screening questionnaires such as the popular Children's Sleep Habits Questionnaire (CSHQ) [33]. But the developers of these instruments never claimed they were diagnostic. Their use identifies symptoms and parental concerns in children without clarifying whether insomnia is present. The CSHQ has the added feature of enabling parents to endorse whether items to which they respond actually pose a problem—this can be quite helpful when indeed they complete this portion of the questionnaire. Some children, particularly those with ADHD, may have night-to-night variability in their sleep problems, such that it becomes important to establish whether the duration and consistency of sleep issues with sleep onset and/or maintenance merit identification as insomnia [34].

As noted above, in order to qualify for a diagnosis of insomnia, one must have an adequate opportunity for sleep [1]. There are many situations which result in inadequate sleep which are not intrinsic to the child. Early school start times can cut into sleep in the morning, necessitating early wakings [35]. Alternately, early wake times even in the absence of early school start times can occur. Idiosyncratic daycare arrangements in which parents leave very early so that children must get ready to stay with their grandparents or a sitter prior to leaving for school also disrupt sleep and are not amenable to usual insomnia therapies.

In the world of sleep medicine, other sleep disorders must always be queried. Obstructive sleep apnea (OSA) may not keep children from falling asleep but has the potential to disrupt sleep and affect sleep quality. This should always be screened for, even with a presenting complaint of sleeplessness, due to the potential for overlap [36]. What is one to do with the restless sleeper? Restless legs syndrome is difficult to diagnose in children but may delay sleep onset, as well as provoke night wakings and diminish restful sleep. Restless legs syndrome and the related periodic limb movement disorder are discussed in depth in Chap. 10.

An interesting question to pose to parents is whether children who "wake" during the night are in fact not fully awake, as parasomnias may require a somewhat different approach and interventions than insomnia (documented in detail in Chap. 7). A child in this category may appear somewhat awake but require far less parental intervention than the true night-waker. Classically, the non-REM parasomnias such as sleepwalking and night terrors should not affect sleep quality, but anecdotally, parents of some children with disabilities report impact on daytime behavior. Other sleep and medical disorders may trigger parasomnias by promoting partial arousals, and obstructive sleep apnea, restless legs syndrome, gastroesophageal reflux, and anxiety are potential culprits which are all common among children with disabilities [37].

Other medical disorders can also interfere with sleep and perhaps better account for sleeplessness [38]. The itchiness of atopic dermatitis (or scabies, or bedbugs) is difficult to sleep through [39]. Allergic rhinitis also affects sleep quality

[40]. Gastroesophageal reflux may worsen during the night, as lying flat eliminates gravity as protective against reflux. There may be fewer distractions from the discomfort of dental caries or chronic or severe constipation. Children with disabilities affecting their expressive language may be particularly vulnerable to discomfort that they cannot convey to adults.

Healthy sleep habits are discussed in detail in Chap. 28. When discussing sleep hygiene, it is important to stress to parents that practicing good sleep habits is necessary, but not always sufficient, to improve their child's sleep. This is particularly crucial for the parents who report that they have tried working on better sleep habits for their children (or "tried everything") without results and abandoned the project. Good sleep habits are required groundwork, but not necessarily a stopping point, for better sleep, and additional interventions without this foundation may be hobbled.

Circadian sleep disorders are addressed in detail in Chap. 9. Suffice it to say that a shifted schedule can give the appearance of insomnia, excessive daytime sleepiness, or both. However, circadian tendencies are also worth addressing. Some children have chronotypes that are shifted earlier, or later, than typical for age without reaching the level of a disorder [41]. In a study comparing measures of chronotype in prepubertal children, morningness/eveningness tendencies did not deviate significantly from a normal Gaussian distribution in prepubertal children [41]. Young children tend to be shifted earlier. When parents share the expectation (or hope) that their preschooler should wake up well after 6 AM, this issue is usually better addressed by time, and the onset of formal education, than by medication. Likewise, children who reach puberty experience a delayed circadian rhythm, shifted to later bedtimes and wake times, that is biological as well as behavioral [42]. Their need for a somewhat later bedtime may be physiologically appropriate rather than obstinate or pathological. The young adult with spastic quadriplegic cerebral palsy who arrives from the group home with the staff's complaint that he takes a long time to fall asleep, even with medications, should perhaps not be put to bed at 7 PM for their convenience.

Evidence for recommendations for required sleep times and duration is imperfect. Recommendations remain controversial, with some authors suggesting that "no matter how much sleep children are getting, it has always been assumed that they need more" [43, 44]. This has not stopped the National Sleep Foundation and the American Academy of Sleep Medicine, among others, from publishing guidelines for recommended sleep durations for different age ranges summarized in Table 5.1 [45–47].

All published recommendations, further, apply to typically developing children; there is not much to reflect whether children with various NDD have similar requirements. Research on short sleep and its consequences has become popular in adult sleep medicine, though that has not necessarily translated down to pediatrics yet. Adult "short sleepers" studied likely represent both people with a genuinely shorter sleep need and also those who are simply not getting enough sleep, a heterogeneous group [48]. Adolescents in particular likely still need more sleep than adults, and most are getting much less than their parents think they need to function [49].

A more common scenario that has triggered a national conversation is developmentally inappropriate school start times for middle and high school students [35]. Students who have undergone the circadian shift to later bedtimes documented in puberty have difficulty with the earlier wake times required in many communities for middle and high school. The American Academy of Pediatrics has endorsed school start times no earlier than 8:30 AM for this age group [50]. Grassroots advocacy groups such as Start School Later, in partnership with sleep medicine researchers and clinicians, continue to lobby school districts around the country [35]. Anecdotally, sometimes students who attend schools out of their home districts, either public or private, to receive appropriate special education services, face a lengthy bus ride that requires them to wake excessively early regardless of a reasonable school start time. Long daytime naps to compensate for early wake times should be discouraged.

Table 5.1 Summary of total recommended sleep duration over 24 h, including naps, for children

Age	Recommended (hours)	May be appropriate[a]; uncertainty[b] (hours)	Not recommended (hours)
Newborns (0–3 months)[a]	14–17[a]	11–13, 18–19[a]	<11, >19[a]
Infants (4 months to <1 years)	12–15[a]; 12–16[b]	10–11, 16–18[a]; 16–18[b]	<10, >18[a]; <12, ≥18[b]
Toddlers (1 to <3 years)	11–14[a, b]	9–10, 15–16[a]; 10–11, 14–16[b]	<9, >16[a];<10, >16[b]
Preschoolers (3 to <6 years)	10–13[a, b]	8–9, 14[a]; 13–14[b]	<8, >14[a]; <10, >14[b]
School-aged children (6–13 years)[a]; (6 to <13 years)[b]	9–11[a]; 9–12[b]	7–8, 12[a]; 12–13[b]	<7, >12[a]; >13[b]
Teenagers (14–17 years)[a]; (13–18 years)[b]	8–10[a, b]	7, 11[a]	<7, >11[a]; <8, >10[b]
Young adults (18–25 years)[a]	7–9[a]	6, 10–11[a]	<6, >11[a]

[a]Hirshkowitz et al. [45]
[b]Paruthi et al. [47]

One important question to ask about a sleep complaint is whether it represents a sleep disorder, or a life disorder that manifests in sleep problems, among other things. For the young child not yet in school, with no set schedule other than the late-skewed schedule of her family, inconsistent discipline, and near-constant electronics exposure, the standard interventions of pediatric sleep medicine will be inadequate. One might ask why a child with global dysregulation of behavior should be expected to adhere to a bedtime routine and sleep peacefully through the night, when no other elements of her daily routine run smoothly. A combination of enrollment in preschool, necessitating a more consistent wake time, and behavioral therapy to reinforce structure and good habits may be a better start. Chaotic family environments are frankly challenging.

Guidelines

There are few guidelines available for identification and treatment of insomnia among children, let alone children with NDD. The American Academy of Sleep Medicine practice parameters for behavioral treatment of bedtime problems and night wakings in infants and young children studiously avoid the use of the term "insomnia," though noted that longitudinal research suggested that some infant sleep problems become chronic [4]. These guidelines support behavioral interventions as effective. The Autism Treatment Network and National Initiative for Children's Healthcare Quality collaborated to develop a clinical practice pathway on evaluation and treatment of insomnia in children with autism, acknowledging the paucity of research, and ultimately this document stands as one of the only pieces of consensus clinical guidance on pediatric insomnia in any condition [38]. This is reviewed at greater length in Chap. 11.

In terms of evaluation, based on guidelines developed for adult sleep medicine, a detailed history remains the gold standard [51]. Actigraphy may be indicated as an adjunct to a detailed history, physical examination, and subjective sleep diary (which, in children or young people with NDD, may be patient or parent-recorded) to assist with diagnosis and assessment of severity or to guide diagnosis with patients and families who might otherwise unable to provide an accurate account of their sleep patterns [52]. Polysomnography is not routinely indicated in the evaluation of insomnia in the absence of symptoms of sleep-disordered breathing or movement disorders [51]. Nor is other laboratory or radiographic testing recommended routinely in the absence of symptoms of other comorbid disorders [51].

Treatment

Behavioral treatments for sleep can be effective for children with NDD as well as typically developing children, and specific recommendations are described in detail in Chap. 28. Delivery of these treatments, given a paucity of trained clinicians, is a challenge. There is evidence that a standardized pamphlet alone is not adequate as treatment for childhood insomnia and has been proposed as a control condition for studies (perhaps a caution to busy practices dispensing educational handouts) [53]. Cognitive behavioral therapy for insomnia (CBT-I) is a highly effective treatment for insomnia in adults involving not only sleep hygiene education but also stimulus control instructions and sleep restriction therapy [54]. Stimulus control aims to reinforce the association between the bed and sleep, retraining the brain away from "undesirable associations such as wakefulness, frustration, and worry" [51]. Sleep restriction compresses the time in bed into a deliberately shorter duration, increasing sleep drive and consolidating sleep [51]. Elements of adult-style CBT-I may have applications for older children and adolescents with cognition in the average range, likely with adaptations [55, 56]. Interestingly, the effectiveness of CBT-I among adolescents as well as adults is not limited to psychophysiologic insomnia but extends also to what was formerly known as "secondary" insomnia, insomnia with comorbid medical or psychiatric conditions [54, 57]. This effectiveness of the same treatment across traditional subtypes actually led to the conflation of the so-called primary and secondary insomnias. Adaptations for pediatrics, including for children with NDD, are being developed. The Zurich 3-step method, described by Oskar Jenni's group, is to some extent a pediatric variation of this [58]. It involves educating parents about regular sleep-wake rhythms (the circadian process regulating sleep), adjusting bedtimes to meet individual sleep needs (the homeostatic process regulating sleep), and the use of strategies that encourage the child to fall asleep on his own. These steps yielded significant improvements in nocturnal wake duration, sleep duration, variability of sleep onset and offset, and parent ratings of internalizing and total behavior problems.

With the caveat of the brochure study above, it can be helpful to provide suggestions as to further reading for some families. One may do this not only as treatment but potentially as prevention for children at risk who do not yet have sleep problems. Table 5.2 highlights a few favorite recommendations and is by no means a comprehensive listing.

The Sleep Toolkit educational materials freely available on the Autism Speaks website have relevance for children with conditions other than autism as well and detail what a bedtime routine should accomplish as well as sleep needs and the rationale for encouraging children to sleep independently [59].

Table 5.2 Selected resources for use with families

Title	Author	Year	Audience
Sleep Better!: A Guide to Improving Sleep in Children with Special Needs	M. Vincent Durant	2013	Parents of children with NDD
Solving Sleep Problems in Children With Autism Spectrum Disorders: A Guide for Frazzled Families	Terry Katz and Beth Malow	2014	Parents of children with ASD
Take Charge of Your Child's Sleep: The All-In-One Resource for Solving Sleep Problems in Kids and Teens	Judith Owens and Jodi Mindell	2005	Parents of children with ADHD, among others
What to Do When You Dread Your Bed: A Kid's Guide to Overcoming Problems With Sleep	Dawn Huebner and Bonnie Matthews	2008	Children 6–12 with anxiety and their parents

Clinicians need to vet their written materials carefully, as general handouts about sleep hygiene may be geared toward adults (avoiding alcohol at night is not relevant for 3-year-olds, one hopes), overwhelming, or inaccurate. In approaching families such as Jeremiah's, in which a bedtime routine is in place, it is important to recognize that "sleep hygiene" is necessary, but not always sufficient for treatment of insomnia.

While behavioral treatment is generally regarded as first line, medication treatment surfaces often in discussion and is treated in more detail in Chap. 29 [60]. Medication use is frequent in children with NDD and sleep problems, and a registry-based study showed associations between its use and both lower questionnaire-reported quality of life and more problematic behaviors during the day [61]. It was not determined whether the children in question had more challenging behaviors prior to being prescribed medication, whether the medications didn't adequately change sleep to improve these conditions, or whether significant improvement in sleep didn't budge quality of life or behaviors [61]. In considering prescribing for sleep, clinicians must discern the source of parental interest in treatment, whether it be to preserve or restore child or family function or to pursue less realistic goals (parent or other caregiver desires for inappropriately early bedtimes for their children or late-morning wake times). When is it appropriate to start medication? Some sleep medicine professionals propose never, or rarely, asserting that medication works temporarily and does not change underlying behaviors. Others are more lenient and see this as a way to alleviate parental suffering, but the decision must be approached critically and cautiously. Likewise, when should medications be stopped? Children with neurodevelopmental disabilities can accrete medications like ships accumulate barnacles, and once on, medications can be difficult to scrape back off.

Unfortunately, in the world of insomnia, at times it may be necessary to consider when nothing else seems to work. How should clinicians advise families whose child won't sleep, despite any strategies recommended, either due to inability to implement those strategies effectively or ineffectiveness despite strenuous efforts?

Conclusions

Insomnia is at the heart of any discussion of sleep problems in children. It affects children of all ages and with all types of disabilities. Clinicians must identify and offer strategies to children who do not sleep and their families, and researchers must explore how insomnia is provoked and maintained in children.

Future Directions

Basic information on sleep needs of children, and children with NDD, is lacking. Do children who are cognitively functioning at a younger age require the sleep that would be expected for their chronologic age or their developmental age? Are there some children with NDD who simply need much less sleep than would be expected for their ages? One of the nagging issues in pediatric sleep is what to do with the child who does not sleep and doesn't seem to be bothered by it.

The longitudinal course of insomnia is also a question. Recent research suggests more persistent sleep symptoms are associated with depression, ADHD, and externalizing behaviors, though not with anxiety [62]. What can families expect for their children's insomnia over time?

Parents often have questions about their child's sleep quality. Measurement of sleep quality is trickier than sleep quantity. It is a topic of interest more broadly in sleep medicine but with applications in children with NDD as well. The ability to measure "sleep health" and gauge relative quality of sleep could be of particular interest as it develops [63].

Protocolization and manualization of behavioral treatments would be useful for consistency. Group therapy and internet approaches to make behavioral treatments more available and feasible for families are being explored [56, 64]. Research examining delivery of CBT-I in adolescents discerned that feedback specifically about sleep efficiency and bedtime improved sleep efficiency, while other types of feedback showed smaller or even counterproductive effects [65]. Enriched training of pediatric clinicians in the treatment of insomnia is crucial given the prevalence of this problem and likely need for stepped care, starting with non-sleep specialists and escalating to specialists as needed, with the

knowledge that availability of pediatric sleep specialists is limited due to small numbers and high demand [66].

Better understanding of the causes of insomnia should prompt the development of more rational therapies. Medication is a constant question, and specifics are addressed in detail in Chap. 29. There is little evidence available on which to base recommendations for pharmacologic treatment of insomnia in children, and all prescriptions are off-label. More rigorous trials of medication for sleep in children are sorely needed, even if they go the way of a recent well thought-out migraine trial, and fail to show significant differences in effect between accepted treatments and placebo [67]. Better guidance on decisions about medication use for insomnia, including when to start and how long to use, would also be appreciated. It is anxiety-provoking for parents (and clinicians) to consider weaning a medication for a child whose chronic sleep disturbance has remitted with the prescription, yet none of us wish to continue prescribing for a child forever. Likewise, melatonin (treated elsewhere in this book in Chap. 31) is often offered as an effective, inexpensive, and mostly benign therapy for delayed sleep onset; yet its widespread use, sometimes long-term, is a large, uncontrolled experiment, particularly among children with NDD.

Clinicians may think of medication and other therapies as symptomatic treatment for an unpleasant situation. But does insomnia in childhood have long-term physical and mental health effects, as has been suggested for insomnia in adults? [10]. Does sleep loss in the developmental window have temporary, or more permanent, cognitive impact? If these are concerns, do behavioral or pharmacologic treatments mitigate any later damage?

Finally, what role could prevention play? Could more proactive counseling of parents of children with disabilities known to be at higher risk of sleep disturbance head off some of the habits that make insomnia more pernicious and persistent? Would propagation of small group trainings and parents working in solidarity with clinicians lead to more restful nights? [68].

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Sleep-Related Breathing Disorders

6

Michael A. DeMarcantonio, Aliza P. Cohen, and Stacey L. Ishman

Introduction

Sleep-related breathing disorders (SRBDs) are common and affect children of all ages. The presentation of these disorders varies from relatively benign snoring to airway obstruction and hypercarbia. SRBDs are divided into four broad classifications that include obstructive sleep apnea (OSA), central sleep apnea (CSA) syndromes, sleep-related hypoventilation disorders, and sleep-related hypoxemia. Children diagnosed with any of these conditions experience abnormal respiration that is either centrally mediated or caused by upper airway obstruction.

In patients with neurodevelopmental disabilities (NDDs), reported prevalences of SRBDs range from 20% to 79% (Table 6.1) [1–6]. If left untreated, these disorders can result in both systemic and cognitive deficits that may exacerbate baseline deficits. In an effort to avoid this clinical scenario and facilitate an accurate and timely diagnosis, we will present an overview that lays the foundation for this broad, and often complex, topic.

M. A. DeMarcantonio · A. P. Cohen
Division of Pediatric Otolaryngology – Head and Neck Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

S. L. Ishman (✉)
Upper Airway Center, Division of Pediatric Otolaryngology – Head and Neck Surgery, and Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Department of Otolaryngology-Head and Neck Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, USA
e-mail: stacey.ishman@cchmc.org

Establishing a Diagnosis

History

Clinical History

The pediatric office visit offers an excellent opportunity to identify patients with an SRBD. With this in mind, the American Academy of Pediatrics Guideline recommends universal screening for snoring in all children [7]. If snoring is present, the guideline suggests that a detailed sleep history should be performed, focusing on witnessed snoring and apnea events, the sleep environment, and associated sleep problems. Parents of children with an SRBD may report disturbed sleep, gasping, and witnessed apneas. The absence of witnessed apneas does not, however, preclude an SRBD, and as many as one-third of children with CSA have no history of witnessed apneas, desaturations, or abnormal breathing [8].

Parents should be questioned about sleep duration, including typical time to bed and wake times, sleep habits such as bedtime routines, and the setting in which children sleep (e.g., whether they share a room or a bed and whether a television is present) in order to identify modifiable patterns and behaviors. They should also be queried about parasomnias such as night terrors, nightmares, sleepwalking, and enuresis. Secondary enuresis, in particular, has been strongly linked to OSA. In a study by Brooks et al. [9], 47% of children with a respiratory disturbance index (RDI) >1 reported enuresis compared to 17% of children with normal sleep studies ($P = <0.05$).

It is also important to screen for daytime behaviors, including hyperactivity, inattention, and sleepiness. A recent meta-analysis reported that symptoms associated with attention-deficit/hyperactivity disorder (ADHD) are significantly associated with primary snoring and OSA [3]. In light of these findings, the presence of ADHD symptoms should

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Table 6.1 The prevalence of obstructive sleep apnea or sleep-disordered breathing in conditions associated with neurodevelopmental delay

Condition	Prevalence	Criteria
Cleft palate [1]	22%	Sleep-disordered breathing
Angelman syndrome [2]	30%	Obstructive sleep apnea
ADHD [3]	25–35%	Obstructive sleep apnea
Cerebral palsy [4]	58–67%	Sleep-disordered breathing
Down syndrome [5]	30–50%	Obstructive sleep apnea
Prader-Willi syndrome [6]	80%	Obstructive sleep apnea

prompt detailed questioning regarding SRBD symptoms. Overall, daytime sleepiness is less common in children than in adults; however, excessive sleepiness is frequently reported in children with Prader-Willi syndrome (PWS), cerebral palsy (CP), and Down syndrome (DS) [10–12]. Children with OSA and obstructive hypoventilation syndrome are more likely to complain of daytime sleepiness than children with central apnea events. There are, however, a myriad of causes for daytime sleepiness that are unrelated to SRBDs, the most common being poor sleep hygiene. The possibility of hypothyroidism should be considered in complicated medical patients with sleep complaints. Thyroid dysfunction is more common in children with ADHD (5.4%) and PWS (20–30%) than in typical children [13, 14] and is even more common in patients with DS; 40% of all children with this syndrome have abnormal thyroid studies, and 7% present with overt clinical hypothyroidism [15].

Standardized Questionnaires

Efforts to quantify the signs and symptoms of SRBDs have led to the development of a number of sleep questionnaires. However, these questionnaires are limited by their variable sensitivity and focus only on sleep-disordered breathing (SDB). The Pediatric Sleep Questionnaire (PSQ) is widely accepted and thought to have the best ability to predict the presence or absence of OSA. Although this questionnaire has excellent sensitivity (83%) and specificity (87%), it was validated only in healthy children [16]. In a recent study [17] in which the PSQ was used to study children with craniofacial deformities, the majority of patients were syndromic (54.7%), and Pierre Robin sequence was the most common diagnosis. Authors reported a 28% prevalence of likely OSA overall, with rates above 50% in patients with facial cleft and Treacher-Collins and Apert syndromes. Formal validation of this tool, however, has not been carried out for children with NDD and would be problematic given that questions regarding attention would be hard to answer for these children.

The Children's Sleep Habits Questionnaire (CSHQ) has been shown to have a sensitivity and specificity of >70% for SDB in otherwise healthy elementary school children [18]. However, Shott et al. [19], utilizing a questionnaire based on the CSHQ, reported a sensitivity of only 23% and a specificity of 61%.

The OSA-18 has been developed to measure SDB quality of life and was validated in otherwise healthy children [20, 21]. It was subsequently validated in children with syndromic craniosynostosis after being translated into Dutch and was found to be reliable and valid [22].

Elsayed and colleagues [11] used components of several different validated surveys to evaluate 100 children with CP. Symptoms of SDB were identified in 44% of the study population, with school-age children more commonly affected than younger children. It is, however, important to acknowledge the limitations of sleep questionnaires. Few surveys have been used specifically for the evaluation of children with an NDD. In addition, results may be confounded in children with NDD by the behavioral components of the questionnaires. Future study and validation is required prior to widespread implementation.

Physical Exam

General Exam

The physical evaluation should begin with observation of general behavior and sleepiness. Children with obesity hypoventilation syndrome (OHS) in particular may fall asleep easily and appear to be somnolent. Evaluation of body mass index (BMI) is important, as children with obesity are four to six times more likely to have OSA than non-obese children [23]. In children with DS, BMI is associated with an increased risk of OSA, even after adjusting for age and sex [24]. However, the association between obesity and SRBDs may not always be as straightforward. In children with PWS, researchers have demonstrated a lack of association between an elevated apnea-hypopnea index (AHI) and obesity [25].

Head and Neck Examination

A thorough head and neck examination should be considered, as should an evaluation of voice and speech. These evaluations should include as assessment of hyponasality, which may be associated with a lack of nasal airflow due to obstruction at the nose or nasopharynx (e.g., adenoid hypertrophy). The presence of retrognathia and/or micrognathia should be noted, especially for children with other craniofacial issues, as these conditions are more common in children with upper airway obstruction [26]. Midface and maxillary hypoplasias are features of children with DS, Crouzon syndrome, and Angelman syndrome.

The oral cavity and oropharyngeal exams should include an evaluation of dentition, dental occlusion, tongue, palate, and tonsil size and position. Brodsky et al. [27] popularized

a four-point grading system for tonsil size. Using this scale, grade 0 tonsils are surgically absent, grade 1 are located within the tonsillar pillars, grade 2 extend just beyond the tonsillar pillars, grade 3 extend >50% toward the midline, and grade 4 make contact at the midline. This grading system has been shown to have both acceptable inter-observer and intra-observer reproducibility [28]. Relative macroglossia, a condition in which a patient has a normal-sized tongue in a small oral cavity, is common in children with DS. This finding is frequently seen in combination with hypotonia and glossoptosis in children with significant upper airway collapse [29]. The palate should also be evaluated for any evidence of midline defects; these include overt clefts of the hard and soft palate, soft palate submucosal clefting, and the presence of a bifid uvula. Also, dental occlusion should be evaluated using Angle's classification of malocclusion. This classification system defines occlusion as class I (normal), class II (overbite), and class III (underbite). In a small series, class II and III malocclusion significantly correlated with OSA on polysomnography (PSG) [30].

A thorough nasal examination should include evaluation of the nasal mucosa and structures. Signs of mucosal edema or inflammation may indicate a concurrent diagnosis of allergic rhinitis. These findings should be further investigated, as a 2013 systematic review reported a significant association between allergic rhinitis and SDB [31]. Anterior rhinoscopy may also demonstrate other causes of obstruction such as inferior turbinate hypertrophy (Fig. 6.1), septal deviation, or nasal polyps.

Endoscopy

For children in whom nasal pathology is assumed to be a primary issue, nasal endoscopy may be considered; this allows for the detection of posterior septal deviations, visualization of the maxillary sinuses and osteomeatal complexes, and identification of nasal masses, obstruction, or polyps.

More commonly, flexible laryngoscopy is utilized to visualize the entire upper airway, including the nasal cavity, adenoids, oropharynx, pharyngeal walls, base of tongue, lingual tonsils, hypopharynx, supraglottis, and glottis. In young infants, the endoscopic exam should be used to evaluate for nasal obstruction from pyriform aperture stenosis or choanal atresia. Visualization of the adenoid pad is easily performed, well tolerated even in young children, and well correlated with nasal obstruction [32]. For children with NDD, the likelihood of glossoptosis and lingual tonsil hypertrophy is increased. Lingual tonsil hypertrophy is frequently seen in children with DS, children who have undergone previous adenotonsillectomy (T&A), and children with obesity [29, 33].

Laryngomalacia is also well visualized with flexible endoscopy. It is characterized by dynamic supraglottic collapse secondary to shortened aryepiglottic folds and redundant arytenoid mucosa (Fig. 6.2). It is common in children with DS, affecting up to 50% of these children [34]. There should also be a high index of suspicion for laryngomalacia in patients with CP who present with upper airway obstruction [35]. Moreover, it has been reported that the generalized hypotonia seen in children with CP may result in later and more severe presentation of laryngomalacia [36].

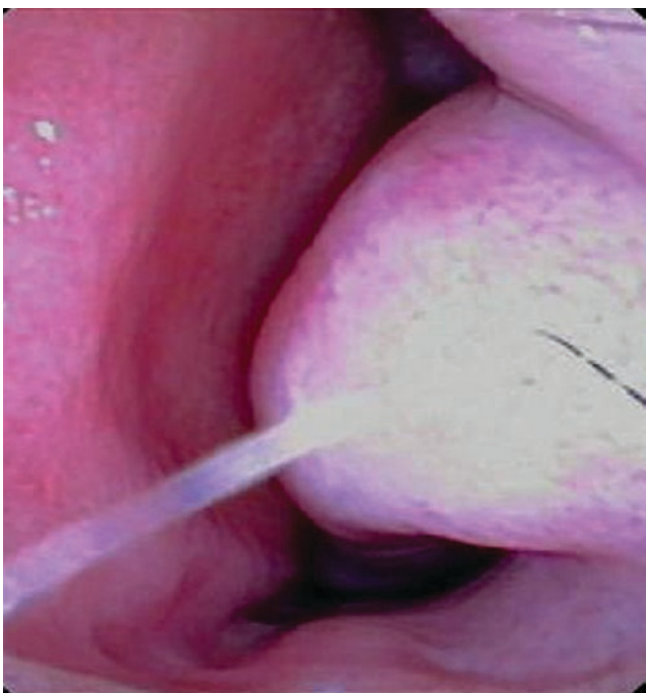

Fig. 6.1 Inferior turbinate hypertrophy

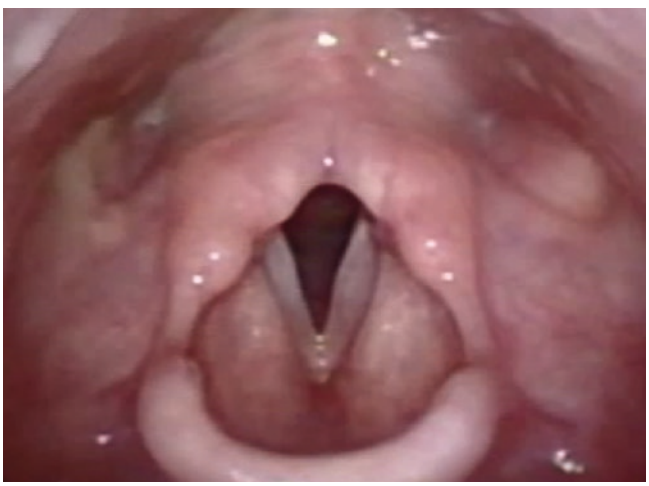

Fig. 6.2 Laryngomalacia with shortened aryepiglottic folds and redundant arytenoid mucosa

Diagnostic Studies

Laboratory Studies

Laboratory studies are generally not required in the workup of SRBDs, except for children with OHS. These children should undergo an arterial blood gas study to confirm daytime hypercapnia. Blood gas studies may also demonstrate a compensatory respiratory acidosis and hypoxemia [37]. They should also undergo a complete blood count to identify possible polycythemia associated with chronic hypoxemia, as well as thyroid function tests to rule out severe hypothyroidism, which can result in alveolar hypoventilation [38].

Imaging

For children with OSA, lateral neck X-rays have been utilized to evaluate adenoid size. A 2011 systematic review supported the utility of lateral films in children [39]. However, there has been a concerted effort to reduce the radiation exposure of children secondary to imaging studies. In a study by Pearce et al., CT scans were associated with a small but real risk of leukemia and brain cancer [40]. Although the radiation dose from a neck film is notably lower than the dose from a CT scan, these findings highlight the need to limit unnecessary studies. As a result it is currently recommended that lateral neck films be reserved for children who cannot tolerate flexible nasal endoscopy [41]. For infants in whom pyriform aperture stenosis or choanal atresia is suspected, CT imaging without contrast is usually obtained.

Children with idiopathic CSA should undergo imaging of the brain (generally MRI) to rule out a neurologic source for their CSA. A 2011 study [8] of 25 children with primary CSA found that the diagnostic yield of MRIs exceeded 50%.

Sleep cine magnetic resonance imaging (cine MRI) is a useful imaging technique to evaluate children with OSA after T&A. This modality allows for high-resolution examination of the upper airway during drug-induced sleep (Fig. 6.3). Images are collected over a 2-minute period and combined to create a real-time movie that demonstrates airway dynamics. One advantage of the study is that it allows multiple overlapping areas of obstruction to be evaluated simultaneously [42]. This study is typically employed in the 33% of patients who have persistent OSA following T&A [43, 44]. Cine MRI has been employed to successfully identify areas of obstruction in children with DS [45]. The limitations of this modality are that it does not identify obstruction well in the nasal passages or the larynx and that cost and availability are major concerns.

Drug-Induced Sleep Endoscopy

Since the 1990s, drug-induced sleep endoscopy (DISE) has also been used to identify areas of airway obstruction, predominantly in children with OSA on PSG after T&A or in children in whom tonsils and adenoids are small and considered nonobstructive. DISE allows for dynamic examination of the airway during sleep from the nares to the trachea, and it has been shown to be valid and reliable in both adults and children [46–49]. This procedure involves performing flexible fiber-optic examination of the airway while patients receive anesthetic agents to induce sleep (Fig. 6.4).

This procedure is useful for children with a high likelihood of persistent OSA after T&A, such as those with DS, in whom 30–50% reportedly develop persistent or recurrent OSA following T&A [29]. The hypotonia and anatomic abnormalities associated with other NDDs are also likely to contribute to a persistent OSA after surgery.

Polysomnography

In-laboratory PSG is the gold standard for the diagnosis of OSA in children and has been demonstrated to have acceptable test-retest reliability in children [50, 51]. The American Academy of Pediatrics (AAP), the American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS), and the American Academy of Sleep Medicine (AASM) recommend PSG prior to operative intervention in high-risk patients such as children with obesity, DS, PWS, craniofacial abnormalities, and neuromuscular disease [7, 52, 53]. These guidelines also emphasize the need for repeat postoperative evaluation and PSG in children with a high risk for persistent SRBDs after treatment, as is common in children with NDDs. PSG involves the simultaneous monitoring and recording of multiple physiologic parameters, including electroencephalography, electrooculography, and electromyography (EMG) [54]. Airflow is also monitored via nasal pressure transducer, thermistor, and/or end-tidal capnograph, to determine when respiration has been interrupted [54]. Additional monitoring devices include pulse oximetry, electrocardiography, and surface limb electromyography (EMG) monitoring. Monitors are also placed on the patient's abdomen and chest to detect respiratory effort, allowing for the differentiation between central and obstructive apneas.

The ideal pediatric PSG setting should be child-friendly, with pediatric waiting rooms and age-appropriate beds. It is also essential that accommodations be available for parents [54]. Technicians should be aware that children with NDD may require a significant amount of parental comforting or intervention by child-life specialists in order to optimize the study. Staffing may also be increased for children with NDDs, especially those with behavioral issues.

In children, an apnea is defined as two or more consecutive breathing cycles without airflow [55]. Hypopneas are defined as a reduction in airflow of ≥30% associated with either an arousal or an oxygen desaturation ≥3% [55]

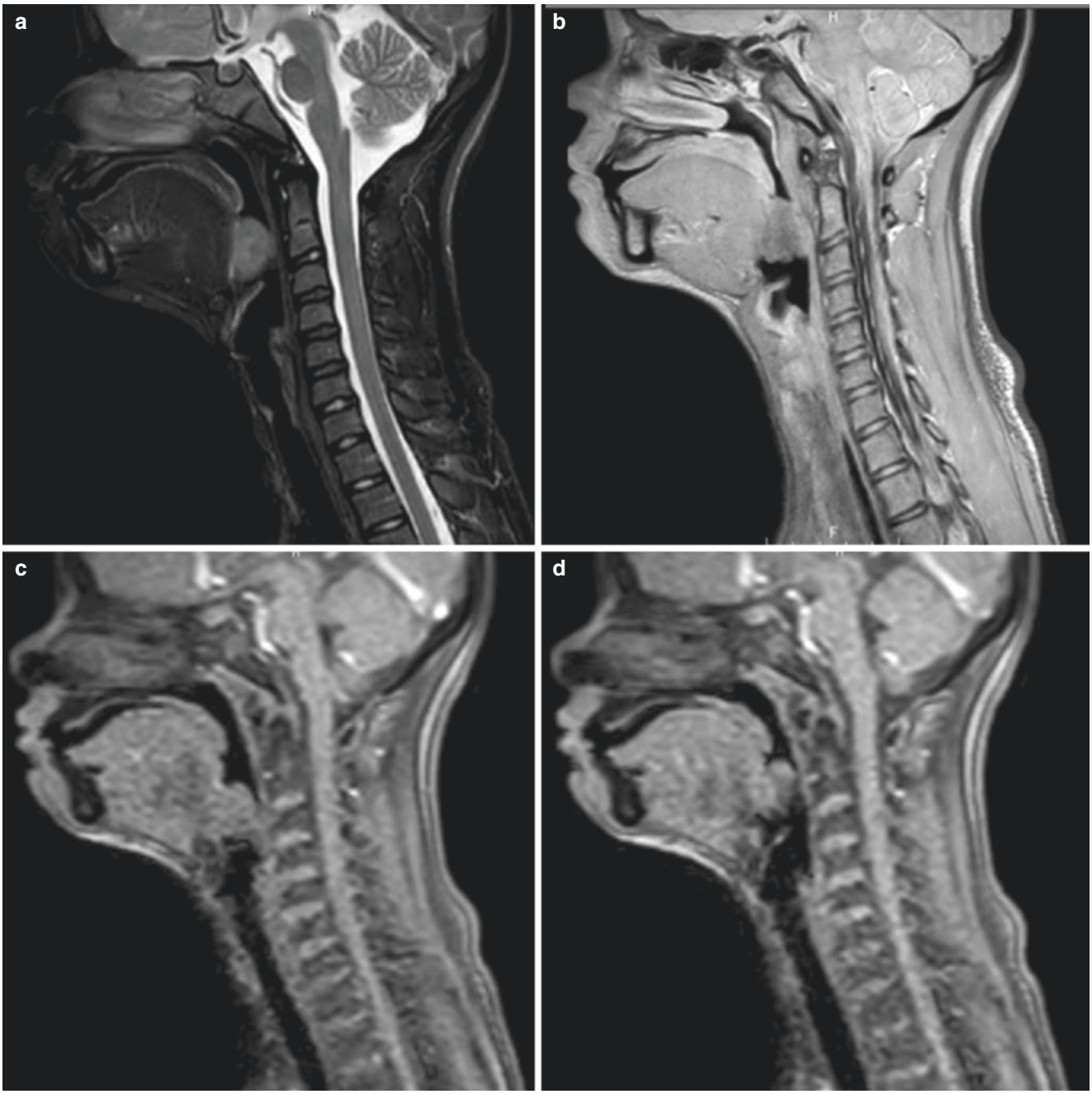

Fig. 6.3 Sagittal cine MRI of the upper airway. This MRI demonstrates lingual tonsillar hypertrophy in both T2 (**a**) and T1 images (**b**). It also demonstrates dynamic obstruction from lingual tonsils during inspiration (**c**) and expiration (**d**)

(Table 6.2). Apneas and hypopneas are further characterized as central or obstructive, based on the absence or presence of respiratory effort. Apneas and hypopneas are tabulated as events per hour and reported as indices, including the apnea-hypopnea index (AHI), obstructive apnea-hypopnea index (oAHI), and central apnea index (CAI) (Table 6.3) [55]. Based upon normative data, an obstructive AHI >1 is considered abnormal [7, 56]. The severity of OSA is subsequently categorized as mild when the obstructive AHI >1 and <5, moderate OSA when the obstructive AHI ≥5 and <10, and severe OSA when the obstructive AHI ≥10. CSA is diagnosed when the central apnea-hypopnea index is ≥5 events/

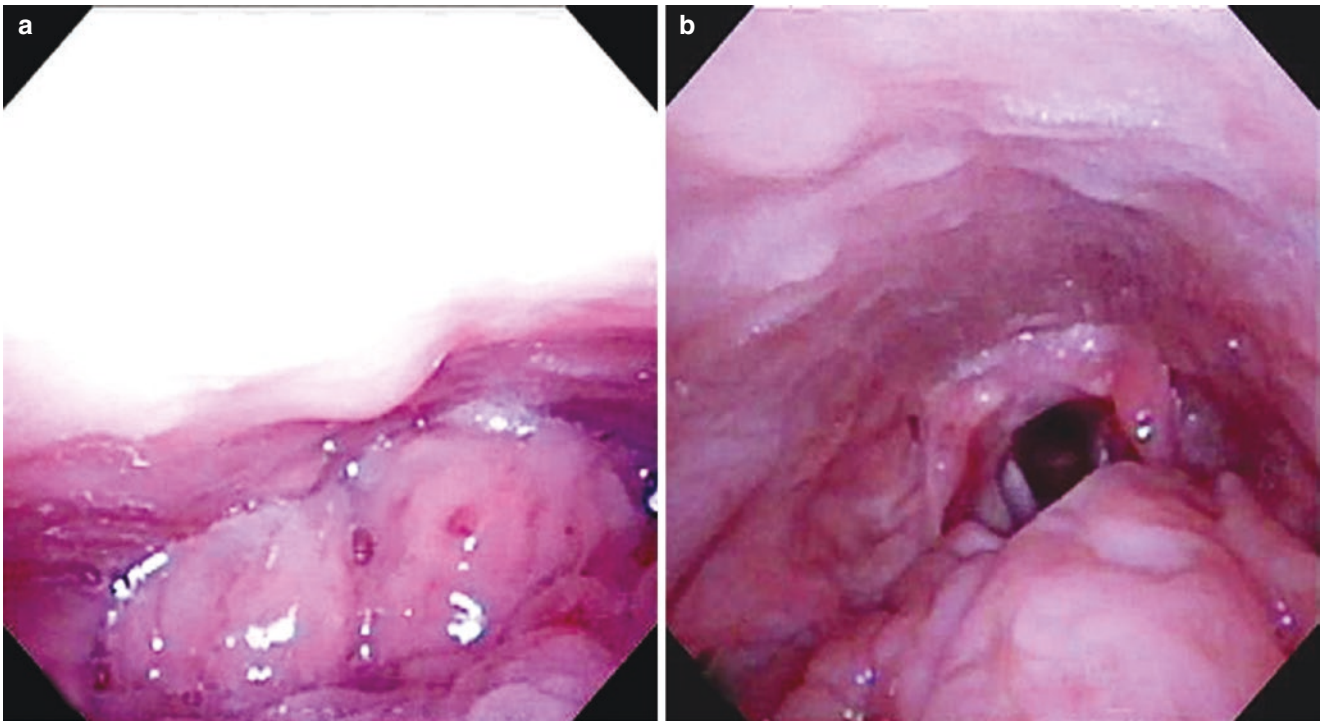

Fig. 6.4 This is a hypopharyngeal image taken during drug-induced sleep endoscopy. Image (**a**) demonstrates complete airway obstruction by the lingual tonsils, while (**b**) demonstrates persistent airway obstruction at the level of the lingual tonsils despite jaw-thrust maneuver

Table 6.2 Definitions of common terms used to describe respiratory events seen in sleep-related breathing disorders (SRBDs) [55]

Term	Definition
Obstructive apnea	Absence of airflow for 2 breaths associated with the presence of respiratory effort
Hypopnea	A reduction in airflow of ≥30% along with either an arousal or an oxygen desaturation ≥3% from the baseline
Central apnea	Absence of airflow without respiratory effort for 2 breaths in addition to:
	For children >1 year old: duration >20 s *or* an arousal *or* ≥3% oxygen desaturation
	For children <1 year old: decrease in heart rate to <50 beats per minute for at least 5 s *or* decrease in heart rate to <60 beats per minute for 15 s
Hypoventilation	25% of the total sleep time is spent with pCO2 >50 mm Hg
Respiratory effort	An arousal that is associated with increased respiratory effort, snoring, and related arousals increased pCO2 for the duration of two breaths

Hg mercury, *pCO2* partial pressure of carbon dioxide

Table 6.3 Definitions of common terms used to describe polysomnography parameters [55]

Term	Definition
Apnea-hypopnea index (AHI)	The number of apneas and hypopneas per hour of sleep averaged over the total sleep time
Obstructive apnea-hypopnea index (oAHI)	The number of obstructive apneas and hypopneas per hour of sleep averaged over the total sleep time
Central apnea index (CAI)	The number of central apneas per hour of sleep over total sleep time
Respiratory distress index (RDI)	The number of apneas, hypopneas, and RERAs per hour of sleep averaged over total sleep time
Oxygen desaturation index (ODI)	The number of arterial oxygen desaturations/hour (typically >3–4%)

hour. Some labs score respiratory effort-related arousals (RERAs). A RERA is defined as an arousal that is associated with increased respiratory effort, snoring, and increased peripheral arterial carbon dioxide ($PaCO_2$) for the duration of two or more breaths (Table 6.2). RERAs per hour are frequently added to the AHI and reported as the respiratory distress index (RDI) (Table 6.3).

Oxygen desaturations, defined as a decrease of 3% or 4%, are also tabulated and may be reported as the oxygen desaturation index (ODI) (Table 6.3). Standard PSG studies also report the percentage of sleep when CO_2 levels are >50 mm Hg. Hypoventilation is diagnosed in children when CO_2 levels are >50 mm Hg for >25% of the total sleep time [55].

Obstructive Sleep Apnea

Case Vignette #1

History: The parents of an 8-year-old girl with DS reported that their child had mild snoring but no history of apnea. They noted some increase in disruptive behavior at school and the recent onset of nocturnal enuresis.

Diagnostic workup: Physical examination revealed obesity, macroglossia, and tonsillar hypertrophy. PSG was performed, revealing an AHI of 18, with an obstructive AHI of 16.5 events/hour.

Treatment: The patient underwent T&A, with resolution of symptoms. Postoperative PSG revealed persistent OSA, with an AHI of eight events/hour and an obstructive AHI of 7.5 events/hour.

Key Points

History

- All children should be screened for snoring in conformity with AAP recommendations.
- Secondary enuresis is more common in patients with OSA than in healthy children.

Diagnostic Workup

- Obesity increases this child's risk of OSA and hypoventilation.
- Neither clinical history nor questionnaires are sufficient to differentiate snoring from sleep apnea. PSG is the gold standard for diagnosis.

Treatment

- T&A is first-line therapy for OSA.
- This patient is at increased risk of persistent OSA and should also undergo postoperative PSG.

Additional diagnostic procedures (DISE, cine MRI) may be necessary to determine further treatment options for this child. OSA is reported to occur in 2–4% of children and is defined as a complete or partial upper airway obstruction during sleep with respiratory effort. The diagnostic criteria for pediatric OSA from the AASM require (1) the presence of snoring or (2) labored, paradoxical, or obstructed breathing during sleep or (3) sleepiness, hyperactivity, behavioral problems, or learning problems during the day [57] In addition to having one of these symptoms, the patient must have a PSG that demonstrates either one or more obstructive apneas, mixed apneas, or hypopneas or a pattern of obstructive hypoventilation for at least 25% of sleep time. This pattern of obstructive hypoventilation must be associated with hypercapnia (partial pressure of CO_2 in arterial blood >50 mm Hg and with either snoring, flattened inspiratory nasal pressure, or paradoxical thoracoabdominal motion). Risk factors for this disorder include a history of prematurity, male sex, obesity, and NDDs [53, 55, 56, 58–60]. Studies of children with NDDs have found that OSA is diagnosed in greater than 50% of those with DS, PWS, and craniofacial syndromes such as Goldenhar, Apert, and Crouzon syndromes and Pierre Robin sequence [6, 17, 61]. However, authors of these studies also note that these prevalence numbers are likely underestimated because of inconsistent evaluation and screening of affected children. Pijpers and colleagues [62] reported that when children with syndromal craniofacial synostosis were screened for OSA, the number of children recognized to have OSA doubled from 26% to 53%. Persistent OSA is also common in children with craniofacial anomalies, obesity, and CP [63, 64].

For children with untreated OSA, there is concern for both cardiovascular and neurocognitive sequelae. The consequences of hypertension in particular may be long lasting, with pediatric hypertension increasing the likelihood of elevated blood pressure and metabolic syndrome in adulthood [65]. Children with OSA are also at an increased risk of psychosocial problems, including poor socialization, poor school performance, and aggressive behavior [66]. In children with DS, OSA has been linked to a reduction in verbal IQ score and disruptive school behavior [67, 68]. Moreover, OSA disease severity in these children has been linked to diminished visuoperceptual skills such as spatial orientation [69]. With increased OSA severity, psychosocial problems associated with OSA may also worsen. Research has shown that in children with PWS, increased OSA severity is associated with increased daytime inactivity and autism-related behavior [10].

Management

T&A is first-line therapy for children with OSA and is effective in 66% of patients [43]. Given that children with NDDs are deemed high-risk surgical candidates, the AAP and the AAO-HNS recommend hospital admission after T&A as well as follow-up to evaluate for possible persistent disease. Incomplete resolution of OSA is more common in children with NDD, especially for those with DS, PWS, and craniofacial abnormalities [67, 70, 71].

For children with persistent or recurrent OSA after T&A, a number of medical and surgical options exist. Continuous positive airway pressure (CPAP), medications, weight loss, and surgery are all treatment options, and the selection of the appropriate option depends on the site of obstruction and the degree of OSA. Nasal CPAP has been approved for use in children since 2006. This therapy can be effective; however, finding an appropriately sized mask is difficult in children with craniofacial issues or in those who are small, as few masks are made specifically for children. Additionally, research indicates that CPAP adherence is often suboptimal, with one multicenter study [72] reporting that usage in a setting with standardized support was only 3.8 h per evening. Moreover, even when CPAP is tolerated, there is concern that prolonged CPAP usage may contribute to long-term craniofacial changes [73].

The use of medications for the treatment of OSA may be effective in children with mild or low moderate disease severity. A 6-week course of nasal steroids has been shown to reduce the AHI by an average of 4.9 events/hour in children with OSA and adenotonsillar hypertrophy [74]. Similarly, oral montelukast has been shown to reduce the AHI by 1.8 events/hour after 12 weeks of use [75]. A large retrospective study [76] of 752 children, with mild OSA, reported an 80% response rate to a combined intranasal corticosteroids and oral montelukast. For the 445 children who underwent PSG before and after surgery, the reduction in the obstructive AHI was 3.1 events/hour. Resolution of OSA was seen in 62% of children.

Weight loss should also be considered and is strongly advocated for overweight and obese children. Medical weight loss programs are first-line therapy in this regard. Increasingly, however, bariatric surgery is being performed in adolescents with severe OSA. Although outcomes in children are limited, bariatric surgery has been shown to result in significant improvement in OSA severity in adults [77].

Further surgery may be considered for children with persistent OSA following T&A, especially if they are not good candidates for CPAP due to nocturnal seizures, drooling, or other safety concerns. It typically addresses obstruction at the base of the tongue, the palate, or both and often requires that cine MRI or DISE be carried out to determine the site of obstruction. For children with DS or obesity, lingual tonsillar enlargement has been identified as a common site of obstruction after T&A [33, 45]. For infants with laryngomalacia or older children with sleep-state-dependent laryngomalacia, supraglottoplasty should be considered. A systematic review of supraglottoplasty outcomes (after T&A) reported OSA resolution rates of 58–72% [78]. Durvasula et al. [79] evaluated supraglottoplasty outcomes in children with NDDs and syndromic children and found that 67% had resolution of OSA after surgery; however, in children with CP, surgical failure was more common.

Central Sleep Apnea Syndromes

Case Vignette #2

History: The parents of a 3-month-old male reported a history of PWS and stridor, but no history of apnea or acute life-threatening events.

Diagnostic workup: Physical examination revealed global hypotonia and audible inspiratory stridor with mild retractions. The rest of the physical examination was unremarkable. Tonsils were small (1+).

PSG was performed and showed an obstructive AHI of nine events/hour with a CAI of eight events/hour.

Treatment: The patient was started on 1/8 L of oxygen. Repeat PSG showed a residual CAI of 2.5 events/hour.

Key Points

History

- Children with PWS are at increased risk of CSA.

Diagnostic Workup

- The patient required PSG to determine the type (central versus obstructive) and severity of apnea prior to intervention.

Treatment

- Oxygen therapy has been demonstrated to be effective in children with PWS and CSA.
- A single study reported that patients with OSA and CSA may have improvement in both conditions with treatments traditionally used for OSA, such as adenotonsillectomy or supraglottoplasty.

CSA is defined as a reduction or cessation of breathing without associated respiratory effort. This may manifest as an apnea with ≥90% reduction in airflow or as a hypopnea where there is a 30 to <90% reduction in airflow. Except in infants or young children, central events should be associated with one or more of the following symptoms: sleepiness, difficulty falling or staying asleep, awakening short of breath, snoring, or witnessed apneas. Overall, CSA occurs in approximately 5% of children undergoing PSG [8]. The *International Classification of Sleep Disorders* has delin-

eated nine subgroups of CSA syndromes. Those that are most commonly seen in children include primary CSA, CSA of prematurity, primary CSA of infancy, and CSA caused by a medical disorder (Table 6.4). Each of these CSA syndromes is described below.

Primary Central Sleep Apnea

Primary CSA is idiopathic CSA that meets the general criteria for CSA and is not associated with Cheyne-Stokes breathing. In cases in which there are central and obstructive apneas, >50% of these apneas must be central events in order to be classified as CSA.

Management

In patients with primary CSA, effective supportive therapies include supplemental oxygen and CPAP [80–82]. Baldassari and colleagues reviewed the effect of T&A on 101 children with both OSA and CSA. Following T&A, children experienced a significant reduction in both obstructive and central apnea events; 90% of children with mild CSA (defined as a CAI >1 and <5) had complete resolution of the disease [83].

Primary Central Sleep Apnea of Prematurity

Primary CSA of prematurity is defined as central apnea demonstrated on PSG in an infant <37 weeks' conceptional age at the time that symptoms are first noted and are not explained by associated sleep, medical, or neurologic conditions. The diagnostic criteria require that an apneic or cyanotic episode be observed or that a sleep-related central apnea, desaturation, or bradycardic episode be detected using hospital monitoring. In addition, monitoring (including, but not limited to PSG) must demonstrate recurrent central apneas >20 seconds or periodic breathing for ≥5% of total sleep time. Immaturity of the respiratory control system is considered to be the primary reason for primary CSA of prematurity, and the prevalence of this condition is related to gestational age and birth weight [84]. It is diagnosed in nearly all infants born at <29 weeks or with a birth weight of <1000 g, 54% of infants born at 30–31 weeks, 15% of infants born at 32–33 weeks, and 7% of infants born at 34–35 weeks [84]. This condition typically resolves by 36–40 weeks' conceptional age [85]. Literature describing the relationship of this disorder to subsequent development is scant. A review of 19 infants with post-hemorrhagic hydrocephalus found that 26% had central apneas [86]. A study of 60 premature infants with observed CSA reported that 27 (45%) were confirmed to have CSA on PSG; the majority of these children had perinatal asphyxia or intraventricular hemorrhage [87].

Table 6.4 Sleep-related breathing disorders divided by category as delineated in the *International Classification of Sleep Disorders* of the American Academy of Sleep Medicine (3rd Edition) [57]

Sleep-related breathing disorders	Categories
Obstructive sleep apnea disorders	Obstructive sleep apnea, adult
	Obstructive sleep apnea, pediatric
Central sleep apnea syndrome	Central sleep apnea with Cheyne-Stokes breathing
	Central apnea due to a medical disorder without Cheyne-Stokes breathing
	Central apnea due to high-altitude periodic breathing
	Central apnea due to a medication or substance
	Primary central sleep apnea
	Primary central sleep apnea of infancy
	Primary central sleep apnea of prematurity
	Treatment-emergent central sleep apnea
Sleep-related hypoventilation disorder	Obesity hypoventilation syndrome (OHS)
	Congenital central alveolar hypoventilation syndrome
	Late-onset central hypoventilation with hypothalamic dysfunction
	Idiopathic central alveolar hypoventilation
	Sleep-related hypoventilation due to a medication or substance
	Sleep-related hypoventilation due to a medical disorder
Sleep-related hypoxemia disorder	Sleep-related hypoxemia
Isolated symptoms and normal variants	Snoring
	Catathrenia (sleep-related groaning)

Primary Central Sleep Apnea of Infancy

The diagnostic criteria for primary CSA of infancy mirror the criteria for primary CSA of prematurity (defined above) except that the onset of symptoms occurs ≥37 weeks' conceptual age. As with primary CSA of prematurity, immaturity of the respiratory control system is considered to be the primary reason for this condition. Symptomatic CSA occurs in 0.5% of infants, whereas 2% of healthy asymptomatic full-term infants will have at least one observed central event [88]. Most children are diagnosed clinically, and the diagnosis is confirmed by overnight PSG and the exclusion of other sleep, medical, or neurologic disorders that may result in CSA. Older infants can present with an acute life-threatening event (ALTE), which prompts evaluation. Prolonged apnea events will cease for some children by 43 weeks' conceptional age [88], but for others, these events may take several years to resolve. The presence of laryngomalacia in infants should also raise concern for possible CSA. In a study by Tanphaichitr and colleagues, infants with laryngomalacia were found to have a CSA prevalence of 46.3%. In this study, children with underlying neurologic disease, hypotonia, or a syndrome were 2.5 times more likely to have CSA than otherwise healthy children; however, this finding did not reach the level of statistical significance (Odds ratio = 2.5, $P = 0.13$) [89].

Central Sleep Apnea Due to a Medical Disorder

CSA is frequently identified in children with neurologic diseases or deficits. For example, 68% of children with a Chiari II malformation are diagnosed with CSA [90]. CSA has also been reported in children with PWS and epilepsy disorders. For children with PWS, CSA is more common in infancy (43%) than in children older than 2 years of age (5%) [91]. CSA has also been reported in patients with Rett syndrome and may occur with apneas while awake [92]. D'orsi et al. [93] note that nocturnal CSA events may be mistaken for seizure activity in children with Rett syndrome.

Management

Full-term and premature infants with CSA are generally managed with supportive therapy. Depending on the severity of disease, interventions include observation, oxygen supplementation, and pharmacologic therapy. Observation may be employed when children have mild CSA and are in a monitored setting. Oxygen therapy may be utilized to support infants until CSA resolves. The utility of oxygen therapy for CSA in children with NDDs has only been demonstrated in PWS. In a study of 10 infants with PWS, Urquhart and colleagues reported a reduction in median CAI from 15.9 to 4.4 events/hour using supplemental oxygen [94]. Both caffeine and theophylline have been used as central nervous system stimulators in children with CSA. Currently, caffeine is preferred because of its longer lasting effect and safety profile [95].

Sleep-Related Hypoventilation Disorders

Sleep-related hypoventilation is characterized by decreased gas exchange and elevated levels of CO_2 (i.e., hypercapnia) during sleep or both during wakefulness and sleep in children with obesity hypoventilation syndrome. Hypoventilation during sleep is defined as >25% of total sleep time with the CO_2 level ˃50 mm Hg, whereas awake hypoventilation is defined as $PaCO_2$ >45 mm Hg. Clinicians should be aware of the increased risk of hypoventilation in children with severe OSA, obesity, or DS [96, 97].

There are six hypoventilation disorders delineated in the *International Classification of Sleep Disorders*: obesity hypoventilation syndrome (OHS), congenital central alveolar hypoventilation syndrome (CCAHS), sleep-related hypoventilation due to a medical disorder, late-onset central hypoventilation with hypothalamic dysfunction, idiopathic central alveolar hypoventilation, and sleep-related hypoventilation due to medication or substance. Our discussion will be limited to OHS, CCAHS, and sleep-related hypoventilation due to a medical disorder.

Obesity Hypoventilation Syndrome

Children with OHS have hypoventilation when awake and asleep [98]. To meet the diagnostic criteria for this disorder, children must have an awake $PaCO_2$ >45 mm Hg as well as severe obesity, with a BMI >95th percentile and no additional reason for hypoventilation [99]. OHS is estimated to occur in 10–20% of obese adults, and 80–90% of patients with OHS have coexisting OSA [57]; however, OHS has been infrequently reported in children and has not been reported specifically in children with NDDs [100].

Congenital Central Alveolar Hypoventilation Syndrome

CCAHS, formerly known as Ondine's curse, is a rare genetic disorder characterized by failure of automatic central respiratory control during sleep that is associated with a *PHOX2B* gene mutation [101]. This condition has an estimated incidence between 1:10,000 and 1:200,000 live births, and only a few hundred cases have been reported worldwide [102, 103]. Children born with CCAHS are usually healthy-appearing infants with cyanosis or feeding difficulty. Occasionally, these children are undiagnosed until they have cardiovascular collapse. Associated autonomic abnormalities may also be noted, including

Hirschsprung disease and neural tumors such as neuroblastoma. Daytime hypoventilation may also be seen. Virtually all of these children require mechanical ventilation during sleep, and some will also require daytime mechanical ventilation [104]. Documentation of nocturnal hypoventilation and *PHOX2B* testing are required to establish a definitive diagnosis. This condition has been described in one patient with DS [105].

Sleep-Related Hypoventilation Due to a Medical Condition

In this disorder, sleep-related hypoventilation is present along with lung disease, cardiac disease, chest wall abnormalities, or a neuromuscular disorder. OHS and CCAHS must also have been ruled out. This condition manifests in children with Chiari malformation when hypoventilation is thought to result from brainstem herniation [106]. In children with PWS, neurologic deficits may result in pathologic hypoventilation.

Management

Children with OHS should all be screened for OSA. Although subsequent treatment is often multifaceted, it generally includes CPAP. Weight loss, either medical or surgical, is also important for these patients [107]. CCAHS is a lifelong medical condition. Nearly all children require positive-pressure ventilation via tracheostomy in infancy. As they age, nocturnal mechanical ventilation, bi-level positive airway pressure, and diaphragmatic pacing may be management options [108].

Sleep-Related Hypoxemia

Sleep-related hypoxemia is diagnosed when nocturnal arterial oxygen saturation levels are ≤90% for ≥5 min in children or ≤88% for ≥5 min in adults, without sleep-related hypoventilation. Although CSA or OSA can be present, sleep-related hypoxemia is diagnosed only if it is believed that neither of these disorders is the primary cause of the hypoxemia. This condition is thought to be secondary to neurologic or parenchymal lung disease. Sleep-related hypoxemia has been documented in children with PWS but may represent an underreported entity in other forms of NDD [109–111].

Management

Sleep-related hypoxemia is treated with nocturnal supplemental oxygen therapy. Evaluation of daytime oxygenation should be carried out in order to determine if daytime oxygen supplementation is also required. Treatment of the underlying pulmonary or neurologic disease may also improve this condition over time.

Snoring

Habitual snoring is reported by parents in 7.5% of children [59]. In patients referred for PSG, snoring (previously referred to as primary snoring) will be diagnosed in up to 40% of children [112]. In these patients audible snoring is appreciated during the study with an AHI <1. Patients with NDD appear to have similar prevalence rates, with primary snoring reported in 40% of children with ADHD and 29% of children with DS [112, 113]. Snoring is often considered a benign entity; however, multiple studies have demonstrated cognitive deficits in children with snoring compared to non-snoring controls [114, 115]. It should be noted that while children with habitual snoring scored lower than controls in these studies, the majority of scores remained within the normal range [116]. Children with habitual snoring have also been reported to have behavioral impairment, similar to that seen in children with OSA, when compared to controls [116, 117].

Management

There is no reliable way to distinguish primary snoring from OSA by history in children [118]. PSG is currently the only definitive way to rule out OSA and confirm a diagnosis of snoring. Presently, prospective research is required to evaluate possible treatment options to address the morbidity associated with primary snoring.

Conclusion

SRBDs are commonly seen in children with NDDs, and expeditious treatment requires a thorough diagnostic approach. The workup should include a detailed clinical history, a focused physical examination, and overnight PSG. Treatment options include surgical therapies, positive airway pressure, and oxygen supplementation. Because children with NDDs are at an increased risk of persistent and recurrent SRBDs following treatment, they require close ongoing follow-up to monitor disease resolution. Timely and appropriate management of SRBDs in children with NDDs is essential for minimizing associated morbidities.

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Parasomnias

7

Ariel A. Williamson and Thornton B. A. Mason II

Case Vignette

Rayshaun is an 11-year-old boy with a history of developmental delay, current diagnosis of attention-deficit/hyperactivity disorder (ADHD), and concerns for abnormal arousal responses from sleep. His mother reported that these events have been occurring "since he was a baby." During these periods Rayshaun appears to have a different respiratory state. His eyes are open and he stares but has minimal to no movement. More recently, he has sat up in bed and perhaps appeared confused, but he has not cried out or vocalized. He may remain in this staring position for some 20–25 min according to his mother's report. There may be some associated increase in motor tone, but no tongue biting or incontinence. There are no associated clonic movements. These episodes occur approximately three times per month.

A routine, awake EEG study was arranged prior to the office visit and showed no epileptiform discharges or any clinical or electrographic seizure activity. There was no further evaluation for these spells in the interim leading up to an office visit specifically to discuss them.

Rayshaun's typical sleep schedule is a bedtime of 7:30 pm on school nights and 9:30–10 pm on weekends and in the summertime. His wake time is 6:00 am. Some nights he has a sleep latency that lasts several hours, particularly on those evenings where he goes to bed prior to 8:00 pm. His mother is not aware of consistent paradoxical effort, although he sometimes may have some labored breathing. He does not snore. There is no history of sleepwalking. As a very young child, the patient had some episodes of screaming from sleep that might have represented either sleep terrors or nightmares.

Rayshaun shares a room with his 8-year-old brother but sleeps in his own bed (the lower bunk of bunk beds). There is a TV and video game system in their room. Rayshaun reports occasional nighttime awakenings during which he entertains himself with TV or video games before falling back to sleep. He drinks caffeinated beverages in the afternoon, such as 16 oz of iced tea or 12 oz of Mountain Dew soda, three to four times per week.

With regard to his medical history, Rayshaun was born at term. He has never been hospitalized, and his only surgery was a repair of an umbilical hernia. There is a family history of seizures in his maternal aunt (but none recently), paternal aunt (deceased), and 13-year-old sister, who has epilepsy but has been tapered from valproic acid therapy and is currently seizure-free. Rayshaun takes long-acting methylphenidate 27 mg daily and standard-release methylphenidate 7.5 mg each afternoon to manage his ADHD. He is enrolled in sixth grade and receives special education services through an Individualized Education Program (IEP).

On the review of systems, there are no otolaryngologic, gastrointestinal, cardiovascular, or musculoskeletal issues reported. On physical exam, vital signs were normal, and he was normal weight. His general physical exam demonstrated a moderately crowded airway, Mallampati class III. Tonsils were mildly enlarged (grade 2+/4). Lungs were clear to auscultation bilaterally. The heart had a regular rate and rhythm without murmur. Extremities were normal. Cranial nerve examination was unremarkable. He had no pro-

A. A. Williamson
Sleep Center, Divison of Pulmonary Medicine, Department of Child and Adolescent Psychiatry and Behavioral Sciences, Children's Hospital of Philadelphia, Philadelphia, PA, USA

T. B. A. Mason II (✉)
Departments of Neurology and Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, USA
e-mail: masont@email.chop.edu

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nator drift, and his tone was symmetric. Strength appeared full on confrontational testing. Sensation was normal to light touch. Myotatic reflexes were symmetric without clonus. There were some mild contralateral (mirror) movements with rapid effort, and rapid alternating movements were mildly slow bilaterally.

The impression is that of an 11-year-old with a history of developmental issues, ADHD, and concern for nighttime arousals from sleep. Rayshaun has never had daytime seizures or any history of febrile seizures when he was younger, but there is a family history of epilepsy. His mother reports these episodes of arousals from sleep have been present since early infancy, and they do not have features that clearly support nocturnal seizures. On the other hand, it would be unusual if these episodes of sitting up overnight were confusional arousals, given that he remains so still by his mother's report without any vocalizations and no real agitation. In order to evaluate further, an overnight polysomnogram was performed.

The overnight polysomnogram showed normal sleep efficiency and normal sleep stage distribution (Fig. 7.1). The number of arousals from sleep was normal. There was mild snoring. No significant central apneas occurred, and there were no obstructive apneas or hypopneas. Respiratory gas exchange was normal. The periodic limb movement index was normal. Rayshaun had a brief (45 s) arousal from slow-wave sleep during which he opened his eyes, sat up and vocalized softly, and then stretched and laid down to return to sleep rapidly. The EEG was normal throughout, with no clinical or electrographic seizures noted.

To help manage arousal parasomnias, behavioral sleep medicine recommendations were made. In order to avoid prolonged sleep latency, his bedtime was shifted to approximately 9 pm nightly. His mother was asked to move the television and video games from the patient's room as they may distract him from having a consistent sleep pattern. Rayshaun was encouraged to eliminate all caffeinated beverages including iced tea.

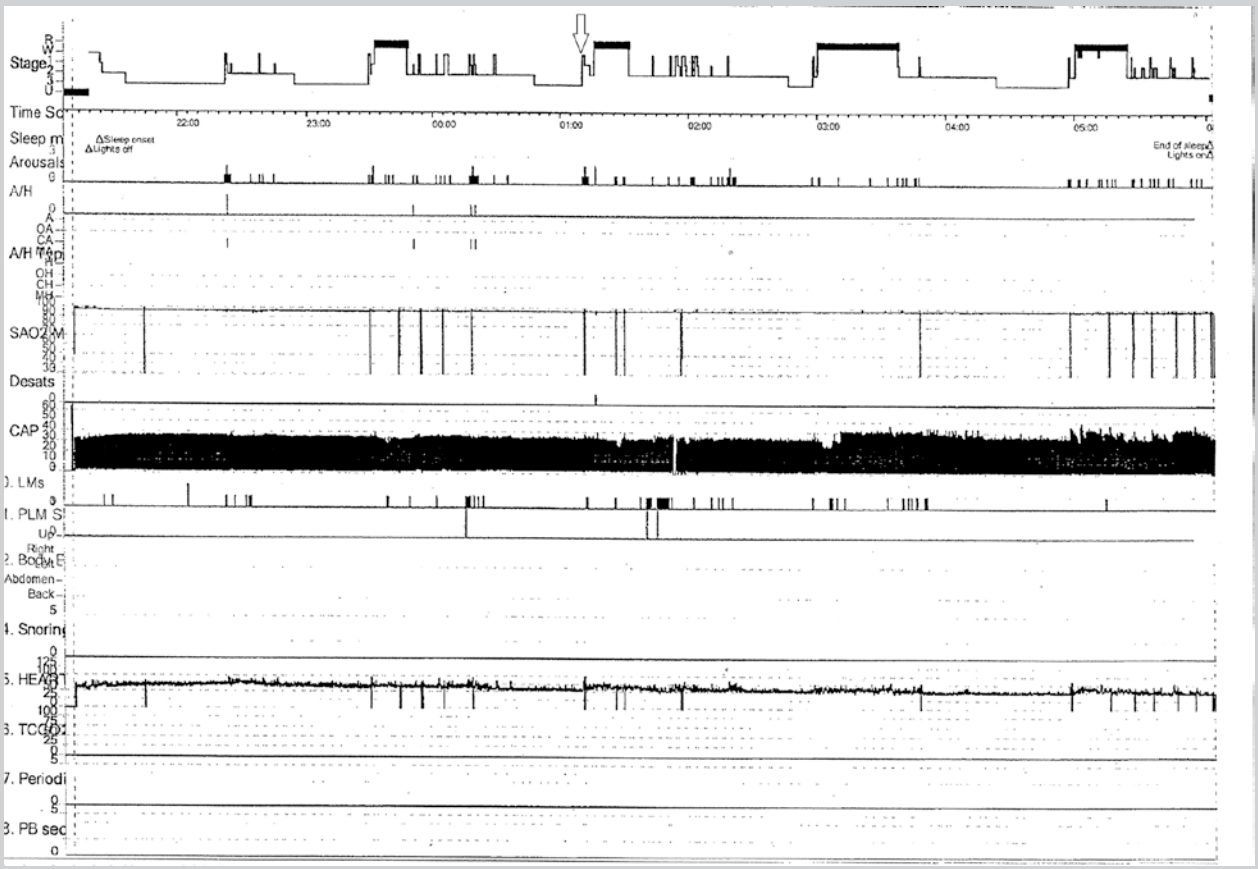

Fig. 7.1 Summary of overnight polysomnography. Snoring occurred, without associated obstructive sleep apnea. Intermittent artifact was seen in the pulse oximetry (SAO_2) and heart rate (*heart*) channels. Several brief central apneas were seen (within normal limits). At epoch 488 (open arrow, top), the patient had a brief (45 s) arousal from slow-wave sleep where he opened his eyes, sat up and vocalized softly, and then stretched and laid down to return to sleep rapidly. The EEG was normal throughout, with no clinical or electrographic seizures noted

Overview of Parasomnias

The *International Classification of Sleep Disorders*, third edition (ICSD-3), defines parasomnias as "undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousal from sleep" [1]. Parasomnias are commonly encountered in typically developing children and adolescents [2–4] and include a number of different sleep-related behaviors, cognitions, and emotions, from sleep talking or rhythmic movements during sleep to vivid and disturbing nightmares [1]. Although parasomnias tend to diminish with increasing age [4, 5], frequent, dangerous, or prolonged parasomnias can result in disrupted sleep, injury, or other negative psychosocial consequences, both for those experiencing the event and for others in the home [1]. As parasomnias vary in their behavioral complexity, level of physical arousal, and timing during sleep, the ICSD-3 broadly classifies these episodes into three diagnostic categories. These categories are (1) events occurring during non-rapid eye movement (NREM) sleep, (2) events occurring during rapid eye movement (REM) sleep, and (3) other parasomnias [1]. This chapter will review NREM-related and REM-related parasomnias, with a focus on the behavioral manifestation, incidence, and clinical management of these disorders among youth with neurodevelopmental conditions.

Subtypes of NREM-related and REM-related parasomnias and associated ICSD-3 diagnostic criteria are shown in Table 7.1.

Table 7.1 ICSD-3 diagnostic categories of and criteria for parasomnias

ICSD-3 disorder	Summary of ICSD-3 diagnostic criteria
NREM-related parasomnias	
Disorders of arousal	Broad features
	Recurrent episodes of incomplete awakening from sleep
	Lack of responsiveness to others' efforts at intervention or redirection during the episode
	Limited or no associated cognition or dream imagery
	Partial or complete amnesia of the episode
	Not better explained by another sleep disorder, mental or medical condition, or substance use
	Occurs in the first third of the night
	Confusion and disorientation upon waking
	Distinguishing features
	Confusional arousals
	Mental confusion or confused behavior while the child is in bed
	Absence of terror or ambulation outside of bed
	Sleepwalking
	Ambulation and other complex behaviors outside of bed
	Sleep terrors
	Episodes of abrupt terror, usually beginning with a loud vocalization
	Intense fear and signs of autonomic arousal
Sleep-related eating disorder	Recurrent episodes of dysfunctional eating that occur after an arousal during the main sleep period
REM-related parasomnias	
REM sleep behavior disorder	Repeated episodes of sleep-related vocalization and/or complex motor behaviors
	Documented to occur during REM sleep via PSG or, based on dream enactment, presumed to occur during REM sleep
	PSG demonstrated REM sleep without atonia
	Not better explained by another sleep disorder, mental or medical condition, or substance use
Nightmare disorder	Repeated occurrences of extended, extremely dysphoric, and well-remembered dreams that involve threats to survival, security, or physical integrity
	Child is oriented and alert after waking from dream
	Dream experience or sleep disturbance caused after waking from dream causes clinically significant distress or impairment in social, occupational, or other areas of functioning
Recurrent isolated sleep paralysis	Recurrent inability to move the trunk and all of the limbs at sleep onset or upon awakening from sleep
	Episodes last seconds to a few minutes
	Episodes cause clinically significant distress including bedtime anxiety or fear of sleep
	Not better explained by another sleep disorder, mental or medical condition, or substance use
Other parasomnias	Exploding head syndrome
	Sleep-related hallucinations
	Sleep enuresis
	Parasomnia due to a medical disorder
	Parasomnia due to a medication or substance
	Parasomnia, unspecified

ICSD-3 International Classification of Sleep Disorders, Third Edition [1], *PSG* polysomnography; all diagnostic criteria are adapted from ICSD-3

NREM-related parasomnias include disorders of arousal (confusional arousals, sleepwalking, and sleep terrors) and sleep-related eating disorder. Generally, disorders of arousal involve recurrent, partial awakenings from sleep, as well as unsuccessful attempts by others to redirect or console the individual, a lack of associated cognitive or dream imagery, and inability to recall the event the next morning [1]. These events are not better accounted for by psychiatric or medical conditions, substance or medication use, or other sleep disorders [1]. Disorders of arousal tend to occur during non-REM, slow-wave (N3) sleep, in the first third or first half of sleep, and vary in their duration from a few minutes to as long as 30 or 40 min [1, 6]. Individuals experiencing a disorder of arousal are not consciously awake but appear awake, talking or yelling during these events with their eyes open, or engaging in routine, complex behaviors (e.g., walking, urinating, opening doors) [1]. Similar to disorders of arousal, sleep-related eating disorder, another NREM-related parasomnia, involves enacting a routine behavior (eating), with a partial or complete loss of conscious awareness, the potential for bodily injury, and an inability to recall the event the next morning [1].

REM-related parasomnias occur during REM sleep and, as such, tend to appear in the final third of sleep [1, 7]. REM-related parasomnias include REM sleep behavior disorder (RBD), nightmare disorder, and recurrent isolated paralysis [1]. RBD involves a loss of the typical atonia associated with REM sleep, resulting in recurrent, often violent and combative, vocalizations or movements during REM [1, 6]. Whereas disorders of arousal (from NREM sleep) are characterized by disorientation upon waking, a lack of dream imagery, and difficulty recalling the event, individuals experiencing RBD are alert after waking and can recall their dream content, which usually aligns with the observed RBD behaviors [1]. Similar to disorders of arousal, however, RBD can result in serious bodily injury to the self and to bed partners [1, 7]. Nightmare disorder also involves recall of dream content and alertness after waking, but is not associated with movement during sleep [1, 7]. Nightmare disorder is characterized by repeated, vivid, and frightening dream content during REM that awakens the patient from sleep and that has a clinically significant impact on patient mood and functioning [1]. Finally, recurrent isolated paralysis refers to the inability to perform voluntary bodily movement when falling asleep or waking from sleep, in the absence of narcolepsy, other sleep disorders, medical or psychiatric problems, or medication or substance use [1].

Office Evaluation for Parasomnias

A thorough office evaluation is needed for a child with any parasomnia. Because parasomnias occur out of sleep, a child's recollection of events is often very limited and fragmented at best. Usually, the child will not remember any details of what transpired, and children with neurodevelopmental disabilities (NDD) may have further difficulty describing an event sequence. Parents should be questioned regarding how soon after initial sleep onset these events are noted (keeping in mind that non-REM parasomnias are typically most prominent in the first third to half of the night, whereas REM parasomnias often occur in the second half of the night) and whether episodes may also be seen during naps as well as at night [6].

Parents should also be asked to describe in detail the movements and behaviors that typically occur. It is important to ask whether the movements are rhythmic or highly stereotyped and whether the movements occur at different times through the night; these features, if present, may support epilepsy rather than parasomnias [6]. The relationship between epilepsy and sleep is complex. For example, many studies have shown that non-REM sleep activates interictal discharges in partial epilepsies, and indeed sleep spindles and spike-wave discharges share common mechanisms through thalamocortical circuitry [8]. In nocturnal frontal lobe epilepsy, however, the onset of seizures (ages 10–20 years) is later than the typical onset of parasomnias, and events tend to be more frequent (sometimes every night and multiple times during the same night) and shorter (typically lasting 20–30 s) as compared to parasomnias. Arousal parasomnias do not show the dyskinetic or dystonic postures typically associated with nocturnal frontal lobe epilepsy, and complex motor sequences are not stereotyped in individual patients with parasomnias as they are in patients with seizures [8, 9]. To complement the parents' descriptions, home videos are often very useful for identifying and classifying parasomnias. While the general elements of behavior (e.g., crying, agitation) may be similar across different nights for a patients with arousal parasomnias, the sequence and range of complex movements/behaviors vary [10]; for a patient with nocturnal seizures, serial video clips would be expected to show a recurrent and highly stereotyped pattern (with each clip looking the same).

Sleep diaries, in which parents record sleep periods, arousals/awakenings, and parasomnia events, help provide a more detailed history. Sleep diaries have been shown to be quite reliable regarding children's sleep schedules [11] (e.g., sleep onset, morning rise time), but validity drops for sleep quality measures such as night wakings. Actigraphy could be used to complement sleep diaries and has an advantage as a cost-effective, nonintrusive method to gather objective activity in a child's typical environments. Artifact in actigrams, however, can pose challenges related to device removal, induced external movement, and motionless wakefulness [11]. With sleep diary and actigraphy data taken together, periods of relative sleep deprivation may be found to be associated with increased arousal parasomnias. Possible triggers for parasomnias include obstructive sleep apnea and/or peri-

odic limb movements in sleep. It is important to query symptoms of obstructive sleep apnea, such as snoring, gasping, and pauses in breathing during sleep. The sleep history should be accompanied by a comprehensive physical and neurological exam, to look for features that would be associated with an underlying sleep disruptor. For obstructive sleep apnea, features such as adenotonsillar hypertrophy, nasal obstruction/nasal septal deviation, retrognathia/micrognathia, midface hypoplasia, a narrow hard palate with crowded dentition, and macroglossia should be considered [6]. Obesity and central hypotonia also increase the likelihood of obstructive sleep apnea. For periodic limb movements in sleep, features such as peripheral neuropathy or myelopathy should be considered, along with possible associated symptoms of restless legs syndrome. Overnight polysomnography (PSG) has a value in the evaluation of patients with arousal parasomnias, specifically to determine if there is an intrinsic sleep disruptor, such as obstructive sleep apnea or periodic limb movements in sleep. If these underlying disorders are treated, the frequency of parasomnias may decrease [41]. Of note, however, the parasomnias that are reported by parents may not be witnessed on PSG. A PSG that does not include a parasomnia event does not exclude parasomnias that are supported by parental report, home video recordings, and clinical evaluation during the office visit.

Multiple studies support a genetic predisposition for arousal parasomnias, so it is important to ask about affected family members. In studies of sleep terrors, a possible autosomal dominant disorder was seen in a three-generation family [12]. Kales et al. reported that the prevalence of sleepwalking and sleep terrors in first-degree relatives of patients with sleep terrors was ten times greater than in the general population [13]. If both parents were affected, they estimated a 60% chance of a child being affected [13]. Proposed modes of inheritance for sleepwalking include multifactorial models, autosomal recessive inheritance with incomplete penetrance, and autosomal dominant inheritance with variable/reduced penetrance. Based on the data from the Finnish Twin Cohort, Hublin et al. reported that >1/3 of sleepwalking in adults and >1/2 in children are attributable to genetic factors; both additive and dominant genetic effects were proposed [14]. In a small, family-based study, Lecendreux et al. found a positive association between the HLA-DQB1*05 subtype and sleepwalking, suggesting a possible further interaction between the immune system and sleep [15]. The familial traits responsible for familial parasomnias such as sleepwalking have not been fully defined, but one retrospective analysis showed that all of the study patients who had parasomnias also had sleep-disordered breathing and anatomical craniofacial (including maxillary and/or mandibular) risk factors for sleep-disordered breathing [16]. From their genome-wide linkage analysis for sleepwalking in a four-generation family, Licis et al. reported the first genetic locus for sleepwalking at chromosome 20q12-20q13.12, although the specific gene involvement and relevance to individuals in other families need to be elucidated [17].

NREM-Related Parasomnias

Behavioral Manifestations and Prevalence in Typically Developing Children

Due to shared diagnostic features (see Table 7.1), the three disorders of arousal are thought to represent a spectrum of NREM-related parasomnias [6, 18]. Indeed, confusional arousals, sleepwalking, and sleep terrors have been found to co-occur, particularly among children and adolescents. For instance, whereas the co-occurrence of sleepwalking and sleep terrors was only 0.3% in a large sample of adolescents and adults ages 15–100 years [5], a study of children ages 3–13 years revealed an association of 0.21 for sleepwalking and sleep terrors, with 17% of children who endorsed sleepwalking showing sleep terrors and 36% of children with sleep terrors reporting additional sleepwalking [3].

Despite their similarities, the disorders of arousal can be distinguished by their behavioral manifestations, with some subtle differences in their age of onset and prevalence [3, 4, 18]. Confusional arousals refer to movements and vocalizations (talking, crying, whimpering, etc.) in bed, with the child often sitting up and appearing confused and agitated during the event [1, 6, 18]. These episodes have an average duration of 5–30 min [6, 18]. Confusional arousals tend to emerge between the ages of 2 and 10 years but are more common among in early childhood [1, 6, 18, 19]. In typically developing children, the prevalence rate for confusional arousals is approximately 17.3%, with no noted sex differences [3]. Confusional arousals decrease in prevalence to a rate of 2.9–4.5% among individuals ages 15 years and older [1, 5].

Instances of sleepwalking frequently begin as a confusional arousal [1] and involve the individual leaving the bed, although in young children, sleepwalking may appear as crawling around the crib or bed [18]. Some individuals become agitated while sleepwalking and may bolt out of bed and scream, whereas others appear calm and engage quietly in routine behaviors, such as walking down the stairs or urinating [1, 18]. Sleepwalkers can easily injure themselves by walking into objects around the home or by unlocking doors and windows and walking outside [6, 18, 19]. Sleepwalking typically emerges between 5 and 10 years of age [18], with few sex differences found in prevalence rates [3]. Although a longitudinal study of Swedish children ages 6–16 years indicated that sleepwalking affected 40% of the sample [20], recent studies of children have shown prevalence rates of

approximately 11–14.5% [2–4]. Sleepwalking occurs in 2–4.3% of older adolescents and adults [1, 5].

Unlike confusional arousals and sleepwalking, sleep terrors begin with a loud, piercing scream, accompanied by intense physiological reactivity (e.g., rapid and shallow breathing, sweating, tachycardia, etc.), fearfulness, and agitated movements [1, 6, 18]. Sleep terrors usually emerge between 2 and 10 years of age [18]. Prevalence rates for sleep terrors in typically developing child samples show substantial variation across studies, often due to differences in study samples and methodology [4]. Sleep terrors have been found to impact as many as 39.8% of preschoolers ages 2.5–6 years [4], with prevalence rates in the literature noted to be as low as 1–6.5% [1] and as high as 9.3–17.3% in studies of youth ages 3–13 years [2, 3]. Sleep terrors are less common after age 15, with an average rate of 2.2% among individuals aged 15–100 years [5].

Prevalence Among Children with Neurodevelopmental Disabilities

There are some data to suggest that NREM-related parasomnias are more prevalent among certain populations of youth with neurodevelopmental impairments. For example, several studies have noted significantly higher scores for youth with autism spectrum disorder (ASD) than for typically developing youth on the frequency of parent-reported symptoms suggestive of parasomnias (e.g., "wakes up screaming approximately 2 hours after going to sleep") [21–23]. Of note, this work examined reporting on broad sleep questionnaires and did not compare rates of verified NREM-related parasomnia diagnoses across groups. However, Ming and colleagues [24] recently compared PSG data for 23 children with ASD and 23 age-matched controls and found that those with ASD evidenced significantly higher rates of disorders of arousal than control children. This study also found that parent-reported parasomnias on sleep questionnaires corresponded with PSG evidence of NREM-related parasomnias, such that of the 14 children with ASD who experienced PSG-recorded parasomnias, 11 of them also had parent-reported night crying or screaming episodes [24].

Importantly, there have been some inconsistent findings in this literature, with several studies showing no increased parent-reported parasomnia prevalence among children with ASD [25–27]. Research similarly indicates inconsistencies in the prevalence of parent-reported NREM-related parasomnias among children with Down syndrome, likely due to variation in the sample size, characteristics, and specificity of parent-reported measures being used to identify sleep concerns [27]. For example, two studies have shown that parents of children with Down syndrome report higher mean levels of NREM-related parasomnias on sleep questionnaires than rates reported by parents of typically developing youth [28, 29], whereas some work indicates low prevalence rates among these youth (i.e., 3%) compared to prevalence data in normative samples [30]. In a child with neurodevelopmental disorder, a positive family history of parasomnias may indicate additive risk for further parasomnias.

In a recent meta-analysis of 61 studies examining sleep problems in youth with multiple disabilities, Tietze et al. [31] reviewed some additional evidence linking parasomnias with specific neurodevelopmental conditions, such as cri du chat syndrome [32], Angelman syndrome [33–35], and cerebral palsy [36], although there were no data to indicate that parasomnias are consistently found in or more prevalent among these populations. Relevant to the occurrence of NREM-related parasomnias, one study of 49 youth under age 15 with Angelman syndrome (AS) and their age-matched controls demonstrated prevalence rates of 5.41% for both sleepwalking and sleep terrors in youth with AS in the 6 months prior to the study compared to rates of 3.14% and 1.34% for these disorders, respectively, among controls [33]. A larger study of 290 youth with AS documented that 1.7–4.9% of parent reporters endorsed that their child "frequently" or "always" evidenced symptoms consistent with sleep terrors, such as "wakes up screaming during the night and cannot be calmed down" and "is not awake when screaming at night" [34]. In children with cerebral palsy, a prevalence rate of 8.1% has been shown for experiencing disorders of arousal in the 6 months prior to the study, although in this study, specific parasomnia subtypes were not distinguished [36]. Overall, while there are no large-scale population-based studies that show increased prevalence of NREM-related parasomnias among youth with neurodevelopmental problems, a proportion of children with different neurodevelopmental conditions do appear to experience these events more frequently than typically developing youth [24, 31, 33, 34]. However, additional studies are needed to determine specific and more nuanced differences in NREM-related parasomnia frequency (i.e., number of times per week) as well as the severity and duration of NREM-related parasomnias among typically developing youth and those with neurodevelopmental conditions.

Classification Challenges

Classification of NREM-related parasomnias in children with neurodevelopmental disabilities can be challenging for caregivers and medical professionals. One salient issue noted in the literature is that few pediatric sleep questionnaires have been validated for children with neurodevelopmental problems [31, 37]. Although Ming et al. [24] have provided some evidence that questionnaire-based parent-reported NREM-related parasomnias correspond with observed PSG

data, few studies have specifically examined the psychometric properties of commonly used sleep research measures in heterogeneous samples of children with disabilities. While this issue is not as problematic in clinical settings, where any screening measures are typically followed by parental interviews and often PSG, validity studies for screening questionnaires are needed for research purposes [31].

Interview procedures for identifying NREM-related parasomnias can also be complicated by child and caregiver factors. A number of neurodevelopmental disorders present with comorbid deficits in cognitive functioning and communication skills, making it difficult to ask youth to describe their sleep experiences [31, 37]. Given that a critical diagnostic feature of NREM-related parasomnias is that the child cannot recall the event in the morning [1], assessing this criterion in youth with more severe neurodevelopmental and related cognitive impairments is challenging.

Relying on caregiver reports of child behavior can also be difficult when classifying NREM-related parasomnias. Research has shown that parents of children with neurodevelopmental and sleep problems often do not seek treatment, under the assumption that sleep disturbances are associated with the underlying neurodevelopmental disorder and therefore unlikely to change [37, 38]. These assumptions could contribute to underreporting of child sleep disorders and, in turn, a lack of appropriate diagnosis and treatment. Other caregivers may be unable to distinguish between characteristics of the sleep disorder and the daytime behavior of some children with neurodevelopmental disorders [27, 31]. This may be especially challenging in the context of evaluation for NREM-related parasomnias. For example, distinguishing whether a child is having a disorder of arousal versus a REM-related parasomnia versus an agitated but otherwise normal night waking could be challenging with a child who is nonverbal, routinely engages in stereotyped behaviors, or is not interactive with others during daytime hours. As described further below, a consideration of whether there is a history of seizures is also important when assessing any child for NREM-related parasomnias. For parents of children who have both neurodevelopmental conditions and associated seizures, differentiating seizure behavior and NREM-related or REM-related parasomnias may be particularly difficult due to broad similarities in the behavioral manifestations of these events.

Safety Issues

Safety can be a significant concern when children are experiencing frequent, dangerous, or violent NREM-related parasomnias [6, 7, 18, 39]. Caregivers can take different precautions at home to prevent injuries to the child or others, depending on the child's nighttime behaviors. Caregivers can remove bedside furniture or toys or place the child's mattress on the floor to enhance safety of the child during a confusional arousal or when the child is emerging from bed during an episode of sleepwalking or sleep terror [6, 39]. Parents can place a bell or an alarm on the child's door to alert others at home of sleepwalking episodes so that the child can be redirected to bed [6]. Additionally, families should consider locking or covering windows, securing the front door, and installing an alarm system to prevent children from leaving the house or from hurting themselves while walking downstairs [6, 18]. Locks may need to be installed higher than usual so children cannot reach these during event. Families should also lock up or remove firearms at home and should be sure to lock and store firearms unloaded to prevent their being discharged during a disorder of arousal [39].

Some bedroom and home conditions may present additional challenges for families trying to maintain safety during NREM-related parasomnias. For example, families who live in an apartment complex may have difficulty obtaining approval from management to install precautions like dead bolts at home and should receive support and justification from their medical provider if this is problematic. Families with pools or other backyard spaces in particular should take measures to ensure that the child cannot access these locations during an episode. Children who experience NREM-related parasomnias and share a bedroom with one or more family members may inadvertently hit, kick, or startle others in the room when these events occur. Caregivers can educate others in the home to avoid interaction with the child when an episode is occurring and consider rearranging room-sharing conditions when there is a risk of serious injury or frequent sleep disruptions for family members. Specific to children with neurodevelopmental conditions who engage in self-injurious behaviors during these events, such as the head banging or body rocking often seen in children with ASD, parents may consider having the child wear a helmet or placing protective padding (e.g., pillows, etc.) in or around the bed [40], as long as this does not promote increased sensation-seeking behaviors.

Modifying and Contributing Factors

Both individual and environmental factors can contribute to the incidence of NREM-related parasomnias in children. Importantly, environmental factors such as insufficient sleep, stress, or changes to the individual's typical sleep conditions (i.e., sleeping in a new or noisy location) are associated with NREM-related parasomnias [6, 18]. As noted above, research also indicates a genetic basis for parasomnias, with studies showing that children who sleepwalk or have sleep terrors are more likely to have first-degree relatives who also have a history of NREM-related parasomnias [13, 41]. Child age is

additionally thought to impact NREM-related parasomnias, given their increased prevalence in childhood as opposed to during later adolescence and adulthood [18]. In their examination of adult sleepwalking, Oliviero et al. [42] proposed that adult sleepwalkers could have increased immaturity in their neural circuits, synapses, or receptors compared to non-sleepwalking adults. Recently, in a sample of 72 children, Nevsimalova and colleagues [43] found that a perinatal risk history and comorbid developmental problems, such as ADHD, an intellectual disability, or a learning disability, were significantly associated with the incidence of NREM-related parasomnias. The authors concluded that these findings support the idea that NREM-related parasomnias could evolve as a result of underdeveloped neural circuitry among younger children and those with neurodevelopmental conditions [43], although additional studies are necessary to further examine this hypothesis.

The presence of other medical problems, and untreated sleep disorders in particular, can trigger NREM-related parasomnias [18, 41, 43]. Guilleminault et al. retrospectively examined factors that precipitated sleepwalking and sleep terrors in a sample of youth aged 2–11 years and found that when children with NREM-related parasomnias were treated for comorbid sleep-disordered breathing or restless legs syndrome, their parasomnias were eliminated [41]. Conversely, youth in the study with REM-related parasomnias whose comorbid sleep disorders were left untreated showed no change in their incidence of parasomnias, suggesting that the sleep disruptions caused by the presence of other sleep-related movement or breathing disorders may trigger NREM-related parasomnias [41]. Nevsimalova et al. also found that children with NREM-related parasomnias were more likely to have other co-occurring sleep disorders [43].

Additional medical concerns such as fever, illness, or reflux [18, 43], or the use of medications associated with sleep disruption, such as psychotropic, stimulant, or antihistamine medications [1, 5, 6], may also increase the incidence of NREM-related parasomnias. The occurrence of NREM-related parasomnias in adulthood is associated with psychiatric problems, such as symptoms of depression and anxiety [5]. There is little work to suggest that this association occurs among children, although Guilleminault et al. found that young children with separation anxiety were more likely to sleepwalk and have sleep terrors [41], and Fisher et al. found a small association between persistent sleep terrors and psychotic experiences in a large sample of 12-year-olds [2].

Overall, sleep disorders are multifactorial in nature, particularly among youth with neurodevelopmental conditions [31, 37]. Some factors specific to youth with neurodevelopmental disabilities could impact the etiology and maintenance of NREM-related parasomnias. For example, several studies have shown that greater cognitive impairments among youth with neurodevelopmental conditions have been associated with increased frequency and severity of sleep disturbances and disorders [22, 31, 44]. As sleep fragmentation, insufficient sleep, and breathing- or movement-related sleep disorders can contribute to the incidence of NREM-related parasomnias [6, 18], it is reasonable that youth with neurodevelopmental conditions who experience more associated cognitive impairments and, in turn, more frequent sleep disruptions or disorders may be at greater risk for experiencing NREM-related parasomnias.

There is some work to suggest that increased pain can trigger parasomnias in youth with neurodevelopmental conditions. Bidirectional relations between pain and poor sleep have been found in diverse populations of youth with chronic pain and other medical conditions [45]. In a sample of youth with intellectual and developmental disabilities, Breau and Camfield showed that children with higher pain scores showed significantly more frequent night wakings, signs of sleep-disordered breathing, and parent-reported parasomnias on the Children's Sleep Habits Questionnaire (CSHQ) relative to those with lower pain scores [46]. Tudor and colleagues have also found a relationship between pain and increased incidence of parasomnias among children with ASD [47]. In their study, pain was predictive of diminished sleep duration, parasomnias, and sleep-disordered breathing on the parent-reported CSHQ [47]. Sleep fragmentation or insufficient sleep as a result of pain in youth with neurodevelopmental conditions could trigger parasomnias, although studies that examine interrelations between pain and the prevalence of diagnosed NREM-related parasomnias in particular are needed.

Differential Diagnosis

The differential diagnosis of paroxysmal events during the night includes epilepsy (such as nocturnal frontal lobe epilepsy), parasomnias, sleep-related movement disorders, sleep-related dissociative disorders, and psychogenetic non-epileptic seizures [48]. As detailed in the ICSD-3, sleep-related movement disorders include restless legs syndrome, periodic limb movement disorder, sleep-related leg cramps, sleep-related bruxism, and sleep-related rhythmic movement disorder. Questionnaires could be considered for sorting out the differential diagnosis, but the complexity of nocturnal events can pose challenges. In a study of children with ASD, 14 of 21 had polysomnography evidence of a parasomnia; questionnaire was shown to have a sensitivity of 64.7% but a much lower specificity of only 33.3% [24]. While many seizures may be easily distinguished from non-epileptic events on the basis of history, some epileptic seizures, such as those seen with nocturnal frontal lobe epilepsy (NFLE), may be difficult to diagnose. A Frontal Lobe Epilepsy and Parasomnias (FLEP) scale was developed and tested in

adults, not children, with initial findings supporting the use of the scale's clinical features for reliably diagnosing NFLE [49]. However, a subsequent study highlighted the inadequacy of some items from the scale, which could, for example, increase the likelihood of mistaking REM behavior disorder for seizures [50].

If epilepsy is considered, an expanded EEG montage is needed, with options including a sleep-deprived EEG, video-EEG as inpatient, or ambulatory continuous EEG recording. While ambulatory EEG recording has the appeal of potentially greater convenience and lower cost, there are several limitations: contamination of the EEG signal by artifacts (loose leads, muscle activity, movement), an often reduced number of channels available for the recording, and no concurrent video documentation to review behavioral manifestations [51]. An additional challenge is that the EEG in NFLE can be normal, with deep discharges missed by scalp electrodes or discharges obscured by movement artifact [48]. Moreover, the presence of epileptiform discharges (spikes, sharp waves) may not be correlated with clinical seizures. In ASD, for example, the baseline prevalence of epileptiform discharges is high, ranging from 15–20%, up to 59.4%, in different studies [52, 53]. By extension, epileptiform discharges in an EEG of an autistic child with paroxysmal nocturnal events would not necessarily indicate nocturnal seizures. In cases where the diagnosis is difficult to establish, prolonged video-EEG monitoring can increase the yield of captured events and allow recognition of subtle but consistent findings on either the EEG or seizure semiology. Also, recording multiple events allows an increased likelihood of capturing an event in which electrographic activity builds/evolves to the point of being detected by scalp leads or an event without obscuration by muscle artifact [48].

Management

Among typically developing children, evidence-based approaches for treating NREM-related parasomnias include parental psychoeducation, treatment of any comorbid sleep disorders, sleep extension, and scheduled awakenings [6, 18, 54]. In some cases, medications can also be used to treat NREM-related parasomnias [6, 7, 18]. Parental psychoeducation and reassurance about the benign nature of most NREM-related parasomnias can be useful, as can providing caregivers with information about maintaining child safety and avoiding prolonged interactions with the child during the event [6, 18]. As Guilleminault et al. have shown, managing comorbid sleep disorders such as sleep-disordered breathing problems or restless legs syndrome can resolve sleepwalking and sleep terrors in children [41]. Given that youth with neurodevelopmental conditions tend to show an increased prevalence of sleep-disordered breathing and insomnia, which can result in insufficient sleep [31], parents of these children may benefit from additional psychoeducation about the risk for parasomnias in the context of other untreated sleep disorders.

Some studies have shown that group or individual parental psychoeducation about broad sleep problems is useful for parents of children with neurodevelopmental conditions. Stores and Stores examined the benefits of brief parent instruction about child sleep problems in a sample of young children aged 7 months to 4 years with trisomy 21 [55]. Compared to children with trisomy 21 whose parents received no sleep instruction, children with trisomy 21 whose parents received psychoeducation showed fewer behavioral sleep problems at 6-month follow-up [55]. Malow and colleagues compared group-administered versus individually administered parent psychoeducation about sleep problems for youth ages 2–10 years with ASD and found that parent-reported insomnia, sleep latency, and parasomnias on the CSHQ decreased in both groups following sleep education [56]. It should be noted, however, that parasomnias and other sleep disorders were not assessed objectively via video recordings or other measures.

Because sleep deprivation has been found to contribute to the incidence of NREM-related parasomnias, extending children's sleep duration to ensure that they receive an adequate amount of total sleep for their age is useful [54]. Guidelines for recommended child sleep needs at different ages can be found at http://sleepfoundation.org/how-sleep-works/how-much-sleep-do-we-really-need. To implement sleep extension, caregivers can set a consistent bedtime and waketime schedule that allows for enough total sleep per night [54]. Sleep extension may be difficult to implement among children with neurodevelopmental conditions, potentially due to differences in their sleep needs and habits [31, 38, 44]. For example, meta-analytic data indicate that youth with ASD tend to have less total sleep time, increased sleep latency, and diminished sleep efficiency than their typically developing peers [44]. Children with ASD and intellectual disabilities in particular showed diminished total sleep time relative to other youth with ASD and to typically developing peers, indicating that these cognitive and behavioral differences may contribute to differences in child sleep duration [44].

Case studies have shown that anticipatory or scheduled awakenings can be used to prevent NREM-related parasomnias [57–59]. This strategy is helpful when parents can identify a particular time at which the NREM-related parasomnia typically occurs each night [6]. In this approach, parents wake the child up 15–20 min before the event usually occurs and have a brief, comforting interaction with the child before putting him or her back to bed [18, 54]. Generally, there are few large-scale studies that show the efficacy of behavioral techniques in treating various sleep difficulties in youth with neurodevelopmental conditions [38, 55, 56]. However,

Durand reported on the benefits of scheduling awakenings and sleep extension in resolving frequent sleep terrors experienced by three children with ASD [60]. This is a low-cost, low-risk, but sometimes high-effort intervention that many families are willing to try.

Pharmacological intervention for the treatment of arousal parasomnias should be reserved for those rare, protracted cases with no associated sleep disorder, with frequent parasomnias, and with a threat of injury to patients/others [6]. Medications that have been used successfully include benzodiazepines and tricyclic antidepressants [61]. Examples of benzodiazepines used in adults for disorders of arousal include clonazepam, temazepam, and estazolam [62]. While benzodiazepines may reduce slow-wave sleep, they may also be effective for parasomnias by decreasing the likelihood of arousals [61]. Low-dose clonazepam has been reported as effective in controlling arousal disorders in children. A dose of 0.125–0.5 mg can be given at bedtime [18]. In some cases, a 3–6-week course of treatment may be curative, allowing the medication to be discontinued [63]. Potential side effects like paradoxical hyperactivity and drooling may occur in children with neurodevelopmental disabilities who are treated with benzodiazepines [18], so using the lowest effective dose may be advised. Benzodiazepines can be challenging to wean, and distress due to rebound parasomnias may prolong the process.

REM-Related Parasomnias

REM Behavior Disorder

REM sleep behavior disorder (RBD, also known as REM sleep motor disorder) involves combative or aggressive enactment of dreams. Instead of the expected REM sleep atonia, patients with REM sleep behavior disorder show complex movements that can be vigorous and sometimes violent. REM sleep behavior disorder in adults tends to have a male predominance, with onset usually in the sixth to seventh decade of life [6]. REM sleep behavior disorder is not commonly reported in children but can occur. While in a dream state, patients with REM behavior disorder may injure themselves or their bed partners by punching, grabbing, or kicking [64]. In some cases, the resulting trauma (e.g., ecchymoses, lacerations, and fractures) may be severe and perhaps even life-threatening. Patients with REM sleep behavior disorder report that their dreams have more intensity, action, and violence than typical dreams [65]. With RBD, there is variable loss of the general muscle paralysis typically associated with REM sleep, but all other major features of REM sleep remain in place. Motor control in RBD is more anomalous in general, and manifestations also include periodic limb movements and nonperiodic limb twitching in NREM sleep. Indeed, in adults with RBD, approximately 75% of patients have periodic limb movements during REM sleep [1].

While uncommon, REM sleep behavior disorder (subclinical, idiopathic, and symptomatic) has been documented in children and adolescents with onset as early as infancy [66]. In children, RBD may occur in the clinical setting of narcolepsy. RBD has also been seen in childhood neurological disorders such as juvenile Parkinson disease, olivopontocerebellar degeneration, and brainstem tumors [65, 67]. Other pediatric disorders associated with REM sleep behavior disorder or subclinical REM sleep behavior disorder based on case reports and case series include Tourette syndrome, xeroderma pigmentosum, Moebius syndrome, Smith-Magenis syndrome, and infantile spasms [65, 66, 68]. Clues to REM sleep behavior disorder in children include nightmares associated with body movements, trauma from movements during sleep, and vivid dream recall associated with limb/body movement. Thirumalai et al. were the first to document RBD in children with ASD; they reported RBD in 5 of 11 children studied [69]. There have not been further reports of a similarly increased prevalence of RBD in children with ASD. A shortcoming of the Thirumalai et al. study was that medications were not specified and medications such as selective serotonin reuptake inhibitors and tricyclic antidepressants may trigger RBD [68, 70].

Persistent elevated muscle tone and movement throughout REM sleep are demonstrated on polysomnography, including distinctly increased phasic EMG activity (REM sleep without atonia [RWA]) [65]. The placement of additional EMG leads during polysomnography may be helpful in revealing increased movements of the arms, legs, and trunk. As summarized in the ICSD-3, evidence-based data for detecting RWA in the setting of RBD show that any (tonic or phasic) chin EMG activity combined with bilateral activity of the flexor digitorum superficialis muscles in >27% of REM sleep 30-s epochs reliably distinguishes RBD patients from controls [1]. Reports of REM without atonia in pediatric patients with RBD, however, may rely exclusively on chin EMG tone in overnight polysomnography to assess muscle tone augmentation/sustained tonic muscle activity [68, 69]. In childhood RBD, the value of additional EMG monitoring from muscles of the forearm has not been established [71]. Pediatric polysomnography reports do not routinely comment on the presence of REM without atonia/RBD, so if there are clinical concerns for RBD prompting polysomnography, the referring clinician should share these with the sleep laboratory and sleep medicine provider interpreting the study.

Clonazepam suppresses phasic REM EMG activity, and most adults with RBD improve with low-dose therapy (0.5–2 mg taken at bedtime); in this clinical setting, clonazepam is reported to be efficacious and safe [65]. Typically,

relapse of REM behavior disorder occurs rapidly upon discontinuation of clonazepam [72]. Melatonin given in a range of 3–9 mg in adults is reported to restore REM atonia and may be effective as monotherapy for REM behavior disorder or successful in combination therapy with clonazepam. Melatonin may be especially considered for treatment of REM behavior disorder when there is an incomplete response to clonazepam or there are concerns that clonazepam could potentially exacerbate daytime sleepiness or aggravate existing dementia [73]. In a series of five pediatric cases of REM sleep behavior disorder, clonazepam given in bedtime doses of 0.25 mg has been reported to be completely effective in eliminating the parasomnia [74]. Elsewhere, clonazepam in children with RBD has been described as potentially fully effective, with melatonin at times also leading to resolution of symptoms [68].

Nightmares

Nightmare disorder is the repeated occurrence of dreams that have vivid, intense, and extremely disturbing or frightening content and typically wake the individual up from sleep [1, 6]. Nightmare content tends to involve threats to safety or survival [1]. Nightmares are usually accompanied by feelings of dysphoria, including fear, anxiety, and sadness, and may result in difficulty returning to sleep, particularly for children [1, 18]. In order to meet criteria for nightmare disorder, the experience of the dream or the resulting sleep disruption must result in a clinically significant impairment in function [1]. Examples of functional impairments include mood disturbance, bedtime resistance, cognitive or behavioral problems, or daytime sleepiness or fatigue [1]. ICSD-3 diagnostic criteria for nightmare disorder are summarized in Table 7.1.

In contrast to descriptions of NREM disorders of arousal, individuals can recall nightmare content upon waking and do not tend to appear confused when waking, although they may similarly call out during sleep, sweat, and move in bed when having a nightmare [18]. Further distinguishing these events from disorders of arousal, nightmares tend to occur in the second half of the night, when REM sleep is more common [1, 6]. Differentiating nightmares from a confusional arousal may be difficult in children, as some do appear disoriented after waking from a nightmare [75]. It may be especially challenging to identify whether children with NDDs are having nightmares and to separate these experiences from confusional arousals. As noted above in the context of classifying NREM-related parasomnias, deficits in child cognitive function and communication often result in difficulty eliciting diagnostic information from the child, such as whether he or she can recall the nightmare content upon waking.

Nightmares are common among younger children, with 30–90% of children aged 3–6 years experiencing occasional nightmares and 5–30% experiencing frequent nightmares [6]. Older children also experience nightmares fairly regularly. Recently, Fisher and colleagues examined the prevalence of nightmares in a large birth cohort of 6796 children, with repeated assessments of parent-reported child nightmares between ages 2.5 and 9 years and child-reported nightmares at age 12 years [2]. Of the sample, 37% of youth had parent-reported nightmares at multiple (three or more) child assessment periods, while 24.4% of youth at age 12 reported having nightmares in the 6 months prior to the study's data collection [2]. It is important to note that occasional nightmares in children do not indicate the presence of nightmare disorder [1]. According to the ICSD-3, nightmare disorder has a prevalence of 1–5% in preadolescent children, with 2–8% of the general population experiencing frequent nightmares [1]. Nightmares appear to equally impact males and females during childhood [6], with studies showing an increased prevalence of nightmares among female adolescents and adults [76–80].

Precipitating factors for nightmare disorder include a genetic predisposition for the disorder, as well as coincident psychopathology. Twin studies have shown that there is a genetic basis for frequent nightmares and that individuals with a history of persistent childhood nightmares are more likely to experience continued nightmares in adulthood [1, 81]. Nightmares are more prevalent among children and adults with psychiatric disorders, such as anxiety and posttraumatic stress disorder (PTSD) [1, 76, 77, 81, 82]. Fisher et al. have also provided some evidence for persistent nightmares over the course of childhood as an indicator of risk for psychotic experience at age 12 years [2]. Posttraumatic nightmares are a diagnostic symptom of PTSD, but the appearance of these events should not be considered an indicator of nightmare disorder unless the individual meets the necessary ICSD criteria for this condition as well [83]. Associations between frequent nightmares, psychopathology, and nightmare-related distress may also vary in magnitude according to the study design (longitudinal versus correlational) and whether parents or children report [77].

Contrary to some parental expectations, cross-sectional studies of nonclinical child samples indicate that time spent watching television and specific television content are not significantly associated with increased nightmare frequency in children, although youth often report having "bad dreams" about what they have viewed on television or through other media [77, 84, 85]. Additional studies on this topic are needed, given that there may be individual differences in children's sensitivity to violent stimuli and the degree to which media content impacts nightmare frequency [84]. For example, children with ASD may report idiosyncratic reactions to content that their parents would not typically antici-

pate to provoke fear or anxiety. Longitudinal studies are also needed to show whether increases in viewing violent media over time predict the onset or increased frequency of nightmares among children [84]. As such, management of nightmares may include limiting exposure to frightening stimuli during the day and especially prior to bedtime [18]. To help manage child nightmare disorder, it is also recommended that parents provide reassurance to children who wake with a nightmare [18, 54]. Of note, this technique should be reserved for children who require reassurance following nightmares, and not those who seek reassurance due to broad difficulties, independently falling and staying asleep throughout the night.

Cognitive-behavioral techniques to decrease distress and fear resulting from nightmare stimuli have been successful in both child and adult populations [75, 86, 87]. Imagery rehearsal therapy is one cognitive-behavioral strategy that has been associated with reduced nightmare frequency and enhanced sleep quality in adults with nightmare disorder or recurrent, PTSD-related nightmares [86]. This approach involves education about sleep, writing or discussing a dream narrative that positively changes a frightening aspect of the nightmare, and daily imaginal rehearsal of the new, positive dream imagery [86]. Two studies have adapted this technique for children. St-Onge et al. reported on diminished nightmare frequency in 9- to 11-year-old children at posttreatment and 9-month follow-up relative to no-treatment control children [88]. Simard and Nielsen also provided evidence that for children aged 6–11 years, enrollment in the study was associated with an initial and sustained decrease in nightmare frequency and related distress prior to treatment and demonstrated that imagery rehearsal treatment was associated with further reductions in nightmare-related distress [89]. Sadeh has summarized other cognitive-behavioral strategies for treating nightmares in children that have been effective in reducing nightmare frequency and related distress [75]. These interventions include systematic desensitization, relaxation techniques, and eye movement desensitization [75].

As is the case with other behavioral interventions for childhood sleep problems, few approaches have been evaluated among children with neurodevelopmental conditions [31, 37, 38]. Case studies suggest that cognitive-behavioral approaches to treating recurrent PTSD-related nightmares are beneficial for adults with intellectual disabilities. In their review of PTSD treatment for individuals with disabilities, Mevissen and de Jongh [90] identified two case studies [91] that successfully applied imagery rehearsal therapy to treat nightmares in adult women with mild intellectual disabilities who had experienced sexual assault. It is reasonable to assume that children with neurodevelopmental impairments with adequate cognitive and communication skills could benefit from cognitive-behavioral approaches to treating nightmare disorder; however, effective examples of this approach with youth who have neurodevelopmental conditions are needed.

Assessing the Impact of Parasomnias on Daily Functioning

In treating NREM- and REM-related parasomnias, it is critical to assess the impact of these disorders on child functioning. As noted above in the sections on the classification of parasomnias among youth with neurodevelopmental conditions, it may be difficult to assess the functional impact of parasomnias on youth with these conditions because of related cognitive or communication impairments [31, 37, 38]. Additionally, there is a paucity of pediatric sleep disorder screening tools, let alone any that address parasomnia symptoms, that have been validated for youth with neurodevelopmental conditions [31], which may lead to underidentification of parasomnias and other sleep disorders.

In order to assess whether parasomnias negatively impact child functioning, parents of youth with neurodevelopmental conditions and comorbid parasomnias should receive psychoeducation about parasomnias and their potential negative effects on child functional outcomes. Such outcomes include behavioral dysregulation and parasomnia-related distress (for instance, as in nightmare disorder) [7, 18]. Parents should also consider keeping daily sleep logs to document child parasomnias and subsequent daytime functioning [54]. Assessing parental sleep in the context of child parasomnias or any sleep difficulty may also provide insights into broader family functioning [37, 38]. For example, research has demonstrated that parents of youth with comorbid neurodevelopmental conditions and sleep problems tend to show poor sleep habits themselves as well as diminished psychological well-being relative to parents of youth with disabilities who do not have sleep concerns [92]. While no research on this topic has not been specific to parasomnias and reflects broader sleep difficulties, it is reasonable that the presence of untreated child parasomnias could disrupt parent and family sleep. When child self-assessment is limited, assessing the sleep of parents and other family members may therefore be useful in obtaining information about how parasomnias impact daily functioning and whether subsequent treatment has been beneficial.

Future Directions

The review of the literature on parasomnias provided in this chapter suggests several important directions for future research. In particular, studies that aim to validate assessment tools and treatment approaches for parasomnias among heterogeneous groups of youth with diverse neurodevelopmental conditions are needed [31, 37, 38, 56]. There are also impor-

tant questions for future research related to the etiology and prevalence of NREM- and REM-related parasomnias, both for youth with neurodevelopmental conditions and for typically developing youth. Given that the available prevalence literature on parasomnias also often uses parent ratings that vary in their focus on either the frequency or the intensity of parasomnias, studies to disentangle whether parasomnias are more frequent, more severe, or both among youth with neurodevelopmental conditions would be helpful, as would additional studies using more objective (PSG or actigraphy) data. In the future, studies with analysis of EMG data from different muscle groups, especially in patients examined longitudinally over multiple nights, could prove valuable in improving the diagnostic certainty of parasomnias, and especially RBD, in children. Other unresolved PSG issues include the minimum REM sleep duration needed to diagnose REM without atonia or exclude REM without atonia and how to evaluate REM without atonia in the setting of disrupted REM sleep (e.g., with concurrent obstructive sleep apnea and with medications) [1]. Overall, there are few longitudinal studies of pediatric NREM- or REM-related parasomnias. For youth with neurodevelopmental conditions, there are likely bidirectional effects between neurodevelopmental symptoms and sleep problems (e.g., sleep fragmentation, insufficient sleep, untreated parasomnias) [31], which could result in persistently disturbed sleep and poor developmental outcomes. Research that explores these interrelations is needed to determine potential psychosocial and developmental impacts.

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Hypersomnia

8

Samata Singhi, Erin Steinhart, and Kiran Maski

Case Vignette

Andrew is an 11-year-old boy with a history of ADHD and anxiety who presents to neurology clinic with persistent daytime sleepiness since age 9 years. Andrew sleeps approximately 9.5 h at night and falls asleep in class several times per week. Teachers also describe him as having poor attention and working memory and being easily distractible, especially in the afternoons. Mother says he is very irritable and moody in the evenings but does better if he naps for 1–2 h after school and before dinner. Epworth Sleepiness Scale score was 18/24, indicating moderate to severe daytime sleepiness. Andrew was diagnosed with attention-deficit/hyperactivity disorder and has been on 10 mg of Adderall XR since age 10 years. This medication has helped his attention problems and school performance to some degree but has not improved his daytime sleepiness. Mother wonders how much of Andrew's daytime sleepiness is affecting his attention, mood, and school performance and whether an underlying sleep disorder could contribute to his symptoms.

Introduction

Hypersomnia is defined as the inability to stay awake during typical wakeful times during the day and may present as unintended lapses into drowsiness or sleep as well as a persistent desire to sleep [1]. Children may not be aware of their degree of sleepiness so parent and teacher behavioral observations are critical in the evaluation process. Symptoms of daytime sleepiness, which involves a real propensity toward sleep, must be distinguished from fatigue. Fatigue is often described as feeling tired, rundown, never rested, lacking energy, and exhausted. While the sleepiness of hypersomnia may also be associated with fatigue, patients with fatigue generally don't report inadvertent lapses into sleep like hypersomnia patients. Use of open-ended questions, requesting examples of symptoms in specific situations (i.e., whether a child falls asleep in car rides or during boring classes), and obtaining behavioral observations from parents, peers, and teachers can help the clinician distinguish more concerning symptoms of hypersomnia from generalized fatigue. Sleepiness can vary in severity and range from propensity to sleep in low-stimulation environments and with monotonous activity all the way to sudden sleep attacks.

Differential Diagnosis of Hypersomnia

Primary Central Nervous System Hypersomnias

Primary central nervous system hypersomnias can be broadly categorized as either chronic or periodic conditions (Fig. 8.1). Chronic primary hypersomnias refer to conditions in which symptoms of excessive daytime sleepiness are present daily for at least a 3-month period and include narcolepsy type 1 (narcolepsy with cataplexy), narcolepsy type 2 (narcolepsy without cataplexy), and idiopathic hypersomnia. Periodic primary hypersomnias are episodic presentations of exces-

S. Singhi
Department of Neurology, Boston Children's Hospital, Boston, MA, USA

E. Steinhart
Clinical Research Operations, Department of Neurology, Boston Children's Hospital, Boston, MA, USA

K. Maski (✉)
Department of Neurology, Boston Children's Hospital, Boston, MA, USA

Harvard Medical School, Boston, MA, USA
e-mail: kiran.maski@childrens.harvard.edu

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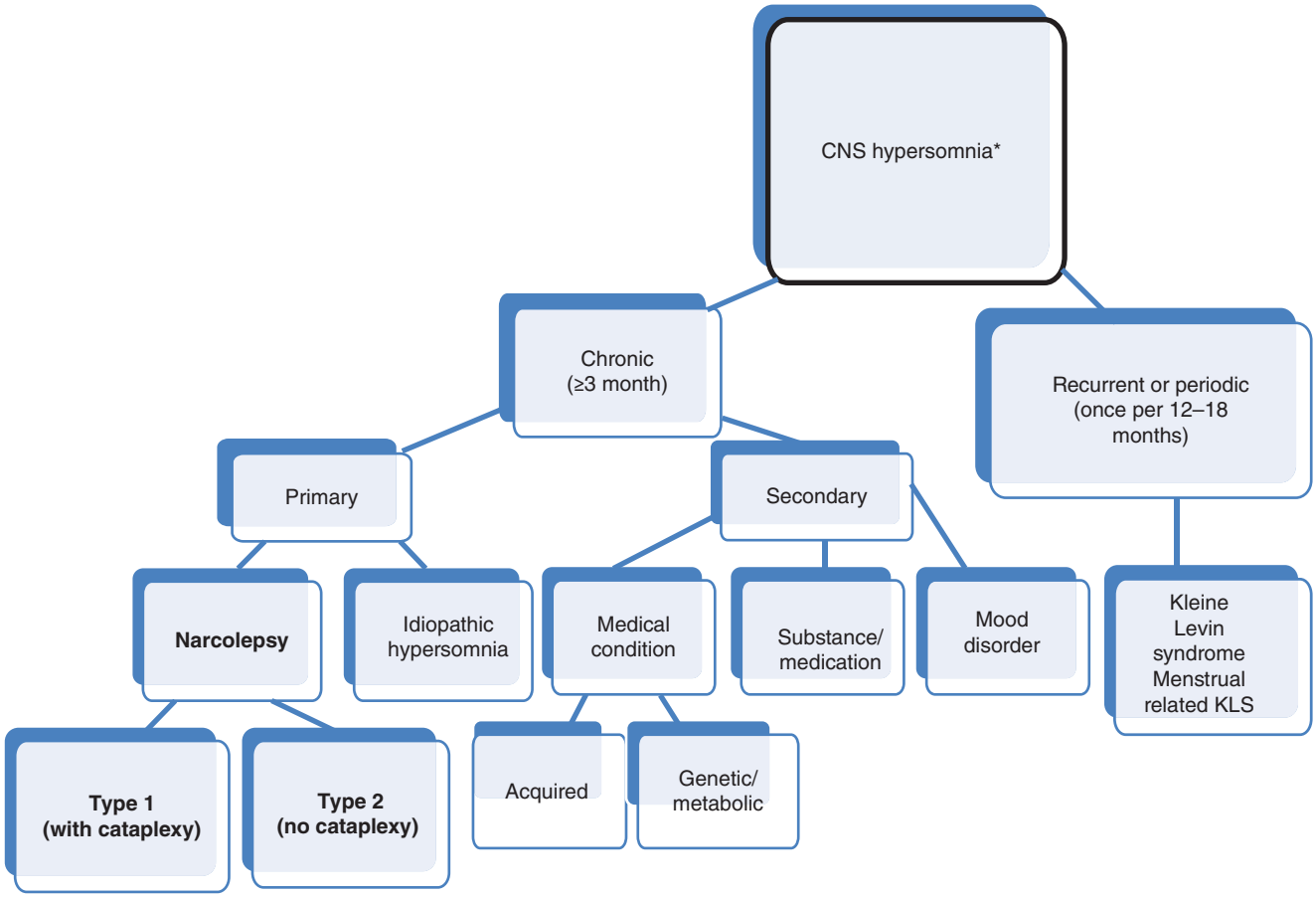

Fig. 8.1 Flowchart of primary and secondary hypersomnia conditions. *Excludes hypersomnia due to insufficient sleep or other primary sleep disorders

sive daytime sleepiness that are generally cyclical in nature and include menstrual-related hypersomnia and Kleine-Levin syndrome.

Narcolepsy Type 1

Narcolepsy type 1 is a rare sleep disorder, occurring in 0.025–0.05% of the population or 1 per 2000 people [2, 3] characterized by excessive daytime sleepiness, hypnagogic (sleep onset) and hypnopompic (sleep offset) hallucinations, sleep paralysis, and cataplexy. Fundamentally, these symptoms are thought to be related to increased rapid eye movement (REM) sleep pressure [4]. In normal REM sleep, dreams occur, and the body becomes functionally atonic, with the exception of eye muscles and the diaphragm. The sleep-related hallucinations and sleep paralysis experienced in narcolepsy are attributed to inappropriate transitions into REM sleep occurring close to waking periods. Similarly, cataplexy is believed to represent the functional atonia characteristic of REM sleep intruding into wake periods. The etiology of narcolepsy is due to loss of hypocretin neurons in the lateral hypothalamus though the cause of this neuronal loss is still unknown [5–7]. A strong association with narcolepsy type 1 and the HLA DQB1*0602 haplotype has been found suggesting an autoimmune etiology [8, 9].

Excessive daytime sleepiness is the core symptom of narcolepsy and is generally the first presenting symptom [10, 11]. In prepubertal children, symptoms of cataplexy have been reported to precede excessive daytime sleepiness though this is a rare presentation [12]. Narcolepsy symptoms most commonly develop in the second decade of life between ages 10 and 19 years of age with a second peak at ages 30–40 [2]. More recently, a rise in prepubertal onset of symptoms has been reported with more dramatic and sudden onset of symptoms [13, 14]. In these cases, excessive nocturnal sleep time, daytime sleepiness, atypical cataplexy, precocious puberty, and rapid weight gain have been noted. Unfortunately, the median time to diagnosis has been reported to be as high as 10.5 years and is attributed to lack of awareness of narcolepsy symptoms and signs [15, 16]. Pediatric narcolepsy can be a particular diagnostic challenge

because of associated neurobehavioral and psychiatric comorbidities discussed later in this section that can lead to misdiagnosis.

Cataplexy involves transient atonia that typically lasts seconds and is triggered by emotional stimuli such as laughter, anger, embarrassment, anticipation, and even pain. During classic cataplexy attacks, the axial muscles are affected, most commonly with transient weakness at the jaw, neck, shoulders, and/or knees. Consequently, cataplexy may be observed as episodic tongue protrusion, jaw slackening, change in speech, head bobbing/head drops, shoulder slumping, knee buckling, and/or falls. Cataplexy can be mistakenly diagnosed as epileptic seizures in the more severe cases, or children may be labeled clumsy in the more subtle presentations [12]. Cataplexy is reported in 65–75% of the patients with narcolepsy [17, 18] and distinguishes the condition of narcolepsy type 1 (narcolepsy with cataplexy) from narcolepsy type 2 (narcolepsy without cataplexy). Cataplexy onset is usually within 3 months to 1 year after onset of sleepiness [11, 19]. More recently, atypical forms of cataplexy have been reported, most notably in prepubertal children [20]. Atypical cataplexy may present with cataplectic facies (ptosis, jaw opening) and even positive motor phenomena resembling tics and/or dyskinesias such as grimacing and repetitive tongue protrusion [20]. This atypical presentation of cataplexy is not emotionally triggered and appears to be more chronic in nature, making it difficult to distinguish from other neurological conditions such as primary movement disorders or neuromuscular disease.

Narcolepsy Type 2

Narcolepsy type 2 shares the symptoms that mark narcolepsy type 1 – daytime sleepiness, hypnagogic or hypnopompic hallucinations, and sleep paralysis – with the exception of cataplexy. Despite this overlap in symptoms, only 24% of patients with narcolepsy type 2 have low CSF hypocretin levels (<110 pg/ml), and only about 40% are positive for the HLA DQB1*0602 haplotype. It has been suggested that this disorder may result from only partial loss of hypocretin neurons or that the disorder is different in etiology altogether [8, 21, 22]. Furthermore, cataplexy can occur years after daytime sleepiness symptoms, so in some cases, narcolepsy type 2 may simply be an early form of narcolepsy type 1. Diagnosis of narcolepsy type 2 can be challenging because symptoms of hypnagogic/hypnopompic hallucinations and sleep paralysis also occur in the general population, notably in settings of shift work and sleep deprivation [23, 24]. Thus, clinical history regarding symptoms, social history including work hours, stressors, sleep duration, and sleep quality are critical for making an accurate diagnosis of narcolepsy type 2. The revised International Classification of Sleep Disorders Manual specifies the diagnosis of narcolepsy (type 1 or type 2) requires typical symptoms and one of two confirmation studies: (1) a nocturnal polysomnogram and multiple sleep latency test (diagnostic of both type 1 and type 2) *or* (2) CSF hypocretin <110 pg/ml (diagnostic exclusively of type 1). The details of this sleep testing are discussed further in this chapter. It is estimated that narcolepsy type 2 represents 15–25% of all reported narcolepsy cases.

Idiopathic Hypersomnia

Idiopathic hypersomnia (IH) is also a condition of excessive daytime sleepiness, with patients reporting daily irresistible sleep periods over a period of at least 3 months without accompanying symptoms of hypnogogic hallucinations, sleep paralysis, or cataplexy. Patients with IH typically report symptoms of sleep drunkenness or sleep inertia (irritability and confusion upon being woken up with repeated returns to a sleep state) and unrefreshing naps [1]. Despite long sleep durations, on average greater than 10 h, patients with IH still have excessive daytime sleepiness. The etiology of this condition is unknown. Patients with IH generally have normal CSF hypocretin levels, and there has been no clear association with HLA typing or preceding infections [25]. In comparison to patients with narcolepsy types 1 and 2, individuals with IH have higher sleep efficiency on polysomnography, longer mean sleep latencies on the multiple sleep latency test, and a tendency to be older at the time of symptom onset [26, 27]. Some reports indicate a familial pattern of hypersomnia, as IH patients commonly report a relative with similar symptoms; however, there is little research about inheritance patterns of IH [1, 26]. Obstructive sleep apnea, delayed sleep phase syndrome, insufficient sleep, and drug use can all mimic the symptoms of idiopathic hypersomnia [25]; therefore close monitoring of typical sleep duration (by sleep charts or actigraphy) and performance of overnight polysomnography and multiple sleep latency testing are essential to provide an accurate diagnosis. Idiopathic hypersomnia typically develops in adolescence and in many cases self-resolves by young adulthood [1]. On the other hand, patients initially diagnosed with IH may later develop other symptoms typical of narcolepsy (hypnagogic/hypnopompic hallucinations, sleep paralysis). In these cases, their diagnoses may be changed to narcolepsy type 2 after repeat sleep diagnostic testing confirms the presence of abnormal sleep onset REM periods.

Kleine-Levin Syndrome (KLS)

KLS is characterized by periodic episodes of severe hypersomnia and behavioral, psychiatric, and cognitive disturbances [1]. It classically affects adolescents. Hypersomnia is the hallmark feature and patients typically report sleeping up to 18–20 h a day [28]. In addition to excessive sleepiness, episodes are marked by slowed processing speed, confusion, regression to childlike behaviors, altered perception/depersonalization, irritability, and anxiety [28–30]. Hyperphagia,

food hoarding, and anorexia have been reported with this condition, suggesting hypothalamic dysfunction. Episodes can last days to weeks interspersed by months of asymptomatic periods [30]. The frequency of episodes tends to decrease with age, and the condition frequently resolves during adulthood. Functional MRI (fMRI) studies have revealed hypoperfusion of the right dorsomedial prefrontal cortex and the right parietotemporal region as well as the hypothalamus, thalamus, and caudate [31].

The etiology of KLS is unknown. There is some evidence that KLS is of autoimmune etiology, though supporting data have been inconsistent in the literature. KLS onset often occurs after an infection, and on occasion subsequent relapses may be preceded by a similar illness [27]. A sample of individuals with KLS has also been noted to be more likely to be positive for the HLA DQB1*0201 haplotype than controls [32], although this finding did not carry over in studies with larger KLS cohorts [32, 33]. Other triggers for the periodic symptoms include travel, alcohol use, drug use, and head trauma [27]. Case studies have revealed that 5% of KLS patients have a family history of the disorder. Factors including prepubertal disease onset, male sex, or postadolescent onset result in longer duration of symptoms during episodes [1, 27]. KLS is so rare that there are limited data to inform treatment recommendations. Medications such as stimulants and antiepileptic medications such valproic acid have shown no or minimal benefit [33, 34]. Recently, one open-label, controlled study in 130 KLS patients showed that lithium treatment decreased the duration and frequency of symptomatic episodes [35]. This therapy is promising for future treatment. Important to management is supportive care with emphasis on maintaining good sleep hygiene (as sleep deprivation may trigger episodes) and educational support [29].

Secondary Causes of Hypersomnia in Children

The most common cause of excessive daytime sleepiness is insufficient amount of sleep [36]. The amount of sleep recommended for children at different ages has thus far been grounded in the results of population-based studies [37] in which typically developing, healthy school-aged children get a median 10 h on average per night and adolescents approximately 9 h. Yet, the average amount of sleep obtained by children per the National Sleep Health Foundation is notably lower. In a national poll of American children, 34% of toddlers, 32% of preschoolers, and 27% of school-aged children were reported to sleep fewer hours than what the parent/caregiver thought they needed [38]. More objective evidence confirms these concerns. In one research study using actigraphy, children ages 4–10 years slept on average 8 h per night compared to the recommended 10 h for this age range [39]. This growing trend of insufficient sleep among children certainly contributes to increased prevalence of daytime sleepiness, with up to 25% of students ages 4–12 reporting falling asleep in class [38]. There have been no large-scale studies of population data assessing sleep duration in children with neurodevelopmental disorders to clarify whether their sleep needs differ from what is recommended by chronological age. Other sleep disorders such as obstructive sleep apneas, periodic limb movements of sleep, nocturnal epilepsy, and parasomnias may sufficiently disturb the continuity of sleep and result in daytime sleepiness.

Developmental disorders such as attention-deficit/hyperactivity disorder (ADHD) and psychiatric disorders constitute up to 35% of total cases of children referred for sleep problems, [40] and thus fatigue and daytime sleepiness are common presenting concerns. Furthermore, clinical research has documented secondary narcolepsy-like symptoms in a number of neurogenetic conditions such as Prader-Willi syndrome [41], Norrie disease [42], Niemann-Pick C [43], and Coffin-Lowry syndrome [44]. Epilepsy, sedating medications, and predisposition to sleep apnea all may contribute to complaints of daytime sleepiness among children with developmental, genetic, and psychiatric conditions. In this section, we briefly review the incidence and potential causes of excessive daytime sleepiness among children with attention-deficit/hyperactivity disorder, depression, and two specific genetic disorders: Smith-Magenis syndrome and Prader-Willi syndrome.

Sleepiness in Children with ADHD

Sleep problems are a common comorbidity in ADHD. Based on parental report, 25–50% of children with ADHD have problematic sleep at night [45–49]. Sleep problems may be the result of hyperactivity, and difficulty settling down for sleep and/or medications used to treat ADHD may result in sleep problems [50]. These sleep disturbances often result in daytime sleepiness and fatigue. A retrospective study of 33 children and their polysomnograms by Goraya et al. revealed that children with ADHD had increased arousal indices, increased wake after sleep onset, and reduced sleep efficiency which correlated with excessive daytime sleepiness and hyperactivity [51]. Likewise, a meta-analysis conducted by Cortese et al. also suggested that children with ADHD have more daytime sleepiness, more movements in sleep, and higher apnea-hypopnea indexes compared to controls [52, 53]. While sleepiness has been reported in patients with primary ADHD [53, 54], it is also important to recognize that sleepiness in otherwise healthy children is well known to manifest as behavioral problems, educational difficulties, or symptoms of attention deficit or hyperactivity [37, 38]. Thus, primary sleep disorders resulting in daytime sleepiness have

the potential to mimic ADHD symptoms. Accordingly, it is important for clinical providers to ask about daytime fatigue and sleepiness and symptoms of primary sleep disorders such as narcolepsy when evaluating a patient with symptoms concerning for attention deficit disorders.

Sleepiness in Children with Smith-Magenis Syndrome (SMS)

Smith-Magenis syndrome (SMS) is a neurodevelopmental disorder caused by an interstitial deletion of chromosome 17p11.2 and associated with cognitive impairments, behavioral problems, dysmorphic features (brachycephaly, midface hypoplasia, "cupid's bow" mouth, prognathism), speech delays with/without hearing impairment, and peripheral neuropathy [55]. Significant sleep problems are reported in 65–100% of SMS patient by parents [56]. Early sleep onset and daytime sleepiness (including "sleep attacks" during which children abruptly fall asleep) are commonly reported in SMS cohort studies, even while patients have short total nocturnal sleep time and repetitive prolonged nocturnal wakings [57]. This atypical sleep pattern and daytime sleepiness are attributed to an inversion of melatonin onset and rise [58–60]: melatonin typically begins to rise in the early evening, and its secretion is then sustained through the night, but some children with SMS have been found to have paradoxically low levels of nocturnal melatonin and high levels of daytime melatonin [60]. Most notably, sleep disturbances were predictive of daytime behavior problems including tantrums and hyperactivity, and only mild improvements have been noted using medications to control behaviors or sleep [60]. Because the circadian rhythm of melatonin synthesis is regulated by the sympathetic nervous system, in one study SMS patients were given a B-adrenergic antagonist to reduce production of daytime melatonin. Results showed a dramatic improvement in both daytime melatonin concentrations and daytime behavior problems [61]. Such findings highlight a novel biological mechanism between sleep disturbances and problematic daytime behaviors in children.

Sleepiness in Children with Prader-Willi Syndrome (PWS)

Prader-Willi syndrome is most commonly caused by deletion in the paternally derived chromosome 15 (q11–q13), but maternal uniparental disomy, imprinting errors, and translocation have also been reported [62]. PWS is characterized by short stature, hypotonia, hyperphagia, early-onset obesity, impaired sexual development, and cognitive impairment [63]. Additionally, excessive daytime sleepiness is frequently noted, both by subjective report and by objective testing (multiple sleep latency testing) among children with PWS [64, 65]. Parents of children with PWS report that their children seem to nap excessively, fall asleep easily, and waken with difficulty [66]. Multiple sleep latency testing has revealed short sleep latency and presence of sleep onset REM periods consistent with narcolepsy in many cases [66–68]. Additionally, 16–28% of children with PWS may also have cataplexy, suggesting secondary narcolepsy due to global hypothalamic dysfunction and hypocretin neuropeptide loss [68]. Sleepiness may also be attributed to the high prevalence of sleep-disordered breathing, including hypoventilation, OSA [69], and central sleep apnea [70] reported among children with PWS. Interestingly, weight loss and reduction of sleep-disordered breathing with continuous positive airway pressure (CPAP) does not always result in reduction of the daytime sleepiness [71]. Use of modafinil, a wake-promoting agent described later in this chapter, has been shown to significantly improve daytime sleepiness among patients with PWS, though larger clinical trials are needed [72].

Hypersomnia and Depression

Depression is a common comorbid condition among children with neurodevelopmental disorders [73, 74] and is another contributing factor to the presentation of EDS. Change in sleep (either insomnia or hypersomnia) is listed as one of the diagnostic criteria of major depressive disorder (MDD) [75], but there have been a limited number of studies investigating the actual frequency of hypersomnia symptoms in MDD. Individuals who report hypersomnia in conjunction with MDD or other mood disorders most often have symptoms that include long sleep time, sleep inertia, and excessive daytime sleepiness [25]. Subjective assessments indicate a high frequency of hypersomnia in the presence of MDD with symptoms of hypersomnia often noted to precede a major depressive episode [25]. However, in the limited number of studies that have used objective measures such as multiple sleep latency testing (MSLT) to assess hypersomnia in mood disorders, mostly normal results are reported. Thus, it is possible that hypersomnia related to depression is a rarer subtype of depression and what patients report as sleepiness may actually be fatigue or lack of energy [25]. On the other hand, individuals with hypersomnia disorders of central origin such as narcolepsy type 1 have high rates of depression (discussed further below) suggesting a bidirectional relationship between hypersomnia and emotional health. Careful patient interview and diagnostic testing with polysomnography and multiple sleep latency testing are often necessary to establish the primary diagnosis.

Neurobehavioral and Neuropsychiatric Comorbidities Associated with Primary Narcolepsy

Children with narcolepsy types 1 and 2 have high rates of behavioral problems and psychiatric conditions. While it is commonly thought that these comorbidities are the results of excessive daytime sleepiness or secondary to poor coping mechanisms after development of chronic disease, it is also possible that these conditions are intrinsic to the disease state itself.

Attention-Deficit/Hyperactivity Disorder (ADHD) and Narcolepsy

ADHD symptoms are present at high rates among children with narcolepsy types 1 and 2 [76, 77]. A recent cross-sectional survey of children under 18 years of age found that 35.3% of children with narcolepsy reported ADHD symptoms compared to 4.8% of control subjects [76]. It is well known that sleep problems including sleep disturbances, insufficient sleep, and daytime sleepiness can result in poorer executive functioning, memory difficulties, inattention, and hyperactivity in children [53, 78, 79]; thus, symptoms of ADHD may be expected among children with narcolepsy. Indeed, excessive daytime sleepiness, insomnia, and fatigue scores among children with narcolepsy were all significantly associated with ADHD symptoms in this cross-sectional study [76]. However, the ADHD symptoms of narcolepsy patients were less likely to improve with treatment of stimulant medications, suggesting that sleepiness alone may not be driving these behaviors. Clinically, practitioners must be aware of the risk of cognitive and behavioral problems in children with narcolepsy and consider neuropsychological testing and formal academic supports in the form of 504 plans or Individualized Education Programs.

Schizophrenia and Narcolepsy

By one report, presentation of narcolepsy type 1 combined with schizophrenia seemed rare, occurring in 1–18 cases in a population of 2 million based on independent prevalence rates [80]. In contrast, another study showed that approximately 10% of adolescent patients with narcolepsy type 1 developed schizophrenia at an average age of 2.5 ± 1.8 years after narcolepsy symptom onset [81]. Patients with both narcolepsy and schizophrenia were younger than those with narcolepsy alone, and the authors suggested that younger age makes these patients more susceptible to "brain autoimmune disease" due to high prevalence of HLA DQB1*03:01/06:02 allele in patients with both narcolepsy and schizophrenia. While schizophrenia may be a potential comorbidity, use of high-dose stimulants has also been shown to be associated with adverse psychotic side effects among patients with hypersomnia conditions [80]. Auger et al. reported increased risk of psychosis (OR = 12), alcohol or polysubstance abuse (OR = 4.3), and psychiatric hospitalization (OR = 3.2) among patients with narcolepsy and idiopathic hypersomnia treated with high-dose stimulants (defined as dosage ≥120% of the maximum recommended by the American Academy of Sleep Medicine Standards of Practice Committee) [82]. Lastly, it is possible that there is a distinct subtype of narcolepsy with psychotic features, a claim which thus far has only been suggested by case reports [83]. Anti-NMDA receptor antibodies have been detected in patients with narcolepsy with psychotic features (with and without encephalitis symptoms), suggesting autoimmune etiology may result in broader neuropsychiatric symptoms [84]. Of great concern is the potential misdiagnosis of narcolepsy as schizophrenia based on reports of hallucinations. While hallucinations are experienced in both narcolepsy and schizophrenia, the hallucinations experienced by patients with narcolepsy are almost always associated with sleep onset/offset (hypnogogic/hypnopompic hallucinations) and more likely to be multimodal in presentation (both visual and tactile) [85].

Mood Disorders and Narcolepsy

Among both adults and children, primary mood disorders are reported in up to 1/3 of patients with narcolepsy and include depression, anxiety, obsessive-compulsive disorder, and social phobia [86]. Among children with narcolepsy, 25% of patients reported depressive symptoms on the Children's Depression Inventory [87]. Symptom burden tended to be higher in those reporting depression, with more frequent hypnogogic hallucinations and sleep paralysis, higher subjective sleepiness scores, and longer duration of symptoms before diagnosis compared with non-depressive patients. However, depressive feelings were not significantly different among patients based on treatment with stimulants for daytime sleepiness or venlafaxine for cataplexy.

These high rates of depression among patients with narcolepsy suggest that mood disorder may be intrinsic to the narcolepsy diagnosis. Interestingly, the sleep architecture of depressive patients without narcolepsy has been reported to include short REM onset latency, increased REM pressure with sleep onset REM periods, and sleep fragmentation – all findings similar to those reported in patients with narcolepsy. Hypocretin deficiency associated with narcolepsy induces cholinergic-monoaminergic imbalance with primary effect on alertness, but such dysregulation has been shown to

directly influence mood as well [88]. Clinically, screening for affective problems among patients with narcolepsy is important, as medications used to treat core symptoms such as stimulants may worsen underlying mood disorder symptoms. Ultimately, allying with mental health providers is often necessary for assessment and management of psychological health.

Evaluating and Diagnosing Hypersomnia

As mentioned above, obtaining a history of duration and quality of nocturnal sleep period is important as is detailed information about duration and frequency of daytime naps and whether such bouts of sleep are refreshing. Use of sleep logs or diaries can be helpful in obtaining longitudinal sleep and wake patterns, as can actigraphy. Physical exam should focus on craniofacial structure, as micro- and retrognathia as well as tonsillar hypertrophy may predispose children to develop obstructive sleep apnea and associated daytime sleepiness.

Questionnaires

There are number of validated questionnaires that are used in the clinical evaluation of hypersomnia. The Pediatric Daytime Sleepiness Scale is an eight-item, self-reported Likert-type questionnaire that measures daytime sleepiness in children ages 11–15 years, with possible scores ranging from 0 to 32. Higher PDSS scores indicate greater daytime sleepiness. Along with being easy to administer, score, and interpret, the PDSS has a high internal consistency and is commonly used in clinical practice [89]. The PDSS has been used in children with epilepsy [90, 91], autism [92], and ADHD [76]. The Cleveland Adolescent Sleepiness Questionnaire (CASQ) has been validated in a broader age range in students aged 11–17 years with known sleep-disordered breathing (primary snoring or obstructive sleep apnea) [93]. Internal consistency of the CASQ was slightly higher than the PDSS but to date has not been utilized in published research with children with neurological or neurodevelopmental disorders. Lastly, the modified Epworth Sleepiness Scale (ESS) is an eight-item questionnaire used to assess levels of EDS in children ages 6–16 years that allows both parents and children to rate the child's tendency to fall asleep during different scenarios [94]. Items are rated from zero to three, with higher scores indicating greater sleepiness. A total score is also obtained, with scores of 10 or more indicative of EDS and median scores of 14 reported specifically among patients with narcolepsy [95]. The modified version of the ESS has not been formally validated but has been used in a number of research studies assessing sleep-disordered breathing [94], hypersomnia associated with brain tumors [96], ADHD [97], multiple sclerosis [98], and narcolepsy [99].

Actigraphy

Actigraphs are watch-like devices that contain a computerized algorithm that measures limb movement to estimate sleep and wake patterns. The sleep onset latency, number and duration of nocturnal awakenings, time in bed, total sleep time, sleep efficiency, and number and duration of daytime naps can all be quantified using actigraphy in children. Actigraphy has been used in children with neurodevelopmental disorders such as ADHD [100, 101] and autism [102–104], though extra training on use and even desensitization protocols may be required [105]. Actigraphy can be helpful for evaluating for insufficient nocturnal sleep and circadian rhythm sleep disorders. Furthermore, actigraphy can confirm the presence of hypersomnia. In one study, group differences among children with narcolepsy type 1 and idiopathic hypersomnia and controls were detected in all actigraphic parameters except sleep onset latency and time in bed, and significant differences were even noted between participants with narcolepsy and idiopathic hypersomnia [106]. Unfortunately, actigraphy is not clinically reimbursed in many countries, limiting its use.

Nocturnal Polysomnography

Hypersomnia is one valid indication for an overnight polysomnogram (PSG), and others include concerns for obstructive sleep apnea, restless leg syndrome, frequent parasomnias, epilepsy, and nocturnal enuresis when an underlying sleep disorder contributing to EDS is suspected. If problems with sleep schedule or hygiene exist, they should be addressed, and hypersomnia reassessed before a sleep study is ordered. Per the International Classification of Sleep Disorders-3 [1], an overnight PSG and multiple sleep latency test (MSLT) are both indicated for the diagnosis of narcolepsy types 1 and 2, but ideally, potential sedating, alerting, or REM-suppressing medications (e.g., clonidine, guanfacine, stimulants, SSRI, SNRIs) need to be weaned off 2 weeks prior to testing. Alternatively, the ICSD-3 criteria permit narcolepsy type 1 diagnosis to be made if CSF hypocretin-1 concentration measured by immunoreactivity is either ≤110 pg/ml or <1/3 of mean values obtained in normal subjects with the same standardized assay.

In children, the specificity of a nocturnal sleep onset REM period (SOREMP, or REM onset latency of ≤15 min) for detection of narcolepsy type 1 is high at 97.3% (95% confidence interval [CI]: 92.2–99.4%), but the sensitivity was

moderate at 54.8% (95% CI: 38.7–70.2%). Overall, the positive predictive value of an SOREMP for the diagnosis of narcolepsy type 1 was 88.5% (95% CI: 69.8–97.4%) [107]. Given the high specificity of a nocturnal SOREMP on the PSG for the diagnosis of narcolepsy, the revised International Classification of Sleep Disorders-3 now allows the presence of a nocturnal SOREMP to be included in the two required SOREMPs for diagnosis of narcolepsy type 1 or 2, formerly factored in from multiple sleep latency testing only [1]. Insufficient amount of sleep and shift work have been associated with findings of nocturnal SOREMPs [108].

Mean Sleep Latency Test (MSLT)

A mean sleep latency test is considered a standard measure of sleepiness, based on the assumption that the length of time it takes an individual to fall asleep is directly related to their degree of sleepiness [109]. During an MSLT, the patient is offered up to five opportunities to nap during the day separated by 2-h intervals during which she/he is not permitted to sleep but may engage in other activities. At each nap interval, the patient is asked to lie down in bed in a dark room and given 20 min during which to fall asleep. Using EEG measures to assess for sleep onset, the mean sleep latency is calculated based on four to five nap periods, where a sleep latency of 20 min is used in calculations for any nap periods where the patient did not fall asleep. Sleep stages are also assessed during the MSLT to determine if the patient enters into a sleep onset REM period (SOREMP) during any of the naps. An MSLT is indicated in all cases where narcolepsy is suspected as well as in instances where a physician is attempting to differentiate between narcolepsy and idiopathic hypersomnia. If other sleep disorders are suspected such as obstructive sleep apnea (OSA) or insomnia, an MSLT is not indicated until an overnight polysomnogram (PSG) has been conducted to rule out these potential causes of sleepiness [109].

Per ICSD-3 criteria, a mean sleep latency of ≤8 min and two or more SOREMPs are required to make the diagnosis of narcolepsy. As noted above, one of these SOREMPs may now be observed on the nocturnal PSG.

Maintenance of Wakefulness Test (MWT)

The MWT is a test that requires a patient to try to stay awake in a dimly lit room over a series of 40 min periods with no stimulation. There are typically four periods in a protocol and patients "fail" if their mean sleep latency is <8 min [109]. This test is used to assess wakefulness and can be useful to determine treatment efficacy of medications used to treat hypersomnia disorders. There are no normative data for children.

Case Vignette, Continued

You refer Andrew to a pediatric sleep lab for testing for a repeat sleep study and multiple sleep latency test. His MSLT takes place approximately 5 months from the time of symptom onset. On his overnight sleep study, he again is noted to have a short sleep onset latency (3 min), a nocturnal SOREMP, periodic limb movements (index 21/h), and five obstructive events in all, for a total apnea-hypopnea index not consistent with OSA. In total, he slept 560 min. On the multiple sleep latency test, his mean sleep latency was 0.5 min, and SOREMPs were noted in all five nap periods. The test results confirm Andrew's diagnosis of narcolepsy in light of his clinical context.

Management of Hypersomnia

Practice parameters for the treatment of narcolepsy and other hypersomnia conditions are available through the American Academy of Sleep Medicine [110] and the European Federation of Neurological Societies [111], but there is little research specifically looking at safety and efficacy of these treatments in children with hypersomnia conditions. Consequently, most medications for hypersomnia are not approved by the Federal Drug Administration (FDA) for children. The guideline recommendations for treatment of narcolepsy and idiopathic hypersomnia conditions are reviewed below.

Daytime Naps/Sleep Hygiene

One to three daytime naps can be very refreshing for people with narcolepsy coupled with sufficient, regular nocturnal sleep. Clinical experience suggests naps should be kept brief, lasting 15–30 min, so patients are easier to wake.

Wake-Promoting Agents

Modafinil is generally considered first-line therapy for treatment of EDS in adults but is not approved for pediatric use because of case reports of Stevens-Johnson syndrome [112]. Although it lacks FDA approval for use in pediatric populations, it is frequently used in practice with good efficacy in children [113]. A few case series and a small double-blinded trial have supported its efficacy in treatment of pediatric narcolepsy [10, 113–115]. Modafinil has also been used successfully for treatment of excessive daytime sleepiness with

minimal side effects in children with Prader-Willi syndrome [72]. Modafinil is a central stimulant of postsynaptic alpha-1 adrenergic receptors [116] thought to work through direct and indirect actions on the dopaminergic system as well as serotoninergic and gamma-aminobutyric acid (GABA) pathways [117]. Side effects include headaches, anxiety, nausea, and insomnia, particularly at the start of treatment. It is a cytochrome p450 inducer so can affect metabolism of other medications. Of note, young women on oral contraceptives must be cautioned that modafinil may reduce the efficacy of the oral contraceptive and additional birth control may be needed.

There are no dosage guidelines in children, but doses ranging from 50 to 400 mg/day, taken in one to two doses in the morning and then at midday, have been successfully used [10, 118]. The *S*-enantiomer of modafinil has a half-life of 3–5 h and the *R*-enantiomer, armodafinil, has a longer half-life of 10–14 h. No head-to-head clinical trials between modafinil and armodafinil have been conducted for the treatment of narcolepsy [119, 120].

Stimulants

Traditional stimulants (D,L-amphetamines and methylphenidate) are evidence-based therapeutic treatments for improving wakefulness and alertness in patients with narcolepsy types 1 and 2 [121, 122]. Stimulants work primarily by increasing monoaminergic neurotransmitters including dopamine, norepinephrine, and serotonin to promote wakefulness. While this increase in norepinephrine and serotonin may help cataplexy, the effect is generally insufficient to eliminate cataplexy. Methylphenidate dosing usually starts at 10 mg each morning and can be titrated up to 40–60 mg, divided into morning and midday doses. Extended release formulations are also available. Amphetamine salts are also used in pediatric populations for treatment of excessive daytime sleepiness with comparable efficacy, and dosing is similar to methylphenidate, but maximum recommended dosing is 40 mg/day [117].

The most frequent side effects of traditional stimulants are loss of appetite, nervousness, tics, headaches, and sleep-onset insomnia. Increased anxiety can occur with these compounds, especially among patients predisposed to mood disorders, but a mood disorder is not a contraindication to use stimulants. At high doses, stimulants may precipitate psychosis and suicidal ideation [82, 123], and close clinical monitoring of efficacy and adverse reactions is recommended. Children who are prescribed these medications should be monitored with regard to blood pressure and weight.

Drug addiction is a common concern of parents with children who have narcolepsy and take stimulants. Reassuringly, one study has shown that patients with narcolepsy being treated with a stimulant had no significant differences in risk taking behaviors compared to patients not undergoing stimulant treatment [124].

Anti-cataplexy Medications

Tricyclic antidepressants (TCAs) were traditionally used for treatment of childhood cataplexy, but now selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine and serotonin and selective norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine are more commonly used [19]. They are usually considered second-line treatment for cataplexy in adults [117]. Venlafaxine has also been successfully used for treatment of hypnagogic hallucinations and cataplexy in children [125, 126]. Venlafaxine has some adrenergic reuptake inhibition that may make it a slightly more alerting drug compared to standard serotonin reuptake inhibitors. Generally, however, this effect is insufficient to control daytime hypersomnia. Increased suicidal ideations have been reported with SSRI and SNRI use, and it is important to monitor mood and concerns of self-harm if used.

Atomoxetine, a norepinephrine reuptake inhibitor which has been used in treatment of ADHD symptoms, can also be considered for treatment of cataplexy in children, although efficacy and safety data are not yet established.

Sodium Oxybate

Sodium oxybate is efficacious for the treatment of cataplexy, EDS, and nocturnal sleep disruption in patients with narcolepsy [99, 114, 127] and is FDA approved for the treatment of adults with narcolepsy type 1 [114]. Its efficacy in children with narcolepsy has been shown in a number of studies for treatment of cataplexy and EDS [114, 127]. The FDA recently approved an indication for its use in children with narcolepsy 7–17 years old. The exact mechanism of how sodium oxybate works is unclear, but it stimulates GABA-B receptors, increasing slow-wave sleep [117]. Treatment is initiated with 2.25 g in two doses taken at night given 2–4 h apart and increased weekly up to maximal dosing of 4.5 g twice nightly or clinical effect.

Side effects of sodium oxybate can be more significant than those experienced with stimulants and include weight loss, dizziness, increased anxiety, hallucinations, and delusions. Of most concern, sodium oxybate can trigger sleep-disordered breathing and hypoventilation and could cause respiratory depression if mixed with alcohol. Hypernatremia-related side effects also need to be monitored. Training and registration processes are required of a provider prior to their prescribing sodium oxybate (Table 8.1).

Table 8.1 Commonly used medications for treatment of narcolepsy symptoms

Drug	Symptoms treated	Commonly used doses	Common side effects
Methylphenidate (IR, ER)	Excessive daytime sleepiness	10–60 mg divided into morning and midday doses	Loss of appetite, nervousness, tics, headaches, and sleep-onset insomnia. Monitor growth
D or L amphetamine (IR, ER)	Excessive daytime sleepiness	10–40 mg/day	Anxiety, depression, psychosis, and suicidal ideations
Modafinil	Excessive daytime sleepiness	100–400 mg/day taken in one to two doses in the morning and at midday	Headaches, anxiety, nausea, and insomnia. Possible Stevens- Johnsons syndrome
Armodafinil	Excessive daytime sleepiness	50–250 mg	Same as modafinil
Sodium oxybate	Excessive daytime sleepiness, nocturnal sleep disturbance, and cataplexy	2–9 g divided in two doses given at bedtime 2–4 h apart	Weight loss, sleep-disordered breathing and hypoventilation, increased anxiety, hallucinations, delusions. Can cause respiratory depression if mixed with alcohol
Protriptyline (TCAs)	Cataplexy	5–10 mg BID/TID	Dry mouth, mood changes, sleep disturbance, potential for QT prolongation, serotonin syndrome
Fluoxetine, paroxetine (SSRIs)	Cataplexy	Fluoxetine 10–40 mg	Sexual dysfunction, mood changes, sleep disturbances. Potential for prolonged QT cardiac interval and serotonin syndrome
Venlafaxine	Cataplexy	37.5–150 mg	Weight gain, mood changes, potential for prolonged QT interval and serotonin syndrome

ER extended release, *IR* immediate release.
Modified from [117, 128]

Back to Vignette: Treatment for Case

His school provided a 504 plan for Andrew to offer accommodations for his diagnosis of narcolepsy type 2. He has the option of taking a 30-min nap in the late morning and after lunch in the school nurse's office. With naps, he is more alert during the day and able to better participate in class and complete homework. He has started higher doses of stimulants (methylphenidate ER 27 mg each morning) for management of daytime sleepiness and ADHD symptoms. Mother reports improved alertness and academic functioning.

Future Directions

Treatment for narcolepsy and other disorders of hypersomnia in adults has been well studied [129], but there is a significant lack of placebo-controlled studies as to the safety and efficacy of these treatments in pediatric populations. Currently there are no evidence-based treatment guidelines for management of narcolepsy or hypersomnia symptoms specific to children, and most treatment recommendations are based on data from adult studies [117]. Several studies evaluating the safety and efficacy of methylphenidate and other stimulants in treating children and adolescents with ADHD exist [48], but there is limited data on their usefulness in treating hypersomnia. Considering that patients with primary hypersomnia conditions are dependent on lifelong medications, longitudinal studies assessing factors such as efficacy, tolerance, cardiovascular outcomes, and growth are needed [117, 129].

The MSLT is standard for assessing sleepiness in patients suspected of having hypersomnia disorders [109]. However, MSLT alone cannot confirm a diagnosis of hypersomnia or narcolepsy, as it must be evaluated in the context of the patient's history. A positive MSLT can be the result of other factors such as delayed sleep phase or insufficient sleep [109, 129, 130]. Future research may be directed to more biological assessments of sleepiness that would produce biomarkers that distinguish narcolepsy from other conditions that produce EDS.

Conclusions and Recommendations

EDS can result in executive functioning problems and behavioral difficulties. It is important to question parents about a child's sleep habits and symptoms of daytime sleepiness when assessing for conditions such as ADHD or problematic behaviors. Because sleepiness is often seen in conjunction with externalizing and internalizing behaviors such hyperactivity, inattention, and emotional dysregulation, disorders of hypersomnia including narcolepsy are often misdiagnosed as primary ADHD [16]. Office-based tools including the Pediatric Daytime Sleepiness Scale and the Epworth Sleepiness Scale can be useful in evaluating a patient's subjective feelings of sleepiness. These assessments can help

determine if the sleepiness is a factor and should prompt further query about typical sleep duration and quality and symptoms of other primary sleep disorders.

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Circadian Rhythm Sleep Disorders

9

Amanda L. Richdale and Emma K. Baker

Abbreviations

AASM	American Academy of Sleep Medicine
AS	Angelman syndrome
ASD	Autism spectrum disorder
ASWPD	Advanced sleep-wake phase disorder
CRSWD	Circadian rhythm sleep-wake disorder
CRSWD-NOS	Circadian rhythm sleep-wake disorder—not otherwise specified
DD	Developmental disability
DLMO	Dim light melatonin onset
DS	Down syndrome
DSWPD	Delayed sleep-wake phase disorder
ICSD	International classification of sleep disorders
ID	Intellectual disability
ISWRD	Irregular sleep-wake rhythm disorder
N24SWD	Non-24-h sleep-wake disorder
NDD	Neurodevelopmental disability
PWS	Prader-Willi syndrome
RS	Rett syndrome
SCN	Suprachiasmatic nucleus
SMS	Smith-Magenis syndrome
WS	Williams syndrome

Introduction

As will be described in this chapter, circadian sleep-wake disorders are sleep disturbances that relate to the timing of sleep and wake across the 24-h day. They include phase-delayed sleep, where sleep onset and wake are significantly later than typical or desired, and also phase-advanced sleep, where sleep onset and wake are significantly earlier than typical or desired, considering the individual's age. Also included are those cases where sleep is interspersed irregularly across 24 h or where the sleep-wake rhythm follows a period that is longer than a standard 24-h day. As we will discuss, the literature on circadian sleep-wake disorders in children with neurodevelopmental disabilities (NDD) is sparse.

Many children with NDD exhibit consistently late sleep onset, night waking, early waking, and/or inappropriate napping, which may be indicative of a circadian sleep-wake disturbance. A case example, which we describe in more detail later, was reported by Piazza and colleagues [1] who described an 8-year-old girl with autism, severe intellectual disability, and severe sleep problems. She had not slept more than 3 h per night from age 5 years and had not responded to regular routines or sleep medications. Irregular sleep onset, night waking, shortened night sleep, some nights without sleep, and daytime napping were all reported, indicative of an irregular sleep-wake pattern. Chronotherapy, a sleep scheduling therapy manipulating bedtimes and wake times over time, was used to correct her sleep-wake cycle, resulting in significant improvement in her sleep. She subsequently averaged 7.9 h of sleep at night, which was maintained at a 4-month follow-up.

The Sleep-Wake Cycle Is a Circadian Rhythm

Sleep and wake are governed by two processes, the homeostatic drive for sleep (process S) and the circadian system (process C) [2]. The circadian system regulates sleep timing, with the master "clock" or pacemaker being in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. The circadian system organises the daily rhythms of physiology and behaviour, of which sleep and wake are one component, via the synchronisation of internal physiological rhythms, so that their timing relative to each other remains constant [3, 4]. This is

A. L. Richdale (✉)
Olga Tennison Autism Research Centre, La Trobe University, Melbourne, VIC, Australia
e-mail: A.Richdale@latrobe.edu.au

E. K. Baker
Diagnosis and Development, Murdoch Children's Research Institute, Parkville, VIC, Australia
e-mail: emma.baker@mcri.edu.au

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accomplished via light-sensitive SCN cells that respond to bright light, the primary zeitgeber, or external time cue. Light arrives at the SCN from the eyes via the retinohypothalamic tract [5]. On average, the endogenous circadian period (tau) in humans is just over 24 h [3], ranging from 23.5 to 24.9 h [5]. Thus, the sleep-wake rhythm typically becomes synchronised to a period of 24 h by being reset each day under the influence of the natural light-dark cycle. Under constant conditions where there are no external zeitgebers, a person's sleep-wake rhythm free-runs at its endogenous period, which generally means that the individual falls asleep at a progressively later time each night, with time of sleep onset gradually moving across the 24-h day [5]. The resetting of the circadian clock is thought to involve the neurohormone, melatonin, which is secreted by the pineal gland. Melatonin levels rise each evening near one's usual bedtime, signalling sleep onset, and decrease as usual wake time approaches. Melatonin is suppressed by bright light, and levels are very low during the day. The night-time rise in melatonin, also called dim light melatonin onset (DLMO), is a good estimate of the degree of circadian advance or delay [5, 6]. The sleep-wake cycle is also tightly aligned with the circadian temperature rhythm, with sleep onset occurring on the falling phase of the daily core body temperature rhythm. Core body temperature drops, and peripheral temperature rises around sleep onset [7].

During the first few months of life, an infant's sleep-wake rhythm becomes synchronised by the light-dark cycle and regular social cues such as feeding [8]. The infant develops a 24-h sleep-wake rhythm, with one consolidated and longer night-time sleep period interspersed with usually two, then one, regular daytime naps. By age 3–5 years, the daytime nap is dropped, and the child exhibits a typical pattern of night sleep and daytime wakefulness [9]. Nevertheless, individuals vary in propensity for the circadian onset of sleep and morning wake times, with morning, intermediate, and evening patterns evident. These patterns or preferences are referred to as an individual's circadian chronotype. Morning chronotypes have a natural preference for early rise times and sleep onset; conversely, evening chronotypes prefer to rise later than average with corresponding late sleep onset. This may result in the morning or evening chronotype's sleep-wake patterns being out of synchronisation with typical societal patterns of school, work, or leisure and may adversely affect the individual's education or employment and socialisation with family and peers [10].

Defining Circadian Sleep-Wake Disorders

As has been outlined in other chapters of this book, sleep difficulties including insomnia, excessive daytime sleepiness, and difficulties with napping are common complaints in children with developmental disorders. These symptoms may also be indicative of a circadian sleep-wake disturbance [3]. Okawa and Sasaki [11] reviewed sleep difficulties associated with developmental disability (DD) and intellectual disability (ID), including circadian sleep-wake rhythm disorders, both with respect to children with more severe ID and known brain impairment (acerebrate children), blind children with moderate to severe ID, and children with ID associated with specific DDs. They reported the presence of sleep electroencephalography (EEG) abnormalities associated with ID and specific DDs, as well as free-running or irregular sleep-wake rhythms in children with severe delay, vision loss and delay, and autism. They concluded that "an understanding of the mechanisms of the human biological clock is indispensable for the treatment of mentally retarded or brain-impaired children" [11, p., 286].

This chapter examines circadian sleep-wake rhythm disorders in children with an NDD. In doing so, we use definitions from the *International Classification of Sleep Disorders*, third edition (ICSD-3) [3], and summarise information about circadian sleep-wake rhythm disorders from ICSD-3 and the *Diagnostic and Statistical Manual of Mental Disorders*—fifth edition (DSM-5) [12]. The ICSD-3 defines a circadian rhythm sleep-wake disorder (CRSWD) as follows:

> The disorder is caused by alterations of the circadian time-keeping system, its entrainment mechanisms, or a misalignment of the endogenous circadian rhythm and the external environment. (p. 189)

The American Academy of Sleep Medicine (AASM) [3] describes seven CRSWDs, while DSM-5 [12] describes six CRSWDs. Shift work disorder and jet lag disorder (ICSD-3) and shift work type (DSM-5) will not be considered further, as they do not typically affect children with NDDs. The five AASM [3] disorders are summarised in Table 9.1 and are similar to those described in DSM-5 [12]. A sleep diary should confirm the abnormal patterns described, and presentation of these sleep schedules should not be better explained by a different current sleep disorder or other medical, developmental, or psychiatric disorder. In all but CRSWD-NOS, symptoms must be present for at least 3 months. In addition, in all CRSWDs, the sleep-wake disturbances involved cause clinically significant distress or impairment in important areas of functioning [3].

Parents' complaints about settling problems and night wakings are common during childhood [13, 14] including in children with an NDD [15] and are generally attributed to environmental or behavioural issues such as poor sleep hygiene and limit setting, lack of appropriate bedtime routines, or, alternately, night-time fears, anxiety, depression, and behavioural problems [16, 17]. Sleep problems are among the most common comorbid issues reported for children with an NDD [18–20]. For some NDDs including autism spectrum disorder (ASD), Rett syndrome (RS), Smith-Magenis syndrome (SMS), and Angelman syndrome

Table 9.1 AASM CRSWDs

CRSWD	AASM brief description
Delayed sleep-wake phase disorder (DSWPD)	A. Phase of the major sleep episode is significantly delayed (late) in relation to desired or required sleep and wake times
	B. Preferred sleep-wake schedule leads to improved sleep, with a advanced phase maintained
Advanced sleep-wake phase disorder (ASWPD)	A. Phase of the major sleep episode is significantly advanced (early) in relation to desired or required sleep and wake times
	B. Preferred sleep-wake schedule leads to improved sleep, with a advanced phase maintained
Irregular sleep-wake rhythm disorder (ISWRD)	Pattern of irregular sleep and wake across 24 h, usually with night insomnia and excessive daytime sleepiness
Non-24-h sleep-wake rhythm disorder (N24SWRD)	History of insomnia and/or excessive daytime sleepiness; asymptomatic episodes due to the 24-h light-dark cycle and the rhythm for sleep-wake propensity being misaligned
Circadian rhythm sleep-wake disorder—not otherwise specified (CRSWD-NOS)	Meets general diagnostic criteria for CRSWD, but not one of the specific subtypes. CRSWD primarily precipitated by medical, neurologic, or psychiatric disorder

Data from the American Academy of Sleep Medicine [3]

(AS), parents also report irregular sleep patterns. These can vary with children sometimes falling asleep relatively quickly but taking hours to fall asleep on other nights, or having shortened night sleep, very early waking (prior to 5 AM), and lengthy periods of night waking during which the child engages in undesirable behaviours [21–24]. Excessive daytime sleepiness is frequently reported in association with Down syndrome (DS) and Prader-Willi syndrome (PWS) [25, 26]. While sleep difficulties in children with an NDD may have similar environmental and behavioural causes to those for other children, they may also be due to conditions associated with the specific developmental disorder (e.g. sleep apnoea associated with DS and PWS) or may be indicative of circadian sleep-wake disturbances. However, the possibility of a CRSWD as the primary reason underlying disturbed sleep in children with an NDD has not often been considered in the peer-reviewed literature. Indeed, other than in ASD, where there has been a burgeoning interest in comorbid sleep difficulties in the past 5–10 years, there is a general lack of literature concerning common sleep difficulties such as insomnia symptoms and their treatment in children with an NDD [15].

Insomnia is a common complaint in individuals with DSWPD. In DSWPD, insomnia typically develops in response to attempts to deal with sleep onset difficulties and societal requirements to wake earlier than desired. Daytime sleepiness is common. Lack of motivation to follow a more "normal" lifestyle may also be present, particularly in adolescents, with resulting treatment resistance [3]. In general, about 10% of patients who complain of insomnia may have DSWPD, and it is most common in adolescents and young adults [3, 12]. Genetic factors may also be involved [12]. Activities that delay bedtime, psychiatric conditions such as mood disorders, familial patterns of late sleep onset, and family dysfunction have been associated with the onset and maintenance of DSWPD. In children, the presence of bedtime resistance may not simply be behavioural but may be an indicator of an evening chronotype and a consequent lack of sleep readiness at the time parents set for bed. AASM notes that among the NDDs, children with ADHD or ASD may be vulnerable to DSWPD and that *little is known about the natural history of the clinical entity of DSWPD in the paediatric population* (p. 195) [3]. Indeed, several authors have suggested that DSWPD may explain susceptibility to sleep disturbances in children with ASD [27–30].

Individuals with ASWPD wake earlier than desired and are sleepy in the evening. They may experience partial sleep loss if they do not go to bed at their desired early evening bedtime. The disorder is thought to be much less common than DSWPD and also more common in older adults [12], with research in adults with autism suggesting it becomes prevalent after age 30 [31]. The suggested prevalence in adults is 1% [11]; familial patterns are reported [2], with possible *PER2* and *CK1* clock gene involvement [11]. ASWPD has also been reported in ASD [31, 32] and SMS [33]. Typical sleep patterns are often advanced anyway in young children, making ASWPD more difficult to discern. Chronic insomnia, poor sleep hygiene, and lack of appropriate and regular bedtime routines are more likely to underlie an apparent ASWPD, and psychiatric disorders such as depression should be considered [3]. Overall, stringent cases of ASWPD may be rare, though advance-related sleep complaints may be more common [3].

Individuals with ISWRD lack a well-defined circadian rhythm of sleep and wakefulness; instead, their fragmented sleep and wake periods occur variably across the 24-h day, along with frequent napping. Insomnia symptoms or excessive daytime sleepiness is likely to be present depending on

the individual's sleep-wake patterns. According to AASM [3], ISWRD is more likely to be seen in adults with dementia and in children with NDD, but prevalence remains unknown [12, 34]. Factors that may contribute to ISWRD include a lack of exposure to external zeitgebers such as light and dark or regular socialisation patterns [3], and it is associated with neurodegenerative and neurodevelopmental disorders [12]. A key factor in ISWRD is the lack of a predictable, single, long consolidated period of sleep as would typically be expected to occur each night. Among children, a chaotic home life resulting in poor sleep hygiene and irregular sleep schedules may also contribute to the development of ISWRD. Children with ASD, AS, Williams syndrome (WS), RS, and SMS may be at an increased risk for ISWRD. However, little is known clinically about the course and impact of ISWRD in children [3].

In N24SWRD, sleep and wake times are not entrained to the 24-h day and appear to free-run. The individual has a circadian period which is generally greater than 24 h, which may fall outside the range in which the circadian pacemaker can be reliably entrained. Such individuals typically report insomnia and daytime sleepiness, interspersed with asymptomatic periods when their sleep-wake periods happen to cycle around to coincide with those of their social surroundings [3]. The most commonly recognised cause of N24SWD is total blindness where photic cues for light and dark cannot reach the circadian pacemaker [3, 12]; psychiatric disorders associated with social isolation are also a risk factor [12]. Children with severe intellectual disability and blindness are also at risk. Some cases have been reported in specific NDDs including RS [35], ASD [36], and AS [37], possibly due to failure to entrain to social and environmental zeitgebers. According to ICSD-3 [3], N24SWRD is rare in typically developing children and may be associated with an endogenous circadian period closer to 25 h than 24 or inadequate daytime light exposure, excessive evening light exposure, or reduced exposure to other environmental cues. These latter factors may be associated with psychiatric conditions like social anxiety or medical conditions associated with long periods of inactivity. DSWPD is also a risk factor for the development of N24SWRD and may also be confused with N24SWRD. Like ISWRD, little is known clinically about the course and impact of N24SWRD in children [3].

Finally, CRSWD-NOS is used to describe disturbed sleep in an individual with a circadian sleep-wake rhythm that does not meet full criteria for a specific CRSWD. CRWSD-NOS is typically associated with medical conditions, psychiatric conditions, medication, or substance abuse. Individuals with neurodegenerative disorders and children with NDDs are also at risk of CRSWD-NOS. The specific manifestations of the disrupted sleep-wake patterns vary across individuals [3].

Given the frequency of reported sleep problems in children with an NDD and that sleep difficulties such as delayed sleep onset, night waking, early waking, and daytime napping in these children may be indicative of a circadian sleep disturbance, it is surprising that little attention has been paid to whether or not a CRSWD is present. Consideration of CRSWDs may help inform treatment, which is likely to be different from that indicated for sleep onset and night-waking difficulties associated with a more typical insomnia diagnosis. The following section describes reports of the presentation of CRSWDs in children with an NDD or sleep difficulties that may fit criteria for a CRSWD.

Intellectual Disability

In 1981, Okawa, Sasaki, Nakajima, and Takahashi [38] reported on a 12-year-old boy with a developmental age of no more than 7 months with low muscle tone and enlarged lateral ventricles, who could not stand and was largely bedridden. He had no obvious aetiology that would account for his delay. The boy showed *prolonged wakefulness for 2–6 days (p. 65)*, followed by similar periods of several days of sleep. The rhythm *repeated every 10–15 days for several months*, and he *then switched into an irregular sleep-wake pattern (p. 65)*; his sleep was independent of seasonal influences. On PSG, the boy had distinct sleep and wake EEG patterns. His body temperature rhythm was greater than 24 h but was stable despite his sleep-wake patterns. Thus, this boy appeared to be internally desynchronised, and his pattern of sleep was not influenced by external environmental factors; his sleep-wake pattern may best be classified as CRSWD-NOS.

In a later paper, Okawa, Takahashi, and Sasaki [39] described sleep-wake patterns in a group of 12 children with severe brain damage experienced perinatally (six cases) or between 6 months and 3 years of age. The children were now aged 3–14 years and presented with a range of circadian sleep-wake disturbances. Nine children were reported to experience seizures; all were bedridden and with vegetative disturbances, and thus, they appeared profoundly delayed. All the children showed REM sleep on PSG, but in seven cases, NREM sleep was monostage (e.g., difficult to distinguish normal NREM sleep stages), and only one child showed normal NREM sleep stages. In these profound cases of brain dysfunction, two types of circadian sleep-wake rhythm patterns were described: consolidated sleep and dispersed sleep. Consolidated children showed a distinct circadian sleep-wake pattern with a night-time sleep period and an afternoon nap, but their total sleep was generally reduced. However, two of these five children showed phase shifts indicative of a free-running rhythm and thus possible N24SWRD. Children with a dispersed pattern had no

optimal sleep time across 24 h and could not stay awake for 6 h at a time; they also had a tendency to hypersomnia, and six showed monostage NREM sleep. Thus these seven children appeared to fit criteria for ISWRD.

A group of 14 young children aged 9 months to 4 years with moderate to severe ID and a lack of consolidated, daily sleep were described by Guilleminault et al. [40]. Nine of the children had seizures, seven had cerebral palsy, and one had macrogyria; none had a known metabolic disorder. All children had adequate vision and were responsive to light. Sleep problems were reported from birth, with up to 3 h of noncontinuous night quiet periods and 30 min periods of quiet and sleep during the day. At the time of evaluation, all children were medicated (sleep medications and/or anti-epileptics), their sleep problems were very disturbing to their families, and treatment, including behavioural approaches, had not been successful. Based on sleep logs, these children slept for an average of 6 h in 24, with an average of only 3.2 h nocturnal sleep, and were not responding to sleep medications. Night behaviours included screaming, yelling, and periods of activity. The dominant pattern of sleep was fragmentation, with the longest sleep period between 8 PM and midnight and scattered periods of sleep varying from 15 to 80 min tending to cluster between 8 PM and 8 AM. Thus, these children all appeared to exhibit an ISWRD associated with their ID. The 12 children on a hypnotic medication were switched to chloral hydrate, and treatment with light therapy with a behavioural programme was attempted, with gradual withdrawal of chloral hydrate when an appropriate sleep pattern was apparent. This was successful for 5 of the 14 children, with a consolidated period of night-time sleep. At a 2–5-year follow-up, sleep improvements were maintained [40].

From this small number of studies, children with moderate to profound ID, often with comorbid seizures, may present with disorganisation of the circadian system resulting in irregular sleep patterns. These disorganised sleep patterns may or may not be amenable to typical sleep treatments.

Intellectual Disability and Blindness

Four girls aged 4–12 years with moderate to severe ID and congenital blindness were reported to have a CRSWD; all girls showed various EEG abnormalities on sleep PSG [41]. Three children had N24SWRD and the fourth had an ISWRD. One 10-year-old girl with seizures and moderate ID showed a free-running rhythm with a 24.8-h period, as well as apnoeic episodes during waking. Her epilepsy was successfully controlled, and attempts were made to entrain her sleep-wake rhythm with both light therapy and strict scheduling but were ineffective. A second girl, aged 12 years with severe ID and seizures and no response to light had a free-running sleep-wake rhythm with a 24.3-h period. Control of her seizures with an evening dose of nitrazepam (a nitrobenzodiazepine) together with forced daytime activities resulted in entrainment to a 24-h cycle. The third case was a 7-year-old girl with seizures, very enlarged ventricles, and light and dark recognition only who was extremely impaired. She had a sleep-wake rhythm with a period that varied from 25 to 30 h. Forced awakening resulted in entrainment to a 24-h period, but when active treatment was stopped, her entrainment drifted. The last girl was 4 years old with moderate ID and an ISWRD. She had one extended sleep period at sometime between midnight and midday, as well as naps between midday and midnight, and showed a rhythm period of 24.5 h. Forced awakening together with appropriate daytime activities eventually resulted in her rhythm becoming entrained to a 24-h period. Thus, strict scheduling activities were able to resynchronise the girls' sleep-wake cycles to a 24-h period in two of the four cases. It is unclear whether brain damage affecting circadian pacemakers or an inability to synchronise to weaker zeitgebers such as social cues due to their significant ID prevented the other two girls' entrainment.

A case study report by Sadeh and colleagues [42] of a blind adolescent with profound ID and severe behavioural problems including self-injurious behaviours as well as sleep problems concluded that the boy had a concomitant sleep-wake schedule disorder. A subsequent letter to the editor [43] expressed disagreement and suggested that bipolar disorder better met the described presentation. In their reply, Sadeh and Anders [44] defended the diagnosis of sleep-wake schedule disorder. They also noted that bipolar disorder and sleep schedule disorders could be related and that pharmacological treatment for the former may also affect the circadian pacemaker. This case illustrates the relationship between blindness, ID and mood disorders, the difficulties associated with differential diagnosis, and the potential for medication to affect the circadian system.

Smith-Magenis Syndrome (SMS)

While research on sleep in this syndrome remains sparse, individuals with SMS have chronic sleep difficulties, which usually begin early in life and are a significant predictor of behavioural problems. Early bedtime, night waking, early morning waking, shortened sleep, and daytime sleepiness [45, 46] suggest that sleep is phase advanced [45] or has an irregular rhythm [46]. These sleep problems are thought to be due to an inverted melatonin rhythm [45, 47, 48], though this is not found in all individuals [48]. Thus the reported melatonin rhythm abnormality in SMS may not be due to an intrinsic dysfunction in the circadian clock but rather may be related to genetic variation in melatonin regulation [48].

One of the genes included in the interstitial deletion at 17p11.2 associated with SMS is the *RAI1* (retinoic acid

induced 1) gene, or a heterozygous mutation of *RAI1*. *RAI1* has been implicated in altered melatonin secretion [46], and mice with *RAI1* deletion show altered circadian rhythmicity. Williams et al. [46] have shown that *RAI1* is a regulator of *CLOCK* (master regulator of the circadian clock) whose protein product heterodimerises with BMAL1. The CLOCK/BMAL1 complex regulates a range of downstream genes that modulate circadian rhythms. Thus, Williams et al. believe that the deletion or mutation of *RAI1* with consequent dysregulation of the expression of circadian genes leads to the inverted melatonin rhythm thought to be responsible for the sleep-wake rhythm abnormalities found in SMS. A combination of treatment with controlled-release melatonin at bedtime and using a beta-adrenergic antagonist to block melatonin in the morning has been effective in phase delaying both sleep onset and morning wake time in children with SMS to a more typical sleep schedule [49].

Autism Spectrum Disorder (ASD)

Inanuma [50] reported that compared to age controls, 33 children with ASD aged 1–8 years had irregular sleep-wake patterns, with highly variable sleep onset and wake times, night waking, significant daytime napping, and shortened night sleep, particularly children less than 4 years. However, perusal of the monthly sleep plots provided suggests that these children did have a longer, consolidated night sleep period; thus, they did not appear to meet criteria for ISWRD and may best be described as having CRSWD-NOS. Similarly, Segawa [36] plotted the sleep-wake rhythm of 63 children aged 1–12 years, compared with their siblings over a 6-month period. Irregular sleep-wake rhythms were reported with late sleep onset and morning waking, daytime naps, and short nighttime sleep in the children with ASD, suggesting DSWPD or CRSWD-NOS, with one case of a free-running rhythm (N24SWRD). Segawa [36] reported that regular play therapy and/or 5-hydroxytryptophan (5-HTP) administration improved or alleviated the children's sleep patterns. As 5-HTP is a precursor to both serotonin and melatonin syntheses, this suggests either serotonin neurotransmitter system involvement in these circadian sleep-wake anomalies or melatonin phase delay.

Later researchers have continued to report irregular sleep-wake patterns in children with ASD. Wiggs and Stores [30] examined sleep in 64 children with ASD using actigraphy and concluded that at least some of their children met criteria for DSWPD. Souders et al. [29] described the sleep of 59 children with ASD with intellectual abilities ranging from severe intellectual disability to average intellect. Children with autism had longer sleep latency, longer night wakings, and shorter total night sleep than controls. They concluded that 18% of children had ICSD-2 Insomnia due to Pervasive Developmental Disorder (PDD), that is, they could find no explanation for the children's sleep problems other than that they had an autism spectrum disorder [51]. They speculated that this may be due to a delayed or reduced-amplitude melatonin rhythm or clock gene abnormalities. These research reports suggest increased CRSWDs and, given the increased sleep latency, most probably DSWPD. Nevertheless, although some children have a significantly delayed bedtime suggestive of DSWPD, they may wake at an acceptable time. This is consistent with individuals on the autism spectrum, on average having reduced total sleep [15, 21]. Reasons for reduced total sleep are unknown, and it is possible that shifting sleep onset to an earlier time may then result in early morning waking. Some children with ASD are also early wakers. It is not always clear whether children with ASD and reduced total sleep are sleep deprived. Sleep timing and quantity often vary in ASD children from what is considered typical, and it is difficult to know whether or not some of these children meet the criteria for a CRSWD. However, addressing these sleep issues is paramount for families.

A case study described an 8-year-old girl with autism, severe intellectual disability, omphalocele, feeding problems, aggressive and self-injurious behaviours, and severe sleep problems [1]. She had stopped sleeping more than 3 h per night at age 5 years, even though she was on both clonidine and chloral hydrate for sleeping and kept a regular daily routine. Prior to inpatient treatment, the child had irregular sleep onset, night waking, shortened night sleep including some nights without sleep, and daytime napping. Inspection of the sleep data provided suggested ISWRD. Her medications were withdrawn. The girl underwent chronotherapy, a sleep scheduling therapy manipulating bedtimes and wake times over time to correct her sleep-wake cycle. She was placed in bed beginning at 3.30 AM, when she was most likely to be asleep, and left in bed for 10 h. Her bedtime was first successively delayed by 2 h and then 1 h per night until 9:00 PM bedtime was reached. No daytime naps were permitted, and her normal daily routine was maintained during her wake period. The child then maintained a regular bedtime routine for sleep at 9:00 PM and was woken at 7:00 AM each morning. There was significant improvement in both sleep and behaviour, and by completion she averaged 7.9 h of sleep during her scheduled night sleep time. Improvements were maintained 4 months later.

Thus there is good evidence that at least some children with ASD may be at an increased risk for CRSWDs possibly due to a phase-advanced or phase-delayed melatonin rhythm, reduced amplitude melatonin rhythm, or clock gene abnormalities. Bourgeron [52] provide a review and theoretical account of this, and several authors have reported abnormalities in melatonin [53–56]. This has led to the use of bedtime melatonin which can successfully improve sleep onset latency and in some cases night waking in children with ASD

(for reviews, see Guénolé et al. [57] and Rossignol and Frye [58]). However, a recent paper by Goldman et al. [59] reported that while melatonin successfully treated sleep onset latency difficulties in nine high-functioning boys with ASD, there was no evidence of abnormality in the melatonin rhythm that might account for their sleep problems. This group has since published a second paper showing that DLMO in 7 of 28 individuals with ASD and normal cognitive functioning aged 11–26 years (M = 15.6 years) did not differ from 7 controls [60]. The authors suggested that the success of melatonin in treating these children may be due to its soporific and anti-anxiolytic effects [59]. This is particularly pertinent as anxiety symptoms as well as diagnosed anxiety disorders are significantly elevated in individuals with ASD. Abnormal circadian sleep-wake patterns in children with ASD and more severe intellectual disability may be due to associated brain damage, an abnormality in the melatonin rhythm, and failure to pick up on social and environmental zeitgebers that assist with rhythm synchronisation, anxiety, or some combination of these factors.

Williams Syndrome (WS)

WS is a deletion syndrome involving chromosome 7q11.23 [61] and is generally associated with mild to moderate ID. While there are a few studies of sleep in WS, disturbed sleep including long sleep latency, night waking, reduced total sleep, and poor sleep efficiency, as well as restless sleep and periodic limb movements, has been reported [61–63].

Sniecinska-Cooper et al. [64] measured sleep using actigraphy and a sleep questionnaire and salivary melatonin and cortisol at 4:00–6:00 PM, bedtime, and wake time (afternoon and bedtime values were normalised against morning values) in 25 children aged 4–11 years with WS. The children with WS showed increased sleep latency, increased time awake at night, increased sleep fragmentation, increased movement, and a tendency to lower sleep efficiency; total sleep time was not reported. While the ratio calculated from bedtime to afternoon melatonin samples increased in the control group, this was not seen in WS children; at bedtime the WS children also showed a higher level of cortisol than controls, with the drop in cortisol from afternoon to bedtime being less pronounced in WS, suggestive of higher arousal. Overall, higher bedtime melatonin levels in the control group were related to better sleep parameters, but no similar relationships were found in the WS group. Lower cortisol was associated with shorter actigraphic sleep latency in both groups. Both reduced melatonin and increased cortisol at bedtime may account for long sleep latency in WS.

A sample of 25 children with WS (6–17 years) was assessed using the Sleep Disturbance Scale for Children (SDSC) and melatonin as measured by day and overnight urinary 6-sulfatoxymelatonin (6-SM), as well as measures of behaviour and memory [65]. On the SDSC, 65% of the children had disturbed sleep, while 6-SM did not show the expected day-night change with no increase in 6-SM in the overnight void. The authors reported that based on 6-SM excretion, 26% of children had a normal melatonin rhythm, 21% had a delayed rhythm, and the remaining 53% had an absent melatonin rhythm. Insomnia symptoms (sleep onset and maintenance) were significantly correlated with 6-SM levels, and the authors suggested that abnormality in the melatonin synthesis pathway with subsequent low melatonin levels may account for disturbed sleep in WS.

Thus, melatonin and cortisol rhythms may be delayed or absent in WS [64, 65], or as suggested by Sniecinska-Cooper et al. [64], cortisol and melatonin rhythms may be desynchronised. These recent findings suggest that children with WS are at risk for CRSWD, but they require replication.

Fragile X Syndrome (FXS)

Fragile X syndrome (FXS) is the most common inherited cause of intellectual disability, with full mutation prevalence being about 1:2500 [66]. There is a higher prevalence of FXS in males, and FXS carries an increased risk for anxiety disorders and ASD. Affected individuals have an expansion of the CGG trinucleotide repeat on their X chromosomes, with full mutations involving >200 CGG repeats and pre-mutation ≥55 repeats [67]. Parent-reported sleep problems occur in 30% or more of children [68–70], primarily delayed sleep onset and night-waking difficulties; irregular bedtimes and morning wake times were also common [68]. Variable sleep patterns together with elevated melatonin both overnight and during the day were also reported in a small sample of boys [71]. Moreover, peak melatonin levels occurred later in boys with FXS compared to controls, suggesting a possible delay of melatonin secretion and the sleep-wake rhythm. Thus, both the kinds of sleep behaviours reported and suggested abnormality in melatonin secretion may indicate circadian sleep-wake difficulties in at least some children with FXS, but further research is required.

Angelman Syndrome (AS)

AS is a chromosome 15 disorder involving the *UBE3A* gene; in 70% of cases, there is a deletion of maternally derived genes. The condition has a lifelong impact, and children are severely developmentally delayed; significant sleep problems are one of the associated conditions reported [72]. Parent-reported sleep problems include sleep onset and sleep maintenance difficulties and overall poor sleep quality. Sleep-disordered breathing, excessive daytime sleepiness,

and parasomnias are also reported, and the use of sleep medication is common. Rates for a range of sleep problems vary from around 40% to 70% [73–75]. Sleep difficulties have been documented in a small sample using both actigraphy and PSG, confirming that long sleep onset latency, long periods of night waking, poor sleep efficiency, and increased sleep fragmentation are present [76]. There is limited evidence that sleep onset and night-waking difficulties may be behaviourally maintained, with a report that behavioural interventions are helpful [77].

CRSWDs have also been reported for children with AS, though studies have been limited by small sample sizes. In particular, DSWPD, ISWRD, and N24SWRD have been reported in children with AS [37, 78]. Takaesu and colleagues [37] assessed CRSWDs and the melatonin profile in eight children (6–17 years) and seven adults (20–27 years). All AS participants were confirmed to have 15q11–q13 deletions on a DNA test. A total of eight AS patients (six children) received a diagnosis of a CRSWD. In particular, three children received a diagnosis of ISWRD, two of N24SWRD and one of DSWPD. Melatonin was sampled across a 24-h period, with a 4-hourly sampling rate, and the AS group showed significantly lower melatonin levels at all time points except at 8:00 AM. The amplitude of the 24-h serum melatonin level was dampened in the AS group. In particular, the greatest difference was observed between the peak serum melatonin levels. In comparing those children with AS and a CRSWD to children with AS without a CRSWD, peak melatonin levels were significantly higher in the latter group.

A recent study [79] found that pharmacological reversal of *UBE3A* silencing repaired functional circadian physiology in mouse models of AS. *UBE3A* encodes a HECT domain E3 ubiquitin ligase (E6-AP) [79]. Ubiquitin is a small protein that in a multistep process is added to and thus regulates the action of target substrate proteins [80] including circadian clocks [79, 81]. The clock transcription factor BMAL1 is an ubiquitinylation target of E6-AP, supporting the role of *UBE3A* in the regulation of the circadian clock [79, 81]. In particular, reactivation of paternal *UBE3A* in AS brain slices restored circadian periodicity, specifically in E6-AP-deficient neurons, leading the authors to conclude "that deficiency of neuronal E6-AP activity leads to defective ubiquitinylation of clock proteins that alters circadian-clock-mediated behaviour and metabolism" and that these alterations likely underlie the sleep disorders that are associated with AS [79].

Rett Syndrome (RS)

While RS was classified as a pervasive developmental disorder under earlier editions of the DSM, its cause is now known to be due to mutations in the *MECP2* gene, with specific mutations determining severity of clinical presentation and affecting primarily females [23]. Autistic features are common [82]. Sleep problems were first reported as associated with RS by Glaze and colleagues [83]. Reported difficulties include late sleep onset, night waking, and early morning waking; however, daytime napping is common, resulting in relatively normal total sleep time over a 24-h period [84]. Disturbing night-time behaviours such as laughing, screaming, and teeth grinding, as well as actual seizures, are also reported [23]. Sleep architecture and sleep efficiency appear to be relatively normal on PSG [85] in a group of 30 RS girls recruited into a polysomnography study; however, they were not referred for sleep problems. Given reports elsewhere of frequent poor sleep, it is likely there is considerable interindividual variability.

Night-time sleep problems and increased daytime napping suggest that sleep may not be well consolidated in RS, and two papers from the 1990s reported on melatonin treatment for poor sleep [35, 86]. Using actigraphy to monitor sleep over 10 weeks in nine girls with RS, immediate-release melatonin was administered an hour prior to bedtime using a double-blind, placebo-controlled, crossover protocol. The girls presented with long sleep onset latency, night wakings, reduced total night-time sleep, and reduced sleep efficiency. No free-running or non-24-h sleep-wake patterns were observed. Treatment significantly reduced sleep onset latency and improved total sleep and sleep efficiency in the more severely affected girls. However, there was considerable individual variation in response. The second study [35] examined the effects of melatonin in two children; prior to treatment, the first girl (age 7 years) had a free-running rhythm and 6-h delayed melatonin cycle, and the second girl (13 years) had a fragmented sleep-wake rhythm, with a normally timed but relatively low melatonin peak. Oral melatonin prior to bedtime resulted in a considerable improvement in the sleep-wake cycle in the first girl, while in the second child, the authors believed that melatonin had primarily a soporific effect. Cessation of melatonin resulted in return of sleep difficulties, and melatonin administration was recommenced.

Melatonin Treatment for Sleep Difficulties in Children with an NDD

The administration of exogenous melatonin has been widely reported as a successful approach for treating sleep onset difficulties in children with DD (see Schwichtenberg and Malow [87] for a review). Melatonin has both chronobiotic (phase-shifting) and soporific (sleep-inducing) effects, and it is the latter that is argued to assist in reducing sleep onset difficulties. In particular, sleep onset latency is usually reported to decrease significantly after short-term trials [87]. However,

the findings regarding wake after sleep onset and total sleep time are conflicting [87]. In particular, in a randomised double-blind placebo-controlled trial by Gringras and colleagues [88], it was found that melatonin significantly reduced sleep onset latency in children aged 3–15 years at a 12-week follow-up. However, sleep efficiency did not improve significantly, and although there was a statistically significant increase in total sleep time, the difference was not clinically significant. Moreover, children in the melatonin group woke significantly earlier (29.9 min earlier) at follow-up compared to baseline. Thus the chronobiotic mechanisms of melatonin likely phase-shifted the sleep-wake rhythm rather than acting through soporific effects. Similar results were found in a randomised double-blind placebo-controlled study that assessed the efficacy of 3 mg of melatonin in improving insomnia symptoms in children with ASD and/or FXS. Melatonin not only increased sleep duration but also shifted sleep onset times earlier (42 min) compared to placebo, further suggesting that melatonin acts as a chronobiotic.

In the study by Takaesu and colleagues [37], six AS subjects were treated with 1 mg of melatonin for their CRSWD. Melatonin was taken orally between 6:00 pm and 7:00 pm for 3 months. The results indicated that the free-running rhythm associated with N24SWRD in two AS subjects was completely suppressed after commencing melatonin treatment and two of the three ISWRD subjects decreased the frequency of daytime napping and increased nocturnal sleep duration. These subjects also had significant improvements in their sleep quality. Of note, sleep was assessed via parent-report sleep logs and not via more objective measures of sleep.

Mouse models have suggested that melatonin may exert anxiolytic effects [89]. Thus it is possible that sleep improves in children with NDDs treated with melatonin by reducing anxiety symptoms. Children may then be able to fall asleep and return to sleep after waking without the need to alert their parents. However, further research is required using objective measures of sleep and anxiety.

Currently there is no consensus on the required dosage and type of melatonin (immediate versus controlled release), and this may differ for each child's presenting sleep problem. Moreover, long-term safety outcomes of melatonin have not been rigorously assessed, as fast-release melatonin is not registered for child use, with no long-term safety data for children. Animal studies show melatonin can affect the reproductive system, immune system, and metabolism, and it may interact with other medications prescribed for children [90]. There is some evidence for the safety of prolonged-release melatonin (trade name Circadin) in children [91], though it is not recommended in Australia [92]. Consequently the use of melatonin in paediatric samples should be approached with caution until appropriate safety data become available [92]. However, when a CRSWD has been identified, melatonin may be useful in helping phase-shift sleep to more appropriate times and may also help to improve sleep quality, particularly in children with very disturbed sleep patterns and melatonin atypicalities (e.g. AS, SMS, and WS). Prior to melatonin treatment, a comprehensive sleep assessment including assessment of endogenous melatonin levels, where possible, should be undertaken to determine the most appropriate dosage and timing of administration. Behavioural treatments and chronotherapy in conjunction with melatonin are also likely to be beneficial in improving sleep patterns [93]; the additive effects of behavioural treatments may improve problematic sleep habits which melatonin cannot treat.

Conclusions and Recommendations

Overall, common symptoms of sleep onset delay, night and early morning waking, and daytime sleepiness or increased napping are not only indicators of insomnia, but they may also indicate a CRSWD in children with an NDD or ID. N24SWRD and ISWRD are frequently reported, and DSWPD is reported in children with ASD; however, CRSWDs are not always considered in the interpretation of sleep problems. Prevalence rates and presentations also appear to differ across different NDDs. Those with more severe ID (e.g. AS and RS) may be more prone to the development of CRSWDs as they may not use environmental zeitgebers effectively to entrain their sleep-wake rhythms [94]. Moreover, psychopathology symptoms such as anxiety and depression may also account for CRSWDs in children with an NDD, particularly those who are cognitively able. Supporting the presence of CRSWDs, melatonin rhythm abnormalities have also been reported in some rare chromosomal disorders, and melatonin is used with some success in treating delayed sleep onset, though the mechanism of action is disputed, with chronobiotic effects being most likely.

Future Directions

Overall, further research is required that aims to objectively assess sleep in children with an NDD and to classify these sleep problems based on current diagnostic criteria (e.g., ICSD-3). With the emergence of home DLMO kits [95, 96], assessment of endogenous melatonin levels is more easily accessible and will assist in delineating CRSWDs in NDDs. Assessment of DLMO will also assist in determining whether melatonin levels are deficient around the sleep onset period and whether supplemental melatonin will be efficacious in treating sleep problems. While melatonin is reported to be effective in treating several sleep difficulties, particularly sleep onset delay, the mechanism of action is unclear, and studies assessing the long-term safety of exogenous

melatonin, particularly fast-release preparations, are lacking. Further research is also required to determine the efficacy and long-term safety of melatonin for sleep disturbances in children with NDDs and the types of sleep disturbances which it most successfully treats.

All sleep interventions should include attention to sleep hygiene principles, which are discussed elsewhere in this volume (see also Jan et al. [97]). Melatonin has the advantage of being easy to administer, and its efficacy in a particular case will generally be quickly established. Nevertheless, in view of potential long-term safety concerns, other means of shifting the sleep-wake rhythm should be explored. While there is little research in children, both chronotherapy and light therapy can be used to phase shift the sleep-wake rhythm.

We have detailed Piazza's case study using chronotherapy [1], and it is clear that such an approach requires significant support. Light therapy, in which bright morning light results in phase advance (moving sleep onset to an earlier time) and bright evening light in phase delays (moving sleep onset to a later time), can be applied (see Guilleminault et al. [40]). In typically developing children, mean age 10 years, a recent report [98] comparing melatonin and bright light therapy for chronic sleep onset difficulties showed that 30-min morning exposure to bright light (500 nm peak wavelength, 8000 lux) fixed to a cap, thus allowing movement, was successful in advancing sleep onset time, with modest effects on sleep latency, but that overall, melatonin (3 mg) was a superior treatment. Nevertheless sleep latency still exceeded 30 min in both the melatonin and bright light groups, there were treatment adherence issues in both groups, and the authors noted that research on treatment protocols for light therapy in children is needed. Having a child regularly outdoors in bright morning light (possible in summer months), with strong daily routines, may also assist if the sleep rhythm is delayed or irregular. Indeed, sleep hygiene recommendations include getting sufficient daylight at appropriate times of day [97]. Of course, what is needed is more research into the frequency and presentation of CRSWDs in children with NDDs and research into the efficacy, effectiveness, and acceptability of treatment methods other than melatonin, as well as investigation of optimal melatonin protocols and dosage.

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Sleep-Related Movement Disorders

10

Ann Reynolds

Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
AHI	Apnea-hypopnea index
ASD	Autism spectrum disorder
DD	Developmental delay
EMG	Electromyogram
FDA	Federal Drug Administration
GP	Growing pains
ID	Intellectual disability
NDD	Neurodevelopmental disabilities
OSA	Obstructive sleep apnea
PLMD	Periodic limb movement disorder
PLMI	Periodic limb movement index
PLMS	Periodic limb movements of sleep
PSG	Polysomnogram
PSQ	Pediatric sleep questionnaire
RCT	Randomized control trial
REM	Rapid eye movement
RLS	Restless legs syndrome
RMD	Rhythmic movement disorder
RMMA	Rhythmic masticatory muscle activity
SRB	Sleep-related bruxism
SRMD	Sleep-related movement disorder
SSRI	Selective serotonin reuptake inhibitors
TD	Typical development

Case Vignette

David is a 3-year-old with an autism spectrum disorder, limited speech, daytime irritability, limited diet, and severe symptoms of insomnia. He had difficulty settling for sleep and maintaining sleep. He was described as a restless sleeper and did not snore. His parents were not sure if he kicked his legs at night, but his blankets were often twisted up and lying on the floor by morning. They felt that he was always on the go but may be more "wired" at night. His sleep disruption caused significant dysfunction for his family. David's mother met with a psychologist to discuss sleep hygiene and was able to implement some of the strategies. He made some improvement in initiating sleep but continued to have night wakings one to two times per night, seven nights per week. His serum ferritin was 17 ng/mL (normal 10–60) with a normal erythrocyte sedimentation rate. The psychologist worked with David and his parents on desensitization for a polysomnogram (PSG). He had a successful study which showed no respiratory abnormalities but a periodic limb movement index of 12 per hour. He was treated with ferrous sulfate, 3 mg/kg/day divided twice per day for 3 months. His ferritin was checked again and was 28 ng/mL. His night waking was improved, such that he was waking only one night a week.

Introduction

Sleep problems are very common in children with neurodevelopmental disabilities (NDD), with prevalence rates of approximately 50–80% [1–4]. The etiology of sleep problems in children with NDD is complex as a child's sleep may be impacted by multiple factors. A multidimensional approach is indicated. Sleep-related movement disorders (SRMD) are a potential cause of sleep problems which may

A. Reynolds
Pediatrics, University of Colorado Denver,
Children's Hospital Colorado, Aurora, CO, USA
e-mail: ann.reynolds@childrenscolorado.org

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be overlooked in children with NDD. Unfortunately, SRMD have not been adequately studied in children with NDD, and their true prevalence is unknown.

Sleep-related movement disorders include restless legs syndrome (RLS), periodic limb movement disorder (PLMD), sleep-related bruxism, and sleep-related rhythmic movement disorder, among others (Table 10.1). With the exception of RLS, these disorders typically involve "relatively simple" stereotyped movements that disrupt the initiation or maintenance of sleep or lead to daytime symptoms/behaviors associated with inadequate sleep. These movements should be differentiated from complex behaviors during sleep such as parasomnias. For a movement such as bruxism, which also occurs during wakefulness, to be classified as a sleep-related movement disorder, it should only be done if the movement is present exclusively during sleep or "significantly different" during sleep [5]. Sleep-related leg cramps, benign myoclonus of infancy, propriospinal myoclonus at sleep onset, sleep-related movement disorder due to a medical condition, sleep-related movement disorder due to a medication or substance, and sleep-related movement disorder, which are unspecified, will not be discussed in detail (Table 10.1). Isolated symptoms and normal variants, including excessive fragmentary myoclonus, hypnagogic foot tremor, alternating leg muscle activation, and sleep starts (hypnic jerks), will not be discussed [5]. RLS and PLMD will be described separately, but due to the significant overlap between them, they will be combined for discussion of the prevalence, etiology, and treatment in children with NDD.

Research addressing SRMD in children with NDD is limited. This is most likely related to multiple factors, including a lack of awareness that these disorders may play a role in sleep problems in children with NDD. Children with NDD often have developmental or behavioral issues that are presumed to be the sole reasons for their sleep difficulties. They may also have repetitive movements during the day such as bruxism, rocking, or stereotypies. Determining whether these daytime movements are different during sleep or contribute to sleep problems can be challenging. Children with NDD frequently have difficulty communicating

Table 10.1 Sleep-related movement disorders

Restless legs syndrome (RLS)	Restless legs syndrome is characterized by an urge to move the legs associated with uncomfortable sensations which are worse at rest and in the evening and relieved by movement[a]
Periodic limb movement disorder (PLMD)	Repetitive stereotypic movements of the limbs during sleep characterized by extension of the great toe with partial flexion of the ankle, knee, and hip associated with disturbance of sleep or daytime behavior and not better explained by another sleep disorder[a]
Sleep-related bruxism (SRB)	Rhythmic grinding/clenching of teeth during sleep associated with abnormal wear on the teeth, jaw pain, temporal headache, and/or jaw locking in the morning. SRB is separate from daytime bruxism, but both may be present in the same individual[a]
Sleep-related leg cramps	Sleep-related leg cramps, or "charley horses," are painful leg cramps that occur around bedtime and are relieved by stretching
Sleep-related rhythmic movement disorder (RMD)	Repetitive, rhythmic, and stereotyped movements of large muscle groups during sleep or just before sleep which negatively impact sleep or daytime function or potentially lead to injury[a]
Benign myoclonus of infancy	Repetitive myoclonic jerks of the limbs, trunk, and body that occur only during sleep in infants up to 6 months of age and can be stopped by waking the infant
Propriospinal myoclonus at sleep onset	Jerks of the abdomen, trunk, and neck which occur during drowsiness and interfere with initiating sleep
Sleep-related movement disorder due to a medical condition	Sleep-related movements associated with difficulty initiating or maintaining sleep secondary to a medical condition. This diagnosis may be used prior to establishing a medical diagnosis; otherwise it should only be used if the movements require "independent attention." If an individual meets criteria for another sleep disorder, such as RLS, the other sleep disorder diagnosis should be used
Sleep-related movement disorder due to a medication or substance	Sleep-related movements associated with difficulty initiating or maintaining sleep secondary to the use of a medication or substance or withdrawal of a medication which require "independent attention." If an individual has symptoms consistent with another sleep disorder, such as RLS, as a result of medication or substance use, then the other sleep disorder diagnosis should be used
Sleep-related movement disorder, unspecified	Sleep-related movements that do not fit other classifications may be used when a psychiatric condition is suspected but not yet confirmed

Based on the International Classification of Sleep Disorders, 3rd ed. [5]
[a]See text for a more detailed discussion

symptoms, a skill which is critical to enable diagnosis of RLS. They also have difficulty cooperating with polysomnography (PSG) which is essential for making a diagnosis of PLMD. These factors lead to the difficulty making a reliable diagnosis of a sleep-related movement disorder, which in turn leads to the difficulty conducting research to establish the prevalence of and treatments for SRMD in individuals with NDD.

Restless Legs Syndrome and Periodic Limb Movement Disorder

Restless Legs Syndrome

Restless legs syndrome (RLS) is a sensorimotor sleep-related movement disorder which is primarily defined by an urge to move the legs. The urge to move the legs is usually associated with "uncomfortable or unpleasant sensations" in the legs. The term "dysesthesia" has been used. These vague/indistinct symptoms are difficult to describe for adults and even more so for children with NDD. The urge to move the legs (and sometimes arms) must be associated with rest, relieved by movement, and worse in the evening. The symptoms cannot be due to another condition such as arthritis or myalgia and must cause significant "distress," disruption of sleep, or impact on daytime function. Specifiers are available for severity and clinical course of symptoms. "Mimics" of RLS such as dermatitis and growing pains in children must be considered [5, 6].

RLS has been reported to occur in 2–4% of children [5, 7]. RLS can be difficult to diagnose in children as it is a diagnosis which is based on a description of symptoms by the individual. The presence of RLS in children was initially recognized because adults with RLS reported that their symptoms started in childhood [8]. Updated pediatric RLS criteria were published in 2013 [7] after the adult criteria were updated in 2012 by the International Restless Legs Syndrome Study Group [6]. The pediatric criteria stipulate that the description of the urge to move the legs should be in the "child's own words" such as "need to move," "got to kick," or "too much energy" [7, 9, 10], and the clinician should be aware of ways that children might describe the urge to move their legs. Words that may be used by children to describe dysesthesia include "bugs, ants, spider in the legs, weird/funny feelings, tingle, wiggly, oowies, boo-boos, tickle, and shaky" [5, 7, 10]. Language and cognitive function are now used instead of age to determine the ability to use the RLS criteria in a child. Typically a language level of at least 6 years is needed in order to describe symptoms of RLS. Prompts such as "Do your legs bother you?" are encouraged; however, it is also important that questions are not leading as some children may answer yes because they feel that it is expected. Asking a child to draw a picture of how their legs feel can be helpful as well [8, 9, 11]. The criteria for probable and possible RLS were also updated in 2013. A child meets the criteria for probable RLS if the child has an urge to move legs which is worse at rest and relieved by movement but is not worse at night [7]. About two thirds of children with RLS may describe unusual feelings in their legs during the day as well as at night, usually when sitting in school or in the car. In order to clarify that symptoms are worse at night, it can be helpful to ask about the duration of sitting needed to produce symptoms during the day vs. at night [5, 11]. A child meets criteria for Possible RLS if the child appears to have limb discomfort and movement when sitting or lying down which is worse in the evening and appears to be relieved by movement. The Possible RLS diagnosis may be considered when children do not have the language to communicate an urge to move or discomfort [7]. Approximately 63–74% of children with RLS have periodic limb movements of sleep (PLMS) based on a single night of PSG [12]; about 90% of adults with RLS will have PLMS on PSG performed over multiple nights [5]. RLS is more common in individuals with a family history of RLS or PLMD in first-degree relatives. PLMS and family history increase confidence in a diagnosis of RLS but are no longer considered essential when making a diagnosis of RLS because of the lack of availability of biologic family history for some children [7].

Individuals with RLS have a greater prevalence of attention-deficit/hyperactivity disorder (ADHD), depression, and anxiety [5]. A retrospective review of children with definite or probable RLS found that 64% had at least one psychiatric or NDD diagnosis. The retrospective nature of the study precluded conclusions regarding the role of psychotropic medications in the etiology of RLS. A multidisciplinary approach to the management of RLS may be indicated in order to optimize management of both the psychiatric/developmental disorder, especially with respect to medication management, and RLS [13]. Other conditions that may be associated with RLS are narcolepsy, migraine, obstructive sleep apnea (OSA), and thyroid disease. While a diagnosis of "secondary RLS" has been proposed when RLS is associated with conditions such as iron deficiency or pregnancy, ultimately the pathophysiology, family history, genetics, and clinical course do not support a "secondary" classification. Clear "precipitating factors" in RLS include the following: iron deficiency, pregnancy, chronic renal failure, prolonged immobility, and some medications. Possible "exacerbating factors" in RLS include sleep deprivation, peripheral neuropathy, pain, caffeine, tobacco, and alcohol [5].

Differentiating RLS from growing pains (GP) is problematic in children as there is overlap between the disorders [10, 14]. GP are common and have been reported to occur in 2.6–49.4% of children. The variability of reports is pre-

sumed to be secondary to a lack of well-defined diagnostic criteria. Both RLS and GP occur primarily in the legs, tend to occur later in the day, and tend to be hereditary. GP have a younger peak age of 4–6 years old and by definition are painful, intermittent, and bilateral [10]. Children with growing pains were found to be more likely to have PLMS on PSG than children without growing pains in a retrospective chart review of patients referred for sleep problems, mainly snoring [14]. Subjects who reported restless sleep were also more likely to have GP and PLMS in that study. The authors postulated that growing pains may "lie on the phenotypic spectrum of RLS" [14]. A working group has been formed to establish consensus for more precise diagnostic criteria for GP which should improve understanding of the overlap between RLS and GP [10].

Periodic Limb Movement Disorder

PLMS are repetitive stereotypic movements of the limbs during sleep that occur in clusters lasting for minutes up to an hour. They usually occur in the lower extremities and are characterized by extension of the great toe with partial flexion of the ankle, knee, and hip. Cortical arousals, autonomic arousals, and awakenings may occur before, during, or after these movements. The diagnosis of PLMS in children requires an elevation in the periodic limb movement index (PLMI), scored via polysomnography (PSG), of greater than 5 per hour [5, 15]. Periodic limb movements of sleep are evaluated using surface electromyogram (EMG) of the anterior tibialis muscle and should be scored as defined by the latest American Academy of Sleep Medicine manual for the Scoring of Sleep and Associated Events. They should not be scored when associated with respiratory events such as apneas or hypopneas [5]. In order to make a diagnosis of periodic limb movement disorder (PLMD), sleep problems or impairment in daytime function must be present in addition to PLMS. A diagnosis of PLMD should not be given if another diagnosis better explains insomnia or hypersomnia: for example, a diagnosis of PLMD cannot be made in the presence of narcolepsy, untreated OSA, or REM sleep behavior disorder, as PLMS are often associated with these disorders [5]. An evaluation for narcolepsy should be considered in children with PLMS and daytime sleepiness [7]. In addition, PLMD should not be diagnosed in an individual who meets criteria for RLS; however, a diagnosis of PLMD may change to a diagnosis of RLS as a child develops the ability to describe symptoms of RLS. PLMS have been proposed as an endophenotype of RLS [5, 7, 12]. While the literature on PLMS in individuals with NDD is limited, several small studies have documented the presence of PLMS on PSG in children with ASD, ADHD, and other disabilities [5, 16–24].

Making a diagnosis of PLMD requires a high index of suspicion, as self-report and parent report are not considered sensitive or specific for PLMS [5]. Screening tools for PLMD have limited value in children with typical development and have not been validated in children with NDD. The Pediatric Sleep Questionnaire (PSQ), PLMS subscale, includes six items which are differentially weighted. The items include restlessness of the legs when in bed, growing pains that are worst in bed, usually getting out of bed (for any reason), waking more than twice per night on average, feeling unrefreshed upon waking up, and waking with morning headaches. It was validated on 113 subjects undergoing PSG for concerns about sleep-disordered breathing. Children with NDD were excluded. A PLMS score >0.33 had a sensitivity for PLMI ≥5 of 0.79, a specificity of 0.56, a positive predictive value of 0.38, and negative predictive value of 0.89. It had reasonable internal consistency, Cronbach's $\alpha = 0.71$, and test-retest reliability, $p = 0.62$, $P = 0.0026$, $n = 21$. The items which were most predictive included having restless legs, growing pains, night waking, and morning headache. The authors caution that the tool is more useful in research to capture children at risk for PLMS than for use in a single patient in a clinical setting [25]. Of note, when taking a history, hypnic jerks (also known as sleep starts) may mimic PLMS but are only present during the transition to sleep and are shorter and not "periodic" [5]. At this time, physiologic measures are required to make a diagnosis of PLMD.

A polysomnogram (PSG) is considered "standard" care when a child is suspected of having PLMD and may be an "option" when a child is suspected of having RLS but the language level of the child is not adequate to describe symptoms of RLS [26]. Having said this, night-to-night variability in PLMS has been reported in children, such that multiple nights of PSG may be needed for detection [27]. PLMS are uncommon in children with typical development; therefore, the presence of PLMS on a PSG is noteworthy [5]. PLMD may go undetected in individuals with NDD given the challenges of performing PSG in this population, who may have difficulty tolerating the monitoring involved due to tactile sensitivities or anxiety in novel situations. Desensitization strategies can be very helpful in preparing a child with NDD for a PSG; therefore, consideration of the use of PSG should not be disregarded in children with NDD. Due to concerns about night-to-night variability of PLMS [11] such that a single night of PSG might not capture PLMS, or when PSG is not an option, the use of leg actigraphy may be considered. Leg actigraphs, which use three-axis motion sensors to record leg activity, can measure PLMS and have been validated versus PSG in adults [28, 29]. However, interpretation may require manually setting the amplitude threshold [28]. Leg actigraphs have been proposed for use in children but have not been validated in the pediatric population [8].

Restless Legs Syndrome/Periodic Limb Movement Disorder Pathophysiology

Dopamine function in the brain, iron status, and genetic predisposition are implicated in the etiology of RLS and PLMD [5]. Early-onset RLS is clearly associated with a positive family history of RLS in first-degree relatives, which favors an autosomal dominant inheritance. However, more complex explanations involving both genes and environment have been proposed. Polymorphisms found to be associated with RLS include *BTBD9*, *MEIS1*, *MAP2K5/LBXCOR*, and *PTPRD* [5, 30, 31]. Dopamine is presumed to be involved in RLS and PLMS, as most patients with RLS have at least an initial response to L-dopa or dopamine-receptor agonist therapy [5, 32]. Autopsy, functional MRI and positron emission tomography studies have also supported the role of dopamine in RLS [5]. Iron plays an important role in dopamine function in the brain: it is a cofactor for tyrosine hydroxylase, an enzyme involved in dopamine synthesis [33]. Iron also has a role in synaptic density, myelin synthesis, and energy production in the brain [5]. Both RLS and PLMS are associated with iron deficiency, specifically, a serum ferritin level of less than 50 ng/mL [11, 34]. Evidence also suggests that central nervous system iron status may be even more important than peripheral iron status in the pathophysiology of RLS [35–37].

Potential risk factors for RLS and PLMS of particular interest in children with NDD are iron deficiency and also the use of psychotropic medications such as selective serotonin reuptake inhibitors (SSRI) and dopamine antagonists such as atypical antipsychotic medications. Children with NDD, and more specifically, children with ASD, are at risk for iron deficiency due to feeding issues such as restricted diets, food neophobia, and mealtime rituals, all of which may be associated with decreased dietary iron intake and which are reported in as many as 70–90% of children with ASD [38–42]. Iron deficiency (low ferritin levels) has been reported in 8–52% of children with ASD [43–45]. A study of diet and nutrition in children from five sites around the United States found that 8% of subjects had ferritin levels less than 12 ng/mL and 90% had ferritin levels below 50 ng/mL [46]. However, normal values for ferritin are much lower in young children than in adults, with normal values in some labs reported to be 10–60 ng/mL. Low ferritin levels, therefore, may increase the risk for RLS/PLMS in this population. Children with NDD often take psychotropic medications to manage psychiatric comorbidities and maladaptive behaviors. These medications may have a negative impact on sleep. SSRIs have been associated with RLS and PLMS in adults, although the mechanism of action for this adverse effect is unclear [47]. A retrospective chart review of 1023 children who underwent PSG in Poland found an association between PLMS and SSRI use in children. In that study, PSG was performed to evaluate for sleep-disordered breathing or daytime sleepiness, and movements were not scored if they occurred within 1 s of snoring or arousals. PLMS were found in 13 of 41 children (31.7%) taking SSRIs compared with 77 of 982 children (7.8%) who were not taking SSRIs [48]. Atypical antipsychotic medications are frequently used to treat maladaptive behaviors in children with NDD, and risperidone and aripiprazole have a Federal Drug Administration (FDA) indication to treat irritability and aggression in children with ASD. There have been case reports, one for risperidone and one for olanzapine, reporting symptoms of RLS and PLMS which improved or resolved on discontinuation of those medications [47, 49, 50]. Atypical antipsychotic medications are dopamine antagonists, so that blockade of dopamine is the presumed mechanism of action for development of RLS/PLMS with atypical antipsychotics [50]. Of interest, aripiprazole, which has both dopamine agonist and antagonist activity, has been reported both to worsen and alleviate symptoms of RLS [51, 52]. Symptoms of RLS may be mistaken for akathisia, a known side effect of atypical antipsychotics. However, akathisia should not worsen more markedly at night [50]. Children with limited iron intake, especially from heme sources of iron such as beef, and those taking psychotropic medications should be monitored for SRMD.

Restless Legs Syndrome/Periodic Limb Movement Disorder in Individuals with Genetic Disorders, Intellectual Disability, and Epilepsy

The literature regarding the prevalence of RLS/PLMD in individuals with NDD due to genetic disorders, intellectual disability (ID), and epilepsy is sparse and usually limited to small case series or descriptive studies reporting PLMS found during PSG. A retrospective chart review found that 4% of children with definite or probable RLS had ID and 6.7% had a learning disorder [13]. Increased rates of PLMS have been noted in individuals with Williams syndrome. A report of seven children with Williams syndrome found that they had higher PLMI (14.9 ± 6.2) than ten matched controls (2.8 ± 1.9) [53]. However, in a larger study of children with Williams syndrome ($n = 35$), there was no difference in PLMI between children with Williams syndrome and controls [54]. Thirteen girls with Rett syndrome were found to have higher mean PLMI (9.52 ± 1.89) than controls (2.81 ± 1.1) [55]. Children with Angelman syndrome ($n = 10$) were noted to have a higher prevalence of PLMI >5 than children with ID both with seizures ($n = 13$) and without seizures ($n = 15$), with rates of 70%, 38.46%, and 46.67%,

respectively. All groups had a higher prevalence than has been reported for the general population. These data are difficult to interpret due to small numbers, potential bias due to recruitment from sleep centers, and the presence of sleep disordered breathing in some subjects [24]. The same group also evaluated 11 children with idiopathic ID and epilepsy compared to 10 children with typical development and no sleep issues. These study subjects with ID and epilepsy had a mean PLMI of 4.2 ± 5.1; however, only three had a PLMI >5 (27%) with two of those subjects also having an apnea-hypopnea index (AHI) >2, consistent with sleep-disordered breathing [56]. Children with Down syndrome are known to have a high prevalence of sleep-disordered breathing/OSA. A study using the Pediatric Sleep Questionnaire (PSQ) [25] found that 21% of children with Down syndrome had elevated scores on the sleep-related movement problem section of the PSQ, the PSQ PLMS subscale score. The children with Down syndrome were about 2.6 times more likely to have a sleep-related movement problem on the PSQ if they also had ASD or enlarged tonsils and adenoids [57]. These results should be viewed with caution as the PSQ PLMS subscale score has low specificity [25]. Another small study reported that children with Down syndrome (n = 11) had mean leg movements of 8.3 ± 6.5 per hour, compared to a control group (n = 13) with 1.8 ± 1.1 movements per hour. In addition, arousals and awakenings were more likely to be associated with limb movements than with sleep-disordered breathing in the children with Down syndrome [58]. These PSG studies have low numbers and potential ascertainment bias; however, PSG should be considered in children with NDD who have insomnia.

Restless Legs Syndrome/Periodic Limb Movement Disorder in Children with ASD

The literature regarding RLS and PLMS in individuals with ASD is limited. No studies of RLS in children with ASD have been completed. However, a retrospective chart review of children with definite or probable RLS found that 4.8% had an ASD which is greater than the 1–2% expected in the general population and may be an underestimate due to the difficulty making the diagnosis in children with communication disorders [13]. There has been no study specifically looking for PLMS in children with ASD; instead, there have been studies which included PSG with EMG of the anterior tibialis muscle in children with ASD [16, 18–22, 59]. There may be a higher prevalence of PLMS in children with ASD [16, 18–22, 59]. Seven studies, most very small, reported rates of PLMS ranging from 0% to 38% [16, 18–22, 59] (Table 10.2). Five of the seven studies did not include sleep disturbance as an inclusion criteria; therefore, many subjects were low risk for any findings on PSG. Many of these studies were looking for differences in REM sleep in individuals with ASD and did not require sleep problems for inclusion. Two studies found no children with increased PLMI (sleep issues were not prerequisite for inclusion in these), and five found abnormal PLMI (greater than five PLMs per hour) in 20–38% of subjects. One of the studies which included developmental delay (DD) and typical development (TD) control groups found no statistical differences in mean PLMI between groups: ASD = 5.19 ± 7.04, DD = 4.59 ± 3.42, and TD = 2.79 ± 3.86 [59]. Two of these studies did include children with sleep disturbances, with one evaluating night waking in children suspected of having REM sleep behavior disorder [20, 21].

Table 10.2 PLMS in children with autism spectrum disorders

Study	PLMS evaluated	Sleep issues prerequisite	*N*	Age	Number with PLMS > = 5/h
Godbout et al. [18]	Yes	No	8 Asperger	7–53	3 (38%)
Thirumalai et al. [21]	Yes	Yes	11 ASD: night waking	3–9	4 (36%)[a]
Limoges et al. [19]	Yes	No	16 ASD: IQ >82	16–27	5 (31%)
			16 control		1 (6%)
Bruni et al. [16]	Yes	No	8 Asperger	7–15	0
			10 autism		0
			12 typical		0
Malow et al. [20]	Yes	Yes/no	10 ASD: poor sleepers		2 (20%)
			11 ASD: good sleepers		3 (27%)
Giannotti et al. [22]	Yes	No	20 ASD: regression	5–10	0
			18 ASD: no regression		
Lane et al. [59][b]	Yes	No	68 ASD	2–7	35%
			16 DD		44%
			18 typical		17%

[a]Two of those also diagnosed with obstructive sleep apnea (OSA), one with REM sleep behavior disorder and one with PLMS as the primary diagnosis

[b]Respiratory parameters not measured

In addition, in a retrospective chart review of children with ASD who also had a documented PSG and ferritin levels compared these children to matched controls. The children with ASD had PLMS 47% of the time vs. 8% in controls, and their ferritin levels were significantly lower than those of controls, 27 mg/dL vs. 86 mg/dL. Among children with ASD, lower serum ferritin was associated with decreased sleep efficiency [60]. Most children with insomnia do not undergo PSG unless disorders such as OSA are suspected; therefore, PLMS may go undetected as a potential cause of sleep disruption that affects daytime behavior.

Restless Legs Syndrome/Periodic Limb Movement Disorder Is Children with ADHD

Both adults and children with RLS have a higher prevalence of symptoms of ADHD than the general population; likewise, individuals with ADHD have a higher prevalence of RLS [5]. Dopamine and iron have been implicated in the pathophysiology of both disorders [61–63]. Studies in children have been mixed but most have found an association between RLS/PLMS and ADHD [13, 23, 64–66]. In a retrospective chart review of individuals with definite or probable RLS, 25% had a diagnosis of ADHD [13]. A meta-analysis of PSG data found that children with ADHD had more PLMS than control children [23]. However, one study of 31 medication-naive children with ADHD and no comorbid psychiatric disorders, NDD, or medical conditions (including "chronic sleep disorders") found no difference in PSG compared to 26 control children. The PLMI did vary between first and second night of PSG in both groups. Parents of children with ADHD did report more sleep problems on the PSQ [67]. ADHD has also been associated with low serum ferritin levels/iron deficiency and low brain iron on MRI in children [61, 62, 68–71]. There are no studies of iron treatment for RLS in children with ADHD. A small study of 23 children with ADHD with serum ferritin levels <30 ng/mL who were randomized (3:1 ratio) to ferrous sulfate (80 mg/day) or placebo found improvement in ADHD symptoms with iron therapy [72]. Issues which complicate the association between these conditions include overlap in diagnostic criteria between ADHD and RLS as in children who report an urge to move during the day, especially when in school, the role of comorbid psychiatric disorders such as anxiety, the use of psychotropic medications which can impact RLS/PLMS, and the impact of poor sleep on attention.

Restless Legs Syndrome/Periodic Limb Movement Disorder Treatment

Both non-pharmacologic and pharmacologic treatments are used to treat RLS/PLMD in children [11, 64]. Very little research has been done to evaluate these therapies. Even less literature exists regarding treatment of RLS/PLMD in children with NDD specifically (Table 10.3). Lifestyle changes such as appropriate sleep habits, elimination of caffeine and medications which exacerbate RLS/PLMS, and daytime exercise are suggested for children with RLS based on information from the adult literature [73–75]. Currently, there is no FDA-approved drug to treat RLS in children. Ropinirole, pramipexole, rotigotine (dopamine agonists), and gabapentin enacarbil are FDA approved to treat adults with moderate to severe RLS. Iron is a well-accepted treatment for RLS in adults with a ferritin level of less than 50 ng/mL and has been recommended in children [11, 75].

Table 10.3 Treatment for restless legs syndrome/periodic limb movement disorder

Healthy sleep habits	Recommended in children but no trials [10, 11]
Physical exercise (not too much)	Small RCT in adults [73], RCT in adult hemodialysis patients [74], recommended in children but no trials [10]
Avoidance of caffeine, nicotine, alcohol	Recommended in adults but no trials [75]
Avoidance of SSRIs, antihistamines, neuroleptics	Recommended in children but no trials [10, 11]
Iron (ferrous sulfate)	One open-label trial in ASD [76]
Gabapentin	Chart review for *insomnia* in children with ASD [77], RCT in adults with RLS [78, 79]
L-dopa	One small RCT in ADHD [80], one case series in ADHD [81]
Clonidine	Recommended in children with RLS and difficulty initiating sleep but no trials [11]
Clonazepam	Case series in Williams syndrome and PLMS [53]

All evidence is based on small RCT or small case series. These would all be considered "off-label" use and should be used with caution. No evidence on long-term efficacy and safety in children [64]

Treatment with 3 mg/kg/day of elemental iron divided into two doses for 3 months has been recommended as an initial treatment for RLS in children when serum ferritin levels are <50 ng/mL [11, 34]. Sustained improvement for 1–2 years after treatment is reported [11, 34, 82]. Twenty-five children with PLMS and serum ferritin levels less than 50 ng/mL were treated with 3 mg/kg/day of ferrous sulfate, and 19 (76%) reported significant subjective clinical improvement. In the children who responded to iron therapy, there was a significant decrease in PLMI (pre = 27.6 ± 14.9 PLM/h vs. post = 12.6 ± 5.3 PLM/h; $P < 0.001$), with an increase in serum ferritin concentrations (pre = 40.8 ± 27.4 ng/mL vs. post = 74.1 ± 13.0 ng/mL; $P < 0.001$). There was no mention of serious adverse events [83]. A retrospective chart review of 97 subjects found that children treated with iron (typically but not exclusively 3–4 mg/kg/day of elemental iron divided into twice per day dosing) for ferritin <30 were more likely to show improvement in RLS symptoms than those who did not. Of those treated with iron, initial ferritin levels were lower in the group who responded, median 18.9 vs. 27.4 ng/mL ($p = 0.005$). More children who used non-

pharmacologic therapies which included iron improved than those who did not, 46% vs. 19% (p = 0.03). There were methodological concerns including a high loss to follow up and potential placebo effect. The authors discuss the fact that serum ferritin levels in children are lower than in adults; therefore, using the adult cutoff of 50 ng/mL for treatment with iron may not be appropriate for children. They proposed using a ferritin of 30 as a cutoff in children [84]. An open-label study reported low to low normal ferritin in children with ASD who also had restless sleep, and both ferritin levels and subjective report of restless sleep improved with oral iron treatment (6 mg/kg/day of ferrous sulfate). Of note, 27% of participants developed gastrointestinal symptoms during the study. However, only 2 (5%) withdrew due to "side effects." It should be noted that 3 (7%) withdrew due to refusal to take the supplements [76]. The main side effect of oral iron is gastrointestinal distress, which occurs in 5–60% of patients [85–88]. Iron should not be given with food which interferes with absorption. Iron can be given 30 min before a meal or 2 h after. In order to improve compliance, children who need to take iron with something other than water in an attempt to hide the taste can take iron with a liquid containing Vitamin C, such as orange juice. Vitamin C is also recommended to improve absorption in the presence of inhibitors such as calcium, grains, or tea [89]. Ferritin levels should be followed to avoid the risk for iron overload, particularly if there is a family history of hemochromatosis [90, 91]. Checking levels after 3 months and then every 3–6 months has been suggested. In addition dose adjustments should be made to keep ferritin levels above 50 [82]. Ferritin is an acute phase reactant; therefore, levels should be obtained when the child is not ill, and a marker of inflammation such as an erythrocyte sedimentation rate or C-reactive protein should be obtained at the same time. If there is a poor response in ferritin level after the use of oral iron supplements, consider poor absorption as a potential cause in addition to poor compliance. Gastrointestinal and inflammatory disorders such as celiac disease can interfere with iron absorption. Intravenous iron has been suggested for individuals with RLS/PLMD who do not tolerate or respond to oral iron. Two RCTs in adults found mixed results with intravenous iron infusion [92, 93]. A retrospective chart review of intravenous iron sucrose in 16 children with RLS/PLMD categorized 15 of 16 children as having "systemic or neurologic comorbidities." Follow-up information was only available for 12 of the 16 subjects, and of those, 10 (62.5%) showed improvement in sleep based on parent report. Two subjects had some gastrointestinal symptoms, and the mean rise in ferritin after one dose was 29.3 ng/mL. Anaphylaxis is a potential side effect of intravenous iron; however, lower molecular weight iron preparations may have fewer serious adverse events. Further study is ongoing in this area [94]. When oral iron is used to treat symptoms of RLS/PLMD, parents should be educated about the risk of toxicity from overdose with iron supplements, in addition to gastrointestinal side effects, and the need for monitoring of serum ferritin levels to avoid iron overload.

The use of medications in children with RLS/PLMD should be reserved for children with moderate to severe symptoms which significantly impact sleep or daytime function [11]. A small randomized controlled trial (RCT) in children with RLS and ADHD found that L-dopa improved RLS symptoms. Baseline differences in ADHD symptoms between the groups were a notable limitation of this study, though [80]. In addition, a case series found improvement in ADHD symptoms after treatment of RLS with dopamine agonists [81]. Dopamine agonists can cause daytime sleepiness, hallucinations, disinhibited or compulsive behaviors, and nausea. All of these symptoms could have significant impacts on daily function in children with NDD. They can also lead to augmentation, worsening of RLS symptoms with spread to other body parts as well as progressively earlier onset of symptoms in the evening. Augmentation may respond to dose adjustments. There is little information about long-term use of dopamine agonists in children [11]. Gabapentin enacarbil has FDA approval for the treatment of moderate to severe RLS in adults. It is a prodrug of gabapentin. Studies in adults have found that gabapentin can improve symptoms of RLS [78, 79]. Gabapentin is FDA approved as an anticonvulsant in children. A retrospective chart review of 23 children, most with NDD, who were treated with gabapentin for insomnia found improvement in 78% [77]. Clonidine or other medications used to treat sleep may be helpful for children with RLS and significant difficulty initiating sleep [11].

Sleep-Related Bruxism

Sleep-related bruxism (SRB) is defined as rhythmic masticatory muscle activity (RMMA) characterized by repetitive grinding or clenching of teeth during sleep which is associated with at least one of the following: abnormal wear on teeth, jaw pain, temporal headache, and jaw locking in the morning [5]. Sleep-related bruxism is considered a separate entity from daytime bruxism, but both may be present in the same individual. SRB may be primary or alternatively, secondary to a medical disorder, psychotropic medications, caffeine, alcohol, or drugs of abuse [5]. Therefore, when bruxism is associated with cerebral palsy, intellectual disability, or Down syndrome, it is considered secondary SRB [5]. Sleep bruxism is found in around 14–17% of children with some studies reporting prevalence as low as 6% and others as high as 50% [5, 95, 96] and is more common in children than in adults. Many prevalence studies exclude children with NDD, chromosomal anomalies, or psychiatric

disorders. However, SRB may be no more common in individuals with NDD than in children with typical development [97, 98]. Episodes of SRB are frequently preceded by arousals on PSG with increased sympathetic activity. SRB, PLMS, and arousals are proposed to have a "common underlying neurophysiological mechanism" [5, 96, 99]. While PSG can confirm SRB, it is not typically recommended as standard evaluation to make the diagnosis [26]. However, SRB often occurs in individuals with OSA [100]; therefore, PSG should be considered if OSA is a potential concern. An association has been found between SRB, OSA, and maxillary transverse deficiency/"crossbite" in children. Crossbite occurs when there is lateral malocclusion such that either the upper or lower teeth are closer to the cheek than the opposing teeth. Rapid palatal expansion has been used to treat OSA in children with maxillary transverse deficiency. An observational study of rapid palatal expansion in 32 children with maxillary transverse deficiency but not sleep concerns found a reduction in RMMA on PSG in 65% of the children with no change in sleep or AHI [100].

Bruxism can result in wearing down of the teeth, tooth or jaw pain, and temporal headache. In most children, SRB resolves on its own without treatment. Occlusal splints/dental guards are typically used in adolescents or adults to prevent wear on the teeth. Stress reduction, improvement in sleep habits, and cognitive behavioral therapy have been used to treat SRB in adults [98, 101]. Children with NDD and SRB should have regular dental care and should be monitored for jaw pain. Pain or change in behavior or feeding may be signs of dental trauma secondary to SRB in children with NDD and SRB.

Sleep-Related Rhythmic Movement Disorder

Sleep-related rhythmic movement disorder (RMD) is characterized by repetitive, rhythmic, and stereotyped movements of large muscle groups during sleep or just before going to sleep. These movements must negatively impact sleep or daytime function, or potentially lead to injury, in order to rise to the level of diagnosis as a disorder. If the rhythmic movements are not associated with negative effects on the child, then the term "disorder" is not used. The movement types include body rocking, head banging, head rolling, body rolling, leg rolling, and leg banging. Most infants, children, and adults who engage in RMD do not have NDD. Rhythmic movements not primarily associated with sleep can lead to a diagnosis of stereotypic movement disorder instead. RMD typically starts in infancy and subsides by age 1–2 years. It is only present in 5% of 5-year-olds. The potential relationship between mechanisms involved in RMD in children with typical development and stereotypies in children with NDD is unknown and deserves further study [5]. The prevalence of RMD in individuals with NDD has not been studied.

Areas of Uncertainty/Future Directions in Sleep-Related Movement Disorders

The diagnosis of RLS and PLMD in children with NDD is problematic. Difficulty with communication of symptoms in children with NDD makes the diagnosis of RLS particularly challenging. Development of a tool which uses behavioral observation to diagnose RLS in young children and children with NDD has been proposed [102, 103]. At this time, the diagnosis of PLMD requires PSG, which is expensive, potentially difficult for children with NDD to tolerate without preparation, and challenging to access in many communities. Physiologic measures and biomarkers are needed. Leg actigraphy should be studied in children as a method to aid in the diagnosis of PLMD [8]. Genetic testing may also prove useful in the future as polymorphisms associated with RLS/PLMD have been identified [30, 31]. Neuroimaging may increase understanding of underlying mechanisms of SRMD in children with NDD. In addition, treatment studies are much needed to address SRMD.

Conclusions and Recommendations

Clinicians who provide care for children with NDD should be aware of the potential for SRMD to impact sleep in these children. Because children with NDD may have difficulty communicating symptoms of RLS, and because a diagnosis of PLMS requires PSG, these diagnoses can be easily missed in children with NDD. These factors lead to the difficulty both in making a reliable diagnosis of sleep-related movement disorders and also in conducting research. Higher rates of PLMS on PSG have been reported in small studies of children with NDD and ASD. An association between RLS/PLMS and ADHD in children has been reported. Children with ADHD may be at increased risk for RLS/PLMD due to possible common etiological pathways involving dopamine and iron. In addition, considerable overlap exists between RLS and ADHD, especially when considering that children with RLS often report an urge to move when at rest during the day such as when sitting in a classroom. Risk factors which may be associated with possible RLS/PLMD in children with NDD are growing pains, PLMS on PSG, first-degree relatives with RLS/PLMD, limited intake of easily absorbed forms of iron/meat, and low serum ferritin. Making a diagnosis of sleep-related bruxism and sleep-related rhythmic movement disorders is problematic as these behaviors are

often present during the day as well as during sleep in individuals with NDD. Sleep is integral to optimal development and daytime function, physical health, and to quality of life of individuals with NDD and their families. The etiology of sleep problems in children with NDD is multifactorial; therefore, an awareness of SRMD is critical to effectively manage sleep problems in this population. Therefore, further study is needed to understand the impact of SRMD in individuals with NDD.

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Part III

Neurodevelopmental Disabilities

Autism Spectrum Disorder

11

Margaret C. Souders, Whitney T. Eriksen, Amanda E. Bennett, Raghuram Prasad, and Stefanie Zavodny

Introduction

The high prevalence of inadequate sleep in children worldwide has caused great alarm, and the effects of inadequate sleep may be even more pronounced in children with neurodevelopmental disorders, including autism spectrum disorder (ASD) [1–4]. ASD is a complex neurodevelopmental disorder that has seen a marked increase in the prevalence over the past 30 years with a current rate of 1 in 59 children in the United States (US) [4–6]. One in 42 boys and 1 in 189 girls are identified as having ASD, a 4.5:1 sex ratio [5]. ASD is thought to have high heritability, and autism risk may be sexually dimorphic, with most genetic studies consistent with a female protective effect [4, 7–10]. The recurrence risk in families ranges from 10% to 25%, with a birth interval of less than 18 months increasing risk [11, 12]. Substantial heterogeneity exists in the degree of intellectual ability, social and communication impairments, and collection of behavioral symptoms [4]. Cognitive ability varies, with 31% of individuals with ASD having IQ scores in the range of intellectual disability (IQ ≤70), 23% in the borderline range (IQ = 71–85), and 46% in the average or above average range of intellectual ability (IQ >85) [4, 5]. ASD is a lifelong disorder that has major implications for the quality of life of the individual with ASD as well as his family, resulting in tremendous added responsibility on the part of public health and education systems [4, 13, 14].

In 1943, Leo Kanner first described children with significant impairments in social interaction, restricted and repetitive behaviors, and often unusual sensory responses to environmental stimuli as having autism [15, 16]. Over the past two decades, there has been progress in conceptualizing autism as a spectrum and an identity, delineating the variability in the phenotype and genotype [4]. In the 1990s, experts achieved consensus on the core deficits central to its definition and established an agreement between the two major diagnostic systems, the 4th edition of the *American Psychiatric Association (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* and the 10th edition of the World Health Organization (WHO) International Classification of Diseases [17, 18]. Their consensus on the core deficits for ASD prompted the development of two widely accepted, internationally recognized clinical diagnostic tools, the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview (ADI) [4, 19].

Autism is currently conceptualized as a spectrum in the DSM-V (2013). Previously, the DSM-IV described three categories of pervasive developmental disorders which included autism, pervasive developmental disorder-not otherwise specified (PDD-NOS), and Asperger disorder. The DSM-V merged these categories into the single diagnostic category of autism spectrum disorder [20]. The diagnostic criteria for ASD in the DSM-V describe two groups of characteristics: (1) persistent deficits in social communication and social interactions across contexts and (2) restricted, repetitive patterns of behavior and unusual responses to sensory stimuli [20]. The refinement of the DSM criteria along with the development and dissemination of diagnostic tools has had several results: (1) stimulation of greater public awareness; (2) encouragement of local, state, and national

M. C. Souders (✉)
Biobehavioral and Health Sciences Department, University of Pennsylvania, Philadelphia, PA, USA

Child and Adolescent Psychiatry, The Children's Hospital of Philadelphia, Philadelphia, PA, USA
e-mail: souders@email.chop.edu

W. T. Eriksen · S. Zavodny
School of Nursing, University of Pennsylvania, Philadelphia, PA, USA

A. E. Bennett
Developmental and Behavioral Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, PA, USA

R. Prasad
Clinical Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Department of Child and Adolescent Psychiatry and Behavioral Sciences, Autism Integrated Care Program, The Children's Hospital of Philadelphia, Philadelphia, PA, USA

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policy development on the screening, diagnosis, and treatment of ASD; and (3) the generation of very skilled ASD providers [4]. These critical developments as well as possible epigenetic and genetic phenomena have contributed to the increasing prevalence of ASD worldwide [4].

What Is Insomnia and What Is the Prevalence of Insomnia in Children with ASD?

Insomnia in children is defined as sleep-onset delay (sleep latency) of more than 30 min per night, on average, and/or frequent prolonged night wakings with impaired daytime functioning [21]. Prolonged night waking alters sleep efficiency, which is defined as the percentage of total sleep time during the episode potentially filled by sleep [time asleep/(total time in bed – time to fall asleep)]. A sleep efficiency of 85% or greater is considered a benchmark for a good night's sleep [21]. Insomnia in children with ASD occurs across all cognitive levels, and its prevalence may be as high as 60–86%, up to two to three times greater than among typically developing (TD) children [2, 21–27]. Insomnia in children with ASD is often a primary concern for parents and is one of the predominant reasons for why many families seek help [28]. Moreover, insomnia in children with ASD has been found to alter their parents' and siblings' sleep and add great burden to their families' lives [29]. A recent meta-analysis of sleep data in children with ASD showed small but measurable differences in sleep parameters using objective measures of actigraphy and/or polysomnography (PSG) [30]. Actigraphy is a miniaturized wristwatch-like microcomputer that senses physical motion and generates a signal each time it is moved (accelerated). It is generally placed on the wrist and can also gather accurate data when placed on the shoulder of the child's pajama shirt. Due to tactile sensory differences, many children with ASD prefer the shoulder placement over the wrist [26, 31]. The stored movement data can be transferred to a computer for interpretation and conversion into sleep parameters. Studies utilizing actigraphy and PSG with children with ASD have found shorter sleep time, longer sleep latency, and decreased sleep efficiency as compared to control groups [30].

What Are the Hypotheses for the High Prevalence of Insomnia in Children with ASD?

Sleep problems in ASD have many possible neurobiological, medical, and ecological mechanisms, and multiple mechanisms are likely to be the cause in any given child [4, 21, 23, 26, 32, 33]. Behavioral insomnias of childhood (BIC) are the most common extrinsic causes of insomnia for children in general and for children with ASD in specific [26, 33–35]. Children with ASD are uniquely vulnerable to sleep problems, perhaps due to the underlying biological and behavioral rhythms of ASD that may predispose children to both extrinsic and intrinsic stressors that threaten sleep [9, 26, 32, 36]. Hypotheses regarding intrinsic causes of insomnia in children with ASD include the following: (1) brain organizational and maturational differences, (2) circadian-relevant genes, (3) abnormal melatonin secretion, and (4) arousal dysregulation. Intrinsic hypotheses for insomnia will be presented first and followed by extrinsic causes of insomnia in children with ASD [4].

Brain Wave Organization and Maturational Differences

Intrinsic causes of insomnia may involve differences in brain wave organization and maturation identified by polysomnography (PSG). PSG, the collective process of monitoring and recording physiologic data during sleep, is considered the gold standard for objective measurement of sleep. It can include, but is not limited to, electroencephalographic activity (EEG), electrooculogram (EOG), electromyographic activity (EMG), rhythm electrocardiogram (ECG), airflow via thermistor nasal pressure, and/or pneumotachograph and oxygen saturation via pulse oximetry [37]. The early PSG studies in children, from 1969 to 1976, included children with ASD aged 22–52 months and showed EEG activity that lacked organization in slow-wave sleep and undifferentiated sleep, defined as the absence of sleep spindles during NREM which results in a lack of a clear delineation between REM and NREM sleep [38–40]. In 1976, Tanguay and colleagues found that spindle EEG activity was found during REM in children with ASD, but not in the same-age controls, suggesting that sleep stages were not well differentiated. These findings were similar to PSGs of normal preterm infants and infants less than 18 months, suggesting a maturational defect in children with ASD. Four subsequent studies, from 1999 to 2002, reported higher rates of undifferentiated sleep, muscle twitching during rapid eye movement (REM) sleep, high rates of periodic limb movements in sleep (PLMS), and REM sleep behavior disorder [41–44].

In 2006, 21 children with ASD were compared to 10 TD controls utilizing 2 nights of PSG and a sleep questionnaire [45]. The ASD cohort was divided into two groups, "good sleepers" and "poor sleepers," as reported by their parents. The results showed no significant differences between the good ASD sleepers and TD controls on the sleep questionnaire domains or sleep architecture. However, poor sleepers with ASD showed prolonged sleep

latency and decreased sleep efficiency on the first night of PSG and increased scores on the insomnia domains of the questionnaire. Interestingly, there were no significant differences between the second night of PSG for the poor ASD sleepers (n = 11) and TD controls (n = 10). More recently, in 2010, a study completed in the Clinical Research Center of the National Institute of Health compared 50 children with ASD who had a mean age of 4.8 years, with age-matched controls (15 TD children and 13 children with developmental delay) [46]. The results showed statistically significant shorter total sleep times, greater slow-wave sleep percentage, and much lower REM sleep percentage. The authors concluded that a deficiency of REM may indicate an abnormality in neural organization in young children with ASD and is consistent with findings from the 1960s to 1970s.

Despite multiple methodological limitations of these studies, the accumulated findings are considerable. These studies highlight the possibility of central nervous systems maturational and organizational differences. In addition, higher rates of parasomnias are found in children with ASD as compared to typically developing controls, including muscle twitches, muscle activity during REM, and PLMS observed during PSG. These findings may implicate dysfunction in excitatory monoaminergic pathways and other core neurotransmitters. In total, these findings support the hypothesis of complex intrinsic neurobiological differences that alter sleep, sleep behaviors, and sleep quality in children with ASD.

Circadian-Relevant Genes

Another emerging hypothesis for intrinsic causes of insomnia in children with ASD includes circadian-relevant gene anomalies resulting in biological and behavioral rhythm disturbances [4, 9, 32, 47–50]. In humans, sleep and wakefulness are regulated by an endogenous circadian clock in the brain, the suprachiasmatic nucleus (SCN) [9]. This master clock orchestrates a circadian rhythm system of positive and negative feedback loops that alter clock gene expression [9]. Clock genes PERIOD (PER 1, 2, 3), TIMELESS, NAPS2, and cryptochromes (CRY1,2) interact and are activated by clock proteins CLOCK and ARNTL/BMAL1 [51–54]. In 2002, clock/clock-related gene anomalies were first suggested as possible contributory factors in the etiology of core deficits of ASD involving temporary synchrony and social timing deficits [47]. Results from genetic linkage studies from families with more than one child with ASD implicated chromosome 2q as a possible site, and region 2q37 has indeed been found to include the hPER2 gene which codes for circadian rhythms in humans [47]. More recently, PER2 was identified as one of the candidate genes for the 2q37 deletion syndrome in humans, which results in the phenotype of ASD, dysmorphic features, and sleep problems [55]. In addition, two clock gene variants involving PER1 and NPAS2 were found to be associated with a 110-member autism cohort from Autism Genetic Resources Exchange [56]. Most recently, the coding regions of 18 canonical clock genes and clock-controlled genes were sequenced in 28 participants with ASD, and PER2, PER3, and TIMELESS variants were found to be associated with ASD [9]. However, the results from these studies were limited by small sample sizes and/or lack of significance after corrections for multiple analyses. The identification of rare mutations in clock genes with functional alterations in ASD participants warrants further investigation with large sample sizes and a well-described ASD sample [4]. Moreover, some researchers suggest the possibility that clock genes and clock gene-gene interactions may serve a dual role with respect to sleep and the control of oscillators associated with social communication and concurring brain development [4, 47].

Abnormal Melatonin Rhythms, Peaks, and Receptor Sites

Abnormal melatonin levels have been hypothesized to play a role in insomnia in children with ASD. Melatonin is synthesized in the pineal gland and received in the SCN by receptors MTNR1A and MTNR1B, which are involved with multiple functions including sleep induction, circadian and seasonal rhythm regulation, and immune function [9]. A delayed melatonin rhythm has been hypothesized to be associated with prolonged sleep latency, and low melatonin amplitude has been associated night waking in children with ASD [32]. Multiple investigators have identified abnormal levels of melatonin or a major metabolite of melatonin (urinary 6-sulfatoxmelatonin) in the urine, serum, or plasma of individuals with ASD [32, 48, 57–61].

It is also hypothesized that low melatonin levels and sleep-onset delay in children with ASD may be related to mutations in melatonin synthesis pathway genes or changes to regulatory regions of melatonin receptor sites [4, 60, 62–64]. A recent study evaluated variation in two melatonin pathway genes, acetylserotonin O-methyltransferase (ASMT) and cytochrome P450 1A2 (CYP1A2), and observed higher frequencies of variants than found in the general population for individuals with ASD [62]. Moreover, two studies investigated regulatory regions of melatonin receptors MTNR1A and MTNR1B in individuals with ASD and detected base changes in upstream regulatory regions of these receptors, suggesting that these genes were interesting candidates for ASD [63, 64].

However, one of these studies found base changes in the regulatory regions in both the ASD participants and controls. On the other hand, both studies detected V124I mutations in ASD participants only [63, 64]. Taken together, a combination of abnormal production, increased breakdown, and abnormal receptor sites of melatonin may help explain prolonged sleep latency and night wakings in children with ASD. However, these studies were limited by small sample sizes, indicating a need for further study with larger samples [62–64].

To date, 16 treatment studies have shown strong support for the effectiveness of short-term use of exogenous melatonin, dose range 0.5–15 mg, with most studies using a 3–5 mg dose 30 min prior to desired sleep onset, to improve sleep in children with ASD [4, 49, 65–80]. This body of evidence supports the use of melatonin and extended release melatonin in children with ASD after environmental and behavioral strategies have been implemented and are insufficient in improving sleep. However, some children with ASD do not respond to melatonin, and other families find that melatonin loses its effectiveness over time [26, 73]. In addition, a recent study by Goldman and colleagues (2014) found no differences in endogenous melatonin samples comparing children with ASD and insomnia (n = 9) and typically developing children in maximal melatonin concentration and time to peak concentration [81]. These outcomes suggest that other hypotheses and opportunities for intervention regarding insomnia in children with ASD should be explored [4].

Arousal Dysregulation in Insomnia

Current thinking on insomnia in general regards the disorder as one of hyperarousal. Early work hypothesized that insomnia was an internalization of emotional arousal [82–86], and recent research has focused on two lines of inquiry: cognitive arousal and increased somatic/physiological arousal. The theory of cognitive arousal hypothesizes that increased cognitive activity (thinking and worrying while trying to fall asleep) prevents the initiation of the sleep process [83, 85, 86]. The theory of physiological arousal posits that there is greater activation of the sympathetic nervous system in patients with insomnia compared to good sleepers [87]. A few small studies have characterized biomarkers of sympathetic outflow and revealed that increased heart rate, body temperature, heart rate variability, and higher levels of norepinephrine have been correlated with insomnia [82, 87, 88].

Hyperarousal and Insomnia in ASD

Since the earliest descriptions of ASD, it has been suggested that individuals with ASD may have difficulties with basic neurophysiological processes of attention and arousal. Children with ASD have been described by clinicians and therapists as being either “hypo” or “hyper” aroused by internal and external stimuli. Arousal theories remain at the heart of clinician dialogue. Hutt and colleagues in 1964 were the first to hypothesize that autism involved chronically high arousal levels [89]. Dawson and Lewey (1988) described a general over-arousal and narrow range of optimal arousal in autism [90]. Recent advancements in the field of neuroscience and the understanding of neural circuits have renewed interest in the arousal theories of ASD. There is growing evidence that ASD is associated with arousal dysregulation and dysregulation of the autonomic nervous system (ANS).

The ANS is divided into three divisions: sympathetic, parasympathetic, and enteric branches. ANS hyperarousal may be related to sympathetic hyperarousal, parasympathetic under-activation, or atypical interaction of the two systems. A few small studies have evaluated sensory arousal and sympathetic tone using electrodermal activity (EDA) in children with ASD compared to controls, and the results were inconsistent. Two studies observed larger tonic EDA in response to sounds [91, 92], while two other studies found no changes in response to auditory stimuli [93, 94]. However, Ming and colleagues [95] investigated autonomic dysfunction using a NeuroScope, a device that measures brainstem activity and quantifies cardiac vagal tone, blood pressure, and heart rate in real time, and found that all children with ASD had elevated sympathetic tone [95].

More recently, there has been greater attention by clinicians and researchers to recognizing co-occurring psychiatric disorders in children with ASD. A high prevalence of anxiety and/or ADHD, considered disorders of arousal, has been identified in multiple studies in children with ASD [96–101]. In addition, a recent study found blunted EDA response to anxiety tasks in a high anxiety group with ASD as compared to both a low anxiety group with ASD and a TD group, suggesting atypical ANS function in some children with ASD, specific to sympathetic activity [102]. Taken together, the high prevalence of high arousal psychiatric disorders, unusual responses to sensory stimuli, and insomnia in children with ASD may provide a greater understanding of a cluster of symptoms that can be identified as arousal dysregulation.

Norepinephrine and Prefrontal Cortex Cognitive Abilities

One neural system that could account for both arousal dysregulation and cognitive challenges described in ASD is the locus coeruleus-norepinephrine system. Over past 20 years, multiple studies have documented the dominant role of norepinephrine in regulating the working memory and attentional functions of the prefrontal cortex [103–105]. The locus coeruleus, a pontine nucleus, is the source of a widely divergent projection system that provides the majority of all norepinephrine to the brain and is the sole source of norepinephrine in the cortex [104, 105]. This system is activated by diverse sensory and autonomic stimuli, and its activation is associated with forebrain arousal [106, 107]. Electrophysiological studies in rats and nonhuman primates suggest that there is an inverted U-shaped relationship between the locus coeruleus, neuronal discharge, and prefrontal cortex cognitive abilities [100, 101].

This U-shaped model provides a framework for better understanding the arousal dysregulation and "hyper" and "hypo" arousal symptoms in children with ASD. When the locus coeruleus neurons are in a phasic mode, they are very responsive to sensory stimuli, a state associated with optimal performance in tasks requiring focused attention [108]. However, levels of locus coeruleus discharge and norepinephrine outside the optimal range are associated with poor performance. High levels of norepinephrine (i.e., high tonic activity) are associated with hyperarousal [108]. Given these characteristics of the norepinephrine system, ASD symptoms related to arousal and abnormal sensory responses could result from locus coeruleus-norepinephrine dysfunction. The "hyper" or over-aroused child with ASD has behavioral symptoms of inattention, impulsivity, high activity, anxiety, panic, and insomnia.

While insomnias in children with ASD are predominantly identified as falling under the category of behavioral insomnia of childhood (BIC), which is thought to be caused by external factors such as limit setting and sleep-onset associations, some studies have identified that children's anxiety, fears, worries, and sensitivities to environmental stimuli may also contribute to their insomnia [23, 26]. In our previous work, we collected data from 97 families that included a comprehensive sleep history, environmental assessment, sleep questionnaires, and 10 nights of actigraphy for each child. Some parents were able to implement behavioral strategies with fidelity and were also able to make ecological changes to the environment. Despite these interventions, parents voiced that their children continued to have anxiety and worries at night and appeared to be in a hyperactive state [26]. We hypothesize that the "hyperaroused state" experienced by a subgroup of children with ASD may be linked to insomnia [26]. We concluded that in order to develop more precisely targeted sleep treatments for children with ASD, arousal dysregulation would need to be specifically addressed [4].

Extrinsic Causes of Insomnia in Children with ASD

Behavioral insomnias of childhood (BIC) are the most common causes of insomnia in children and in children with ASD [26, 33–35]. Sleep-onset association type is characterized by the child's dependency on a specific stimulus, whether person, object, or setting for initiating sleep or returning to sleep. Limit setting type is characterized by bedtime stalling or refusal behaviors that are a result of difficulties with limit setting by the caregiver. The stalling and refusal behaviors can escalate each night and become quite disruptive. These behaviors may be inadvertently reinforced by postponing bedtime and providing a child with 1:1 attention [26]. Caregivers of children with ASD often will trial multiple ideas to help their child fall asleep and may establish bedtime conditions that inadvertently perpetuate chronic insomnia [26].

The insomnia model denoted by Spielman and colleagues (Fig. 11.1) describes predisposing, precipitating, and perpetuating factors significant to the development and maintenance of insomnia [109]. *Predisposing factors* include genetic, physiological, or psychological phenomena that confer differential susceptibility to individuals [109]. *Precipitating factors* include physiological, environmental, or psychological stressors which push an individual over a hypothetical insomnia threshold to produce acute symptoms [109]. *Perpetuating factors* include behavioral, psychological, environmental, and physiological factors that prevent the individual from re-establishing normal sleep [109]. In pediatrics, health providers have often focused on BIC. In an attempt to help their children fall asleep at night, parents often inadvertently create middle insomnia, difficulty falling asleep after waking up in the middle of the night, because they created conditions such as sleeping with the child, backrubbing, and attending to them as they fall asleep, which would need to be replicated in the middle of the night.

Based on the Spielman model of insomnia (Fig. 11.1), the neurobiological and neuropsychiatric vulnerability of children with ASD can represent predisposing factors which position children with ASD closer to the hypothetical threshold of insomnia than their typically developing peers. Precipitating factors could include (1) environmental stresses

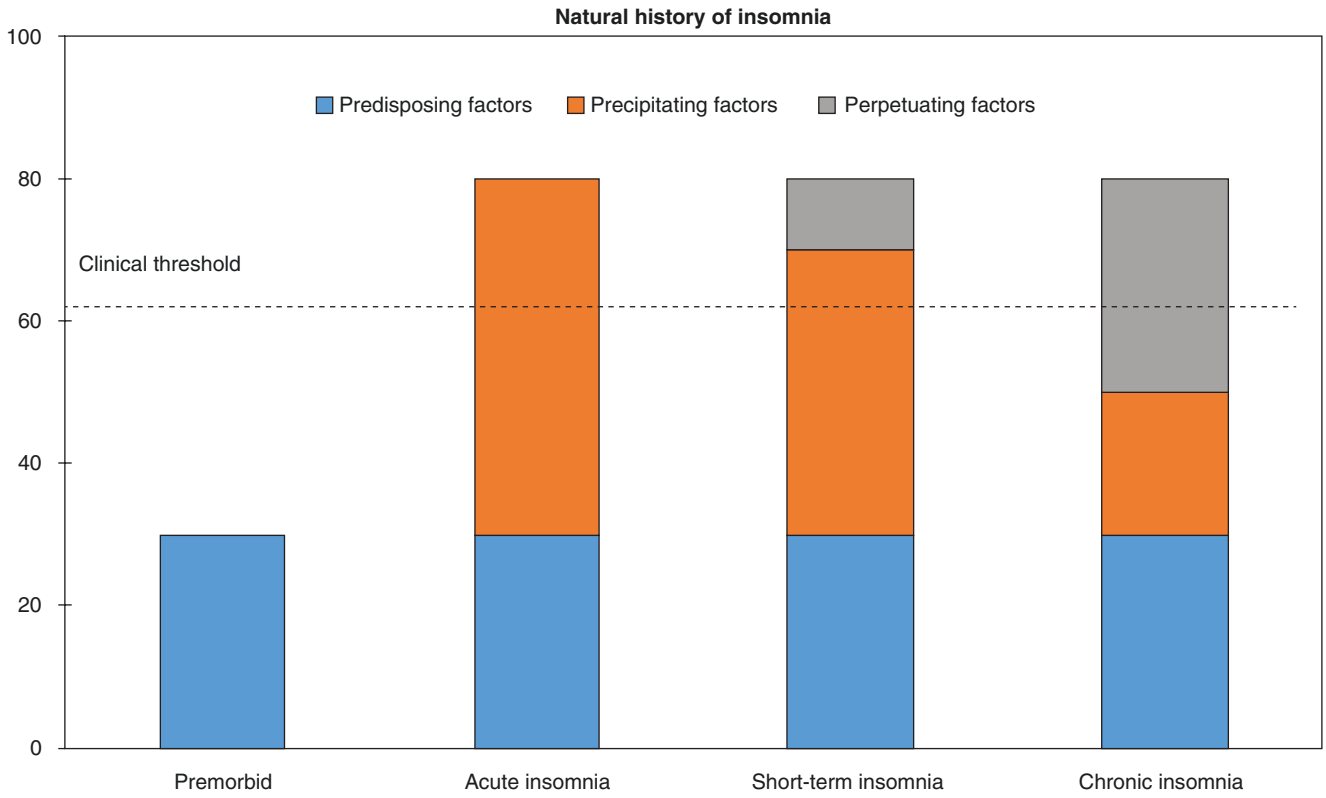

Fig. 11.1 Spielman's insomnia model. The clinical threshold for insomnia is illustrated with a dashed line. The insomnia model describes predisposing (blue bar), precipitating (orange bar), and perpetuating (gray bar) factors significant to the development and maintenance of insomnia. (Illustration based on Spielman et al. [109])

such as changes in evening routine, (2) psychological stressors such as a difficult day at school, or (3) physiological stressors such as being sick, any of which could push a child with ASD over his threshold into insomnia. In attempting to treat the child's insomnia, parents may inadvertently introduce perpetuating factors, such as sleeping with the child in their bed and rubbing their back, which can create a sleep-onset association disorder. For this reason, caregivers of children with ASD and insomnia often will need the support of healthcare providers in identifying the child and parents' specific predisposing, precipitating, and perpetuating factors.

The Autism Treatment Network (ATN) recognized that it is critical for clinicians to be well trained in delivering sleep care to this vulnerable population. The ATN Sleep Committee compiled evidence-based ecological and behavioral strategies, resulting in the development of a practice pathway. The practice pathway published by Malow and colleagues [110] and developed by the ATN Sleep Committee and the National Initiative for Children's Healthcare Quality recommends a clear outline for identifying, evaluating, and managing insomnia in children and adolescents with ASD.

Practical Approaches to Sleep Problems in Children with ASD

The ATN practice pathway was devised from a thorough review of the state of the science and included 20 intervention articles studying individuals with ASD with sample sizes of 10 or greater [4, 110]. The pathway was based on a consensus of sleep experts that captured best practices for an overarching methodology to implementing comprehensive sleep care by primary care providers or ASD specialists [110]. The pathway was tested at four pilot sites across the United States. It takes a ten step approach (see below) including screening for and treating medical conditions that may be related to poor sleep and identifying signs and symptoms of obstructive sleep apnea and its risk factors. A pilot phase showed that barriers to using the ATN pathway included lack of time during a clinic visit and limited clinician knowledge of and comfort with both assessment and management of insomnia [110]. The following case study illustrates key concepts to increase provider comfort with the assessment and management of insomnia in children with ASD.

Practice Pathway Ten-Step Approach [110]

1. Screen all children with ASD for insomnia with sleep questionnaire annually.
2. Identify any parent or child sleep concerns and discuss.
3. Screen for medical conditions that may be contributing to insomnia, and refer to appropriate subspecialist.
4. Treat any medical conditions significantly affecting sleep before continuing with the practice pathway.
5. Determine the willingness and capacity of the family to implement a sleep intervention.
6. The first-line approach is parent education about environmental modification, positive bedtime routines, and behavioral strategies.
7. Introduce the ATN Sleep Tool Kit and educational materials with visual schedule.
8. If the family is unable or unwilling to follow environmental and behavioral strategies, consider consultation to a sleep specialist.
9. Pharmacological interventions may be considered, starting with melatonin.
10. Timely follow-up in 2–4 weeks for all interventions.

Annual reassessment for all children with ASD

Medical Conditions Contributing to Sleep Problems [110]

Gastrointestinal Disorders

Reflux
Constipation
Pain

Respiratory Disorders

Sleep-disordered breathing
Allergies
Asthma

Neurological Disorders

Epilepsy/seizures
Restless legs syndrome/abnormal movements

Skin and Integumentary Disorders

Dental issues
Eczema/itching
Sensitivity to textures/light/sound

Nutrition

Hunger
Iron deficiency
"Growing pains"

Obstructive Sleep Apnea (OSA) Signs/Symptoms and Physical Risk Factors

OSA Signs and Symptoms

Snoring/loud breathing
Snorting/gasping for breath
Periods of apnea (child stops breathing temporarily)
Unrefreshing sleep/daytime sleepiness

Physical Risk Factors

Obesity
Large tonsils/and/or adenoids
Hypotonia
Micrognathia (small or receding chin)
Palatal defects

Introduction to Case Vignette

This is the case of a child with ASD and anxiety disorder who participated in an insomnia study [111]. The study involved an intervention designed as a supplement to the ATN Sleep Tool Kit, a 1-h education session with emphasis on ecological approach and establishing positive evening routines [112]. The study included a home-based weekly intervention delivered by nurses which included three components: (1) positive evening routines with visual schedule;

(2) a faded bedtime protocol that has children go to bed when they are irresistibly sleepy, equating sleepiness with their bedroom (stimulus control); and (3) supplemental calming techniques. We also incorporated the Bedtime Pass from the ATN Sleep Tool Kit, a technique used to encourage a child to self-soothe with calming activities during night wakings. When the child wakes at night, he can choose to either trade in the pass for a hug or attention from a parent or keep the pass and claim a reward in the morning. When the child gets out of bed, the parent is taught to redirect the child to bed and take the Bedtime Pass. The environmental changes, bedtime routines, and calming activities were tailored to each child and family, based on their arousal/anxiety profile, sleep characteristics, and the family's identified goals.

Based on the idea that a subgroup of children with ASD are in a hyperaroused state, we developed a module consisting of instructions for calming techniques to supplement the ATN Sleep Tool Kit [33] and address the internal factors that threaten sleep and decrease their arousal levels. The calming module includes 12 individualized soothing and relaxing activities that are selected by the parents/patients with ASD: (1) observing your breathing exercise; (2) progressive muscle relaxation; (3) yoga poses; (4) massage; (5) Moody Cow activities; (6) mindfulness exercises; (7) Worry Box/Worry Doll; (8) taking a warm bath; (9) gentle rocking or swinging; (10) quietly reading a book; (11) self-soothing, soothing the five senses; and (12) quietly saying prayers.

These activities have been found to be successful in calming individuals with arousal/anxiety symptoms.

Case Vignette

Identifying Information and Presenting Concerns

On joining our study, K.J. was a 9.5-year-old boy with a diagnosis of ASD, as well as obesity, insomnia, mild seasonal allergies, mild eczema, and intermittent daytime irritability. He frequently became agitated with small changes in routine throughout the day as reported by his school teachers and parents. This irritability would escalate into a tantrum one to two times per day. The tantrums comprised of screaming, crying, and flopping to the floor. He had no history of aggression, self-injury, ADHD, depression, psychosis, or mania. Parents did report that K.J. worried all the time and they had concerns about anxiety.

Social History

K.J. was living with his married parents and older brother, aged 11 years, in a comfortable, suburban home outside a major metropolitan area. Both K.J. and his brother were adopted as infants and were not biological siblings. No information was available on K.J.'s biological mother. His parents completed graduate school; his father was a program director in a high school and his mother was a school psychologist.

Birth History/Early Years

K.J. was an easy baby who fed well and slept well. He was identified as having developmental delay at age 2, and his language and social development seemed to plateau. He was diagnosed with ASD at 3 years old, and his ADOS score was 17, in the range of autism. K.J. received intensive applied behavior analysis and developmental therapies weekly in the preschool years and transitioned to special education in first grade. He had a history of frequent ear infections and received bilateral myringotomy tubes at age 4 years with annual follow-ups with an otolaryngologist. He did not have large tonsils or adenoids and did not have symptoms of obstructive sleep apnea.

Current History

At the time of the study, K.J. was a rising fourth grader in a special education classroom with an Individual Education Program. He had weekly speech language and occupational therapy. His full scale IQ was 105. He was followed by a psychiatrist for his ASD and disruptive behaviors and was taking 6 mg of extended release guanfacine and 6 mg of extended release melatonin at 8 PM daily. He also took 10 mg of cetirizine daily in the morning for seasonal allergies. Despite the use of sleep medications, K.J. continued to take over 1 h to fall asleep and woke up frequently at night. Parents reported that the medications worked at first, then stopped working despite increased doses. He previously tried clonidine for sleep, but it would only help him fall asleep, then he would wake back up in 1–2 h. For the duration of the study, he continued his prescribed medications, and parents agreed to avoid changes to his medications.

K.J. was active in a football little league during the summer and often swam in the family's pool in their backyard. Despite his level of physical activity, K.J.'s body mass index was in the 99th percentile, and both parents voiced concerns about his weight. He received a nutrition consult and participated in a healthy weight program for children. Parents had implemented a

healthy diet for the past 6 months. However, he continued to gain weight. Parents reported that K.J. occasionally snored with cold symptoms but did not snore regularly. K.J. was screened for all the medical conditions contributing to sleep problems (above), and his medical history was otherwise unremarkable except for mild allergy symptoms and very mild eczema on his elbows treated nightly with an emollient moisturizer.

Screen for Sleep Concerns and Associated Psychiatric Disorders

Sleep Environment

Though he had his own bedroom, K.J. slept with his brother in his brother's room on adjacent twin beds in the middle of the room. The bedroom was cool (room temperature 65 °F), overall dark though with a blue night light, and quiet, with an overhead fan on for white noise. K.J. had heightened auditory sensitivity, so he also wanted the TV on in the living room for white noise. K.J. frequently complained about his brother disturbing him in the evening and during the night.

Sleep Questionnaire

K.J.'s mother completed the Children's Sleep Habits Questionnaire (CSHQ), a 33-item questionnaire with 8 subscales that reflect key sleep domains, help clinicians identify specific sleep problems, and guide behavioral and environmental strategies to improve sleep. Higher scores indicate more sleep problems. A cutoff of 41 for total subscale scores has a sensitivity of 0.80 and specificity of 0.72 [113]. Table 11.1 below shows the expected score for good sleepers with no sleep problems (minimal score of 33) [113] and K.J.'s CSHQ score of 63. K.J.'s score indicated serious sleep problems and warranted referral to a sleep expert.

K.J.'s CSHQ revealed high scores for multiple subscales: bedtime resistance, parasomnias, night wakings, and daytime sleepiness. A closer look at the individual questionnaire items revealed that K.J. had difficulties settling down, struggled with bedtime routines, and feared sleeping alone. He needed his parents at night and woke with scary dreams (Table 11.1). In addition, he had frequent tooth grinding (bruxism), which has been associated with anxiety in children and adults and may be a reflection of an underlying anxiety disorder [114]. Taken together, these elevated subscales reflected both intrinsic and extrinsic sleep problems, earning sleep diagnoses of BIC and sleep anxiety.

Table 11.1 Children's sleep habits questionnaire: expected scores and K.J.'s scores

Subscales	Minimal score	K.J. baseline score	Significance
Bedtime resistance	6	11	Moderate bedtime resistance –struggles at bedtime
Sleep-onset delay	1	2	Prolonged sleep latency
Sleep duration	3	6	Parental concern about inadequate sleep
Sleep anxiety	4	7	Afraid to sleep alone, away from home, needs parents
Night wakings	3	8	Wakes frequently at night, moves to parents' bed
Parasomnias	7	11	Restless, grinds teeth, scary dreams
Sleep-disordered breathing	3	4	Occasional snoring with colds
Daytime sleepiness	8	14	Takes a long time to be alert in morning, falls asleep watching TV and riding in car, seems tired
Total score	33	63	Above 41 has been used as a cutoff for sleep problems

Anxiety Interview and Questionnaire

The study psychologist interviewed K.J. and his mother with the Pediatric Anxiety Rating Scale (PARS) [115]. His 7-point total severity score was 24, indicating anxiety. His mother also completed an anxiety questionnaire, the Screen for Child Anxiety Related Disorders (SCARED). A score above 25 indicates an anxiety disorder, and K.J.'s total score was 43 [116].

Baseline Actigraphy

At baseline, K.J. went to bed at 9:45pm, took 36.5 min to fall asleep, and woke just before 7:00am (Fig. 11.2). Over the nine nights observed with actigraphy, K.J. averaged 550.7 min (9.17 h) in bed a night, consisting of 368.9 sleep minutes (6.14 h) and 181.8 wake minutes (3.03 h).

Feedback on Actigraphy Data

Notably, on reviewing his actigraphy with K.J. and his family and discussing his frequent, prolonged night wakings, K.J. "confessed" to coming downstairs to watch TV and eating cookies in the middle of the night

when he couldn't sleep. He was able to provide evidence (in hidden empty cookie wrappers) of his behavior, which came as a surprise to his parents: they had not believed him able to unlock the safety baby gate at the top of the stairs to let himself downstairs. This also helped put into perspective K.J.'s mother's struggles to help him lose weight.

The Intervention

After reviewing his sleep habits and actigraphy data with K.J. and his parents, the study team implemented the intervention (Table 11.2). First, we introduced the visual bedtime schedule from the ATN Sleep Tool Kit, combining the family's current evening routine with two targeted interventions selected by the family from the calming module: quietly reading a book and saying prayers. K.J. had already been taking a bath in the evening, bringing his total "calming activities" during Weeks 1–3. These activities were placed on a visual schedule Velcro board.

During Week 2, we encouraged him to sleep in his own room and implemented significant environmental

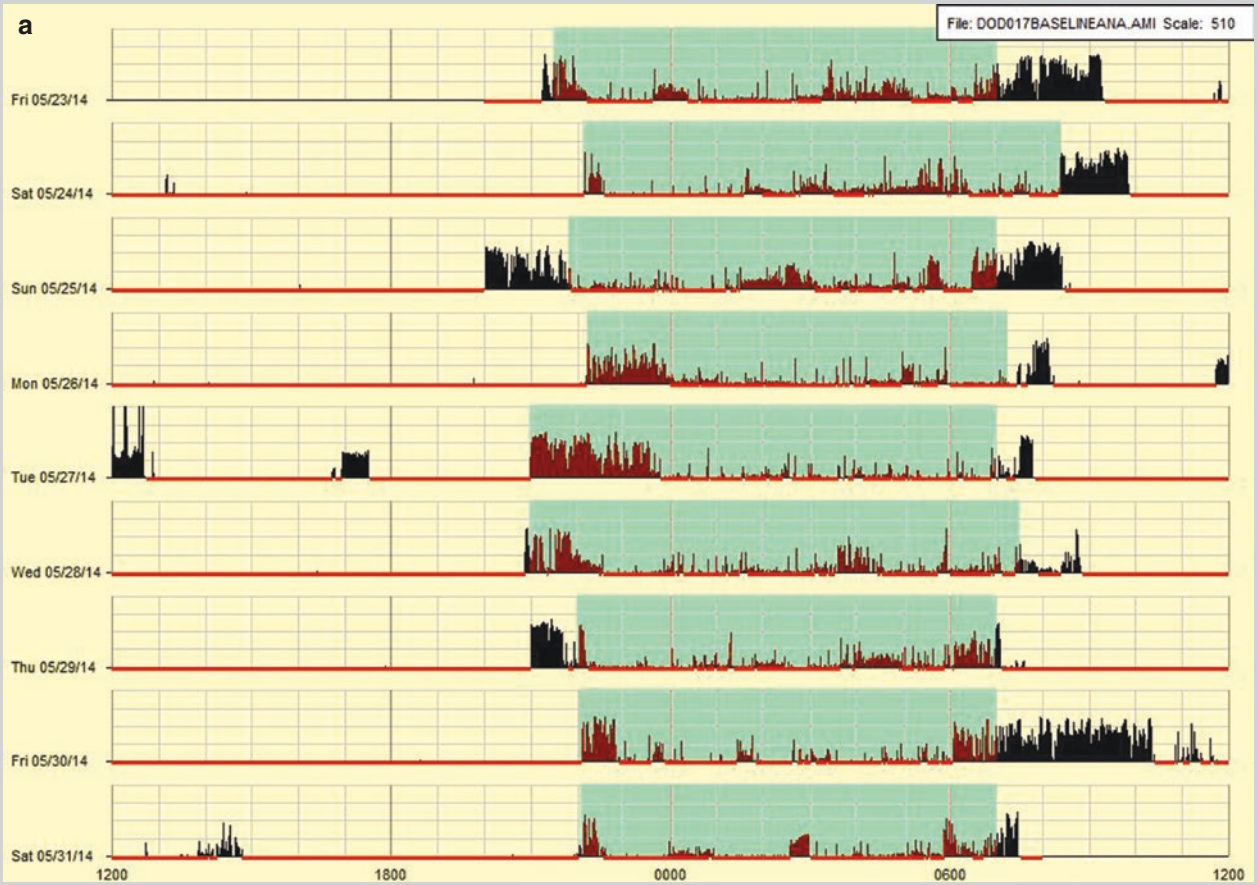

Fig. 11.2 (**a**) Baseline actigraphy. Nine nights of actigraphy. X-axis is military time with midnight (0000) being in the center of the x-axis. Y-axis is the days of the week starting with Friday 5/23/14 to Saturday 5/31/14. (**b**) Week 8 post-intervention actigraphy. Nine nights of actigraphy. X-axis is military time with midnight (0000) being in the center of the x-axis. Y-axis is the days of the week starting with Thursday 9/4/14 to Saturday 9/12//14. Actigraphy is a miniaturized wristwatch-like microcomputer that records motion. After motion is transduced into an analog electric form, it is digitized and stored. Each child was monitored with a MicroMini Motionlogger actigraph (AMA-32) in the zero-crossing mode from Ambulatory Monitoring, Inc. (Ardsley, NY). The actigraph was activated with the Act Millennium 3.10.49 (ACTME) software program in Mode 18, with 1-min epoch intervals, and was able to collect data for 22 days, 16 h, and 0 min. Actigraphic raw data were translated into sleep measures with the Action-W software version 2.5.30 and Actigraphic Scoring Analysis program for an IBM-compatible PC. Each night the blue-shaded area represents the time the parent reported the child was in bed. The black lines represent time the child is wearing the actigraph watch. The height of the lines each night represents the degree of movement detected by the actigraph at each time point

Fig. 11.2 (continued)

Table 11.2 Standard care plus TAB for K.J.

	Interventions
Ecological	Own room with bed up against the wall
	White noise
	Night light
	Ceiling fan
	Removed stuffed animals
Positive routines	Bath and teeth brushing
	PJs
	Light snack
Bedtime Pass	Rewards chosen
	Figurines
Calming activities	Rocking in chair and reading a book
	Deep breathing
	Yoga legs in bed
	Weighted blanket

changes. We made a plan to bring his bedroom into compliance with ideal sleeping standards (cool, dark, and boring). Notable changes included heavier curtains to block out light at night paired with a red night light in the hallway and his door slightly ajar. It is important to note that the night light is red, because blue light creates an alerting effect on the brain and may prevent melatonin production. He continued to use a fan at night to serve as white noise and keep the room cool. We removed many stuffed animals from the bed saved for two or three special "snuggies," placed a rocking chair in the room for reading time, and designated the many books in the room as a "before bed only" activity. Additionally, during Week 2 the study team worked with K.J. to practice deep breathing exercises and "Yoga for Insomnia" poses to do at night with his family. K.J. particularly liked doing "yoga

legs" paired with the deep breathing exercises and would practice them in bed before going to sleep and again when he woke up in the middle of the night.

In Week 3, the study team taught the family massage to use before bedtime, but K.J. didn't respond to the technique, and it was removed that same week. The family also introduced a "Bedtime Pass" from the Sleep Tool Kit with much success. K.J. was easily redirected the first night using the pass and enjoyed either a small action figure or the ability to choose his favorite breakfast, pancakes, the following morning. Over the course of the Weeks 2 and 3, K.J. successfully transitioned from only doing calming activities such as reading in his rocking chair in his bedroom to staying the entire night in his own bedroom.

Final adjustments to the bedtime routine were made in Week 4, with the addition of a weighted blanket at the family's request. Each week we monitored the family's use of the interventions and provided feedback on how to implement them consistently, especially with chaotic, changing summer schedules. By the 4th week, his family was consistently implementing the visual schedule, with set times every night for medication and bed time, and allowing the other calming activities to shift with the family's evening activities. In this way, they promoted flexibility but kept a predictable "flow" from dinner to bedtime. From Week 4 to Week 8, no significant changes were made to K.J.'s interventions.

Table 11.3 K.J.'s data – actigraphy and CSHQ

Measure	Baseline	Week 4	Week 8	Change
Actigraph data				
Starting time	21:44:50	21:58:01	21:52:00	+00:07:10
Ending time	6:54:34	7:27:06	7:03:00	+00:08:26
Duration	550.71	570	551	+0.29
Activity mean	36.71	24.65	15.88	−20.83
Wake minutes	181.8	140.57	63.5	−118.3
Sleep minutes	368.9	429.43	488.44	+119.54
% sleep	67.28	75.22	88.53	+21.25
Sleep efficiency	78.21	90.01	95.24	+17.03
Sleep latency	36.52	20.57	17.83	−18.69
Child sleep habits questionnaire				
Bedtime resistance	11	6	6	−5
Sleep-onset delay	2	1	1	−1
Sleep duration	6	5	5	−1
Sleep anxiety	7	5	5	−2
Night wakings	8	3	4	−4
Parasomnias	11	10	11	0
Sleep-disordered breathing	4	5	4	0
Daytime sleepiness	14	12	10	−4
Total core	63	47	46	−17

Results

At Week 4 K.J.'s sleep showed substantial improvements in sleep latency and sleep time (Fig. 11.2). He went to bed at 9:58 PM, took 20.5 min to fall asleep, and woke at 7:27 AM (Table 11.3). Over the seven nights of actigraphy, K.J. averaged 570 min (9.5 h) in bed a night, consisting of 429.4 sleep minutes (7.15 h) and 140.5 wake minutes (2.34 h), reflecting an increase of 60 min (1 h) of sleep per night. Additionally, his scores on the CSHQ improved for bedtime resistance and night wakings.

By Week 8 (Table 11.3), K.J. saw further improvements, specifically in sleep consolidation and sleep minutes. He went to bed at 9:52 PM, took 17.8 min to fall asleep, and woke at 7:03 AM. Over the nine nights of actigraphy, K.J. averaged 551.2 min (9.19 h) in bed a night, consisting of 488.4 sleep minutes (8.14 h) and 63.5 wake minutes (1.05 h), reflecting an additional increase of almost1 h per night.

Case Summary

Based on baseline sleep interview, actigraphy, and CSHQ data, K.J. had both early insomnia (prolonged sleep latency) and middle insomnia (frequent night wakings). Intervention had a dramatic improvement on his sleep and resolved his early and middle insomnia (Table 11.3). K.J. and his family were able to implement the sleep protocol with fidelity. Parents were able to implement ecological approaches and had the resources to provide an optimal sleep environment. His parents' perceptions of his sleep habits also improved, based on CSHQ, from a total score of 63–46, but they continued to report parasomnias, sleep anxiety, and mild daytime sleepiness. Although by Week 8, K.J.'s sleep had increased from 6 to 8 h per night on average, the National Sleep Foundation recommends 9–11 h of sleep per night [117] for a child of K.J.'s age, resulting in inadequate sleep time and residual daytime sleepiness. The plan was for parents to continue the interventions, slowly fade his sleep start time back to 8:45–9:00 PM in order for him to have a 9–10 h sleep opportunity, and discuss his medications with his psychiatrist. We also referred the family to a psychologist to address his anxiety with cognitive behavioral therapy.

Future Directions

Exciting future research could investigate clock genes and clock-controlled genes and their relationships with ASD using big genetic data sets and deep phenotyping. Deep phenotyping that includes characterization of sleep problems, arousal symptom clusters analysis, and biomarkers of arousal including catecholamines, stress hormones, and the ANS would give us a greater understanding of the causes of sleep problems in ASD and is urgently needed.

The next steps for the dissemination of the ATN practice pathway for sleep in children with ASD will need to address local, state, and national barriers to implementation of ecological and behavioral sleep treatment with fidelity. This will require a paradigm shift in the healthcare arena to mobilize resources to train providers and empower families and communities to implement ecological and behavioral care to improve sleep in children with ASD.

Conclusions

This chapter provided an overview of the state of the science of sleep in children with autism spectrum disorder (ASD) and hypotheses for the high prevalence of insomnia in this vulnerable population. We presented an ecological approach for promoting optimal sleep using a case presentation. The strongest evidence to date on promoting sleep in ASD is on sleep education, behavioral interventions, and exogenous melatonin.

The case presentation highlights the dramatic improvement in sleep achievable with an intensive educational, ecological, and behavioral approach implemented by well-trained providers and highly motivated parents. To be effective this intervention demands commitment to a non-pharmacological approach by the provider and parent and requires confidence that behavioral change is possible. Moreover, in our experience, ecological changes are quick and cost-effective, and parents are very receptive to such environmental changes.

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Attention-Deficit/Hyperactivity Disorder

12

Nicole Ali, Fiona Davidson, Marilyn MacPherson, and Penny Corkum

Case Vignette: Ben

Following a comprehensive assessment through an ADHD clinic, Ben, a 10-year-old boy, was started on a long-acting stimulant for the treatment of ADHD-combined type. Even before initiating medication, he already had mild difficulties falling asleep. His routine was to play video games for 1 h before bedtime, identified as being "between 9:00 and 9:30 p.m." Parents acknowledged that Ben would "push the limit," so it was not uncommon that he would not actually be in bed until almost 10:00 p.m. He was still awake when they went to bed at 11:00 p.m. and then would fall asleep soon after. In the morning, Ben rarely woke on his own, but roused quickly when awakened at 7:00 a.m. for school.

Following initiation of stimulant medication, Ben was followed up in clinic 4 weeks later. His parents reported significant improvement in his ability to focus at home. His teacher also commented that Ben was doing well at school, and she had already noticed an improvement in some of his grades. However, Ben was complaining of having a harder time falling asleep: even after his parents went to bed, he would lie awake for another hour or two, until midnight or 1:00 a.m. His parents also noted that Ben was harder to rouse in the mornings. Because of some appetite suppression, they decided not to give his medication until after he had finished his breakfast, so he generally took his medication between 8:30 and 8:45 a.m.

The initial approach was to encourage parents to administer his medication earlier in the morning. They were given the option of giving it to him at 7:00 a.m., when they went in to wake him, or as soon as he started eating breakfast, at 7:30 am. As this particular medication should be effective for 12 h, this would ensure that any rebound effect of the medication would resolve before bedtime. In addition, Ben and his parents were encouraged to move video game use to earlier in the evening and to limit his amount of daily screen time to 60–90 min.

When reassessed 4 weeks later, Ben's family reported that giving the medication with breakfast had been effective in returning him to his previous routine, such that he was usually falling asleep by 11:00 pm. However, he continued to have difficulty waking in the morning. His parents did not view the video games as a contributing factor, so they hadn't changed this activity. The importance of healthy sleep practices was discussed with both Ben and his parents. Considering that an appropriate sleep duration for children between 6 and 12 years of age should be 10–11 h, Ben was clearly not getting enough sleep, either now or before he started medication. After brainstorming with his family about better sleep routines, Ben was agreeable to refraining from watching television, playing video games, or going on the computer after 7:00 p.m. When reassessed 6 weeks later, Ben's sleep was no longer a concern, and he was well rested and easy to rouse in the morning.

N. Ali · F. Davidson · P. Corkum (✉)
Department of Psychology and Neuroscience, Dalhousie University, Halifax, NS, Canada
e-mail: penny.corkum@dal.ca

M. MacPherson
Pediatrics, Colchester East Hants Health Center, Truro, NS, Canada

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Introduction

For many families, weekdays are packed with work, school, and extracurricular activities. Finding the right balance between all of these *and* getting adequate sleep can be difficult but is tremendously important for both children and adults. In the case above, by changing his evening habits and shifting the balance between stimulating activities and bedtime, Ben and his family remedied his sleep issues. Given that many sleep problems may be the product of busy lives or lack of knowledge regarding how much sleep is needed, it is important to educate parents and children about healthy sleep habits, as with Ben's family. Many children with ADHD have insomnia or other sleep problems, which will be discussed in this chapter. Children with ADHD are more likely to have sleep problems than their typically developing (TD) peers, and these issues can be made worse by the stimulant medications used to treat ADHD, as in Ben's case. This chapter will explore why considering sleep problems is an important part of treating and managing ADHD.

According to the DSM-5, the prevalence of ADHD is about 5% among children and 2.5% among adults, with twice as many boys as girls receiving this diagnosis [1]. ADHD can present as predominantly inattentive, predominantly hyperactive and impulsive, or if both inattentive and hyperactive/impulsive features are prominent, as combined type. The inattentive presentation manifests with symptoms such as difficulty sustaining attention at work/play, not following through on directions, disorganization, distractibility, carelessness, and forgetfulness. Features of the hyperactive/impulsive presentation include fidgeting, constant movement, excessive talking, interrupting, and running about or jumping at inappropriate times. In order to be diagnosed with ADHD, symptoms must be severe enough to interfere with everyday function and be present for at least 6 months. In addition, symptoms must be evident across more than one setting, such as both at home and in school. Symptoms must also present prior to the age of 12 years (diagnoses made in adolescence and adulthood require reflecting on childhood behavior) but are usually apparent earlier. Although symptoms may be suspected in preschool-aged children, they are often difficult to distinguish from typical behaviors for this age group. For this reason, ADHD is often first diagnosed in school-aged children [1].

Sleep problems are very common in children with ADHD, so much so that in the earlier DSM-III-R, they were used as part of the diagnostic criteria [2]. Although sleep problems were subsequently removed from the list of criteria for ADHD in DSM-IV [3], there are clear relationships between ADHD and sleep [1]. Between 25% and 75% of children with ADHD are reported to have problems with sleep [4]. In two separate studies, approximately three-quarters of parents of children with ADHD reported significant sleep problems [5, 6]. In one of those studies [6], the majority of children with sleep problems had sleep problems of moderate to severe intensity. More severe problems were related to lower daily functioning and lower quality of life scores. Additionally, more severe sleep problems were associated with more severe ADHD symptoms [6]. It is likely that this is a reciprocal relationship, in which children with more severe ADHD have more severe sleep problems as a consequence of ADHD, and inadequate sleep, in turn, makes the ADHD symptomology worse. A study found that children with ADHD, as well as controls, when sleep restricted by 1 h per night for six nights, end up displaying more attention problems on a direct measure of attention, the continuous performance task [7].

There are a number of different sleep problems that may present in children with ADHD, such as insomnia, obstructive sleep apnea, circadian rhythm sleep/wake disorders, and restless legs syndrome. While all of these sleep problems can occur in healthy children, they are more common for children with ADHD and most likely have more severe detrimental effects on daytime functioning for this population.

Evidence Base: ADHD and Sleep Problems – The Not-So-Odd Couple

"He'll sleep well tonight!" is the sort of comment that is often made when we observe a child with seemingly boundless energy – not unlike comments often made about children with ADHD, particularly those with the hyperactive/impulsive or combined subtypes. These children are described as if they are driven by a motor, and it may stand to reason that they would crash into bed at the end of the day and sleep for 10 h straight. Unfortunately, given how commonly children with ADHD suffer from sleep problems, this may not actually be the case.

As mentioned, symptoms of ADHD may contribute to the development of insomnia, while poor sleep can worsen symptoms of ADHD. Moreover, poor sleep can affect memory, attention, concentration, and emotional regulation, which can further intensify symptoms of ADHD [8]. In fact, some of the symptoms of insomnia are closely related to symptoms of ADHD. According to the DSM-5, impairment of cognitive performance, including the areas of attention, concentration, and memory, is a diagnostic feature of insomnia [1]. Cognitive performance is also affected by ADHD [1]. Additionally, physiologic arousal is considered an associated feature of insomnia, which is likewise demonstrated in the tendency of children with ADHD to fidget and have difficulty staying in their seats [1].

There is also a common etiological pathway between ADHD and some physiological sleep problems, with overlap between the neurotransmitters responsible for sleep/wake and those responsible for attention [9, 10]. Table 12.1

Table 12.1 Shared space, shared resources

	Relationship with ADHD	Relationship with sleep
Shared space		
Thalamus	Smaller regional volumes in certain areas associated with lower attentional scores	Responsible for sleep spindles and synchronization
Shared resources		
Dopamine	Management of psychomotor function and reward seeking	Role in wake
Serotonin	Role in the exploration of environment	Role in wake
GABA	Responsible for arousal reduction and emotional regulation	Role in sleep (both REM and NREM)

outlines a few of the shared pathways between ADHD-related behaviors and problems associated with sleep. For instance, the thalamus, which is responsible for sleep spindles and synchronization in sleep, may also play a role in ADHD. A study examining the morphology of the thalamus found that certain regions have a smaller volume in those with higher scores of inattention [11]. There are also some neurotransmitters that play roles in both ADHD and sleep [12–14]. Dopamine and serotonin are both factors in waking [12]. Dopamine is also related to areas of functioning impacted by ADHD, namely, psychomotor function and reward seeking [13]. Likewise, in addition to contributing to the wake state, serotonin is related to exploration of the environment [13]. It is possible that the overstimulated psychomotor functioning, excessive reward seeking, and exploration that are often symptomatic of ADHD could be related in part to dopamine and serotonin levels, which may also interfere with sleep by promoting wakefulness. Another neurotransmitter worth mentioning is GABA, which is responsible for reducing arousal and regulating emotions [13], both of which can be a struggle for children with ADHD. GABA also has a role in sleep [10]. Given the overlap in etiological pathways between ADHD and insomnia, wherein hormones and brain morphology related to sleep function are also related to symptomology of ADHD, sleep issues could potentially make ADHD treatment more complicated. However, on a positive note, this means that there is an opportunity to improve ADHD symptoms by treating the sleep problems and vice versa.

Studies have shown that problematic sleep – in particular, insomnia – is more common in children with ADHD than in TD children [15–17]. Children with ADHD are more likely to suffer from fragmented sleep, lower sleep efficiency, daytime sleepiness, bedtime resistance, prolonged sleep-onset latency, nightmares, restless sleep, nighttime awakenings, and hypersomnia [15–17]. Differences between children with ADHD and TD children in sleep are even more significant when comparing children with ADHD on stimulant medications to TD children. In fact, children with ADHD on stimulant medications had significantly more difficulty with sleep than other children with ADHD who are not on medication (e.g., in waking in the morning and restless sleep) [15]. In addition to stimulant medications, there are other factors that can make a child with ADHD more likely to have sleep problems. For instance, a comorbid disorder, such as anxiety [15], increases the likelihood of sleep problems for TD children and further compounds the already increased chances of sleep problems in children with ADHD. Furthermore, children who have the combined presentation of ADHD, with significant features of both inattention and hyperactivity/impulsivity, are more likely to have sleep problems [15]. Other possible contributors to sleep problems include comorbid medical disorders, such as asthma, and poor sleep practices [9, 18]. While poor sleep practices are not unique to families with children with ADHD, they may be more common as parents themselves may struggle with structure and limit setting given the genetic risk [1] for familial contributions to ADHD.

Assessment and Diagnosis: Things Are Not Always What They Seem

With the knowledge that sleep problems are common among children with ADHD, care must be taken to not simply dismiss any sleep issues in a child diagnosed with ADHD as being simply part of the package. Not only should the sleep problems themselves be targeted for treatment, but consideration of other potential diagnoses should be made as well. Consider the case of Jack, who was referred for an ADHD evaluation but also suffered from sleep deprivation.

Case Vignette: Jack

Jack is a 6-year-old boy who was referred for an ADHD assessment by his parents after his teacher expressed concern about Jack being very inattentive in the class setting. The school psychologist conducted a behavioral observation and noted that Jack presented as inattentive but not hyperactive or impulsive. A psychoeducational assessment found that he was meeting grade-level outcomes and had no learning disabilities. It was noted that Jack was inattentive during testing and also that he mouth breathed and constantly rubbed his eyes and nose. Further questioning of his parents revealed that he was a restless sleeper, had a chronic cough which was worse during sleep, and frequently complained of itchy eyes and nose and itchiness in the back of his throat.

After completing the comprehensive evaluation, it was found that Jack met criteria for ADHD-inattentive presentation based on both parent and teacher semi-structured diagnostic interviews. He did not reach criteria for any other mental health problems. However, he was also suspected to be sleep deprived, and in light of his significant allergy symptoms, it was recommended that he be evaluated for environmental allergies prior to having a diagnosis of ADHD formalized. Allergy testing revealed allergies to trees, grasses, dust mites, cats, and dogs, all of which he was exposed to regularly. Environmental changes and regular treatment with an antihistamine medication were successful in treating his allergy symptoms. His sleep improved and he appeared better rested. His attention span and school performance also improved. One year later, questionnaires filled out by his teacher and parents no longer supported an ADHD diagnosis.

As in Jack's case, assessment can be complicated by the overlap in symptoms and features between ADHD and sleep problems. Recall that impairment in cognitive performance, specifically *attention, concentration,* and *memory* are features of insomnia. These impairments could easily mimic or exacerbate certain symptoms of ADHD, such as difficulty sustaining *attention*, avoidance of activities requiring *sustained mental effort*, and being *forgetful* about routines. In Jack's case, allergies resulted in restless sleep, and the subsequent sleep loss led to difficulty paying attention. In this way, it appeared that ADHD was present even when it was not, and had Jack not been assessed for allergies before diagnosing ADHD, time could have been wasted treating the wrong problem, possibly using unnecessary (and potentially ineffective) medications.

It is also possible for ADHD-related behaviors to make it *appear* as if a sleep disorder is present. For example, see Fig. 12.1. Children with ADHD often struggle with school and may be prone to school avoidance. These children may resist bedtime because they associate it with having to get up for school and may also struggle to fall asleep because of school-related worries and anxieties. A combination of the sleep loss and desire to avoid school can make rousing in the morning difficult for these children, and they may then be tired throughout the day. This daytime sleepiness, in turn, could make concentration and attention even more challenging, making school more difficult, and exacerbating the entire problem [19]. In this case, the main problem is ADHD, but without fully understanding the motivations behind the child's behaviors, a sleep disorder such as insomnia or circadian rhythm disorder might be misidentified.

It is necessary to rule out primary sleep disorders on the list of differential diagnoses when conducting an ADHD assessment, as in Jack's case [20, 21]. When assessing a child's sleep, it is important to gather information about timing (i.e., going to bed, getting up), snoring, daytime behaviors, sleep refusal/resistance, and anxieties (e.g., dark, separation) [22]. A brief and easy way to administer screening measure for sleep problems in children was developed by

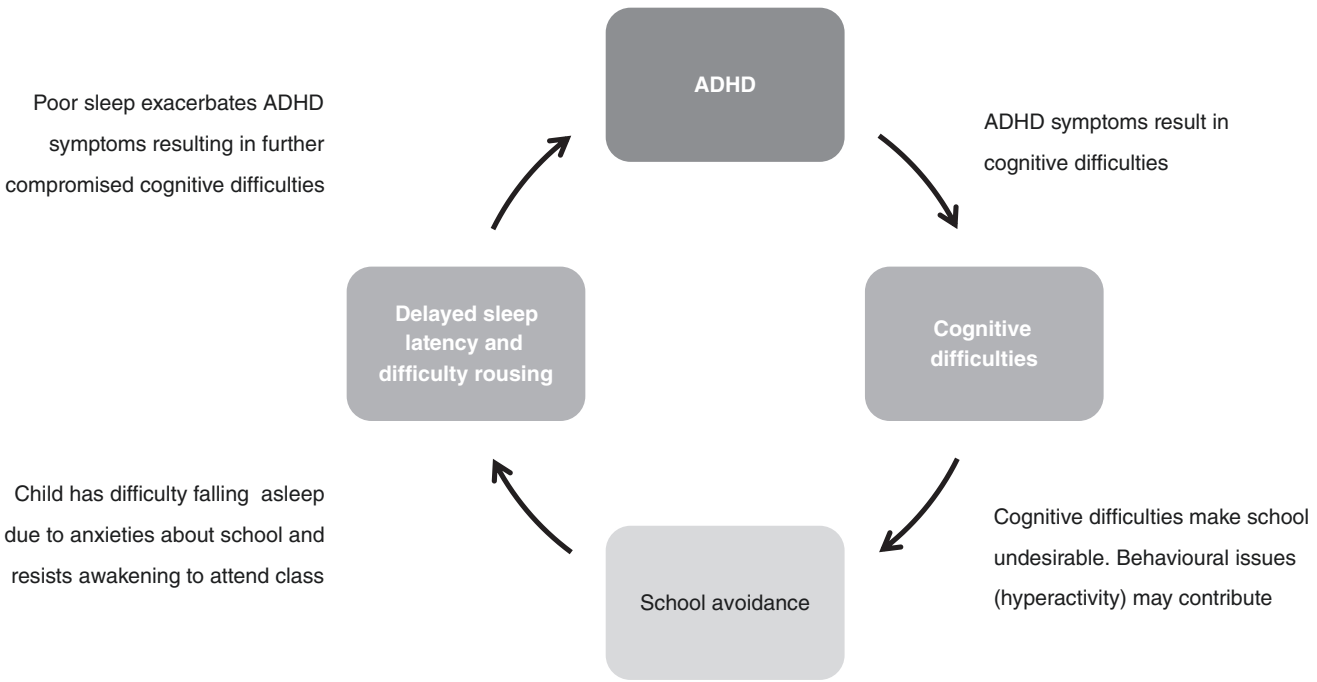

Fig. 12.1 Reciprocal influence

Owens and Dazell and is known by its mnemonic, BEARS. This screening tool involves asking both parents and school-aged children about *B*edtime problems, *E*xcessive daytime sleepiness, *A*wakenings during the night, *R*egularity of sleep/wake times and sleep length, and *S*noring and nighttime breathing [10]. If there are concerns, then sleep diaries are a good way to collect data on children's sleep, with free and downloadable versions available online. For an example, see Fig. 12.2. This specific comprehensive, child-friendly diary collects information about what activities the child did before bed, caffeine consumption, sleep-onset latency, night awakenings, sleep duration, daytime energy and wakefulness, ability to concentrate, nodding off, and naps. It also includes age-appropriate information about the importance of sleep. For any sleep diary, it is recommended that 2 weeks of sleep data be collected in order to observe patterns that may help to determine the type of sleep problem as well as to identify any predisposing, precipitating, and perpetuating factors.

While many children with ADHD have insomnia as discussed above, there are some other sleep disorders that are

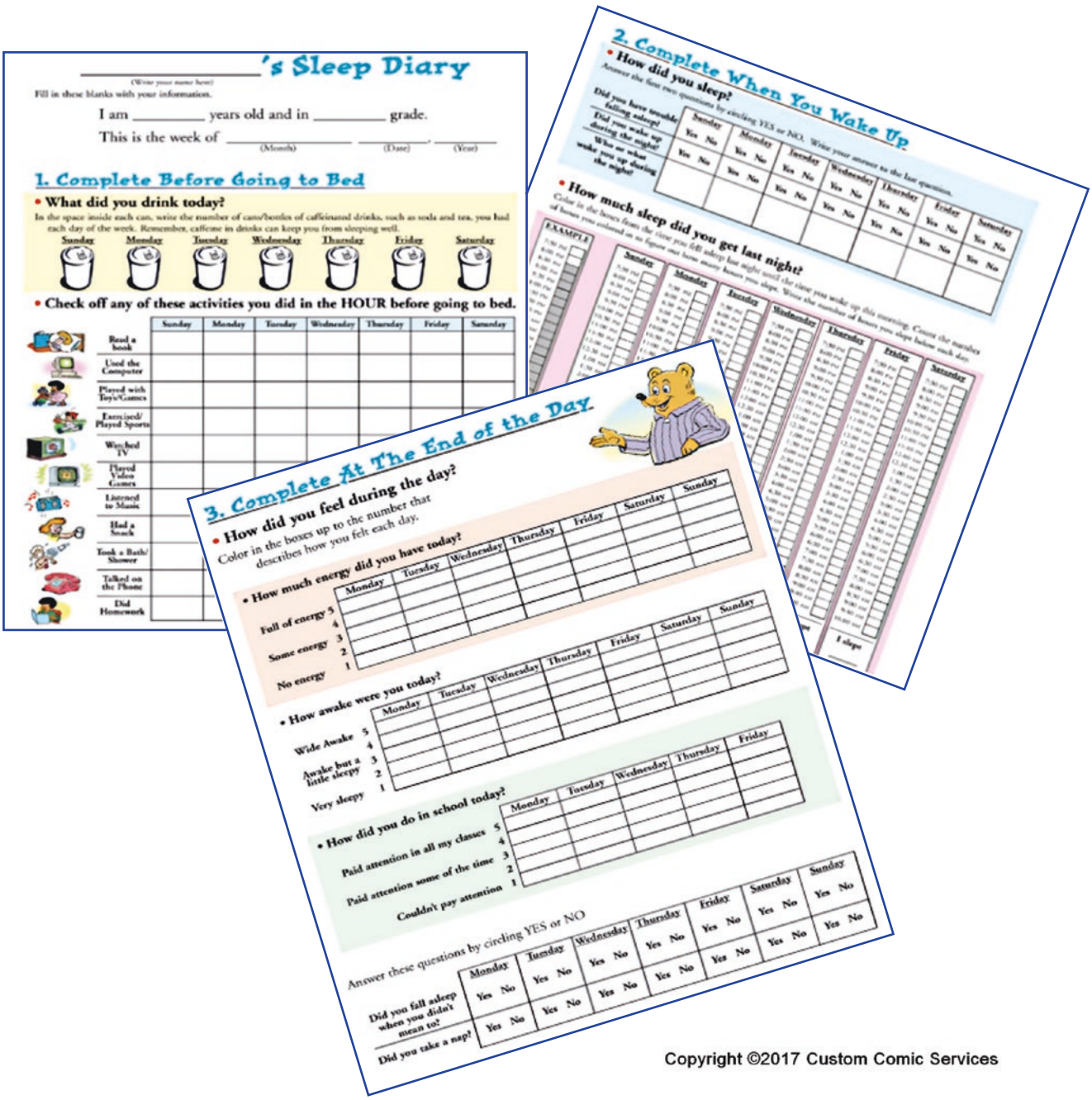

Fig. 12.2 Example sleep diary. (From SleepForKids.org. For further information, visit the National Sleep Foundation at SleepForKids.org or SleepFoundation.org)

particularly common in children with ADHD. Children with ADHD are more likely than TD children to have restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) [21, 23]. RLS causes the individual to feel an urge to move their legs in periods of inactivity/rest in order to counter unpleasant sensations. RLS often results in difficulty initiating and maintaining sleep and daytime sleepiness [1]. While the prevalence of RLS in children in general is around 2% [24], nearly half of adults with ADHD also have RLS, and a quarter of adults with RLS also have ADHD [25]. It is suspected that in most adult cases, RLS has been present since childhood, although it may have been dismissed as "growing pains." Studies have shown that nearly half of children with ADHD have at least *symptoms* of RLS [26]. Thus, it is fair to assume that RLS is quite common among children with ADHD and may be a lifelong problem. The most commonly reported symptoms for children aged 8–11 with definite RLS based on diagnostic criteria are an inability to stay still, inability to get comfortable, poor/interrupted sleep, pain, inadequate sleep quantity, and difficulty rousing. The reported symptoms are similar in adolescence, only pain is less likely to be reported, while daytime sleepiness and difficulties concentrating are more common [24]. PLMD is a disorder that is closely related to RLS. Children with PLMD experience involuntary, repetitive leg movements while they sleep, resulting in disrupted sleep and possible arousals [20]. PLMD occurs in about 90% of people with RLS, so it is no surprise that PLMD also occurs in a large number of children with ADHD despite only being present in just over 1% of the general population of children [1, 27, 28].

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder in which the affected individual has complete or partial obstruction of breathing during sleep [20]. As with RLS, statistics show that OSA is found more commonly among children with ADHD [1], although this needs to be interpreted with some caution, as a review of reviews concluded that while there is an increase in sleep apnea index in ADHD samples, it is present at a non-pathological level [29]. One of the main indicators of OSA is snoring. Snoring appears to be more common in children with ADHD than TD children. In fact, children with ADHD symptoms who also have OSA and are treated with adenotonsillectomy may no longer meet the criteria for ADHD at follow-up [30]. Children with OSA may also have symptoms such as daytime mouth breathing, difficulty swallowing, and poor speech articulation [1]. Also as with RLS, OSA often results in daytime sleepiness [1].

Another relevant sleep disorder for children with ADHD is circadian rhythm disorder and, in particular, delayed sleep phase syndrome. This disorder is characterized by out-of-sync sleep/wake cycles resulting in difficulty falling asleep and rousing at culturally expected times. However, if allowed to follow one's own schedule, a child with a circadian rhythm disorder could sleep for an appropriate duration [1, 18]. A study was conducted in which children with ADHD and sleep-onset problems were randomly assigned to either receive melatonin or placebo [31]. Melatonin is a supplement with soporific effects (e.g., induces sleepiness) and can also be used to help adjust the timing of the circadian clock. In the abovementioned study, approximately half of those receiving melatonin began falling asleep more than 30 min earlier, and less difficulty falling asleep was reported. Very few children reacted negatively to the melatonin (e.g., headaches, dizziness) [31]. This is evidence that, although children with ADHD may be more prone to issues with their sleep/wake cycles, these issues may be corrected with melatonin as opposed to prescription medications. (Note that the potential for melatonin to help with sleep disturbances in children with ADHD extends beyond those with circadian issues and will be further discussed in the *Insomnia Management and Treatment* section.)

If there is a clinical indication of one of the sleep disorders described above, it may be necessary to send the child for polysomnography (PSG) testing [21]. A PSG test records information on sleep stages and physiological measures (e.g., respiration) via electrophysiological measures and is useful in testing for a number of sleep disorders, including sleep disordered breathing and sleep-related movement disorders. While PSG is the gold standard for sleep assessment, there are less intrusive options for assessing some types of sleep problems. An actigraph is a movement capturing device that is worn by the child, but it does not measure respiration or EEG and, as such, cannot be used to diagnose all sleep disorders. However, actigraphs can be useful for diagnosing circadian rhythm disorders and insomnia (e.g., long sleep onset, night awakenings, early morning awakenings). Another measure is videosomnography which involves video-recording a child to assess sleep. This sleep assessment tool may be useful in assessing abnormal sleep behaviors [18].

Like insomnia, the above described sleep disorders may exacerbate ADHD symptoms and treatment of these sleep problems could make ADHD more manageable. It is also possible that other factors may make both a sleep disorder and ADHD worse. For instance, on average, children with ADHD have significantly lower serum ferritin levels than TD children, and there is a nonsignificant trend suggesting even lower levels are associated with comorbid RLS [23]. Comorbid RLS is associated with more severe ADHD symptoms, and low iron can exacerbate both ADHD and RLS symptoms [23, 32]. It is hypothesized that early iron deficiency may be related to decreased dopamine receptors [23]. As stated previously, dopamine plays a role in the sleep/wake cycle, and, thus, there is potentially a complex relationship between sleep problems, RLS, and iron deficiency and the increased risk in children with ADHD.

Because of the many ways that sleep problems and ADHD can be intertwined, it is clearly important to evaluate sleep when first assessing for ADHD and to ensure ongoing monitoring of sleep problems and changes throughout treatment for ADHD. This is important in order to minimize detrimental effects of sleep problems on ADHD symptomology and to properly address any sleep problems that may be present and interfering with treatment of ADHD.

ADHD Medication and Sleep: A Stimulating Conundrum

Stimulant medications are often used in the treatment of ADHD. It is well documented that children on stimulant medications have more sleep difficulties [15, 33–35]. Children with ADHD taking stimulant medication are also more likely to be taking medication for sleep than children with ADHD who were not taking medication for their ADHD symptoms. This relationship may be a reflection of more severe sleep problems related to more severe ADHD symptoms, or more severe sleep problems related to taking ADHD medication, and/or a parental preference for pharmacological treatments [18].

There is evidence to suggest that stimulant medications for ADHD directly interfere with sleep. An experimental study of children with ADHD, with no reported sleep difficulties, demonstrated that when taking immediate-release methylphenidate, children had later sleep onset and shorter total sleep time (TST) by approximately 57 min per night! [34]. This brought the average sleep time down to 8 h and 20 min for these children, 40 min less than the National Sleep Foundation's (NSF) recommended minimum sleep time for children of this age [34, 36]. Similar findings were reported in another study where children taking ADHD stimulant medication fell asleep significantly later and had significantly shorter TST as compared to TD controls and children with ADHD not on medication [34]. Interestingly, in a recent study, children with pre-existing sleep problems had significantly higher levels of sleep disturbance on placebo and low dose, but did not differ from children without pre-existing sleep problems on moderate to high doses of methylphenidate. In fact, a number of the children with pre-existing sleep problems no longer met the criteria of having moderate to severe sleep disturbances once on the higher dose of methylphenidate, while nearly a quarter of the children who did not have a pre-existing sleep problems went on to develop moderate to severe sleep disturbances when taking methylphenidates. Thus, it is extremely important to closely monitor the impact on sleep when starting a child on stimulant medication and to continue to monitor the impact on sleep whenever dosing is changed [37]. As shorter total sleep time alone can have a detrimental impact on performance on executive functioning tasks [38], the potential sleep loss associated with stimulant medication use can be costly. Recall the case of Ben, whose initial mild sleep problems intensified once he started a stimulant-type medication.

Due to the complications stimulant medications can present, it is prudent to consider the pros and cons of using them before prescribing or, in the case where they are already being given, whether daytime benefits outweigh the sleep difficulties that result [39]. While it has been suggested that additional dosing of a stimulant medication later in the day might serve to counter "rebound effects" assumed to be the cause of sleep problems, there is not sufficient evidence to support giving additional doses [21].

Insomnia Management and Treatment: Putting Sleep Problems to Bed

While sleep problems such as RLS and OSA may occur in children with ADHD, the most common sleep problem is insomnia, defined as difficulty getting sleep of adequate quality and/or quantity due to problems with initiating and/or maintaining sleep. In children, this can mean difficulties maintaining and/or initiating sleep *without parental presence*. The DSM-5 does not report prevalence rates of insomnia for children, citing a lack of data; however, it is stated that sleep difficulties in children are likely a product of conditioning, inconsistency, and psychological and medical factors. Insomnia is comorbid with another disorder about 50% of the time [1]. So it becomes very important to conduct assessments to determine whether the child has both ADHD and insomnia and to consider the reciprocal relationship the two share. When discussing insomnia issues in children, the terminology "behavioral insomnia of childhood" (BIC) may be used. There are three types of BIC: limit-setting type, sleep-onset association type, and combined type. In the sleep-onset association type, the child has come to rely on specific associations to fall asleep and to get back to sleep when waking. For instance, he may need his parent present in his room. In the limit-setting type, the child tends to show bedtime resistance, most often because of inconsistent bedtimes being set by parents [40].

Depending on the type of BIC the child is experiencing, different behavioral approaches would be most appropriate. For instance, for children with sleep-onset association type, the best treatment would be graduated extinction methods, in which parents gradually remove their presence (or whatever it is the child has come to associate with falling asleep). If a child has the limit-setting type of BIC, a token system in which the child gets rewarded for staying in bed and gets one pass that allows him to get up out of bed per night can be helpful [41]. Essentially any behavioral interventions aimed

at TD children can be used with children with ADHD, though they may require some individual adaptions or take longer to fully implement.

There are no approved pharmacological treatments for children with insomnia [21, 32]. However, according to a national survey of psychiatrists, one in four children between the ages of 6 and 12 with complaints of insomnia were given pharmacological treatments. The most common pharmacological treatment for children with insomnia was sedative/hypnotic medications, which comprised 45% of cases where medication was prescribed. An additional 23% of treatments included a sedating/hypnotic medication in conjunction with an existing psychotropic medication [42]. For children with ADHD in particular, the most common prescribed medications (either to treat insomnia and ADHD collectively or to target insomnia specifically) are alpha agonists, such as clonidine and guanfacine, and sedating antidepressants, such as trazodone and mirtazapine [42, 43]. An important consideration regarding pharmacological treatments is the danger in equating sedation with sleep [32]. When sleep medications are used, it is important to carefully weigh the pros and cons and to consider the impact of the sedating effect of these treatments. While sleep medication can successfully minimize the effects of poor sleep on the primary diagnosis (e.g., ADHD) and may improve daytime functioning, they commonly result in a "hangover" effect and are actually detrimental to daytime functioning [42]. In other words, while sleep medication may be given with the goal of improving daytime functioning, the resulting impact of eliciting sedation, rather than a natural sleep state, can actually worsen daytime functioning. Finding the proper balance regarding timing and dosage of medication can also be difficult, and there is scant sufficiently rigorous research examining the use of pharmaceuticals to treat insomnia in children with ADHD [32, 44]. Furthermore, in much of the research, while subjective measures of sleep demonstrate improvements when using sleep medications, more objective measures do not reflect any actual change [44]. Given all this, it seems wise that other options for treating sleep problems should trump the use of sleep medications.

Insomnia in children is often also treated with over-the-counter (OTC) medications. The most common OTC medications psychiatrists reported administering to children with insomnia and ADHD were antihistamines (such as those containing diphenhydramine) and melatonin [42, 43]. While there does not appear to be any strong evidence to support the use of antihistamines [44], a study of children with ADHD and insomnia found that 81% of participants responded to either melatonin or a combination of behavioral therapy and melatonin [21]. One explanation of how melatonin works is that it lets the brain know that it is time to slow down and rest to induce sleep onset, and when an individual's chronobiology is working effectively, it is released naturally at nighttime [45]. As children with ADHD can have delays in the timing of natural melatonin secretion, they may benefit from taking OTC melatonin before bed [10, 18, 32, 44–46]. Studies focused on children with ADHD and insomnia tended to administer doses between 3 and 6 mg, often based on child's weight [45, 46]. Commonly available melatonin preparations are often fast release, taking less than an hour to be absorbed and are usually taken approximately 20 min before bed [45, 47]. Immediate-release, sublingual forms that can be taken during night awakenings, as they are immediately absorbed, and slow-release forms that may also help with not only sleep onset but also night awakenings should be taken 1–3 h before bed [47]. However, the bulk of the research in children with ADHD has focused on the standard, fast-release melatonin, and studies are needed to examine whether the slow-release and/or sublingual forms could successfully treat night awakenings. While melatonin is a promising treatment, there are potential minor aversive effects such as dizziness, headaches, nausea, bedwetting, nightmares, and daytime drowsiness. However, these effects are uncommon and often resolve without discontinuing melatonin. In some studies, no differences were found between children taking melatonin and children taking a placebo. An increased risk for seizures in children with neurological disorders and comorbid seizure disorders has been questioned; however, more often the number of seizures remains the same or decreases. Finally, it is recommended to use melatonin with caution in children taking antihypertensive or sedative-hypnotic medications due to the potential for lowering blood pressure [46].

Currently there do not to appear to be any well-designed studies to compare and contrast behavioral and pharmacological interventions in isolation. However, given that there are no FDA-approved medications to treat insomnia in children, and that studies focusing on behavioral interventions have noted significant improvements, it seems best to use behavioral interventions as a first line of treatment [21, 22, 32, 39, 45, 48]. In cases where behavioral intervention alone is not successful or only marginally helpful, melatonin is the most supported pharmaceutical treatment. Studies have found promising results regarding the use of behavioral treatments for insomnia in children with ADHD specifically [21, 48]. One of the most common behavioral interventions for school-aged children with sleep problems is to improve upon healthy sleep practices (also known as "sleep hygiene"). This may involve addressing diet and timing of meals/snacks, amount and timing of physical activity, the bedroom environment (e.g., lighting), and the use of electronics [21]. The use of electronics may be an important intervention point for children with ADHD in particular, as demonstrated with Ben. Children with ADHD have been found to spend more time watching television and to be more likely to have a television in their bedroom [49]. Other important interventions may include focusing on positive bedtime routines: having consistent bedtimes, using quiet "winding down" activities, and ensuring positive interactions occur between child and

parent/caregiver. Children with ADHD may require clearly defined, structured schedules to help them prepare for bedtime. A posted list of the steps may be useful [21].

Regardless of the choice of behavioral treatment, it is important that it is tailored to the child's symptomology and developmental abilities [21, 39, 48]. There are also important familial considerations, such that it may be necessary to provide parents with education about healthy sleep practices. (Recall that Ben's parents did not initially believe electronics were a contributing factor to his sleep problems.) It is also important to know about family composition: for instance, if the child's parents have separated and share custody, treatment will be more successful if both homes are willing to follow the same treatment plan. Thus, it is important to gather information about family background and context. Cultural background and parent-child relationships will also come into play in tailoring the behavioral treatment [32, 49]. Many behavioral insomnia problems are contextually based in the parent-child relationship and are addressed through this relationship. It is important to understand the parents' sleep beliefs, how easily they can be modified, the potential negative impacts, and the misconceptions about sleep. Parents should be provided with good strategies for improving sleep and encouraged to implement consistent sleeping schedules [22, 48]. Sleep education for the entire family is the most important intervention [22]. Table 12.2 contains the

Table 12.2 ABCs of SLEEPING

	Core concept	Details and recommendations
A	**Age appropriate**	It is important that children go to bed and wake up at times that ensure that they receive an age-appropriate amount of sleep (see NSF guidelines: https://sleepfoundation.org/press-release/national-sleep-foundation-recommends-new-sleep-times/page/0/1). For children who have outgrown naps (which they usually do during the preschool age period), napping during the day could be an indication that they are not getting sufficient quality and/or quantity of sleep at night
B	**Bedtimes**	Having set bedtimes and wake times, as well routines in the evening and morning, is key to good sleep. It is recommended that bedtimes be no later than 9 PM across childhood
C	**Consistency**	It is very important that these bedtimes and wake times are consistent, even on weekends (i.e., no more than 30–60 min difference between weekday and weekend bedtimes and wake times)
S	**Schedule**	The child's schedule in general is important. In addition to having routines at bedtime and wake time, it is also important that they have consistency throughout their day, including the timing of homework, extracurricular activities, and so forth
L	**Location**	It is important that the child's location for sleep includes a comfortable bed; the room is quiet, dark, and cool; and the location is consistent and familiar. Also, the child's bedroom should only be used for sleeping. Children should not be sent to their bedroom for a time out. The bedroom also should not be too exciting or distracting and should be conducive to relaxation
E	**No Electronics in the bedroom or before bed**	The use of electronics, including both the timing of use and the location, should also be considered – children should not be using stimulating electronic devices (i.e., iPods, cell phones, laptops, etc.) too close to bedtime (most commonly defined as 1 h prior to going to bed), and it is recommended that these items not be placed in the bedroom
E	**Exercise and diet**	Exercise and diet are both important factors that should be considered when evaluating sleep hygiene. Physical activity during the day is important to healthy sleep, but should not be undertaken too close to bedtime (defined in the literature as anywhere from 1 to 4 h prior to bedtime). The child's day should be organized so that there is time for a cooldown period before bedtime, where he slowly comes down from his regular level of activity into a quiet, more restful state. Diet includes caffeine consumption – children should limit or totally eliminate caffeine consumption (i.e., soda) – as well as the timing of meals. Children should not be going to bed hungry, but also should not be consuming a large meal right before bedtime. A healthy balanced diet is also important to the child's sleep as well as to overall health
P	**Positivity**	Positivity surrounding sleep is also an important aspect of sleep hygiene. Parents should have a positive attitude toward sleep and the bedtime/wake time routine, and the atmosphere in the house should be positive, in order to be conducive to creating a positive mood in the child. It is important that this positive mood is relaxing and calming, rather than fun and exciting; we want the child to be winding down before bedtime. Also, tackling frustrating activities right before bed (i.e., math problems for a child who struggles with math) is not recommended, as this may interfere with the child's ability to fall asleep
I	**Independence when falling asleep**	Independence is also important. Once the child reaches an age where she is capable of settling into sleep without her parents, independence when falling asleep should be encouraged, in order to discourage dependence on someone else in order to fall asleep. For children, independence means no calling out and no getting out of bed and, for parents, no responding to their child calling out and returning the child to her room if she does get out of bed
N	**Needs met during the day**	Finally, the needs of the child should be met throughout the day. This refers to both the child's emotional needs (i.e., love, support, hugs, etc.) and basic physiological needs (i.e., thirst, hunger, etc.)
G	**All of the above equals a Great sleep!**	

ABCs of SLEEPING, a useful mnemonic for remembering the elements of healthy sleep practices and for educating parents about the importance and purpose of these practices. By focusing on concepts such as getting an age-appropriate amount of sleep, having consistent bedtimes and wake times, ensuring the bedroom is appropriately prepared for sleep (dark, comfortably cool, quiet) and free of electronics, having the child eat a healthy diet, promoting proper exercise, working to make the bedtime experience positive and independent, and attending to the ABCs of SLEEPING can help a child achieve great sleep [8, 50].

Improving sleep practices may be sufficient to improve sleep problems when stimulant medications are being given. However, if this alone is insufficient, it may be useful to consider altering the dosage, timing, and/or type of medication [19, 39]. As is demonstrated in Ben's case, both alterations to the timing of his medication and practice of healthy sleep habits were needed to fully improve his sleep issues.

Future Directions: Are There Sweet Dreams Ahead?

While children with ADHD are at increased risk for sleep problems, there are effective treatments that have been successfully implemented with this population. Continued research into treatments for sleep problems in children with ADHD will be extremely valuable. While some sleep problems common to children with ADHD such as RLS may require other treatments, education around healthy sleep habits and other such behaviorally based interventions can still be helpful. In order to reduce the barriers to access to these treatments, eHealth (web-based) interventions would be ideal.

As for pharmacological treatments for sleep problems in children with ADHD, in particular for those with insomnia, evidence base is limited for prescription medications. Iron supplements, for RLS, and melatonin for sleep rhythm and insomnia, more generally, do have empirical support. However, it would be useful to see some large-scale studies comparing behavioral interventions to these over-the-counter treatments in order to determine which treatments are superior and under which circumstances a child may be better suited to one, the other or both.

The most important message to emerge from the current knowledge base is that symptoms of poor sleep and symptoms of ADHD are so intertwined that it makes thorough assessment and evaluations extremely important in order to implement appropriate treatment plans and that behavioral interventions are the best first course of action (and may be sufficient in many cases).

Guidelines to Assessment and Treatment: Pay Attention! Stay Awake!

1. Be aware that some sleep problems may mimic ADHD symptoms. Because poor sleep has a negative impact on cognitive abilities such as memory, attention, and concentration, children who have poor sleep may appear to have issues with inattention and even hyperactivity/impulsivity associated with ADHD.
2. Be aware of the reciprocal relationship between sleep problems and ADHD. Just as poor sleep can mimic or worsen symptoms of ADHD, ADHD can lead to poorer sleep due to arousal, lower iron, difficulty following routines, etc.
3. If there is reason to believe there may be a physiological sleep disorder present, such as OSA or RLS, testing should be done in a sleep lab to rule in or out this sleep disorder. Treating these disorders when present should make ADHD treatments (*if* the child does have ADHD) more successful.
4. If the child with ADHD has trouble initiating or maintaining sleep, consider behavioral interventions and education in healthy sleep practices (see the ABCs of SLEEPING). Useful behavioral interventions include extinction, graduated extinction, and token systems with response cost.
5. If sleep problems persist even after ruling out sleep disorders such as OSA and RLS/PLMD and implementing healthy sleep practices and appropriate behavioral interventions, consider using melatonin as a sleep aid with continued behavioral intervention.
6. Sleep should be evaluated before starting any stimulant medications for the treatment of ADHD. In the case of medication-induced insomnia, consider changing dose quantity, timing, or type of medication. The daytime advantages of the medication should be weighed against the effects on sleep.

Conclusions and Recommendations: Thoughts to Sleep On

Sleep problems are a common complaint for children with ADHD. It is important to first ascertain whether the child does in fact have ADHD and whether there is a comorbid sleep disorder. Consideration of sleep disorders in the differential diagnosis of ADHD is important. In the case of insomnia, whether it is a primary diagnosis or a byproduct of ADHD, behavioral intervention is recommended as the best treatment option because it is safe and, with the proper modifications for the child's ability and symptoms, can be effective. In cases where behavior intervention and modifications

for healthier sleep practices alone are not sufficiently effective, melatonin could be considered alongside continued behavioral intervention. Again, there is scant evidence of any other approved, effective pharmaceutical treatments for sleep problems in children with ADHD. By identifying and treating sleep problems, their negative effects on ADHD symptomology can be minimized or completely eliminated. Further, having a well-rested child may help make treatments for the ADHD easier to implement and more effective.

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Cerebral Palsy

13

Eugenio Mercuri and Domenico M. Romeo

List of Abbreviations

CP	Cerebral palsy
CSHQ	Children's Sleep Habits Questionnaire
DIMS	Disorders of initiation and maintenance of sleep
EDS	Excessive daytime sleepiness
EEG	Electroencephalogram
GMFCS	Gross Motor Function Classification System
NDDs	Neurodevelopmental disabilities
OSA	Obstructive sleep apnea
PSG	Polysomnography
PSQ	Pediatric Sleep Questionnaire
QOL	Quality of life
REM	Rapid eye movement
SDB	Sleep-disordered breathing
SDSC	Sleep Disturbance Scale for Children
SWTD	Sleep-wake transition disorders
TD	Typically developing

Introduction

Cerebral palsy (CP) represents the most frequent cause of physical disability in childhood, affecting more than 2 per 1000 live-born children [1]. It consists of a group of disorders of movement and posture caused by a nonprogressive interference, lesion, or abnormality of the immature brain, which is often accompanied by impairment of sensation, cognition, and communication [2]. In recent years, interest has grown in the description and diagnosis of sleep disorders in children with CP, with reports that sleep disorders are more frequent in CP than in typically developing (TD) children [3–19]. The prevalence of sleep disturbances in CP varies from 19% to 63% according to different studies, which have involved different types of sleep disorders and ages of subjects and seem related to a multifactorial etiology including muscle spasms, musculoskeletal pain, decreased ability to change body position during the night, visual impairment, epilepsy, and side effects of antiepileptic drugs [3–7]. Other comorbidities, such as motor and cognitive impairment and psychiatric problems, increase the risk of developing abnormal patterns of sleep [6–9]. As the presence of sleep disorders influence the quality of life of all the family [10, 11], correct diagnosis and treatment could improve not only the well-being of children with CP but also of their caregivers. The focus of the present chapter is to provide a critical overview of sleep disorders associated with CP with a specific focus on the diagnosis and treatment.

Case Report

Antonio is a 6-year-old boy with cerebral palsy and sleep disturbance. Born at 31 weeks' gestational age, he developed periventricular leukomalacia and spastic diplegia with motor and cognitive impairment and behavioral issues. He is classified at a Level 1 on the GMFCS and has a full-scale IQ of 60. On the Child Behavior Checklist, he showed mainly externalizing disorders (aggressive behavior and attention problems). No epilepsy or clinical seizures have been reported. His parents reported significant sleep issues, mainly difficulties in getting to sleep at night, feeling afraid when falling asleep, and waking up several times per night. He completed the Sleep Disorders Scale for Children (SDSC) , a questionnaire specifically designed to assess sleep disturbances in children, with the following results: Total Score 85, Disorders of Initiating and Maintaining Sleep 76, Sleep Breathing Disorders 79, Disorders of Arousal 70, Sleep-Wake Transition Disorders 70, Disorders of Excessive Somnolence 77, and Sleep Hyperhidrosis 57. He had a normal sleep electroencephalogram (EEG).

Parents were advised to promote a good bedtime routine and to provide a dark and quiet environment, reducing

E. Mercuri (✉) · D. M. Romeo
Pediatric Neurology Unit, Policlinico Gemelli, Catholic University, Rome, Italy

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activities such as watching television during the lead-in to bedtime. After 2 months of specific behavioral intervention with parent training, the parents reported an improvement in sleep behavior, but the child continued to wake up at least two to three times per night; melatonin was started with a dosage of 2.5 mg, 20–30 min before bedtime. Parents reported a further improvement of quality and quantity of sleep, especially in sleep latency and nighttime sleep duration, with a notable reduction in the nocturnal episodes of waking up (down to one to two times per week). After 3 months the parents completed again the SDSC with the following results: Total Score 58, Disorders of Initiating and Maintaining Sleep 60, Sleep Breathing Disorders 58, Disorders of Arousal 58, Sleep-Wake Transition Disorders 45, Disorders of Excessive Somnolence 53, and Sleep Hyperhidrosis 57. No side effects of melatonin were reported.

Prevalence

There is no consensus on the prevalence of sleep disorders in children with CP, due to heterogeneity of the types of sleep disorder assessed, methods of assessment, and the presence of other comorbidities. Published data using screening questionnaires reflecting the overall quality of sleep in children with CP [5–7, 12, 19, 20] identified an abnormal total sleep score in 19–30%, with at least one clinically significant sleep disorder in 40–63% at school age, and a lower prevalence in preschool children. In terms of specific sleep disorders, disorders of initiation and maintenance of sleep (DIMS), sleep-wake transition, excessive daytime somnolence (EDS), and arousal, as well as sleep-disordered breathing (SDB), were all reported with a prevalence between 10% and 24%. Difficulties in settling a child to sleep might lead to actions that play a role in perpetuating insomnia, such as rocking or patting [20]. In another study [19], the most frequent sleep disorders reported were bruxism (32.8%), leg movements (29.5%), nocturnal enuresis (24.6%), and sleep-disordered breathing symptoms like snoring (36.1%). Furthermore, obstructive sleep apnea (OSA) and habitual snoring have also been reported in children with CP, potentially reaching a very high incidence (>60%) [21]. DIMS is more frequent in children with spastic quadriplegia, dyskinetic CP, or severe visual impairment [5]. In terms of severity of motor function as measured by the Gross Motor Function Classification System (GMFCS), insomnia and sleep-disordered breathing (SDB) were more common in children with grades V and IV (severe motor impairment), bruxism was more common in GMFSC grade III, and nightmares and sleepwalking were more common in GMFSC grades I and II (mild motor impairment) [1].

Etiology

Sleep disorders in children with CP can be related to the primary motor impairment due to muscle spasms, musculoskeletal pain, and decreased ability to change body position during the night, but other risk factors can be identified.

Epilepsy is well known to predispose to sleep disorders [22, 23]. It is found in approximately 50% of children with CP. The interaction between epilepsy and sleep disorders is not completely understood. Different studies have confirmed that sleep problems were more prevalent in children with active epilepsy; conversely, sleep disturbances, especially sleep deprivation predispose to an increase in the frequency of seizures [22, 23]. These effects vary considerably with the type of seizure disorder, including its etiology and comorbidities. Direct effects are most likely in severe forms of epilepsy with frequent, difficult to control seizures especially of a convulsive type [22]. Nocturnal seizure discharge in temporal/frontal lobe epilepsy can cause parasomnias interfering with nighttime sleep structure and causing excessive daytime somnolence and worsening sleep apnea [21–23].

Sleep organization in children with CP was characterized by abnormal sleep EEG, sometimes with the absence of rapid eye movement (REM) sleep, low incidence of sleep spindles, or high percentage of wake after sleep onset [16]. Antiepileptic drugs can affect sleep quality and daytime alertness and could modify sleep architecture. However, some studies demonstrated that sleep disorders could be more associated with persistent seizures than with antiepileptic drugs [3–7]. In these studies, seizure-free epileptic children, who were all receiving antiepileptic treatment, reported no increase of excessive daytime somnolence. On the other hand, daytime drowsiness was much more strongly associated with persistent seizures than with antiepileptic drugs, perhaps due to a disruptive effect of seizures on sleep physiology or to an expression of postictal effects.

The severity and type of motor impairment is also strongly associated with specific sleep disorders. Children with spastic quadriplegia and with dyskinesia were more affected by DIMS, due to pain related to stiffness and contractures or involuntary movements. Motor problems of the dyskinetic form of CP could lead to motor restlessness during sleep, linked to a dopaminergic dysfunction or to basal ganglia lesions that could account for hyperkinesia, hypnic jerks, and bruxism [24, 25]. On the other hand, the brainstem dysfunction described in children with dyskinetic CP may affect the architecture of sleep, potentially in disturbances of REM sleep [8].

Brain lesions, especially if affecting cortical and subcortical structures related to the central visual pathway, can cause impairment of several aspects of visual function, such

as visual fields or acuity. This is described as *cortical visual impairment* and occurs in approximately 20–50% of children with CP. It has been reported that concomitant visual impairment in children with CP can also affect the timing and maintenance of sleep through the lack of light perception resulting in altered melatonin secretion and potentially a free running circadian rhythm [4]. Furthermore, the presence of behavioral problems in these children could contribute to sleep wake cycle disorders, as reported in a recent study showing a positive correlation between difficult morning awakening and visual impairment [19].

Behavioral and psychological problems are also known to affect the quality of sleep both in children and their families. Several studies reported a high incidence of behavioral problems in children with CP, such as aggression and attention problems or withdrawal and somatic complaints, and the association between behavior and sleep disorders has largely been reported even in children without disabilities [26–28]. Two studies [6, 7] reported a specific association between sleep disorders and behavior in children with CP both in preschool and elementary school, confirming that behavioral problems were often associated with abnormal sleep disorders, especially internalizing disorders such as withdrawal and somatic complains. In a large study of preschool children with CP, specific sleep disorders such as SDB, bruxism, and EDS were associated with psychiatric problems [19]. Another study related sleep problems in children with CP to maternal depression, showing that mothers who had children with sleep problems were more likely to have difficulty sleeping themselves [11]. Insomnia, excessive daytime sleepiness, and GMFCS score severity were associated with lower quality of life (QOL) in children with CP [10]. Sleep disturbances in children with CP influence not only their caregivers' sleep but also their siblings', who show shorter sleep and more difficulty falling asleep compared to their peers [29]. In a study exploring sleep disturbances in children with CP and their siblings using a structured questionnaire, children with CP scored significantly higher than their siblings in most of the scores, but siblings reported a higher prevalence of DIMS than children in the general population. Furthermore, a high/abnormal total score in CP was significantly associated with reduced sleep duration and increased sleep latency in caregivers [30].

Anatomical factors, as glossoptosis, adenotonsillar hypertrophy, recurrent aspiration pneumonia, and gastroesophageal reflux, are reported in children with severe CP and could contribute to sleep-related breathing disorders, causing sleep fragmentation and hypoxemia [3, 5]; habitual snoring and sleep apnea have been reported with a high prevalence in children with CP [5, 21, 31].

Diagnosis

Several methods have been proposed to assess sleep disturbances in children with CP to investigate developmental changes in sleep behaviors and to identify differences between TD children and those with CP.

Polysomnography (PSG)

Polysomnography (PSG) is considered the gold standard sleep measurement [32]. According to international guidelines [33], electrodes are placed at specific locations on a child's body (scalp, face, neck, chest, and legs), for continuous electrophysiological recordings of brain activation, eye movements, skeletal muscle activation, and cardiac function. In addition, respiratory monitoring is measured using an oronasal thermal sensor for airflow, esophageal manometry or more commonly, respiratory inductance plethysmography for respiratory effort, pulse oximetry for oxygen saturation, and transcutaneous or end-tidal PCO_2 monitoring to measure hypoventilation. These electrophysiological data provide a range of information about sleep: how long the child takes to fall asleep, total sleep time, how well the child slept overall, nocturnal awakenings, limb movements during sleep, and breathing difficulties [32]. PSG has been used in few studies of children with CP especially to assess OSA and to follow improvement after specific treatments [34–36]. In children with severe CP [9], obstructive apnea, decreased ability to change body position, and interictal epileptiform discharges are prevalent during sleep, with significantly more respiratory disturbances per hour of sleep, fewer changes in body position during the night, and interictal epileptiform discharges averaging 23.3% of total arousals.

The limitation of this method in routine clinical practice is that it requires placement of electrodes by a specialist and usually requires that a child stay overnight in a sleep laboratory, a procedure which is costly and inconvenient for some families.

Actigraphy

Actigraphy is an increasingly popular method of assessing habitual sleep-wake patterns, using a watch-like movement sensor to assess activity levels as a proxy for likely sleep and wake [32]. It allows data collection over different days for sleep measurement within a child's natural environment; therefore, compared to PSG, actigraphy is less costly and invasive than PSG. Actigraphy data provide information about the length of a child's sleep, whether he experienced

any awakenings, and how efficient his sleep was overall. Actigraphy is not a suitable method for the diagnosis of disorders in which sleep is fragmented: for example, the detection of limb movement events in children with periodic limb movement disorder is not accurate. Furthermore, in children with OSA, actigraphy fails to reliably identify breathing abnormalities, while PSG is the gold standard for diagnosis [32]. Recently it has also been validated to monitor physical activity during walking in children with CP and could be used in rehabilitation research and clinical practice [37].

Sleep Electroencephalography (EEG)

EEG has been used to measure sleep activity both in clinical and research settings in children with neurodevelopmental disabilities (NDDs) [32]. Specific age norms in sleep EEG could be useful in identifying NDDs: slow-wave activity during sleep increases over the first years of life with a peak before puberty, followed by a decline during adolescence, as it is generated and maintained by thalamocortical and cortico-cortical networks. Children with CP who have lesions affecting these networks could be identified by the assessment of sleep EEG. The same findings could be identified for sleep spindles, a characteristic feature of non-rapid eye movement (NREM) sleep that is related to the same network activities. In one study, more than 50% of children with CP and mental retardation showed the absence of NREM sleep and REM sleep, either extremely low incidence of sleep spindles or the presence of extreme spindles or an abnormally high percentage of wake after sleep onset [16]. Using a compressed spectral array during nocturnal sleep, researchers also observed periodic changes of delta (slow wave) and spindle rhythm powers related to intelligence quotient, with a significant decrease in the developmental quotient in CP patients with neither delta nor spindle rhythm powers found during nocturnal sleep [38]. Furthermore, among people with athetoid CP [8], there has been reported a marked decrease in rapid eye movements during REM sleep.

Questionnaires and Sleep Diaries

Both types of instruments are widely used to ask parents or children to reflect on daily or weekly sleep behavior. Questionnaires are easy to administer and straightforward to score and sometimes report normal values or ranges for comparative purposes. Diaries require a daily report of sleep and wake times [32]; they are time-consuming to complete, and their results can be difficult to interpret, as there are no normal values or times that exist for comparison. Clinicians frequently opt to use questionnaires instead of PSG and/or actigraphy because of their time- and cost-effective nature, as well as their relative ease of administration, but these may sacrifice accuracy of diagnosis for both SDB and DIMS. Several standardized scales are available to identify sleep disorders in childhood, but only few have been used in children with CP [39–41].

The Pediatric Sleep Questionnaire (PSQ) [39] is mainly used to screen for childhood sleep-related breathing disorders; it contains 48 items related to OSA symptoms. Subscales include the Sleep-Related Breathing Disorder scale, a measure of SDB. Furthermore, it has been used to study the association between quality of sleep and QOL in 41 children with CP and in 91 TD controls age 8–12 years [10], reporting risks for sleep disruption and lower QOL in children with CP; insomnia was often associated with a low psychosocial QOL, whereas excessive daytime sleepiness predicted lower physical QOL. On the other hand, no effects of sleep variables on QOL were observed among the TD group.

The Children's Sleep Habits Questionnaire (CSHQ) is designed for school-age children, and it is one of the most common tools used for assessing sleep problems in children [40]. It is an up to 45-item, parent-rated questionnaire that assesses the frequency of behaviors associated with common pediatric sleep difficulties as they have occurred during a "typical" recent week. Items cluster into eight subscales that relate to common sleep problems in children: Bedtime Resistance, Sleep-Onset Delay, Sleep Duration, Sleep Anxiety, Night Wakings, Parasomnias, Sleep-Disordered Breathing, and Daytime Sleepiness. In addition, all ratings are summed to create a total sleep disturbance score, for which a score of over 41 identified 80% of a clinical sleep disorders sample and is often used as a cutoff for abnormality. A study comparing CSHQ scores between 40 children with CP, aged 4–12 years, and 102 age-matched TD children showed that children with CP had higher scores for Sleep Anxiety, Night Wakings, Parasomnias, and SDB subscales [11].

The Sleep Disturbance Scale for Children (SDSC) [41] looks at sleep disorder symptoms over the previous 6 months in children between 3 and 16 years [42]; it consists of 26 items in a Likert-type scale with values 1–5 (higher numeric values reflect higher severity of symptoms). The sum of scores provides a total sleep score with a possible range from 26 to 130; a T-score of more than 70 (>95th centile) is regarded as abnormal and a score <70 or less as normal. The original factor analysis yielded six sleep disturbance factors representing the most common areas of sleep disorders in childhood and adolescence: (a) DIMS, (b) sleep breathing disorders (SBD), (c) disorders of arousal (sleepwalking, sleep terrors, nightmares), (d) sleep-wake transition disorders (SWTD) (hypnic jerks, rhythmic movement disorders, hypnagogic hallucinations, nocturnal hyperkinesias, bruxism),

(e) disorders of excessive somnolence, and (f) sleep hyperhidrosis. The SDSC represents the most frequently used questionnaire in studies of sleep in children with CP, with more than 700 children [5, 7, 11, 13, 20] assessed in different studies. Compared with normative data, children with CP showed higher total SDSC scores, with specific sleep disorders as DIMS, SDB, and SWTD; the sleep disorders were closely correlated to motor and cognitive impairment, behavioral problems, and epilepsy.

Treatment

Recent reviews have confirmed the absence of studies on sleep intervention specifically for children with CP [3, 15]. Most of the published research on intervention has been related to other NDDs, with only a few including participants with CP [15]. In these studies, it is recommended that the treatment for sleep disorders should begin by establishing good "sleep hygiene," through parent-based education and behavioral interventions [3, 43, 44]. This should be followed by promoting a structured, age-appropriate bedtime routine and providing a dark and quiet environment. Potentially stimulating activities such as watching television and vigorous play should be avoided during the lead-in to bedtime. Maintaining regular bedtime and waking times may strengthen and entrain circadian mechanisms to promote rapid sleep onset near the desired bedtime.

Behavioral interventions adopted by parents should be used in case of disruptive behaviors [43, 44]: *extinction (systematic ignoring)*, placing children in bed and then ignoring (directly or gradually) any inappropriate behaviors, with the exception of concerns regarding safety or illness; *positive routines*, creating quiet but enjoyable bedtime routines with fading of bedtimes toward children's time of habitual sleep onset; and *parent education and anticipatory guidance*, educating parents and caregivers about early childhood sleep and the treatable influences that may promote or disrupt it.

Osteopathy and Massage

These therapies are among of the most used alternative medicine therapies for children with CP. The effects of osteopathy on sleep disorders in CP have been evaluated in two studies [45, 46]. In the first, the authors assessed 142 children with CP, 71 of whom were treated with osteopathy, for 6 months. No statistical differences were found for motor function, quality of life, pain, or sleep between children who had cranial osteopathic treatment and those who did not [45]. In the second study, the authors treated 50 children with CP using either osteopathic manipulation or acupuncture [46]; after a period of 6 months, 96% of the parents reported an improvement, especially in the use of arms or legs, and a more restful sleep in both the osteopathic and acupuncture groups. In both studies, however, no structured questionnaires or other sleep measures as actigraphy or PSG were used.

The literature on the use of massage specifically for children with CP is sparse and controversial: some studies supported the benefit of massage therapy for spasticity and also improved muscle tone, range of motion, and cognition [47], while others failed to find any benefit [48]. In a recent study, 100 families of children with CP responded to a survey documenting that 80% of their children with CP had received massage at least once. Of these families, 86% reported that massage helped to relax their children's muscles, 71% that it improved quality of life, 30% that it decreased their child's pain, and 23% that it improved sleep [49]. An improvement in sleep behavior was reported in another study enlisting 70 parents in a parent-training program for massage in children with CP, with improvements in eating and mobility also claimed [50]. However, neither study used a control group, which limits more definitive conclusions.

Surgery Treatment

Children with CP are commonly affected by OSA, due to anatomical factors that lead to airway obstruction [3–5, 17, 21]. Different surgical techniques, such as adenotonsillectomy, soft-tissue reduction combined to skeletal expansion of the mandible, uvulopalatopharyngoplasty, and tongue-base suspension, have led to significant improvement of OSA in children with CP, with reduced apnea/hypopnea indices and improved oxygen saturation [17, 35, 51, 52]. However, in the case of severe airway obstruction, especially at older ages, children with CP could require tracheostomy [53].

Treatment for Spasticity

Baclofen and botulinum toxin are medications frequently used for spasticity in children with CP. Over the last few years, some studies have also explored a possible role of these treatments in improving sleep behavior. Intrathecal baclofen delivered by implanted pumps has been demonstrated to reduce the frequency of night wakings and sleep apnea and to improve sleep in general in children with spastic CP within 6–9 months after treatment, probably due to the resulting reduced muscle spasms and improvement of pain and mobility [18, 54, 55]. Rare and generally temporary side effects, such as constipation, excess lethargy, urine retention, pressure sore, and deteriorating swallow, were reported.

The effect of botulinum toxin injections on sleep has been studied in 26 children with non-ambulatory quadriplegic CP

who had significant spasticity and pain at the hip level [56]. These subjects received botulinum toxin injections at the adductor magnus, medial hamstrings, and iliopsoas muscles. All the children reported significant improvement at the Pediatric Pain Profile after 3 months of the treatment; furthermore, families reported an improved sleep pattern of the child, especially in terms of the reduction of the frequency of night wakings and need for turning because of sleep discomfort. No significant side effect was reported after treatment.

Melatonin and Other Drugs

Drug treatment of sleep disorders in children has received remarkably little scientific study, and there is a lack of well-designed controlled studies, despite widespread use in this age group [43]. Melatonin (N-acetyl-5-methoxytryptamine), a tryptophan-derived molecule, is a chronobiotic drug essential for the regulation of the sleep-wake cycle. During the day, human synthesis of melatonin is limited. When it becomes dark, norepinephrine liberated by the beta-adrenergic receptors in pinealocytes improves its secretion [3, 43]. It has been proposed that melatonin may have significant therapeutic effects in circadian rhythm sleep-wake disorders such as jet lag disorder and sleep-wake cycle disturbances in blind people and shift workers. There are various studies of melatonin usage in pediatric sleep disturbances, most of them confirming its role in improving sleep quality, reducing sleep-onset latency, and increasing total sleep time [3, 57–63], but none has included exclusively CP patients. Some studies have reported results on the use of melatonin in NDDs, including CP [58–63]. Wasdell et al. [58] used a starting 5 mg dose of melatonin in 51 children affected by different NDDs, with a gradually increased increment of the dose until the therapy showed optimal beneficial effects. Sleep characteristics were measured by wrist actigraphs and caregiver completed diaries. The children showed an improvement in both total nighttime sleep and sleep latency of approximately 30 min. Significant improvement in children's sleep was also observed in clinician and parent ratings.

In a randomized, double-blind, placebo-controlled 6-week trial of melatonin versus placebo in 20 children with NDDs, 90% fell asleep more quickly when receiving melatonin than placebo with a significant reduction of sleep latency [59]. In a third study, melatonin was used in 49 children aged 1–13 years affected by CP, epilepsy, and other NDDs; children under 5 years of age were started on 2.5 mg, and those ≥5 years started on 5 mg; this was increased by 2.5 mg at intervals of 3 days up to a maximum dose of 7.5 mg (<2 years) or 10 mg. Parents completed sleep diaries before and after treatment, and the majority showed significant improvement in total sleep time and in nighttime sleep duration and sleep latency [60]. A recent clinical trial confirmed the efficacy of melatonin in the treatment of sleep disorders in 275 children with NDDs, with doses ranging from 0.5 to 12 mg for a period of 12 weeks, again reducing sleep latency and increasing total sleep time [61].

As melatonin is a generally safe treatment with few adverse side effects reported, it could therefore be considered a first line of treatment of sleep disorders in children with CP, especially involving sleep onset [63]. As it has been reported that in a limited number of cases of severe neurologically disabled children melatonin can potentially increase seizure activity [62], there has been some discussion on whether its use should be limited in children with CP with comorbid active epilepsy [15]. Across disorders, additional research including larger groups of children with specific disabilities/syndromes is needed to draw disability-specific conclusions [63].

Gabapentin is an antiepileptic medication whose mechanism of action has not fully been described but may involve interactions with voltage-gated calcium channels and modulation of GABA biosynthesis. It has been used for the treatment of partial seizures, neuropathic pain, and restless legs syndrome. In adults with primary insomnia, gabapentin improves sleep quality, increasing slow-wave sleep and sleep efficiency [64]. Recently it has been used in treating refractory insomnia in 23 children with a mean age of 7 years and a diagnosis of NDDs in 87% (including one child with CP); gabapentin was started at an average dose of 5 mg/kg, with a maximal dose of 15 mg/kg at bedtime; at follow-up the 78% of the children showed a sleep improvement, with adverse effects in 6 children [65].

Conclusions

Sleep disorders are common in children with cerebral palsy. Its characteristic and comorbid features, such as motor impairment, pain, cognitive impairment, behavioral problems, or epilepsy, are all important risk factors for the development of sleep disorders. The use of questionnaires, primarily the SDSC to date, is widely reported to identify sleep disturbance, even if a more structured in-depth interview or objective assessment, using PSG or actigraphy, provides better information on sleep disorders and allows a more accurate diagnosis.

No sleep interventions specifically designed to improve the sleep of children with CP are reported in the literature. Instead, strategies to improve sleep depend mainly on clinical experience and include sleep hygiene and/or specific drugs such as melatonin, a commonly prescribed drug for disturbed sleep in children with neurological dysfunction. An effective treatment has the potential to improve not only the well-being of the child but the well-being of a whole family [3–5, 15, 29, 30].

Future Directions

Randomized placebo-controlled trials should be proposed to establish efficacy, safety, and pharmacokinetics data of melatonin in children with CP to test the hypothesis that oral melatonin has an impact on sleep behavior in this population [66].

Further clues may also come from the correlation with brain imaging and with the pattern of brain lesions underlying CP; only a few studies have examined how specific brain damage or hypoxic events that are common causes of CP can affect sleep architecture [6, 8], such as how a dopaminergic dysfunction or a lesion of the basal ganglia, typical of the dyskinetic form of CP, could lead to motor restlessness during sleep that could account for hyperkinesia, hypnic jerks, rhythmic movement disorders, and bruxism [24, 25]. Research into this neglected field is needed in order to implement appropriate and efficient interventions which will allow children with CP and their families to get back to sleep.

Practice Points for Sleep Disorders in Children with CP

- Prevalence: 19–63% according to different studies
- Etiology: Primary motor impairment, visual impairment, epilepsy and antiepileptic drugs, severity of motor impairment, and psychiatric problems
- Diagnosis: Questionnaires (SDSC) in routine clinical practice to screen for sleep disorders; PSG as needed; and actigraphy in research studies
- Treatment: Parent-based education about sleep and behavioral interventions, melatonin (0.5–5 mg)

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Down Syndrome

14

Maria Cecilia Melendres and George T. Capone

Case Vignette

Nicky is now a 19-year-old boy with Down syndrome who has been followed in the pediatric sleep clinic since he was 9 years of age for obstructive sleep apnea. He had previously undergone an adenotonsillectomy at age 4 years. He presented to sleep clinic due to loud snoring, neck hyperextension during sleep, frequent awakenings at night, and falling asleep in school. His sleep study was consistent with obstructive sleep apnea, and he was started on continuous positive airway (CPAP) therapy. Nicky had significant difficulty with CPAP at the start. He often took it off in the middle of the night, and compliance checks were low. With assistance of behavioral psychologists and Nicky's parents, CPAP compliance gradually improved over a period of 2–3 years. He is now using it for more than 8 h nightly. His father reports that Nicky is now more awake and alert during the day. He believes that if Nicky's sleep apnea was not adequately treated, he would not be as active or as healthy and would have a lot more restless sleep. His father is constantly encouraging parents of children with DS to have them evaluated and treated for sleep apnea.

Introduction

Down syndrome (DS) is a chromosomal disorder that occurs in approximately 1 in 800–1000 live births. Most often DS results from complete trisomy of chromosome 21, due to nondisjunction during gamete formation. A small number of cases result from either complete or partial translocation of chromosome 21 to another chromosome, typically in the D (13–15) or G (21–22) group [1]. Persons with DS also experience a higher prevalence of health comorbidities including congenital, acquired, and aging-related medical conditions [2]. Guidelines for regular health maintenance and preventive medical screening have been set forth by the American Academy of Pediatrics [3]. Children and adolescents with DS experience much higher rates of sleep disorders including sleep-related breathing disorders (SRBD), sleep pattern disturbances, sleep fragmentation, and behavioral-based sleep disorders [4].

Clinical Features/Etiology

Children with DS have several clinical features which potentially lead to disturbed sleep and/or increased risk for sleep-disordered breathing [5]. Since nocturnal sleep has an important role in a child's learning as well as behavior and daytime function, it is important to diagnose and manage sleep disorders early in children who already have deficits in these areas. Sleep disruption may exacerbate learning and behavior difficulties that are already inherent to children with DS.

Sleep in children with DS has been shown to differ from sleep in typically developing children. In particular, studies of sleep architecture have shown decreased percentage of rapid eye movement (REM) sleep, decreased REM activity, increase in time to initiation of REM sleep (REM latency), more frequent night awakenings and arousals, and decreased sleep efficiency [6, 7]. The lower REM sleep in children with DS

M. C. Melendres
Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

G. T. Capone (✉)
Down Syndrome Clinic and Research Center, Neurodevelopmental Medicine, Kennedy Krieger Institute, Baltimore, MD, USA
e-mail: capone@kennedykrieger.org

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perhaps puts them at a disadvantage as REM sleep is thought to be functionally related to learning [8]. It is speculated to facilitate the consolidation and retrieval of prior learning.

The overall rates of sleep disturbance in children with DS range from 31% to 54%, higher than what is reported in typically developing children [4]. These sleep disturbances are not limited to sleep-related breathing disorders but also include non-respiratory and behavioral sleep disorders such as difficulties in initiating (reported in 51.8% of DS patients) or maintaining sleep (69.4%), excessive daytime sleepiness (54%), impaired circadian rhythm, and increased level of irritation or anxiety [9, 10]. These symptoms are not always brought to the attention of healthcare givers as parents may assume that these difficulties with sleep are part of their child's syndrome [9–11]. These behavioral sleep problems can have a significant impact on the child's daytime functioning, as well as the well-being of the family. It is thus useful to screen all children with DS for any evidence of sleep disturbance, including bedtime difficulties, night awakenings, excessive daytime sleepiness, or fatigue [4]. Management of these disturbances requires a comprehensive evaluation of the family's current sleep practices, as well as identification of medical and/or psychiatric disorders that can contribute to sleep difficulties.

Up to 25–30% of children and adolescents with DS also have a comorbid psychiatric or neurobehavioral condition [12]. Children with DS may manifest restless sleep and sleep pattern disturbances that can impact attention and learning, and exacerbate daytime emotional and behavior regulation [13]. Higher parent ratings of sleep disturbance correlated with greater impairment in executive function in a small, healthy cohort of adolescents and young adults with DS [14]. More specifically, a significant association between the amount of time spent in slow wave sleep and several measures of achievement and adaptive behavior has been reported [15].

The most widely studied sleep disturbance in children with DS is sleep-disordered breathing. Sleep-disordered breathing is thought to be a continuum reflecting increasing upper airway resistance (Fig. 14.1). On one end is primary snoring, which is the mildest form of sleep-disordered breathing. At the other end is the obstructive sleep apnea syndrome [16]. Upper airway resistance syndrome and obstructive hypoventilation are intermediate conditions between these two extremes. Primary snoring is defined as snoring that is not associated with gas exchange abnormalities, excessive arousals, or daytime symptoms. Obstructive sleep apnea syndrome is a disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction (obstructive apnea) that disrupts normal ventilation during sleep and normal sleep patterns [17]. It has an estimated prevalence of about 1–4% in otherwise typically developing children [18]. In children with DS, the prevalence of obstructive sleep apnea (OSA) is much higher, ranging from 24% to 79% in population-based samples and up to 97%

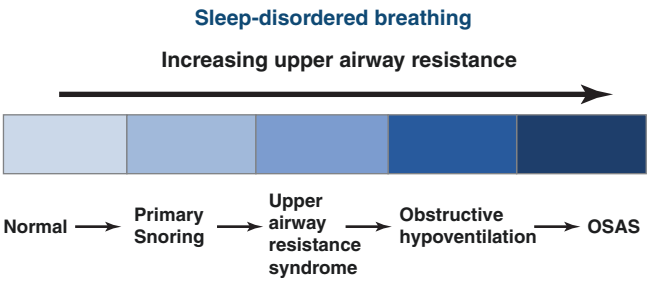

Fig. 14.1 Spectrum of sleep-disordered breathing reflecting increasing upper airway resistance

in those referred for a history of snoring [10]. This increased prevalence continues into adulthood as well, with most patients having a severe degree of OSA [19]. In typically developing children, OSA peaks between the ages of 2 and 6 years of age, corresponding to the period during which the tonsils and adenoids are largest in relation to the underlying airway size. In DS, a higher prevalence of OSA has been described even in young infants, together with correlations between OSA and prematurity, congenital heart disease, dysphagia, GERD, and other GI conditions [20, 21]. Infants with DS and GI issues, co-occurring dysphagia and CHD have a higher likelihood of also having OSA. It is recommended that at least once during the first 6 months of life, then at each well-child visit during childhood, symptoms of obstructive sleep apnea and behavioral problems that could be associated with poor sleep should be discussed with parents [3].

The etiology of obstructive sleep apnea is multifactorial, and it is thought that a combination of anatomic, neuromotor, and other factors (including racial, hormonal, metabolic, and genetic) is involved [22]. Children with DS are at higher for risk for obstructive sleep apnea because of physical, neurologic, and medical features that can contribute to a smaller upper airway, increasing their predisposition to upper airway obstruction during sleep [23, 24]. Physical features include midfacial and mandibular hypoplasia, macroglossia which may be either absolute (true macroglossia) or relative (relatively large tongue compared to the small size of their oral cavity), and lymphoid hyperplasia (including lingual tonsillar hypertrophy). In addition to these structural factors, children with DS usually have hypotonia. This decreased muscular tone throughout the body can predispose to glossoptosis, or the tongue falling back and obstructing the airway. This also contributes to hypopharyngeal collapse during sleep. In addition, obesity is a known risk factor for obstructive sleep apnea syndrome. The higher prevalence of obesity or overweight in children with DS than in the general pediatric population puts them at higher risk for OSA [25]. Hypothyroidism is another condition more commonly seen in children with DS than the general population, and which has shown some association with OSA [26]. Thyroid function should be routinely checked in children with DS diagnosed to have OSA.

Symptoms of Sleep-Disordered Breathing

- Nighttime symptoms
  - Snoring
  - Difficulty breathing
  - Restless sleep
  - Nighttime sweating
  - Enuresis
  - Sleeping in unusual positions (sitting up, bent at waist)
- Daytime symptoms
  - Mouth breathing, nasal obstruction, and hyponasal speech
  - Upper respiratory tract infection and recurrent ear infections
  - Difficulty with swallowing
  - Behavior and learning problems (inattention, impulsivity, irritability)

Obstructive sleep apnea causes both nighttime and daytime symptoms. Snoring and difficulty breathing are the most common nighttime symptoms of OSA. The snoring in children with DS is usually loud and occurs nightly. It is present in almost all children with DS who have sleep apnea. Parents may describe increased respiratory effort associated with lack of airflow. Some parents may describe this as struggling to breathe and restlessness during sleep. Other symptoms include secondary nocturnal enuresis, sweating, and sleeping in unusual positions such as with the neck hyperextended, sleeping propped up on several pillows, or sleeping in a sitting position (Fig. 14.2). Daytime symptoms are usually related to adenotonsillar hypertrophy and include mouth breathing and hyponasal speech in which the child sounds as if he has nasal congestion. Children with OSA may also exhibit behavior and learning problems. Symptoms of attention-deficit/hyperactivity disorder and mood irritability are common among children with OSA.

Diagnosis of obstructive sleep apnea is done using polysomnography. This entails an overnight stay in a sleep laboratory, during which time various physiologic parameters are measured simultaneously. As children with DS may not tolerate the monitoring sensors used during a study, it is useful to introduce what to expect prior to the test, to enable some degree of preparation and possibly better tolerance of the procedure. A sleep study is indicated if a child with DS exhibits the symptoms of obstructive sleep apnea, especially when other risk factors such as obesity are present on examination. In addition, it is recommended that all children with DS (regardless of the presence or absence of symptoms) undergo a sleep study by age 4 years [3], since there is usually poor correlation between parent report of symptoms of sleep-disordered breathing and polysomnogram results [15].

Untreated obstructive sleep apnea poses the risk of neurocognitive, behavioral, cardiovascular, and metabolic consequences [27]. As children with DS already have deficits in these areas, OSA may result in more profound effects in these children. Children with DS and OSA/sleep pattern disturbances demonstrated lower verbal IQ scores and more cognitive inflexibility compared to those without OSA [28]. A possible relationship between OSA severity (AHI) and communication skill has been recently noted as well [29]. Most of these studies are from small, clinically ascertained samples.

It is tempting to speculate that undiagnosed sleep-related breathing disorders (SRBD) or other sleep disturbances are also causally related to neurobehavioral disorders in this vulnerable and susceptible population, but this has not been conclusively demonstrated nor has it been well studied. Whenever behavior problems involving mood, irritability, anxiety, inattention, distractibility, loss of developmental skills (regression), hypo- or hyperactivity, and fatigue manifest in children without a prior history, focused questioning about sleep patterns and hygiene and diagnostic testing for sleep apnea should be considered. As reported by us previously, children with DS and comorbid neurobehavioral disorders manifest a high incidence of sleep disturbances according to parent report. Even in the absence of diagnostic testing by overnight polysomnogram, a majority of these children appeared to benefit from psychotropic medications given at bedtime to improve insomnia and sleep consolidation in addition to daytime maladaptive behaviors [30, 31]. Laboratory-based investigation of larger cohorts needs to be undertaken in order to tease apart the separate contributions of hypoxemia, disturbed breathing, and sleep fragmentation in children with DS both with and without neurobehavioral problems.

Previously unpublished data obtained from children with DS 3–13 years of age presenting to our outpatient clinic for initial evaluation suggests the following:

- In a cohort of DS children with externalizing disruptive behavior problems, 16/38 (42%) also had OSA on overnight polysomnogram. While 22/38 (58%) did not have OSA, half of those without OSA (11/22) manifested >7/h spontaneous arousals on overnight polysomnogram.
- As expected, in this same cohort, children with OSA had a higher apnea-hypopnea index (AHI), more central apneas (CA), and a higher arousal index (ArI) compared to those without OSA.
- According to the parent-reported Sleep Disturbance Scale for Children [32], none of the six subscale scores differed significantly between those children with and without OSA.

Fig. 14.2 Children with Down syndrome and unusual sleep positions, including sleeping "folded over" (clamshell position) (**a**) and also sleeping with neck and upper trunk in hyperextension (**b**)

- On the parent-reported Aberrant Behavior Checklist (ABC-C), all children scored high on the hyperactivity and irritability scales, consistent with our previous findings in children with ADHD and disruptive behaviors [31]. However, significant differences were not apparent between those with and without OSA.

Management

The first line of treatment for childhood obstructive sleep apnea is adenotonsillectomy [33], including among children with DS. Adenotonsillectomy is indicated if a child has obstructive sleep apnea documented on an overnight sleep study, has some degree of adenotonsillar hypertrophy, and has no contraindications to surgery [33]. In children with DS, adenotonsillectomy for OSA also leads to improvement in OSA, but not to the same degree as in typically developing children [34, 35]. Adenotonsillectomy in typically developing children is curative in about 80% [36]. In contrast, about 50–73% of children with DS will have persistent obstructive sleep apnea following adenotonsillectomy [35], requiring further treatment.

Children with DS may require a higher level of care in the immediate postoperative period, as they are at higher risk for postoperative complications. Potential complications of adenotonsillectomy for OSA include complications related to anesthesia, bleeding, pain, fever, infection, and pulmonary edema. Children with DS are also at risk for respiratory complications such as upper airway obstruction and oxygen desaturations, in addition to potentially needing a longer period to tolerate adequate oral intake, leading to longer hospital stays [37]. The American Academy of Pediatrics recommends admitting children at high risk to a hospital for observation following surgery for OSA, including those with DS [33]. In addition, evaluation with a follow-up sleep study after adenotonsillectomy is recommended in children with DS [38], given the higher likelihood of incomplete cure. This study should be done 6–8 weeks after surgery to allow for adequate healing of the surgical site.

In those with a significant degree of OSA persisting after surgery, further airway evaluation through flexible endoscopy, sleep video fluoroscopy, cine computed tomography (CT), or cine sleep magnetic resonance imaging (MRI) may be done to identify other sites or causes of airway obstruction that may be amenable to further surgery [39, 40]. In children with DS, there may be multiple sites of persistent obstruction and may include adenoid regrowth, glossoptosis, lingual tonsillar hypertrophy, and/or hypopharyngeal collapse [11]. Surgical procedures which may be done include revision adenoidectomy, lingual tonsillectomy, uvulopalatoplasty, genioglossus advancement, tongue reduction or radio

frequency ablation of the tongue base, rapid maxillary expansion, and tracheostomy [41, 42].

For children with DS who are not candidates for surgery, or in whom OSA has persisted after surgery, positive airway pressure (PAP) therapy is used. Two modes of PAP therapy can be used to treat obstructive sleep apnea: continuous PAP (CPAP) and bi-level PAP. A CPAP machine delivers air at a constant pressure through a nasal mask to keep the airways open. Bi-level PAP has two pressures set, an inspiratory and an expiratory pressure. Both CPAP and bi-level PAP have been shown to be effective in childhood OSA [43], but CPAP is used more commonly. PAP therapy significantly decreases the number of obstructive apneas and improves oxygenation, snoring, and sleepiness. As PAP therapy entails the use of a nasal mask during every sleep period, compliance is often suboptimal. Initiating PAP therapy may be particularly difficult in children with developmental disabilities, such as in Nicky's case, above. As such, behavioral therapies have been developed, with about 75% of children successfully tolerating PAP after behavioral intervention [44] (Fig. 14.3). Ideally, behavioral training for PAP therapy in children with developmental disabilities should begin prior to PAP therapy initiation by involving a behavioral therapist even during the initial mask fitting. The therapist can also help identify the type of distraction and reinforcement contingencies that can be used for the child [45]. In instances when a behavioral therapist is not available, the family can also work with a respiratory therapist who has significant experience working with children with DS. It is typically recommended that the child be taught first to tolerate the mask while awake, prior to attempting to use it during sleep. Ongoing parental education and support throughout all stages of therapy is a prerequisite to successfully implementing PAP therapy in children.

In addition to behavioral therapy for the child, adherence may be improved by minimizing side effects from PAP use. Complications from PAP use include those related to an ill-fitting mask such as skin breakdown and eye irritation from air leak. Nasal symptoms such as congestion or irritation may be improved by providing heated humidification with the machine [46].

Compliance Information 2/13/2015 - 5/13/2015

Compliance Summary

Date Range	2/13/2015 - 5/13/2015 (90 days)
Days with Device Usage	90 days
Days without Device Usage	0 days
Percent Days with Device Usage	100.0%
Cumulative Usage	30 days 11 hrs. 39 mins. 55 secs.
Maximum Usage (1 Day)	9 hrs. 48 mins.
Average Usage (All Day)	8 hrs. 7 mins. 46 secs.
Average Usage (Days Used)	8 hrs. 7 mins. 46 secs.
Minimum Usage (1Day)	1 hrs. 37 mins. 30 secs.
Percent of Days with Usage >= 4 Hours	97.8%
Percent of Days with Usage > 4 Hours	2.2%
Total Blower Time	30 days 11 hrs. 39 mins. 55 secs.

Hours of Usage

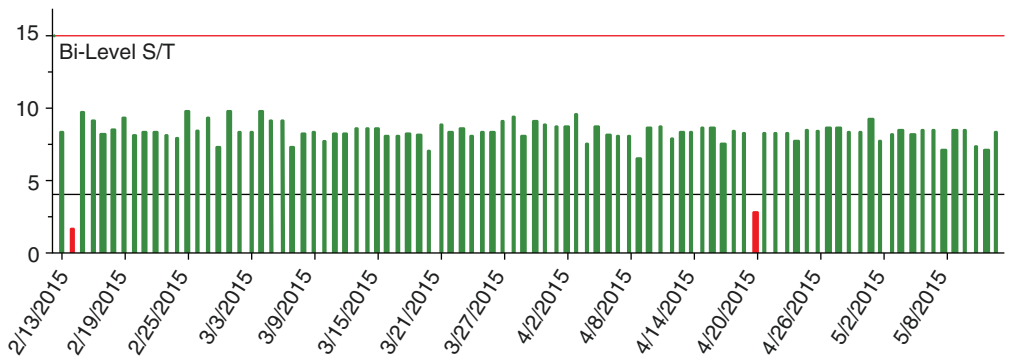

Fig. 14.3 PAP compliance card download on a previously noncompliant child with Down syndrome following behavioral therapy showing that the child used his PAP machine on all days, with an average daily use of more than 8 h

Weight loss is an important aspect of the management of obstructive sleep apnea in obese children. Thyroid function should be checked and hypothyroidism should be treated if present. Symptoms related to gastroesophageal reflux, or reactive airway disease also require aggressive management. The use of intranasal steroids is an option for those with mild OSA who have contraindications to surgery and in those with mild residual OSA following adenotonsillectomy [33].

Summary

In summary, children with DS are higher risk for both behavioral and physiologic sleep problems. Parents may not routinely bring these sleep disturbances to attention with the belief that these are inevitable consequences of the syndrome. Management of these sleep disorders impacts the child's health as well as overall functioning of the family.

Clinical Pearls

- Children with Down syndrome are at higher risk for sleep-disordered breathing (SDB).
- Both respiratory and non-respiratory sleep disorders are more common in children with Down syndrome compared to typically developing children.
- Children with Down syndrome should be screened for sleep disorders during each well-child visit beginning in infancy.
- Obstructive sleep apnea in children with Down syndrome is less often cured by adenotonsillectomy than in typically developing children.
- Children with evidence of sleep disturbance/fragmentation without SDB often benefit from both behavioral and medical therapies that promote sleep consolidation.

Future Directions

An initial sleep study to screen for sleep-disordered breathing is recommended starting at age of 4 years for children with DS who are not symptomatic. For children under 4 years, it is reasonable to screen based on presence of symptoms, risk factors, or other comorbidities. The next frontier may be adults with DS over 21 years of age and guidelines for rescreening based on risk factors.

Research is also needed to establish whether children with DS exhibit improvement in behavior or neurocognitive functioning following treatment for OSA. We believe this is true for some symptoms, but not clearly demonstrated as of yet. Further, type of treatment presents another variable: surgical treatment vs. CPAP vs. medication, to address issues with sleep consolidation and potentially daytime behavior targets. Hypoglossal nerve stimulation, an implantable medical device used in select populations as an alternative to CPAP for treatment of OSA, is starting at this writing in clinical trials for people with DS and OSA also. Studies using airway management are needed. Our clinical experience is that the behaviors most likely to improve are fatigue, mood, irritability, oppositional resistance, impulsivity-hyperactivity, and some disruptive behaviors. In terms of neurocognitive domains (executive function), improvement in attention, organization, and initiative are most likely. The behaviors that are less likely to improve include symptoms of autism spectrum disorder, self-injurious behaviors, obsessive-compulsive disorder, stereotypy, and severe ADHD or disruptive behaviors. More studies are needed to address pharmacologic management of sleep in this population, as most of the above behaviors can show a nice response to a well-chosen medication.

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Spina Bifida and Chiari Malformations

15

Adetayo Adeleye, Aaron Hockley, and Valerie Kirk

Abbreviations

AHI	Apnea-hypopnea index
CM	Chiari malformation
CPAP	Continuous positive airway pressure
CSF	Cerebral spinal fluid
MMC	Myelomeningocele
OSA	Obstructive sleep apnea
PSG	Polysomnography
SRBD	Sleep-related breathing disorder

What Is Spina Bifida?

Key Points

1. Patients with spina bifida are at risk for sleep-related breathing disorders from early infancy through adulthood.
2. Breathing abnormalities in these patients are varied – polysomnography is often needed to establish an accurate diagnosis.
3. Patients with spina bifida are also at risk for sudden death during sleep.

Spina bifida, more accurately referred to as myelomeningocele (MMC), is a specific type of neural tube defect. This broader term typically encompasses the milder forms of caudal neuropore failure also, such as spina bifida occulta and meningocele. In MMC, the spinal cord (myelon), its covering (meninges), and the vertebral arches develop abnormally early in gestation [1, 2]. The neural tube is the embryonic structure that later gives rise to the brain and spinal cord, together forming the central nervous system. The shaping, folding, and midline fusion of the neural tissue of the brain and spinal cord occur early in gestation through a process called primary neurulation [3]. MMC is a defect in this process that results from failure of fusion in the caudal region of the neural tube during the 4th week of embryogenesis, resulting in defective closure of the neural tube in the vertebral column. The visually evident result is a "herniation" in the back of the infant through which the spinal cord and/or meninges protrude. Similar defects of fusion in the cranial region of the neural tube result in anencephaly. In humans, anencephaly and MMC are the most commonly occurring neural tube defects [2]. The severity of clinical symptoms associated with MMC is determined by the particular nerves involved (i.e., the level of the defect) and the degree of damage and/or associated maldevelopment. Children with MMC have neurologic deficits at the level of the defect and below, resulting in varying degrees of muscle paralysis, bladder and bowel problems, loss of skin sensation, and spine and limb deformities [1]. Clinically, they are often classified according to the level of their spinal defect.

A Chiari malformation (CM) is present in 95% of patients with MMC [4]. This developmental brain abnormality consists of varying degrees of hindbrain herniation through the foramen magnum at the base of the skull. The more severe Type II CM is very often present with MMC and consists of a caudal descent of the cerebellar vermis, fourth ventricle, and the lower brain stem [5]. A brief discussion about what is currently known about isolated Type I CM, which is milder, and SRBD is included at the end of this chapter.

Normal Control of Breathing

Three basic elements are important for the normal control of breathing:

A. Adeleye (✉) · V. Kirk
Department of Paediatrics, Alberta Children's Hospital/University of Calgary, Calgary, AB, Canada
e-mail: adetayo.adeleye@albertahealthservices.ca

A. Hockley
Clinical Neurosciences, University of Calgary, Calgary, AB, Canada

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1. Sensors (chemoreceptors)
2. A central controller (brain)
3. Effectors (respiratory muscles)

Chemoreceptors respond to changes in the chemical composition of the blood and/or cerebral spinal fluid. Central chemoreceptors are situated in the brain and respond primarily to changes in hydrogen ion concentration. When the blood PCO_2 rises, CO_2 diffuses into the CSF from the cerebral blood vessels and is converted to carbonic acid. Carbonic acid releases hydrogen ions which stimulate these receptors resulting in increased ventilation and a subsequent reduction in the PCO_2. Peripheral chemoreceptors are located in the carotid bodies of the respiratory system and heart and respond primarily to changes in oxygen, carbon dioxide, and hydrogen ion concentrations in the blood. These sensors gather information and feed it to the brain, or central controller, whose function is located primarily in the pons, medulla, and parts of the cerebral cortex. These centers coordinate the information and in turn send impulses to the respiratory muscles which facilitate ventilation. Together respiration is controlled via a negative feedback system [6].

Risk Factors for Sleep-Related Breathing Disorders

Type II CM is usually associated with progressive hydrocephalus as well as a variety of neurologic abnormalities due to central and peripheral nervous system dysfunction. These abnormalities potentially have profound effects on respiratory functions, causing derangements in control of breathing and in upper airway muscle function. As the brain stem controls the central respiratory pattern, upper airway musculature, and arousal mechanisms, patients with Type II CM may have any or all of the following: central apnea, central hypoventilation, obstructive apnea, and/or deficits in arousal to asphyxia [7–9]. Other specific symptom complexes that are present in patients with CM can include isolated vocal cord paralysis (usually secondary to increased intracranial pressure); vocal cord paralysis with other cranial nerve deficits, such as swallowing problems; and lastly, stridor or dysphagia associated with apnea and/or cyanosis [4].

Additional factors known to increase risk for SRBD and obstructive sleep apnea (OSA) include adenotonsillar hypertrophy, obesity, scoliosis, aspiration, neuromuscular abnormalities, restrictive and/or obstructive lung disease, and craniofacial abnormalities [10]. Incidentally, patients with MMC can develop several of these risk factors as a result of their underlying condition. MMC may result in leg weakness and paralysis, sensory loss, bowel and bladder dysfunction, and orthopedic abnormalities (e.g., clubfoot, contractures, hip dislocation, scoliosis, and kyphosis) [3]. As a consequence, these children may be non-ambulatory, become deconditioned, develop scoliosis, and have increased weight gain. Patients with MMC may also have restrictive pulmonary disease as a result of kyphoscoliosis and/or diminished respiratory muscle strength due to lower motor neuron lesions.

Abnormalities in Control of Breathing in MMC

Infants with MMC often have abnormal ventilatory patterns. Davidson Ward et al. studied a group of 18 asymptomatic infants with MMC during sleep. At the time of study, the infants had a mean age of 9 months and no clinically apparent apnea or hypoventilation. Recordings of their ventilatory patterns showed that study infants had longer episodes of apnea than healthy control infants [11]. In another publication, these investigators reported on the hypoxic and hypercapnic arousal responses of a group of seven symptomatic infants with MMC and CM who had already undergone tracheostomy and posterior fossa decompression [12]. Eleven studies to assess hypoxic arousal were performed in seven infants with MMC and hypoxic arousals occurred in only two of those studies (18.2%), whereas eight of the nine healthy control infants (89%) aroused to hypoxia. Arousal to hypercapnia occurred in only three of eight studies completed on six infants with MMC (37.5%). In comparison, all of the seven healthy infants studied aroused to hypercapnia. They concluded that infants with MMC, CM, and apnea or hypoventilation have arousal deficits to respiratory stimuli. These abnormalities in ventilatory control were confirmed in a later study of 26 infants with MMC by Petersen et al. [4].

A number of subsequent studies have shown that children with MMC have abnormal ventilatory responses to increased CO_2 or decreased oxygen levels. Swaminathan and colleagues went on to show that the ventilatory abnormalities noted in infancy persisted into later life. They studied 14 patients with MMC and CM at a mean age of 18. They showed that hypercapnic ventilatory responses were significantly diminished in the group with MMC compared with control values. They speculated that the CM interferes with central chemosensitivity (hypercapnic ventilatory response) and central integration of chemoreceptor output [13]. More recently, peripheral chemoreceptor function in older children with MMC was noted to be abnormal in a report by Gozal et al. [14].

Together these studies suggest fundamental abnormalities in the way central and peripheral chemoreceptors respond to and integrate information about breathing. This is not surprising, as the chemoreceptors are located in centers of the brain that may be impacted by the traction and compression that occurs on the brain stem in patients with MMC and CM.

Sleep-Related Breathing Disorders and Myelomeningocele

It is now well established that children with MMC often have SRBD. In response to a clinical observation that asymptomatic children with MMC often had severely abnormal polysomnograms (PSG), Robert Brouillette, the medical director of the Montreal Children's Hospital Sleep Laboratory, designed a series of methodical clinical projects in the late 1990s. Brouillette et al. were the first group to study the prevalence and type of SRBD in this population. Their first paper in the series, published by Waters et al. [15] in 1998, described the overall prevalence of SRBD in a spina bifida specialty clinic population. Questionnaire data was obtained on 98% of the clinic population, and PSG was performed on 76% of the 109 children in the clinic. Fewer than half of these children (37%) had normal PSG findings, and 20% had moderate to severe SRBD. The most common type of SRBD in this group was central sleep apnea (12/17). The remainder had a more typical OSA pattern, and fewer still had hypoventilation only.

In the Montreal cohort, there was a higher risk of SRBD among those children who had spina bifida that was associated with additional risk factors. The children with a higher-level neurological defect (L2 or above), scoliosis, and restrictive lung disease were among those with the highest risk of SRBD, as well as those who were non-ambulatory [15]. These risk factors are intertwined: there is a high risk of developing a spinal curvature for non-ambulatory children, and severe scoliosis can contribute to restrictive lung disease in the absence of other risk factors [16]. The combination of neurological, motor, and structural abnormalities of the spine in children is often associated with a high-level MMC defect and therefore confers the highest risk situation for SRBD in this population. An additional, seemingly unrelated risk factor for SRBD in the clinic population studied was a prior posterior fossa decompression surgery (odds ratio 3.5) [15]. This finding may reflect a selection bias, as children with MMC who undergo decompression are more likely to have severe symptoms in general.

These findings from the Montreal group described above raised the next clinical question – if SRBD was so frequent in children with MMC, was it being identified and treated? To answer this question, MMC clinic directors across North America were asked to complete a survey [17]. Over 200 surveys were distributed to clinic directors in both Canada and the United States. Eighty-six clinic directors (41%) completed the survey, representing data on 13,349 children with MMC. Although 67% of the sites confirmed they had access to diagnostic testing for SRBD, only 7.5% of these children had undergone any form of cardiorespiratory or sleep-related diagnostic testing. Overall, 418 (3.1%) of children enrolled in one of these 86 clinics had been identified as having moderate to severe SRBD. Again, central apnea was the most frequently reported type of SRBD (36.1%), followed by obstructive sleep apnea in 28% and hypoventilation in 7.2%. Mixed central and obstructive abnormalities on PSG were reported in 28.7% [17].

Clinic directors were also asked about causes of death in their clinic population as part of the survey. Three hundred eighty deaths over the previous 10 years were confirmed. The leading reported causes of death in this group were sleep-related and responsible for 21.5% of all deaths: SRBD (12.8%) and sudden unexplained death during sleep (8.9%) [17]. Given the high prevalence rate of SRBD in children with MMC and the significant mortality related to it, Brouillette's group sought to prove that treatment was available and effective for children with both MMC and SRBD (Fig. 15.1).

A multicenter, cross-sectional study design was used to collect data from seven pediatric sleep centers across North America and Australia [18]. Each center reviewed the health records of children with MMC and known SRBD who had been identified by PSG in their laboratory. Data was collected on a total of 73 children with both MMC and moderate to severe SRBD. The risk factors identified by Waters et al. were included in the data collection: 60% had lesions above L3, 75% were non-ambulatory, 72% of those with prior pulmonary function testing showed evidence of moderate to severe restrictive lung disease, and 49% had undergone prior posterior fossa decompression. As with both previous study populations, OSA and central apnea were the most frequently identified abnormalities on PSG (30/73 and 25/73, respectively). Hypoventilation was identified in 12 of the 73 subjects.

Among children with OSA and MMC, roughly a third had undergone adenotonsillectomy, the first-line therapy for typically developing children with OSA. It was effective in only 29% of this group. Continuous positive airway pressure (CPAP) therapy was successfully used in 85% of these children with obstructive sleep apnea.

Children with central sleep apnea as the primary SRBD diagnosis underwent a variety of treatments: methylxanthines (treatment was deemed successful in two of nine patients [22%]), supplemental oxygen therapy (effective in preventing hypoxemia in three of six patients without additional treatment), and positive airway pressure (successful in all seven patients for whom it was prescribed). Six children in this group had primary hypoventilation during sleep, and all were treated with supplemental oxygen at night. Half of these children continued to have significant hypercarbia which was treated with nasal positive airway pressure. Posterior fossa decompression surgery was the primary or secondary treatment for eight children with obstructive sleep apnea and another four with central apnea. Only 25% in each group showed any improvement in their breathing during sleep. The rate of significant complications postoperatively was high (25%), raising a number of questions that the study design could not address.

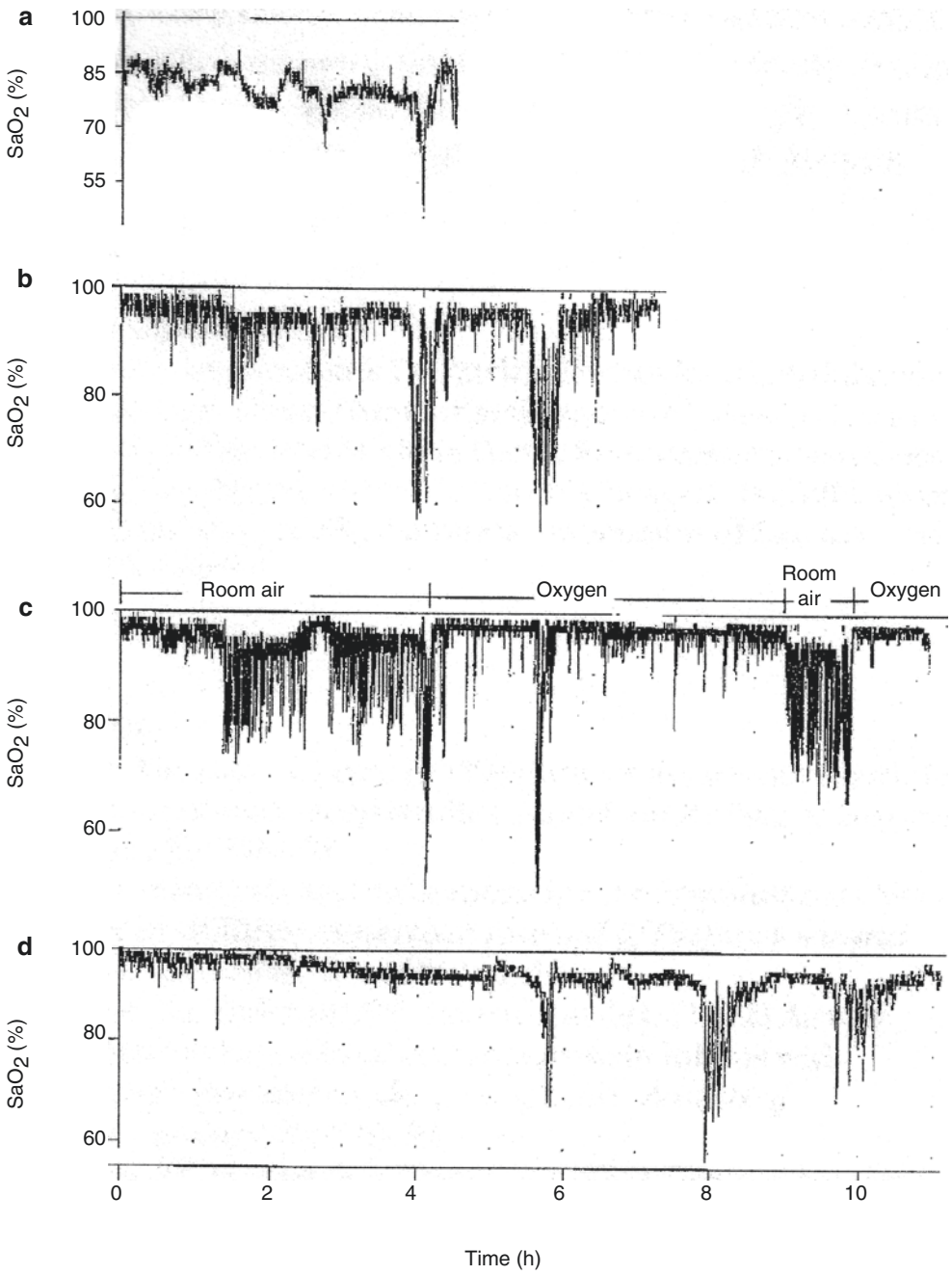


Fig. 15.1 Overnight oximetry tracing in four children in whom SRBD was not suspected until screening was done. (**a**) 17-year-old girl with MMC at L2, marked scoliosis, restrictive lung disease – PSG showed low baseline saturation with further desaturation in REM sleep, (**b**) 3-year-old girl with repaired left diaphragmatic hernia, MMC at T4-PSG showed REM sleep-related central apnea with severe desaturations, (**c**) 7-year-old girl with MMC at T10-PSG showed central apnea, and (**d**) 9-year-old boy with MMC at T12-PSG showed severe central apnea (Kirk 1999)

This series of clinical studies from the Montreal Children's Hospital established the following specifics about SRBD in children with MMC:

1. Moderate to severe SRBD is frequent in children with MMC [15].
2. Diagnostic testing was not routinely performed in this high-risk group [17].
3. Death related to SRBD is common in this population [17].
4. Treatment for SRBD is effective in children with MMC [18].

Little additional literature has been published with respect to SRBD in this population. Alsaadi et al. reported PSG findings on 16 children with MMC. The most frequent form of SRBD was central apnea, followed closely by OSA. Sixty-eight percent had moderate to severe SRBD; however, this was a referred population and not a clinic cross-sectional prevalence study [19]. A high prevalence rate of SRBD in children with MMC has also been confirmed by Gozal et al. in a separate report [10]. This paper compared peripheral chemoreceptor function in ten older children with MMC to

age and sex matched controls. As part of the study design, all underwent PSG and half were found to have significant SRBD [14]. More recently, Patel et al. described the PSG findings in a large cohort of children and young adults. The PSG testing and scoring criteria differed from the pediatric studies above, so their findings with respect to type of SRBD are not directly comparable, but they did report a high prevalence of SRBD in this population in keeping with previous reports. In addition, a subgroup analysis of nine subjects who had PSG performed both before and after decompression surgery was done. All PSG indices indicative of severity showed a trend toward improvement after the surgery, though none of these met statistical significance. Perioperative course and complications were not reported [20]. Table 15.1 summarizes available data on SRBD in MMC.

Marcus et al. [21] comprehensively reviewed the cognitive and behavioral implications of untreated SRBD. In addition to creating risk factors for SRBD, the brain and spinal cord abnormalities associated with MMC also affect learning, typically displayed through problems with perceptual-motor skills, numerical reasoning, attention, memory, and organization; nonverbal learning disability; attention-deficit/ hyperactivity disorder; and problems with executive function [1, 3].

Currently, the only published report on electroencephalographic findings during sleep in children with MMC is a case report. Battaglia et al. described two children with MMC, aged 5 and 7 years, who had a spike-wave pattern on electroencephalographic (EEG) monitoring noted during slow-wave sleep. Given the potential impact of spike-waves on cognitive development in children, this short paper should raise our awareness and attention to the non-sleep staging characteristics of the EEG data obtained during PSG in children with MMC [22].

Table 15.1 SRBD frequency and type in children with MMC

	SRBD (%)	CA (%)	OSA (%)	Mixed (%)	Hypoventilation
Waters 1998	52 (62)	47 (57)	18 (22)	52 (62)	0
N = 83					
Kirk 1999[a]	418 (100)	150 (36)	117 (28)	121 (29)	29 (7)
N = 418					
Kirk 2000[a]	73 (100)	25 (34)	30 (41)	0	12 (16)
N = 73					
Gozal 1995	5 (50)[b]	4	1	1	0
N = 10[b]					
Alsaadi 2012	11(68)	11	0	0	0
N = 16					
Patel 2015	42(81)	29	71	Not scored	Not measured
N = 52					

Both central apnea and obstructive apnea have a high prevalence in children with MMC. Detailed PSG data was not available in all reports cited

[a]Selected population of children with MMC and SRBD

[b]Percent of referred population with moderate to severe SRBD

Sudden Death in MMC

Despite evidence showing improved overall survival of infants with MMC into adulthood [23], these infants and children continue to be at risk for sudden unexplained death. Jernigan and colleagues performed a retrospective analysis of 106 subjects with MMC, aged 19–30 years. Six of these subjects (all young women) experienced sudden death (5.6%). As all six were found unresponsive in bed with no history of antecedent illness, the deaths were presumed to be sleep-related. Using multivariate analysis, female sex, sleep apnea, and midbrain elongation ≥15 mm on magnetic resonance imaging were associated with a higher risk of sudden death. In addition, subjects with sudden death were more likely to have had sleep apnea and used CPAP. No PSG data was available on these subjects so information regarding type and severity of SRBD was not included in the report [24]. Chronic tonsillar herniation and hydrocephalus have also been associated with sudden death in adult patients with myelomeningocele [25, 26].

Type I Chiari Malformation and SRBD in Children

Key Points

1. Chiari 1 malformation is a risk factor for SRBD.
2. The associated SRBD can be central, obstructive, or both.
3. Preliminary reports suggest treatment with posterior fossa decompression can be effective for improving SRBD.

There is currently limited published data on the impact of Type I CM and SRBD in children. Type I CM differs from Type II: the cerebellar tonsils, not vermis, experience caudal descent, occasionally with an elongation of the fourth ventricle. There is no descent of the brain stem or fourth ventricle as seen in Type II CM [5] (Fig. 15.2 and Table 15.2).

Historically, most subjects with Type I CM have gone undiagnosed or have presented in adulthood with non-dermatomal occipital headache or neck pain that is aggravated by the Valsalva maneuver, exertion, cough, and/or postural changes. The hypothesized pathophysiology for the classic

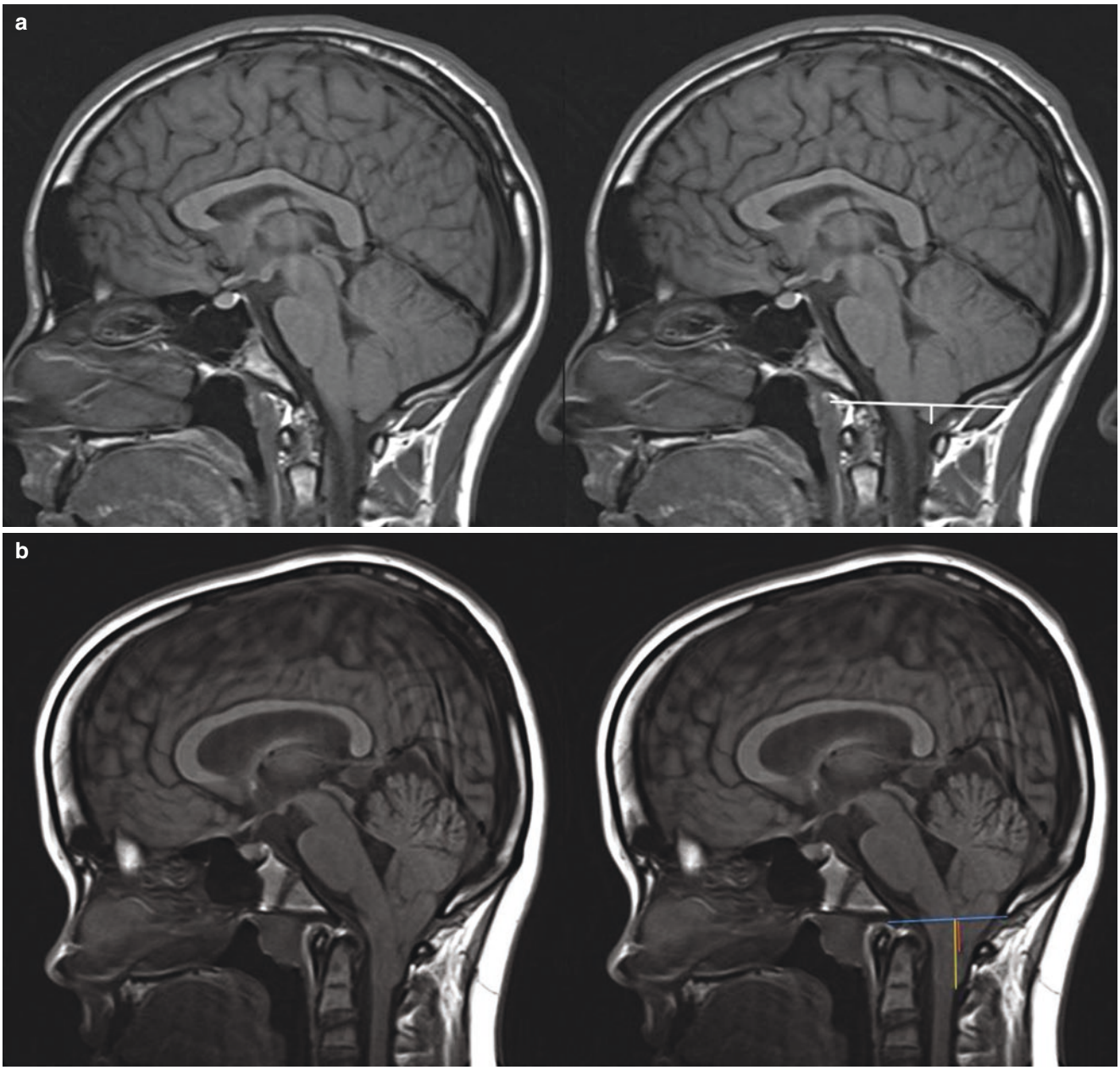


Fig. 15.2 MRI images of Chiari Type 1, Chiari Type 1.5, and Chiari Type II. (**a**) Left: Midsagittal T1 MRI showing cerebellar tonsil descent of 7 mm below the basion-opisthion line, consistent with Chiari 1 malformation. Right: How the measurement of tonsillar descent is performed. (**b**) Left: Chiari 1.5 malformation. Right: Demonstration of tonsillar (yellow) and obex (red) descent beneath the basion-opisthion line. (**c**) Left: Chiari 2 malformation – Inferior displacement of the medulla oblongata into the spinal canal with kinking of the upper cervical spinal cord (yellow arrow), herniation of the diminutive tonsils deep into the cervical spinal canal (red arrow), and associated syrinx (green arrow). Right: Associated hydrocephalus

Valsalva or exertional occipitocervical headache is that of impaired flow of cerebrospinal fluid (CSF) [27]. During exercise there is increased cerebral blood flow resulting from a higher partial pressure of carbon dioxide in arterial blood (PaCO2), resulting in downward pressure through the foramen magnum, thereby worsening the foramen magnum crowding and impairing CSF flow. Similarly, during a Valsalva maneuver, venous drainage is impaired and could result in increased foramen magnum crowding and resultant headache. As young children are less likely to complain or articulate these symptoms, the diagnosis has been made less frequently in this age group. The natural history of asymptomatic Type I CM is unknown [5]. This holds particularly true in pediatric patients in whom tonsillar descent can occasionally diminish over time – and even disappear – as the posterior fossa expands during growth. A group of 22 chil-

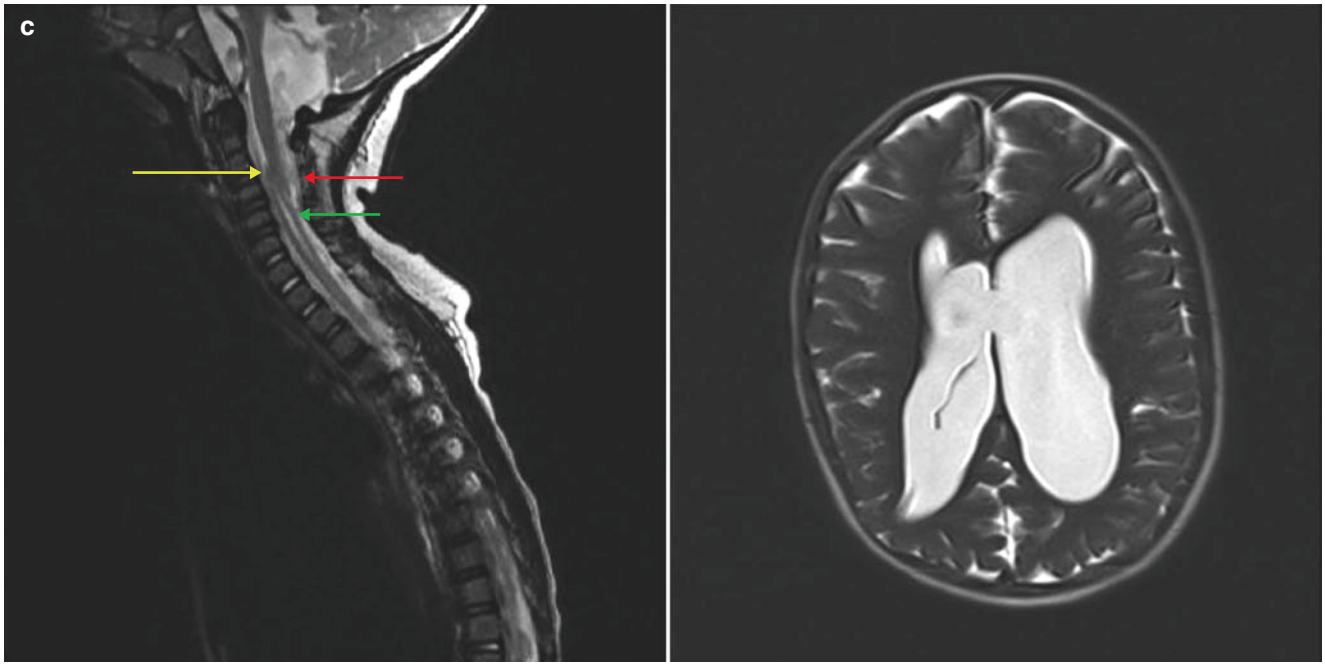


Fig. 15.2 (continued)

Table 15.2 The common Chiari malformations

Chiari type	Definition	Associated features	Common symptoms
1	Cerebellar tonsil herniation >5 mm inferior to the foramen magnum (FM)	Syringomyelia	Occipitocervical headache
		No associated brain stem herniation or other CNS anomalies	Pain in the back and shoulders
			Motor and sensory symptoms
1.5	Cerebellar tonsil herniation and herniation of the brain stem through the foramen magnum (defined as obex beneath the FM) [35]	Similar to Chiari 1, less well defined as a group	Poorly defined, similar to Chiari 1 but potentially more severe
		Potentially more severe and refractory symptoms	Possible SRBD
2	Herniation of cerebellar vermis, cerebellar tonsils, brainstem, and fourth ventricle	Myelomeningocele	Brain stem symptoms
		Hydrocephalus	Myelopathy
		Syringomyelia	SRBD
		Other brain anomalies	

The Chiari malformations differ with respect to what neural tissue is displaced, or herniated, through the foramen magnum as well as their associated features and symptoms (Data from [35, 36])

dren without symptoms (n = 11) or with intermittent mild symptoms (n = 11) were followed for a mean of 5.9 years. Seventeen (77.3%) either had their symptoms improve or remained asymptomatic. The remaining five (22.7%) had clinical worsening, three of whose symptoms were severe enough to require operative decompression [28].

From a control of breathing and SRBD point of view, one would anticipate some of the same abnormalities in pediatric patients, but little has been reported in children. Adult-based literature suggests there is a significant risk for SRBD; however, these studies have included populations with both Type I and Type II CM defects [29–31]. Narang et al. recently reported on a cohort of 68 children with Type I CM who were referred for PSG over a 6-year period. Almost all (66/68) had respiratory symptoms at the time of PSG (88% with mouth breathing, 63% with snoring), and 85% of them had at least one neurological or developmental finding (50% with headache, 21% with gait or balance abnormalities). In this symptomatic group of children, 49% met criteria for SRBD. Their findings were very similar to those reported by Waters et al. for children with MMC. Central apnea (18%) and OSA (18%) were the most frequent PSG findings, followed by hypoventilation (9%). Moderate to severe SRBD (apnea-hypopnea index [AHI] ≥ 5 respiratory events/hour)

was present in 29% of this cohort [32]. Similarly, Losurdo enrolled 53 consecutive pediatric patients with Type I CM and performed PSG which revealed SRBD in 13 (24%) of these patients. Significant risk factors for SRBD included the presence of syringomyelia, hydrocephalus, and/or neurologic symptoms. Interestingly, the development of SRBD was independent of the size of the tonsil herniation [33]. The data for adults is sparser, but a 2006 study enrolled 16 consecutive patients with Type I CM and syringomyelia for overnight PSG and found SRBD in 75%, which was predominantly central; notably, postoperative PSG in six patients showed a significant improvement in the central apnea index [34] (Table 15.3).

Our own lab was sensitized to the relationship between SRBD and Type I CM when a 10-year-old boy with longstanding severe OSA was noted to have a new finding of frequent central apneas on a follow-up PSG. He had been treated with CPAP for a number of years. Because of the finding of central apnea, an MRI study was performed confirming the presence of his Type I CM. His SRBD resolved following a decompression procedure. Collaboration with our neurosurgical colleagues has resulted in a pilot project looking at PSG findings in children with Type I CM at baseline and at specific points in time post-decompression surgery. Early results from our group have shown a significant decrease in the AHI in patients with significant SRBD and Type I CM who have undergone posterior fossa decompression and duraplasty surgery (expansion of the posterior fossa dural compartment by sewing in a synthetic patch; unpublished data). Clearly, the level of suspicion for these conditions and communication and collaboration with neurosurgery is imperative for treatment both of children with MMC and those with isolated Chiari Type I defects.

Future Directions

Although the characteristics of SRBD in children with MMC are fairly well characterized, we are only beginning to clinically appreciate the potential impact of more subtle brain abnormalities (Chiari 1, 1.5) on breathing in children. Although some preliminary reports suggest a high prevalence of SRBD in children with Chiari 1 defects, these have been referred (symptomatic) populations. A number of unanswered questions remain:

1. What is the prevalence of significant SRBD in asymptomatic children with Chiari 1 and 1.5 malformations?
2. What is the predominant form of SRBD in this population?
3. What is the role of posterior fossa decompression and duraplasty in this group?

Table 15.3 SRBD and Chiari 1 malformations

	SRBD (%)	CA (%)	OSA (%)	Hypoventilation (%)
Narang 2015	33 (49)	12 (18)	16 (24)	6 (9)
$N = 68$				
Losurdo 2013	13 (24)	5 (6)	6 (11)	2 (4)
$N = 53$				
Gagnadoux 2006[a]	14 (75)	7 (50)	7 (50)	No data
$N = 16$				

Preliminary findings suggest that the prevalence and distribution of type of SRDB in children with Chiari 1 malformations may be similar to that seen in children with MMC and Chiari II malformations

[a]Adult subjects

Case Vignette

The following case highlights some of the challenges encountered in regard to SRBD in this patient population. Melinda was born at 31 weeks gestational age due to preterm labor. The pregnancy was complicated by antenatal diagnosis of MMC which was surgically repaired in utero at 24 weeks gestational age. At birth, she was noted to have associated Type 2 CM, microcephaly, congenital heart disease (atrial septal defect and ventricular septal defect), and hypertension. She was admitted to the neonatal intensive care unit and had a relatively unremarkable course. Melinda was first referred to the respiratory service at the time of her discharge (10 weeks of age) for ongoing management. At this time, her overnight oximetry in room air showed a low baseline mean oxygen saturation (around 90%) with intermittent desaturations (oxygen nadir of 60%). She was treated with supplemental oxygen and caffeine, underwent frequent overnight oximetry monitoring and clinical assessments, and was discharged home.

Concurrent with discharge, Melinda was referred to the sleep clinic for concerns of possible OSA given her history of CM. She was noted to be clinically stable with no symptoms of SRBD. The plan was made to proceed with PSG, but closer to 1 year of age. An overnight oximetry study done just prior to her PSG is shown below (Fig. 15.3). At 11 months of age, mean oxygen saturation on room air was 97%. There continued to be clusters of desaturations during sleep (minimum recorded saturation of 85%).

PSG studies were performed when she was 14 and 21 months of age, respectively (Table 15.4). During the first PSG study, the AHI was in the severe range for age. Events clustered predominantly during REM sleep and were primarily obstructive in nature (Fig. 15.4).

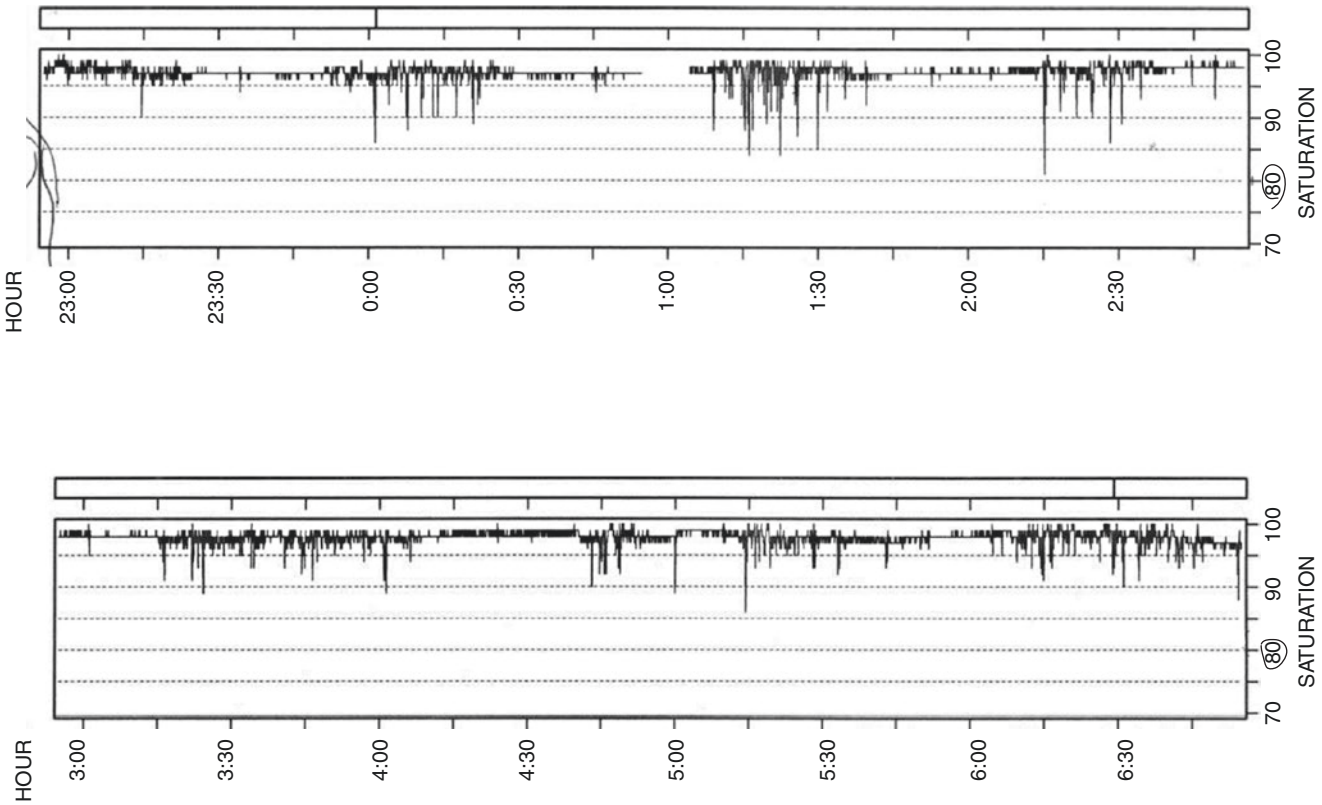


Fig. 15.3 Graphic overnight oximetry recordings. Regularly occurring clusters of desaturation are observed through the night. This pattern is characteristic for REM-related SRBD

Table 15.4 Illustrative case – PSG diagnostic analysis data

PSG variables	1st PSG	2nd PSG
Central apneas	5/1.1	5/1.3
Count/index (events/hour)		
Obstructive apneas	13/2.8	0/0
Count/index (events/hour)		
Mixed apneas	21/4.5	6/1.6
Count/index (events/hour)		
Hypopneas	22/4.7	9/2.3
Count/index (events/hour)		
Apnea + hypopnea (AHI)	13.1	5.2
Total sleep time (TST)	279 min	230
Sleep efficiency	80%	47%
Mean oxygen saturation (maximum/minimum)	94.3%	93.5%
	(98%/85%)	(98.8%/85.4%)
Percentage of TST with oxygen saturation <90%	0.5%	0.4%
Mean $ETC0_2$	37 mmHg	39.1 mmHg
(maximum / minimum)	(40 mmHg/35 mmHg)	(41 mmHg/38 mmHg)
Mean $TCPC0_2$	37 mmHg	37.4 mmHg
(maximum/minimum)	(40 mmHg/35 mmHg)	(41 mmHg/35.1 mmHg)
Percentage of TST CO_2 >50 mmHg for $ETC0_2$ and $TCPC0_2$	0% and 0%	0% and 0%

There was a significant improvement in respiratory events, total sleep time, and measures of gas exchange between the first and second PSG – both done in the 2nd year of life

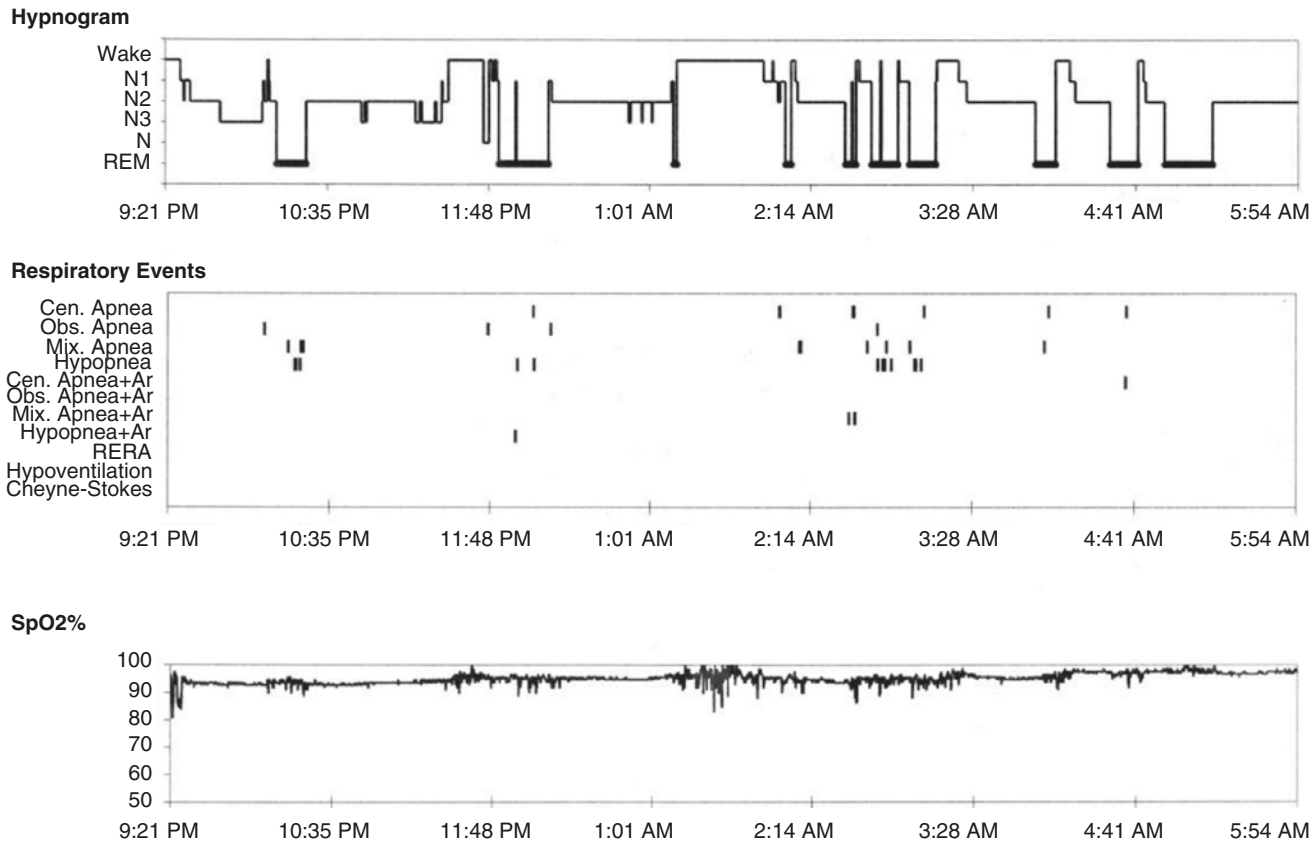
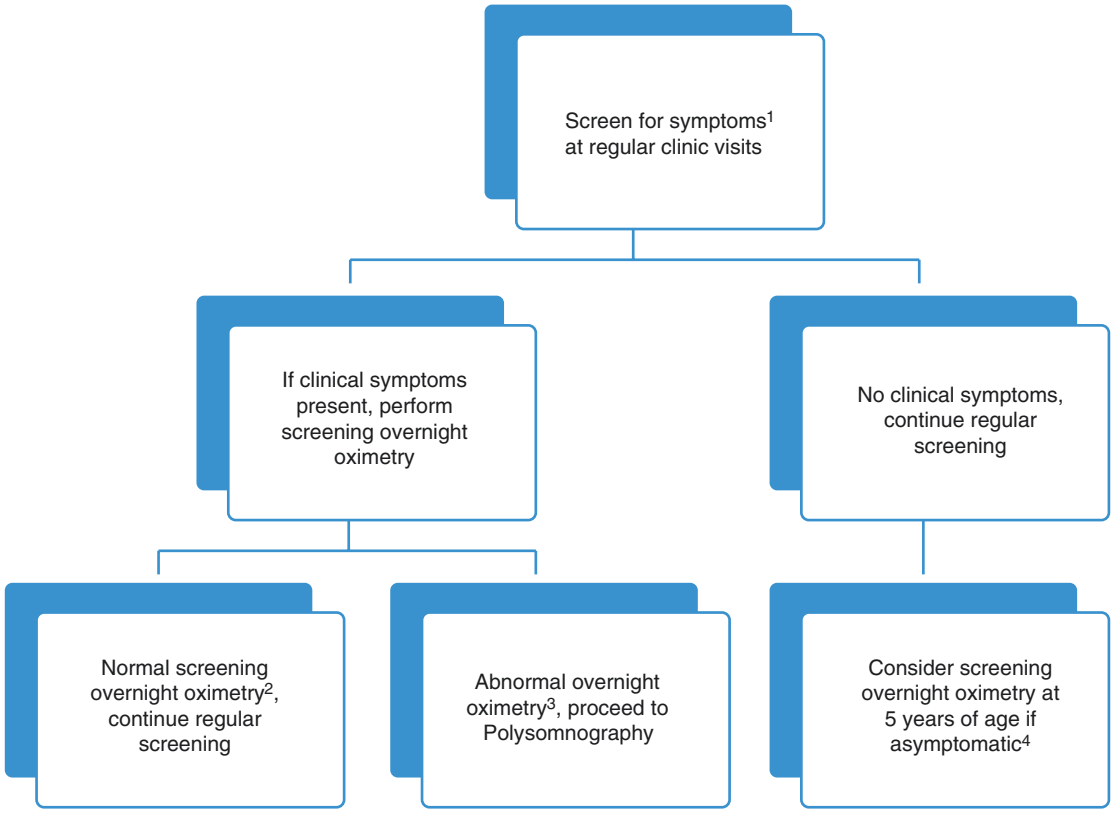


Fig. 15.4 Graphic summary of initial PSG data. Sleep architecture, distribution of respiratory events, and oxygen saturation trending during the first PSG recording graphically illustrate the relationship between sleep stage and respiratory events

There was no evidence of nocturnal hypoventilation or hypoxemia on the diagnostic study. A treatment study with CPAP was challenging due to mouth leaks around the mask and subsequent inability to optimize treatment pressures. Ongoing oxygen supplementation was recommended on a temporary basis, pending a repeat PSG. An upper airway assessment did not identify any surgical options. Findings of the follow-up PSG study 7 months later are shown in Table 15.4. Of most significance, the overall AHI had decreased to the mild to moderate range for age. Given her improvement and the difficulties encountered in mask fitting, no treatment was attempted on the follow-up study. Gas exchange remained relatively well preserved. A decision was made by her sleep physician to follow her progress clinically and repeat another PSG in a year's time, highlighting the importance of ongoing regular surveillance for sleep symptoms.

Based on our experience, we propose a schematic screening algorithm for SRBD that may be used in children with MMC (Fig. 15.5).



1. Enquire about abnormal breathing pattern; snoring, noisy or irregular breathing, cyanosis during either sleep or wake, unexplained pulmonary hypertension, and unexplanied poor growth.
2. Ensure baseline oxygen saturation is > 94 to 95%, with no clusters of desaturations to suggest REM-related breathing disorder or obstructive sleep apnea.
3. Oximetry does not meet criteria outlined above.
4. Symptoms to consider at an older age would include snoring, unexplained fatigue, frequent night awakenings, and morning headaches. The development and/or worsening of the following conditions may also increase the risk for SRBD: obesity, ambulatory status, scoliosis, seizure disorders, and hydrocephalus.

Fig. 15.5 Suggested schematic screening algorithm for SRBD in children with MMC. Suggested clinical approach to children with MMC with limited access to PSG. If symptoms and clinical suspicion are present and overnight oximetry does not reveal abnormalities consistent with SRBD, full overnight polysomnogram is indicated

Clinical Pearls

1. Sleep-related breathing disorder (SRBD) can be present in the absence of parent-reported symptoms.
2. Regular screening by history for SRBD is important; intermittent objective assessment is also recommended.
3. Clusters of desaturations on overnight oximetry are a sensitive and specific indicator of the presence of REM-related SRBD.

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Prader-Willi Syndrome

16

Barbara Y. Whitman and Mary E. Cataletto

Case Vignette

J.R. is a 12-year-old boy with Prader-Willi syndrome who has been followed in a primary care practice. He is referred to you as his developmental pediatrician for evaluation because of inattentiveness, short temper, difficulty following directions, and falling asleep in school. His parents report that he has always been difficult to manage and is "prone to temper tantrums." Although he has never liked school nor done well academically, these problems seem to have escalated over the past school year. His teacher thinks he is sleeping to avoid schoolwork that is difficult for him. Since he reacts to being awakened with tantrums, she is recommending a transfer to a more restrictive school environment, a move his parents oppose.

Your assistant reports that J.R. was asleep in the waiting room and that other children were frightened by loud noises he made as he slept. You review his history and find that he has a long-standing history of snoring, snorting respirations during sleep with witnessed apneas. He is currently receiving growth hormone replacement therapy. Your examination reveals a narrow bifrontal diameter, a high-arched palate, mild micrognathia, dental malocclusion, and 3+ tonsils. His body mass index (BMI) is +3 standard deviations (SD) above the mean for age. The remainder of the examination is noncontributory.

B. Y. Whitman (✉)
Department of Pediatrics, Saint Louis University School of Medicine, St. Louis, MO, USA
e-mail: barbara.whitman@health.slu.edu

M. E. Cataletto
Clinical Pediatrics, Stony Brook University School of Medicine, Stony Brook, NY, USA

Pediatric Pulmonology and Sleep Medicine, NYU – Winthrop Hospital, Mineola, NY, USA

Introduction to Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is a complex neurogenetic disorder originally described in 1956 [1]. The incidence of PWS is estimated to be between 1/10,000 and 1/25,000 live births [2]. However, in infants with hypotonia 0–24 months of age (mean age 8 months), prevalence rates for Prader-Willi syndrome have been reported at 10.7% [3]. PWS results from a silencing of paternally contributed genes on chromosome 15 q11.2–q13. Silencing can result from a frank deletion of the critical region on the paternally contributed member of the pair of chromosomes, a maternal disomy (two copies of maternal chromosome 15, no paternal copy), or rarely, from an imprinting center mutation. This last situation involves a complex genetic mechanism in which a specific region of a chromosome must be "reset" with each generation. In the case of PWS, this reset does not occur in the PWS-specific region of chromosome 15, resulting in the disorder. The diagnosis of Prader-Willi syndrome is made by genetic evaluation. DNA methylation analysis is recommended as the first step in the genetic evaluation of the child with suspected PWS, followed by genetic determination of the causal molecular class, which is important for both genetic counseling and correlation of genotype-phenotype-related concerns [4].

Previously clinicians focused on the clinical phenotype and subsequent course of the disorder, which varies over time. Infancy and early childhood are characterized by infantile hypotonia, often accompanied by feeding difficulties and failure to thrive, an abnormal body composition including a markedly reduced muscle mass, facial and body dysmorphisms, hypogonadism, and developmental issues. Sleep-disordered breathing has been reported across the life span with central apneas occurring more frequently in infants [5, 6]. Between 2 and 3 years of age, significant changes in fat distribution, followed by increased appetite and food intake, emerge, resulting in morbid, and at times, life-threatening obesity [7]. These early concerns are followed by short stature and endocrinopathies. Cognitive

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impairments and characteristic learning difficulties become evident in early childhood, accompanied by emergent behavior difficulties that increase across time, with a particular escalation noted in early adolescence. Behavioral characteristics most often include emotional lability, temper tantrums, stubbornness, compulsivity, and difficulty handling change [8]. Finally, the majority of those affected have hypothalamic-pituitary abnormalities resulting in both growth and sex hormone deficiencies. Until recently, a markedly decreased life span was expected, primarily resulting from obesity-related complications. With improved management, the early introduction of growth hormone replacement therapy and heightened vigilance for, and early treatment of, sleep-disordered breathing, an improved life span, and quality of life, are now evident. Nonetheless, mortality rates in Prader-Willi syndrome, estimated at 3% per year across the age range [9], are still higher than in control individuals who also have an intellectual disability [10].

Case Vignette, Continued

Evaluation of Sleep

J.R.'s history of habitual snoring, witnessed apnea in sleep with associated hypersomnolence, his poor focus, and irritability presents the physician with a high index of suspicion for obstructive sleep apnea. Findings on physical examination support this concern with evidence of obesity, as well as a narrow oropharynx with high-arched palate and enlarged tonsils.

J.R. was referred to a pediatric sleep specialist at a specialty Prader-Willi center who conducted a nocturnal polysomnogram (NPSG or overnight sleep study). The in-laboratory, attended PSG is considered the gold standard for the evaluation of sleep-disordered breathing in children and includes video recording as well as noninvasive monitoring of multiple physiologic variables, including electroencephalography (EEG), pulse oximetry, oronasal airflow, chest and abdominal wall movements, and end-tidal carbon dioxide (CO_2). Specific scoring criteria are available for the interpretation of polysomnograms in children [11].

In this clinical case scenario, the sleep study showed evidence of moderate sleep-disordered breathing (obstructive type), which was noted to be worse during REM sleep. No significant brady- or tachydysrhythmias were reported.

Case Progression

J.R. was referred to a pediatric otolaryngologist (ear, nose, and throat, or ENT doctor) at the center. ENT specialists are important members of multidisciplinary teams at Prader-Willi centers, providing important insights about the anatomy of the upper airway and determining whether surgical options are appropriate for an individual child. J. R.'s examination revealed both enlarged tonsils and adenoids, and he was felt to be an acceptable surgical candidate for adenotonsillectomy, which is often first-line treatment for obstructive sleep apnea (OSA) in children. He underwent a preoperative cardiology evaluation for cor pulmonale, a potential complication of OSA, which was negative; J.R. begun on a weight management program comprised of both exercise and nutrition.

J.R. was admitted to the hospital where he had an uneventful perioperative course and was followed postoperatively by both his surgeon and sleep specialist. He continued to exhibit signs and symptoms of sleep-disordered breathing at his 6-week postoperative visit.

Postoperative assessment with a repeat polysomnogram to evaluate for the presence of residual OSA is indicated for high-risk children such as J.R. who demonstrated a significantly abnormal baseline polysomnogram, obesity, and craniofacial dysmorphology including a high-arched palate, micrognathia, and dental malocclusion, all of which decrease the size of the oropharynx [12]. Therefore, J. R. underwent a postoperative sleep study 8 weeks after his surgery. Despite a mild weight loss and the adenotonsillectomy, the repeat PSG continued to show moderate OSA although the apnea-hypopnea index (AHI) was mildly decreased compared to the preoperative study. A titration study with continuous positive airway pressure (CPAP) was performed with J.R., and an effective pressure was determined. He was started on home CPAP with good results.

CPAP is an effective therapeutic option for children who have objective evidence of OSA following adenotonsillectomy [13]. The CPAP system delivers air under pressure to an airway predisposed to collapse (a common finding in PWS due to upper airway hypotonia), in order to stent open the airway. It can interface with a nasal or full-face mask or nasal pillows. Masks and pillows come in different sizes and are fitted to the individual child. Compliance with using CPAP appliances can be problematic; behavioral interventions may help to improve adherence. It is often helpful to introduce the child to the system prior to starting therapy. Other intervention options, including rapid maxillary expansion, a specialized orthodontic procedure, may be appropriate for selected patients. Weight loss continues to be an important component in the therapeutic plan postoperatively until an appropriate weight is achieved and maintained.

Overview of Sleep-Disordered Breathing with a Focus on Children with Prader-Willi Syndrome

Early reports of Prader-Willi syndrome identified syndrome-specific sleep abnormalities in the form of reduced arousal responses and central apneas, particularly in infants [14], and excessive daytime sleepiness among those school-aged and older. Subsequently, abnormalities of sleep architecture and sleep-disordered breathing, including both oxygen desaturations and obstructive apneas, were identified [15, 16] (Table 16.1). An extensive literature documents an association between sleep disorders and cognitive difficulties, decreased schoolwork performance, and behavior/psychiatric difficulties in the general population. While similar associations are described in individuals with PWS, a sleep-related etiology for behavior challenges is often overlooked within the context of the known marked behavioral difficulties common to this group of children.

Obstructive Sleep Apnea

While children with Prader-Willi syndrome can display a number of complex sleep disorders, affected individuals are especially at risk for developing sleep-disordered breathing with a reported prevalence as high as 89% [17] compared to a 1.2% [18] prevalence reported in the general pediatric population. Obstructive sleep apnea (OSA) constitutes the most common presentation [19]. Predisposing factors for children with Prader-Willi syndrome include craniofacial configuration, hypotonia, increased viscosity of secretions, obesity, and growth hormone therapy [20]. Adenotonsillar size in relationship to a narrower oropharyngeal space is specifically a consideration [21]. Abnormal ventilatory responses to hypoxia and hypercarbia contribute to hypoventilation, augmenting the cardiorespiratory consequences regardless of the cause [22, 23]. While the etiology of the abnormal ventilatory responses remains unclear, the prevailing hypothesis is a dysfunction of the primary peripheral chemoreceptors and/or defective afferent pathways leading to the central controllers [24].

Adenotonsillar hypertrophy is the most common etiologic factor responsible for obstructive sleep apnea in the general pediatric population, whereas among those with Prader-Willi syndrome, the etiology of obstructive apnea is most likely multifactorial.

In the current clinical practice guideline on diagnosis and management of OSA authored by the American Academy of Pediatrics Subcommittee on Obstructive Sleep Apnea Syndrome, OSA is defined as "a disorder of breathing characterized by prolonged partial upper airway and/or intermittent complete obstruction (obstructive apnea) that disrupts normal ventilation during sleep and normal sleep patterns and is accompanied by symptoms or signs of OSA" [25].

The preferred testing for the diagnosis of obstructive sleep apnea in children is an attended, in-laboratory nocturnal PSG because it provides an objective and quantitative look at important cardiorespiratory variables during different sleep stages and in different sleep positions, as well as an assessment of sleep patterns. This is a noninvasive procedure and is generally well tolerated by children. During a nocturnal PSG, equipment leads (wires that are placed and temporarily glued to specific locations on the head and body that feed information back to a PSG machine) are placed to determine sleep stages, as well as to monitor nasal and oral airflow, heart rate, respiratory rate, pulse oximetry, and end-tidal CO_2. Overnight polysomnograms are then evaluated against standardized criteria for establishing the diagnosis and classifying the severity of obstructive sleep apnea [26] (Table 16.2). Shorter studies, such as nap studies (PSG monitoring for a time period equal to the duration of a daytime nap), are limited by their failure to provide an opportunity to evaluate all sleep stages; overnight studies using pulse oximetry only are limited by evaluating only one parameter and do not confirm the presence or absence of sleep. Furthermore, oximetry does not address ventilation. Therefore, neither is appropriate for diagnosis of sleep-disordered breathing.

Questionnaires may be helpful in screening children for sleep-disordered breathing; however, current evidence demonstrates that neither patient history nor questionnaires adequately correlate with PSG for the diagnosis of obstructive sleep apnea in children. A 2011 review by Spruyt and Gozal [27] of available pediatric sleep questionnaires found that only the Sleep Disorders Inventory for Students (SDIS) and the Sleep Disturbance Scale for Children (SDSC) fulfilled psychometric criteria. While these tools can complement other components of an assessment, PSG remains the gold standard for diagnosing the presence of OSA as well as for monitoring treatment response.

Table 16.1 Previously identified sleep abnormalities including sleep-disordered breathing in a Prader-Willi syndrome population

Abnormalities of sleep architecture	Decrease in sleep onset
	Decrease in REM latency
	Sleep onset REM periods
	Decrease in NREM sleep instability
	Longer durations of total sleep
Abnormalities of sleep-related breathing	Underarousal
	Abnormal respiratory rate when exposed to hypoxic stimuli
	Central apnea
	Obstructive apnea
	Oxygen desaturations
Other sleep abnormalities	Excessive daytime sleepiness
	Narcolepsy

Table 16.2 Diagnostic and severity classification of obstructive sleep apnea in children

Severity	Apnea index (events/h)	SpO_2 nadir %	$PaCO_2$ Peak (torr)	$ETCO_2$ > 50 Torr (%TST)	EEG arousals (events/h)
Mild	1–4	86–91	>53	10–24	>11
Moderate	5–10	76–85	>60	25–49	>11
Severe	10	≤75	>65	≥50	>11

Modified from Katz and Marcus [26] with permission from Elsevier
EEG electroencephalography, *$ETCO_2$* end-tidal carbon dioxide, *$PaCO_2$* partial pressure of carbon dioxide in arterial blood, *SpO_2* blood oxygen desaturation levels, *TST* total sleep time

Management

Adenotonsillectomy is widely recognized as the treatment of choice for obstructive sleep apnea in children with enlarged tonsils and adenoids who are medically acceptable candidates for surgery. While most children improve with this therapy, outcomes may be less favorable in obese children such as those with PWS [28]. In addition, children with a diagnosis of OSA undergoing adenotonsillectomy have a higher incidence of respiratory complications in the early post-op period as compared to children without OSA [29]. Pavone et al. reported that 4/5 patients with PWS undergoing adenotonsillectomy experienced at least one of the following postoperative complications: delayed emergence from anesthesia, hemorrhage and respiratory complications requiring reintubation, and/or need for supplemental oxygen [30]. In contrast, a later study did not identify significant postoperative complications in this population [31]. It should be kept in mind that both of these studies reported small patient cohorts. These differences may also reflect improvements in anesthesia and surgical management over time and the increased awareness of the special concerns related to children with Prader-Willi syndrome. Late surgical complications may include velopharyngeal/velopalatal insufficiency [32, 33]. It is recommended that children with Prader-Willi syndrome and obstructive sleep apnea requiring adenotonsillectomy be referred to a specialty center with a multidisciplinary team familiar with the syndrome.

Published experience with adenotonsillectomy in children with PWS suggests that while adenotonsillectomy may be effective in most children with PWS and mild to moderate OSA, complete resolution of OSA may not be achieved, especially in those with severe OSA and in those with comorbid obesity [34, 35]. Therefore, follow-up sleep studies are recommended in these high-risk patients at least 6–8 weeks postoperatively under the following circumstances:

- Preoperative diagnosis of moderate or severe OSA
- Sequelae of OSA (e.g., pulmonary hypertension, cor pulmonale)
- Obesity
- Persistent OSA symptoms

Children found to have significant residual apnea on follow-up PSG as well as children who are not surgical candidates should be considered for continuous positive airway pressure (CPAP), a noninvasive ventilatory support system. CPAP stents the pharyngeal soft tissue of the posterior pharyngeal wall, which can lessen or eliminate the obstruction causing the apnea. We recommend that CPAP titrations be performed under the direction and supervision of a pediatric sleep specialist.

Once titrated, adaptation to and compliance with the device is often problematic, especially in children with developmental disabilities and genetic syndromes [36]. Modest benefits have been reported with behavioral interventions [37], including "gradual exposure to CPAP in a supportive setting, as well as anticipatory troubleshooting of typical difficulties and child responses to the challenges of using CPAP" [38]. Overall, however, the current literature is limited regarding successful strategies to improve CPAP compliance in children.

Independent of other treatment interventions, weight loss strategies should be initiated in all children with OSAS who are overweight or obese as there is a clear association between weight loss and improvement in sleep apnea [39]. It must be recognized that affecting weight loss in this population is particularly difficult due to both a reduced metabolic rate and a markedly reduced caloric need in the presence of constant hyperphagia. Thus, weight loss will be slower and more difficult to achieve, although critical.

Additional Sleep Disorders Common in PWS

Excessive daytime sleepiness (EDS) is a frequent finding in individuals with PWS, occurring independent of both BMI and nocturnal sleep status [40]. In studies based on subjective report, the prevalence estimates range from 52% to 100%, with greater prevalence in childhood through the pubertal age, a plateauing in adulthood, and occurring more frequently in those whose PWS results from a paternal deletion [41]. Mimicking narcolepsy, the sleepiness results in naps during rest and inactivity [42]. While the exact mechanism underlying EDS in this population is unclear,

the lack of correlation with other sleep disorders suggests central mechanisms, most likely hypothalamic dysfunction or hypocretin deficiency [43, 44]. Independent of obesity status, central hypersomnolence should be considered in individuals with PWS who fail to respond to either surgery or CPAP and have persistent daytime sleepiness. Modafinil has US Food and Drug Administration (FDA) approval for treatment of sleepiness due to narcolepsy, OSA, and shift work disorder in adults; however, it is not FDA approved for use in children for any indication. Nonetheless, while randomized controlled trials among children with Prader-Willi syndrome and central hypersomnolence are lacking, there are published case reports of successful use of modafinil [45, 46].

Growth Hormone Replacement Therapy and Obstructive Breathing Disorders

Infants and young children with PWS are at higher risk for respiratory difficulties and unexplained sudden death than children without PWS. The etiology of the respiratory problems in PWS seems to be multifactorial in origin but primarily related to insufficiency of respiratory muscles resulting from a genetically driven reduced muscle mass, severe hypotonia, and pharyngeal narrowness [47]. In addition, because of hypotonia-related insufficient airway protection, many infants experience feeding-associated aspiration-induced respiratory problems. While aspiration risks can often be managed by repositioning the infant during and after feeding, nonetheless, the increased risk for respiratory difficulties remains.

The majority of individuals with PWS demonstrate classic growth hormone deficiency even at birth, including reduced muscle mass and strength, low energy expenditure and reduced linear growth even in the presence of obesity, and reduced serum levels of IGF-1 (a serum marker for growth hormone levels). Randomized, controlled studies of growth hormone replacement therapy in the late 1990s documented accelerated growth velocity, increased muscle mass and strength, decreased fat mass, increased physical activity, and even behavior improvements [48–50]. As a result, during the past two decades, growth hormone replacement therapy (GHRT) with daily injectable recombinant human growth hormone has become standard of care for most affected children (and many adults). Crucially, research also demonstrated improved respiratory function [23, 51], even in very young infants treated with GHRT. As a result, in the year 2000, the pharmaceutical companies Pharmacia and Upjohn obtained FDA approval for GHRT for this population. Soon thereafter, there emerged several reports of sudden unexpected death in children with PWS in the early phases of growth hormone treatment [52, 53].

While several theories were hypothesized to explain these deaths, the prevailing etiologic theory centered on GH-mediated tonsillar or soft tissue hypertrophy, increased fluid retention, and soft tissue edema resulting in fatal obstructive sleep apnea. While OSA as a result of GHRT-induced tonsillar hypertrophy previously had been documented in other populations, the available, albeit, sparse evidence in PWS individuals at that point indicated that GHRT improved respiratory function. Further, available data indicated the overall mortality rate of GH-treated PWS patients was lower than that of untreated PWS patients. Nonetheless, the temporal relationship between seven fatal events worldwide and initiation of GHRT led Pharmacia and Upjohn to issue a safety warning on May 30, 2003 [54], indicating that GHRT is contraindicated in patients with PWS who are severely obese or have severe respiratory impairment. This resulted in a number of physicians refusing to or significantly delaying GH treatment to this population.

Subsequently, a number of controlled studies, both cross-sectional and longitudinal, have addressed the following questions:

- Does GHRT raise the risk for OSA in those with PWS?
- What is the increased risk, if any, of sudden unexpected death associated with GHRT?

Collectively, these studies indicate that initiating GHRT does not increase the risk of OSA in *most* individuals affected by PWS. However, there does appear to be an increased risk of obstructive events among those who develop treatment-induced elevated serum IGF-1 levels. Thus, current guidelines recommend a baseline PSG prior to initiating GHRT, especially for those with obesity and hypotonia, with treatment for obstruction as indicated, followed by a repeat PSG 2–6 months after initiation of GHRT and subsequent adjustment of dose if IGF-1 levels exceed two standard deviations greater than the mean for age and gender [55].

Lessons Learned About Sleep Disorders and Prader-Willi Syndrome

- Clinicians should have a high level of vigilance for both sleep-disordered breathing and other sleep disorders in children with Prader-Willi syndrome.
- Routine screening for sleep-disordered breathing is recommended.
- While many sleep questionnaires are available, none is diagnostic.
- The diagnosis of obstructive sleep apnea is made by overnight polysomnogram.

- Adenotonsillectomy is recommended as the first-line treatment in children with PWS and OSA with evidence of adenotonsillar hypertrophy who are deemed acceptable surgical candidates. Residual apnea may be present post-operatively, and follow-up sleep studies are recommended.
- All overweight and obese children with sleep apnea should have weight management and follow-up as part of their treatment plan.

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Rett Syndrome

17

Amee A. Patel and Daniel G. Glaze

Clinical Vignette

A.J. is a 4-year-old female with Rett syndrome (MECP2 mutation T158M) who presents to the sleep clinic for difficulty falling asleep and staying asleep. During the night, she wakes up laughing and oftentimes moves her arms in the air while trying to go back to sleep. Her parents are concerned as this behavior prevents A.J. from going back to sleep and disrupts sleep for other family members. During the day, A.J. is sleepy and not able to participate in activities with her siblings or in her physical and occupational therapy. A.J. sleeps only 4–5 h during the night and then 2–4 h during the day, for a total of 6–9 h of sleep per 24-h period. Her family is requesting recommendations.

Introduction

Rett syndrome (RTT) is a severe neurodevelopmental disorder that affects 1/10,000 females and is rarely diagnosed in males. There are more than 250 known genetic MECP2 mutations that are associated with RTT [1]. A mutation in the MECP2 gene, located on the X chromosome (Xq28), is identified in 95% of individuals with typical RTT. MECP2 encodes for the methyl-CpG-binding protein 2 (MECP2) and is expressed in all organs. However, it is predominantly expressed in the central nervous system (CNS), thus supporting the early clinical symptoms of neurologic regression described below [2].

Following an initial period of apparent normal development, there is a period of neurologic regression between 6 and 18 months. During this time, there is loss of verbal communication skills and purposeful hand motor skills. The development of repetitive stereotypic hand movements occurs, and an abnormal apraxic/ataxic gait is common. Autistic features may be seen in some individuals with RTT during this time. Following this period of regression, the girls appear to plateau. They have better eye contact and social interactions; however, the core features do not improve to any significant degree. Ninety percent or more of individuals with RTT experience epilepsy, growth failure, gastrointestinal problems such as gastroesophageal reflux and chronic constipation, and autonomic dysfunction including breathing abnormalities and motor dysfunction. The incidence of sudden unexpected death is increased in individuals with RTT over the general population. However, in over 70% of individuals with RTT, the prognosis for life expectancy is good, with survival into the fifth decade. There is no approved or proven treatment for RTT, and at this time, management is symptomatic.

Sleep and Rett Syndrome

Sleep is a normal, active physiologic process that is vital for adequate growth and development. In the general population, sleep disorders affect approximately 25% of all children at some point during childhood [3]. A recent study of individuals with neurodevelopmental disorders, such as RTT, autism, Angelman syndrome, etc., identified a significant prevalence of sleep problems [4]. Sleep problems have been identified in 80–94% of individuals with RTT [5, 6]. Despite the length of time elapsed since the first report of RTT in 1966 by Andreas Rett, the exact mechanism, genetic predisposition, and phenotype of its associated sleep disorders are still unknown. Sleep problems may develop before or at the time of regression. More than one primary sleep

A. A. Patel
Pediatrics, Children's Sleep Center and Pediatric Pulmonary Medicine, Texas Children's Hospital/Baylor College of Medicine, Houston, TX, USA
e-mail: axpatel1@texaschildrens.org

D. G. Glaze (✉)
Pediatrics and Neurology, The Children's Sleep Center, The Blue Bird Circle Rett Center, Bioethics Committee, Texas Children's Hospital/Baylor College of Medicine, Houston, TX, USA
e-mail: dgglaze@texaschildrens.org

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disorder, such as sleep-disordered breathing or periodic limb movement disorder, as well as medical problems including epilepsy, gastroesophageal reflux, or constipation, may occur simultaneously or in succession and contribute to fragmented sleep.

Poor quality of sleep as a result of sleep problems promotes poor cognition, behavioral problems, mood disturbances including irritability, and overall decreased quality of life during the day. Oftentimes, hyperactivity and inattentiveness may occur as a result of insufficient sleep or poor quality of sleep. Sleep problems in individuals with RTT can also be disruptive and/or frightening to a girl's family, resulting in increased stress and poorer overall quality of life for all family members.

Sleep Characteristics

Several studies have identified that individuals with RTT have sleep disturbances in the form of multiple nighttime awakenings along with behaviors such as nocturnal laughter or screaming. A large Australian study using the Australian Rett Syndrome Database (ARSD) and various sleep questionnaires identified sleep problems in over 80% of individuals with RTT. The most commonly reported sleep problems included nocturnal laughing, teeth grinding, and nocturnal seizures [5]. Other nocturnal behaviors seen in this population included non-rapid eye movement (NREM)-related parasomnias such as confusional arousals and night terrors. NREM-related parasomnias typically occur during the first third of the major sleep period. These episodes result in incomplete awakening from sleep and typically the individual does not respond to efforts to awaken her by a family member. There is also partial or complete amnesia of the episode. For episodes of confusional arousals, the individual may continue to appear confused and disoriented for several minutes or longer following the episode. Night terrors are characterized by episodes of abrupt terror, typically beginning with an alarming scream. There are autonomic signs associated with night terrors such as mydriasis, tachycardia, tachypnea, and diaphoresis. Similar to confusional arousals, the individual is not able to remember the event afterward. In general, NREM-related parasomnias increase in frequency and severity during periods of insufficient sleep as well as when the individual is abruptly awoken during the episode.

The frequency of specific sleep problems is associated with age. Young children (0–7 years of age) with RTT are more likely to have more nighttime awakenings than older children with Rett syndrome. Daytime napping and nighttime seizures increase with age, while nocturnal laughter, teeth grinding, and nighttime screaming decrease with age.

Individuals with RTT have irregular sleep onset times as well as total daytime sleep that is longer when compared to typically developing individuals [7]. The age-related decrease in total and daytime sleep expected in typically developing children is not present in individuals with RTT. It is suspected that this is most likely related to the arrested brain development that is expected in individuals with RTT [7, 8].

A 2001 cohort study using validated sleep diaries reported that individuals with RTT showed an irregular sleep-wake pattern, prolonged sleep latency, multiple awakenings during the night several times per week, as well as poor sleep quality [8]. In addition, this study identified that individuals with seizures had significantly more daytime sleep and a higher percentage of total sleep time occurring during the day than those without seizures. Individuals with RTT who were ambulatory had a higher sleep efficiency and less daytime sleep than those who were not ambulatory [8]. This suggests that daytime function, as well as comorbid conditions such as seizures, contributes to the overall sleep characteristics found in individuals with RTT.

Genotype/phenotype correlations regarding the severity and frequency of sleep problems in individuals with RTT have been reported. Young et al. found that the frequency and type of sleep problems varied according to the mutation type. Sleep problems were most reported in individuals with large genetic deletions, as well as with either p.R294X or p.R306C mutations. Nighttime laughter was most common in those with large genetic deletions, p.R168X, and more recently with p.R106W [5, 6]. Daytime napping was most reported in those individuals with p.R270X, p.R255X, and p.T158M mutations. There was no relationship between a specific genetic mutation and nocturnal screaming or with nocturnal seizures [5]. These findings suggest that different mechanisms contribute to the phenotypic expression of sleep problems in individuals with RTT.

PSG Findings

Normal development of the sleep/wake cycle begins in the newborn period. In the 1st month, the sleep/wake cycle revolves around feeding times. Gradually, the cycle begins to adjust to light exposure to follow a day-night cycle. Major sleep periods begin to occur during the night, with less sleep time during the day. The sleep periods during the day decrease to daytime naps with the major sleep period at night. Around age 4–5 years, the naps begin to phase out, resulting in only one major sleep period at night.

Normally body movements occur throughout sleep, which help individualize the different stages of sleep. Larger gross motor movements occur in lighter stages of sleep. As the sleep cycle progresses, these movements evolve into twitches. The twitching movements gradually increase during rapid eye movement (REM) sleep, as well

as in the latter parts of the night. As the brain develops, the unique characteristics of the different sleep stages mature. The gold standard for objectively identifying sleep architecture is the polysomnogram (PSG). During scoring of a PSG, wakefulness, NREM sleep, and REM sleep are identified. Clinically, individuals with RTT exhibit a normal development of sleep from the newborn period until the time of neurologic regression.

Total sleep time is similar in younger children with RTT in comparison to typically normal developing children, whereas older children with RTT have decreased total sleep time [9]. Individuals with RTT also gradually sleep more during the day; thus, the total sleep time in a 24 h period is increased compared to typically developing individuals [10].

NREM 1 and NREM 2 sleep is decreased in younger children with RTT, which may be due to a decreased sleep latency period [9]. In older individuals, NREM 1 and NREM 2 sleep occurred in similar proportions to typically developing individuals [9]. The characteristic findings of NREM 2 sleep of K complexes and spindles eventually were not distinguishable in older children due to the neurologic dysfunction. However, in adult women with RTT, K complexes may reappear.

Slow-wave sleep (particularly NREM 3 sleep) in individuals with RTT is generally similar to typically normal developing individuals. It occurs in higher amounts during the first part of the night. However, in older individuals with RTT, slow-wave sleep occurs during the latter part of the night [11–13]. There is also an increase in slow-wave sleep, a trajectory opposite to the typical pattern, in which the amount of slow-wave sleep decreases as age increases toward adulthood. In regard to REM sleep, studies have shown that there is a decrease in the percentage of REM sleep and that REM sleep latency is longer in individuals with RTT compared with controls [9].

EEG abnormalities are common in individuals with RTT; however, there is variability in the type of EEG activity. EEG activity is normal before the age of 3 and before clinical symptoms of regression [14–16]. As clinical symptoms of regression begin, the background EEG activity and occipital dominant rhythm gradually begin to slow during wakefulness and during sleep [16, 17]. Subsequently, the background EEG activity consists of irregular slow waves and becomes increasingly disorganized. Expected sleep characteristics such as spindles and K complexes during NREM 2 sleep are lost.

In addition, spikes, polyspikes, and spike and wave discharges gradually become more prominent first during NREM sleep and then during wakefulness, as the disease progresses [15, 18, 19]. Epileptiform abnormalities occur mostly in the central region and gradually involve the temporal region. There are also reports of the involvement of the parasagittal region of the brain [15].

Respiratory Pattern During Sleep

Individuals with RTT have a characteristic breathing pattern that occurs predominantly during periods of wakefulness. Interestingly, this respiratory pattern is not present during the newborn period [20]. The brain stem, which regulates control of breathing, is intact during sleep [17, 20]. The characteristic pattern involves intermittent periods of hyperventilation with decreased partial pressure carbon dioxide (pCO_2) values and periods of breath holding.

The respiratory pattern tends to be disorganized with mild to moderate oxygen desaturations. The events are followed by an increase in respiratory effort, followed by a return to baseline oxygen saturation values [9]. The resulting hypoxemia may be significant enough to provoke a seizure or syncope, but the respiratory abnormalities occurring during wakefulness are independent of seizure activity [9, 21, 22]. There are also episodes of respiratory pauses during which individuals with RTT are calm and indeed, enjoying a particular activity [9, 20]. Stereotypic hand movements are intermittently present during periods of disorganized breathing and also during normal respirations but are not typically present during sleep [9].

During sleep, the respiratory pattern is generally organized and continuous breaths. Oxygen saturation values are typically within normal range. Periodic breathing is minimal during sleep. End-tidal pCO_2 values are in the normal range [9]. Children and adults with RTT may demonstrate upper airway obstruction in the form of snoring and obstructive sleep apneas, as well as central sleep apnea on PSG. Central apneas may be present during the transition from wakefulness to sleep and during REM sleep as a result of the preceding periods of hyperventilation or hyperpnea [12, 23]. As per the American Academy of Sleep Medicine, scorable central apneas in children are characterized by decreased respiratory effort and flow for 20 s or more or at least two breaths in duration but associated with a 3% oxygen desaturation or an arousal. The prevalence of sleep-disordered breathing appears to be higher in individuals with RTT than in typically developing individuals [4, 24].

Evaluation of Sleep Disorders

Evaluation of sleep disorders in individuals with RTT begins with a complete history and physical examination. Initial history from a caregiver can direct the diagnostic evaluation and plan. History of sleep characteristics includes how long it takes for the child to fall asleep and whether she is able to maintain sleep through the night. The number of hours of sleep achieved per sleep period will direct the physician as to whether the child is sleep deprived. Events during sleep will also help guide whether a further evaluation is warranted. For example, snor-

ing, gasping or choking for air, and excessive daytime sleepiness are all suggestive of sleep-disordered breathing. Frequent jerking movements or leg movements may be a sign either of seizures or periodic limb movement disorder.

The child's bedroom environment should also be assessed as part of the sleep history. Some children have televisions, toys, phones, and other siblings in the room with them, any of which may distract them from initiating sleep. In addition, having caregivers outline where and when bedtime starts may provide insight into possible barriers to sleep, such as starting bedtime too early or too late. A comprehensive history should include daytime and nighttime sleep schedule, timing and duration of naps, bedtime routine, and contributing factors such as any caffeine intake. Identifying the overall impact on family dynamics also helps differentiate how aggressive an intervention should be.

A review of medications should be undertaken. This includes medications that have already been tried to help treat the sleep problems as well as medications prescribed to treat other medical conditions such as attention-deficit/hyperactivity disorder or seizures. Oftentimes, such a review will reveal probable medication side effects of insomnia or daytime sleepiness, which can be alleviated after adjusting dose or time of administration.

Physical examination can identify craniofacial abnormalities such as micrognathia, retrognathia, pectus deformities, nasal turbinate hypertrophy, and tonsillar or adenoidal hypertrophy in children with RTT as well as those with typical development – all of which can contribute to sleep-disordered breathing. Physical examination also helps direct evaluation and treatment of medical problems such as seizures, which are common in RTT. Gastrointestinal problems, such as chronic constipation and gastroesophageal reflux, occur in almost 100% in individuals with RTT and must be considered and treated as these problems are frequently associated with night awakenings and disruption of sleep. In addition, individuals with RTT may experience the same sorts of problems experienced by typically developing children and adolescents. As an example, uncontrolled or chronic nasal congestion can contribute to snoring and frequent awakenings. Nocturnal coughing as a result of postnasal drip can present with erythema and/or cobblestoning of the mucosa of the posterior pharynx. Occasionally, despite a thorough sleep history and physical examination, diagnostic studies may be indicated. Table 17.1 summarizes the available diagnostic tools that may help identify sleep problems in individuals with RTT.

Table 17.1 Diagnostic tools to help identify sleep problems in individuals with Rett syndrome

Diagnostic tool	Indication for test
Polysomnography	Sleep-disordered breathing
	Titration of positive airway pressure therapy to optimize treatment of sleep-disordered breathing
	Seizure activity during sleep
	Atypical or self-injurious parasomnias
	Periodic limb movement disorder
Sleep log/diary	Variable sleep/wake pattern
Actigraphy	Assessing multi-day rest-activity patterns
	Circadian rhythm disorders
Video and expanded EEG	Atypical behaviors
	Nocturnal seizures
	Atypical parasomnias/atypical movements

Overnight PSG is the gold standard diagnostic tool for most sleep medicine experts. This study includes EEG monitoring, pulse oximetry, oronasal airflow, abdominal and chest wall movement monitoring to record respiratory effort, leg electromyography to determine leg movements, pCO_2 monitoring, and video recording. PSG is indicated to diagnose sleep-disordered breathing such as obstructive sleep apnea, central sleep apnea, and sleep-related hypoventilation, as well as to titrate positive airway pressure in children [25]. PSG is also indicated to diagnose periodic limb movement disorder, to confirm the diagnosis of an atypical or potentially injurious parasomnia, and to differentiate an atypical parasomnia from nocturnal seizures [26]. Occasionally, video EEG and/or an expanded EEG may be helpful in identifying atypical seizures.

Sleep logs or sleep diaries are useful to determine if there are specific sleep-wake patterns from day to day as well as to identify circadian rhythm sleep disorders. They are sometimes used in tandem with actigraphy. An actigraph is a device that is worn on the wrist that estimates periods of sleep versus wakefulness based on pattern of movements. It is best utilized with a sleep log/diary, which can be particularly helpful in situations when there is artifact recorded on actigraphy monitoring.

Lastly, home sleep testing in an unattended setting may be helpful in assessing for obstructive sleep apnea using one to several physiologic parameters. Currently, there are few studies documenting the use of home sleep testing in individuals with RTT. However, home testing may be helpful in children with a high pretest probability of obstructive sleep apnea who may not tolerate being in a sleep laboratory or for whom a standard PSG is not readily available due to long wait times, transportation issues, etc. In addition, pediatric sleep labs are not universally available; many sleep labs are not experienced in studying medically complex children like individuals with RTT.

Treatment of Sleep Disorders

Treatment of sleep disorders in children with neurodevelopmental disorders in general can be challenging. Sleep problems in this population can be quite persistent if left untreated. Management begins with addressing the contribution of medical problems, primary sleep disorders, behavioral problems, and the impact of medications. Such management may improve the sleep issues, but these tend to be chronic with respect to their clinical course [4, 6, 7]. Table 17.2 illustrates the various treatment options available to treat sleep problems in individuals with RTT.

Medical problems such as epilepsy, chronic otitis media, respiratory problems such as chronic cough or allergic rhinitis, and GI abnormalities such as constipation or gastroesophageal reflux should be addressed first. Daytime behavioral problems should also be managed as they could interfere with nighttime routines and cause difficulty with winding down for bedtime. A review of any medications that have potential side effects of insomnia or daytime sleepiness has been previously noted. Timing of medication administration should also be reviewed and modified as needed.

More than one sleep problem may be present during the initial evaluation of sleep problems. Therefore, treating sleep disorders such as sleep-disordered breathing will improve overall sleep quality as well as increase total sleep time. Daytime function and behavioral problems may also improve as a result.

For obstructive sleep apnea, evaluation of the upper airway is the initial step. In children, adenotonsillar hypertrophy is the most common cause of obstructive sleep apnea. If the child is not a surgical candidate and there is significant daytime impairment, or the caregiver wishes to pursue nonsurgical options, then positive airway pressure therapy is initiated. In addition, positive airway pressure therapy may be an option if surgery is not curative and residual OSA continues to cause daytime impairment, such as daytime sleepiness or behavioral problems. This may be provided in the form of continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BPAP) with or without a backup rate. Typically, the positive airway pressure therapy is delivered through a nasal interface as opposed to a full-face mask in order to prevent episodes of aspiration during sleep.

Table 17.2 Treatment options available for individuals with Rett syndrome who have sleep problems

Treatment modality	Examples
Treating medical problems	
Epilepsy	Anticonvulsants
Gastroesophageal reflux	Acid suppressing medications (proton pump inhibitors, histamine type 2 receptor antagonists)
Constipation	Optimization of dietary fiber intake, laxatives, stool softeners
Allergic rhinitis	Nasal steroids, antihistamines
Treating primary sleep disorders	
Sleep-disordered breathing	Adenotonsillectomy; positive airway pressure therapy
NREM related parasomnia	Avoid periods of insufficient sleep, avoid abrupt awakening during episode; maintain good sleep habits
Periodic limb movement disorder	Iron supplementation; gabapentin
Management of daytime behaviors	Consistent daytime schedule
	Limit setting
Adequate sleep hygiene	Consistent bedtime routine
	Avoid caffeine
	Avoid strenuous or vigorous activity before bedtime
Behavioral approaches	Gradual extinction
	Scheduled awakenings
Relaxation techniques	Massage therapy
	Music therapy
	Pet therapy
	Weighted blankets
Medications	Melatonin
	Alpha agonists (clonidine)
	Antidepressants (trazodone)
	Hypnotics (zolpidem)
	Anticonvulsants (gabapentin)
	Benzodiazepines (clonazepam)
Caregiver education	Provide understanding of sleep problems
	Establish reasonable goals and expectations
	Provide resources/support groups

For NREM-related parasomnias, reassurance is provided to the caregivers that the episodes do not result in further neurologic insult and will self-resolve with improved sleep quality and sleep time. In addition, caregivers are provided with instruction to avoid abruptly awakening the individual during episodes, as this may further exacerbate parasomnias as well as increase their frequency. The caregiver can gently console the individual during the episode and then allow her to fall back asleep.

Modifying and promoting good sleep habits have been shown to dramatically improve insomnia in individuals with RTT [27]. Caregivers should maintain a consistent bedtime and wake time, incorporate a bedtime routine in which there is limited exposure to electronics, limit strenuous physical activity prior to bedtime, and limit caffeine and exposure to bright light in the evenings. Exposure to bright light after dark promotes a later bedtime with subsequent delay in sleep onset.

Behavioral approaches are beneficial in treating sleep problems in individuals with RTT. This includes extinction of the unwanted behaviors, such that a child is allowed to cry or fuss for an allotted period of time. With gradual increases in the increments of time, the individual eventually will learn to self-soothe and fall asleep without caregiver intervention. For undesired behaviors such as nocturnal laughter, confusional arousals, or nocturnal screaming, scheduled awakenings prior to the unwanted event may be helpful. This technique is especially beneficial if the timing of the unwanted behavior consistently occurs at the same time during the night. Other behavioral interventions include relaxation approaches such as massage therapy, music therapy, or pet therapy. Weighted blankets may be helpful in diminishing environmental stimuli and allow an individual to initiate sleep.

Currently, there are no medications that are FDA approved for the treatment of sleep problems in children. A few studies have shown that supplemental melatonin along with decreasing time to sleep onset also increases total sleep time and improves daytime cognitive function [28–30]. In addition, several pharmacologic agents have been used off-label in children and adults as an alternative or in conjunction with melatonin (Table 17.2).

Lastly, sleep education for caregivers is strongly recommended as it establishes an understanding and acceptance that sleep problems in individuals with RTT are common. Expectations and reasonable goals by the caregiver should be established as an initial intervention for the sleep problems. Caregivers should also feel comfortable expressing their frustration in respect to their child's sleep patterns, as most caregivers worry about their children's sleep and do not sleep well as a result.

Future Directions

Sleep problems are common in individuals with RTT contributing to poor quality of life for both individuals with RTT as well as for the caregiver(s). Sleep difficulties often present around the time of developmental regression. The genotypic and phenotypic presentations of RTT have been linked to the types of sleep problems; however, the actual mechanism contributing to sleep problems is not clear. Areas of research that can identify the exact mechanism for the sleep problems may help direct therapy. Currently, there is limited use of home sleep testing, which may benefit individuals with RTT, particularly those with significant barriers to transportation, long wait times, and developmental and behavioral issues that may prevent full PSG monitoring. Research on the use of sleep-promoting medications in individuals with RTT is necessary as this may ultimately improve overall quality of life in individuals with RTT as well as their families.

Clinical Pearls

- Individuals with RTT of all ages frequently experience sleep problems, which are oftentimes not addressed and are chronic.
- Sleep problems associated with RTT include insomnia, irregular sleep/wake schedules with daytime sleepiness, NREM-related parasomnias, and sleep-disordered breathing, including both obstructive and central sleep apnea.
- Sleep problems typically are described by caregivers as multiple nighttime awakenings, daytime napping, nighttime laughing, abnormal movements of the upper extremities, and/or nocturnal seizures.
- Evaluation of sleep problems includes a detailed history and physical examination along with evaluation of bedtime routine and description of the nighttime behavior during sleep, as well as daytime consequences as a result of poor quality sleep.
- Treatment of sleep problems includes identifying and managing primary sleep and medical problems as well as incorporating behavioral approaches in maintaining good sleep habits such as maintaining a consistent bedtime routine and avoiding daytime naps.
- Currently, there is no approved sleep-promoting medication to treat sleep problems in children. However, melatonin has been shown to be useful in individuals with RTT who have difficulty initiating and/or maintaining sleep. Off-label use of medications for sleep, such as antidepressants, hypnotic agents, and anticonvulsants, requires further study.

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Williams Syndrome

18

Paige Kaplan and Thornton B. A. Mason II

Overview of Williams Syndrome

Williams syndrome (Williams-Beuren syndrome or WBS) is a congenital disorder caused by deletions of multiple contiguous genes on the long arm of one chromosome 7 (del 7q11.23) [1]. There is a distinctive pattern of developmental delays, personality and behavior, physical phenotype, and multiorgan involvement [2, 3]. Williams syndrome is panethnic. Its incidence is approximately 1:8000, but it is likely underdiagnosed. Classically, a child with Williams syndrome is born post term, with birth weight and length in or below the lower half of the normal range.

The physical characteristics of Williams syndrome include subtle facial dysmorphism, regardless of racial background. In infancy and early childhood, the face is round or oval, sometimes with facial asymmetry, with periorbital puffiness (not edema); upward growth of the medial part of the eyebrows ("medial flare"); epicanthic folds, irides that are often blue and have a stellate, lacy pattern; strabismus; flat nasal bridge with a broad nose tip and anteverted nares; poorly defined philtrum that may be long; wide mouth; full lips with diminished or absent Cupid's bow and protuberance of the lower lip; "low-set," full cheeks; deep nasolabial creases; flat malar area; and small chin (Fig. 18.1). Nasolacrimal duct obstruction may cause excessive "tears." In later childhood and adulthood, the facies becomes long and gaunt. The body is characterized by sloping shoulders, short stature, and relatively short limbs. There may be cervical kyphosis, exaggerated lumbar lordosis, occasional scoliosis, and radioulnar synostosis (preventing rotation of the forearm). The skin is very soft with fine creases. The hair is thick and curly and becomes prematurely gray. Inguinal and umbilical hernias are common. Often there is less body fat in childhood or adolescence, due to increased resting energy expenditure. In later childhood and adolescence, patients become overweight.

The infant with Williams syndrome is hypotonic with joint laxity (except for tight heel cords) and hyperreflexia. There is early onset of feeding difficulties and failure to thrive. The infant is constantly irritable for several reasons: (1) pain from esophagitis, caused by frequent gastroesophageal reflux, compounding the feeding problems; (2) idiopathic hypercalcemia in approximately 15% (that usually resolves after infancy); (3) constipation; and (4) tactile defensiveness (irritability on being touched). By the end of the 1st year, irritability and vomiting diminish or resolve. There are still significant feeding problems, due to low tone, and difficulty chewing and swallowing coarser foods. The hypotonia and joint laxity improve in childhood. Hypertonia develops in about a third of children and is more prevalent (85%) in adults. Mild, moderate, or severe contractures develop in childhood in approximately 50%. Their gait is characteristically wide based, with the upper part of the body leaning forward and a tendency to toe-walk, even in the absence of joint contractures. Chiari I sequence (malformation) occurs, with significant displacement of the cerebellar tonsils below the level of the foramen magnum; this malformation likely occurs in Williams syndrome because of a small posterior fossa with a normal-sized cerebellum and could place affected patients at increased risk for sleep-disordered breathing.

The range of IQ in Williams syndrome is broad, with an average score of 50–60. A large number of individuals have borderline normal IQ scores, and a few are in the normal range (up to 114 in one report). However, IQ scores do not reflect the unique profile of strengths and weaknesses in

P. Kaplan
Genetics Division, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, USA

T. B. A. Mason II (✉)
Departments of Neurology and Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, USA
e-mail: masont@email.chop.edu

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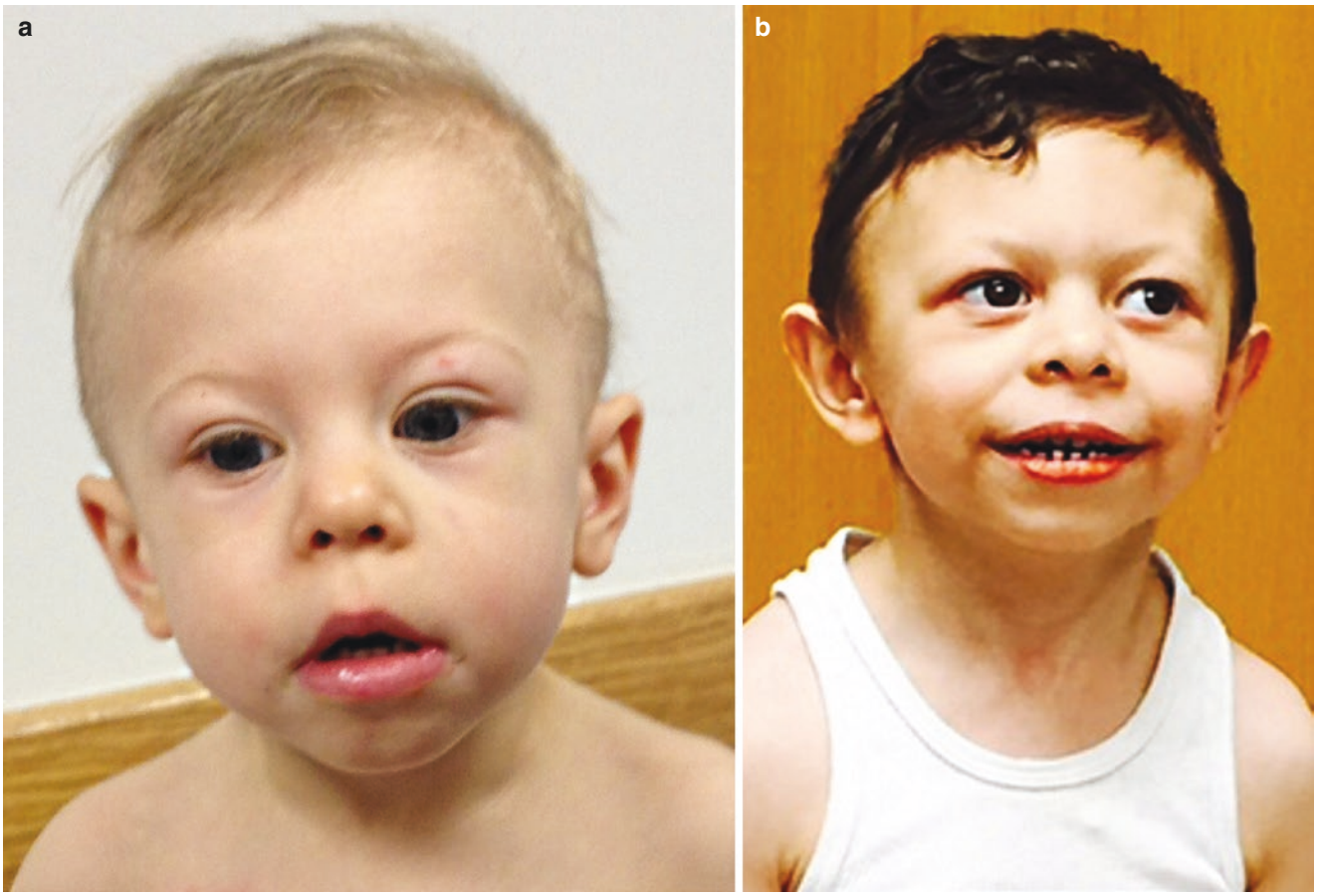

Fig. 18.1 Infant (**a**) and young child (**b**) with Williams syndrome. Note typical facial features – broad forehead, periorbital soft-tissue fullness, anteverted nares, long philtrum, decreased Cupid's bow of upper lip, "pouty"-everted lower lip, and "low-set" cheeks

cognitive skills [4, 5]. Weaknesses involve "visual-motor" skills or visual-spatial construction (spatial location and motion) and problem-solving, especially mathematics. The cognitive strengths of WBS are in verbal and auditory skills, including auditory short-term memory. Severe delays in language development are expected: first words emerge, on average, at 21 months and sentences at 3–4 years. Combination of words into phrases begins at the same stage as in typically developing children, when they know approximately 50–100 words. Most children with Williams syndrome have fluent and distinctive language at 4–5 years with emotional content; prosody is distinctive because of exaggerated emotion and rhythms and unusual, subtly inappropriate words and idioms and grammatical problems. Attention-deficit/hyperactivity disorder (ADHD), idiopathic hyperacusis, and easy distractibility affect most children.

Children with Williams syndrome are very sociable – indeed, they typically show uninhibited, and often inappropriate, friendliness. In contrast to children with autism, children with Williams syndrome naturally and instantly make eye contact, even in early infancy, detect emotions in other people, and show empathy. In young children, most aggressive behavior seems to be due to frustrations in communication or in performing a given task. WBS children often perseverate with repetitive comments or questions. Despite their friendliness, often toward strangers, they suffer from tremendous anxiety and fear, even in early childhood. Disabling anxiety may be present in adults with WBS, and they may have an increased prevalence of other psychiatric disorders, including depression and obsessive-compulsive behavior.

One of the most important causes of morbidity and early death is narrowing (stenosis) of arteries. Many or all arteries are narrowed in Williams syndrome, but these stenoses may not have clinical effects. In a large series, clinically important stenosis affected peripheral (branch) pulmonary arteries (PPS) in 64%, supravalvar aorta (SVAS) 51%, aortic arch (coarctation) in 21%, and pulmonary valve in 16%. Stenoses may develop in other arteries (descending aorta, renal, mesenteric, subclavian, or cerebral arteries) even in the absence of PPS or SVAS [6]. Cardiac lesions are not uncommon: ventricular septal defect (VSD) occurs in 21% and mitral valve abnormalities (MV prolapse) in 15%. Most arterial narrowing is present at birth or early infancy.

Severe hypertension and cardiac hypertrophy, from narrowing of the great vessels, peripheral pulmonic arteries, and/or renal arteries, as well as rigidity (non-compliance) of arteries, may cause cardiac failure. Sudden death may occur and is associated with cardiac catheterization and/or anesthesia in about half of cases. Causes include deficient cardiac output from severe cardiac ventricular outflow obstructions or myocardial infarction/arrhythmia due to coronary artery stenosis. In recent decades, early diagnosis, preventive treatment, and appropriate vascular surgery have reduced morbidity and mortality. Rarely, strokes due to narrow cerebral arteries in young children or adults cause transient or permanent hemi- or para paresis, additional impairment of cognitive function, and occasionally, death. The cerebral arterial stenosis can develop in the absence of SVAS and other arterial narrowing. There is risk of sudden death with anesthesia in patients with Williams syndrome [7] that appears related to cardiac hypertrophy secondary to vascular stenosis or coronary artery stenosis [8]; anesthesia should be administered by cardiac anesthesiologists.

Other systemic involvement can affect the gastrointestinal system (gastroesophageal reflux and chronic constipation are common; rectal prolapse is less common but can be very debilitating), the renal system (increased urinary frequency in 32%, uninhibited detrusor muscle contractions or bladder dyssynergia in 10%, and radiologic "nephrocalcinosis," reported usually without renal stones or dysfunction), and teeth (small with spaces between teeth, absence of some teeth, and malocclusion). Short stature is common in Williams syndrome, sometimes evident at birth. Early puberty in males and females is common [9]. Sleep problems are prevalent and will be reviewed here.

Early diagnosis of Williams syndrome is important so that anticipatory management can help prevent severe problems and improve long-term outcomes. A multispecialty clinic for Williams syndrome patients can offer integrated, anticipatory care by medical personnel with expertise in cardiology; genetics; physical, occupational, and speech therapies; nutrition and feeding; developmental pediatrics; psychiatry; nephrology; ophthalmology; gynecology; orthopedics; neurology; neuroradiology; and sleep medicine. A list of clinics is available on the Williams Syndrome Association website, www.williams-syndrome.org.

Williams syndrome support groups, such as the Williams Syndrome Association, have been established by parents in many countries. They provide emotional support and information to patients, their families, and allied professionals; encourage research; and increase public awareness of Williams syndrome.

Sleep-Wake Patterns and Sleep Architecture

Questionnaire Studies

There are multiple questionnaire-based studies that support sleep problems in children with Williams syndrome. Mason et al. (2011) used a parent-report sleep questionnaire, adapted from Arens et al. (1998) that included 13 items to evaluate respiratory status, body/limb movements, and arousal/awakenings during sleep, as well as restless legs syndrome symptoms while awake [10, 11]. Comparing responses for 35 subjects with Williams syndrome vs. 35 typically developing matched controls, subjects with WBS were significantly more likely than controls to have difficulty falling asleep, general restlessness, repetitive leg movements, frequent and prolonged nighttime arousals, and inability to keep still before sleep [10]. Ashworth et al. (2013) used the Children's Sleep Habits Questionnaire and actigraphy (see below) to compare sleep among children with Williams syndrome, Down syndrome, and typically developing children [12]. The authors found that compared to typically developing controls, children with WBS had more sleep problems related to sleep onset delay, sleep duration, and night wakings. Children with WBS were also much more likely than typically developing children to move into another person's bed during the night, have bedwetting, and complain of body pain overnight.

Axelsson et al. (2013) compared 18 toddlers with Williams syndrome to 18 typically developing children (over the age range of 18–48 months). Parents completed questionnaires including the Brief Infant Sleep Questionnaire, Child Behavior Checklist, Infant Sleep Vignettes Interpretation Scale, Pittsburgh Sleep Quality Index of Parents, MacArthur Communicative Development Inventory for Infants – Words and Gestures, and the Major (ICD-10) Depression Inventory [13]. Based on these parent responses, children with WBS had shorter nighttime sleep duration, more night wakefulness, more night wakings, and later bedtimes and took longer to settle compared with age-matched typically developing children. There were no significant differences found in measures of maternal sleep quality and mood between mothers of typically developing and Williams syndrome children. However, up to 50% of mothers in both groups had scores indicative of poor sleep quality. In addition, the sleep quality scores of the mothers of the children with Williams syndrome were significantly related to their children's night wakefulness and night wakings [13].

Annaz et al. (2011) focused on school-aged children, surveying parents of children with Williams syndrome (ages 6–12 years, n = 64), comparing findings with 92 age-matched controls [14]. The instruments used included the Child Sleep Habits Questionnaire and sections of the

Pediatric Sleep Clinic Questionnaire. The authors reported that children with Williams syndrome were significantly more affected by sleep disturbances including bedtime resistance, sleep anxiety, sleep onset delay, frequent night waking, and excessive daytime sleepiness. Exploring changes with chronological age, the authors found that the subjects with Williams syndrome had decreases in sleep problems with age at a much slower rate in comparison with typically developing children.

Given that sleep problems are common in children with developmental disabilities as well as in the general population, it is important to compare questionnaire findings across different groups, so that control groups also include subjects with other special needs. Einfeld et al. used the Developmental Behavior Checklist to assess sleep, among other parameters [15]. The study included 70 subjects with Williams syndrome (average age 9.2 years) and 454 control subjects with intellectual disabilities (average age 12 years). The control group tended to have more severe intellectual disability than the Williams syndrome group. For the category of sleep ("sleeps little/disturbed sleep"), subjects with Williams syndrome were not significantly different than controls [15]. Ashworth et al. (2013) compared scores for the Children's Sleep Habits Questionnaire between children with Down syndrome and children with WBS and found that children with Down syndrome had significantly increased bedtime resistance, sleep anxiety, parasomnias, and sleep-disordered breathing. Moreover, the Children's Sleep Habits Questionnaire total score was significantly higher for those children with Down syndrome compared to subjects with Williams syndrome [12].

Objective Assessments

Actigraphy is a noninvasive technique that provides objective assessments of activity levels, from which sleep-related parameters can be derived. Advantages of actigraphy include ease and simplicity of recording and feasibility of recording data over multiple days in the home environment. Ashworth et al. included actigraphy in their study, with the actigraph being worn on the non-dominant wrist for a week in study subjects; concurrent sleep diaries were completed to support analyses of actigraphy data. Compared to typically developing children, children with Williams syndrome had earlier bedtimes and longer sleep latencies, although there was a wide interindividual variability in the latter parameter. The mean sleep latency of 48 min in the Williams syndrome subjects was twice that of both typically developing and Down syndrome subjects [12]. Interestingly, children with Down syndrome had multiple actigraphy measures supporting sleep disturbance that were significantly different compared to both the typically developing and Williams syndrome subjects, including night wakings, wake after sleep onset, sleep efficiency, moving time, and fragmentation. As the authors suggest, sleep-disordered breathing (e.g., obstructive sleep apnea) could have been an important factor resulting in sleep disturbance that was not objectively assessed in the study [12]. Thus, while both developmental disorder groups were found to have sleep problems, actigraphy measures showed differing profiles between subjects with Down syndrome versus Williams syndrome.

In a study of adolescents and adults with Williams syndrome, 95% reported feeling tired, and approximately 35% had excessive daytime sleepiness, based on the commonly used Epworth Sleepiness Scale score cutoff of 10 or greater [16]. Mean sleep onset latency was prolonged at 37.7 min, and sleep efficiency was decreased compared with normal values (average 74%). This study's limitations included the absence of a control group and no polysomnography data to support actigraphy results. The authors also noted potential biases associated with self-report data, specifically related to the personality features of individuals with Williams syndrome (strong desire to please others and give answers that they think others want to hear) [16].

There have been few studies using overnight polysomnography to assess sleep architecture and other parameters in children with Williams syndrome. Arens et al. (1998) studied seven subjects with Williams syndrome described by parents as often or always having symptoms suggestive of a movement arousal sleep disorder and ten age-matched controls. They found that the subjects with Williams syndrome had significantly increased wake after sleep onset (as a percentage of total sleep time), decreased Stage 1–2 (N1/N2) sleep, and increased Stage 3–4 (N3) sleep compared to controls; however, no significant differences were seen in total sleep time, sleep efficiency, sleep latency, or arousal/awakening indices [11]. A subsequent study of 35 subjects with Williams syndrome and 35 gender, ethnicity, and age-matched typically developing subjects (age range of 2–18 years) showed that children with Williams syndrome had significantly decreased sleep efficiency, with a mean difference between matched pairs of 4.5%. Wake after sleep onset was also statistically greater in Williams syndrome [10]. The authors also found that slow-wave (N3) sleep was increased as a percentage of total sleep time compared to controls, with a mean difference of 4.6%; there were no significant differences in N1, N2, or REM sleep between the two groups [10]. Gombos et al. (2011) performed two consecutive full-night polysomnograms on nine Williams syndrome subjects ages 14–28 years and nine matched controls; the first night was used for acclimation to polysomnography, so that only the data from the second night were analyzed [17]. They found that Williams syndrome subjects had decreased total sleep time, decreased total sleep efficiency, increased wake time after sleep onset, and increased slow-wave sleep and

decreased REM sleep as percentages of total sleep time. The authors also observed that sleep in their Williams syndrome subjects appeared qualitatively more fragmented in general, with more awakenings and less cyclic sleep architecture than in typically developing subjects. However, there were no significant differences between the two groups in the number of sleep cycles, average REM period duration, or average sleep cycle duration [17]. Taken together, these studies support increased wake after sleep onset (which may in turn result in decreased sleep efficiency) and increased slow-wave (N3) sleep as consistent findings in subjects with Williams syndrome from early childhood through young adulthood.

Periodic Limb Movements in Sleep

Periodic limb movements in sleep are determined by overnight polysomnography and are scored from surface anterior tibialis electromyography leads using standardized criteria for movement amplitude, duration, and frequency. Since periodic limb movements may disrupt sleep in some children, Arens et al. wondered if restless sleep in some patients with Williams syndrome could be related to these movements. Indeed, the authors found an association between periodic limb movements in sleep and Williams syndrome. In a subset of children with Williams syndrome who were screened for possible movement arousal disorder, the mean periodic limb movement index was fivefold greater in the group with Williams syndrome compared to the control group (14.9 vs. 2.8); in addition, the periodic limb movement arousal and periodic limb movement-awakening indices were significantly higher than in the control group. Five of the Williams syndrome subjects were treated with clonazepam, and an immediate and sustained improvement was noted by parents in four of these. After 3–6 months of treatment, three Williams syndrome patients underwent repeat polysomnography, during which significant decreases in the periodic limb movement index, period limb movement arousal index, and periodic limb movement-awakening index were seen [11].

A subsequent study of children with Williams syndrome and controls found significant correlations between parental reports of repetitive leg movements during sleep and periodic limb movements in children with Williams syndrome on polysomnography [10]. The study, however, did not show that the periodic limb movement index and periodic limb movement arousal index differed significantly between the group with Williams syndrome and controls [10]. A contributor to the discrepancy between the studies may have been referral bias, as the only children with Williams syndrome described by parents as often or always having symptoms supportive of a movement arousal disorder had polysomnography in the Arens et al. study [11]. In another study, Gombos et al. reported that subjects with Williams syndrome had a significantly higher number of leg movements per hour, but the leg movements did not meet criteria for being described as periodic. Ultimately, the periodic limb movement indices were low in both groups, and there was no significant difference between them [17]. Goldman et al. (2009) reported in their study of adolescents and adults with Williams syndrome that 13.6% of 23 subjects had unpleasant leg sensations when lying down at night, suggestive of restless legs syndrome symptoms. Individuals with restless legs syndrome in the general population often have periodic limb movements in sleep, but polysomnography was not included as part of the study, so the prevalence of periodic limb movements in sleep could not be assessed in their subjects [16].

Sleep-Disordered Breathing

The respiratory parameters in the Arens et al. study were overall normal in subjects with Williams syndrome compared to control subjects, including the apnea index, apnea/hypopnea index, baseline oxyhemoglobin saturation, and saturation nadir. While the mean end-tidal CO_2 value was mildly elevated in subjects with Williams syndrome compared to control subjects, it was still within the normal range. One subject with Williams syndrome was noted to have mild upper airway obstruction associated with transient oxyhemoglobin desaturation to 88% [11]. Similarly, in the Mason et al. study, the mean obstructive apnea-hypopnea index, the number of subjects with an obstructive apnea-hypopnea index >1 event per hour, and total apnea-hypopnea index were not significantly different between subjects with Williams syndrome and controls. Those subjects, however, were found to have greater respiratory-related arousals than control subjects, and such arousals may contribute to decreased sleep efficiency [10].

EEG Features

Gombos et al. (2011) reported that EEG spectra during sleep in subjects with Williams syndrome showed higher delta and slow-wave activity over the frontopolar leads bilaterally in terms of both absolute and relative power compared to age- and sex-matched typically developing controls. The authors also noted a region-independent decrease in relative alpha and sigma power. The delta activity and slow-wave activity increases in subjects with Williams syndrome might have been related to increased slow-wave sleep, but the authors suggested that these changes could also have reflected fatigue or delayed maturation [17]. Subsequently, further analyses of sleep EEG in subjects with Williams syndrome compared to controls suggested a decrease in alpha/low sigma power,

as well as a redistribution of 8–16 Hz EEG power toward faster frequencies, which was felt to be a characteristic feature of Williams syndrome [18]. More recently, Bódizs and colleagues studied 21 subjects with Williams syndrome across a range of ages (6–29 years) and compared these to 21 typically developing subjects matched for age and sex. The authors reported an accelerated age-dependent sleep architectural impairment affecting sleep efficiency, wake after sleep onset, and wake time [19].

Endocrine Markers

Sniecinska-Cooper et al. (2015) determined melatonin and cortisol levels in children with Williams syndrome to explore a possible relationship between the circadian rhythm of the expression of these hormones and sleep patterns [20]. The authors compared 25 children with Williams syndrome with 27 typically developing controls matched for age and gender. For each subject, saliva was collected at three time points over a day (4–6 PM, shortly before customary bedtime and after awakening for the day). The levels of salivary cortisol and melatonin were analyzed by enzyme-linked immunoassays. Sleep patterns were analyzed by actigraphy and the Children's Sleep Habits Questionnaire. The authors found high individual variability in the amount of melatonin secreted in both groups, and no significant differences between the groups in samples collected in the afternoon or at bedtime. Comparing the ratios between bedtime and afternoon samples, there was a less pronounced rise in melatonin levels before sleep in the group with Williams syndrome compared with the typically developing group. A similar cortisol ratio evaluation showed that the group with Williams syndrome had less of a drop in cortisol at bedtime, as well as a higher normalized value of cortisol at bedtime. From a sleep standpoint, subjects with Williams syndrome had significantly increased sleep latency, increased movement time, increased wake time, and more sleep fragmentation on actigraphy compared to controls. On the Children's Sleep Habits Questionnaire, parents reported that 15% of subjects with Williams syndrome previously had sleep problems, and 65% had current sleep problems (23% of these children occasionally). None of the parents of typically developing children indicated that subjects currently or previously had sleep problems. In summary, the authors concluded that abnormalities in secretion of melatonin and cortisol may be underlying factors or contribute to sleep problems in individuals with Williams syndrome [20].

Management

The approach to assessment and management of sleep disorders in children with Williams syndrome should include, where appropriate, overnight polysomnography for evaluation of primary sleep disorders (such as obstructive sleep apnea and/or periodic limb movements in sleep). In turn, if an intrinsic sleep disruptor is found, then management should be initiated; there may be a role for follow-up overnight polysomnography to monitor treatment response or interim progression. After assessing for primary sleep disorders and excluding medical issues (e.g., pain, gastroesophageal reflux, etc.), parents of children with Williams syndrome should be provided with education and guidelines for behavioral intervention. This approach may mirror steps recommended for families of children with other neurodevelopmental disabilities and include creating a quality sleeping environment, promoting self-soothing skills that allow the patient to initiate sleep and maintain sleep independently, adopting a consistent sleep/wake schedule, and optimizing parent-child interactions [21].

There are no sleep medications that have been trialed specifically in the Williams syndrome population through designated studies. As with other children who have neurodevelopmental disorders and sleep issues, melatonin can be tried. It would be reasonable to start with a low dose (0.5–1 mg) at bedtime for hypnotic effect and titrate as needed. Over-the-counter preparations of melatonin that include other active ingredients should be avoided, and extended release melatonin preparations could be considered for children with sleep-maintenance insomnia features [21, 22]. Wasdell et al. (2007) reported the first randomized, placebo-controlled crossover study to demonstrate that controlled-release melatonin is an effective and safe means of treating sleep initiation and maintenance issues in children with neurodevelopmental disorders. Controlled-release melatonin 5 mg (initial trial) increased total sleep duration by approximately 30 min and shortened sleep latency by about the same amount. In the subsequent open label portion of the study, doses as high as 15 mg were used in some subjects [22].

Future Directions

For the child in the office with Williams syndrome, the evaluation and treatment of sleep problems is an important component of overall management. Indeed, optimizing sleep may expand developmental potential and greatly improve quality of life for the patient and the patient's family. Future research should be aimed at teasing out the genetic contribu-

tions to disturbed sleep in Williams syndrome. For example, circadian rhythms may be disturbed, as reflected by endocrine studies, leading to disrupted sleep patterns. Further work is needed to validate the techniques of saliva collection in younger children for cortisol and melatonin assays [23]. Similarly, endocrine studies might be confirmed in larger subject groups. Further assessment of daytime sleepiness as it relates to endocrine changes is needed, as well as determining actual endocrine values during sleep.

As with other parameters including EEG spectral power changes, it will be critical to determine what changes in sleep patterns may be unique to Williams syndrome (in the setting of 7q11 haploinsufficiency) versus non-specific changes seen broadly in populations of children with neurodevelopmental disabilities. Additional studies are needed to replicate findings that support or define characteristic sleep-related Williams syndrome phenotypes. While general approaches to management of sleep problems in Williams syndrome are certainly helpful, targeted interventions in the future could be introduced to improve sleep and daytime functioning more specifically in children with Williams syndrome based on a knowledge of downstream genetic effects.

Case Vignette

Sally is an 11-year-old girl with a history of Williams syndrome, insomnia issues, and obstructive sleep apnea.

Her history includes adenotonsillectomy at age 2 years for obstructive sleep apnea symptoms. An overnight polysomnogram performed in the months after surgery showed borderline/mild obstructive sleep apnea (obstructive apnea-hypopnea index 1.7 events per hour). Because of her developmental issues, she was placed in a self-contained classroom for her main courses. She repeated the first grade and had a one-on-one specialist in the classroom. She has received multiple services at school as well as privately, including speech therapy, occupational therapy, and social skills training.

At age 5 years, she was seen in the sleep center for anxiety around bedtime, when she would cry and scream for up to an hour. Her mother began allowing Sally to fall asleep in her parents' bed, where she would fall asleep quickly and remain until morning. On nights when she was able to fall asleep in her own bed, Sally would typically wake overnight and move into her parents' bed, again staying for the night. She did not have symptoms at that time of snoring, paradoxical effort, gasping in sleep, or witnessed apneas. If she did not get adequate sleep, she was reported to be irritable and fatigued the following day. Overall, she had hyperactivity and poor concentration during the day. Given her anxiety and sleep onset association insomnia, behavioral recommendations were made, including setting up a separate bed in the parents' room and stressing the importance of sleeping in her own bed, whether in her room or her parents' room. It was also recommended that the family use a timer to let her know how long she should remain in her bedroom before being allowed to move into her parents' room. It was to start at 3 min, and if Sally cried out prior to timer going off, it would be reset; her parent would check on her during the 3 min interval as a positive reinforcement. It was also suggested that the patient have playtime during the day in her room to help lessen her anxiety there. Melatonin was added and helped with sleep onset issues. She gradually developed greater independence, falling asleep more quickly, and sleeping in her bedroom most nights. Melatonin was subsequently discontinued, and behavioral recommendations included the use of a "good morning light" (a bedroom lamp set with a timer for the desired wake time) in order to help her understand when she was permitted to leave her room in the morning.

At age 10, Sally had developed increased snoring and difficulty breathing during sleep and underwent repeat overnight polysomnography to assess for obstructive sleep apnea. The study demonstrated sleep architecture findings of decreased sleep efficiency (due to an increased sleep latency and multiple awakenings), and increased arousals and awakenings, with many arousals related to respiratory events. There was severe obstructive sleep apnea, with an obstructive apnea-hypopnea index 25.5 obstructive events per hour (normal <1.5 events per hour). Central apneas and periodic breathing were not increased. Baseline oxyhemoglobin saturation was normal; the oxyhemoglobin saturation nadir was mildly abnormal. The periodic limb movement index was normal.

Sally was evaluated in the sleep center office for continuous positive airway pressure (CPAP) therapy initiation. After an interval of desensitization for mask use habituation, she was placed on an empiric regimen of 5 cm H_2O CPAP. She then underwent a CPAP titration that showed resolution of obstructive sleep apnea on CPAP 9 cm H_2O. Her mother reported that Sally's behavior was improved on CPAP, and download of the home machine showed excellent adherence; her mother reported, however, that she was placing the patient's CPAP mask after the patient was asleep and

struggled put the mask back on after the patient awoke overnight. It was decided that her mother would make CPAP part of the "tuck-in" routine at bedtime, and Sally would try to fall asleep with the mask on. She also was to practice wearing her CPAP mask while awake (such as while watching television). Her CPAP use improved gradually, such that the most recent download of her home machine showed use for 30 consecutive nights, with an average use of over 7 h per night.

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Tuberous Sclerosis Complex

19

Tanjala T. Gipson

Case Vignette

DC is a 2-year-old young boy with tuberous sclerosis complex (TSC) with restless sleep in his new bedroom. His restlessness is worsened by illness. His father's goal for DC's sleep is that he would not scream and wake up frequently as his parents' sleep is being interrupted when they awaken to console him. DC also has epilepsy treated with vigabatrin and has been seizure-free since infancy. An EEG obtained to determine if his restlessness was due to subtle seizure activity was negative, and he was referred to our center's Sleep Clinic for further evaluation and recommendations.

DC was diagnosed with parasomnias, unusual events occurring during or around sleep. Night terrors are a kind of parasomnia during which children cry out and appear markedly frightened during sleep. As such, his family was advised that the events would improve over time with adjustment to his new environment. It was recommended that they not enter his room to intervene and consider adjusting his bedtime to 30 min earlier. Iron labs, ordered to rule out a potential etiology of restless sleep, were normal. Three months later, his restless sleep resolved.

Introduction

Tuberous sclerosis complex (TSC) is a genetic syndrome occurring in 1/6000 live births that may either be inherited in an autosomal dominant manner or develop spontaneously. It is classified as a neurocutaneous disorder due to the predominance of brain and skin manifestations and is clinically diagnosed based upon the presence of major and minor features (Table 19.1) [1]. Autism (61%) [2, 3], intellectual disability (45%) [4], and epilepsy (up to 90%) [5–7] are comorbidities linked to this condition. The neurobiology of TSC lies in loss of regulation of the protein kinase mammalian target of rapamycin (mTOR). Typically, the genes *TSC1* and *TSC2* encoding hamartin and tuberin, respectively, form a complex that functionally serves to activate and deactivate mTOR, a protein that mediates cell growth among other functions. An inherited or spontaneous mutation in either *TSC1* or *TSC2* renders mTOR constitutively active. It is this excessive activity of mTOR that has been linked to the major and minor features as well as the comorbidities associated with TSC [8]. The effects of mTOR on the brain are multiplicative (Fig. 19.1) [9–16]. In terms of sleep dysfunction in TSC, the disruption of the balance of gamma-aminobutyric acid (GABA) and glutamate, the brain's most abundant neurotransmitters, is of particular interest. GABA mediates inhibition, while glutamate is responsible for excitation in the synaptic activity of the brain. An appropriate balance is necessary to achieve optimal learning and maintain freedom from seizures [17, 18]. Preclinical evidence suggests that GABA activity is too low in TSC [14, 19–21]. In addition to epilepsy it is plausible that this imbalance may also result in the sleep disturbances so commonly observed in this population. Fortunately, there are targeted therapies for TSC; however, they have not been studied primarily for sleep disturbances in this population to date.

T. T. Gipson
Tuberous Sclerosis Center of Excellence,
LeBonheur Children's Hospital, Memphis, TN, USA
e-mail: tgipson@uthsc.edu

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Table 19.1 Tuberous sclerosis complex – major and minor features

Major features	Minor features
Cortical dysplasias >3	Dental enamel pits
Subependymal nodules >2	Hamartomatous rectal polyps
Subependymal giant cell astrocytoma	Cerebral white matter radial migration lines
Hypomelanotic macules (3 or more)	Gingival fibromas
Shagreen patch	Nonrenal hamartoma
Facial angiofibromas >3 or cephalic plaque	Retinal achromatic patches
Multiple renal nodular hamartomas	"Confetti" skin lesions
Nontraumatic ungual fibromas >2	Multiple renal cysts
Cardiac rhabdomyoma	
Pulmonary lymphangioleiomyomatosis (LAM) and/or renal angiomyolipomas[a]	

Definite TSC, 2 major or 1 major plus 2 minor features; possible TSC, 1 major or >2 minor features
[a]When both pulmonary LAM and renal angiomyolipomas are present, they are counted as one major feature of TSC

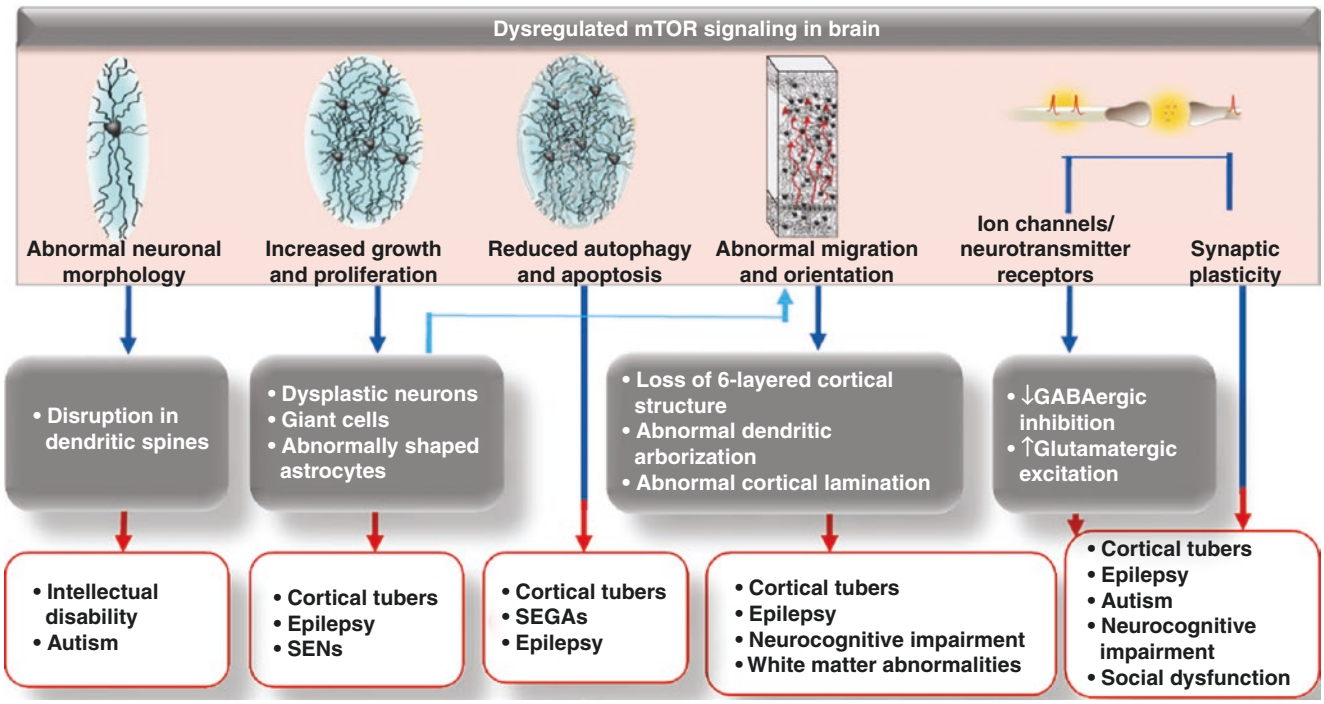

Fig. 19.1 Illustration depicting the neurobiological impact of dysregulated mTOR (mammalian target of rapamycin) (© 2018 Novartis AG)

Evidence Base

Diagnosis

Clinicallydefinite TSC is characterized by the presence of the combination of two major *or* one major and two minor features. Clinically possible TSC is present when there is one major *or* two minor features. Genetic testing is useful in determining whether there is a mutation in *TSC1* or *TSC2*; however, there are individuals with no mutation identified who have a clinical diagnosis of TSC. To date, the literature suggests that mutations in *TSC2* as compared to those in *TSC1*, and spontaneous as opposed to inherited mutations, are associated with greater phenotypic severity [22, 23]. A correlation between the protein effects of these mutations and cognitive outcomes was discovered in a recent review [24].

After confirmation of a TSC, diagnosis begins a lifelong schedule of surveillance studies as the major and minor features of TSC can appear throughout life. Guidance exists for the frequency of surveillance studies [25]. Among the recommendations, neuroimaging is warranted as individuals are at risk for the development of three different types of brain

lesions – subependymal nodules, cortical tubers, and subependymal giant cell tumors (SEGT). Subependymal nodules line the ventricles of the brain and have not been often associated with pathology. SEGTs often initially appear to be subependymal nodules but are distinguished by their contrast enhancement on brain MRI and localization near the foramen of Monro. Although benign and slow-growing, enlargement often leads to obstruction of CSF resulting in hydrocephalus, headaches, and seizures. Cortical tubers are abnormal aggregations of neuronal and glial cells that often appear early on but are most prominent after the age of 2 years when myelination is mostly complete (Fig. 19.2). These lesions have been associated with epilepsy and neurodevelopmental outcome [27–31]. Abdominal imaging is mandated for life as individuals may commonly develop renal lesions – cysts, carcinoma, and/or angiomyolipoma.

Benign growths have also been reported in other solid organs. At least two cases of insulinoma have been reported in TSC [32, 33]. Sleepiness associated with increased seizure frequency was reported in one of them emphasizing the need for heightened vigilance for unusual causes of sleep disorders in this population [32]. In another case, calcified subependymal nodules in the brainstem were associated with central and obstructive sleep apnea associated with hypoxia-induced seizures [34]. Further, a young girl with TSC, high-functioning autism, and expressive language delay was found to have electrical status epilepticus during sleep (ESES) emanating from the temporal lobe on sleep EEG [35]. REM interictal epileptiform discharges were associated with the ictal EEG and largest tuber with good outcomes noticed after epilepsy surgery in another individual with TSC [36].

In addition to neurological diagnostics, evaluations are also indicated by ophthalmology, genetics, dentistry, nephrology and/or urology, dermatology, and cardiology.

Management

Ongoing, timely surveillance and early treatment with targeted therapeutics for the known features and associated comorbidities of TSC are the primary aims of management in this population.

Sleep Disturbances in TSC

In adults with TSC, the majority had epilepsy, and 31% reported a sleep disorder in a questionnaire-based study. Insomnia was associated with obstructive sleep apnea and restless legs syndrome. Daytime sleepiness correlated with the presence of mental health medications, depression, and antisocial behavior. Using medications for epilepsy correlated with daytime sleepiness, anxiety, and inattention [37]. In a series of pediatric patients with TSC who underwent two overnight polysomnographic studies, consistent sleep abnormalities included decreased REM sleep, shorter total sleep time, higher number of awakenings and stage transitions, reduced sleep efficiency, and increased wakefulness after sleep onset and stage 1. Epileptic events related to sleep and large temporal or bifrontal tubers were associated with these abnormalities [38].

We employ a three-in-one approach (functional, symptomatic, and organic) to assessing sleep difficulties in individuals with TSC. A functional assessment, often administered by behavioral professionals, seeks to identify if there are any variables in the environment that may maintain the sleep dysfunction [39]. For example, a child who gets up from bed and is given a cup of milk for soothing may stay up later to seek the attention of this interaction with the parent. Symptomatic assessments in TSC focus on the severity and adequacy of treatment of epilepsy as seizures often interrupt sleep in this population. Finally, an organic assessment relates to the identification and treatment for TSC-specific features, such as subependymal giant cell tumors.

Epilepsy

Epilepsy occurs in as many as 90% of individuals with TSC and may often be refractory [40–42]. Infantile spasms, a catastrophic type of epilepsy, have been treated with vigabatrin [26, 43–48]. This medication is an irreversible inhibitor of GABA transaminase and thus functions to restore GABA levels that are abnormally low in this population likely explaining its higher rate of efficacy among those with TSC. Further, evidence supports a role for vigabatrin in refractory complex partial seizures associated with TSC [49]. Clobazam also functions to target abnormally low GABA levels and has also been found to be helpful in this group [50].

SEGAs and Renal Angiomyolipomas

Subependymal giant cell astrocytomas (SEGAs) and renal angiomyolipomas have been historically monitored until growth was associated with either increased in intracranial pressure or hematuria, respectively. However, everolimus has now been FDA-approved and indicated for both tumors allowing medical management when tumors are as small as 3 cm [51, 52]. Trials are ongoing to determine if everolimus is useful for epilepsy [53]. Sirolimus, another mTOR inhibitor, has been approved for the treatment of pulmonary lymphangioleiomyomatosis [54]. A clinical trial of a topical version of sirolimus for facial angiofibromas has been completed and is awaiting an FDA decision [55].

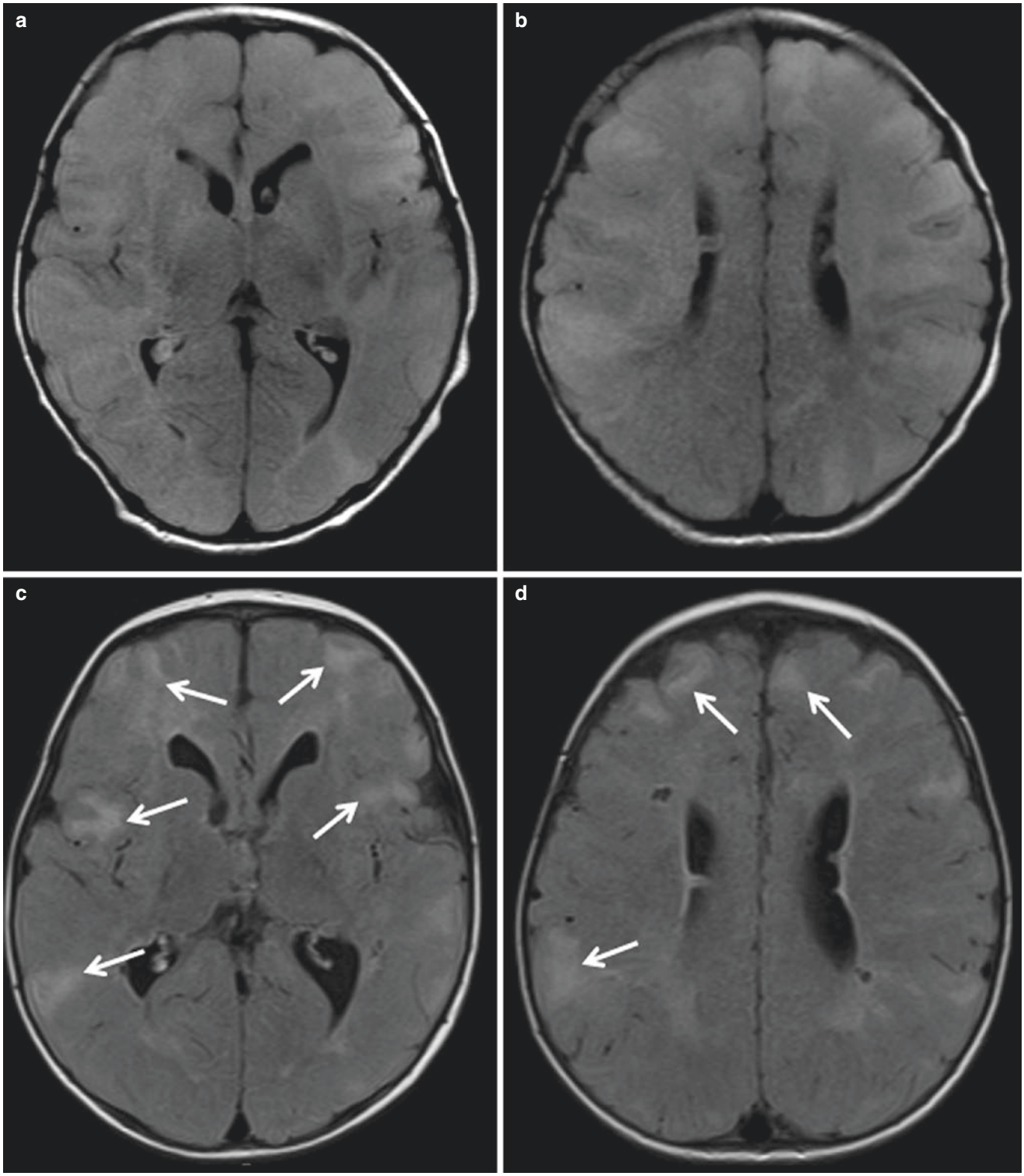

Fig. 19.2 (**a**) and (**b**) Axial FLAIR (fluid attenuated inversion recovery) images of a 1-month-old infant with tuberous sclerosis complex reveal multiple FLAIR hyperintense lesions representing tubers and involving the cortical and subcortical white matter of the bilateral frontal and parietal lobes. Additionally, multiple subependymal nodules were observed in the body of the lateral ventricles and the left foramen of Monro (not illustrated). (**c**) and (**d**) Matching, axial FLAIR images of the same child at 14 months of age reveal again multiple cortical and subcortical FLAIR hyperintense tubers within the bilateral frontal and parietal lobes (white arrows in (**c**) and (**d**)) (From Gipson et al. [26]. Reprinted with permission from Elsevier Limited)

Areas of Uncertainty (Future Directions)

Diagnosis

As sleep in TSC is not commonly studied, future studies are needed to focus on best practices for the effective screening and diagnostic evaluation of sleep disorders in this population. Validation of measures such as the TAND checklist [56] and the three-in-one approach used in our center could prove useful for screening. Diagnostic evaluation may require a comprehensive approach to include polysomnogram, EEG, or a combined study as well as a thorough investigation for both rare and common tumors associated with TSC. It is uncertain if this should be applied uniformly to the entire population at discrete intervals or just as difficulties arise.

Management

The applicability of traditional behavioral and sleep interventions to individuals with TSC warrants further study. Melatonin, for example, seems to work as a simple sedative in children and adults with TSC but does not correct any abnormalities in secretion of melatonin [57]. Prolonged-release melatonin tested in a group of individuals with neurodevelopmental disorders including a few with TSC was well tolerated in the majority of patients and positively impacted multiple facets of sleep – sleep latency, duration, quality, and frequency of awakenings [58]. In a randomized, placebo-controlled trial with crossover of seven individuals with TSC with sleep disorders compounded by epilepsy and learning difficulties, increased total sleep time and a trend toward better sleep onset time was associated with treatment using 5 mg of melatonin [59]. Contrastingly, melatonin improved not only total sleep time and sleep latency but also decreased the number of night awakenings in a study of individuals with intellectual disabilities including some with TSC using a dose range of 0.5–9 mg [60].

Using vigabatrin or everolimus to target the potential mechanism of sleep disturbances in TSC by restoring the imbalance of GABA/glutamate is a unique opportunity for this population and worthy of study in well-designed clinical trials.

Guidelines

The clinical consensus guidelines for TSC have recently been updated for medical management and cognition [1, 25].

Conclusions and Recommendations

Clinicians treating individuals with TSC should be vigilant in monitoring for the development of sleep disturbances. Although sleep disturbances in TSC are very common, they are infrequently studied. Therefore, the approach for screening, diagnosis, and treatment does not differ from the general population. However, the burden and localization of neurologic disease and the impact of epilepsy and rare tumors are unique aspects of TSC that must be considered during the diagnostic work-up. Fortunately, neurobiologically targeted medications are available for TSC and may provide an opportunity for actual disease *modification*. Therefore, well-designed clinical trials are warranted.

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Sleep and Epilepsy

20

Dragos A. Nita and Shelly K. Weiss

Abbreviations

ADNFLE	Autosomal dominant nocturnal frontal lobe epilepsy
AED	Antiepileptic drugs
BRE	Benign Rolandic epilepsy
CPAP	Continuous positive airway pressure
CSWS	Continuous spike-wave during sleep
DRE	Drug-resistant epilepsy
EDS	Excessive daytime sleepiness
EEG	Electroencephalography
EMU	Epilepsy monitoring unit
GTC	Generalized tonic clonic
IED	Interictal epileptiform discharges
JME	Juvenile myoclonic epilepsy
LKS	Landau-Kleffner syndrome
NDD	Neurodevelopmental disabilities
NPO	Nil per os (nothing by mouth)
OSA	Obstructive sleep apnea
PLMD	Periodic limb movement disorder
PSG	Polysomnography
REM	Rapid eye movements
RLS	Restless leg syndrome
SE	Sleep efficiency
SL	Sleep latency
SUDEP	Sudden unexpected death in epilepsy
SWS	Slow-wave sleep
TST	Total sleep time
VNS	Vagus nerve stimulation
WASO	Wakefulness after sleep onset

D. A. Nita · S. K. Weiss (✉)
Department of Pediatrics, Division of Neurology, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada
e-mail: dragos.nita@utoronto.ca; shelly.weiss@sickkids.ca

Introduction

Children with neurodevelopmental disabilities (NDD), regardless of the etiology, often have associated comorbidities. Among them, epilepsy is very common, and those children who have epilepsy frequently experience seizures during sleep. Seizures can occur both during daytime sleep and nocturnal sleep. It is known that children with epilepsy (even those without NDD) have significantly more sleep problems than their siblings or healthy controls [1]. It is essential for clinicians who work with children with NDD to understand how to evaluate and manage children who have epilepsy, particularly nocturnal epilepsy. Sleep can be disrupted either by the ictal event (seizure) and/or by the interictal (between seizures) abnormal brain activity. This disruption can result in daytime problems including (but not limited to) problems with memory, learning, behavior, attention, and daytime fatigue.

The incidence of epilepsy in children with NDD varies depending on the etiology of the child's intellectual delay as well as the severity. In many children, there is a relationship between those who have a lower intelligence having a higher incidence of seizures. An example of this correlation is reported in children with autism and epilepsy [2]. This correlation is understandable as, irrespective of the etiology of a child's NDD, increasing severity of cognitive delay is associated with more pathology in brain circuitry.

Epilepsy

Seizures are common in childhood, affecting 4–16% of children before 16 years of age [3]. Epilepsy (which is characterized by recurrent seizures due to a genetically determined or acquired brain disorder) is also a common neurological condition in pediatric populations with an estimated lifetime prevalence of 1% [4]. Seizures result from electrical hypersynchronization of neuronal networks in the cerebral cortex. Seizures are divided into two types, generalized, where the ictus originates in all regions of the brain simultaneously,

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and focal/partial, where the ictus originates in one focal region of the brain and can potentially spread to other areas. In order to provide an understanding of the intricate relationship between sleep and epilepsy in children with NDD and to have an approach to the clinical management of children with this comorbidity, a brief review follows outlining common epilepsy definitions (Table 20.1).

Seizures and Sleep

The connection between seizures and sleep has been recognized well before the era of evidence-based medicine, since the time of Hippocrates and Aristotle. In the modern era with advancements in the evaluation of children and adults with epilepsy, using neurophysiologic monitoring including polysomnography as well as continuous video EEG monitoring, much has been learned about the bidirectional relationship between sleep and epilepsy.

Sleep and epilepsy have two essential attributes in common. They are mediated by specific electrical oscillations of the brain networks and mediated by the same intrinsic cellular properties, sleep representing physiologic brain rhythms while seizures represent the evolution of normal oscillations into pathological patterns. Secondly, sleep and seizures share the same neuronal network, comprising the cerebral cortex, the thalamus and reticular thalamic nucleus, and the ascending modulatory systems from brainstem and forebrain. Thus it becomes obvious that the same mechanisms mediate both the different states of vigilance and the transformation of normal rhythms into paroxysmal epileptic activities. In addition, there are other factors influencing the bidirectional relationship between seizures and sleep such as the effects of antiepileptic medication (which can either stabilize sleep or contribute to changes in sleep architecture and daytime alertness) and the effect of other surgical or neuromodulatory therapies on sleep, as well as the effect of primary sleep disorders on seizures and epilepsy.

Table 20.1 Common epilepsy definitions

Term	Definition
Interictal epileptiform discharges (IED)	IED are brief, intermittent, and distinctive waves or complexes, present between seizures in the EEG recordings of people with epilepsy
Seizure	Seizures are paroxysmal clinical manifestations secondary to the presence of abnormal, excessive, synchronous electrical cellular activity in the brain
Epilepsy	Clinical condition characterized by a predisposition toward recurrent unprovoked seizures
Epilepsy syndrome	An epilepsy syndrome is an association of various clinical and electrographical EEG features that are specific for a particular type of epilepsy. Such features include age of onset, types of seizures commonly seen, part of the brain involved, clinical course, genetic etiology
Drug-resistant epilepsy (DRE)	DRE is a type of epilepsy in which seizure freedom cannot be achieved after two well-tolerated, appropriately chosen antiepileptic drugs were taken for an appropriate period of time

Effect of Sleep on Seizures

Stages of Sleep Have Different Effects on EEG and Seizures

The transition from wakefulness to slow-wave sleep (SWS) is a consequence of a blockade of afferent synaptic volleys at the thalamic level and a deprivation of the cerebral cortex of external signals. This blockade promotes rhythmic high-amplitude, slow-oscillatory activities in the corticothalamic networks that underlie the slow waves seen on the EEG during SWS. In contrast activated states such as wakefulness and REM sleep are characterized by a desynchronized, low-amplitude EEG reflecting neurons being closer to the firing threshold, ensuring in this way an accurate transmission of information and an increased responsiveness to stimuli. This is why during sleep, when the cortical states are characterized by highly synchronous activities, there is an increased propensity for the spreading of the interictal discharges and seizures, given that at the cellular level these types of activities can seamlessly develop from the cortical slow oscillations. However, during the awake state and REM sleep, which are both activated cortical states, neurons are steadily depolarized and are more resilient to the spread and expression of both interictal discharges and seizures.

In clinical practice it is very important to assess the propensity for seizure both during sleep and wake. This is why it is common to evaluate a child with epilepsy by obtaining an EEG during sleep. Gibbs and Gibbs, pioneers in the use of EEG for the diagnosis and treatment of epilepsy, were the first to demonstrate the activation of interictal discharges by sleep and recognize the value of sleep clinical EEG recordings in obtaining a diagnosis of epilepsy as well as localization of the ictal onset. They reported that interictal epileptiform discharges were observed in about 36% of awake EEGs, but this number increased to 82% during sleep [5]. This finding remains true today.

Non-REM sleep is a powerful activator of interictal discharges [6]. The IEDs may or may not be present during wakefulness, but they increase at sleep onset, attain their maximum incidence during SWS, and can even become continuous in certain patients, producing an electrographical pattern called continuous spike-wave during sleep (CSWS) or electrographic status epilepticus during sleep (ESES). During REM sleep they are rare and usually localized to the most epileptogenic areas. The field of an interictal discharge

typically enlarges as sleep deepens and is strictly localized during REM sleep in patients with focal epilepsy. The fact that REM sleep is highly resistant both to the expression of interictal epileptiform discharges and to their cortical spread is useful in determining the seizure onset zone in patients with medically refractory epilepsy undergoing evaluation for epilepsy surgery [7].

For patients with generalized epilepsy, sleep is a less important activator, but a similar pattern of the expression of interictal discharges can be seen in most idiopathic generalized epilepsies. During slow-wave sleep, generalized interictal epileptiform discharges typically become more disorganized, and sometimes spike-wave discharges are replaced by higher-amplitude lower-frequency polyspikes. The findings seen during REM sleep are similar with the awake findings and are characteristic for the particular type of epilepsy [8].

Sleep Deprivation Provokes Seizures

Sleep deprivation is recognized as a provoking factor for seizures, and it is used in clinical practice to increase the likelihood of capturing EEG abnormalities in patients with suspected epilepsy. Whether the activation of the interictal epileptiform discharges is produced by the sleep deprivation per se or is the effect on an increased time spent during SWS, sleep after sleep deprivation remains a subject of debate. While most clinicians consider that the degree of activation of IEDs by sleep deprivation is similar with that produced by natural sleep captured during routine procedures, there are also evidences that sleep deprivation is a stronger activator than natural sleep [9].

Sleep Disorders in Patients with Epilepsy

Sleep disorders that are common in patients with epilepsy can contribute to poor seizure control due to inadequate quantity and/or sleep disruption. Sleep disruption and consequent increase in seizures can have many deleterious effects including problems with memory, learning, attention, behavior, and increased daytime fatigue. It is well recognized that sleep is important for learning and cognition, as has been studied in children with epilepsy [10, 11]. The clinician must be cognizant of the evaluation for any type of sleep disorders (e.g., insomnia, circadian rhythm disorder, sleep apnea, parasomnias as outlined in this textbook) when evaluating a child with epilepsy.

An example of a sleep disorder that should not be missed is obstructive sleep apnea (OSA). Obstructive sleep apnea treatment has been shown to improve seizure control in pediatric and adult patients with epilepsy and OSA [12–14]. In a retrospective review of 27 children with epilepsy and OSA, 10 subjects became seizure-free, and 3 had a significant reduction in seizures after surgical treatment (tonsillectomy and adenoidectomy). In a second smaller retrospective case series of nine children with NDD who also had OSA and epilepsy, seizure frequency was reduced in five of the nine children in the first year after treatment for OSA without any changes in AED treatment [15].

In a referred sample of adults with epilepsy, one third were found to have OSA [16]. The factors that may contribute to this high incidence are the weight gain seen with the use of specific antiepileptic drugs in parallel with a relatively decreased level of physical exercise. In addition, some AEDs may act as depressants of the central nervous system and may decrease the airway tone (especially barbiturates and benzodiazepines). The fragmentation of sleep and the sleep deprivation seen in patients with OSA lead to more frequent seizures, and conversely treating OSA can lead to better seizure control and even a decrease in the frequency of the interictal epileptiform discharges [12, 13, 17].

Adult patients with OSA have different treatment strategies and have been studied more thoroughly. In an adult cohort, the treatment of OSA with continuous positive airway pressure (CPAP) in patients with focal epilepsy not only normalized the apnea-hypopnea index but also produced a marked reduction in spike rate [17], thus supporting the hypothesis that OSA may increase the excitability of the cortical networks.

Effect of Seizures on Sleep

Seizures Alter Sleep Architecture, Leading to Hypersomnia, Sleep Fragmentation, and Arousals from Sleep

The normal sleep architecture and its continuity are essential for the normal daytime functioning of the individual, memory consolidation, and attention. These processes are affected when sleep architecture is disrupted. It is easier to study adult patients in a sleep laboratory as there are better defined normal values to which to compare the data. Adult patients with epilepsy experience a variety of alterations of the normal sleep architecture such as increased wake after sleep onset, increased number of arousals, decreased duration of REM sleep, and prolonged REM sleep latency [18, reviewed in 19].

There are several studies documenting the adverse effects of epilepsy on sleep patterns in children. In one study of 105 children with epilepsy (66% with developmental delay and 23% with autism), there were a number of changes in sleep patterns reported and sleep behavior when compared to controls. These changes included increased rates of both parent-child room sharing and co-sleeping as well as higher rates reported by parent questionnaire of parasomnias, night waking, shorter sleep duration, increased daytime sleepiness, and increase in sleep onset delay and in bedtime resistance [20]. These results highlight the importance in balancing parents' desire to co-sleep with their child who has nocturnal seizures with establishing good sleep practices (which is outlined in Chap. 28).

Children with NDD and epilepsy have a greater incidence of sleep problems and reduced sleep efficiency compared to children without epilepsy. In several studies, it is reported that there are some factors related to the epilepsy accounting for this association (e.g., nocturnal seizures, DRE, generalized seizures, and certain epilepsy syndromes) as well as comorbid factors (e.g., presence of developmental delay), increased anxiety related to sleep, and an increased incidence of behavior problems [1, 19, 21–23].

Many children with epilepsy complain about poor sleep quality and daytime sleepiness. While most of the time these are attributed to the secondary effects of the AED, a particular attention should be directed to children with mild seizures, on AED monotherapy, with normal AED serum levels, and with well-controlled seizures given that they may represent a primary sleep disorder [24]. These changes can impact children with NDD more than normal individuals given the preexisting burden of the disease on their daily functioning. Indeed, many children with NDD already have daytime problems with attention and memory, and they can be exacerbated not just by nocturnal seizures but also by an increased incidence of interictal discharges.

Approach to the Evaluation of Epilepsy in Children

There may be many influences affecting sleep in children with NDD and epilepsy as discussed above and outlined in Fig. 20.3.

Case Vignette #1

A 6-year-old boy with developmental delay and autism presents with a 6-month history of regression. A previous routine EEG captured only wakefulness and was significant for the presence of IEDs (Fig. 20.1). Interictal abnormalities are seen in a large proportion of children with autism. The history of autistic regression prompted an overnight sleep EEG that demonstrated a very pronounced activation of the IEDs by sleep and the presence of continuous spike-wave during sleep (CSWS) (Fig. 20.2). This pattern resolved in the follow-up EEG after he was placed on medication, and this was associated with a significant improvement in his developmental skills.

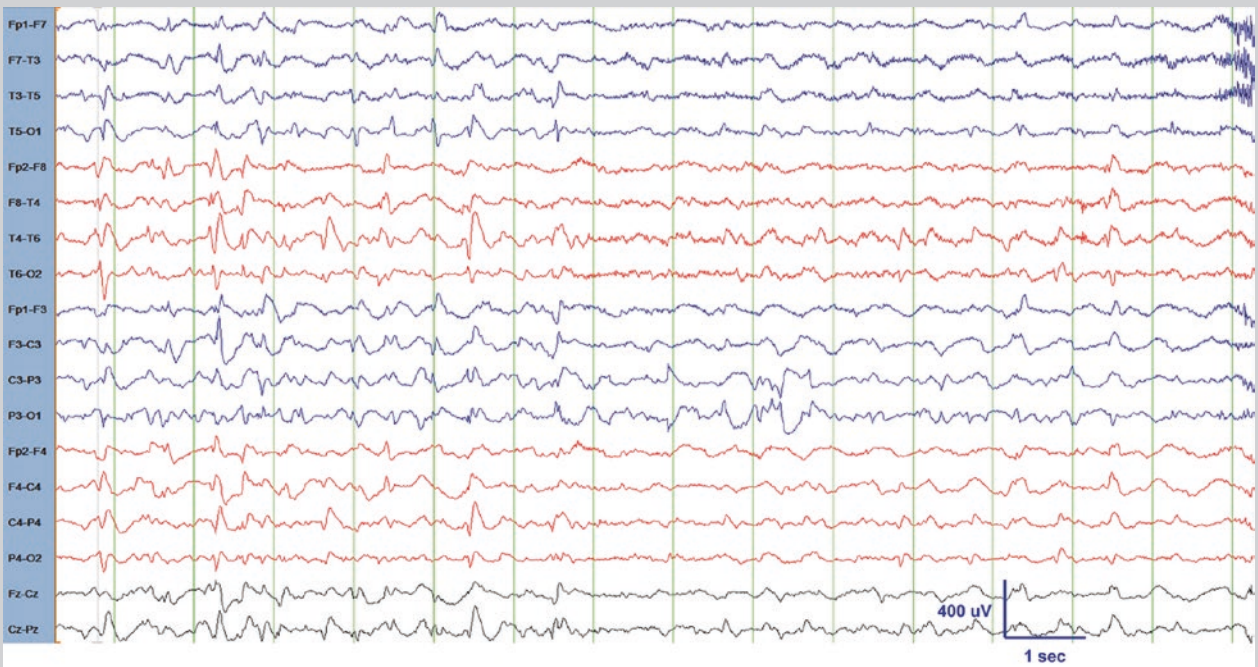

Fig. 20.1 Awake EEG in a 6-year-old boy with developmental delay and autism (15 s, 21 channels, anteroposterior bipolar montage)

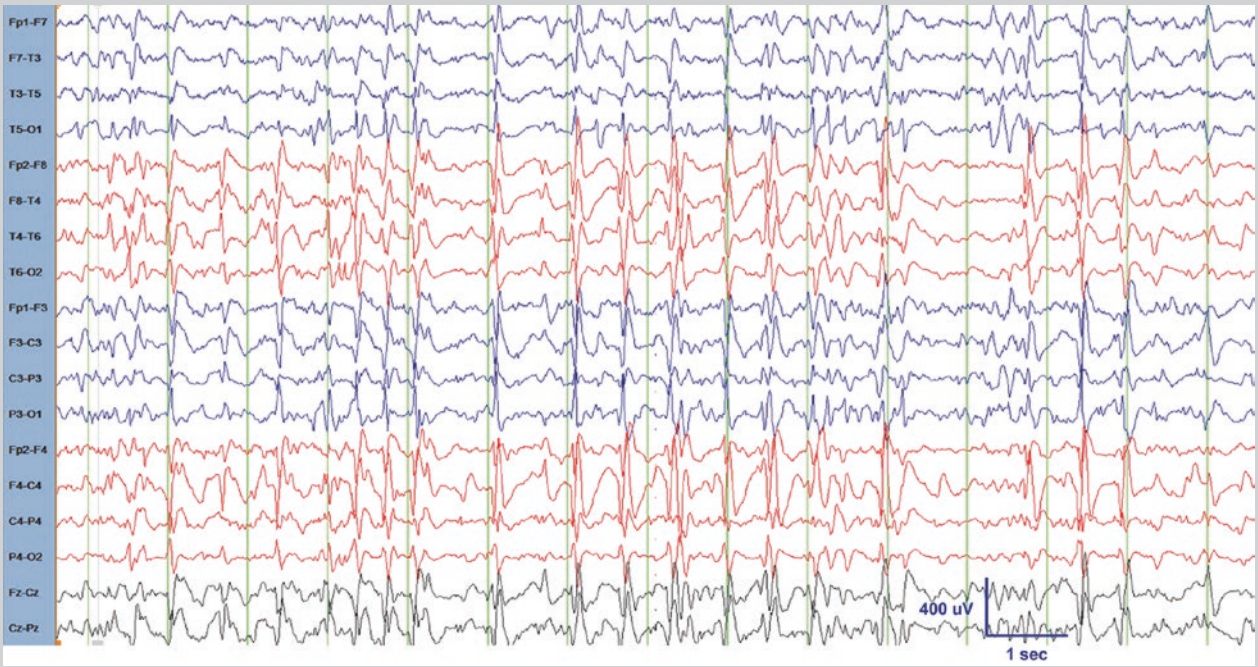

Fig. 20.2 Continuous spike-wave during sleep captured during a sleep recording in the same patient, responsible for his regression (14 s, 21 channels, anteroposterior bipolar montage)

Comment

It is important for the clinician involved in the care of children with NDD, epilepsy, and sleep pathology to be aware of all these reciprocal interactions between seizures, sleep architecture, sleep deprivation, and possibility of sleep-activated interictal discharges. Although commonly children with this pattern will have seizures, other symptoms may include autistic behavior, regression, auditory agnosia, and/or deterioration in school performance. Many clinicians consider the terms CSWS and ESES interchangeably. CSWS/ESES is an epileptic encephalopathy with >85% spike-wave index.

Epilepsy Syndromes with Seizures Related to Sleep

Certain epilepsy syndromes have a specific pattern of seizures in relation with sleep. These are outlined in Table 20.2.

Evaluation of Children with Nocturnal Seizures

A detailed review of the evaluation of a child with NDD and possible nocturnal seizures is beyond the scope of this chapter. A careful clinical history and physical examination is required, followed by neuroimaging (usually a MRI), and EEG that captures both wake and sleep. In some cases, an overnight EEG and/or polysomnographic evaluation are also indicated.

There are a variety of neurophysiologic evaluations that can be used to diagnose seizures from other episodic non-ictal behaviors (Table 20.3). It is also important to differentiate localization related (focal) seizures from generalized seizures. These tests may include a daytime routine EEG (usually under 1 h) with sleep captured, an overnight video EEG recording, or an overnight polysomnography recording. In some clinical settings, the PSG includes either an expanded EEG montage or a full EEG recording. It is important for the clinician to understand the advantages and disadvantages of these evaluations in order to make informed decisions as to which evaluation is indicated.

Practical Tips to Obtain EEG and PSGs in Children with NDD

Sleep Deprivation

Often it is useful to obtain sleep during a daytime EEG recording to evaluate interictal discharges. This can be done

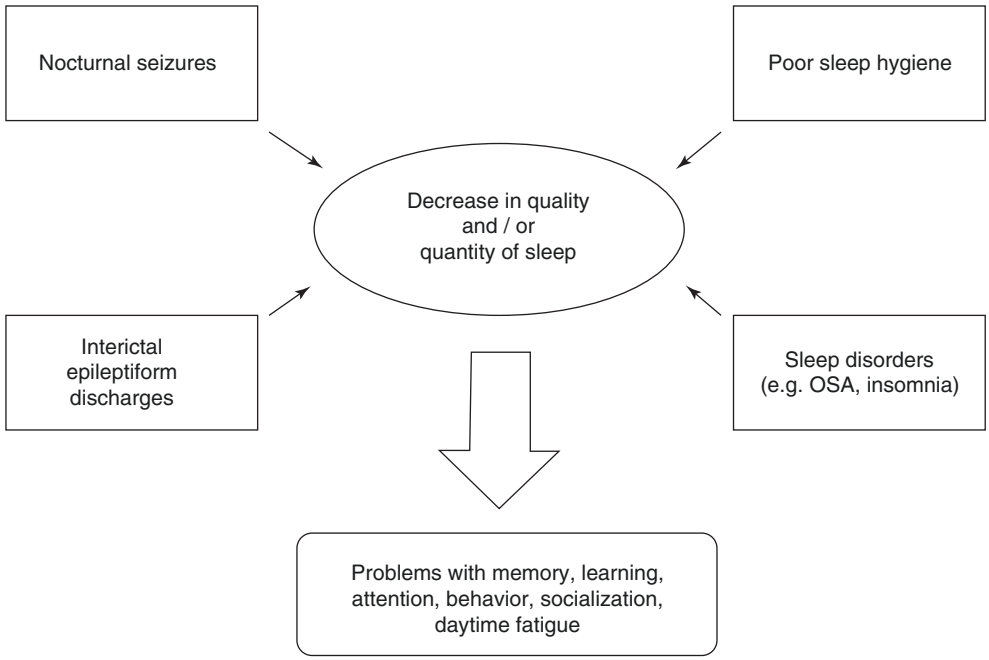

Fig. 20.3 Factors influencing sleep in children with NDD and epilepsy

Table 20.2 Epilepsy syndromes with seizures related to sleep

Infantile spasms	Infantile spasms are a developmental epilepsy syndrome with onset between 3 and 18 months of age, characterized by an abnormal, chaotic, EEG background (hypsarrythmia), seizures consisting of flexor-extensor spasms of the body, and associated developmental delays. Hypsarrhythmia pattern may be present exclusively during sleep. The clinical spasms occur in clusters usually on awakening
Epilepsy with generalized toni clonic (GTC) seizures on awakening	Generalized epilepsy characterized by onset of generalized convulsive seizures between the ages of 5 and 40 years (peak 11–23 years). Seizures may be frequent and occur usually in the morning 1–2 h after awakening. Sleep deprivation, fatigue, and alcohol lower threshold for seizures
Juvenile myoclonic epilepsy (JME)	JME is characterized by myoclonic, absence, and GTC seizures that occur in the morning. Myoclonus is observed upon awakening and may evolve into generalized seizures. EEG is dominated by generalized, high-amplitude polyspike-wave discharges, frequently precipitated by photic stimulation
Benign occipital lobe epilepsy	The early onset benign occipital lobe epilepsy, also known as Panayiotopoulos syndrome, is characterized by prolonged periods of autonomic instability and generalized or hemiconvulsive seizures during sleep
Benign Rolandic epilepsy (BRE)	BRE, also termed benign epilepsy with centro-temporal spikes, is the most common focal epilepsy syndrome in children. Onset is between 3 and 13 years of age, and remission occurs in adolescence. Two thirds of children have seizures exclusively from sleep. On EEG, central and temporal lobe spikes are seen, which may be independent and bilateral with a horizontal dipole, prominently activated by sleep
Landau-Kleffner syndrome (LKS)	LKS is an acquired epileptic aphasia with language regression or auditory agnosia secondary to the presence of epileptiform activity in the temporal lobes. Onset is usually between 3 and 9 years of age. Motor seizures are rare, but epileptic abnormalities are present over the anterior temporal lobe and are enhanced by sleep. Frequently, a CSWS pattern is present during sleep
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)	ADNFLE is an autosomal dominant epilepsy, produced by a mutation in the genes coding for the subunits of the nicotinic acetylcholine receptor (CHRNA4 or CHRNB2). Onset is in adolescence or young adulthood. The clinical manifestations include sudden awakenings with dystonic or dyskinetic movements, complex behaviors, and sleep-related violent behaviors. EEG findings include ictal epileptiform abnormalities predominantly over frontal areas in one third of patients or rhythmic slow-wave activity over anterior cortical areas in another half of the patients. Non-REM parasomnias have a high incidence, affecting about one third of the patients with ADNFLE

Table 20.3 Investigations used in the evaluation of child with nocturnal seizures

Investigation	Advantages	Disadvantages
Routine awake EEG without sedation	Fast, without much disruption in child and family routine	May not record sleep or sleep-activated interictal discharges
Routine daytime EEG with sedation	Will capture sleep in daytime test and more likely to record interictal discharges	Child will require a period of NPO prior to evaluation and will require time to recover from the sedation
Sleep-deprived EEG	May not need sedation, or (in authors experience – unpublished) may be able to acquire sleep with combination of sleep deprivation and oral melatonin	May be able to capture sleep (avoid sedation) with sleep deprivation + melatonin only and, therefore, will not require as long to recover from test
Overnight video EEG	Will record all stages of sleep including N3. If seizures occur frequently may record event	Disruption of routine for child and family
Prolonged video EEG evaluation in epilepsy monitoring unit (EMU)	Diagnosis of seizure – if event occurs frequently but not every night, will increase chances of capturing event	Significant disruption to family
		Not able to evaluate for sleep disorders as listed below in PSG
Ambulatory EEG	Can provide continuous EEG that is not disruptive to family in the home setting	Does not have video, so unable to diagnose or characterize seizures
Overnight polysomnography	Evaluate sleep architecture and rule out sleep problems such as OSA, non-REM arousal disorder, PLMD	Not as useful to evaluate for IEDs or seizures as EEG montage is limited
Home monitoring of sleep	Systems available to evaluate oxygen saturation	No system currently available that can evaluate sleep disorder
Actigraphy	Can evaluate sleep vs. wake	Technology currently not able to evaluate seizures or sleep architecture

TIP: In addition to the above, having the parent record an event suspicious for a seizure or parasomnia on a cell phone or video camera can be very helpful in the evaluation of a child with potential epilepsy.

Case Vignette #2

A 3-year-old girl with Rett syndrome and no history of clinical seizures was referred for an overnight polysomnogram (PSG) to the sleep laboratory to rule out sleep apnea. The findings included borderline obstructive sleep apnea, mild central sleep apnea, and sleep fragmentation, as well as slow spike-and-waves throughout sleep. Following the PSG, to further evaluate her abnormal EEG activity, the child underwent an overnight EEG with a full montage to evaluate for either clinical or subclinical seizures and to further define her interictal discharges. The child did not have any seizures during the EEG recording, but this evaluation allowed for a better appreciation of her IEDs, which showed increased discharges during sleep that were multifocal. Snapshots of the PSG and EEG are shown below to illustrate the different information that is obtained from a PSG with an expanded EEG montage vs. a 21 channel EEG recording (Figs. 20.4, 20.5, and 20.6).

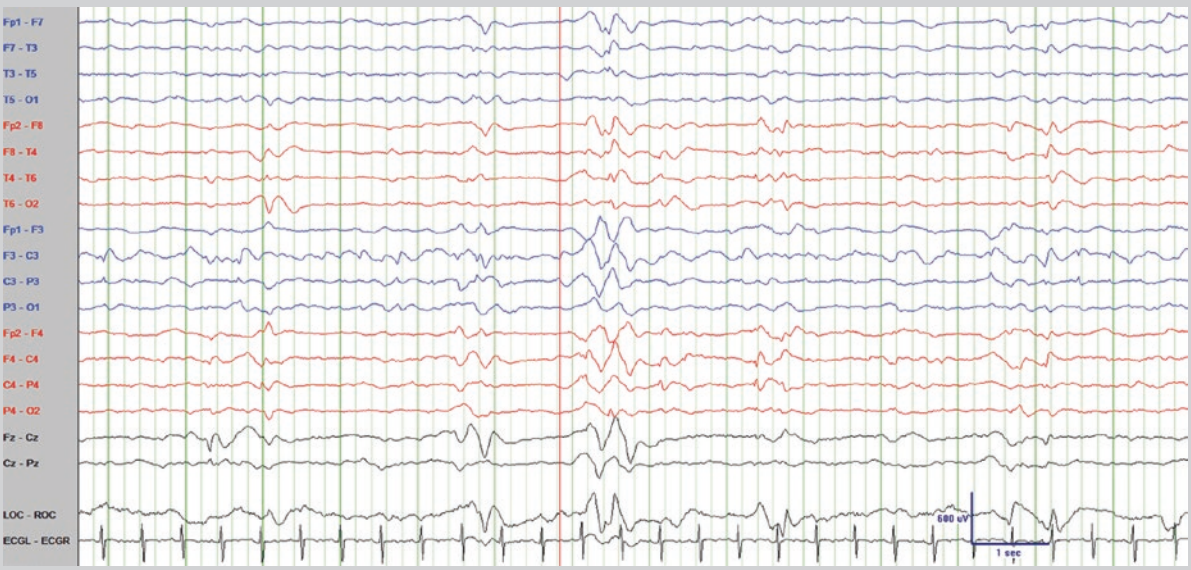

Fig. 20.4 Epoch of wake on EEG with 21 channel EEG recording (14 s, 21 channels, anteroposterior bipolar montage)

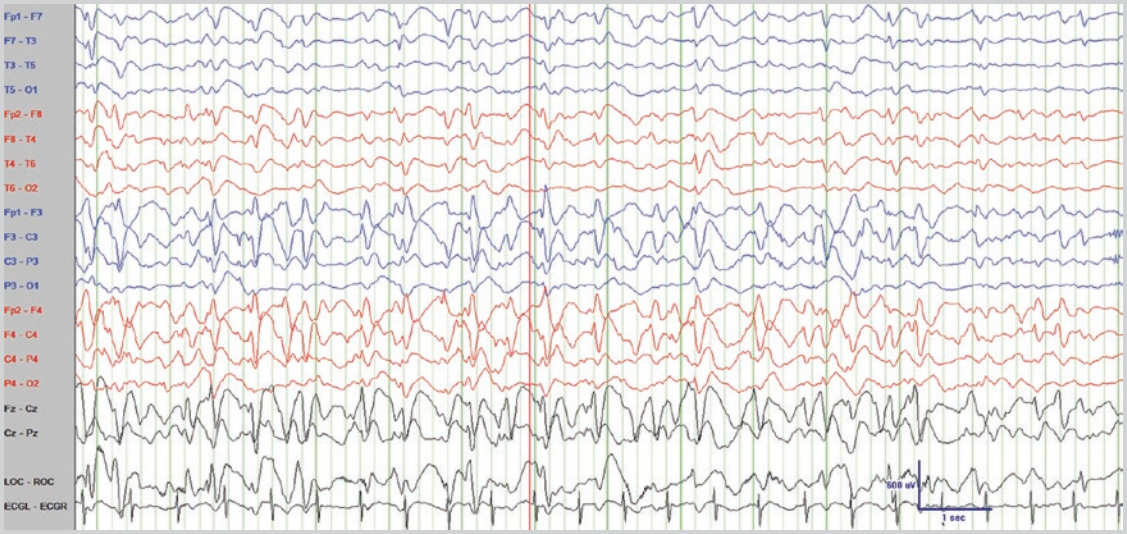

Fig. 20.5 Epoch of sleep demonstrating activation of IEDs on EEG with 21 channel EEG recording (14 s 21 channels, anteroposterior bipolar montage)

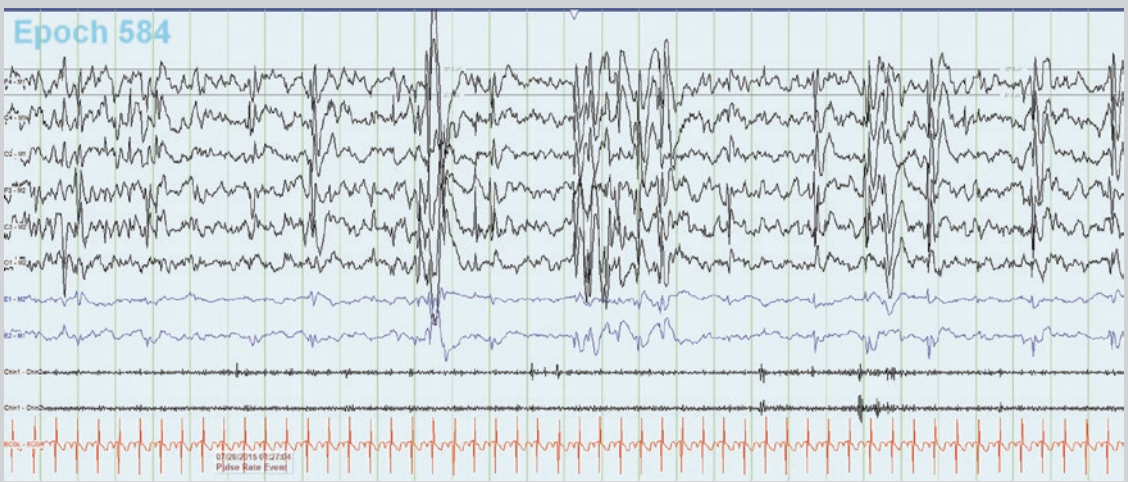

Fig. 20.6 Epoch of PSG during N2 sleep demonstrating the presence of IEDs (14 s, six channels, referential montage)

Comment

Clinicians must be cognizant of the limitations of PSG in the evaluation of both interictal discharges and nocturnal seizures. In some laboratories, the PSG will be done with an expanded EEG/seizure montage but this will not include (in most) a 21 channel EEG recording. Although one will see abnormal spike-wave activity (as demonstrated in this example), it will not be possible to evaluate the localization or extent of the IEDs. In addition, due to movement artifact and limited EEG coverage during a PSG, the ictal features of a frontal lobe seizure may not be able to be appreciated. Therefore, it is often necessary to perform both evaluations: a PSG to evaluate for primary sleep disorders, and also an EEG or overnight EEG to evaluate for ictal and interictal activity.

by sleep depriving a child before the EEG. The method of sleep deprivation (e.g., number of hours) may vary from one neurophysiology laboratory to another. Sleep deprivation, combined with scheduling the EEG at the child's usual nap time, can be used and may avoid the need to use a sedative medication for the EEG.

Use of Melatonin

There is limited evidence in the literature for the use of sleep-inducing agents, such as melatonin, to obtain sleep recordings during a daytime EEG [25–27]. In the authors' experience (not published), the combination of sleep deprivation with oral melatonin for children who are both typically developing as well as those with NDD can be helpful in obtaining sleep during a daytime EEG recording.

Practical Technical Tips

The same tips as outlined in Chap. 3 on PSG are useful in the evaluation of a child with NDD for an EEG. For a further excellent practical summary of technical tips, see Paasch et al. [28].

Treatment Options for Children with Epilepsy

There are several options in the treatment of children with epilepsy. Medical management is the first line. Children are generally started on a single antiepileptic drug chosen by the clinician as most appropriate for the seizure type with the highest efficacy and least side effects. If the first AED fails as monotherapy, then a second AED is added or substituted.

Epilepsy surgery is reserved for patients with DRE, who failed at least two properly chosen AEDs, well tolerated by the patient, and trialed for an appropriate period of time. Procedures used may include resective procedures (e.g., corticectomies, lobectomies), disconnection procedures (e.g., hemispherotomies, multiple subpial transections), and laser ablation. Many children with NDD and structural brain abnormalities benefit from these procedures, and the presence of a NDD is not a contraindication for surgery.

Children with DRE who are not candidates for surgery may benefit from the ketogenic diet and/or implantation of neuromodulating devices such as the vagus nerve stimulator (VNS).

Case Vignette #3

An 8-year-old girl who was diagnosed with autism at the age of 2 years is referred for consideration of epilepsy surgery. The girl is nonverbal but can communicate using signs and functions at the cognitive level of a 4-year-old. She has many stereotypies and significant socialization issues as well as anxiety. At the age of 5 years, she developed complex partial seizures which usually occur upon waking but can also occur during wake. Despite a trial of two AEDs, the child continued to have seizures. She underwent neuroimaging and was found to have a small left hippocampus with increased signal on FLAIR sequence (Fig. 20.7), most likely consistent with mesial temporal sclerosis. Next, the child underwent a video EEG which captured four seizures. All seizures consistently arose from the left temporal lobe. The child also underwent a neuropsychological evaluation, limited by her cooperation, anxiety, and cognitive challenges, which showed global delay in both verbal and visual memories. Following these evaluations, she underwent a left mesial temporal resection, and the pathologic diagnosis was subpial gliosis in the left temporal lobe and left hippocampal sclerosis. Following surgery, the seizures resolved without any new deficit in her memory or learning. She continues to have challenges related to her ASD, anxiety, and cognitive delay. The child remained on AEDs following surgery for 2 years, until the age of 10 years, at which time she was successfully weaned off her AEDs.

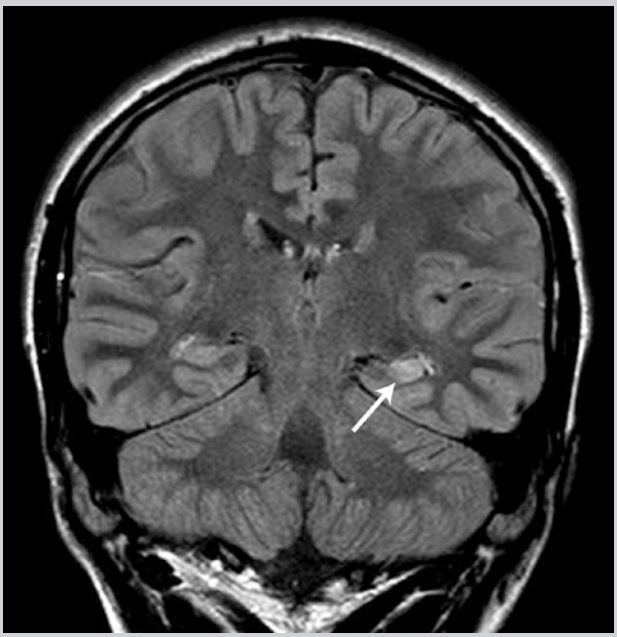

Fig. 20.7 Coronal FLAIR MRI sequence demonstrating abnormal signal in left mesial temporal lobe and left hippocampus with associated volume loss. Arrow indicates increased signal on FLAIR sequence in left hippocampus

Comment

This case illustrates that when a child has medically refractory epilepsy, it is important to refer the child for consideration of surgical options to decrease or eliminate seizures. The presence of NDD (as evident in this child) should not preclude evaluation for epilepsy surgery.

Antiepileptic Drug Treatment and Sleep

The goal of antiepileptic pharmacotherapy is to control seizures by achieving a prolonged seizure-free state. A clinician will choose the most appropriate medication after evaluation of the child's seizure type, epilepsy syndrome, and consideration of potential drug side effects. Other considerations in choosing an AED include the preference for monotherapy, choosing an AED with minor interference with sleep, administration of the minimal effective dose, and attention to the timing of drug administration [29, 30]. Considering all of these variables will be important to try to maximize good sleep and decrease daytime somnolence in children with epilepsy.

There are few studies evaluating the effect of AEDs on sleep architecture in children with epilepsy. It is also difficult to evaluate this association, as it is unknown if the sleep architecture is altered primarily by the AED or by underlying brain abnormality causing the child to have seizures. In one study [31], children with epilepsy were evaluated by polysomnography. Sleep architecture seemed to be influenced by the number of AEDs, with children having decreased REM sleep and decreased sleep efficiency if treated with two or three AEDs. Further research on the effect of AEDs on the sleep architecture of both children who are typically developing and those with comorbid neurologic/cognitive challenges is needed.

What has been shown in studies of adults with epilepsy is that AEDs may have differing effects on sleep, with some causing detrimental effects, and others stabilizing sleep [29]. It may be difficult to definitively determine these effects on people with epilepsy, as it is difficult to separate the effect on sleep from a drug itself vs. the effect on sleep from decreasing both ictal and interictal activities. Drowsiness is one of the most frequent side effects of AEDs [29, 30]. In some children this will be a transient effect, experienced with the introduction of the drug or titration of AEDs to higher doses.

Antiepileptic drugs have variable effects on sleep architecture, but most AEDs do affect sleep architecture. In a recent evidence-based systematic review on the effects of epilepsy treatments on sleep, gabapentin, tiagabine, pregabalin, clobazam, and carbamazepine were found to reduce sleep latency and/or improve sleep efficiency [32]. Phenobarbital, valproic acid, and high-dose levetiracetam aggravated daytime sleepiness, whereas topiramate and zonisamide did not. Some of the known effects of AEDs on sleep are summarized in Table 20.4.

Sleep After Epilepsy Surgery

The literature focusing on sleep architecture after epilepsy surgery is sparse. In one adult study that evaluated sleep before and after epilepsy surgery [33], no signifi-

Table 20.4 AED effects on sleep

	Awake/arousals	N1	N2	N3	REM	SE/TST	SL	WASO
PB	–		+		–		–	
PHT		–	+		–	–	–	
VPA	0	0	0	0	0	0	0	0
CBZ	–	0	0	+	–	+	–	
ESM		+		–	+			+
BZD	–	–	+	–			–	–
VGB	–							
GBP	–	–		+	+			
LTG				–	+			
TPM	0	0	0	0	0	0	0	0
FBM	0	0	0	0	0	0	0	0
LEV			+		–	+		–
PGB	–	–	–	+	–	+		–
ZNS	0	0	0	0	0	0	0	0
TGB				+		+		

Data from Refs. [29, 30, 32]

PB phenobarbital, *PHT* phenytoin, *VPA* valproic acid, *CBZ* carbamazepine, *ESM* ethosuximide, *BZD* benzodiazepines (e.g., lorazepam, diazepam, clonazepam, clobazam), *VGB* vigabatrin, *GBP* gabapentin, *LTG* lamotrigine, *TPM* topiramate, *FBM* felbamate, *LEV* levetiracetam, *PGB* pregabalin, *ZNS* zonisamide, *TGB* tiagabine, *SE* sleep efficiency, *TST* total sleep time, *SL* sleep latency, *WASO* wakefulness after sleep onset, + increase, – decrease, 0 no effect found, empty cells – no data

cant changes were seen. However, in a group of patients with postoperative Engel classes I and II, increased total sleep time (TST) and reduced arousals were seen, while no changes were present in the subjects who continued to have frequent seizures [34]. Therefore, we can speculate that it is probable that after successful epilepsy surgery, children's sleep would improve, as would daytime somnolence. However, this has not been directly demonstrated to date.

Sleep in Children on Ketogenic Diet

The ketogenic diet is a high-fat, low-carbohydrate diet used in children and adults with DRE. It was shown that ketogenic diet improves sleep quality in children with DRE [35]. In a cohort of 18 children with refractory epilepsy, at the onset of the diet, there was a significant decrease in TST, mainly due to decreased N2, while REM sleep duration was increased. At 12-month follow-up, there was a further increase in the duration of REM sleep and a decrease of daytime sleep [35].

Sleep in Patients with Vagus Nerve Stimulators

Vagus nerve stimulation is an adjunctive therapy usually reserved for patients with drug-resistant epilepsy who are not candidates for epilepsy surgery. VNS effects are produced by the application of current pulses to the vagus nerve, thus modulating CNS excitability. VNS alters sleep architecture, and the continuous stimulation is associated with increased awakenings and wake after sleep onset (WASO), increased N1 sleep stage, and decreased REM sleep [36, 37].

The VNS device is activated at preset intervals to deliver pulses for a certain duration of time. During these periods, there is a decrease in airflow and breathing effort. In a cohort of 16 adult patients with intractable epilepsy who underwent VNS implantation and had formal PSG before and after VNS placement, an apnea-hypopnea index (AHI) >5 was observed in five patients, only one of whom had preexisting sleep apnea [38]. Similar findings have been reported in children with epilepsy. The intensity of the stimulation is correlated with the severity of VNS-related respiratory events, and a reduction in the stimulation frequency can ameliorate these events.

Evaluation for Sleep Disorders in Children with NDD

It is well known that any cause of sleep deprivation can trigger more seizures. Therefore, when a child with NDD has epilepsy, it is imperative to evaluate for the presence of other sleep disorders. All of the sleep disorders outlined elsewhere in this book may be present in a child with seizures. The most common are behavioral insomnia (outlined in Chap. 5 and elsewhere) or the presence of obstructive sleep apnea or parasomnias. Treating the underlying sleep disorder and improving the continuity and duration of sleep may decrease the frequency, duration, or intensity of the nocturnal seizures. Some case examples to illustrate these comorbidities follow.

Sleep, Epilepsy, and OSA

Case Vignette #4

A 5-year-old boy is seen by his pediatrician for noisy breathing and snoring at night. The child was born at 32 weeks' gestation and developed periventricular leukomalacia which has resulted in spastic diplegic cerebral palsy, mild cognitive impairment, and attention deficit disorder. At the age of 2 years, he also began to have complex partial seizures during both wake and sleep. In addition, he continued to have frequent seizures despite several trials of AEDs. After evaluation (history and physical examination), the child was referred for an overnight polysomnograph which showed the presence of moderate obstructive sleep apnea. After referral to an otolaryngologist followed by a tonsillectomy and adenoidectomy (T&A), his parents reported resolution of his snoring and improvement in his sleep duration. He continued to have both wake and sleep seizures; however without any increase in AED dose or changes to his medications, the frequency of both wake and sleep seizures decreased by 50%.

Comment

As outlined in Chap. 6 on sleep-related breathing disorders, always take a history of signs of OSA, and consider PSG if there is clinical suspicion of OSA. Most children with NDD, even when there is severe intellectual impairment, can be evaluated in a sleep laboratory. However, if a child is unable to cooperate, and there is clinical suspicion of OSA, it is still worthwhile to refer for an otolaryngology consultation for consideration of T&A.

Sleep, Epilepsy, and Parasomnias

Case Vignette #5

A 5-year-old child with fetal alcohol spectrum disorder, developmental delay, and seizures was referred as he had recently begun to wake several times per week (often within 60 min of falling asleep) with an inconsolable cry. When parents went to the child's room, they found that he was tachycardic, tachypneic, and diaphoretic. Parents were not able to determine if the episodes are seizures, as they did not resemble his typical semiology during a seizure. There were no abnormal rhythmic movements and no clear automatisms. After an episode, which lasts 5–15 min, he settled back to sleep and had no memory of the event in the morning. An overnight EEG that captured these episodes showed no electrographical correlate.

Comment

This case illustrates that children can have both slow-wave arousal parasomnias (as described above) and seizures. The clinician must be able to differentiate these two phenomena as the evaluation and management differ greatly.

Parasomnias in Children with Epilepsy

Parasomnias (especially slow-wave arousal disorders) are commonly seen in children with epilepsy and seizures, especially frontal lobe epilepsy, and may be difficult to differentiate from each other. Adult patients with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) have a high incidence of arousal parasomnia (up to 30%), and 12% have REM behavioral disorder [39, reviewed in 40]. Parasomnias may be present in other focal epilepsies, but the incidence is low. The non-REM parasomnia (also called arousal or slow-wave parasomnia) events tend to be longer, have different patterns, and occur during the earlier part of the night, developing during stage N3 sleep (Table 20.5). Seizures tend to be shorter and highly stereotypic. They may occur multiple times throughout the night, from various stages of sleep [40, 41]. The following table outlines some clues in the clinical history and neurophysiologic evaluation to differentiate a child who is having non-REM arousal parasomnias from nocturnal frontal lobe seizures.

Sleep, Epilepsy, and Insomnia

In children with epilepsy, sleep disturbances are mostly studied through parental questionnaires, and there are few if any objective studies available in the literature assessing the specific incidence of insomnia. In adults, insomnia is present in up to 55% of patients with epilepsy [42]. Incidence in children is estimated at approximately 11% based on the number of children with bedtime difficulties and families that report increased parent/child interaction during the night [43]. The presence of insomnia correlates with the number of AEDs, used, and both factors are predictors of poor quality of life [44].

Table 20.5 Non-REM arousal parasomnias versus nocturnal frontal lobe seizures

Feature	NREM arousal parasomnias	Nocturnal frontal lobe seizures
Age of onset	Usually <10 years	Variable: usually childhood or adolescence
Time of onset	Usually within first 2–3 h of sleep onset	Randomly, at any time of the night
Number of attacks/night	1 or 2	Variable, can be >3
Duration (mean)	Seconds to 30 min	Generally short, often <2 min
Stereotypy	Absent	Present
Recall of event	Impaired unless child awakened during parasomnia by parent/caregiver	Can either be impaired (if secondarily generalized) or preserved
Post attack state	Will generally fall back to sleep quickly	May or may not fall back to sleep quickly
Sleep stage	Usually occurs from N3	Usually occurs from N1 or N2, occasionally N3
EEG during event	No IED or seizure activity	IED or seizure may or may not be present. May be obscured by movement artifact

Sleep, Epilepsy, and RLS/PLMD

There are few studies on the incidence of restless leg syndrome (RLS) and periodic limb movement disorder (PLMD) in children with epilepsy. In adults it is reported that 35% of adults with epilepsy may have RLS, and 15% may have PLMD [45]. In one study, 10% of children with epilepsy (out of 40 involved in the study) had periodic limb movements of sleep; however, further research is needed as this was a population referred to a sleep center because of various sleep complains [46]. Since PLMD may result in fragmented sleep and thus increased risk for seizures, consideration should be given to evaluation and treatment of children with possible PLMD/RLS.

Sleep, Insomnia, and EDS

Excessive daytime sleepiness (EDS) is the most common sleep/wake complaint among people with epilepsy, typically attributed to the effects of AEDs and seizures. Several studies have found that one third to one half of the population with epilepsy reports EDS. EDS seems to be related more frequently to undiagnosed sleep disorders than to epilepsy-related factors, and although it affects the quality of life of children with epilepsy, it can be improved by treating comorbid primary sleep disorders [47].

Sudden Unexpected Death in Epilepsy (SUDEP)

It is important to review sudden unexpected death in epilepsy (SUDEP) in a chapter on sleep and epilepsy in children with NDD as unfortunately, this is an unpredictable cause of fatality which when it occurs, is often associated with sleep in this population. SUDEP is a "sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy with or without evidence for a seizure and excluding documented status epilepticus in which postmortem examination does not reveal a toxicologic or anatomic cause for death" [48]. Children and adults with epilepsy have a 20-fold increased risk of sudden death compared to the general population. The incidence is as high as 9.3 per 1000 patient-years among patients with DRE evaluated for epilepsy surgery or VNS [49]. Refractory seizures, frequent generalized tonic-clonic seizures, and the presence of major neurologic impairments are considered to be its main risk factors in the pediatric population [40]. Respiratory abnormalities, such as central and obstructive apneas, hypoventilation, hypercapnia, and desaturation with acidosis, bradypnea, and tachypnea, and cardiac abnormalities, such as postictal changes in heart rate variability, ictal bradycardia, asystole, repolarization anomalies, and atrial fibrillation, have been proposed as putative mechanisms for SUDEP [40, 50]. In addition, cerebral shutdown seen as postictal EEG suppression may represent another mechanism of SUDEP. The evidence currently available for possible mechanisms for SUDEP and potential preventative mechanisms is outlined in a recent review by Massey and colleagues [51].

What Is on the Horizon That May Help Children with NDD Who Have Sleep-Related Epilepsies?

There is ongoing research with the goal of developing new technologies that may be able to detect and abort seizures. At the current time, there is no device that is safe and effective and available for patients. Some families use service dogs trained to detect their child's seizures and alert an adult. At this time, there is no reliable device or other method (including service dogs) to reliably alert a parent when a child has a seizure during sleep.

Conclusion

Epilepsy is a common comorbidity in children with NDD, and although seizures may occur both during wakefulness and sleep, they frequently occur during sleep. There is a well-established bidirectional relationship between sleep and epilepsy, with epilepsy and interictal discharges disrupting sleep and sleep disorders exacerbating seizures. There are also mimics of seizures that occur during sleep, most importantly slow-wave arousal parasomnias. It is important for clinicians to be aware of these associations and evaluate children with epilepsy for sleep disorders. The treatment of sleep disorders in this population can have profound effects by decreasing seizure frequency and improving sleep quality and quantity which will result in improved memory, learning, attention, and quality of life.

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22q11.2 Deletion Syndrome

21

Paula Goldenberg

Sleep is the golden chain that ties health and our bodies together—Thomas Dekker

Case Vignette

Liam, a full-term infant boy, presented at 2 weeks of age with frequent tonic seizures with hypocalcemia and low parathyroid levels. His evaluation revealed no structural brain lesions, electroencephalographic (EEG) abnormalities, or additional metabolic abnormalities. This was managed with calcium glubionate supplementation later weaned due to presumed late-onset neonatal hypocalcemia. Muscle twitching developed 3 months later with hypocalcemia. Calcium supplementation was reinitiated, and due to possible concern for DiGeorge syndrome, an echocardiogram was performed, which showed normal anatomy.

In the interim, Liam had delayed milestones in gross and fine motor and expressive and receptive language. He started early intervention services at 8 months of age. Other concerns included nasal regurgitation, gastroesophageal reflux disease, difficulty transitioning to solid feeds, mild laryngomalacia, frequent infections in day care, with recurrent otitis media and sinusitis requiring close follow-up, and anxiety with fears of the dark as well as insects. At 14 months of age, Liam was seen by a developmental pediatrician who ordered a fluorescence in situ hybridization (FISH) study, which showed a 22q11.2 deletion. Immunologic studies showed decreased CD4+ and CD8+ T cells with normal antigen response and normal immunoglobulins. A genetics evaluation detected low nasal bridge, overfolded helices, low-set rotated ears, and micrognathia.

Expressive speech developed at age 2 years. As a young child, Liam developed leg and foot pains which occurred once a night for months: waking suddenly, crying and screaming in pain, and then falling back asleep 30–60 min later. He showed no evidence of pain during the day and had an unremarkable physical examination and normal calcium levels. No measures helped this pain, including wearing supramalleolar orthoses or shoe inserts during the day, using warm washcloths, massaging or stretching during episodes, and giving ibuprofen at bedtime.

Neurocognitive testing initially showed a low-average verbal intelligence quotient (IQ) and borderline performance IQ. Later his verbal IQ tested in the borderline range. Liam received special education services and was diagnosed with attention-deficit/hyperactivity disorder (ADHD) and depression at age 3 years and 6 years, respectively. At age 6 years, he also developed muffled speech at times of fatigue, and velopharyngeal insufficiency was diagnosed and subsequently repaired by sphincter pharyngoplasty. At age 13 years, he developed idiopathic thoracic scoliosis, which progressed despite bracing, ultimately requiring a T2-L2 fusion at 16 years.

Liam completed high school with vocational training in culinary arts. Despite his challenges, he had talents and interests including basketball and skateboarding.

Introduction

22q11.2 deletion syndrome (22q11DS) is caused by a contiguous gene deletion that is associated with a wide phenotype encompassing virtually all body systems [1]. The diagnosis of 22q11DS includes previous clinically described diagnoses such as DiGeorge (MIM 188400),[1] velocardiofa-

P. Goldenberg
Medical Genetics, Massachusetts General Hospital, Boston, MA, USA
e-mail: pgoldenberg2@mgh.harvard.edu

[1]Online Mendelian Inheritance in Man, http://www.omim.org

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cial (MIM 192430), Takao or conotruncal anomaly face, autosomal dominant Opitz G/BBB (MIM 145410), Cayler cardiofacial (MIM 125520), and Sedlácková and velofacial syndromes. Discovery of the 22nd chromosome deletion was first described in three unrelated patients with DiGeorge syndrome who had an unbalanced translocation involving the pericentric long (q) arm of chromosome 22 [2]. Later, with the development of the *TUPLE1* fluorescent in situ hybridization (FISH) probe [3], 22q11.2 deletion was found to be associated with all of the above clinical syndromes [4–7]. The deletion of the 22q11.2 region is typically a common 3 Mb deletion and less commonly a 1.5 Mb deletion. There are no consistently replicated genotype-phenotype correlations.

The birth prevalence of 22q11DS was previously thought to be 1:4000–1:6000 births but has also been reported in 1 in 992 low-risk pregnancies in a large prenatal study [8]. There is wide variability of phenotype and severity, and it is thought to be vastly underdiagnosed in individuals with milder features [9]. Physicians should have a low threshold for testing for this condition, which today is typically diagnosed by chromosomal microarray testing, which has a higher sensitivity [10].

Inheritance is either autosomal dominant, through a parent that also has the deletion (10%), or de novo (90%). The phenotype can be quite varied, even within the same family: for example, some members with the same size deletion have heart defects, while others do not; some have more severe malformations and morbidity and mortality, whereas others may have minimal findings. So, while an infant who is severely affected has a specific 22q11.2 deletion, that child's college-degreed parent may have the same deletion and minimal features, such that 22q11.2DS likely would have never previously been diagnosed. Due to the high recurrence risk (50% risk of 22q11DS in each pregnancy), the 22q11DS international health management guidelines for patients of all ages recommend genetic testing to all parents of children diagnosed with 22q11DS [11]. There are guidelines for health care for adults [12], so that any adult with 22q11DS should also have syndrome-specific health-care management. Since there are conditions that could become apparent at any time including thyroid disorders and hypoparathyroidism, all patients with 22q11DS are recommended to have additional health-care management with syndrome-specific care [11–13].

The broad phenotype of 22q11DS is reflective of the multiple described clinical syndromes associated with 22q11DS. Parathyroid hypoplasia/aplasia and thymus hypoplasia/aplasia causing immunodeficiency are the hallmarks of DiGeorge syndrome [14]. Abnormalities of the palate, congenital heart defects, and certain facial features are characteristic of velocardiofacial syndrome [4], which was also associated with learning disabilities and psychiatric problems including schizophrenia [15]. Congenital cardiac outflow tract abnormalities (e.g., tetralogy of Fallot), certain facial features, and mild intellectual impairment were described as conotruncal anomaly face syndrome [16, 17]. Genitourinary abnormalities (e.g., hypospadias, cryptorchidism), esophageal dysmotility, laryngotracheal abnormalities, and hypertelorism are described in autosomal dominant Opitz G/BBB syndrome [7], and asymmetric crying facies, unilateral hypoplasia of the depressor angularis oris muscle, and congenital heart defects are hallmarks of Cayler cardiofacial syndrome [5]. Characteristic facial features with hypernasal speech, submucous cleft palate, and other palatal defects can be seen in velofacial or Sedlácková syndrome [4]. All associated features can be seen in patients with 22q11DS.

Overview of Features of 22q11DS

Patients with 22q11DS can have a much broader phenotype than mentioned above. Common features of this syndrome will be described, especially those with a possible impact on sleep. Table 21.1 summarizes these features for the reader's quick reference.

Facial Features of 22q11.2 DS

The facial features of patients with 22q11DS vary with age. Characteristic dysmorphic findings include midface

Table 21.1 Common comorbidities of 22q11DS that may affect sleep

HEENT	*Airway*: tracheomalacia, laryngomalacia, subglottic stenosis
	Palate: cleft palate, VPI (velopharyngeal insufficiency) and postoperative complications
	Craniofacial features: differences of the oropharynx, midface hypoplasia, micrognathia
	Oropharyngeal hypotonia
Respiratory	Aspiration
Cardiac	Heart failure from congenital heart disease
Gastrointestinal	Dysphagia, GERD, constipation
Musculoskeletal	Cervical spine abnormalities leading to central sleep apnea
	Nocturnal leg/foot pains
Neurologic	Seizures and epilepsy
Psychiatric	Anxiety, depression, psychotic disorders
Endocrine	Hypothyroidism, hyperthyroidism, hypoparathyroidism
Immunologic	Otitis media, sinusitis, pneumonia, viral and fungal infections
	Autoimmune inflammatory arthropathy

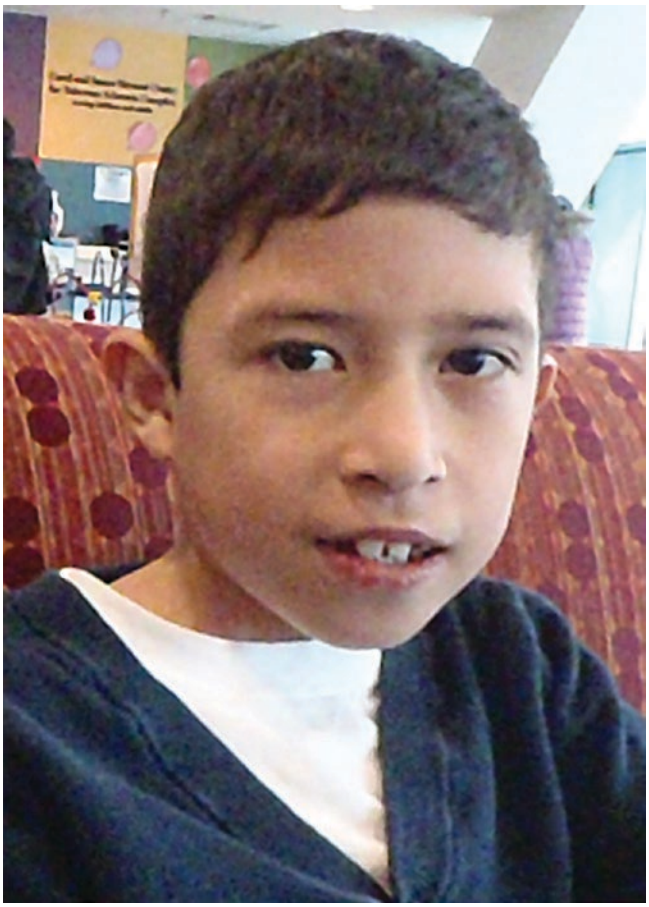

Fig. 21.1 A 9-year-old boy with 22q11 deletion and facial features including midface hypoplasia and micrognathia, ears low-set and posteriorly rotated with overfolded helices, hypertelorism, hooding of eyelids, and bulbous nasal tip with hypoplastic alae nasi

Fig. 21.2 A 4-year-old girl with 22q11 deletion and facial features including slight midface hypoplasia and micrognathia, low-set and rotated ears with overfolded helices, hooding of eyelids, slight upslant of palpebral fissures, and bulbous nasal tip with hypoplastic alae nasi

hypoplasia, hypertelorism (widely set pupils), upslanting palpebral fissures, hooded appearance of the eyes, low nasal bridge, bulbous nose, hypoplastic alae nasi, micrognathia, and low-set, posteriorly rotated ears which may overfolded, thickened, or protuberant [18] (Figs. 21.1 and 21.2). In babies these features may not be easily detected, and in patients of color, there should be suspicion of 22q11DS in individuals with characteristic anomalies, even if facial features are not apparent [19–21]. Patients with 22q11DS resemble each other and as well as their own families. Clinicians should not hesitate to test both parents regardless of whether a child resembles one parent more strongly.

There are other genetic conditions with craniofacial features similar to the 22q11DS phenotype that are associated with sleep apnea. Published reports include Marfan syndrome [22], and Down syndrome [23, 24]. These two syndromes have some facial features overlapping those commonly seen in patients with 22q11DS, including midface hypoplasia and retrognathia or micrognathia.

Airway Anomalies and 22q11DS

Airway anomalies are common in 22q11DS, including tracheomalacia, laryngomalacia, subglottic stenosis, bronchomalacia, and laryngeal web [25, 26]. A study of infants 0–17 months in the general population with obstructive sleep apnea found 27% of patients had laryngo- or tracheomalacia [27], so certainly these conditions may cause sleep apnea in patients with 22q11DS.

Vascular ring can be associated with 22q11DS and may lead to cardiovascular airway compression [28]. The diagnosis of a vascular ring may occur in children with later diagnosis of 22q11DS and should always be suspected in children with respiratory or feeding disorders [28]. Transthoracic echocardiography may be insufficient to define a vascular ring, and patients with dysphagia or airway concerns with known aortic arch anomalies may require CT angiogram or MR angiography to be fully evaluated for a vascular ring [29].

Craniofacial Anomalies and 22q11DS

Patients with 22q11DS commonly have a palate abnormality or palatal dysfunction (69%). Structural palate abnormalities include overt cleft palate (11%), submucosal cleft palate (16%), cleft lip with/without cleft palate (2%), and bifid uvula (5%) [1]. 22q11DS is known to be associated with Pierre Robin sequence, which is commonly associated with obstructive sleep apnea [30]. Palatal anomalies are commonly associated with sleep apnea, either pre- or postoperatively, in the general population [31, 32].

The general population birth prevalence of craniosynostosis is widely thought to be 1:2500, and the birth prevalence in infants with 22q11DS is closer to 1% or slightly less than 1 in 100 [33]. As with facial structure differences seen in patients with 22q11DS, craniosynostosis can lead to alteration of nasopharyngeal anatomy and present an additional risk for obstructive sleep apnea (OSA) in the general population. A prospective cohort study found 68% of patients with syndromic craniosynostosis (associated with Apert, Crouzon/Pfeiffer, Muenke, and Saethre-Chotzen syndromes) had OSA, and OSA was especially common in patients with midface hypoplasia who had Apert and Crouzon/Pfeiffer syndromes [34]. Sleep-disordered breathing can also be seen in patients with non-syndromic craniosynostosis [35].

Palatal dysfunction is commonly seen in 27% of patients with 22q11DS [1] and is characterized by velopharyngeal incompetence in which the palate does not seal the nasopharynx from the oropharynx, leading to symptoms including hypernasal speech, nasal regurgitation, and air leakage through the nose during speech.

Operative procedures to correct palatal clefts or velopharyngeal insufficiency can be associated with postoperative obstructive sleep apnea in patients with 22q11DS [36] as well as in the general population [37, 38].

Cardiac Defects and 22q11DS

Between 74% and 79% of patients with 22q11DS have congenital cardiac malformations, primarily of the outflow tract, most notably tetralogy of Fallot, truncus arteriosus, and interrupted aortic arch type B [1, 39, 40]. Few studies of sleep pathology or quality have been conducted on children or adults with congenital heart defects in the general population for comparison. Sleep apnea has been described in patients with Marfan syndrome [22] and may be associated with increased aortic dilation in these patients [41]. We do know that patients with 22q11DS may have increased aortic dilation, even those that do not have congenital cardiac defects [42].

Gastrointestinal Concerns with 22q11DS

Gastroesophageal reflux disease (GERD) is commonly seen in patients with 22q11DS, as is chronic constipation [43]. GERD is more commonly experienced in horizontal positions, such as while sleeping, and adults in the general population report sleep interruption or disturbance due to heartburn symptoms [44]. Infants with GERD in the general population also have sleep interruption [45].

Dysphagia, or abnormal swallow function, is often seen in patients with 22q11DS. Infants and young children very commonly have feeding problems requiring feeding therapy or tube feedings. Of interest, a mouse model of 22q11DS has been shown to have dysphagia, aspiration, and nasopharyngeal regurgitation and has demonstrated inflammation of the ears, and nasal and respiratory tract, which is interesting as if also present in humans; this inflammation may further narrow respiratory passages and contribute to OSA. The authors provided images of wild-type vs. LgDel 22q11 model mice, showing clear abnormalities in the development of the cranial nerves directly involved in feeding and swallowing (V, IX, X) [46].

Another potential cause of dysphagia is a vascular ring, which, while relatively rare in 22q11DS, is still much more prevalent than in the general population and is underdiagnosed. Should vascular ring be suspected based on clinical symptoms with negative echocardiogram, a cardiac magnetic resonance imaging (MRI) study may be considered [28].

Constipation is an ongoing concern for many patients with 22q11DS, causing significant distress for patients and their families. Many children are on daily regimens and/or managed by gastroenterologists. Hirschsprung's disease has been described in some patients [47]. A relationship between constipation and sleep seems plausible but has not been described in the medical literature.

Endocrine Anomalies and 22q11DS

Both adults and children with 22q11DS have increased risk of endocrine abnormalities, including hypoparathyroidism, Grave's disease, and hypothyroidism.

Hypocalcemia is a common condition in patients with 22q11DS, and up to 60–80% of patients may experience hypocalcemia in their lifetimes, usually caused by parathyroid insufficiency [48, 49]. Patients with 22q11DS commonly have hypocalcemia from parathyroid insufficiency as newborns. It is now known that hypoparathyroidism and hypocalcemia can occur in people with 22q11DS at *any* point in the life-span, with pregnancy, growth spurts, critical illness, and surgery (e.g., depleted calcium in blood

transfusions). Hypocalcemia also may be present with mild stressors in patients who are chronically mildly insufficient in parathyroid hormone. Providers need to be vigilant regarding this risk. Symptoms of hypocalcemia include numbness around the mouth, "pins and needles" sensations, twitching muscles, unusual or unexplained weakness or irritability, muscle cramps or spasms, and seizure history (characteristically tonic seizure). Laryngospasm causing stridor and airway obstruction and prolonged QT interval may be associated with severe hypocalcemia. Patients with 22q11DS may not have any symptoms yet have laboratory findings of hypocalcemia or hypoparathyroidism [50]. Thus, routine screening and a low threshold for laboratory evaluation are recommended [11, 50].

Hypothyroidism and Grave's disease are typically autoimmune rather than congenital in patients with 22q11DS, so these conditions may occur at any point in the life-span. A cross-sectional study of 78 adults with 22q11DS in a relatively young sample with mean age of 31.5 years (SD 10.5) found 20.5% had hypothyroidism and 5.1% had Grave's disease [51]. Hypothyroidism and hyperthyroidism are also commonly seen in pediatric patients with 22q11DS: in one study, 7.7% had hypothyroidism, 1.8% had Grave's disease, and 42% had subclinical or prodromal thyroid disease which progressed to overt thyroid disease [52].

Children with 22q11DS frequently have short stature, and syndrome-based growth charts have been developed [53–55]. Typically adults with 22q11DS have normal stature, so childhood short stature may reflect constitutional growth delay. Growth hormone deficiency may be present in 4% of patients with 22q11DS [56].

Immune Disorders and 22q11DS

Patients with 22q11DS commonly have an immunodeficiency (77%) and 67% of patients with 22q11DS have a T-cell deficit [1]. Individuals with immunodeficiency rarely have life-threatening infections ("partial DiGeorge"); however, less than 1% of patients with 22q11DS have no T cells, a life-threatening condition treated with thymus transplant ("complete DiGeorge"). Patients with mild T-cell lymphopenia generally have improved immune function by the age of 5 years. All babies should be evaluated immunologically prior to the administration of live vaccines [11].

Primarily patients with 22q11DS have frequent viral and respiratory infections including otitis media, pneumonia, and sinusitis, which can interfere with restful sleep. Fungal infections are also common and were significantly associated with the postoperative course in patients with 22q11DS in comparison to other cardiovascular postoperative patients, likely contributing to the increased length of stay in patients with 22q11DS in comparison to other patients with the same heart defects [57]. Patients with 22q11DS and the lowest T-cell counts had the largest immunologic improvement over the first year of life [58]. Overall patients have decreased naïve CD4 populations, blunted T-cell decline, and increased autoimmune disease, including inflammatory arthropathies [59], which are known to be associated with daytime fatigue [60] and sleep fragmentation [61–63] in patients in the general population.

Orthopedic Concerns and 22q11DS

Scoliosis is commonly seen in patients with 22q11DS. One center reported three patients with 22q11DS and scoliosis during early childhood. Vertebral anomalies reported in patients with 22q11DS may be a risk for scoliosis, and another possible factor may be hypotonia of the paravertebral musculature. The usual age of detection of scoliosis is during rapid growth during adolescence. Nearly half of adults with 22q11DS have a history of scoliosis based on record review [51]. However, only a minority of that group required surgery (6%). While the effects of scoliosis on sleep have not been studied specifically in patients with 22q11DS, restrictive lung disease has been reported in patients with severe scoliosis [64].

Cervical spine anomalies are nearly universally seen in patients with 22q11DS and are primarily asymptomatic [65, 66]. There is also reported cervical spine instability (increased segmental motion, increased occipital-atlantal motion, increased atlantoaxial motion, increased C2–C3 or C3–C4 motion) [65, 66]. One patient with 22q11DS and a history of OSA with central sleep apnea had multiple cervical spine anomalies with compression at C1 and cervical instability. Operative repair and cervical spine fusion improved this patient's central sleep apnea [67]. The management guidelines for patients with 22q11DS recommend five-view plain films to screen for cervical spine anatomy in children with 22q11DS at age 4 or older [11].

Neurological Concerns and 22q11DS

Patients with 22q11DS have a higher prevalence of seizures than the general population. This is expected, as many patients have seizures triggered by hypocalcemia, which can be an initial presentation or seen as a new finding in established patients with known diagnosis of 22q11DS [68–71]. Additionally, anatomically there are more patients with cortical dysgenesis and polymicrogyria than would be expected [72, 73], providing anatomic foci for seizures.

Unprovoked seizures and epilepsy are also more common than expected in both children and adults with 22q11DS. In a group of 343 patients with 22q11DS age 2–42 years old, 27 had unprovoked seizures that were primarily focal in nature, and the majority of patients (24/27) met criteria for epilepsy [74]. A retrospective case series of adult patients with 22q11DS found nearly 40% of patients had recurrent seizures (both provoked and unprovoked) and about 5% met criteria for a diagnosis of epilepsy [51].

Patients with 22q11DS nearly universally have hypotonia and benefit from a developmental approach to gross and fine motor delays, including physical and occupational therapy [75]. For example, patients with adult-onset Pompe disease, which affects neuromuscular function, have no particular airway changes but adult-onset respiratory muscle disease and hypotonia, with symptoms of daytime sleepiness and fatigue. These patients can have both hypoventilation and OSA [76], suggesting that hypotonia contributes to OSA.

Neurodevelopmental Concerns

There is variability in cognitive ability in people with 22q11DS, just as there is in the general population. Whereas the median IQ in the general population is 100, median full-scale IQ is in the 70s in cohorts described with 22q11DS [77, 78], a leftward shift of the bell curve of IQ. Relative areas of weakness include nonverbal learning, mathematics, abstract concepts, and reading comprehension. Areas of strength include reading, spelling, and memorization of lists [78, 79].

Patients with 22q11DS have prominent expressive speech delay, with delayed onset of babbling and subsequent delayed initiation of expressive language. Families often bridge communication difficulty with the use of sign language and augmentative communication methods. Patients with 22q11DS often have delays in receptive language, fine motor, and gross motor milestones as well.

Psychiatric Concerns and 22q11DS

Patients with 22q11DS can have behavioral problems that are also frequently seen in children or adults with sleep disturbances in the general population. Environmental stress is commonly experienced by patients of all ages with 22q11DS due to difficulty with communication and poor reading of nonverbal cues. Many pediatric patients with 22q11DS experience daily life stressors including bullying and school problems due to learning differences. These stressors heighten anxiety symptoms and interfere further with acquisition of learning and adaptive functional skills [80].

Environmental stress is associated with poor sleep quality, disrupted sleep architecture, and shortened sleep duration in individuals in the general population, so it is reasonable to believe that stress has similar effects in people with 22q11DS [81].

A systematic review of seven studies with over 300 pediatric participants with 22q11DS [82] compiled data of standard diagnostic psychiatric interviews. Some patients with 22q11DS had no psychiatric diagnosis (36%). Children and adolescents with 22q11DS very frequently had ADHD (38%); anxiety disorders, including generalized anxiety disorder and obsessive compulsive disorder (39%); and depressive disorders (major depression 8%; depressive mood disorders 12%). Bipolar disease and schizophrenia were rarely seen (1.7% and <1%, respectively); however, the authors noted four studies reporting possible prodromal, psychotic-like, or schizotypal traits in 21.9% of 96 subjects with 22q11DS.

A recent cross-sectional study of 112 children and adults with 22q11DS, recruited from a large syndrome-specific 22q11 center, conducted multiple psychiatric screening measures (such as the Kiddie Schedule for Affective Disorders and Schizophrenia) in patients with 22q11DS age 8 years through adulthood [83]. The neuropsychiatric measures showed a high burden of psychopathology overall (79%): 42% with two or more psychiatric comorbidities and 16% with three or more psychiatric comorbidities. In this study, ADHD was present in nearly one-third of patients, stable across age groups. Anxiety disorders were present in 34%; mood disorders, primarily depressive, in 14%; and psychotic disorders in 11%. Psychosis was reported primarily in late adolescent and adult participants; however, 47% were assessed to be psychosis-prone with subthreshold symptoms on prodromal measures, primarily in the ages of 8–23 years.

Under-ascertainment in adults with 22q11DS is a significant issue, as the genetic testing for 22q11 deletion only became available in the 1990s, and this condition is underdiagnosed in adults [84]. Additionally, in the past there was increased mortality with cardiac surgeries, and a large number of patients with 22q11DS have serious heart defects needing complex repairs and may not have survived. People with 22q11 deletion syndrome may have only subtle facial features and not be suspected of having 22q11DS [85]. Psychiatric studies of adults with 22q11DS tend to have difficulty with ascertainment bias, as only more psychiatrically involved adults may be diagnosed or under continuing care for their psychiatric disorders. Thus, there are few studies looking at the prevalence of ADHD, depression, anxiety, and psychosis in adult populations with 22q11DS. A large study of combined international 22q11DS patients, primarily recruited by psychiatric specialists, found adults age 26 and above with 22q11DS (n = 115) to be affected by anxiety (26%), 15–20% affected by depression, and 16% over age 18 years affected by ADHD [86]. These psychiatric conditions may be exacerbated by or cause sleep disorders.

The most striking and concerning psychiatric comorbidity is of psychotic disorders in adolescents and adults with 22q11DS. Adult prevalence studies suggest 23–41% of adults are affected by psychotic disorders, inclusive of schizophrenia [51, 86, 87]. There is a lack of published, large prospective cohort studies that might be helpful in identifying early risk factors, as well as true incidence and prevalence.

The correlation of sleep abnormalities with these psychiatric features has not yet been studied specifically in patients with 22q11DS. Many of these described psychiatric conditions and side effects of psychiatric medications can potentially negatively affect sleep both quantitatively and qualitatively in patients with 22q11DS.

Evidence for Sleep Disorders and 22q11DS

Anecdotally, it has been known for some time that individuals with 22q11DS have sleep difficulties. "Increased need for sleep" was listed as a feature of 22q11DS in the health-care management guidelines for patients with this syndrome [11]. The same guidelines recommended that "Regular, early bedtime and more hours of sleep than other same-aged individuals can help reduce irritability and improve learning and functioning." Unfortunately, no more detailed characterizations, citations, or data in support of this recommendation were provided.

Patients with 22q11DS have multiple conditions that can put them at risk of sleep disruption (Table 21.1). Palatal clefts and velopharyngeal insufficiency; craniofacial anatomic differences including micrognathia, midface hypoplasia, abnormal oropharyngeal anatomy, and alignment; and oropharyngeal hypotonia are all craniofacial anatomic contributors to sleep-disordered breathing and obstructive sleep apnea. Leg pains, similar to growing pains, are reported by families, interrupting sleep of both children and their parents, and possibly herald future development of restless legs syndrome or periodic limb movement disorder.

Sleep disturbance in the general population has many effects in children (excessive daytime sleepiness, learning problems) [88] and in adults (excessive daytime sleepiness, motor vehicle collisions, cardiovascular morbidity, hypertension, diabetes, metabolic abnormalities, erectile dysfunction) [89, 90] and may induce early cognitive decline in the elderly [91]. Adults with 22q11DS may need increased sleep to avoid irritability and depression [11, 51], which are symptoms that may overlap with sleep-disordered breathing. Larger, population-based studies of 22q11DS and sleep are needed to clarify the prevalence of OSA, central sleep apnea, restless legs syndrome, and periodic limb movements of sleep in a broad patient population with 22q11DS.

Sleep-Disordered Breathing and 22q11DS

Sleep-disordered breathing (SDB) is a spectrum from snoring to obstructive sleep apnea (OSA). In the general population, about 11% of children have habitual snoring by parental report, and 1–4% have OSA on polysomnogram [92]. Craniofacial malformations, including cleft palate, are commonly associated with SDB. In a craniofacial sample of 575 patients (syndromic and non-syndromic) [93], overall 28% had snoring, and 20% had sleepiness. Overweight was *not* associated with positive screening for snoring or sleepiness in a specialty craniofacial clinic.

22q11DS is commonly associated with craniofacial anomalies including cleft palate and velopharyngeal insufficiency [1], potentially exacerbated by hypotonia of the oropharynx. In 21 patients with 22q11DS [94], 48% had a positive screening for snoring on the Sleep-Related Breathing Disturbance Scale of the Pediatric Sleep Questionnaire, and 43% had daytime sleepiness, results which were out of proportion to their frequency within the general craniofacial population of 28% with snoring and 20% with sleepiness. Also, in a cohort of patients with syndromes and cleft lip and/or cleft palate (n = 178) given the Pediatric Sleep Questionnaire [32], 50% of 26 patients with 22q11DS had an abnormal screening for obstructive sleep apnea, in comparison to 32% of the cleft lip and/or palate group overall. In both studies at different institutions, patients with 22q11DS had the highest risk for positive screens for obstructive sleep apnea.

Patients with 22q11DS commonly have velopharyngeal insufficiency (VPI) either in the presence or absence of overt or submucous cleft palate [1]. Symptoms and signs of VPI include nasal regurgitation with minimal force, for example, in infants when spitting up, and a hypernasal speech quality. VPI is due to poor function of the velopharyngeal region to seal the pharynx off from the nasal region. Any number of surgical procedures may be used to correct VPI, including pharyngeal flap, Hynes pharyngoplasty, sphincter pharyngoplasty, palatoplasty (including z-plasty), and posterior pharyngeal augmentation. Surgeries may be performed either singly or in combination. The surgical procedures chosen are based on palatal function on nasoendoscopy and possibly carotid artery placement on computed tomography (CT) scan. All surgical procedures can be associated with postoperative development of OSA. In a retrospective review of 43 pediatric patients with 22q11DS referred to craniofacial clinic [36], 28 were found to have hypernasality suspicious for VPI, and of these patients, 7 were given a trial of speech therapy. The remaining 21 patients had operative procedures for VPI (pharyngeal flap [15], sphincter pharyngoplasty [3], Furlow palatoplasty [2], combination of Furlow palatoplasty and sphincter pharyngoplasty [1]). Postoperatively eight patients began snoring, six of whom underwent polysom-

nography. OSA was found in four patients, two of whom went on to require continuous positive airway pressure (CPAP) intervention.

In another retrospective review of 323 patients with 22q11DS [95], 57 had polysomnograms (PSGs), of which 39 studies were preoperative: 21 of those patients had OSA (55%), much higher than the general population prevalence of OSA of 1–3%. Of 17 postoperative patients with 22q11DS who underwent PSG following VPI repair, 9 had OSA (53%). Unfortunately, large pre-/postoperative sleep studies or sleep studies of a consecutive general patient group with 22q11DS have not as yet been done.

Hypotonia of the oropharynx is part of the spectrum of generalized hypotonia in patients with 22q11DS and may also be associated with sleep-disordered breathing and obstructive sleep apnea. It may be helpful to consider populations with other specific genetic and metabolic syndromes in comparison. Patients with Prader-Willi syndrome are another group who have oropharyngeal hypotonia, but assessing this factor in isolation in them is difficult given obesity in this population [96]. Patients with infantile and adult-onset Pompe disease do not generally have obesity, but do have progressive hypotonia from alpha glucosidase deficiency and glycogen accumulation in muscle. Patients with Pompe disease also have sleep-disordered breathing and obstructive sleep apnea [76, 97, 98].

Growing or Leg Pains and 22q11DS

Growing pains are commonly seen in patients in general pediatrics, with a prevalence of approximately 37% in the general population [99]. They are the most frequent recurrent musculoskeletal pain in children between 4 and 14 years of age. There are diagnostic criteria for growing pains (Table 21.2) [100, 101]. It is interesting that growing pains can be associated with later development of periodic limb movements in sleep and that these conditions are highly heritable in the general population [102].

While there are no published studies of nocturnal leg pains in children with 22q11DS, this is a well-known phenomenon in the parent community and a frequent topic on social media and LISTSERVS. Families describe children waking on a near-nightly basis screaming and crying in pain, and their distress persists for 30–60 min despite comfort measures (e.g., warm washcloths, massage). Some families have had custom orthotics made for presumed pronation-related pain due to hypotonia with variable results, likely due to the time-limited course of the pain. Others may try premedicating with acetaminophen or ibuprofen before bedtime, to no avail. Children who are verbal may ask for specific measures; however, nothing seems to abate the pain during an episode. These nightly episodes occur over periods of weeks to months. Typically, children have no residual pain the morning after an episode.

Table 21.2 Characteristics of growing pains

Characteristics of pain	Inclusion criteria	Exclusion criteria
Frequency and duration	Intermittent pains once or twice per week, *rarely daily*, totally pain-free in between the episodes; individual episodes lasting 30 min–2 h	Pain that is persisting or increasing in severity with time
Site	Commonly in calf muscles	Pain involving joints
	More rarely in anterior thigh muscles, shins, and popliteal fossa	Unilateral extremity pain
	Affects both limbs	
Time	In the evenings and nights	Daytime pain
		Nocturnal pain that persists in the morning
Physical examination	Normal	Signs of inflammation

Adapted from: Mohanta [100]. With permission from Indian Pediatrics

Nocturnal leg pains in patients with 22q11DS do bear a strong resemblance to growing pains; however, growing pains are typically less frequent than the pains reported by parents of children with 22q11DS. Practitioners should also be aware that there is a possibility that patients are having symptoms from hypocalcemia, potentially due to nocturnal growth hormone release, and that the pains may be due to carpopedal spasm and paresthesias. Patients with growing pain symptoms should have the following labs when having night sleep pains:

- Ionized calcium or serum calcium and albumin with calculated correction
- Magnesium
- Phosphorus
- Intact parathyroid hormone level

A polysomnogram during a period of growing pains/nocturnal leg pain may help determine whether a child is experiencing growing pains, by documenting whether the child has periodic limb movements of sleep, which can be related to periodic limb movement disorder, or support a symptomatic diagnosis of restless legs syndrome.

Future Directions

Patients with 22q11DS are at risk for sleep difficulty due to their medical comorbidities summarized in Table 21.1. In addition, in craniofacial patients, sleep-disordered breathing and obstructive sleep apnea has been described. More studies

are needed to ascertain the risk of SDB in patients of all ages with 22q11DS, both with and without craniofacial anomalies. Recurrent leg pains, exceeding the criteria for growing pains, not only interrupt sleep in childhood but possibly may also indicate an unstudied risk of periodic limb movements of sleep. Research is needed to further understand the leg pains to find out whether this phenomenon is merely more severe growing pains versus heralding periodic limb movement disorder of sleep or restless legs syndrome. There is no clinical research on sleep in adults with 22q11DS, or people with 22q11DS and psychiatric conditions. A better understanding of sleep problems and needs of people with 22q11DS would likely inform clinical health guidelines and approaches in this population.

Conclusions

Patients with 22q11DS have significant risk of sleep disturbance from numerous medical comorbidities which can include craniofacial including airway, respiratory (aspiration), cardiac, gastrointestinal (reflux, dysphagia, constipation), musculoskeletal (hypotonia, cervical spine anomalies), neurologic (seizures and epilepsy), psychiatric (mood disorders, schizophrenia), endocrine (thyroid disorders, hypoparathyroidism), and immunologic (frequent infections) problems.

In addition, there are several recent studies in children with 22q11DS followed in craniofacial clinics that demonstrate that these patients do have sleep-disordered breathing (SDB).

There are no current guidelines for suspicion and assessment of sleep in patients with 22q11DS. Given the high likelihood of sleep-disordered breathing in this population, possibly up to 55% in the few abovementioned studies, practitioners are recommended to have a low threshold for assessing sleep in patients with this diagnosis. Addressing sleep problems may alleviate not only daytime sleepiness but also the irritability and temper problems that are commonly described in patients with 22q11DS.

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Fragile X Syndrome

22

Rebecca Kronk and Robyn A. Filipink

Introduction to Fragile X-Associated Disorders

William is an 8-year-old young man with a full mutation of FXS. He has no siblings; his mother is divorced and works shifts as a nurse's aide at a local nursing home. He is enrolled as a first grader at the public elementary school in the neighborhood. William has social anxiety and speech delay with a mild speech articulation disorder. Otherwise, William is healthy except for sleep onset and maintenance issues. His sleep routine is variable depending on his mother's work schedule and who is babysitting him while his mother is at work. His mother tries to have a bedtime routine, but this is disrupted when she is working evenings and various caregivers (e.g., grandfather, neighbor) are there to assist. In particular, his grandfather will let William fall asleep on the couch while watching TV, and forgets to give him his melatonin. Due to his anxiety, William will wake up around 2 a.m. almost every night, with or without his melatonin, to be sure his mother is home and in her room. Teachers report that William is often very sleepy in school, so his mother has begun to keep him home on days that they have had a particularly rough night, and she feels he is too tired to attend. On those days, he will intermittently nap on the couch, which leads to a delayed bedtime later in the evening. As a result, both day and evening schedules are disrupted not only for William but his mother as well. His health-care provider has suggested increasing the dose of melatonin, but William's mother is hesitant to do so. She often states that they are "in a vicious cycle and no one understands" all the factors that affect their lives.

Fragile X Syndrome Full Mutation

Fragile X Syndrome (FXS) is considered part of a family of related disorders (Fig. 22.1) mapped to the Xq27.3 site within the 5′-untranslated region of the Fragile X mental retardation 1 (FMR1) gene. A CGG expansion of >200 repeats within this region results in a full mutation as well as gene silencing resulting in a loss or decrease in the amount of gene product known as the Fragile X mental retardation 1 protein (FMRP). FMRP is responsible for dendritic pruning; in its absence, there is an increased number of immature dendritic spines that alter the strength and function of the synapses and overall neuroplasticity [1, 2]. The degree of methylation and the remaining amount of available protein determine clinical severity rather than the number of expanded CGG repeats. However, mosaicism can occur in both the size of expansion and methylation pattern, resulting in phenotypic variability.

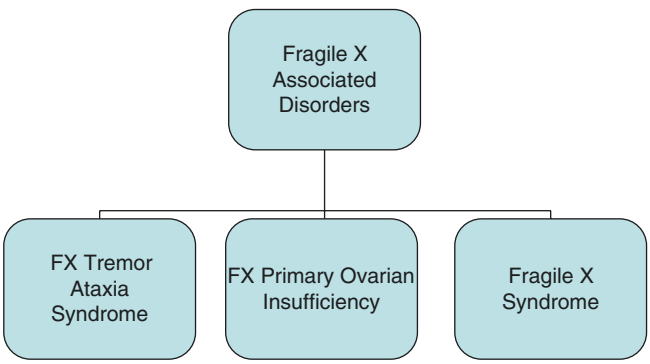

Fig. 22.1 Fragile X-associated disorders

R. Kronk (✉)
Nursing, Duquesne University, Pittsburgh, PA, USA
e-mail: kronkr@duq.edu

R. A. Filipink
Fragile X Clinic, Movement Disorders Clinic, Tourette Syndrome Clinic, Division of Child Neurology, Children's Hospital of Pittsburgh, Pittsburgh, PA, USA

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FXS is the leading known inherited cause of intellectual disability and the most common known genetic cause of autism spectrum disorders. It occurs in every ethnic group and in both genders; however, females have milder symptoms. It has been estimated that 1:5000 males are born with the full mutation [3]; females may have a slightly lower incidence, ranging from 1:4000 to 1: 6000. A Fragile X DNA probe, reported by methylation polymerase chain reaction (PCR), can determine the number of CGG repeats and methylation status (https://www.mayomedicallaboratories.com/test-catalog/Performance/35428).

The phenotypic presentation of the full mutation can vary in type and severity of symptoms. A national survey that included 1167 males and 211 females with a full mutation identified a wide range of co-occurring conditions, listed from highest to lowest in frequency: intellectual disability, attention problems, anxiety, hyperactivity, autism, self-injurious behaviors, aggression, seizures, and depression [4]. All conditions had a higher occurrence rate among males except for depression.

Premutation Allele

In addition to the full mutation, the FMR1 gene has two additional mutational allele categories, premutation and intermediate. The typical number of CGG repeats is between 5 and 44, with 29 or 30 CGG repeats as the most common length of the normal allele. In this normal allele category, an AGG triplet occurs after every 9 or 10 CGG repeats which appears to stabilize the region, preventing expansion upon transmission [5].

The premutation allele ranges from 55 to 200 CGG repeats. Studies show prevalence rates vary widely [6–9]. The Centers for Disease Control and Prevention (CDC) reports 1:151 females and 1:468 males in the United States carry the premutation. Expansion of the premutation allele only occurs in transmission from mother to child; a maternal transmission of 56 repeats is the smallest repeat size known to expand to a full mutation [10]. Fathers only transmit an allele to daughters, and there have been no reported expansions to a full mutation from a premutation male.

Among people with an FMR1 premutation, approximately 40% of men over the age of 50 [11] and, although less severely affected, 8% of women over the age of 40 [12] are at risk of developing Fragile X Tremor Ataxia Syndrome (FXTAS), a neurodegenerative disorder characterized by a progressive cerebellar ataxia and intention tremor. The underlying pathogenesis of FXTAS is related to elevated levels of FMR1 mRNA, resulting in neural cell toxicity causing dysregulation of several proteins (lamin A/C and alpha B crystalline) [13]. A pathognomonic finding of FXTAS involves MRI white matter lesions of the cerebellar peduncles. Minor diagnostic findings include other cerebellar white matter lesions and moderate to severe brain atrophy [14]. Additional symptoms can include memory loss, anxiety, deficits of executive function, cognitive decline, dementia, peripheral neuropathies, Parkinsonism, and various autonomic dysfunctions (e.g., hypertension, incontinence). Interestingly, individuals with FXTAS have approximately a threefold higher risk of obstructive sleep apnea compared to case controls and also to individuals with FMR1 premutation alleles, but without FXTAS [15]. A study by Summers and colleagues [16] found that the frequency of restless legs syndrome nearly doubled in premutation carriers versus controls. These same individuals reported more sleep pathology on the Pittsburgh Sleep Quality Index and Insomnia Severity Index and a trend toward daytime sleepiness on the Epworth Sleepiness Scale.

Fragile X primary ovarian insufficiency (FXPOI) is a Fragile X-associated disorder that affects approximately 20% of women with a FMR1 premutation allele [17]. This condition displays a range of ovarian dysfunction including early menopause, irregular menstrual cycles, infertility, and premature ovarian failure occurring prior to age of 40 years. Physical changes include those of typical menopause such as hot flashes, insomnia, and increase in anxiety and may also affect sleep.

Intermediate Allele

FMR1 alleles between 45 and 54 CGG repeat lengths are termed the “gray zone” or intermediate allele size. The prevalence of individuals with the intermediate allele ranges from 1:42 to 1:112 in males and 1:35–1:66 in females in the United States [18–20]. While most appear stable, transmission to a full mutation within two generations has been documented [10]. Recent studies have confirmed that maternal alleles with no AGG interruptions lend the greatest risk for instability [21]. Yrigollen and colleagues [22] recommend a predictive model using total CGG length, number of AGG interruptions, and maternal age as the most relevant variables to calculate risk of expansion to a full mutation from either premutation or intermediate allele size female.

Several studies have reported an association of the intermediate allele with Parkinson’s disease [23, 24], and case reports have identified individuals with intermediate alleles who met diagnostic criteria for FXTAS [25, 26]. Bretherick and colleagues [27] revealed significant findings between premature ovarian failure and FMR1 allele sizes between 35 and 54 repeats. In 2012, Renda and colleagues [28] conducted a retrospective review of 1447 electronic health records on people aged 18 years or younger who had DNA testing for an FMR1 gene mutation. They identified 25 children and adolescents with FMR1 gray zone alleles, all of

whom were diagnosed with at least 1 neurodevelopmental disorder, with no other recognized genetic, metabolic, environmental, or structural etiology.

Sleep in Children with Fragile X Syndrome: The Evidence

FMRP is present in dendritic spines and plays an essential role in synaptogenesis. Without FMRP, there is altered synaptic plasticity, defects in dendritic pruning, and increased oxidative stress in the brain [29]. Several studies on Drosophila melanogaster have identified an association between FMRP expression levels and altered circadian and sleep patterns [30–32].

Various studies have investigated sleep in children with FXS alone or in relationship with other neurodevelopmental conditions. Table 22.1 is a brief description of studies, listed in chronological order, whose findings have pertinent clinical applications to FXS.

Studies cited in Table 22.1 should make the clinician aware that children with FXS may have sleep disturbances that fall into three major categories: insomnias, parasomnias, and sleep-related breathing disorders. The most frequently reported sleep problems in children with FXS fall under the category of insomnia: sleep onset delay and problems maintaining sleep. It is essential for clinicians to recognize and assess for sleep difficulties in all children with FXS.

Sleep difficulties are compounded when children with FXS display co-occurring conditions or diagnoses such as obstructive sleep apnea, self-injurious behavior (SIB), anxiety, autism, and sensory issues [33, 39, 40]. The odds of having sleep problems can significantly increase when children with FXS are reported to have fair to poor overall health or quality of mood and limited ability to listen and pay attention, interact with others, and adapt to new situations [39]. Therefore, a referral to a specialist may be warranted (e.g., sleep medicine or otolaryngology) for further diagnostics such as an overnight sleep study, also called polysomnography.

Sleep in Children with Fragile X Syndrome: Diagnosis

Sleep disturbances in children with disabilities likely represent a complexity of interactions involving biological, personal, social, and environmental factors. Therefore, obtaining both qualitative and quantitative data will help identify the presence and nature of sleep problems in children with FXS. Surprisingly, sleep concerns are rarely screened in clinical practice [41–43]. In the medical setting, providers and parents must prioritize concerns and typically focus on the presenting illness, as well as overcoming physical and behavioral challenges such that identification of sleep issues can easily go undetected. In addition, parents of children with special health-care needs may believe sleep problems are expected in their child's condition and gradually adapt to or just tolerate their child's sleep disturbance. Thus, they do not mention their sleep concerns during medical visits. Other barriers that prevent a more thorough assessment of sleep may include limited clinical expertise, time, and resources within the clinical practice and lack of access to empirically based screening tools. The consensus document entitled *Sleep in Children with Fragile X Syndrome* (https://fragilex.org/wp-content/uploads/2012/08/Sleep-in-Children-with-Fragile-X-Syndrome2012-Oct.pdf, 2012) provided by the Fragile X Clinical and Research Consortium (FXCRC) suggests the use of leading questions that may begin a conversation about sleep habits:

- Do you have any concerns regarding your child's sleep?
- Does your child take more than 30 min to fall asleep at bedtime?
- Once asleep, does he/she stay asleep?
- Is your child afraid to sleep alone?
- Does your child seem excessively sleepy during the day?
- Have you heard your child snore or stop breathing during the night?

Depending on responses to the questions, a careful history of sleep habits, including a validated pediatric sleep measure, and a 2-week sleep diary may reveal patterns that will guide treatment options.

Lewandowski, Toliver-Sokol, and Palermo [44] provided an extensive evidence-based review of 21 subjective pediatric sleep measures that can be used in practice. The measures were categorized according to their primary focus: sleep initiation/maintenance (5), daytime sleepiness (4), sleep habits and hygiene (4), cognition/beliefs about sleep (2), and multidimensional (6).

The authors applied criteria developed by the American Psychological Association Division 54 Evidence-Based Assessment (EBA) Task Force and identified six measures as "well-established," eight measures as "approaching well-established," and seven as promising. Four of the well-established measures were considered multidimensional and included the *Brief Infant Sleep Questionnaire* (*BISQ*), the *Children's Sleep Habits Questionnaire* (*CSHQ*), the *Pediatric Sleep Questionnaire* (*PSQ*), and the *Sleep Disturbance Scale for Children* (*SDSC*).

Of the four well-established multidimensional measures, only the *Children's Sleep Habits Questionnaire* (*CSHQ*) has been consistently employed as a clinical assessment and research tool in children with FXS [38, 45, 46]. Its use has also been well-established in other neurodevelopmental conditions such as autism [47, 48] and ADHD [49, 50]. The *CSHQ* has

Table 22.1 Summary of studies listed in chronological order, whose findings have pertinent clinical application to FXS

Author	Journal/year	Title	Population	Measure	Findings
Tirosh and Borochowitz [33]	American Journal of Medical Genetics, 1999	Sleep apnea in Fragile X syndrome	7 subjects ages 6–21 years with FXS	Polysomnography	2 subjects had severe OSA
					2 subjects had mild-moderate OSA
Ferri et al. [34]	American Journal of Medical Genetics, 1999	Heart rate variability and autonomic function during sleep in Fragile X syndrome	7 subjects ages 10–15.2 years with FXS	Polysomnography	In FXS, total sleep time significantly decreased; percent of wakefulness after sleep onset significantly increased compared to controls
			6 age-matched controls		
Gould et al. [35]	American Journal of Medical Genetics, 2000	Melatonin profiles and sleep characteristics in boys with Fragile X syndrome: A preliminary study	14 boys ages 4.7–11 years with FXS	14-day sleep diary; salivary melatonin samples	In FXS significantly greater total sleep variability; greater difficulty maintaining sleep; greater variability and elevated levels of melatonin across circadian cycle
			8 age-matched controls		
Miano et al. [36]	Clinical Neurophysiology, 2008	Sleep phenotypes of intellectual disability: A polysomnographic evaluation in subjects with Down syndrome (DS) and Fragile X syndrome	14 males with FXS ages 7–25 years	Polysomnography to measure sleep macrostructure and cyclic alternating pattern to measure sleep microstructure	FX subjects showed a reduced time in bed; lower number of REM periods; higher percentage of stage 1 NREM; most had disrupted sleep microstructure
			9 subjects with DS ages 8–20 years		
			26 age-matched controls		
Wirojanan et al. [37]	Journal of Clinical Sleep Medicine, 2009	The efficacy of melatonin for sleep problems in children with autism, Fragile X syndrome, or autism and Fragile X syndrome	*N* = 12	4-week, randomized, double-blind, placebo-controlled, crossover design using actigraphy and daily sleep diaries to measure effects of 3 mg melatonin	Melatonin significantly lengthened mean night sleep duration, shortened mean sleep onset latency, and shifted mean sleep onset time earlier
			Ages ranged from 2 to 15.3 years. Three subjects had FXS alone; five had autism alone; three had both FXS and autism; one had FMR1 gene premutation		
Kronk et al. [38]	American Journal on Intellectual and Developmental Disabilities, 2009	Caregiver reports of sleep problems on a convenience sample of children with Fragile X syndrome	90 children (81% male) with a full mutation of FXS ages 3–17 years	Parent completed Children's Sleep Habits Questionnaire (CSHQ) and 14-day sleep diary	47% of children reached a clinical cutoff score on CSHQ indicating need for further evaluation. There was a significantly positive association between snoring and clinical level of sleep issues
					8/17 children receiving medications to aid sleep had clinical CSHQ scores
					Sleep diaries identified irregular bedtimes (86%), irregular morning arousal times (83%), night wakings (53%), and sleep onset delay (50%) as having the highest prevalence
Kronk et al. [39]	SLEEP, 2010	Prevalence, nature, and correlates of sleep problems among children with Fragile X syndrome based on a large-scale parent survey	1295 children with FXS syndrome	Parent survey	32% of children were experiencing current sleep difficulties of whom 84% had two or more sleep problems. Most frequently reported problems were nighttime awakenings and problems falling asleep. 47% of males and 40% of females were taking medication as a sleep aid, but 39% of parents felt medical intervention had none or little effect

Table 22.1 (continued)

Author	Journal/year	Title	Population	Measure	Findings
Symons et al. [40]	American Journal on Intellectual and Developmental Disabilities, 2010	Self-injurious behavior and Fragile X syndrome: Findings from the National Fragile X Survey	489 children with FXS with self-injurious behavior (SIB)	Parent survey	38.7% of males and 46% of females with FXS and SIB had sleep difficulties
					Compared to age-matched controls, males with SIB were significantly more likely to have sleep difficulties, sensory food-related issues, inattention, hyperactivity, autism, and anxiety; females demonstrated significantly higher rates of sensory difficulties, autism, and anxiety

been translated to multiple languages (e.g., Spanish, Chinese, and Hebrew), and its use has been validated in various clinical populations [51–53]. The *CSHQ* can provide information on the quality and nature of the child's wakeful periods, bedtime anxieties, sleep resistance, and parasomnias. With regard to clinical feasibility, the *CSHQ* is available at no cost and easily accessible. It can be completed within 5–10 min and does not require long-term recall. Cost, accessibility, and burden to complete are all considerations that should be taken into account when choosing a pediatric sleep measure.

Polysomnography has been successfully implemented in research studies involving children with FXS. There are documented sleep differences in these small cohorts of children including increased risk of OSA and abnormalities of sleep parameters such as decreased percentage of REM stage sleep [34, 36]. Although not as clinically applicable in the primary care setting, actigraphy has been another objective measure employed in sleep research. Actigraphy has an 85–95% agreement rate with gold-standard polysomnography for sleep-wake scoring [54] and provides the advantage of collecting data within the child's typical sleep setting over time, rather than in the course of a single night in a laboratory setting. Actigraphy data becomes even more useful when monitoring pre- and post-interventional outcomes as demonstrated by Wirojanan et al. [37]. Comparison of actigraphy data from children with FXS to age-matched controls or children from a similar population with or without sleep difficulties may add further perspective and interpretive meaning to results.

Sleep in Children with Fragile X Syndrome: Management and Guidelines

Sleep difficulties rarely follow a simple cause and effect pattern. There are multiple influences including cultural, biological, environmental, and behavioral that can simultaneously improve or deplete the restorative influences of sleep. Altered sleep patterns can occur acutely and resolve with minimal intervention or develop into a chronic condition requiring more intensive interventions. Therefore, a biopsychosocial conceptual framework may be a helpful approach in order to effectively manage the complex nature of sleep disorders. Figure 22.2 provides an example of how sleep difficulties may be viewed based on the International Classification of Functioning, Disability and Health-Children and Youth Version (ICF-CY) [55]. This model takes into account not only a health condition but also the interplay of body functions (i.e., alteration in sleep) in executing activities and involvement in life situations within the context of environmental and personal factors. A multidimensional approach to sleep allows the parent and clinician to identify common goals, partner on interventions, and monitor functional outcomes.

Treatment for sleep disturbances may include behavioral, pharmaceutical, or surgical interventions, such as tonsillectomy and adenoidectomy, depending on the nature and severity of the condition. Typically, treatment for insomnias (e.g., difficulty falling asleep or maintaining sleep) or parasomnias (e.g., enuresis) can begin with the primary care provider. Mindell and Owens [56] offer symptom-based algorithms for evaluating prolonged sleep onset or bedtime resistance and night wakings. Although intended for the general pediatric population, these algorithms can guide clinical decision-making and management plans for children with FXS.

The consensus document entitled *Sleep in Children with Fragile X Syndrome* (2012) provided by the Fragile X Clinical and Research Consortium suggests that better sleep hygiene practices should be implemented by helping parents understand sleep physiology and sleep stages along with recognizing environmental cues. Creating a more predictable schedule by routinizing daytime behaviors such as meals and other activities may also help decrease inherent anxiety in the child with FXS and lead to a more structured bedtime routine. Sleep may also improve as coexisting conditions such as ADHD and anxiety are treated.

If a sleep problem is behaviorally based, then behavioral interventions should be considered as the first line of treat-

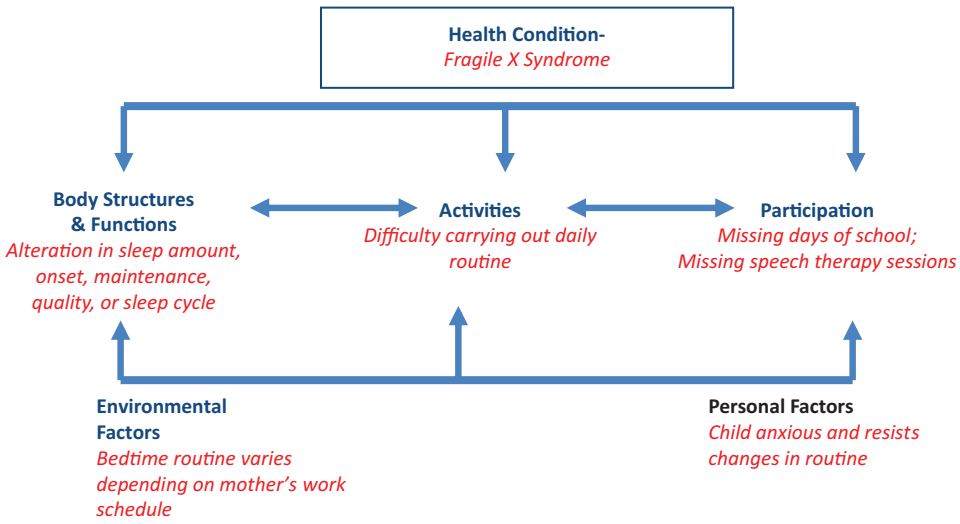

Fig. 22.2 An example of conceptualizing sleep difficulties in children with FXS using the ICF-CY as a biopsychosocial model

ment. Evidence is scant on the effectiveness of behavioral interventions in children with FXS. Weiskop, Richdale, and Matthews [57] conducted a parent training program to reduce sleep problems in children with FXS or autism by addressing bedtime routines, principles of behavior reinforcement, and extinction techniques, and also involving partner support. Ten families completed the program and settling problems, night waking, and co-sleeping were reduced. Improvements were effectively maintained at follow-up. Kronk et al. [39] evaluated caregivers' responses to treatments used and perceived efficacy. Behavioral interventions were most widely used, including environmental changes, bedtime routine changes, and implementing rewards or consequences for behaviors. However, up to 62% of parents felt that they were "a little" to "not at all" helpful. Medical interventions included medication, surgery, or other categories (e.g., herbal supplements, CPAP), and up to 40% of caregivers felt these treatments had effects ranging from "little" to "none." It is essential to determine the perceived effectiveness of treatments from caregivers' perspective. Satisfaction with treatments can improve overall quality of life for both the child and family.

A variety of medications have been documented to treat sleep problems in children with FXS including melatonin, clonidine, risperidone, quetiapine, aripiprazole, mirtazapine, and buspirone [38]. In several studies, parents reported that medications were prescribed to treat sleep difficulties in their children, and their children continued to display significant sleep problems [38, 39]. Etiologic factors influencing response to sleep medications have not been studied in children with FXS. However, Gould and colleagues [35] purported that sleep disturbances in FXS may be related to the hypothalamic pituitary adrenal axis (HPA) and melatonin production. Interestingly, they discovered elevated melatonin levels in saliva samples across the circadian cycle in a small cohort of prepubertal males ($n = 13$) with FXS, which is a counterintuitive finding in relationship to sleep disruption. This study has not been replicated. However, several studies, with larger cohorts, have investigated melatonin levels in children with autism, either with serum or urine samples, and have concluded that nighttime melatonin levels are often decreased compared to controls [58–60].

In a large national survey that included information on 1064 males and 299 females with the full mutation of FXS, Bailey and colleagues [61] investigated the use of medications by symptom (i.e., anxiety, attention, hyperactivity, anger, or aggression) and gender, along with associated child (i.e., age, overall ability, autism) and family characteristics (i.e., income). Less than one third of parents rated medications as "a lot" effective. In children less than 10 years of age, pill swallowing difficulty was prevalent. These studies underscore the need to investigate the biological, behavioral, and social factors influencing the effectiveness of pharmaceutical treatments. In addition, clinicians must consider the dynamics of these factors when routinely assessing for the efficacy of medications used as sleep aids in children with FXS. For a comprehensive review of sleep interventions, primarily pharmaceutical, in children with neurodevelopmental disabilities, refer to Angriman and colleagues [62] and Hollway and Aman [63].

Melatonin

Except for Wirojanan and colleagues [37], who offered a well-designed study that supported the effectiveness of melatonin in children with FXS, there is a paucity of studies investigating the effectiveness of sleep medication specifically in children with FXS. However, Appleton et al. [64] conducted a large multicenter randomized, double-blinded, placebo-controlled parallel-group study of melatonin in children with neurodevelopmental disorders with impaired sleep. Melatonin was started at 0.5 mg, and during the first 4 weeks, the dose could be increased at weekly intervals to

2 mg, then 6 mg, and a maximum of 12 mg. The final effective dose was then maintained. Melatonin was more effective than placebo, reducing sleep onset delay on average by 37 min and increasing total sleep time by an additional 23 min. Interestingly, parents themselves reported less daytime fatigue, but the reduction in sleep latency seemed to result in no measureable improvement in quality of life for families or in the children's behavior over a 12-week period.

Typical dosing of melatonin for children with FXS begins with the lowest dose of 0.5 mg 1 h prior to bedtime. Dosing can be increased weekly by 1 mg to a maximum dose of 3–5 mg. Melatonin also comes in an extended release formulation that can be used to help with sleep maintenance but is limited to children who can swallow a whole tablet or capsule as it cannot be crushed or chewed. It is important to remember that melatonin is not regulated by the FDA and may vary in strength and purity; therefore, suggesting the purchase of pharmaceutical grade melatonin is recommended.

Clonidine

There are no well-controlled studies on the effects of the alpha-agonist clonidine in children with sleep problems. In 1995, Hagerman and colleagues [65] surveyed parents of 35 children with FXS, of whom 37% were using clonidine specifically to treat sleep issues, and nearly half of those parents were satisfied with its use. Clonidine is approved by the FDA as an antihypertensive medication, although its use as a sleep aid in children with neurodevelopmental disabilities has been on the rise. Ming and colleagues [66], in an open-label retrospective study, reported that oral clonidine, with doses ranging from 0.1 to 0.2 mg, was effective in reducing sleep latency in 16/16 subjects with ASD and prolonged sleep initiation. Clonidine improved sleep maintenance in 16/17 children with ASD and sleep maintenance difficulties. Clonidine has been prescribed in children with FXS as well. It should be started at the lowest effective dose (0.025 mg) and incrementally increased to a maximum dose of 0.4 mg per day depending on the age and weight of the child and tolerability. Reported side effects include drowsiness, headache, insomnia, and hypotension. It should not be used with a history of cardiovascular disease or depression, and several drug-to-drug interactions have been documented. Clonidine should not be stopped abruptly as it may cause rebound hypertension.

Sleep in Children with Fragile X Syndrome: Future Directions

Research has identified the presence of sleep difficulties in a subset of individuals with FXS. Further investigations should focus on defining medical conditions that may contribute to sleep problems in children with FXS such as obesity and obstructive sleep apnea (OSA). It is important to note that compared to age-matched controls, male children with FXS have higher rates of obesity [67]. Kronk et al. [38] noted that 34% of children with FXS ages 3–17 years snored loudly with the highest incidence (40%) in children ages 12–17 years. These children may be experiencing OSA contributing to chronic sleep problems. Therefore, future investigations should consider the relationship between sleep and OSA by employing objective measures such as polysomnography (PSG).

Research is necessary to expand our understanding of the subset of individuals with FXS who demonstrate sleep difficulties. Effective treatments, both behavioral and pharmaceutical, must be investigated. There is a need for well-designed double-blind crossover studies investigating the effectiveness of medications and behavioral interventions in treating sleep problems. We must better clarify their psychological and physiological profiles, identify molecular and genetic linkages, and then translate these findings into clinical practice. The immediate and long-term impact of these treatments on family satisfaction and functioning must also be measured and documented. The biopsychosocial complexity of FXS underscores the imperative need to assess treatment outcomes via a multidimensional framework such as the International Classification of Functioning and Health.

Conclusions and Recommendations

Clinicians must be aware that sleep problems occur in children with FXS. Therefore, providing a regular, routine assessment of sleep is a necessary part of the evaluation of a child with FXS. Clinicians can look for future publications by the Fragile X Clinical and Research Consortium (FXCRC) as information from the FORWARD Registry and Database expands our clinical and scientific understanding of FXS https://fragilex.org/our-research/nfxf/forward-registry-database/.

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Intellectual Disability

23

Gregory Stores

Case Vignette

A 3-year-old girl had suffered severe perinatal birth asphyxia causing spastic quadriparesis, epilepsy and global developmental delay. She was said to always have cried a lot, especially at bedtime when she was put down to sleep. In the last 9 months, this problem had worsened, and in addition, she woke repeatedly during the night in a very distressed state. Her parents had been in the habit of letting her go to sleep downstairs in their arms and then allowing her to sleep in their own bed every night. She woke every hour or two and needed much comforting before she settled back to sleep each time. Her sleep was described as restless and she snored most nights. Brief episodes of stiffening during sleep were also reported by her parents without any obvious relationship to the other nocturnal events. She did not actually sleep during the day, but her behaviour was described as generally difficult. Her total time asleep per 24-h period was typically about 7 h compared with the recommendation of 11–12 h for children of her age. Treatment had consisted of baclofen for her spasticity and chloral-containing compounds such as chloral hydrate or melatonin for short periods without any improvement in her sleep. Antiepileptic medication had not been used because her daytime seizures (described as episodes of unresponsiveness for up to 5-min duration) were thought to be infrequent. There was a record of a single generalised tonic-clonic seizure supposedly lasting several minutes before it subsided spontaneously.

Comment: This case illustrates a theme which this chapter emphasises, namely, the need for comprehensive assessment and care in such multiply disabled children. Physical factors, which could have contributed to the child's seriously limited and disrupted sleep, include upper airway obstruction during sleep, nocturnal seizures (tonic seizures in particular may not be recognised as such) and discomfort in bed with difficulty changing position possibly making breathing problems worse. Parenting factors also needed to be modified, in particular the child's dependence on her parents' presence. In fact, further assessment demonstrated that sleep-related breathing problems, discomfort at night and nocturnal seizures did not seem to be significant factors. With persistence, it was possible to improve the child's settling and night-waking problems by means of behavioural methods. This was associated with some initial improvement in her general behaviour, but further attempts to modify the way her parents handled her daytime behaviour problems were considered necessary.

Introduction

The main aim of this chapter is to consider aspects of the relationship between intellectual disability and sleep disturbance, both of which appear to be prominent in children with a neurodevelopmental disorder. Overall rates of intellectual disability and sleep disturbance in such children as a group would be difficult to achieve, and their usefulness is limited in view of the diversity of conditions to which these terms apply. Both appear to be common, but it is more appropriate to consider such rates in each individual neurodevelopmental disorder for which such information is (to a limited extent) available at the present time [1].

G. Stores
Department of Psychiatry, University of Oxford, Oxfordshire, UK
e-mail: gregory.stores@psych.ox.ac.uk

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Whatever the true overall rates of intellectual disability and sleep disturbance might be, for some time now, there have been consistent reports of a strong association between the two. Early accounts about severely intellectually impaired children quoted high rates of serious and persistent sleep problems which were often linked with disturbed behaviour and family difficulties [2]. Since then, this association has been confirmed, for example, by Didden et al. [3], Robinson and Richdale [4], Dorris et al. [5], Lipton et al. [6] and Chu and Richdale [7]. This association is important given the consistent evidence that sleep disturbance in any child can have deleterious effects on development as described later. The predicament of a child with intellectual disability can be worsened by disturbed sleep with additional problems for the family.

Before discussing associations between intellectual disability and sleep disturbance, aspects of the meaning and scope of these two concepts, as well as the potentially harmful effects of sleep disturbance on child development, will be considered briefly.

Intellectual Disability

Definitions and Terminology

Over the years, various terms have been used for intellectual disability, which is now the preferred term in most countries in preference to 'mental retardation'. Schalock et al. [8] have discussed the basis of this renaming. Outmoded terms from the past include idiocy, feeblemindedness, mental deficiency, mental disability, mental handicap and mental subnormality. The prevalence of intellectual disability in children and adolescents has been estimated as 18.30 per 1000, which is considerably higher than in adults [9]. Among individuals with intellectual disability taken as a group, the proportions of mild, moderate, severe and profound impairment have been reported to be approximately 85%, 10%, 4% and 2%, respectively [10].

The American Association on Intellectual and Developmental Disabilities (AAIDD) defines intellectual disability as 'a disability characterized by significant limitations in both intellectual functioning and in adaptive behaviour which covers many everyday social and practical skills. This disability originates before the age of 18' [11]. This definition is compatible with that of the UK Department of Health [12].

In AAIDD terms, intellectual functioning (intelligence) refers to general mental capacity such as learning, reasoning and problem-solving as assessed by intellectual quotient (IQ) testing. In general, an IQ below about 70 has been taken to indicate limited intellectual functioning. Associated deficits in adaptive behaviour are also required for diagnosis and can be assessed by standardised tests. AAIDD emphasises that 'In defining and assessing intellectual disability additional factors must be taken into account such as the community environment typical of the individual's peers and culture' and that 'Professionals should also consider linguistic diversity and cultural differences in the way people communicate, move, and behave'. In keeping with these views, Greenspan and Woods [13], for example, say that defining intellectual disability solely in terms of psychometric test scores is inappropriate for psychiatric and medical disorders. They welcome the DSM-5 attempt to broaden its intellectual disability section by emphasising a medical/neurobiological disorder rather than a disability based on a test score.

Certain terminological distinctions need to be made. 'Learning disability' (sometimes used as equivalent to intellectual disability) should not be confused with 'learning difficulties' (a general term referring to difficulty learning for various reasons, medical and non-medical). 'Learning disability' as used in North America refers to specific developmental delays such as dyslexia, dyscalculia and dysgraphia. In the UK, the term 'special educational needs' usually refers to children who have learning difficulties that make it harder for them to learn than most children of the same age. Such children require assistance that may be educational, medical, psychiatric and/or psychological. 'Children with multiple disabilities' are defined as having two or more disabling conditions that significantly affect learning or other important life functions.

Aetiology

Historical accounts trace from ancient times to the present day the evolving concepts of and attitudes towards intellectual disability [14]. In contrast to the mainly speculative and fanciful notions of earlier times, a modern scientific view can be said to have started with the seventeenth-century English physician and anatomist Thomas Willis (1621–1675) who, incidentally, coined the term 'neurologia'. Willis distinguished between inherited, congenital and acquired causes of what he called 'stupidity', which he differentiated from 'folly', by which he seems to have meant psychiatric disorder, possibly schizophrenia [15]. His many other accomplishments included making observations of various sleep disorders such as insomnia, nightmares, sleepwalking and restless legs syndrome [16].

Increasingly, the causes of intellectual disability are now known to be many and diverse including genetic conditions, metabolic disorders, infections, toxins and trauma. The resulting brain damage or dysfunction may occur in the antenatal, perinatal or postnatal period. In about a third to a half of children with intellectual disability, its cause is not known. Within the neurodevelopmental disorders, the degree of

intellectual disability varies from little or none to profound, and depending on the particular neurodevelopmental disorder, the phenotype can vary considerably in its complexity.

For both clinical and research purposes, generalising about children with a neurodevelopmental disorder or intellectual disability is unhelpful compared with the consideration of specific types of disorder including individual syndromes. However, not all children with a neurodevelopmental disorder have a specific syndrome. 'Non-syndromic intellectual disability' refers to intellectual disability without characteristic dysmorphic features, malformations or other neurological abnormalities.

An account of the *assessment and care of children with intellectual disability* is beyond the scope of this chapter but is available elsewhere [17].

Sleep Disturbance

It is possible that disturbed sleep is a common feature of all neurodevelopmental disorders. However, it has only been reported in a limited number of such disorders because study of sleep aspects of neurodevelopmental disorders is a neglected topic [1].

It should not be thought that people with a neurodevelopmental disorder, including those with an intellectual disability, have types of sleep disturbance fundamentally different from other people. Basically, they have the same range of sleep disorders as other children and adults, but their problems are generally more prevalent and severe and, if untreated, more persistent. Also (as illustrated later), because of the likely multifactorial aetiology of their sleep disturbances, assessment and treatment might be more complicated than in other children. The psychological, social and other adverse effects of the neurodevelopmental disorder itself may be worsened by the sleep disturbance.

It is true that, depending on the degrees of intellectual impairment and communication problems, obtaining subjective clinical details of the disturbance may be difficult and sometimes not possible. For the same reason, compliance with certain diagnostic and treatment procedures can present problems. However overall, in identifying the nature of the sleep disturbance (and therefore, the treatment required), an attempt should be made to utilise modern systems of classification.

The general term 'sleep disturbance' covers both 'sleep problems' and 'sleep disorders', which need to be distinguished from each other for clinical and research purposes. Sleep disturbance can cause shortage of sleep or poor-quality (interrupted or unrefreshing) sleep. 'Sleep behaviour' simply means behaviour associated with sleep which may or may not be problematic.

At any age, the three basic sleep problems (which may interrelate) are as follows:

(a) Insomnia (otherwise referred to as sleeplessness), which takes the form of not readily getting to sleep, difficulty staying asleep and/or waking early and not returning to sleep
(b) Hypersomnolence (excessive daytime sleepiness)
(c) Parasomnias and abnormal sleep-related movements (behaving in unusual ways, having strange experiences or exhibiting unusual movements in relation to sleep)

These sleep problems are not diagnoses in their own right. For appropriate advice and treatment to be chosen, it is necessary to identify the underlying cause of a sleep problem, that is, the sleep disorder. Attempts to treat the sleep problem without accurate diagnosis of the underlying cause are likely to be unsuccessful. The third edition of the International Classification of Sleep Disorders (ICSD-3) [18], the foremost source of information about sleep disorders, is comprised of the following sections. Examples of each encountered in children (although not exclusively) are shown here in brackets.

- Insomnias [behavioural insomnia of childhood].
- Sleep-related breathing disorders [obstructive sleep apnoea].
- Central disorders of hypersomnolence [narcolepsy].
- Circadian rhythm sleep-wake disorders [irregular sleep-wake rhythm disorder].
- Parasomnias [sleep terrors].
- Sleep-related movement disorders [sleep-related rhythmic movement disorder].
- Other sleep disorders [possibly environmental sleep disturbance].
- Appendix A: sleep-related medical and neurological disorders [sleep-related epilepsy].
- Appendix B discusses ICD-10-CM coding for substance-induced sleep disorders.

Clinically valuable and up-to-date details concerning each diagnosis are arranged under the following headings. Treatments are not considered.

- Alternate names
- Diagnostic criteria
- Essential features
- Associated features
- Clinical and pathophysiological subtypes
- Demographics
- Predisposing and precipitating factors
- Familial patterns
- Onset, course and complications

- Developmental issues
- Pathology and pathophysiology
- Objective findings
- Differential diagnosis
- Unresolved issues and further directions
- Bibliography

There is merit in using this system of classification as it is considered more diagnostically specific and up to date than the DSM and ICD classifications of sleep disturbance. The relationship of ICSD-3 to these other classification systems is explained in its Introduction. ICSD-3 covers sleep disorders in both adults and children, but in this edition, paediatric aspects are now given special emphasis.

Developmental Effects of Childhood Sleep Disturbance

There are many potentially serious and widespread consequences of a child's persistent failure to obtain sufficient good-quality sleep. Such consequences can add significantly to the problems and impaired quality of life of children with intellectual disabilities and their families.

1. Emotional state and behaviour can be affected [19]. For example, overtired children are often irritable, distressed and even aggressive, quite possibly seriously disrupting family life. Certain children diagnosed as having attention-deficit/hyperactivity disorder (including some with an intellectual disability) may well have a primary sleep disorder for which stimulant drugs are inappropriate, as they might worsen the sleeping problem. Bedtime can become distressing if associated with upsetting experiences such as nighttime fears. The delayed sleep phase syndrome (which is reported in some with intellectual disability) can lead to mood and other emotional changes. Children's poor sleep may affect interpersonal relationships beyond those with their family. For instance, irritable, difficult or otherwise disturbed behaviour is likely to affect friendships.
2. There is also convincing evidence that cognitive function of children and adolescents can be impaired by inadequate or poor-quality sleep because of harmful effects on concentration, memory, decision-making and general ability to learn [20, 21].
3. Increasingly various physical disorders associated with disturbed sleep are being described [22, 23]. For example, as the production of growth hormone is closely linked to deep NREM sleep, reduction of this type of sleep may affect physical growth. Early-onset obstructive sleep apnoea, which can impair the depth and quality of sleep, may cause failure to thrive in some young children. Persistent sleep loss in particular has been linked in adults and children with physical ill health such as impaired immunity, obesity, hypertension and diabetes.
4. Regarding effects on the family [22, 24], parents may disagree with each other about ways of dealing with children's refusal to go to sleep at the required time or children's insistence on joining parents in their own bed after waking during the night. Because of their own loss of sleep, parents (mainly mothers) may become anxious and depressed and unable to cope. Marital relationships can become seriously strained.

Connections Between Intellectual Disability and Sleep Disturbance in Children with Neurodevelopmental Disorders

Comorbidities (meanings of which are discussed by Bax and Gillberg [25] but defined here simply as the co-occurrence of disorders more frequently than would be expected by chance) are common in neurodevelopmental disorders. They can take various forms, especially physical or psychiatric [26]. As intellectual disability is so common in neurodevelopmental disorders, it can be considered one of the foremost comorbidities. Attention to comorbid conditions can mean complex assessment and management procedures which, however, are necessary to allow adequate insight into the individual child's sleep disturbance and to guide overall treatment requirements.

Clinical Connections

Clinical connections can take a variety of forms.

1. From birth through infancy, the biological clock controlling sleep and wakefulness has to develop in response to perception of environmental indicators of time ('zeitgebers'). This process by which the circadian sleep-wake rhythm is established includes appreciation of the 24-h light-dark cycle and timing of meals and social contacts. Awareness of these indicators may be impaired by maldevelopment of or damage to the anatomical and neurotransmitter systems in the brain involved in the control of sleep and wakefulness described by Brown et al. [27]. Such abnormalities are likely to be associated with intellectual disability.
2. Extensive and severe brain damage produces an 'acerebrate' state in which there is little response to external stimuli and often a highly irregular sleep-wake pattern [28]. In this state, normal sleep phenomena (such as sleep spindles and vertex sharp waves) are usually

lacking, such that it is difficult to distinguish between sleeping and the awake state ('monostage sleep'). Children whose brains are less severely damaged, but whose perception and social awareness are severely impaired, may not entrain their sleep-wake rhythms to a 24-h period and therefore exhibit a 'free-running' circadian rhythm which is not synchronised to zeitgebers, establishing instead an endogenous rhythm of about 25 h.

3. A child who is intellectually disabled may well have difficulty learning good sleep habits. For example, he/she may have limited (if any) understanding of parental efforts to teach good sleep hygiene even in the way described for children with neurodevelopmental disabilities by Jan et al. [29]. In addition, the child might not register or understand the environmental cues about when it is time to sleep.

Polysomnographic Studies

Polysomnographic studies have sometimes explored the relationship between intellectual level and rapid eye movement (REM) sleep, the proportion of which is high in neonates and then decreases as infants mature. It might be expected, therefore, that children with intellectual impairment would have an immature pattern of brain activity with more REM sleep than typically developing children. However, they have been reported to have less, which is compatible with the view that REM sleep is involved in the learning process, although this type of sleep has had various uncertainties raised concerning its biological role [30]. Intellectual disability has also been linked with abnormalities of sleep spindle activity which (like REM sleep) has been associated with the process of memory consolidation [31].

Interesting though such reports may be, studies of mixed groups of children with developmental delays have the disadvantage of involving generalisations across a wide variety of different conditions. A more discriminating approach has examined relationships between intellectual disability and sleep by exploring possible polysomnographic phenotypes, analogous to behavioural phenotypes, in specific developmental disability syndromes. Harvey and Kennedy [32] reviewed the relatively few studies of this type and concluded that differences in sleep architecture appear to be discernible between autism, Down syndrome and fragile X syndrome. Patients with intellectual disabilities appear to have REM sleep abnormalities (including a deficiency) more frequently compared with typically developing controls. How far these various physiological differences relate to clinical sleep disorders has yet to be determined.

Other Factors Which May Accompany Intellectual Disability in the Aetiology of Sleep Disturbance in Children with a Neurodevelopmental Disorder

In addition to limited intelligence, other factors (sometimes in combination) associated with intellectual disability can contribute to sleep disturbance in children. Such factors can be grouped as those intrinsic to the child's basic condition, physical and psychiatric comorbidities, possible medication effects and inappropriate parenting practices. This aetiological complexity can be illustrated by reference to *foetal alcohol spectrum disorders (FASD)* which refers to the range of neurological and other abnormalities that can affect a child who has been exposed to alcohol in utero [33].

Recent studies have assessed the extent of such exposure and its consequences [34], and FASD has been considered the most common preventable cause of intellectual disability worldwide. The overall global prevalence rate of FASD in children and youth in the general population has been estimated as 7.7 per 1000 but with variation from one geographical region to another [35]. Of the various forms of FASD, foetal alcohol syndrome (FAS) is the most severe end of the spectrum with widespread developmental abnormalities.

Points arising from a literature review of sleep in FASD [36] include consistent reports that sleep disturbance is a serious health issue for children with FASD in being common, often severe and persistent. Despite this, the problem has received limited clinical and research attention [37]. Often the nature of the sleep disturbance is not well documented. Although the basic sleep problems may be mentioned (i.e. insomnia, excessive sleepiness, parasomnias or sleep-related movement disorders), underlying sleep disorders as described in ICSD-3 (on which choice of appropriate treatment depends) are inconsistently identified.

A further shortcoming is that often inadequate attention is paid to the possible multifactorial influences on sleep as already mentioned [38]. In FASD, such aetiological factors affecting sleep can be grouped as follows.

1. Damage to brain structures and systems involving sleep caused by the prenatal exposure to alcohol [39] is the prime *intrinsic pathophysiological factor*. For example, experimental animal studies of the effects of alcohol exposure in early development have suggested disruption of the body clock system potentially causing circadian sleep-wake cycle disorders [40]. Consistent with this possibility is the report that a group of children and adolescents with FASD usually had an abnormal melatonin profile [41].
2. A number of recent studies such as [42] have been concerned with various comorbidities associated with

FASD. As many of these comorbidities are capable of disturbing sleep in their own right, they need to be taken into account in explaining the origins of a child's overall sleep disturbance. *Physical comorbidities* capable of disrupting sleep include epilepsy which is particularly common in FASD [43] depending on its type and severity [44]. Deformities and sensory abnormalities associated with FASD [42] are other physical comorbidities which can predispose to sleep disturbance. Various *psychiatric comorbidities* in FASD [42, 45–47] likely to have the same effect include ADHD [48], anxiety, depression and antisocial behaviour [49] and autistic behaviour [50]. The various ways in which intellectual disability and its complications can prevent a child from learning satisfactory sleep habits will generally be related to the degree of intellectual impairment. About two-thirds of all individuals with FASD have mild-to-moderate intellectual disability; the rest are severely affected [51].

3. In view of these comorbidities and the overall paediatric or psychiatric care that children with FASD may well require, various *medications* which can disturb sleep [52] need to be considered. For example, potential causes of insomnia include stimulant drugs for ADHD, pseudoephedrine, theophylline and some antidepressants. Excessive sleepiness may be caused by sedative drugs such as benzodiazepines, major tranquillizers and some antiepileptic drugs.
4. *Parenting factors* can be particularly relevant if a child's sleep is repeatedly disturbed, especially if a child has a neurodevelopmental disorder, because of the parental stress that such a disorder might cause. Possibly because of heightened concern about their child's welfare and safety, parents of children with a disorder such as FASD may have difficulty setting limits to their child's uncooperative behaviour. This may have the effect of inadvertently reinforcing such behaviour at bedtime or during the night by paying the child too much attention, including constantly sharing their bed.

Parents may find it especially difficult to implement other sleep hygiene principles or comply with behavioural treatment procedures if they are anxious or depressed and themselves sleep deprived [24]. In the case of both autism spectrum disorder and FASD, particularly high levels of parenting stress are reported [53]. In view of the domestic circumstances in which foetal exposure to alcohol might have arisen, shortcomings in maternal characteristics and parenting practices might be expected [54].

In any child with a neurodevelopmental disorder and significantly disturbed sleep, the possibility of multifactorial aetiology of the sleep problem needs to be considered and comprehensively assessed. Such an approach is likely to have important implications for the design of the child's treatment programme and overall care.

Aspects of Assessment and Treatment of Sleep Disturbance in Children with an Intellectual Disability

Assessment

Sleep problems may well be overlooked in primary care [55], and it has been said that paediatricians rarely ask about sleep problems [56] or may not possess basic knowledge about children's sleep [57]. In addition, as mentioned earlier, parents (especially of children with intellectual disabilities) may erroneously believe that sleep problems are inevitable and untreatable [4]. Consequently, many opportunities to help such children and their families are likely being missed [58].

Detection and assessment of sleep problems and their causes should be a routine part of paediatric practice and basically the same for all children. Screening should always be included in history taking by means of the following basic enquiries:

- Bedtime resistance or difficulty settling to sleep?
- Waking during the night?
- Breathing problems while asleep?
- Unusual behaviours, experiences or movements at night?
- Difficulty waking up in the morning?
- Being unusually sleepy or 'overtired' during the day?

Further preliminary details can be obtained by means of a sleep questionnaire for completion by parents or other carers, for example, that which was originally compiled by Simonds and Parraga [59] and modified for use with individuals with intellectual disability [60]. Positive findings call for detailed diagnostic assessment with the aim of identifying the child's sleep disorder [61]. Follow-up and repeated screening for sleep disturbance and any aetiological factors following initial assessment should form part of continuing care.

For the diagnosis of certain sleep disorders (e.g. obstructive sleep apnoea or sleep-wake cycle disorders), objective confirmation and clarification of parental reports of symptoms of a sleep problem should be obtained. However, compliance with objective sleep assessments (actigraphy or polysomnography) can be difficult to achieve depending on a child's ability to understand and accept these procedures. However, such difficulties can be overestimated and their risk reduced by staff experienced with children with neurodevelopmental disabilities and with close involvement by parents with the procedures [62].

Treatment

Principles of the treatment of sleep disorders are described elsewhere [63]. Nowadays, a wide range of treatment options is available from which a choice can be made depending on the child's type of sleep disorder. It is the case that the evidence base for many of these treatments – for example, those discussed by Brown et al. [64] – needs to be improved by more high-quality research. In the meantime, in addition to the findings of methodologically sound studies that are available, opinions of respected authorities based on clinical experience can also provide important guidance concerning the management of individual children.

1. Education of parents is important, including explanations of how to promote satisfactory sleep habits in their child. An optimistic view of treatment possibilities should be encouraged, and the chosen sleep treatments should be acceptable to them and within their capabilities. Help and support may well be required to ensure that they persist with treatment as sleep problems (especially sleeplessness) may worsen before they improve.
2. Principles of sleep hygiene help to promote good sleep patterns and have been generally recommended including, as mentioned earlier, for children with neurodevelopmental disabilities [29]. The basic principles include ensuring that the sleeping environment is conducive to sleep in various ways, as well as encouraging certain sleeping practices while avoiding others. Good sleep hygiene can be sufficient in itself in preventing or treating disturbed sleep (notably sleeplessness) but may also be useful as an accompaniment of more specific treatment for a given sleep disorder.
3. It might be assumed that behavioural methods of treatment are likely to be unsuccessful in children with neurodevelopmental disorders which include intellectual disability compared to other children. Richdale and Wiggs [65] have discussed the evidence to the contrary. They argue that such methods have the advantages that they utilise nonverbal means of modifying behaviour and can be individually designed to suit the particular needs and circumstances of each child and family.
4. Indications for the use of pharmacological treatments for children in general with a sleep disturbance have been discussed by Gringras [66]. Hollway and Aman [67] claim that the sleep disorders of developmentally delayed children may also respond to medication, used selectively. Such treatments, if successful, may improve the child's behaviour as well as parental well-being.
5. Other treatments for which there are specific indications include chronotherapy (resetting the biological clock) for circadian sleep-wake cycle disorders; physical methods such as tonsillectomy, continuous positive airway pressure and weight reduction for obstructive sleep apnoea; and psychological or psychiatric help when a child or other family member is seriously disturbed emotionally. Little has been reported about the use of such measures specifically for sleep disorders in children with intellectual disability.

Conclusions

The subject of intellectual disability is very relevant to sleep disturbance in children with neurodevelopmental disorders. However, the subject is also wide-ranging, for which reason it has been necessary to focus this chapter on selected basic aspects. At the present time, information about some of these aspects is incomplete or, indeed, lacking. It is also the case that the evidence base is often limited to clinical consensus rather than the findings of methodologically sophisticated research. Nevertheless, although some of the conclusions drawn may necessarily be provisional, they raise important possibilities for consideration in clinical practice as well as suggesting areas requiring further study.

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Psychiatric Disorders

24

Aditi Kantipuly, Carmen López-Arvizu, and Elaine Tierney

Case Vignette

Karl is a 10-year-old boy with history of high-functioning autistic disorder, mild intellectual disability, and hypothyroidism who came to the clinic with his parents due to excessive morning sleepiness. He lives at home with his parents and 13-year-old sister.

He has a regular bedtime routine that he follows and is to be in bed at 8 PM. Detailed review of nightly routine reveals Karl following a schedule of getting dressed, brushing his teeth, saying prayers, and reading for 20 min. Parents reported that Karl was taking too long in completing his routine: he counted the times he brushed his teeth, and if for any reason he "didn't do it right," he started the process again, delaying his bedtime. Once in bed, he prayed, and his parents noticed he was also extending his prayer time. When asked about this, Karl reported he "has to" include more people in his prayers because "so many bad things happen to them" and he wanted to make sure they "get help." After he was done reading, the lights were turned off and his parent would leave. Karl said he then tried to fall asleep, but the "bad things that happen keep coming." He described images and information from the news that "come into my head, like pictures from the TV news." Although Karl was good at following rules and knows to stay in bed, he was scared and tired at the same time. Finally, Karl described his muscles as being in "knots," which did not let him rest. At school, he was tired, experienced difficulty concentrating, and became irritable at times, which affected both his academic performance and peer interactions.

Karl's parents reported they had the news on in the background while eating dinner and never expected him to understand or pay attention to it. In completing the psychiatric review of systems, Karl worried about "the world coming to an end" and his parents' safety.

Karl was diagnosed with generalized anxiety disorder. He responded well to treatment for anxiety symptoms in the form of cognitive behavioral therapy that included relaxation techniques in combination with parent psychoeducation regarding discussion of current events with him. Karl's sleep pattern then returned to normal.

Diagnosis of Psychiatric Illnesses in Intellectual Disabilities

Having an intellectual disability (ID) does not exempt anyone from psychiatric illness. Both children and adults with ID who have comorbid psychiatric illnesses often have their psychiatric symptoms miscategorized/misidentified as attributable to their ID such that they do not receive appropriate treatment. As such, they can fairly be considered an underserved population [1]. In a typically developing population, the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (*DSM-5*) is used to facilitate psychiatric diagnosis; however, many of the criteria listed there do not apply easily to individuals with ID, due to inability to communicate symptoms that often are subjective in nature and/or require detailed responses to very specific questions. As a

A. Kantipuly
Department of Psychiatry, Kennedy Krieger Institute, Baltimore, MD, USA

C. López-Arvizu · E. Tierney (✉)
Department of Psychiatry, Kennedy Krieger Institute, Baltimore, MD, USA

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: tierney@kennedykrieger.org

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result, the National Association for the Dually Diagnosed (NADD) in association with the American Psychiatric Association developed the *Diagnostic Manual: Intellectual Disability (DM-ID-2): A Textbook of Diagnosis of Mental Disorders in Persons with Intellectual Disability (DSM-ID)* [2].This manual includes a description of each psychiatric disorder and lists symptoms adapted to individuals who might not otherwise be able to report accurately on criteria needed for diagnosis, including sleep-related symptoms. The use of appropriate criteria is crucial in order to accurately diagnose children with ID.

Medication Effects on Sleep

Psychoactive medications frequently used in individuals with neurodevelopmental disabilities might have undesirable effects in sleep that might be an issue of concern for caregivers. Excessive sleepiness is frequently observed with mood stabilizers (valproic acid, lithium carbonate), anti-seizure medications (lamotrigine), antipsychotics (risperidone, aripiprazole), benzodiazepines (diazepam, lorazepam, alprazolam), alpha-agonists (guanfacine, clonidine), and antidepressants (trazodone, sertraline). Sleep disruption, usually in the form of delayed sleep initiation, can occur with stimulant medications (amphetamines, methylphenidate). For example, in children with attention-deficit/hyperactivity disorder, the use of stimulant medication leads to a longer sleep latency, worse sleep efficiency, and shorter sleep duration. It is also important to consider the doses, the administration time, and the formulation of the stimulants administered (extended release versus immediate release) [1]. Judicious use of these drugs is paramount to avoid worsening sleep problems that these patients may already have.

How to Approach Sleep Disturbances in Children with Psychiatric Problems?

Symptoms seen in psychiatric disorders can be secondary to medical disorders and medications. For example, sleep apnea and thyroid abnormalities may lead to symptoms of ADHD and depression, respectively [3]. Symptoms can also be secondary to medications such as mania that can result from steroid administration. Treating the underlying psychiatric disorder may correct much of the sleep abnormality that's present. But, frequently, medications are used to help correct continued sleep disturbances.

Because sleep disturbances are present in many children with psychiatric problems, their identification and treatment are important to improve children's quality of life and clinical outcomes (Table 24.1). The management of primary sleep disorders is very important as they can occur in addition to psychiatric problems [5]. Conversely, treatment of a primary psychiatric disorder may actually improve a child's sleep disturbance and should be undertaken. Sleep hygiene recommendations and behavioral interventions are at the heart of management. Behavioral interventions in children who have problems with initiation of sleep (especially with need for co-sleeping) such as firm schedules or modification of the hour to go to bed, depending on the case; rewards; establishment of limits; avoidance of scary movies or television shows; as well as instillation of positive thoughts and routines are all helpful [5–7]. Discipline and structure are very relevant. Breathing exercises and relaxation techniques can also be helpful [8].

In terms of medication specifically for sleep, it is important to remember that there are no US Food and Drug Administration (FDA)-approved drugs for insomnia in children. Moreover, effects vary: while some antidepressants

Table 24.1 Psychiatric diagnoses in DSM-5 and pertinent sleep abnormalities [4]

Disorder	DSM-5 diagnostic criteria (sleep abnormalities are bolded)
Schizophrenia	Criterion A: 1. Delusions 2. Hallucinations 3. Disorganized speech (e.g., frequent derailment or incoherence) 4. Grossly disorganized or catatonic behavior 5. Negative symptoms (i.e., diminished emotional expression or avolition) At least two of the five symptoms must be present for at least 1 month. One of the two symptoms must be delusions, hallucinations, or disorganized speech
Tourette's disorder	Have two or more motor tics (e.g., blinking or shrugging the shoulders) and at least one vocal tic (e.g., humming, clearing the throat, or yelling out a word or phrase), although they might not always happen at the same time Have had tics for at least a year The tics can occur many times a day (usually in bouts) nearly every day, or off and on Have tics that begin before he or she is 18 years of age Have symptoms that are not due to taking medicine or other drugs or due to having another medical condition (e.g., seizures, Huntington disease, or postviral encephalitis)

Table 24.1 (continued)

Disorder	DSM-5 diagnostic criteria (sleep abnormalities are bolded)
Obsessive-compulsive disorder	A. Presence of obsessions, compulsions, or both: Obsessions are defined by (1) and (2): (1) Recurrent and persistent thoughts, urges, or impulses that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress (2) The individual attempts to ignore or suppress such thoughts, urges, or images or to neutralize them with some other thought or action (i.e., by performing a compulsion)
	Compulsions are defined by (1) and (2): (1) Repetitive behaviors (e.g., handwashing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly (2) The behaviors or mental acts are aimed at preventing or reducing anxiety or distress or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive
	Note: Young children may not be able to articulate the aims of these behaviors or mental acts
	B. The obsessions or compulsions are time-consuming (e.g., take more than 1 h/day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
	C. The obsessive-compulsive symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition
Post-traumatic stress disorder	Criterion A (one required): the person was exposed to death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence, in the following way(s): Direct exposure Witnessing the trauma Learning that a relative or close friend was exposed to a trauma Indirect exposure to aversive details of the trauma, usually in the course of professional duties (e.g., first responders, medics)
	Criterion B (one required): the traumatic event is persistently re-experienced, in the following way(s): Intrusive thoughts **Nightmares** Flashbacks Emotional distress after exposure to traumatic reminders Physical reactivity after exposure to traumatic reminders
	Criterion C (one required): avoidance of trauma-related stimuli after the trauma, in the following way(s): Trauma-related thoughts or feelings Trauma-related reminders
	Criterion D (two required): negative thoughts or feelings that began or worsened after the trauma, in the following way(s): Inability to recall key features of the trauma Overly negative thoughts and assumptions about oneself or the world Exaggerated blame of self or others for causing the trauma Negative affect Decreased interest in activities Feeling isolated Difficulty experiencing positive affect
	Criterion E (two required): trauma-related arousal and reactivity that began or worsened after the trauma, in the following way(s): Irritability or aggression Risky or destructive behavior Hypervigilance Heightened startle reaction Difficulty concentrating **Difficulty sleeping**
	Criterion F (required): symptoms last for more than 1 month
	Criterion G (required): symptoms create distress or functional impairment (e.g., social, occupational)
	Criterion H (required): symptoms are not due to medication, substance use, or other illnesses

(continued)

Table 24.1 (continued)

Disorder	DSM-5 diagnostic criteria (sleep abnormalities are bolded)
Bipolar disorder	For a diagnosis of bipolar disorder, it is necessary to meet the following criteria for a manic episode which may have been preceded by and may be followed by hypomanic or major depressive episodes
	Manic episode: a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy lasting at least 1 week and present most of the day, nearly every day
	During the period of mood disturbance and increased energy or activity three (or more) of the following symptoms are present: Inflated self-esteem and grandiosity **Decreased need for sleep** More talkative than usual or pressure to keep talking Flight of ideas or subjective experience that thoughts are racing Distractibility Increase in goal-directed activity Excessive involvement in activities that have high potential for painful consequences
Separation anxiety disorder	Developmentally inappropriate and excessive fear or anxiety concerning separation from those to whom the individual is attached, as evidenced by at least three of the following: 1. Recurrent excessive distress when anticipating or experiencing separation from home or from major attachment figures 2. Persistent and excessive worry about losing major attachment figures or about possible harm to them, such as illness, injury, disasters, or death 3. Persistent and excessive worry about experiencing an untoward event (e.g., getting lost, being kidnapped, having an accident, becoming ill) that causes separation from a major attachment figure 4. Persistent reluctance or refusal to go out, away from home, to school, to work, or elsewhere because of fear of separation 5. Persistent and excessive fear of or reluctance about being alone or without major attachment figures at home or in other settings 6. **Persistent reluctance or refusal to sleep away from home or to go to sleep without being near a major attachment figure** 7. **Repeated nightmares involving the theme of separation** 8. Repeated complaints of physical symptoms (e.g., headaches, stomachaches, nausea, vomiting) when separation from major attachment figures occurs or is anticipated
Major depressive disorder	Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure Note: Do not include symptoms that are clearly attributable to another medical condition 1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: in children and adolescents, can be irritable mood) 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation) 3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: in children, consider failure to make expected weight gain) 4. **Insomnia or hypersomnia nearly every day** 5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down) 6. **Fatigue or loss of energy nearly every day** 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick) 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others) 9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

(serotonin reuptake inhibitors such as fluoxetine) can have negative effects on sleep patterns, causing insomnia or hypersomnia, trazodone, in comparison, appears to be more effective improving insomnia [9, 10]. Other drugs such as mirtazapine and ramelteon may be effective, but data on their use are scarce [11]. Melatonin may be well tolerated and effective in some children with autism spectrum disorders and neurodevelopmental disabilities, improving sleep duration and decreasing sleep latency [11, 12]. Hypnotics should probably be avoided due to lack to data in children [6]. Indeed, the actual success of many interventions for sleep is unknown due to very limited data [6].

Table 24.2 Tools to assess pediatric sleep

Tool	Considerations
Clinical interview	Potential iatrogenic effects of stimulants and selective reuptake inhibitors
	Responses to bedtime resistance, inconsistent household routines and bedtimes, co-sleeping, caffeine consumption, and evening use of electronic media including computers and mobile phones
Sleep diaries	To be used to calculate key sleep variables such as average sleep-onset latency, variability in sleep times, sleep efficiency, and time spent awake after sleep onset
	Questions to ask include: Sleep initiation Sleep maintenance Middle-of-the-night awakening Nightmares Early awakening and daytime sleepiness The presence and timing of daytime naps should be documented, especially in younger and nonverbal children Parental expectations of total amount of sleep Any perceived changes in mood and energy
	To be obtained from parents and other caregivers including school personnel, daycare providers, and babysitters
Standardized questionnaires	Several questionnaires available from the perspectives of both parent and child
	Parent report *The Children's Sleep Habits Questionnaire* [13] *Sleep Disturbance Scale for Children* [14]
	Child report *Pediatric Daytime Sleepiness Scale* [15] *Sleep Self-Report* [16]

Data from Alfano and Gamble [17]

Evaluation of Sleep Abnormalities Frequently Seen in Children with Psychiatric Disorders

When evaluating sleep disorders in patients who are typically developing and in children with neurodevelopmental disorders, in addition to the workup for sleep disorders detailed in the earlier chapters in this book, the following steps can be added. The psychiatric history of family members should be assessed. The child should be screened for psychiatric disorders that can present with sleep abnormalities, since sleep abnormalities can result from a primary psychiatric disorder that is comorbid with a neurodevelopmental disorder. Drug and alcohol abuse can also interfere with sleep quality, and although there is little research literature about this, having a developmental disability doesn't preclude substance use or abuse, which should always be queried as part of a mental health evaluation. Sleep complaints are often present in psychiatric illness, not necessarily as part of formal diagnostic criteria but often as a manifestation of another symptom (i.e., fear of the dark in anxiety). Therefore, a psychiatric review of systems should include details of duration and quality of sleep. Questions about sleep initiation, maintenance, middle-of-the-night awakening, nightmares, early awakening, and daytime sleepiness are important. The presence and timing of daytime naps should be documented, especially in younger and nonverbal children. Parental expectations of total amount of sleep should also be part of the evaluation. Information should be obtained from the child, parents, and other caregivers including school personnel, daycare providers, and babysitters. A sleep journal is highly recommended and should also include any perceived changes in mood and energy (Table 24.2).

Mood Disorders

Sleep is part of the diagnostic criteria of depression and bipolar disorder; as such, details about its quality and quantity are always part of the psychiatric review of systems (see Table 24.1). These criteria apply to both children and adult regardless of their developmental functioning [4].

Prevalence of major depressive disorder (MDD) from early childhood to adolescence ranges from 1% to 8% [18]. MDD as defined by the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (*DSM-V*) lists insomnia or hypersomnia in its symptom criteria in addition to depressed mood, loss of interest in pleasurable activities, weight changes, psychomotor agitation or retardation, fatigue, feelings of worthlessness, diminished concentration, and recurrent thoughts of death or suicide [4]. Symptoms specific to children include irritability and excessive mood reactivity; however, MDD presents in children in a similar fashion to older patients. According to the DSM-5 criteria used for the diagnosis of major depressive disorder, insomnia or hypersomnia are occurring nearly every day [4]. Interestingly, sleep disturbances correlate with other symptomatology. For instance, agitation and insomnia go together just as hypersomnia tends to be associated with fatigue, hopelessness, and helplessness [19]. Furthermore, there is an impairment in sleep architecture, such as decrease in REM latency and other REM sleep abnormalities [20]. Also, sleep disturbances early in life correlate with the risk of developing MDD later in life [21].

Further, sleep problems correlate not only with symptoms and risk of complications but also with poor response to therapy [22]. In fact, adult patients who attempt suicide are more commonly affected by sleep disturbances [23, 24], and insomnia may be a risk factor for suicidal thoughts [25].

The prevalence rate of pediatric bipolar I and II disorders is difficult to establish. DSM-V lists a combined prevalence rate of 1.8%, for the pediatric population [4]. The mean onset

for the first manic, hypomanic, or major depressive episode is approximately 18 years for bipolar I [4]. Decreased need for sleep is a very common complaint from parents with children with neurodevelopmental disabilities but also of typically developing adolescents with bipolar disorder. Often parents identify sleep disruption retrospectively as a prodromal symptom of bipolar disorder [26, 27]. Bipolar disorder is classified in the DSM-5 as bipolar I disorder and bipolar II depending on the presence of mania or hypomania. Both can present with disordered sleep (decrease need of sleep, e.g., feels rested after only 3 h of sleep) which must be present as a criteria to fulfill diagnosis. With the development of DSM-V, the definition of bipolar disorder is very clear in adults, and the diagnosis in children and adolescents requires taking into account the child's developmental level to better identify the criteria needed for diagnosis. An example of this might be the presence of "grandiosity" as part of mania and the expression of this abnormality of thought being different in a full functioning adult versus a 5-year-old child in which fantastic role-play is normal; the same applies for sleep patterns. Increased sleep-onset latency, multiple episodes of awakening, and decreased need for sleep are also commonly seen in children with bipolar disorder [28, 29]. While acute manic episodes are characterized by decreased need for sleep, it has also been reported that sleep deprivation might play a part in relapse of mania [20]. In fact, sleep disturbances occur in the large majority of children during both manic and hypomanic episodes [30]. During depressive episodes, insomnia and hypersomnia are present [4, 31].

Very few studies have been published regarding characteristics of sleep in children with bipolar disorder. The findings of these studies suggest that children with this condition have more stage 1 sleep and a trend toward reduced stage 4 sleep [32]; lower sleep efficiency, less REM sleep, and a trend toward more awakenings [33]; and decreased sleep efficiency and duration, as well as increased nocturnal activity [34] and longer slow-wave sleep [35]. Sleep disturbances are also present in children of parents with bipolar disorder when compared with controls [36].

Anxiety Disorders

Sleep disorders are seen often in patients with anxiety disorders, and as these are among the most common psychiatric disturbances in children, adolescents, and young adults, it can be inferred how relevant is to recognize and address this problem. Prevalence of anxiety in children and adolescents is 10–20% [37]. The sleep complaints reported in the literature vary according to development, ranging from bedtime refusal, separation anxiety, resistance to sleeping alone, and fear of the dark (directly related to sleep and bedtime routine) to poor academic performance, daytime sleepiness, and irritability (secondary to poor sleep) [31]. Severity of anxiety correlates to functional impairment and sleep disruption and predicts escalating anxiety symptoms [38, 39]. As with MDD, persistent sleep disorders at an early age correlate with the development of anxiety disorders in adulthood [21].

The most common anxiety disorder in children is separation anxiety disorder. Insomnia, nightmares, and refusal to sleep alone are all associated with separation anxiety and as such should be considered in these children [40].

Post-traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is also associated with sleep disturbances. PTSD is becoming a more recognized health problem in our youth. PTSD consists in the development of symptoms following exposure to one or more traumatic events. The clinical presentation varies from fear-based responses to dysphoric mood (DSM-V) [41]. Although now a separate category in DSM-5 from anxiety disorders, PTSD is highly related to and usually comorbid with anxiety. It now belongs to a category named "Trauma and Stressor-related Disorders" [42]. In children, for example, a child suffering from physical abuse can experience fragmentation on his sleep and nightmares [43].

Obsessive-Compulsive Disorder

Children suffering from obsessive-compulsive disorder (OCD) may also be at high risk for sleep disturbances due to anxiety. Shorter total sleep times often characterize children with OCD [35]. OCD-related behavior can interfere with bedtime routines in young children as in the case described above, the need for completing rituals (counting, following a certain order) and the presence of intrusive thoughts of anxious nature keep them awake, and if those thoughts are obsessive and distressing in nature, the diagnosis changes from GAD to OCD [40, 44]. In fact, it appears that in these children, the presence of depression can play an important role in their sleep health [45].

Tourette Syndrome

Ghosh et al. reported on 123 young patients with Tourette syndrome (TS) with and without attention-deficit/hyperactivity disorder (ADHD) aging 21 years and under [46]. Sleep was a frequent issue, with 65% of children in the Tourette-only group and 64% of the group with comorbid ADHD having symptoms suggestive of a sleep disorder [46]. Insomnia was

more common in those with TS and ADHD than in TS-only, but even in the TS-only group, primary insomnia was the most common sleep disorder, affecting 32% [46]. Sleep talking also appears to be common in patients with TS [47]. Sleep disturbances in these patients may also be caused by intrusive thoughts and other emotional disturbances [48, 49].

Schizophrenia

Due to the typical age of onset of schizophrenia in adolescence or young adulthood, it is not a common problem in children. However, sleep disturbances are quite common in patients with schizophrenia, especially insomnia [49]. Individuals with schizophrenia have problems with sleep initiation and maintenance. In patients with schizophrenia, obstructive sleep apnea can be seen as a consequence of the use of neuroleptic drugs, given that these drugs can cause significant weight gain, a risk factor for the development of sleep apnea [50].

Neurodevelopmental Disabilities

Sleep disturbances often are present in children with neurodevelopmental disabilities (as high as 86%) but can be misunderstood and underdiagnosed [11, 51]. Some children who are blind have increased susceptibility to sleep problems due to their difficulty recognizing the changes in light that characterize day and night [11].

Conclusions

Having a neurodevelopmental disability of any kind does not exempt a child from having a comorbid psychiatric disorder. Symptoms that reflect impairment in quality of life should be reviewed carefully and addressed. The identification and treatment of comorbid psychiatric conditions are necessary to address disordered sleep. A psychiatric diagnosis in a nonverbal person is certainly more complicated than in the typically developing population and requires obtaining collateral information from parents or other caregivers, as full participation in a review of systems by the affected individual might not be possible. This should include a review of the daily routine, details of sleep schedule, medical history, and any medications being administered. More studies are needed in children and adults with neurodevelopmental disorders, including longitudinal studies that incorporate clinical interviews, sleep diaries, questionnaires, and multiple informants. These will allow for creation of effective practice guidelines as to how to assess for psychiatric disorders in individuals with sleep symptoms.

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Cancer Survivors

25

Kathy J. Ruble

Case Vignette

John is an 11-year-old white male who was diagnosed with medulloblastoma, including spinal involvement, at age 3 years. His therapy included a gross total resection of his tumor which resulted in a left-sided facial palsy. Surgery was followed by chemotherapy including vincristine, methotrexate, etoposide, carboplatin, cyclophosphamide, and cisplatin, as well as cranial and spinal radiation. John developed a recurrence of his disease which required further radiation and an autologous bone marrow transplant. He completed his treatment at age 5 years and has been followed since that time with serial scans that have shown no further recurrence of his disease. Complications John has experienced since completing his treatment have included continued left facial palsy, neurocognitive difficulties such that he requires special education, functional impairment including difficulties with coordination, hearing loss requiring hearing aids, endocrinopathies including growth hormone deficiency and thyroid dysfunction, and nocturnal enuresis.

At a routine follow-up visit, John's mother stated that she is concerned that she can hear him gasping for breath while sleeping, causing him to wake up multiple times during the night. She also stated that he is sleepy during the day, and his teacher confirmed his daytime sleepiness. His physical exam was normal, with the exception of neurologic findings: his previously noted left facial palsy and moderate ataxia. John's height was less than 3rd percentile, weight 90th percentile, and body mass index (BMI) greater than the 99th percentile according to the Centers for Disease Control and Prevention, 2–20 years growth indices for boys. His routine medications included somatropin (growth hormone) and levothyroxine for treatment of his hypopituitarism.

John was referred to a sleep clinic and underwent polysomnography, which revealed sleep-related central apnea/hypoventilation requiring bi-level positive airway pressure in order to more effectively ventilate. After modifications of the mask to accommodate his facial palsy, he tolerated the nasal interface well, has had no recurrence of his gasping, and reported less daytime sleepiness. John now has more energy and has begun an exercise program in hopes of decreasing his BMI. He will continue to receive care in the cancer survivorship program and routine follow-up through sleep medicine.

Introduction

As survival rates of childhood cancer have reached 80%, there has been an increased recognition of long-term complications, and with them, the need for careful surveillance and identification of interventions aimed at decreasing morbidity in this population [1]. At the current rates of incidence and cure, it is projected that by 2020 there will be nearly 500,000 survivors of childhood cancer in the United States [2].

Chronic health conditions are common among survivors, with an estimated 70% having a grade 1–2 (mild/moderate) condition and 32% having a grade 3–4 (severe/life threatening) condition [3]. Neurodevelopmental complications are among those seen after treatment of childhood cancer, and more than 50% of childhood cancer survivors have some impairment of neurocognitive function. Neurocognitive impairment in this population has been associated with unemployment, lower educational attainment, and inability

K. J. Ruble
Pediatric Oncology Survivorship Program,
Johns Hopkins University, Baltimore, MD, USA
e-mail: rubleka@jhmi.edu

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Table 25.1 Risk factors for neurodevelopmental deficits for common childhood malignancies

Cancer diagnosis	Risk factors
Brain tumor (primary or metastatic)	Tumor location: hypothalamus, posterior fossa
	Surgery: extent of resection and disruption of normal tissue
	Radiation: larger doses and larger field of brain irradiated, younger age at time of treatment
Leukemia/lymphoma requiring CNS prophylaxis	Treatment with intrathecal chemotherapy: younger age at time of treatment, female sex
	Cranial or cranial/spinal radiation: younger age at time of treatment, female sex

to live independently as an adult [4, 5]. Additional neurodevelopmental challenges including cognitive, behavioral, and physical impairments may be seen in children treated for cancer and depend primarily on complications from tumor location and therapies employed. Two groups of survivors who are at particularly high risk for neurodevelopmental complications include children treated for brain tumors or acute leukemia (Table 25.1).

Survivors at Risk for Neurodevelopmental Complications

Brain tumors are the most common type of solid tumor seen in childhood. An estimated 28,000 children in the United States are currently living with a primary brain or central nervous system tumor [6]. The incidence of a primary malignant or nonmalignant brain tumors in children and adolescents ages 0–19 is 5.54 per 100,000, for an expected 4610 new cases in 2018 [7]. A limited number of risk factors for the development of childhood brain tumors have been identified and include genetic and environmental factors. Neurofibromatosis type 1 (NF-1) is the most commonly seen genetic disorder associated with childhood brain tumors, primarily gliomas, which develop in 15–20% of these children [8]. Environmental factors have been much more elusive, with only exposure to ionizing radiation having a definitive association [9].

Overall the most common brain tumors seen in children are low-grade gliomas and medulloblastomas [10]. Low-grade gliomas are slow-growing tumors that can occur anywhere in the brain or spinal cord, and symptoms depend on the location of the tumor but may be present for several months before the diagnosis is made. Surgery is the most common intervention for low-grade glioma, and complete tumor resection can typically be achieved for tumors in the cerebellum and superficial cerebrum which results in an overall survival rate of 90% [11]. Even with a subtotal resection, 58% of children with a low-grade glial tumor may expect no growth of their tumor at 7 years after surgery [12]. For those children for whom complete resection is not possible, or for those with progression of their disease, treatment with chemotherapy or radiation is likely. Radiation for the treatment of low-grade glioma is controversial, and careful consideration of risk versus benefit is warranted – especially in younger children for whom radiation is likely to cause more long-term growth, development, and cognitive complications and those with neurofibromatosis type I due to the risk of secondary tumor induction associated with this genetic disorder [13]. Neurodevelopmental disabilities vary greatly in survivors of low-grade glioma depending on location and size of the tumor, extent of resection, and the use of radiation therapy. Children treated before 7 years of age and those who receive radiation to the temporal lobe/hippocampus are at greatest risk for progressive neurocognitive decline [14]. Additional complications seen in survivors of low-grade glioma include visual impairments (primarily diminished acuity) and Moyamoya syndrome, both of which are associated with tumors occurring along the optic pathway [15, 16]. Moyamoya syndrome, a vasculopathy of cerebral arteries, can result in seizures, hemiparesis, and stroke. Risk factors of developing Moyamoya in survivors of low-grade glioma include radiation at a younger age, treatment of the optic chiasm with higher doses of radiation, and diagnosis of NF-1 [17].

Medulloblastomas arise from the posterior fossa and are most frequently found in the region of the fourth ventricle in the central nervous system. They are fast growing and often obstruct the flow of cerebral spinal fluid, resulting in as many as 80% of children presenting with hydrocephalus at diagnosis. Twenty to 30% of children present with disseminated disease, most frequently in the spinal cord [10]. Treatment of medulloblastoma most often includes surgery, postoperative radiation, and chemotherapy. Survival from medulloblastoma has seen impressive advances, with 5-year survival rates from average-risk patients now reaching 85% and high-risk patients, 70% [18]. Extensive surgical resection has been associated with improved survival, but aggressive resection may result in posterior fossa mutism (PFM) syndrome to some degree in approximately 25% of children, with the vast majority (92%) considered to have moderate to severe intensity of symptoms [19]. PFM typically occurs 1–2 days postoperatively, resulting in rapid onset of loss of speech and emotional lability. These signs are followed by axial hypotonia and ataxia which may be accompanied by brainstem dysfunction, resulting in dysphagia and facial muscle weakness. Most children will have some degree of recovery, dependent on severity of symptoms in the postoperative period. One year after diagnosis, those children initially rated as having severe PFM frequently still had symptoms of ataxia (92%), speech and language difficulties (66%), and global

intellectual dysfunction (59%) [19]. Diminished neurocognitive outcomes are associated with treatment of medulloblastoma independent of PFM. The core cognitive abilities impacted include processing speed, attention, and working memory. Impact is more severe for children diagnosed at younger ages and those treated with radiation [20].

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, accounting for approximately 25% of all cancer diagnoses in children [21]. Improvements in therapy for ALL have led to a 5-year survival rate of 90.4%, for a disease that was nearly universally fatal five decades ago [22]. Much of the improvement in survival rates for ALL is due to the successful prophylaxis of the central nervous system, a known sanctuary site for the disease. In the early years of cancer treatment, cranial or cranial/spinal radiation was the backbone of therapy for central nervous system neoplasms, but as long-term sequelae became more obvious, less toxic therapies, including intrathecal chemotherapy, have been employed [23]. Neurocognitive deficits are the most frequently described neurodevelopmental disability seen after ALL therapy, with risks higher for females and those treated at a younger age [24]. Because radiation to the central nervous system is known to result in neurocognitive deficits after ALL treatment, it is currently utilized in a risk-stratified fashion, reserved for those with high-risk disease or central nervous system relapse. While most studies have shown that the neurocognitive deficits seen with chemotherapy alone are less severe, chemotherapy still has significant impact on brain morphology, resulting in smaller volumes for the hippocampus, amygdala, thalamus, and nucleus accumbens, potentially associated with deficiencies in attention and executive function [25, 26]. Other important neurologic morbidities that have been reported in ALL population include seizures (10.5%), dizziness (33.3%), neuropathies (62.9%), mild ataxia/incoordination (27%), headaches (46.9%), and fatigue (21.6%) [27].

Sleep and Childhood Cancer

Sleep disturbances are emerging as a potential complication with broad health and quality of life (QOL) implications for childhood cancer survivors [17, 28, 29]. Survivors of childhood brain tumors are the population for whom this issue is best described, showing sleep disturbances at a reported prevalence of 38%. Other symptoms reported by brain tumor survivors that may be associated with sleep issues include lack of energy (52%), drowsiness (40%), and lack of concentration (36%) [30]. While the exact mechanisms and prevalence of sleep disturbances in this population are still being defined, some obvious etiologies can be identified.

The hypothalamus plays an integral role in the delicate balance in the neurotransmitters and electrical systems needed to achieve and maintain healthy sleep [31]. Hypothalamic disturbance as a cause of sleep disturbances in this population is highlighted in a recent review of 70 childhood cancer survivors referred for evaluation at a pediatric sleep center: of this group, 50% (35) had tumors in the hypothalamic region/brainstem and an additional 10% (7) had posterior fossa tumors [32]. Sleep disturbances seen in these survivors included excessive daytime sleepiness (81%), apnea (43%), insomnia (17%), and circadian rhythm disorders (5%). Interventions used most frequently in this population included counseling on sleep hygiene and prescription of stimulants for excessive daytime sleepiness, CPAP/BIPAP for sleep-related breathing disorders, and counseling on sleep hygiene and recommendations on melatonin for insomnia and circadian rhythm disorders, all of which reflect standard approaches seen in other populations [32].

Disruption of the central nervous system with surgery and radiation is associated with numerous pituitary hormone endocrinopathies including thyroid, growth hormone, and cortisol deficiency. In addition to the aforementioned hormones controlled and produced in the hypothalamic-pituitary axis, hypocretin is a relatively newly described neuropeptide produced in this region whose deficiency is associated with narcolepsy (a neurologic condition characterized by excessive daytime sleepiness). Altered hypocretin production in childhood brain tumor survivors may further explain some of the sleep disturbances seen in this population, as evidence exists that children with endocrinopathies after treatment report more severe sleepiness [33].

Central sleep apnea can be seen in survivors of tumors affecting the brainstem, thalamus, and hypothalamus [32]. The mechanism for central sleep apnea in this population is likely due to tumor involvement in the respiratory centers of the central nervous system and/or disruption of these centers due to resection of the tumor. The most severe cases of central sleep apnea may require noninvasive ventilation; reports describing the phenomenon in the literature are as of yet rare and limited to case studies [34].

Obesity is yet another complication seen after treatment of brain tumors in childhood, with prevalence ranging from 35% having general obesity to 21% having central obesity, a complication attributed to hypothalamic/hypophyseal damage that results in endocrinopathy and impaired functional mobility (e.g., hemiparesis secondary to tumor invasion or resection) [35]. Obesity is a well-known contributor to sleep disturbances in the general population, and obese adolescent survivors report more symptoms of sleep-disordered breathing and increased snoring volume compared to survivors with average body mass index [36]. Similarly, Mandrell et al. reported that 84% of brain tumor survivors referred for sleep evaluations were obese or overweight at the time of screening [37]. While obesity may be difficult to

control in this population, it is a potentially modifiable consequence that may result in improved health outcomes in sleep and beyond.

The relationship between sleep disturbances and childhood ALL is not as well described as that of brain tumors, but is emerging in studies looking at quality of life issues in this population. In a review of 70 children with cancer referred for sleep evaluations, leukemia survivors represented the second most frequently seen diagnosis in this cohort (26%) after brain tumor survivors; insomnia was the most frequent sleep disturbance in this group (39%), followed by apnea (33%), excessive daytime sleepiness (22%), and circadian rhythm disorders (6%) [32]. Other studies also show that sleep disturbances may effect nearly 50% of ALL survivors and are associated with persistent chronic fatigue, anxiety/depression, pain, and poorer quality of life [38, 39]. Mechanisms for sleep disturbances after ALL treatment are not clearly elucidated, but the shared characteristics with brain tumor survivors hint at the possibility of CNS toxicity as a possible etiology. Gordijn et al. found that higher levels of morning cortisol were associated with fatigue and poorer quality of life in ALL survivors; the authors hypothesize long-lasting changes in the hypothalamic-pituitary axis brought on by stressful life events surrounding the diagnosis and treatment of ALL [40]. Certainly more research is needed to determine if hypothalamic dysfunction is responsible for sleep disturbances in ALL survivors. The risk of sleep-disordered breathing has also been identified after childhood cancer, including in ALL survivors, and the most frequent cause of sleep-disordered breathing in children is anatomical obstruction from tonsils and adenoids [41]. Because contemporary ALL treatment includes chemotherapy for approximately 2.5 years with varying degrees of immunosuppression throughout, hypertrophy of lymphatic tissue in the head and neck may contribute to the etiology of sleep-disordered breathing in this population.

The focus of this chapter has been on childhood cancer survivors, but a mention of sleep disturbances during therapy may help shed light on longer-standing sleep issues in this population. Chemotherapy regimens used to treat childhood cancer often include glucocorticoids, which are known to cause restlessness, agitation, and insomnia. In addition, cytokines produced during treatment have been associated with sleep disturbances in children receiving ALL therapy [42]. Further, interrupted sleep occurs eight times more often during hospitalization than in a home sleep environment [43, 44]. Disturbances in sleep routines such as sleeping in bed with parents or increased screen time usage established during an illness may linger beyond recovery from the malignancy and impact sleep hygiene.

Finally, sleep disturbances in childhood cancer survivors with neurodevelopmental risks may begin in childhood, but it appears they also persist into adulthood, and psychological distress predicts sleep disturbances among adult survivors of childhood cancer [45]. No longitudinal work has been done to evaluate changes in sleep over the decades that children with cancer are expected to survive, but certainly treating sleep disorders in this group could yield benefits throughout the life span.

Future Directions

Research to investigate how sleep disturbances may contribute to late complications and poorer QOL for childhood cancer survivors has just scratched the surface. At current rates of incidence and cure, it is projected that by 2020, there will be nearly 500,000 survivors of childhood cancer in the United States, and studies show that these survivors can expect to have poorer health outcomes and more health-related limitations than their peer group without a cancer history [46]. The most frequently reported complication among survivors is impaired cognitive function [3]. To date the recommendations for addressing neurocognitive deficits in the childhood cancer survivor population have focused on classroom accommodations, remediation, and pharmacologic interventions [47]. While these interventions are important, they fail to address other possible contributors to diminished neurocognitive function which may be modifiable. The effects of sleep disturbances on school performance are well-documented in the general population [48, 49]. Moreover, improvements in cognitive function are seen after interventions to improve sleep in other childhood populations [50–52]. Therefore, future research should focus on better understanding the associations of sleep and neurocognitive function in the survivor population which is already vulnerable to this poor outcome.

In this chapter, we have focused on childhood cancer survivors who have neurodevelopmental compromise, as this population appears to be at greatest risk for sleep disturbances. But the impact of sleep disturbances on health outcomes has wide-reaching influence: for example, insomnia has been associated with increased all-cause and cardiopulmonary mortality rates in adulthood, and sleep apnea is certainly associated with higher rates of cardiac events and morality [53, 54]. Mertens et al. reported that adult survivors of childhood cancer had 8.4 times higher mortality than age-/sex-matched controls from the general population, with cardiac and pulmonary mortality accounting for the majority of non-malignancy deaths [55]. Unlike sleep disturbances, many of the risks for cardiopulmonary complications after treatment for childhood cancer are due to direct organ toxicity of therapy and not currently modifiable; furthermore, the use of cardiopulmonary toxic therapies including chemotherapy and radiation will continue to be necessary for the foreseeable futures. Healthcare providers who care for this

population should incorporate mechanisms to screen for sleep disturbances during routine clinical care and ensure referral to appropriate sleep specialists. Research is needed to evaluate the impact of sleep disturbances on the long-term complications that are most likely to compromise health and quality of life, including cardiopulmonary outcomes.

Long-Term Follow-Up Guidelines for Child, Adolescent, and Young Adult Cancer (version 4) have been developed by a multidisciplinary, international team of healthcare providers to provide evidence-based screening recommendations based on treatment exposures [56]. Currently these guidelines recommend screening for sleep disturbances for survivors who report fatigue; however, there are no specific recommendations on the type or frequency of screening based on specific exposures. As the research on the associations and etiologies of sleep disturbances in the population matures, additional screening recommendations will be expected.

Conclusions and Recommendations

The childhood cancer survivorship community is just beginning to explore the prevalence, etiology, and treatment of sleep disturbances in this population. In this early stage of understanding, children with neurodevelopmental challenges appear to have the greatest risk and may stand to benefit the most from the diagnosis and treatment of sleep disturbances. Attention to sleep in this group is vital and may help to improve many health and quality of life outcomes.

Clinical Pearls

- All childhood brain tumor survivors should be screened for sleep disturbances.
- Survivors with other evidence of hypothalamic disruptions (endocrinopathies) are likely at greater risk of sleep disturbance.
- Overweight and obese childhood cancer survivors should have screening for sleep disturbances.
- Evaluation of sleep should be considered for any survivor in whom fatigue is reported.

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Concussion

26

Janet C. Lam and Jennifer Linton Reesman

Abbreviations

ImPACT	Immediate post-concussion assessment and cognitive testing
MSLT	Multiple sleep latency test
mTBI	Mild traumatic brain injury
PSG	Polysomnogram

Case Vignette

Laurie, a 15-year-old female soccer player is knocked down by a ball kicked at her head. She falls and hits the back of her head on the field. She does not lose consciousness. She is able to get up and immediately complains of a headache. She is assessed by her coach and advised to sit out the rest of the game. She goes home and feels exhausted. Her parents assume it is her usual exhaustion after a game and allow her to go to sleep early that night. She sleeps in late the next morning and follows up with her primary care doctor in the afternoon, who diagnoses her with a concussion. "Complete brain rest" is recommended, and she is advised to rest in the dark. She is advised not to use electronics or do any physical activity and is excused from attending school. She follows up with her doctor after a week and is still having headaches, sleeping during the day, and complaining of difficulty falling asleep at night. She is sensitive to light and does not complete her usual schoolwork due to headaches and tiredness. When she goes to school, she tolerates a couple of hours of time there before recurrence of headaches. Her parents report that she is more irritable than usual and does not engage in her usual social activities with her friends.

Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability in children and adolescents in the United States. According to the Center for Disease Control, more than 248,000 children were treated in emergency rooms in 2009 for sports and recreation-related injuries that included a diagnosis of concussion or TBI. Mild traumatic brain injury (mTBI), otherwise known as concussion, accounts for 70–90% of all traumatic brain injuries [1].

According to the Concussion Consensus Statement [2], concussion is defined by one or more of the following clinical domains:

1. Somatic symptoms (e.g., headache), cognitive (sometimes described as mental fogginess) and/or emotional symptoms (such as anxiety or depression)
2. Physical signs (e.g., loss of consciousness, amnesia)
3. Behavioral changes (notably irritability)
4. Cognitive impairment (e.g., slowed reaction times)
5. Sleep disturbance

Sleep disturbances commonly include difficulty initiating and maintaining sleep (insomnia), excessive daytime sleepiness, and altered sleep-wake cycles. Surveys indicate that up to 38% of children with concussion reported poorer sleep

J. C. Lam, MD, MHS (✉)
Neurology and Developmental Medicine,
Kennedy Krieger Institute, Baltimore, MD, USA

Neurology and Pediatrics, Johns Hopkins University
School of Medicine, Baltimore, MD, USA
e-mail: Lam@kennedykrieger.org

J. L. Reesman, PhD
Neuropsychology, Kennedy Krieger Institute,
Baltimore, MD, USA

Psychiatry and Behavioral Sciences,
Johns Hopkins University School of Medicine,
Baltimore, MD, USA

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during the first month post-injury [3]. The presence and persistence of sleep disturbances over the longer-term recovery period is not clear. A longitudinal study of all levels of traumatic brain injury found that sleep disturbances were present up to 24 months after injury in moderate and severe cases [4]. This study only followed patients for 24 months, so it is possible that sleep disturbances may persist even longer.

Understanding and recognizing sleep problems after concussion is important because sleep disturbances can affect cognitive, emotional, and physical functioning. For instance, insomnia has been shown to exacerbate psychiatric problems, memory, mood, and social functioning [5]. Mood disorders can be comorbid with sleep disorders in patients following concussion. In some cases, a pre-injury history of sleep difficulties or mood disorders may have been present and exacerbated by injury or disruption of routine. Greater anxiety and depression were associated with greater daytime sleepiness, poorer sleep quality, and more naps in patients with brain injury vs controls [6]. Tham et al. [7] found a correlation between depressive symptoms and sleep quality, but their findings were not specific to concussion since both adolescents after concussion and healthy controls were affected.

A commonly used web-based clinical and research assessment tool in the field of sports concussion management is the Immediate and Post-Concussion Assessment and Cognitive Testing (ImPACT: ImPACT Applications Inc., Pittsburgh, PA). This computer-based task typically takes 25 min for administration and includes a demographic section, symptom rating, and six subtests that assess attention, memory, processing speed, and reaction time. Kostyun et al. found that ImPACT neurocognitive test scores for visual memory, visual-motor speed, and reaction time indicated poorer performance in adolescents reporting sleeping more than typical (i.e., 9 or more hours) compared to adolescents who did not report sleeping more than usual [8]. During recovery from concussion, increased sleep may suggest active recovery and decreased neurocognitive functioning during acute recovery.

Adolescents, in particular, are at greater risk of developing sleep problems due to the physiologic changes in their sleep that promote delayed sleep phase, combined with academic and social demands that compete for time with adequate sleep [7]. Tham et al. [4] followed adolescents after concussion and found that they experienced higher rates of sleep disturbances compared to healthy peers at 5 and 12 months post-injury. They reported poorer sleep quality, which was supported with actigraphy data. They had shorter sleep durations (average 6 h), increased wake time at night, and poorer sleep efficiency. Early management of sleep problems may lead to shorter recovery time and reduction of symptoms.

Another risk factor in developing sleep problems is a prior history of sleep problems. Sufrinko et al. [9] found that adolescent and adult athletes who had pre-injury sleep difficulties had decreased cognitive performance and increased symptoms after concussion compared with those who did not have pre-injury sleep problems. They hypothesized that pre-injury sleep problems may increase susceptibility to already compromised cerebral blood flow and metabolism, leading to more severe injury [10]. In related work using animal models of the adolescent brain, structural brain changes in hippocampal volume occurred after chronic sleep deprivation [11]. These changes may be associated with the cognitive and emotional problems displayed with lack of sleep. Sufrinko et al. [9] conclude that there is a cumulative effect of sleep deprivation, brain injury, and affective/cognitive difficulty that results in poorer outcomes after concussion.

Multiple concussions are associated with an increased incidence of insomnia and severity of sleep disturbance [12]. More specifically, the incidence of insomnia increased from 5.6% in patients with no history of concussion to 22.4% after a single concussion to 47.5% for patients after multiple concussions. The frequency and severity of sleep-onset insomnia, sleep-maintenance insomnia, and early morning awakening were all increased after TBI. Sleep-onset insomnia is most prevalent after a first concussion, while maintenance insomnia intensifies after an additional concussion. The number of concussions was found to be a significant predictor of overall insomnia severity. Therefore, as one gets older, the risk for more concussions and also more sleep problems may increase.

Surprisingly, the complaint of sleep disturbances is more common in mild brain injury compared to severe traumatic brain injury. It is unlikely that sleep disturbances are not present in severe injury. Rather, it may be that sleep problems receive less attention compared to the focus on survival and emergency management of a severe injury and the devastating sequelae of long-term physical and cognitive deficits.

There are several challenges to the management of sleep problems after concussion. First of all, the underrecognition of sleep problems and their impact on functioning may result in a lack of guidance or therapy for these problems. Secondly, the belief that complete brain rest is needed until symptoms resolve may lead clinicians to assume that excessive sleep is necessary for recovery for a prolonged period of time, which may actually impair a return to normal functioning. This challenge may relate to a worsening of symptoms in an iatrogenic manner in which a well-intentioned recommendation to rest and sleep during the day may have unintended consequences on sleep and other domains of functioning. Thirdly, sleep problems may become refractory when addressed too late and may prolong recovery and resumption of normal activities.

Evidence Base

Evidence that sleep is impacted after concussion is found from studies using electroencephalography (EEG). A study of infants and toddlers after acute injury showed a reduction of slow-wave sleep and an increase of the sleep spindles found in stage N2 sleep. Rapid eye movement (REM) sleep was not affected [13]. Enomoto [14] found slowing in the occipital area with either delta waves alone or alpha waves mixed with delta or theta waves. These EEG findings have been replicated in adult studies. Schreiber et al. report a higher proportion of stage 2 sleep and lower proportion of REM, as well as shorter total sleep time. The authors hypothesized that these EEG changes correlate with memory difficulties. The level of tiredness after concussion may be so intense as to mimic narcolepsy, with sleep-onset REM periods found on multiple sleep latency tests (MSLT), used to objectively measure sleepiness. Gosselin et al. [15] also report increased delta activity and reduced alpha activity which was correlated with poor sleep quality and daytime impairment.

While the exact etiology of sleep disturbance after a concussion is not well defined, several theories on the mechanism of injury may explain how sleep becomes impacted. For example, the impact of a head injury may result in damage to areas of the brain, such as the hypothalamus and mid and basal forebrain, which regulate sleep. This is supported by alterations in neurotransmitter levels that modulate the sleep-wake cycle [16]. The neuropeptide hypocretin, which is essential for maintaining consolidated sleep and is affected in narcolepsy, may be reduced after concussion [17]. One hypothesis is that injury to the posterolateral hypothalamus results in hypersomnolence since those cells synthesize hypocretin-1, which is important in maintaining a wakefulness state [18].

Diagnosis

The diagnosis of sleep problems in the context of concussion is largely based on history and self-report of symptoms. Symptom checklists, such as the Post-Concussive Symptom Inventory (PCSI) [19], include sleep symptom questions. Given that the reliance on symptom report of children may be difficult to elicit, Sady et al. [20] modified the PSCI to be developmentally appropriate for children of all ages, and different forms have been adapted for different age groups (ages 5–7, ages 8–12, and ages 13–18). A more objective assessment of sleep can be made through the use of actigraphy, which can determine sleep-wake cycles and daytime napping. Though not the standard of practice, a multiple sleep latency test (MSLT) can be used to evaluate the level of daytime sleepiness. If concerns of central or obstructive sleep apnea arise, a polysomnogram can be done.

One must be cautious in overtreating insomnia complaints. Gosselin et al. [15] found that poor sleep quality on the Pittsburgh Sleep Quality Index reported by athletes after TBI was not supported by findings on polysomnogram. Concussed athletes had a normal sleep stage distribution, normal sleep efficiency (>91%), and a mean sleep latency of 15.8 min. However, they found objective findings on waking quantitative EEG which supported symptoms of daytime fatigue. During the waking EEG, there was an increase in the relative delta power and decrease in alpha power, indicating prolonged sleep inertia after waking. Discrepancies between sleep quality perception and objective measures may be partially attributed to central nervous system (CNS) hyperarousal, which is demonstrated by high levels of beta and gamma activity during sleep [15].

Management

The management of sleep problems after a concussion is an important early intervention because sleep disruption is associated with slowed recovery and continued functional impairment [21]. Sleep problems that are not treated may become more persistent and refractory over time. Addressing sleep problems may have a positive effect on recovery and result in a quicker return to physical activity. This is of particular value to student athletes.

Unfortunately, there is a paucity of literature regarding evidence-based management of sleep disorders in children who have suffered a concussion. In a review article by Williams et al. [22], amantadine was recommended for pediatric concussion patients with decreased alertness, decreased arousal, and difficulties with executive function. Melatonin, which can treat insomnia, has been found to protect against focal and global brain injury in animal models [23, 24]. Hypnotic sedatives may also be helpful for insomnia.

Non-medication approaches to managing sleep problems include cognitive behavioral therapy to improve insomnia and light therapy to improve circadian misalignment. Good sleep hygiene, which includes consistent bedtime and wake time, no electronics in bed, and minimizing daytime napping, should be encouraged.

Other comorbidities which contribute to sleep problems include anxiety, depression, and headaches. Medications used to manage these conditions may in and of themselves interfere with the sleep-wake cycle, and their use needs to be monitored carefully.

Areas of Uncertainty

The management of sleep problems related to concussion is often not addressed because it is underrecognized. Studies hypothesize that addressing sleep problems may lead to earlier resolution of symptoms and that ongoing sleep problems may be associated with persisting symptoms.

The role of hypersomnia or excessive daytime sleepiness in recovery from concussion is unknown. Kostyun et al. [8] hypothesize that the brain requires increased sleep to restore its neurometabolic homeostasis to the preinjury level. In animal models, the neurometabolic changes resolve in 7–10 days [25]. They also hypothesize that hypersomnia is a protective mechanism to prevent the brain from engaging in exertional activities that can exacerbate symptoms and prolong the healing process. Further research is needed to define what an appropriate amount of sleep is needed during the recovery process and when total sleep time is expected to revert back to baseline. Certainly, if daytime sleep negatively impacts sleep onset or reduces nighttime sleep, it should be limited.

Future Directions

Given the need to treat sleep disorders which can in turn improve recovery, research is needed on management of sleep problems within the context of concussion. It is not known whether the same sedative hypnotics used to treat sleep problems have a different effect in the context of concussion. It is not clear what effect these agents have on recovery of the metabolic derangements that occur with a concussion.

The pathophysiology of post-traumatic sleep-wake disturbances remains unclear. It is likely a complex interaction between brain lesions, neurotransmitters and hormonal changes, hypocretin level, aging, pain, and genetic predispositions [26]. Even without a clear pathophysiological explanation, sleep problems need to be addressed because they impact recovery. The treating clinician needs to include a careful interview about pre-injury sleep concerns, symptom constellation of sleep problems (i.e., daytime fatigue, delayed sleep onset, fragmented sleep), and sleep patterns.

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Prematurity

27

Sundeep Singh Bola, Fiona Elize Kritzinger, and Indra Narang

Abbreviations

BPD	Bronchopulmonary dysplasia
BSID	Bayley Score of Infant Development
CI	Confidence interval
GA	Gestational age
IVH	Intraventricular hemorrhage
PSG	Poysomnography
RCT	Randomized controlled trial
Ref	Reference number
SCU	Special care unit
SD	Standard deviation
SDB	Sleep-disordered breathing
VLBW	Very low birth weight

Control of Ventilation

Case Vignette

An infant born at 31 weeks gestation required continuous positive airway pressure (CPAP) for 36 h and then was weaned to room air. On day of life 3, the infant was noted to have apneic events with associated bradycardia and desaturation, often requiring stimulation to recover his oxygen saturation. These events occurred during wakefulness and sleep. After alternative causes of apnea, for example, infection and anemia were ruled out, a diagnosis of apnea of prematurity was made, and the infant was loaded with caffeine and commenced on maintenance caffeine therapy.

Definitions

Please see Table 27.1 for additional information on the definitions which follow and others, which are instrumental to understanding the content of this chapter. Preterm birth is defined by the World Health Organization as "babies born alive before 37 weeks of pregnancy are completed" [1]. Additional categories of preterm infants are described in Table 27.1. Apnea, conceptually, is defined as absence of airflow as measured at the mouth or nares. This is further characterized based on the presence or absence of respiratory effort, as described in Table 27.1. Further, the American Academy of Sleep Medicine provides additional definitions of obstructive, central, and mixed apneas based on polysomnographic criteria [2].

Physiology and Control of Ventilation

Respiration is a complex physiologic process that begins in utero with fetal breathing movements, lasts the entire duration of one's life, and ceases at the time of death. It is indeed an incredible phenomenon that relies on multiple sources of input, including behavioral cues, chemoreceptors, and pulmonary mechanoreceptors. Further elaboration on the role of chemoreceptors can be found in the sections which follow. Mechanoreceptors, as the name suggests, respond to mechanical stimuli. For example, stretch receptors provide information to respiratory control centers regarding distension of the airways to avoid, for example, overdistension of the lungs. Integration of these multiple sources of input results in uninterrupted respiration in order to maintain

S. S. Bola
Department of Paediatrics, Markham Stouffville Hospital, Markham, ON, Canada

F. E. Kritzinger
Christiaan Barnard Memorial Hospital, Cape Town, South Africa

I. Narang (✉)
Division of Respiratory Medicine, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada
e-mail: indra.narang@sickkids.ca

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Table 27.1 Definitions

Term	Definition
Preterm birth	Babies born alive before 37 weeks of pregnancy are completed [1]
Extremely preterm	<28 weeks
Very preterm	28 to <32 weeks
Moderate to late preterm	32 to <37 weeks
Obstructive apnea (conceptual definition)	Absence of airflow, with ongoing respiratory effort against an obstructed upper airway
Central apnea (conceptual definition)	Absence of airflow with absent respiratory effort and no airway obstruction
Mixed apnea (conceptual definition)	Absence of airflow with one portion of the event having absent respiratory effort and the other portion of the event having respiratory effort against an obstructed airway
Minute ventilation	Respiratory rate multiplied by tidal volume
Periodic breathing	At least three central apneas or central pauses in breathing which occur in succession, separated by no more than 20 s of normal respiration [3]

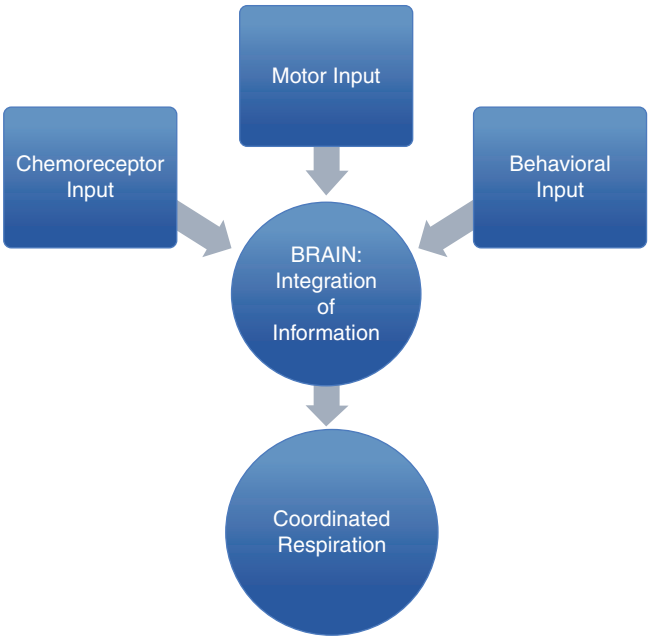

Fig. 27.1 Factors controlling respiration

oxygen and carbon dioxide homeostasis (Fig. 27.1). In times of stress, the respiratory inputs may be altered with compensatory changes in respiration cadence, for example, during exercise or ascent to high altitude. However, both the respiratory rate and tidal volume are also under voluntary control to adapt to the environment and enable activities as required; for example, a diver is able to hyperventilate prior to a dive and then hold his breath while under water. Thus, the versatility offered by the respiratory system is the result of a complex, incompletely understood interaction between the various inputs responsible for respiration, integration of these inputs at a neural level, and the output of a respiratory rhythm that corresponds to one's physiologic demands and voluntary desires.

In the following section, we will briefly review the neural structures involved in respiratory control, the basics of chemoreception, and ventilatory response to hypoxia and hypercapnia and then examine how these differ in preterm infants compared to term infants.

Central Pattern Generators and Respiratory Rhythm Generation

It has long been appreciated that locomotion in vertebrates is mediated by rhythmic activity that is not reliant on sensory input but rather generated by networks of neural structures collectively referred to as central pattern generators (CPGs) [3]. CPGs are responsible for a variety of motor functions ranging from locomotion to generation of rhythmic respiration [4]. What is unique to CPGs is that the output of motor activity remains rhythmic, without requiring rhythmic input. However, this rhythmic activity is not fixed, but rather flexible, and can be modified based on inputs to the system of the CPG [3]. In respiration, for example, changes in oxygen, carbon dioxide, and hydrogen ion levels in the blood result in changes in respiratory cadence and minute ventilation as outlined below. How this rhythm is generated is not entirely clear; possible explanations include the following [5]:

1. Pacemaker neurons.
2. Neural structures, as described below, which behave in a reciprocal inhibitory/excitatory fashion; although either structure on its own may not result in rhythmicity, they may function together to generate rhythmic activity.
3. A combination of these mechanisms.

Neural Structures Involved in Control of Ventilation

The respiratory CPG is composed of two groups of neural structures: the pontine respiratory group and the medullary respiratory group (Fig. 27.2) [4]. The medullary respiratory group is the major location housing inspiratory and expiratory neural structures. The inspiratory neurons are located in the pre-Bötzinger complex and the rostral ventral respiratory group (VRG), and the expiratory neurons are located in the Bötzinger complex and the caudal VRG [6]. Although this is a somewhat simplified explanation, overall, these inspiratory and expiratory structures together behave in a reciprocal inhibitory/excitatory fashion so that when one group is active, it inhibits the other and vice versa, as a means of generating rhythmicity [5]. The pontine respiratory group is thought to communicate with the medullary

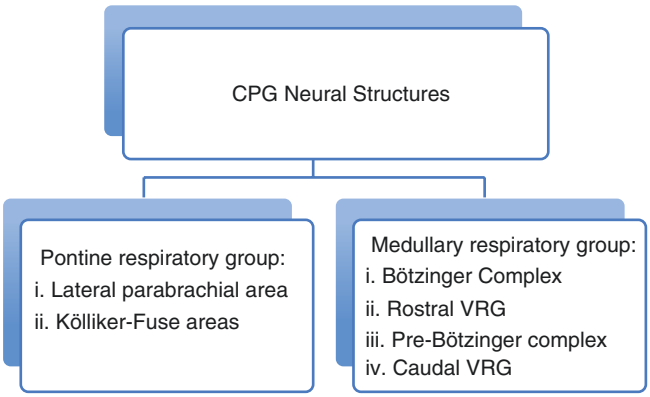

Fig. 27.2 Neural structures involved in respiration. CPG central pattern generators, VRG ventral respiratory group

respiratory groups in order to regulate the transition from inspiration to expiration [5]. Additional sites function to integrate, process, and then relay information from multiple sensory inputs to the medullary respiratory groups allowing modulation of respiration to meet the metabolic needs of the body [6]. Selected sensory inputs are described below. A discussion of the integration sites is beyond the scope of this text.

Chemoreception: Oxygen and Carbon Dioxide

Oxygen

The main site of oxygen chemoreception is the peripheral chemoreceptors located in the carotid body [7]. Hypoxia results in activation of the carotid chemoreceptors, which in turn triggers the release of excitatory neurotransmitters causing an increase in minute ventilation [7]. This increase can be divided into two phases: (1) an initial rapid increase in minute ventilation, followed by (2) a subsequent decline to a new baseline minute ventilation. This new baseline remains higher than the initial minute ventilation in room air [8].

The ventilatory response to hypoxia, although largely controlled by carotid bodies, does vary with carbon dioxide (CO_2) levels; specifically, the ventilatory response to declining inspired oxygen levels in the presence of hypercapnia is much more pronounced than during normocapnia as described in more detail below [9].

Carbon Dioxide

In both adults and children, increasing CO_2/H^+ results in an increase in minute ventilation [7] through stimulation of central and peripheral chemoreceptors [4]. Centrally, the main site of chemoreception for CO_2/H^+ is located in the rostral ventrolateral medulla [10]. Peripherally, the carotid bodies appear to have a role in CO_2/H^+ chemoreception, despite the historical belief that they were exclusively oxygen sensors [4].

Ventilatory Control in the Preterm Infant

Preterm infants have long been observed to demonstrate ventilatory instability, related to immaturity of the neural structures involved in control of ventilation [7]. What would otherwise be perceived as a relatively innocuous stress to a term infant, for example, changes in body temperature, can result in ventilatory instability and apnea in the vulnerable preterm infant [8, 10] as described below.

Oxygen Chemosensitivity of the Preterm Infant

As mentioned above, the mature response to hypoxia is biphasic, but the net effect is an increase in ventilation from baseline [9]. In the fetus, when oxygen delivery via the placenta is reduced, there is a reduction in respiratory movements by the fetus [11]. This response likely serves as a protective mechanism to limit energy utilization in times of hypoxia. However, when the fetus is born, if this response persists, it becomes less functional and potentially detrimental [11] and may be particularly harmful in the preterm infant.

Rigatto et al. studied moderate to late preterm infants (33–37 weeks gestation) exposed to hypoxia (fractional inspired oxygenation [FiO_2] of 15%) and found that they demonstrated an initial increase in ventilation with a subsequent reduction below the baseline ventilation observed in room air [12]. This response is similar to that in adults in that it is biphasic, but notably different in that after the initial rise in ventilation, there is a fall below the baseline ventilation in room air. When more significantly preterm infants were studied, specifically <1500 g with a mean gestational age of 29 weeks, Alvaro et al. demonstrated a response to hypoxia (FiO_2 of 15%) similar to that of the fetus. In these infants, hypoxia resulted in only an immediate and sustained reduction in ventilation [13]. This finding was attributed to the central depressive effect that hypoxia has on respiration in preterm infants [14]. These findings collectively demonstrate the destabilizing effect of hypoxia on the respiration of preterm infants, termed hypoxic ventilatory depression. Preterm infants, with a small functional residual capacity (FRC) and increased metabolic demand and oxygen consumption, are at particular risk of hypoxia. At the end of a tidal breath, the neonate is at a reduced FRC compared to older children and adults. Thus, a neonate requires only a brief pause in respiration to result in hypoxia, with hypoxia having a destabilizing effect on the control of breathing, although the underlying precise mechanisms are not well understood. Conversely, hyperoxia may have a stabilizing effect on the respiratory pattern in preterm infants. Weintraub et al. assessed the effects on respiration when infants of gestational age 27–31 weeks were exposed to incremental increases in FiO_2 from room air to 40% oxygen [14]. In room air, all infants had periodic breathing and apneas. As the FiO_2 was increased,

these infants were noted to have a normalization of their respiratory pattern and a reduction in apneas, while the minute ventilation remained unchanged [14].

Carbon Dioxide Chemosensitivity in the Preterm Infant

Adults, children, and older infants all respond to hypercapnia with an increase in ventilation, and this response is mediated both at a central and peripheral level [15]. Preterm infants also tend to increase their ventilation in response to hypercapnia, but their response is blunted when compared to adults, children, and term and even late preterm infants [16–18]. Frantz et al. demonstrated that preterm infants (29–32 weeks) had a marked reduction in ventilatory response to hypercapnia which improved with post-natal age when compared to late preterm infants (33–36 weeks) [16]. In one study, infants born preterm (mean gestational age of 30.2 weeks) with apnea showed a reduced ventilatory response to CO_2 than gestational age and birth weight-matched controls who did not have apnea [19]. This blunted response, then, appears to represent a risk factor for the development of irregular breathing and apnea. In summary, the ventilatory response to changes in oxygen and carbon dioxide levels documented in preterm infants places them in a position of vulnerability for respiratory instability and apnea. During sleep, with a reduction in ventilation, hypoxemia, and oscillations in CO_2, the preterm infant is at particular risk for worsening respiratory instability with resultant apnea and periodic breathing [18].

Sleep, Normal Respiratory Variants, and Disease States in Preterm Infants

Sleep Architecture in Preterm Infants

There are three types of sleep recognized in the newborn: quiet sleep (QS) (analogous to NREM sleep), active sleep (AS) (equivalent to REM sleep), and indeterminate sleep. QS is characterized by minimal muscle movements and regular breathing cycles. During AS, sucking motions, twitches, smiles, frowns, irregular breathing, and gross limb movements are observed. Indeterminate sleep is the period of sleep that cannot be defined by polysomnogram as either active or quiet sleep.

Sleep organization in preterm infants undergoes significant development between birth and reaching term gestation. Active sleep decreases, and quiet sleep and waking states increase, with gestational age [20–23]. Breathing is more regular in QS, the percentage of AS with rapid eye movements decreases, and awakenings become longer [20–22]. Similar changes are observed in the early weeks after term gestation [20, 24]. Infants born prematurely sleep less and display more alertness and activity at each adjusted age than those born at term. They also have longer sustained episodes of quiet sleep but more body movements and rapid eye movements associated with active sleep [20, 24].

Sleeping and waking patterns of preterm infants have been associated with developmental outcomes. Different measures of sleep-wake states during the preterm period, i.e., the amount of crying, amount of REM during active sleep, sleep cycle length, and amount of nighttime sleep, predict cognitive and motor development at 1 year of age [25–27]. Prematurely born children who show a more rapid decrease in active sleep in the preterm period have higher intelligence quotients and better language and fine motor abilities at 3 years [28].

Mother-infant skin-to-skin contact (kangaroo care) has been shown to change sleep architecture in preterm infants. Infants who received kangaroo care have longer periods of deep-sleep and quiet-awake state and less time in light sleep or drowsy state [29].

Sleep-Disordered Breathing and Preterm Birth

Periodic Breathing

The occurrence of some periodic breathing (PB) is considered normal in almost all newborns [30]. A widely accepted definition of PB is at least three sequential central apneas of at least 3 s duration, with less than 20 s of regular breathing between [31]. PB is hypothesized to be the result of dominant peripheral chemoreceptor activity responding to fluctuations in arterial oxygen tension [32, 33]. Physiological models of PB demonstrate a natural distinction between transient and sustained oscillations, and PB represents high gain in the control loop [34–36]. The "high gain" observed in neonates is the result of chemoreceptor sensitivity to changes in blood oxygen and carbon dioxide levels that leads to sustained oscillations between breathing and apnea, especially during quiet sleep [30, 37–39]. At birth the peripheral chemoreceptors are desensitized by the acute rise in blood oxygen content during the fetal to neonatal transition. The chemoreceptor sensitivity is gradually reset during the first week of life [40]. Therefore, PB rarely occurs in the first 48 h of life and is not considered a precursor to significant apnea [40]. In infants of 32-week gestational age, the fraction of time spent in PB peaks at 7–14 days after birth at 6.5% of the total daily time [41].

Apnea of prematurity (AOP) and PB are distinct entities that differ in character, gestational age, and time of onset and resolution (Table 27.2). Hypoxia may trigger or exacerbate PB and AOP [42], and oxygen administration to preterm infants can decrease both PB and AOP [14, 43].

PB is thought to be benign, but a recent longitudinal study in former preterm infants followed during their first 6 months

Table 27.2 Differences between periodic breathing and apnea of prematurity

	Periodic breathing	Apnea of prematurity
Character of breathing pattern	Regular, cyclical periods of apnea with normal breathing between	Irregular episodes of apneas of varying length, sometimes clustered
Associated bradycardia and desaturation	Rarely significant bradycardia or desaturation	Almost always present and significant
Gestational age predilection	Very common in late preterm and term infants	Uncommon after 34 weeks gestation
Time of onset	After first week of life	Within the first 1–2 days of life
Time of resolution	Persists for several months past term-corrected age	Between 36 and 42 weeks postmenstrual age

post-term showed that PB persisted in 40% [44]. Although in most infants PB was not associated with significant falls in SaO_2, several infants had significant oxygen desaturations and reduced cerebral oxygenation, especially during active sleep [44]. However, the clinical significance of these desaturations associated with PB on neurodevelopmental outcome is unknown.

Apnea of Prematurity

Apnea of prematurity (AOP) is seen as a breathing disorder distinct from periodic breathing, which occurs in infants born before 34 weeks gestational age and usually resolves by 36–40 weeks postmenstrual age (Table 27.2). AOP is demonstrated by short respiratory pauses associated with chronic intermittent hypoxia (CIH) and bradycardia. The frequency of CIH tends to increase after the first week of life and may be sustained over many subsequent weeks [45]. AOP is very common and occurs in 75% of all infants born at less than 32 weeks gestation. Moreover, 90% of infants born before 28 weeks gestation have AOP that usually resolves by 44 weeks postmenstrual age only [46–48].

The pathogenesis of AOP is due to immaturity of the respiratory control characterized by abnormal ventilatory responses to hypoxia and CO_2 as well as immature reflexes and upper airway instability [49]. Apnea is classified as central, obstructive, or mixed depending on the presence of continued inspiratory efforts and upper airway obstruction. In central apnea (CA), there is no inspiratory effort. During an obstructive apnea, inspiratory efforts persist but are ineffective in the presence of upper airway obstruction. During a mixed apnea, there is upper airway obstruction with inspiratory efforts that precedes or follows a central apnea.

Most apneic spells in preterm infants are mixed (50%) or central (40%) [50]. Longer episodes are more likely to be mixed apnea as opposed to short respiratory pauses, which are classified as central apnea.

The management of AOP includes the correction of contributing factors such as hypoglycemia, hypocalcaemia, metabolic alkalosis, anemia, arterial hypotension, hypoxemia, and any other factor that increases work of breathing. Respiratory stimulants, such as caffeine and aminophylline, are effective in reducing the incidence of apnea and periodic breathing but rarely eliminate it. Both therapies are effective, but caffeine is preferred for its oral route of administration, longer half-life, and wider therapeutic range [51]. Concerns regarding potential long-term neurodevelopmental side effects prompted larger, prospective trials that showed no significant side effects. The use of caffeine in preterm infants was related to a decrease in the incidence of patent ductus arteriosus (PDA), decreased duration of noninvasive positive pressure ventilation, decreased incidence of bronchopulmonary dysplasia (BPD), and better neurodevelopmental outcomes at 2 years of age [52–55]. Recent studies have explored the effectiveness and safety of short courses of higher doses (20 mg/kg/day vs. 5 mg/kg/day) of caffeine citrate to ensure successful extubation after 48 h of mechanical ventilation in infants less than 30 weeks gestational age [56]. Extubation failure rates in the treatment group was half that of the placebo group, and duration of mechanical ventilation in infants less than 28 weeks gestation receiving the high dose of caffeine was decreased significantly. No difference in adverse effects was detected in terms of mortality, major neonatal morbidity, death, or severe disability at 12 months [56]. Similar results were seen in a recent study that used even higher doses (40 mg/kg/day loading dose and 20 mg/kg/day maintenance) prior to extubation [57].

In follow-up studies, Marcus et al. studied the long-term effects of neonatal caffeine use on sleep architecture and breathing during sleep in former preterm infants now aged 5–12 years [58]. They found no difference in total sleep time, sleep efficiency, or incidence of obstructive sleep apnea (OSA) between groups randomized to caffeine versus placebo [58].

Finally, in refractory cases of apnea, respiratory support involving nasal continuous positive airway pressure (CPAP), high-flow nasal cannula, or invasive mechanical ventilation may be required to prevent severe hypoxic events and their consequences.

The Relationship Between Gastroesophageal Reflux and Apnea

Apnea of prematurity and gastroesophageal reflux (GER) are both common occurrences in preterm infants, and their causal relationship has been widely debated [59]. GER is the result of transient relaxation of the lower esophageal sphincter. It is physiologically plausible that reflux can trigger apnea as a protective reflex [60, 61]. This hypothesis is supported by a study of Omari and colleagues that showed that a decrease in lower esophageal pressure is associated with

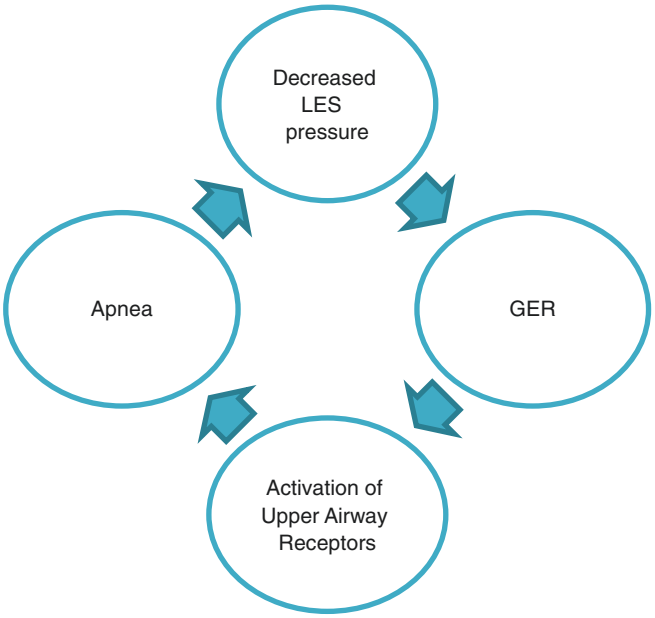

Fig. 27.3 Relationship between gastroesophageal reflux (GER) and apnea, LES lower esophageal sphincter

the onset of apnea in some neonates [62]. Conversely, animal studies have shown that apnea can trigger GER in turn [63]. Figure 27.3 illustrates the hypothesized cycle of apnea and GER.

However, clinical studies designed to confirm this causal relationship have reported conflicting results. This may be in part because earlier studies only used pH monitoring to diagnose GER which is less sensitive as it does not detect non-acid reflux. Recent studies that included multiple intraluminal impedance monitoring in addition to esophageal pH, designed to capture evidence of nonacid reflux as well, did not consistently demonstrate a causal relationship between apnea and GER. A recent review of published literature found that both GER and apnea occur frequently in premature infants, but less than 3% of cardiorespiratory events actually follow a GER event, and GER is not associated with increased duration or severity of cardiorespiratory events [64]. Indeed, it is more common for an episode of GER to follow a cardiorespiratory event (9%) [64].

The role of pharmacotherapy in GER is still debated; more recent studies have highlighted the lack of efficacy of gastric acid inhibitors (GAIs), e.g., proton-pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs), and prokinetics, while other studies raised concern about associated side effects [65–67]. A case-control study of very low birth weight infants showed histamine-2 antagonist (H2RA) use was associated with higher rates of necrotizing enterocolitis [65]. Another neonatal study showed an increased risk of bloodstream infections (relative risk = 4.2) and candidemia (odds ratio = 2.44) with H2RA exposure [68]. Although, GAIs have been well tolerated by infants, recent studies showed a harmful association between the use of GAIs and the development of bacterial enteric infection and community-acquired pneumonia in infants and young children [69, 70].

Pharmacotherapy should only be considered for infants who have evidence of pathological GER with severe symptoms refractory to non-pharmacological treatment, and treatment should be monitored closely and only continued in those with clear benefit.

Sudden Infant Death Syndrome and Prematurity

Sudden infant death syndrome (SIDS) is defined as the sudden and unexplained death of an infant less than 1 year, with the onset of the lethal episode apparently occurring during sleep. A death classified as SIDS remains unexplained after a thorough investigation including a review of the circumstances of death, a clinical history, and a complete autopsy [71]. More than 90% of SIDS deaths occur in the first 6 months of life, with a peak incidence between 2 and 4 months [72]. Although the incidence of SIDS has declined since the introduction of the Back to Sleep campaign in 1994, it remains the leading cause of post-neonatal mortality in North America at approximately 0.5 per 100 live births [73]. Some concern has been raised by the observed increased incidence of plagiocephaly following the introduction of the Back to Sleep campaign [74, 75]. In the only prospective study as of yet, eight factors were associated with an increased risk of deformational plagiocephaly at 7 weeks of age: male gender, first-born birth rank, positional preference when sleeping, head to the same side on chest of drawers, only bottle feeding, positioning to the same side during bottle feeding, tummy time when awake <3 times per day, and slow achievement of motor milestones [76].

SIDS is considered multifactorial in origin, and a "triple risk hypothesis" has been proposed to organize current knowledge. This hypothesis proposes that SIDS results when three factors coincide: a vulnerable infant, a critical developmental period in homoeostatic control, and an external stressor [77]. The final pathway to SIDS is believed to involve immature cardiorespiratory autonomic control, together with a failure of arousal responsiveness from sleep. Several genetic polymorphisms, as well as clinical and environmental risk factors, have been identified [72, 73].

Premature birth is one of most significant risk factors for SIDS. In 1987, the risk of SIDS was 2.32 times greater for extremely premature infants compared with term infants, and although the overall incidence has subsequently decreased, the adjusted odds ratio for SIDS among the most preterm infants (24–28 weeks gestation) is two and a half times higher than for term infants. The risk for SIDS is also increased by 56% in infants weighing less

than 2500 g and also for growth restricted, small for gestational age infants [73].

Although for many years, apnea was thought to be the precursor of SIDS, results of studies such as the Collaborative Home Infant Monitoring Evaluation have shown that it neither precedes nor predicts SIDS [49]. However, concerns have been raised about the possible association between SIDS and PB. Kelly et al. were the first to document excessive PB in cases of "near SIDS" (now known as apparent life-threatening events or ALTEs) and in the siblings of infants who died of SIDS [78, 79]. In a more recent case, excessive PB (30% of total recorded time) was observed in a patient who subsequently died of SIDS [41]. The authors developed a method to quantify PB in large numbers of patients over long periods. Their method can distinguish PB from irregular apnea clusters and may be a helpful method to study the possible link between excessive PB in the newborn and future risk for SIDS [41].

Long-Term Implications of Prematurity on Sleep and Breathing

Many factors contribute to neurodevelopmental outcomes in premature infants, and the impact of AOP on long-term neurological outcome has not been studied systematically. However, available data suggests an increased risk for neurological impairment (defined as a Bayley Scales of Infant Development or psychomotor index score <70, or cerebral palsy or blindness at 3 years of age) in preterm infants less than 32 weeks gestation who required more mechanical ventilation days and had more apnea days (total number of days with at least one apnea recorded per day) after extubation [80]. Existing studies of long-term effects of prematurity on sleep are reviewed in Table 27.3.

The need for further studies is highlighted by recent observations that former preterm infants are more likely to have sleep-disordered breathing (SDB) in later childhood

Table 27.3 Review of studies describing long-term effects of prematurity on sleep

Reference	Description	Subjects included number and age	Main findings
Marcus 2014 [58]	Prospective follow-up of preterm infants born included in double-blind placebo-controlled RCT of caffeine vs. placebo in first 6 weeks of life	201 subjects	Total sleep time unchanged ($p = 0.13$)
		5–12 years of age	No difference in bedtime, time in bed, sleep period, sleep efficiency, sleep-onset latency, wake after sleep onset, or average motor activity during sleep
		Birth weight 500–1250 g	
Janvier 2004 [80]	Prospective follow-up of preterm infants <32 weeks gestation and <1250 g at 3 years of age	175 subjects	Correlation between total apnea days together with male sex with increased probability of neurodevelopmental impairment ($p < 0.01$)
		3 years of age	Correlation between the sum of total days of assisted ventilation and with apnea days with neurological impairment ($p < 0.001$)
		Birth weight 450–1430 g	
		Mean gestational age = 27.6 weeks	
Paavonen 2007 [81]	Retrospective longitudinal study of young adults born preterm at <1500 g. SDB defined as chronic snoring	158 preterm and 169 term controls	Corrected prevalence of SDB 2.2 times higher in preterm group
		Ages 18.5–27.1 years	Maternal smoking an independent risk factor for snoring
Rosen 2003 [82]	Prospective, cross-sectional study in a population-based cohort	850 subjects	Prevalence of SDB = 4.7%
		46% born preterm	SDB was 3–5 times more likely in preterm group compared with term children
		Ages 8–11 years	
Hibbs 2008 [83]	Retrospective study of population-based cohort born at <37 weeks GA who had sleep studies performed between 8 and 11 years of age	383 subjects	SDB (OAI ≥1 or AHI ≥5) 28 (7.3%)
	SDB defined as OAI ≥1 or AHI ≥5	Ages 8–11 years	OAI ≥1 = 23 (6%)
		Mean birth weight 1483 g (range 1041–2040 g)	AHI ≥5 = 52 (13.6%)
		GA 32 weeks (range 29–34)	Unadjusted analyses identified xanthine use, cardiopulmonary resuscitation or intubation, and maternal preeclampsia as risk factors for SDB
			No significant link between gestational age, birth weight, IVH, BPD, or duration of ventilation and presence of SDB

(continued)

Table 27.3 (continued)

Reference	Description	Subjects included number and age	Main findings
Raynes-Greenow 2012 [84]	Population-based cohort study of health-linked records	398,961 subjects	4145 (1.0%) children with a diagnosis of sleep apnea, mean age at first diagnosis 44.2 months
		Ages 2.5–6 years	Preterm significant risk factor for sleep apnea (<32 weeks versus term: hazard ratio 2.74 [95% CI: 2.16, 3.49])
			Small for gestational age subjects were not at increased risk of sleep apnea
Wolke 1998 [85]	Prospective longitudinal study of sleeping problems and feeding experience of preterm and term children during first 5 months after discharge from SCU in Finland compared with cohort from Germany	1057 included in Finland	Night waking at 5 months less frequent for very preterm (25.5%), preterm (40.6%), and term infants (48%) than for term control subjects (56.7–59.9%) in Finland
		Very preterm: 47	No differences in parent-reported sleeping behavior (night wakening frequency, duration of arousals, co-sleeping) based on GA at 20 and 56 months
		Preterm: 258	
		Term: 752	
Iglowstein 2006 [86]	Prospective longitudinal study from birth to 10 years. Sleep behavior data collected by structured interviews. Preterm defined as GA <37 weeks	75 term controls and 130 preterm subjects; mean GA 34.1 weeks (range 27.1–36.8 weeks)	No significant differences in sleep duration (time in bed per 24 h), bed-sharing, night wakings, bedtime resistance, and sleep-onset difficulties
Strang-Karlsson 2008 [87]	Prospective cross-sectional study to determine relationship between VLBW (<1500 g) and quality and amount of sleep in young adults with actigraphy and the basic Nordic sleep questionnaire	167 subjects	No differences in sleep quality or sleep duration
		Ages 19–26 years	VLBW adults went to bed on average 36 min (6–66 min) earlier
		89 VLBW	Lower GA related to longer sleep latency within VLBW ($p = 0.04$)
		78 term controls	
Hibbs 2014 [88]	Population-based longitudinal cohort study to evaluate sleep patterns and quality of sleep in adolescents born preterm and term	501 subjects 43.3%preterm mean (SD) birth weight 1514 g (567 g)	Based on actigraphy: earlier bed times; wake times and earlier sleep midpoints in preterm group ($p < 0.05$)
		Mean GA 31 weeks	Based on PSG: fewer arousals ($p = 0.006$)
		Ages 16–19 years	Questionnaire: more rested in the morning and less sleepiness and fatigue in preterm group

[58, 81–84]. Marcus et al. found a prevalence of OSA of 9.6% in 201 former preterm infants now aged 5–12 years compared with 1–4% of the general population [58]. Although earlier studies raised concerns regarding past exposure to xanthines such as caffeine and theophylline for AOP as a risk for SDB in childhood [83], the aforementioned study by Marcus and colleagues showed no difference in the prevalence of OSA between those who received caffeine and those who were randomized to the placebo arm [58]. Of further interest, the periodic limb movement index was increased in the caffeine group compared with the placebo group, but sleep efficiency was the same in both groups.

Sleep problems other than SDB in the first 6 months seem less common in preterm than full-term infants [85]. Sleep patterns and incidence of sleep problems in the first 10 years of life in historical cohorts did not differ between those born at term or preterm [86]. Even in young adults born prematurely, sleep quality and amount seemed unchanged despite the fact that they were at greater risk for SDB [81, 87]. Interestingly, a more recent study described significantly earlier bed and wake times and fewer arousals in adolescents born prematurely [88].

Summary and Conclusions

Prematurity leads to a period of respiratory instability, especially during sleep. It is important that health-care professionals involved in the care of preterm infants understand not only the normal respiratory physiology and breathing of these preterm infants but also abnormal breathing states that may predispose to short- and long-term morbidity, including poorer neurocognition if left untreated. In particular, increasing evidence suggests that preterm birth may be associated with an increased prevalence of sleep-disordered breathing, specifically OSA. As such, the authors would recommend that preterm children should be screened for sleep disorders in early childhood and those with a high index of suspicion for sleep-disordered breathing, referred to a pediatric sleep center.

Future Directions

Future research is needed to understand the exact mechanisms predisposing to an increased risk of sleep disorders that may further predispose to adverse neurocognition. It

would be helpful to strategize about preventative factors limiting risks of sleep-disordered breathing in this already vulnerable population. Specifically, optimizing respiratory status early on in the lives of these infants may be associated with a reduction in risk for sleep disorders.

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Part IV

Treatment Approaches

Behavioral Sleep Interventions

28

Valerie Paasch, Ximena Celedon Flanders, and Keith J. Slifer

Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
ASD	Autism spectrum disorder
NDD	Neurodevelopmental disability/disabilities
REM	Rapid eye movement

Introduction

Children with neurodevelopmental disabilities (NDD) exhibit behavioral, emotional, cognitive, and sensory-motor difficulties which directly impact their sleep and patterns. Sleep problems such as trouble falling asleep, staying asleep, parasomnias, morning arousal, or early morning waking are commonly seen in children with NDD [1–7]. Disrupted sleep has been associated with intensified daytime behavioral and emotional difficulties. Furthermore, insufficient or inefficient sleep can further cause difficulties with performing activity of daily living.

Sleep problems in children with NDD likely have a behavioral and learning component that is perpetuated through throughout development [8]. While it is not known with certainty what initially causes these issues, abnormalities in circadian rhythms, disturbance in melatonin production, and abnormalities in other hormones or neurotransmitters may also be involved. Other factors involved could include increased sensory sensitivity and lack of bedtime routine. Such factors, individually or in combination, can lead to difficulty initiating and maintaining sleep.

Prior research has shown that behavioral interventions can successfully address sleep problems in typically developing children [9, 10]. Many of the same interventions are currently recommended to address the aforementioned sleep problems in children with NDD. For example, the Sleep Committee of the Autism Treatment Network recommends behavioral intervention as a first-line approach for treating insomnia in children with autism spectrum disorder (ASD) [11]. In terms of acceptability, research has found that parents of children with NDD rate behavioral treatment and melatonin, which is widely used for sleep, similarly [12]. Further, establishing more adaptive bedtime habits and routines have been effective in minimizing and reducing disruptive sleep problems [1, 7, 11]. The purpose of this chapter is to discuss behavioral sleep interventions to address problems falling asleep, problems staying asleep, and problems waking and remaining alert in the morning.

Case Vignette

Kyle is a 2-year-old male with a history of autism spectrum disorder and sleep disturbance. In addition to sleep concerns, Kyle has a history of feeding disorder and disruptive behavior, including tantrums and sibling-directed aggression. He has been receiving behavioral psychology services to address these feeding and behavior concerns. Kyle was referred to interdisciplinary Sleep Clinic given caregiver concern regarding his night wakings and inability to initiate sleep independently.

V. Paasch (✉) · X. C. Flanders
Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Department of Behavioral Psychology, Kennedy Krieger Institute, Baltimore, MD, USA
e-mail: paasch@kennedykrieger.org

K. J. Slifer
Department of Behavioral Psychology, Kennedy Krieger Institute, Baltimore, MD, USA

Department of Psychiatry and Behavioral Sciences and the Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

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Kyle's mother and grandmother attended the assessment, since both caregivers are involved with his bedtime routine. They reported following a consistent evening routine, which included watching a highly preferred television show before going upstairs for bed. Kyle has engaged in a tantrum every night when he transitions away from his television show, and it has sometimes taken a significant amount of time for him to calm. Kyle shares a room with his mother and sister due to a limited number of bedrooms in the home. Due to work schedules, on weeknights, Kyle's grandmother completes his bedtime routine and sleeps in the room with him overnight, while on weekends, his mother completes the routine and remains in the room. In order to fall asleep, Kyle needs a caregiver to rock him in a rocking chair for up to 30 min before being placed in his own bed. There is a nightlight on when Kyle falls asleep; however, it is turned off once his sister falls asleep. Kyle's mother reports trying a variety of prior interventions, such as singing, patting Kyle on the back instead of rocking him, and sitting with him on the floor instead of in the rocking chair; however, Kyle has not fallen asleep under any of these conditions.

Overnight, Kyle wakes frequently and comes to his caregiver's bed where he is able to initiate sleep immediately. If required to return to his own bed, Kyle requires rocking in order to reinitiate sleep, and latency to sleep onset is much longer. If Kyle wakes overnight and a caregiver is not present in the room, he sits on his mother's bed crying and screaming until a caregiver returns to the room to help with sleep reinitiation.

In the morning, Kyle wakes at a consistent time without difficulty. He also takes daily naps. When at home, Kyle must be rocked to fall asleep for a nap; however, at daycare his teachers are able to pat his back without rocking him to help him fall asleep.

Management and Evidence Base: Problems Falling Asleep

Sleep Hygiene

With many of our families, the starting point is to assess a child's sleep hygiene, or the consistent habits to help maximize sleep, because if a child has not established good sleep habits, it will be difficult to get therapeutic traction and see maximum benefit from other interventions [13]. The child's sleep schedule should be consistent throughout the week, with a set bedtime that is the same every night, even on weekends. Ideally, the child will be put to sleep when he is sleepy but not yet asleep, so that the skill of independent sleep initiation can be developed. The child should fall asleep consistently in the same place every night, since changes in environment can shape problematic sleep-onset associations and night wakings. The child's room should be dark, of a comfortable temperature, and free of distractions such as electronics and highly preferred toys, which may motivate or prolong wakings. To further help a child develop appropriate sleep associations, whenever possible, the child's room should be reserved only for sleeping. This means that the bed and bedroom should not be the place of time-outs, homework completion, or daytime play, as all of these activities can create competing associations that weaken the association between the bedroom and sleep. Many children with NDD are noise sensitive, so sound machines, background music, or white noise can be trialed when creating a comfortable sleep environment. However, our experience has been that some children will respond well to having extraneous background noise muffled, while others will find this additional auditory stimulation aversive.

During the daytime, a consistent wake time should be maintained, even on weekends and holidays. For many of our children and adolescents with early wake times for school, this recommendation can be quite challenging. Other recommendations to promote nighttime sleep include either avoiding daytime naps or adjusting their timing as developmentally appropriate, ensuring adequate light exposure during the day, engaging in physical activity before late afternoon, avoiding caffeine in the late afternoon and evening, and avoiding large meals before bedtime.

Addressing sleep hygiene as the sole intervention is unlikely to eliminate sleep problems [14]; however, it has been found to be a beneficial treatment component both for children with attention-deficit/hyperactivity disorder (ADHD) [15] and ASD [14, 16]. Therefore, it is typically most helpful as part of a comprehensive treatment package [14].

Bedtime Routine

Many children with NDD need additional external cues to signal that it is time to wind down and go to bed, as completing a consistent bedtime routine signals that bedtime and sleep are approaching [17]. The bedtime routine should begin approximately 20–30 min before bedtime and should include hygiene activities, such as brushing teeth and putting on pajamas, in addition to a relaxing activity (individualized to the child), such as singing songs or reading a book. The final step of the routine should always end in the child's bedroom. To help provide structure and enforce predictability, many children with NDD benefit from a picture schedule depicting the different steps of their bedtime routine [18].

Visual schedules can be constructed with photographs of the child completing each step of his routine, for greater personalization, or clip art/cartoon pictures can also be used (Fig. 28.1).

When working with children with NDD, it is important to remember that many may have restricted interests or atypical responses to common activities. Many children with NDD become activated by bath time or water play. For such a child, it may be important to move bathing to the morning or as early in the bedtime routine as possible (i.e., before dinner or as the first step in the routine) to provide ample time to wind down. Additionally, many caregivers of children with NDD identify that their child's only calming activities are electronic media or screen-based. This will require additional problem-solving and collaboration with the family to address ways to fade electronics usage at bedtime. Can electronics slowly be faded out of the routine by gradually decreasing the amount of time they are available to the child (i.e., 30 min faded to 25 min faded to 20 min etc. until eliminated)? If the child watches a specific show on the tablet, could he listen to the show instead of watching it on a screen? Can the content of the electronics be adjusted (i.e., transitioning from active games to more passive activities)? Can the brightness and, more specifically, blue light be dimmed on the tablet via tablet settings, app, or special blue light-blocking glasses? Once domains are identified where electronic usage can be adjusted, a structured plan can be created to gradually begin fading them out of the bedtime routine.

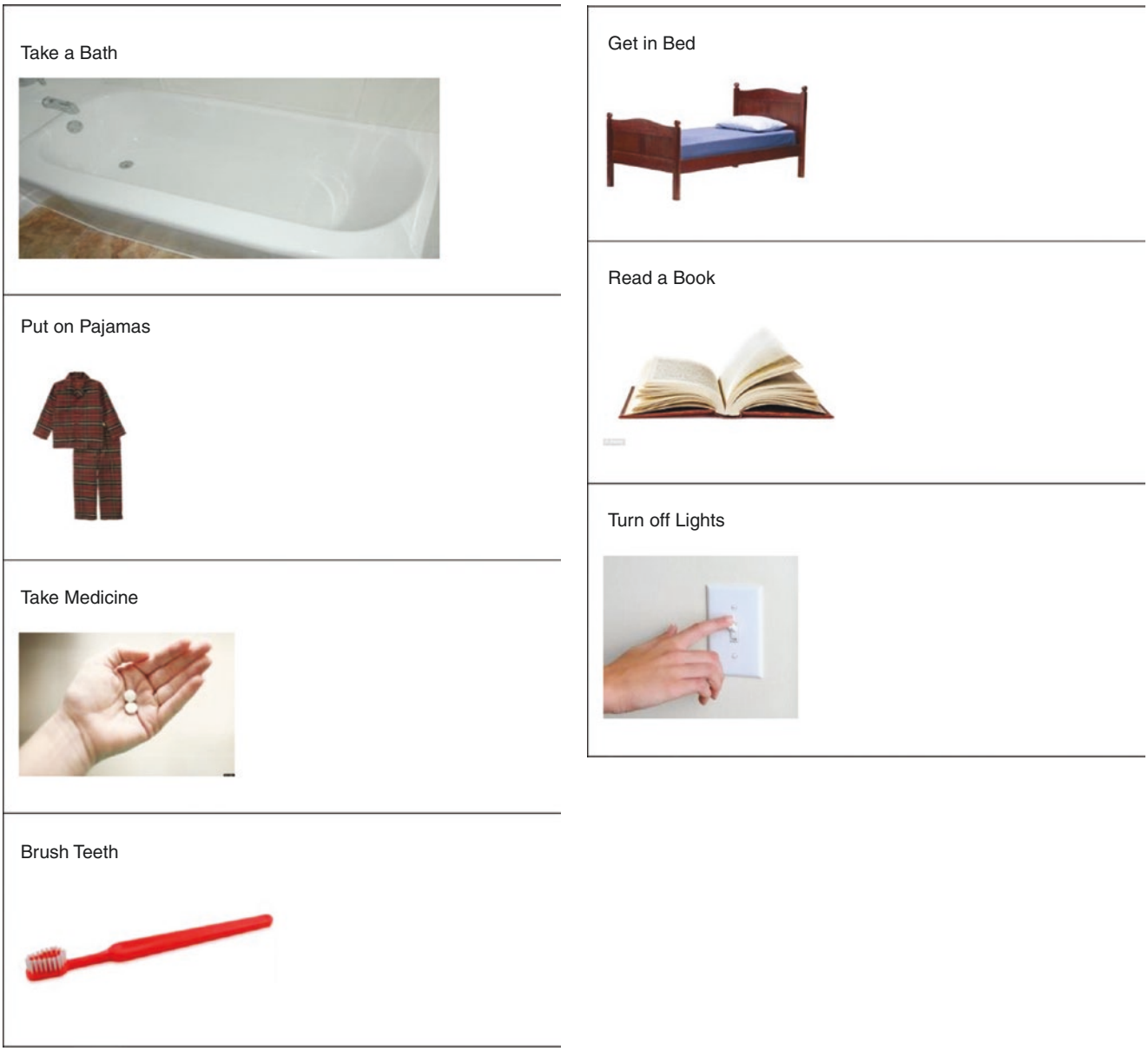

Fig. 28.1 Sample visual schedule for bedtime routine

Delay behaviors, such as refusals or stalling, interfere with completing a bedtime routine for many children. To address these behaviors, a reinforcement plan can be implemented to reward children for following the bedtime routine (i.e., brushing teeth, getting in bed, etc.). Prior to implementation, a reward (i.e., small prize, sticker, or preferred activity the next day) and goal criteria (i.e., number of completed steps, number of points needed, number of successful days) should be established. A structured bedtime routine paired with reinforcement has been found to be a beneficial treatment component for children with ADHD [19] and intellectual disability [20].

Another behavioral intervention that can address delay behavior at bedtime is called "beat the buzzer." During this intervention, a timer is set for a slightly shorter time than the bedtime routine is currently taking to complete (i.e., if the routine currently takes 45 min, initially set for 40 min). If the child completes his routine before the timer sounds, he is provided with a reward. If he does not complete the routine before the goal time, no reward is given. The time on the timer should be gradually adjusted a few minutes shorter each night, as long as the child is successfully meeting his goal in order to shape routine completion to a more preferable duration.

Bedtime Fading

When children have trouble falling asleep once they get in bed, they often begin to associate being in bed with wakefulness, playtime, tantrums, or other daytime behaviors, as opposed to associating their beds with sleep. When a child does have a significantly delayed sleep onset, it is important to ask parents what happens when their child is put to bed at a later time. If the child still takes an extensive amount of time to fall asleep, even when put in bed later, then bedtime fading is not the best intervention to implement. If the parent is unsure what would happen, or reports that the child falls asleep more quickly with a delayed bedtime, then bedtime fading would be an appropriate intervention to trial. (When considering the appropriateness of bedtime fading, additional assessment for delayed sleep phase may also be necessary.)

Bedtime fading involves temporarily delaying the child's bedtime until approximately 20–30 min before he or she is currently falling asleep (i.e., temporarily making bedtime at 10:30 PM if the child currently is falling asleep at 11:00 PM). Problem-solving should be done with the family to identify quiet, non-electronic activities to engage the child during the time between the current bedtime and temporarily later bedtime. When the child consistently falls asleep with an appropriate latency to sleep onset (e.g., 20–30 min), then bedtime should be moved earlier by 15 min. This shaping process (incrementally earlier bedtime) should continue until the child is falling asleep within 20–30 min of his goal bedtime.

Caregivers may initially be hesitant to implement an intervention that delays bedtime for a child who is in need of more sleep. To increase their buy in, it will be important to explain the rationale for this approach. By temporarily delaying bedtime to close to the time the child is currently falling asleep, the amount of sleep the child is getting is not actually decreased, since he was consistently awake during this time anyway. Instead, the association between getting into bed and actually falling asleep soon after is being strengthened. Bedtime fading has previously been found to be an effective intervention for children with ASD [14, 21].

Extinction/"Cry-It-Out" Method

When families come to Sleep Clinic, they have often heard of extinction or the "cry-it-out" method. Many caregivers have tried unsuccessfully to implement this intervention and may fear that this will be the only recommendation given to address their child's delayed sleep onset. Extinction involves the caregiver putting the child in bed, leaving the room, and not returning despite any outbursts or distress the child may express. The goal of extinction is to "extinguish" the outbursts in order to teach the child that protests will neither delay bedtime nor increase bedtime interactions with their caregiver. By learning this, the child is supposed to also learn to fall asleep independently more quickly. Extinction has previously been found to be effective in a small sample of children and young adults with NDD, although parents found the procedure challenging to implement, especially during initial treatment stages [22].

As can be expected, this intervention can be very distressing for caregivers since they are not supposed to comfort their child during the initial stages [23]. When parents use this process, children often escalate their behaviors and protests to gain caregiver attention after being put in bed. Because of this escalation, called an extinction burst, the child may engage in unsafe or self-injurious behavior in an effort to get caregivers to intervene. For example, some children may become so distressed that they vomit or cry. This level of distress is not the goal of this intervention, and it may be unsafe for many children with NDD, medical conditions, or self-injurious behaviors to reach this level of physiological arousal and distress [24]. Furthermore, some children may continue to escalate their behavior to a level that cannot be safely ignored. If the caregiver intervenes and provides attention, they are unintentionally providing intermittent social reinforcement that will make the behavior more likely to occur in the future and likely to escalate quickly in intensity (i.e., "this got mom to intervene last time, so I'll try it again"). Incidentally, the same intermittent reinforcement

schedule will perpetuate delayed sleep onset and simply complicate the problem. Because of these concerns, a more gradual approach to extinction is typically recommended in our clinic for children with NDD.

Gradual Extinction with Caregiver Presence

Another common type of gradual extinction involves fading, or slowly removing, the physical presence of caregivers at bedtime. Similar to the "excuse me" drills described below, children should begin in their own bedrooms, as it is incredibly difficult to fade the child out of a caregiver's bedroom. Many children with NDD are accustomed to falling asleep with caregivers hugging them, rocking them, or providing some other form of deep pressure as they fall asleep. As a result of this apparent need to seek sensory input, children may be unable to fall asleep without these sensory-seeking behaviors.

The first step of fading parental presence at bedtime is determining the current whereabouts of the caregiver and level of physical contact between caregiver and child at bedtime. Is the caregiver in bed with the child? Are they physically touching? The initial step of fading should only be a minor change from current conditions: for example, if previously the caregiver and child have lain in bed together talking, a first step could be to have the room silent once in bed. If previously, the caregiver was in direct physical contact with the child, a first step would be to have the caregiver simply lie next to the child, not in physical contact. As the child tolerates each step in the fading process, he can progress to the next step until the caregiver is ultimately able to remove herself entirely from the child's room. Of note, this intervention involves a time commitment, and parents must remain consistent with implementation. In order to maintain consistency, caregivers should carefully choose when to implement this intervention because they will need physical stamina and emotional energy to follow through on this strategy. Therefore, this intervention should not begin during times of great stress, transitions, illness, or other demands on the caregiver's resources. To the extent possible, caregivers should choose a time when they are well rested and when social and emotional support is available from trustworthy family members or friends. Similar to "excuse me" drills, a reinforcement plan for "following the bedtime rules" can be beneficial. Table 28.1 depicts an example of a sample fading procedure.

Table 28.1 Fading gradual extinction with parental presence: sample fading process

Step 1	Have the caregiver stop verbal interactions with the child once in bed
Step 2	Have the caregiver discontinue active physical contact (back rub, hugging), instead placing a hand on the child
Step 3	Have the caregiver lie next to the child but not engage in physical contact
Step 4	Have the caregiver sit next to the child in bed instead of lying down
Step 5	Have the caregiver sit at the foot of the child's bed
Step 6	Have the caregiver sit in a chair right next to the bed, still within the child's line of vision
Step 7	Have the caregiver systematically move her chair further from the child's bed until she is seated in the doorway
Step 8	Once the caregiver's chair is outside of the doorway, have her begin to say goodnight at bedtime and then leave the room

"Excuse Me" Drills

More often, parents prefer to use a gradual extinction method, whereby they gradually fade, or decrease, the amount of time they are present as the child falls asleep. One type of gradual extinction intervention is "excuse me" drills. With any type of gradual extinction, it is easier to fade a caregiver from a child's room than the child from the caregiver's room, as the caregiver is far more motivated for change than the child. With "excuse me" drills, a caregiver completes the bedtime routine as usual and places the child in bed. When the child is in getting ready to fall asleep (e.g., in bed, quiet, head on pillow, controlled breathing), the caregiver will briefly excuse himself from the room for a reason plausible to the child (i.e., to use the bathroom, check on something in the kitchen, ask the other parent a question) before returning and completing the routine as usual. This approach is especially helpful for highly anxious children because each individual "drill" is a demonstration to the child that they are safe, the caregiver is not leaving indefinitely, and the caregiver can be relied upon to return to provide brief support, reassurance, and praise. Initially, the time-out of the room should be very brief (i.e., a matter of seconds or minutes) based on the child's level of anxiety and behavioral tolerance. The brevity of the caregiver's time outside of the room keeps the child's anxiety from escalating before the caregiver returns. Over time, as the child becomes accustomed to this procedure, the parent's time-out of the room can be gradually increased (i.e., 1 min, then 3 min, then 5 min, etc.). The child learns that the parent is reliably nearby and returns as promised. As the child is able to tolerate his caregiver's time outside the room, that amount of time will continue to be gradually increased until the child "accidentally" falls asleep before his caregiver's return. Once the child is able to regularly fall asleep while his caregiver is out of the room, caregivers can begin saying goodnight and leaving the room after putting the child in bed.

Of extreme importance is the fact that caregivers must be mindful of the time they are out of the room, and they must always return to the child's room following the designated "excuse me" period. This gradual approach attempts to set children up for success by teaching children that (1) they are

capable of falling asleep without a caregiver present and (2) their caregiver is reliable and will return/be there the next morning if they are not present at sleep onset. Depending on the child's level of cognitive functioning, a reinforcement plan for following "bedtime rules" (i.e., staying in bed while the caregiver is not in the room) may add additional incentive for compliance. To maximize success with this intervention, it is important that caregivers not become impatient, overly confident, or distracted when implementing this strategy, thus extending their time-out of the room more quickly than the child is able to tolerate. Doing so may cause the child to become even more anxious or distressed.

Insomnia/Stimulus Control

When children have difficulty sleeping, they often begin associating being in their bed with being awake, watching videos, or playtime. This weakens the association between their bed and sleep. Because of this, it is important to talk to families about stimulus control and reserving the bed, and ideally the bedroom, for sleep. In order to be successful, stimulus control will need to occur both during the day and at night.

During the daytime, children should not be completing homework, playing, or watching television in bed. The goal is to associate the bedroom, and especially the bed, with sleep and no other activities. This is particularly important with respect to electronics in bed, which can be activating rather than calming to the brain. Electronics should be removed entirely from the bedroom, if possible, or at least turned off and removed from the bed an hour before bedtime. Also, at bedtime, the bedroom should not have highly stimulating toys as the presence of these items provides distractions from sleep. Ideally, the child should be allowed only quiet, relaxing, comforting items in bed. Additionally, whenever possible, the bedroom should not be used for time-out or other punishment because it can create anxious or aversive associations with the space, thereby making it more difficult to fall asleep at night.

Overnight, additional efforts need to be made to promote the association between sleep associations and being in bed. For example, in an effort to decrease "clock watching" and anxiety about being awake too long, clocks should be removed from the bedroom or turned away from the child's line of vision. For many children with NDD who obsess on specific times on the clock, pictorial clocks depicting colors (red/green) or images (sun/moon) to cue them as to when they are allowed to wake up may be helpful. For children who have the comprehension and maturity to do so, if they have been in bed and unable to fall asleep for what feels like 20–30 min, they should get out of bed and engage in a quiet, non-electronic activity for approximately 30 min before returning to bed and again attempting to sleep. This process (i.e., alternating effort to sleep with quiet out-of-bed activity) should continue until a child is able to initiate sleep.

Case Vignette: Behavioral Interventions to Address Problems Falling Asleep

As a starting point, education was provided by Sleep Clinic to Kyle's caregivers regarding sleep hygiene, the need for a consistent sleep environment, and the need to address independent sleep onset. Problem-solving was done with caregivers given Kyle's tantrums and avoidance behavior associated with transitioning from watching television to beginning his bedtime routine, as this made it difficult for him to calm at bedtime. It was recommended that all electronics, including television, be discontinued 30 min–1 h prior to bedtime. Instead, they were to be moved earlier in the evening so Kyle did not miss his opportunity to engage in these preferred activities and so that any tantrums associated with those transitions would not occur at bedtime. Additionally, caregivers were encouraged to provide verbal warnings that the transition to bedtime was about to occur. If Kyle had a tantrum during the transition, caregivers were encouraged to continue with the planned routine while using differential attention (i.e., ignoring the tantrum and providing praise and verbal interactions once he was quiet and cooperative).

Potential ways to improve consistency in Kyle's sleep environment overnight were also discussed with caregivers. Caregivers acknowledged that at the time, providing Kyle with his own bedroom or having a consistent caregiver present in the room was not an option. Additionally, because of space limitations, a caregiver would need to remain in the room while Kyle fell asleep in order to complete his sister's bedtime routine with her. Because of this, clinicians and family brainstormed together to identify areas where the family could be consistent. First, to maintain a consistent sleep environment, it was recommended that his nightlight remain on overnight instead of being turned off at time of sleep onset. Second, the family said they could consistently provide Kyle with a large body pillow in his bed to simulate the presence of a caregiver.

Caregivers expressed some concern regarding the potential for an extinction burst (escalation in disruptive behaviors at bedtime) since these changes would significantly change Kyle's current, preferred bedtime routine. Because of this, caregivers were encouraged to focus on consistently implementing these bedtime changes prior to receiving additional behavioral sleep recommendations. They felt this was a manageable plan.

Management and Evidence Base: Problems Staying Asleep

Every sleep-deprived parent knows that getting a child to sleep through the night is just as important as getting that child to fall asleep. Night wakings are a common problem in children and toddlers that persists in up to half, even though physiologically, they should be able to sleep through the night [25]. Approximately one-third of children have recurring difficulty with reinitiating sleep, primarily because they are unable to do so independently [26, 27]. Children who have not learned to fall asleep initially without parental presence and intervention are unlikely to be able to return to sleep independently after a night waking.

Sleep cycles or rhythms alternate between non-rapid eye movement (REM) and REM stage sleep throughout the night about every 1–1.5 h. It is normal for brief arousals or wakings to occur at the end of each sleep cycle. In healthy, typically developing children, these arousals occur multiple times per night and are immediately followed by efficient reinitiation of sleep with little or no conscious awareness that awakening has occurred [25, 28]. Problems staying asleep may occur when some other physiological or environmental event disrupts the efficient return to sleep after what would otherwise have been a brief nighttime arousal. For example, noise from another room, light from a TV, or an uncomfortable room temperature can provide enough stimulation for the child to become more fully awake after an arousal and then have difficulty reinitiating sleep. If the child has fallen asleep with a parent present, he or she will naturally expect that parent to be present on awakening. As a result, the child will cry or call out for the parent, or get up and go looking for the parent, often getting into the parents' bed. Similarly, internal stimuli such as hunger, thirst, anxiety, or pain may disrupt the child's ability to go back to sleep, leading to distress and seeking parental attention and assistance overnight.

When assessing any sleep problems in children, poor sleep hygiene must always be considered. However, if sleep hygiene is established such that the child has a consistent sleep schedule, an appropriate sleep environment, minimal or no stimulant consumption (caffeine or other), and developmentally appropriate napping or appropriately outgrown daytime sleep, yet night wakings occur regularly, the evaluation is not over, and further assessment is warranted.

Sleep-Onset Associations

Whenever a child has consistent night wakings, the source of concern may actually be with the way the child is falling asleep, as opposed to the waking itself. A common reason for recurrent night wakings is a sleep-onset association. Sleep-onset associations refer to the conditions under which we fall asleep and the expectation that how we fall asleep is how we will be awaken: for example, an association that a certain person (e.g., caregiver), activity (e.g., watching television), or environmental cue (e.g., living room sofa) is necessary to fall asleep or to reinitiate sleep. When children only fall asleep while being held or rocked by a caregiver, hearing a bedtime story, or watching TV or cuddling in bed with caregivers, they not only have difficulty falling asleep independently but also may not be able to reinitiate sleep after night wakings without parental intervention. These children have not learned to soothe themselves. When they briefly awaken during the night – and multiple brief spontaneous arousals are a normal part of sleep – to encounter environmental conditions different from those under which they fell asleep (i.e., parent not present; in a different bed and/or room; TV, nightlight, and music turned off; darkened room), they fully wake instead of quickly returning to sleep. When the child awakens with the expectation that these comforting things will be present, only to find the room quiet, dark, and minus the caregiver, he becomes distressed and begins calling out, crying, or searching for his caregiver in an effort to recreate his sleep-onset association to reinitiate sleep. At some point in development, all children, including those with NDD, need to learn healthy and independent sleep-onset associations.

Caregivers can facilitate this process by encouraging good sleep hygiene and a consistent evening and bedtime routine. One important step is to ensure that the child's bedroom environment is the same at bedtime as it will be when child has inevitable brief arousals/wakings during the night. The condition of the room, bed, lighting, temperature, and any ambient noise (music, white noise) should established at bedtime, kept constant during the night, and kept consistent across nights. The child should get in his bed when sleepy but not yet asleep. The child should not fall asleep somewhere other than where he is expected to sleep all night (e.g., caregiver's bed, on couch in front of TV, in the car, etc.) and then be carried to bed asleep, because when he awakens, he will be disoriented by the transition he doesn't remember making. The child should be encouraged to fall asleep independently to lessen the sleep-onset association with caregivers. Extinction or gradual extinction, such as "excuse me" drills or gradual extinction with caregiver presence (both previously discussed in this chapter), are interventions that can be used to encourage this change. It will help to have the child become accustomed to specific environmental stimuli that can be consistently present during the night. Comfort items that can be associated with falling asleep could be a favorite blanket, pillow, stuffed animal, quiet musical toy, or lullaby songs set to play throughout the night. Many times overnight wakings decrease once children are able to initiate

sleep independently at the beginning of the night; however, if necessary, an abbreviated version of "excuse me" drills or graduated extinction with caregiver presence can be implemented with night wakings until the child is able to awaken during the night, tolerate finding himself alone in bed, and reinitiate sleep without parental intervention.

Night Wakings

When children cannot reinitiate sleep without parental intervention, parents may fall back on survival strategies such as co-sleeping, permitting nocturnal eating and drinking, and allowing prolonged interactions with children overnight. Use of these potentially dysfunctional coping mechanisms becomes even more likely with children who have a NDD, such as autism, and/or chronic medical conditions. Most commonly, night wakings are maintained because of sleep-onset associations that children have developed. Sleep-onset associations are the conditions that have become necessary for the child to self-soothe and reinitiate sleep. These associations may involve being held, fed, rocked, sung to, or otherwise soothed by a familiar caregiver [9, 28, 31].

When deciding how to respond to a child's night wakings, first, one must determine if there is something motivating the child to be awake overnight while the rest of the house is sleeping. Is he accessing electronics? Is she able to play (uninterrupted) with a preferred toy? Is he engaging in self-stimulatory behavior? Is she engaging in a preferred or compulsive ritual that caregivers usually limit? If caregivers are able to identify that a child may be waking overnight to engage in preferred activities, then problem-solving will need to be done to find a way to restrict access to these things. For example, can Wi-Fi be turned off or restricted after bedtime? Can parents remove and secure the computer keyboard, video game controller, cable cord, or remote control (while leaving much larger televisions or computers in their typical places) when they go to bed at night? Can the preferred toys complete a bedtime routine of their own, such as being put into a plastic container and taken to the caregivers' room to restrict overnight access? Can a reinforcement plan be implemented to reward the child for adhering to these restrictions?

Also, is the child motivated by special interactions or individualized attention from a caregiver during night wakings? When night wakings are frequent and prolonged, details of the parent-child interactions and the child's behavior should be closely considered. Is the child receiving a significant amount of attention from their caregiver that is otherwise not available during the daytime? Is the child waking in order to see a parent who comes home late after an evening or night shift at work? Is the child waking overnight in an effort to receive extra comfort, snuggles, or preferred activities from their caregiver? Is he hoping to gain access to his caregiver's bed? The goal is always to help the child to learn to self-soothe and fall asleep (or reinitiate sleep) efficiently without excessive dependence on a caregiver [25, 28, 30]. Therefore, if overnight parent-child interactions are reinforcing the child's wakings, both daytime and overnight intervention will need to occur. First, caregivers will need to ensure that they are reserving time every day to engage in quality, child-led activities with their son or daughter. We have recommended at least 15 min daily. This reserved individualized time, sometimes called "special time," teaches the child that he does not need to wake overnight in order to spend time with his caregiver. Second, the quality of overnight caregiver-child interactions needs to be addressed. Verbal exchanges and physical contact should be minimal, and all activities should be boring rather than highly preferred. This shift in interaction teaches the child that preferred kinds of attention and activities with a caregiver are only available during the day, thereby weakening the reinforcing nature of overnight wakings.

Finally, it is important to assess whether overnight wakings occur at a consistent time. If spontaneous wakings appear to be consistently happening at the same time of night, scheduled night wakings (discussed in detail below in the Parasomnias section) could be trialed. Just as with parasomnias, scheduled wakings can be tried 30 min prior to the typical spontaneous overnight waking time.

Parasomnias

Children may exhibit non-REM parasomnias, including sleepwalking, sleep talking, or sleep (night) terrors, episodes of sudden arousal from slow-wave sleep accompanied by autonomic and behavioral evidence of intense fear, agitation, or confusion. Parasomnias typically occur in the earlier part of the night, with no child recall of the events in the morning. In contrast, they are quite memorable for and troubling to parents, who may believe the child is having a nightmare. During a non-REM parasomnia, in contrast to a nightmare, children are likely to avoid comfort rather than seek it. Therefore, caregivers should not attempt to awaken the child, as this may prolong the episode. Instead, the caregiver should supervise the child to ensure safety and gently guide the child back to bed. From a safety perspective, if a child engages in sleepwalking, care should also be taken to ensure that the child's floor stays clear (to minimize injury) and door locks or alarms should be utilized on windows and doors to ensure the child cannot leave the home – especially for children who have eloped from their homes during sleep.

If parasomnias occur during a consistent window of time every night, then scheduled night wakings may be beneficial. Scheduled night wakings involve purposely waking the child

approximately 30 min before the parasomnia typically occurs. These scheduled wakings should be brief, basically just enough for the child to stir, and need not escalate to full wakings, conversations, or other extended interactions. Scheduled night wakings should be trialed for a couple of weeks before skipping a few nights to see if parasomnias have resolved. If parasomnias do not recur when scheduled wakings stop, scheduled wakings can be discontinued and reinitiated in the future if needed. If parasomnias recur, scheduled wakings can be trialed for another week (to see if parasomnias resolve) before discontinuing this intervention. Research has found that scheduled wakings can be an effective intervention for addressing sleep terrors in children with ASD [29].

Nightmares

In the case of night wakings that are less frequent, occur episodically during the latter part of the night when REM sleep is more likely, and involve the child being distressed and recalling frightening or confusing dreams, nightmares are likely. Nightmares are simply frightening dreams that result in awakening from sleep followed by the child being upset and seeking comfort. All children have bad dreams on occasion. Up to 24% of typically developing children have severe and recurrent nightmares, which awaken them and which they recall. Between 2 and 5 years of age, about 20% of typically developing children have significant nightmares and between 6 and 10 years up to 41% [25, 28]. While data at this level of detail are largely unavailable for children with NDD, there is no reason to believe children with NDD have any fewer nightmares, and given their increased risk of having sleep problems in general, they may even have more frequent nightmares. However, many children with NDD lack the communicative ability to describe these experiences to their caregivers. On the other hand, it should be recognized that not all children who report having nightmares actually had them. On those occasions when the child has received comfort and reassurance from a caregiver during a reported nightmare, he may have learned that these reports are a reliable way both to get the caregiver to allow him out of his room and also to gain more access to interactions with adults. Thus, saying "I had a bad dream" can become a learned behavior for a child hoping to bend the typical overnight rules.

Sleep professionals generally do not analyze dreams, but it is sometimes revealing to ask about nightmare content. If the themes are suspiciously the same across time, this may suggest the child has learned to report on these themes as a guaranteed way to get nighttime comfort and attention. However, if reported dreams involve excessive fears of death, injury, or harm to family members, an underlying anxiety disorder may be presenting as a sleep disturbance, and the child should be evaluated by a behavioral health professional for such a condition.

When children have nightmares, they may fear going back to sleep and may begin to avoid or resist going to bed. Initial interventions for nightmares involve briefly comforting the child, reassuring the child that she or he is safe, redirecting the child back to bed, and then prompting use of coping strategies to facilitate reinitiation of sleep (i.e., encouraging the child to "be brave," repeat positive self-statements, listen to quiet music or comforting stories, or practice imagery or deep breathing). Children, who have experienced significant stress or trauma, have anxiety disorders or sleep deprivation, or take medication that may alter their amount of REM sleep are at greater risk for increased REM sleep (i.e., "REM rebound"), which increases the risk of nightmares. Children with NDD and comorbid anxiety or depression may be trialed on anxiolytic or antidepressant medications. Some of these medications can suppress REM sleep, but if discontinued abruptly may lead to a REM rebound effect [10]. Therefore, any intervention that can reduce these risk factors is likely to decrease the frequency of nightmares [25]. For a child with particularly distressing nightmares who has adequate cognitive and verbal abilities, a referral for nightmare imagery modification rehearsal with a psychologist or cognitive-behavioral therapist on an outpatient basis could be appropriate. Imagery modification involves helping the child to use his or her imagination to counter or replace frightening images experienced during a nightmare. One such strategy is helping the child to learn to imagine a more positive ending to a dream (e.g., a superhero appears to help the child defeat the monster; the child asks the troll why he is being mean, then the troll says he is sorry and starts being nice to everyone). Children can also be asked to rehearse the dream by drawing these more positive outcomes.

Additionally, it is important to keep in mind that children with NDD may become anxious and have nightmares about images, characters, television shows, and video games that may not frighten their typically developing peers. Because of this, it may initially be challenging for caregivers to identify the source of fear, and once it is identified, special attention will need to be given to monitoring and restricting the child's daytime access to that content.

Case Vignette: Behavioral Interventions to Address Problems Staying Asleep

As a second step to address Kyle's sleep difficulties, it was decided that caregivers would begin addressing the manner in which Kyle was falling asleep. Education was provided regarding sleep-onset associations as the likely reason why Kyle was unable to independently initiate sleep and why he was seeking out caregivers

during night wakings in an effort to reinitiate sleep. Given the family's prior attempts to fade their presence at bedtime, problem-solving was done to identify a gradual way to implement this change.

Caregivers identified that they would likely be most consistent implementing gradual extinction with parental presence in an effort to address Kyle's sleep-onset association disorder. Given the family's interest in no longer rocking Kyle to sleep, we all agreed this would be their goal. As a beginning step, it was recommended that they began rocking Kyle in their laps on his bed as a way to fade out the rocking chair. Once they were able to successfully make this transition while maintaining a 30 min latency to sleep onset, caregivers were encouraged to begin placing Kyle on the bed instead of their laps while rocking him from side to side. Once this step was achieved, caregivers were encouraged to place Kyle in bed and pat his back until he fell asleep, similar to the current approach at daycare.

To address overnight wakings, caregivers were encouraged to consistently return Kyle to his bed every time he attempted to join them in bed. During these wakings, it was recommended that caregivers engage in soothing behavior (i.e., rocking, caregiver presence) consistent with what they were providing at bedtime to promote Kyle's sleep reinitiation. The possibility of seeing an extinction burst while caregivers implemented these changes was discussed.

Management and Evidence Base: Waking and Daytime Sleepiness

Dysregulated or fragmented sleep, including early morning awakening, daytime napping, delayed sleep onset, advanced sleep onset, and/or frequent nighttime awakenings, may perpetuate excessive daytime tiredness and irritability. Sleep promotion practices are usually aimed at influencing sleep onset, but for those with neurodevelopmental disabilities, early morning risings, difficulties waking, and increased daytime fatigue as potentially manifested in napping may be equally important.

Early Morning

Early morning waking is common in children with advanced sleep-onset patterns, discussed elsewhere in this book. If a child is going to bed too early, this may be the most obvious cause for rising early in the morning. One method to assist with shifting the sleep pattern is trying to shift bedtime later. It is recommended that moving or fading bedtime/sleep onset later be done in 15 min increments every couple of days, to prevent the child from being overtired. Another important aspect to assist with minimizing early morning arousal involves ensuring the bedroom is sleep-friendly, including a comfortable temperature (less than 75°) [10] and room-darkening curtains or blinds. At the same time, family should open curtains or blinds for bright natural light to encourage wakefulness during periods that sleep should not occur. Some children benefit from use of a white noise machine or soft calming music to assist with muffling the sounds of pre-dawn garbage trucks, eager birds, or other external environmental noise that may interfere with the sleep environment.

Difficulty Waking

Children and adolescents who sleep for what appears to be an acceptable amount of time throughout the night but do not feel rested the next day may be slow to start in the morning or may present with excessive daytime fatigue. Difficulties with rising in the morning can be associated with numerous psychosocial and environmental factors, including staying up too late, poor-quality sleep during the night, developmentally inappropriate early school start times, school avoidance, stressful life events, psychosocial functioning, medication side effects, and irregular sleep-wake schedules. Other common causes involve sleep-disordered breathing (e.g., sleep apnea) or other medical difficulties (e.g., seizures). Important to note, children may not display obvious excessive sleepiness during the day but may instead seem more irritable, hyperactive, or inattentive [28]. These effects may be even more pronounced in children or adolescents with NDD.

Scheduling sleep and wake in children, including the duration of daytime naps and bedtimes, needs to take into account developmental, health, social, cultural, and economic considerations, as well the individual needs of families [13]. Every attempt should be made to both maintain sleep/wake regularity. For example, there should not be more than an hour's difference in bedtimes and wake times between weeknights and weekends. Even if a child goes to sleep late, the recommendation is to keep the morning routine and the morning wake time the same, or at least not more than 1 h later than the normal wake time. Although it may appear more humane to allow the child to "sleep in" and catch up on sleep, a regular wake time will prevent the sleep schedule from veering further off-schedule, as can happen when the child who sleeps in subsequently stays up later and later. Consistent sleep-wake schedules may be particularly important for children with NDD, because they are uniquely vulnerable to both sleep and circadian rhythm disruptions [13].

When children continue to have difficulty waking despite attempts to regulate their sleep schedules, caregivers may need to be creative in how they wake their child. Maximum light exposure should be provided (both natural daylight and artificial lighting), ideally slightly before the child's necessary wake time, to help promote wakefulness. Caregivers can also use the child's preferred items, such as

favorite music, television shows, or breakfast items, to motivate the child to wake. Finally, reinforcement programs can be used to reward the child for waking in a timely manner.

Morning routines can further benefit children who have difficulties waking in the morning. A structured morning schedule that is predictable, consistent, and expected can help ease transitions and start the day on a positive note. As with bedtime, it may be helpful to have a visual/picture schedule to assist with step-by-step guidance so that the child knows what happens next. Predictable morning routines tend to be most successful not only when a consistent arousal time is identified but also when the consistent routine (e.g., opening blinds, washing face, brushing teeth, brushing hair, etc.) is adhered to every day, including holidays and weekends.

Napping

Early morning wakings may also occur if a child naps too long or too frequently during the day. Adjusting nap times or gradually shortening nap times may also create sleep pressure and assist with consolidating sleep overnight. Nap patterns are usually established in infancy and often revolve around feeding schedules. Napping becomes less essential as a child becomes older; however, while napping continues, it is important to keep nap times on a regular schedule, waking significantly before the evening hours so as not to interfere with sleep onset at bedtime. Additionally, it is helpful to leverage napping in the association with sleep and bed; naps should be in the child's bedroom and bed whenever possible.

Children who are older and have outgrown the need for a daytime nap should avoid napping unless there is some circumstantial change (e.g., illness, medical condition) or an extremely early wake time for school (e.g., to accommodate a lengthy bus ride). In specific, certain children with NDD may require extra naps or longer nocturnal sleep than their typically developing counterparts. Some fatigue more easily and may fall asleep inappropriately several hours before their regular bedtimes. If this is the case, every effort should be taken to ensure that naps occur as early in the afternoon as possible and are restricted to 20–30 min.

Case Vignette: 3-Month Follow-Up

At Kyle's 3-month follow-up visit, caregivers reported significant improvements in sleep after following recommendations from the previous clinic appointment. Caregivers noted that tantrums at bedtime decreased. Additionally, after following the fading plan, caregivers no longer needed to rock Kyle in order for him to fall asleep, and he had been falling asleep within 15 min. He continued to wake overnight but was able to reinitiate sleep more quickly in his own bed. Furthermore, Kyle started falling asleep independently for naps.

Based on the family's success with prior behavioral sleep recommendations, ways to further improve independent sleep onset were discussed. Once Kyle was in bed, it was recommended that family start using "excuse me" drills to begin slowly and systematically increasing Kyle's opportunity to fall asleep independently. Caregivers were praised for their hard work and dedication to consistently implementing prior recommendations.

Areas of Uncertainty and Future Directions

While extensive research has been conducted on empirically supported behavioral sleep interventions for typically developing children [9], limited quality research has been published on the efficacy of these interventions in children with NDD [11, 24, 31]. Even fewer studies have been conducted on adolescents with NDD [32]. Likely some of this lack of research is due to the heterogeneity of sleep problems in a sample of children with NDD, making it difficult to implement standardized interventions across a sample. Additionally, children with NDD may present with a wide variety of behavioral and sensory concerns, further necessitating the individualization of interventions and making standardization of care challenging. Because of this need for individualization, the majority of studies of behavioral sleep interventions for children with NDD to date have been case studies or case series [8, 32], limiting the generalizability of findings.

When larger-scale studies have been conducted, findings are often variable regarding the intervention's success at addressing sleep concerns in children with NDD [11, 32–34]. In considering this difference in rates of success compared to typically developing peers, it could be hypothesized that comorbid behavioral or medical concerns or other unique characteristics of children with NDD could all play roles. However, there is currently no empirical evidence to say why these differences occur. Additional research is needed given the uncertainty of how well behavioral sleep interventions generalize to children with NDD, both as a group and studied in terms of specific diagnoses, and whether modifications to these interventions may be needed to improve their efficacy [e.g., 14, 31, 33].

Guidelines/Take-Home Tips

1. Addressing sleep hygiene is always a good starting point [13].
2. Individualization of interventions is key [8]. Behavioral sleep recommendations must be adapted not only to the child's individual sleep problems but also the factors maintaining them [35, 36].

Table 28.2 Summary application of behavioral sleep interventions

	Sleep initiation	Sleep maintenance	Parasomnias	Waking/morning
Sleep hygiene	X	X	–	X
Routines	X	–	–	X
Bedtime fading	X	–	–	–
Extinction	X	X	–	–
"Excuse me" drills	X	X	–	–
Graduated extinction with caregiver presence	X	X	–	–
Stimulus control	X	X	–	X
Scheduled waking	–	X	X	–
Reinforcement	X	X	–	X

3. When making recommendations, clinicians must be mindful that families of children with NDD often have many demands placed on them and their time. Because of this, paired with disrupted caregiver sleep, feasibility and caregiver satisfaction must be taken into account when suggesting interventions.
4. Behavioral concerns or medical conditions may also limit the implementation of any interventions that may lead to extinction burst or sudden escalation in behavior. Families may view behavioral interventions using gradual approaches as easier and more acceptable than interventions requiring abrupt change [24].
5. Given the multifaceted nature of sleep problems in children with NDD, no single approach is likely to show results, and multiple interventions including a variety of the previously mentioned behavioral interventions will likely be required to see the full treatment benefit (e.g., [32, 37, 38]). Table 28.2 provides a brief summary on when the application of strategies described in this chapter will be most helpful.
6. Consistency is key. Sleep problems likely developed over time and, because of this, may only resolve over time. Consistent implementation of behavioral recommendations over time is therefore required for success. Because of this, many families find it beneficial to work with an outpatient behavioral therapist or psychologist in order to receive ongoing support and help with problem-solving during intervention implementation.
7. Implementing behavioral sleep interventions with children with NDD is challenging, and the first try is not always successful. A multidisciplinary approach, incorporating both behavioral and medical, will likely improve chances of success.

Conclusions and Final Recommendations

Children with NDD exhibit behavioral, emotional, cognitive, and sensory-motor difficulties that impact their bedtime and wake-time behavior and sleep patterns. Problems with initiation of sleep, sleep associations, night wakings, parasomnias, early morning waking, difficulty waking, and daytime sleepiness are commonly seen in children with NDD impacting their daytime behavioral adjustment and emotional functioning. Abnormalities in circadian rhythms and disturbance in production of melatonin or other hormones or neurotransmitters may be physiologic contributors. Increased sensory sensitivity and lack of bedtime routine can also play roles.

Clearly more research is needed on the factors that individually or in combination can lead to difficulty initiating, reinitiating, maintaining, and awaking from sleep, as well as factors affecting ability to stay awake during the day. Whatever may be the origins of sleep disturbances in children with NDD, there is a preliminary body of research and growing clinical experience demonstrating that behavioral interventions can be helpful alone, or in combination with medical interventions, for treating sleep problems in children with NDD. Many of these interventions are modified versions of interventions that have been empirically validated with typically developing children. Large-scale research on interventions validated specifically for children and adolescents with NDD is sparse and still in its infancy. This is an important gap in the literature in light of the fact that individuals with NDD are at increased risk for medical, behavioral, and sleep problems. While improving sleep hygiene can greatly improve sleep patterns, it is typically not sufficient to solve all sleep problems, particularly for many children with NDD. Furthermore, children with NDD may have restricted interests or atypical responses to common forms of stimulation and activities. Therefore, careful and ongoing collaboration by medical and behavioral health-care staff with caregivers is required to address these additional challenges. The cumulative body of clinical experience known to medical, behavioral, and other health-care professionals has much to offer families toward solving behavioral sleep problems. Compiling this information in a useful format has been a major goal of this chapter.

One important conclusion from the available literature is that children do not automatically fall asleep in healthy ways. Healthy bedtime behavior and sleep patterns must be learned. Due to their unique risks, challenges, sensory, motor, and

behavioral characteristics, children with NDD may require more assistance from caregivers with this learning process. For these reasons, families with children having NDD may need to progress through a process of recognizing that a problem exists, identifying barriers to healthy sleep patterns, brainstorming and testing potential solutions, evaluating preliminary results, and fine-tuning efforts until they are successful. For a sleep-deprived caregiver, who may have other children to care for, this can be a daunting process. The sleep health of all children, especially those with NDD, should be monitored by primary care physicians to allow for early identification, caregiver guidance, and, when indicated, referral for specialized behavioral services to address sleep difficulties as early and efficiently as possible, before years of maladaptive sleep-related behavior patterns and caregiver-child interactions develop. Families often benefit from the assistance of a behavioral psychologist or therapist to support, encourage, and guide them through this process because it can take weeks or months to achieve sleep goals. Whatever environmental or behavior changes are to be implemented by caregivers, it is vital that they have to support and encourage to be consistent and to persist long enough for the child to have the opportunity to learn to behave differently. Unfortunately, all too often, exhausted caregivers become frustrated that changes do not occur immediately and abandon their efforts. It is also important to help them recognize problematic behavioral and sleep patterns early, as early intervention may prevent more complex behavioral sleep problems. Recommended intervention strategies may need to continue and remain consistent as the child develops since managing sleep in a child with NDD is often a long-term project. Therefore, it is important to help prepare caregivers for the ongoing job of helping their child develop healthy sleep patterns.

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Medications

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Lawrence W. Brown

Case Vignette

Melody, a 7-year-old girl with the known diagnosis of Smith-Magenis syndrome was referred for disrupted sleep. Following diagnosis at 14 months when she first presented with developmental delay, the initial treating child neurologist and parents worked diligently to entrain the sleep schedule and used melatonin since age 3. At presentation, bedtime was 8:30 PM with sleep latency under 15 min and only a single brief awakening before sleep offset at approximately 5 AM on an extended-release preparation of 3 mg melatonin given 30 min prior to lights out. However, her parents would frequently find Melody's light on at night. She would take daily brief "power naps" lasting 15–20 min in addition to occasional longer naps of 1–2 h that were equally restful and did not interfere with nighttime sleep. Polysomnography showed decreased rapid eye movement (REM) stage sleep and confirmed an early morning final arousal; there was no apnea or periodic limb movements (PLMS). New episodes of awakening with stiffness, tongue deviation, and right-sided posturing led to an overnight video EEG which did not reveal epileptiform activity but did not capture events of concern. Over the ensuing months, there were no further similar arousals. Behavioral challenges included hyperactivity, skin picking, and tantrums which persisted despite multimodal therapies in a self-contained special education class. Acebutolol was added at age 9 to her extended-release melatonin; this led to increased alertness during the day. For the first time, she needed to be awakened in the morning for school. While medication improved her chronobiologic disorder, she continued to have severe behavioral dysregulation which only worsened as she approached puberty. Sleep and behavioral issues deteriorated despite treatment with fluoxetine. Repeat polysomnography at age 12 now showed an elevated PLM index of 12 events per hour. Serum ferritin of <10 mcg/L was likely explained by heavy menstrual bleeding. Treatment with iron and birth control pills to control menstruation improved symptoms.

Introduction

Considering all of the challenges of raising a child with developmental disabilities, parents may have earned a pass if they try almost anything to encourage or enforce good sleep patterns. Physicians, therapists, and the blogosphere, as well as common sense, assure them that a good night's sleep is essential for optimal functioning, and it is clear to them that their child with a developmental disability is neither sleeping well nor functioning optimally. Parents also know that with their own sleep deprivation comes increased irritability and more anxiety, which they cannot afford. What to do? Even though there are few parents who want to expose their child to any medication, exhausted and desperate ones will try almost anything deemed safe and effective by "experts," whether based on strong clinical studies, limited evidence, or just anecdotal endorsement. This chapter will review the scientific basis, where it exists, for medication for sleep in this population. It will also outline the known safety and efficacy for both formulary and over-the-counter medications commonly used to promote smooth sleep initiation and maintain efficient sleep consolidation in children, especially those with developmental disorders. It must be acknowledged at the outset that few if any of these approaches are Food and Drug Administration (FDA) approved for the purpose of supporting sleep. Because many pediatric pharmacotherapies of

L. W. Brown
Neurology and Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, PA, USA
e-mail: brownla@email.chop.edu

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all sorts are not FDA approved for use in children, pediatric clinicians have long been familiar with this problem and comfortable enough weighing the data and outlining to families the pros and cons of off-label administration until more complete data become available.

Organizing a discussion of sleep disturbances in children with developmental disabilities is a major conundrum. While there are instances in which a particular clinical problem is highly associated with a specific disease state (e.g., sleep-disordered breathing and Down syndrome or chronobiologic disturbance in Smith-Magenis syndrome), the issues under discussion should not be limited to a recitation of genetic conditions – and not all children with these disorders are affected to the same degree. But it is equally important that a discussion of medications to treat a syndrome like periodic limb movement disorder (PLMD) emphasizes the association with attention-deficit/hyperactivity disorder (ADHD) in a book about children with developmental disabilities. This is true even if PLMD is not unique to ADHD, nor necessarily a major contribution to disability for many affected children with ADHD, or even true in the majority of children with the neurobehavioral syndrome. Indeed, none of the sleep-related challenges in children within the broad spectrum of developmental disabilities are unique to the presenting disorder. Therefore, the chapter will focus on medications commonly used for disorders of initiating and maintaining sleep, parasomnias, and their daytime consequence of excessive sleepiness – which is also rarely encountered as an independent symptom of its own. It will also try to provide an overview of the known effects on sleep for medications commonly used for other purposes in children with epilepsy, autism, and ADHD.

Before initiating a discussion of medications, it is important to remember that pharmacologic treatment should never be the goal but, rather, a temporary mechanism to achieve relief of symptoms. If a family comes for a consultation with a chief complaint that they need a medication (for any clinical problem), it is tempting to immediately eject them from the office. While that has never occurred in this clinician's practice, I do explain that it is the clinical concern that should be the chief complaint – which must then be put it into context and followed by a careful history and full examination, followed sometimes by laboratory studies where indicated – before a differential diagnosis can be developed. Only then can we discuss the strategies to address the problem, and only if medication is a reasonable option can we talk about the risks and benefits of drug treatment with specific goals and plans on how to monitor its outcome as part of a comprehensive plan.

Treatment of Insomnia

The lack of approved medications by the FDA has never stopped clinicians who treat children from prescribing medications or recommending nonprescription drugs. In one survey, more than 75% of primary care pediatricians surveyed recommended nonprescription medications for pediatric insomnia and greater than 50% had prescribed a medication specifically for sleep. After children with transitory indications such as acute pain and travel, the most common stated indication for usage was in children with developmental disabilities [1]. A survey of child and adolescent psychiatrists confirmed the common use of prescription or nonprescription medications for sleep among children with a variety of psychiatric disorders including developmental disabilities such as ADHD, autism spectrum disorder, and intellectual disability [2]. Antihistamines were the nonprescription medications most commonly recommended for treatment of insomnia in children, and alpha-agonists (especially clonidine) were the medications most frequently prescribed.

In 2004 the National Sleep Foundation in collaboration with Best Practice Project Management, Inc. convened a conference to evaluate the role of pharmacologic management of pediatric insomnia; results were reported in *Pediatrics* in 2006 [3]. While the discussion extended to all children, there was a specific focus on vulnerable populations, highlighting developmental disabilities, particularly neuropsychiatric disorders including ADHD, autism, epilepsy, and Tourette syndrome. The conference did not review evidence for specific drugs but rather outlined the problem, made recommendations for the design of clinical trials including ethical considerations when dealing with children, and discussed the priorities for future research. They pointed to autism spectrum disorders as having one of the highest priorities due to its prevalence, chronicity, and frequent lack of responsiveness to behavioral sleep approaches. Children with ADHD were also identified as another high priority group also due to the high prevalence and evidence that this group is the most likely receive off-label hypnotic therapy.

Another group of experts, many of them the same, had previously met under the auspices of the American Academy of Sleep Medicine in 2003 with representation from the American Academy of Pediatrics and the Food and Drug Administration; results were published in the Journal of Clinical Sleep Medicine in 2005 [4]. From the outset it was stated that any discussion of drug management must be prefaced by reinforcing the primary role of good sleep hygiene, with pharmacologic intervention largely considered adjunctive. The panel went on to describe the "ideal" hypnotic as one with high oral bioavailability, predictable kinetics, quick onset of action, and rapid metabolism – but sufficiently long to allow once nightly dosing without producing residual daytime sedation. This ideal drug would also have no effect on normal sleep architecture as well as no rebound, tolerance, or withdrawal with few side effects and no drug-drug interactions. Finally, this medication should be available in convenient doses and multiple formulations, including palatable liquids. It was concluded that in the absence of such a drug,

rational treatment must rely on the best match between clinical circumstances and the particular properties of the available medications. Again, the panel emphasized that medication should never be the first nor the sole strategy and should be used in the context of a comprehensive treatment program, except for very self-limited circumstances such as travel. Other important points included the fact that sleep problems in infants and young children are almost always related to asynchrony between the child's sleep development and parental expectations, so that medication is rarely, if ever, indicated. Adolescents should be screened for substance abuse and pregnancy prior to initiation of therapy since many recreational substances have synergistic properties when combined with hypnotics, and hypnotics are potentially harmful to developing fetuses. All patients need to be screened for concurrent use of over-the-counter remedies since some contain similar ingredients under different brand names, and there are also potential drug-drug interactions. Medications should be prescribed only for short-term usage (i.e., without refills) unless there is reassessment of target symptoms and evaluation of patient adherence with both the behavioral as well as pharmacologic plan.

As with the later panel, the experts noted that sleep disturbances were a prominent part of the lives of many children. Across a variety of neuropsychiatric and medical conditions, they emphasized contributions of family stress, caregiver interactions, peer relations, medical needs, sedating or activating medications, physical challenges, and psychiatric comorbidities. They pointed to common situations such as pain or abnormal motor activity that could cause insomnia. At the same time, they recognized that children with developmental disabilities were prone to the same emotional, behavioral, medical, and circadian sleep disorders as typically developing children, so that more common causes of insomnia also need to be primary considerations even in this vulnerable population.

Still, children with neurologic disorders and specific genetic, psychiatric, or behavioral syndromes can be predisposed to particular types of insomnia. Total blindness is associated with free-running circadian disorder. Smith-Magenis syndrome includes a disruption of normal circadian melatonin release leading to poorly organized sleep patterns. Williams syndrome appears to have a higher incidence of periodic limb movement disorder. Rett syndrome has prolonged sleep latency and fragmented sleep. Children with ADHD often have sleep onset and maintenance insomnia which can correlate with obstructive apnea, periodic limb movement syndrome, or stimulant medication rebound. As previously stated, none of these associations are diagnostic nor are all children with proven genetic conditions as listed above affected. However, at the very least, it helps families (and clinicians) to have an increased level of suspicion and to recognize early if there are symptoms of sleep disorder, in order that a full evaluation must address this common association. It is worth reiterating that those with developmental disabilities are not immune to the common disorders that affect neuro-typical children; evidence from systematic reviews suggests that most pediatric sleep problems respond well to behavioral treatments, and these should be tried first before embarking on a course of medication [5].

Medications Commonly Used to Treat Insomnia

Melatonin Receptor Agonists

Melatonin

Although not a prescription drug and widely available even in supermarkets, there have been more placebo-controlled trials for melatonin in the treatment of pediatric insomnia than there have been for any sleep-promoting drug licensed by the FDA. Its use was first popularized in the 1990s in children with intellectual disability, and it has been a mainstay of treatment for pediatric clinicians, not only for children with ADHD and autism spectrum disorders but for typically developing children as well.

Melatonin, also discussed in Chapter 31, has relatively short-acting sleep-promoting properties, with a half-life of approximately 1 h. This makes it much more effective in treating initial insomnia than sleep maintenance insomnia or terminal insomnia. It is best administered approximately 30 min before lights out, and it works best when timed with normal circadian rhythms; therefore, it should be used in the evening and not at other times of day. Appropriate dosing of this exogenous hormone therapy is hard to gauge, not only because it is unclear how much is absorbed, but ready access to unregulated distribution without FDA oversight means that there is little quality control; outside analysis has shown that some pills contain far less or none of the active ingredient. Melatonin is thought to be sedating in dosages of 1 mg or more; the most commonly available form may be a 3 mg tablet, although many formulations and doses are available. Most research studies have used doses of 2.5–10 mg when treating initial insomnia, but doses as low as 0.5 mg have been clinically effective, and as high as 15 mg have proven safe without evidence of significant adverse events in children with severe neurodevelopmental disabilities [6].

There have been few adverse effects from melatonin except for occasional reports of enuresis, depression, and excessive daytime somnolence. A single small series reported as a letter to the editor raised the specter of increased seizures in children with profound developmental delay and epilepsy, but this has never been replicated, and the actual report is sketchy without mention of concomitant medications, EEG confirmation, or even precise dose of melatonin [7].

Melatonin has been widely studied in a variety of neurodevelopmental disorders for more than two decades [8]. These studies have mostly described small populations and have been open label without confirmation by measurements of the hormone or its metabolites. Increasingly, there have been more rigorous investigations in various populations. A study endorsing melatonin's safety and efficacy was performed in medication-free children with ADHD and sleep difficulties using a placebo-controlled, double-blind model with outcome measures that included actigraphy and salivary melatonin levels [9].

There is a randomized, double-blind, placebo-controlled crossover study of children with autism spectrum disorder and/or fragile X syndrome whose parents reported significant sleep disturbance. While the study supported the efficacy and tolerability of melatonin treatment, the design had structural flaws, and there was considerable data loss and poor compliance in some participants [10]. More recent studies looking at salivary melatonin and urinary metabolites of this hormone demonstrated the feasibility of the approach, but at this time the high interindividual variability of diurnal melatonin concentrations challenges clinical application [11].

There are some unique situations in which melatonin can be directly therapeutic. Melatonin can be extremely effective for children with total blindness who have a free-running cycle which typically progressively delays their sleep-wake schedule over time, leading to periods of severe dissonance between their need to sleep and the environmental expectations. It can be very frustrating for a child to be up all night and unable to stay awake at school; melatonin can be used to help entrain their circadian rhythms as demonstrated in adults [12]. Another condition is Smith-Magenis syndrome, in which children have a major sleep disturbance with a phase shift of the circadian rhythm of melatonin and a paradoxical diurnal secretion of the hormone. In one study, treatment with melatonin at night (6 mg) followed by the beta-adrenergic antagonist acebutolol (dosed at 10 mg/kg) in the morning significantly improved sleep onset, reduced nocturnal awakenings, increased sleep duration, and delayed sleep offset in the morning [13]. While there have been no double-blind controlled trials in the disorder, melatonin, with adjunctive acebutolol if necessary, has become widely accepted and standard of care [14].

While most research reports of melatonin usage have studied the immediate release preparation, there are also extended-release formulations, including one which is approved for marketing in the European Union. In one study of the long-term effectiveness and safety, 88 children with severe neurodevelopmental disorders including Smith-Magenis syndrome, autism, Rett syndrome, tuberous sclerosis, intellectual disability, and other disorders were studied over 6–72 months. Within 3 months, subjects showed a significant reduction in sleep latency and nocturnal awakenings, increase in sleep duration, and a dramatic improvement in sleep quality reported by 90% of parents, without serious adverse events or treatment-related comorbidities. Still, the study was limited by the open-label design and had no objective measures of sleep such as polysomnography or actigraphy and there was absence of a placebo control group [15]. Subsequently, a much larger study employing similar rigorous structure confirmed the value of the extended-release preparation of melatonin. In this recent report on 125 children and adolescents with autistic spectrum disorder and Smith-Magenis syndrome (SMS), they only enrolled those whose sleep failed to improve on behavioral intervention. This trial included sleep measures using a validated caregivers' sleep and nap diary and a composite sleep disturbance index. After 13 weeks of double-blind treatment, participants slept on average 58 min longer at night with extended-release melatonin compared to 9 min on placebo. Sleep latency decreased by 40 min on average versus 12.5 min with placebo [16].

Ramelteon

Ramelteon is a melatonin receptor agonist, the first of its class, approved for use in adults in the treatment of insomnia. Its package insert lists no restriction on duration of use. Selective binding to melatonin receptors promotes sleep and helps to maintain a normal sleep-wake cycle. Although the half-life is only 1–2.5 h, there is an active metabolite. There is one available pill (8 mg) which is FDA approved for adults only, and off-label use in children may require smaller doses. Common side effects include dizziness, nausea, daytime somnolence, and fatigue. The only commonly expected drug-drug interaction is with fluvoxamine, since that medication inhibits CYP1A2. This is the same pathway for ramelteon's metabolism, so concurrent use can lead to dramatic increases in ramelteon levels. While not approved for children, there is at least one small report describing its effectiveness in children with autism [17].

Antihistamines

Diphenhydramine

Of all medications provided to children with difficulty in settling, diphenhydramine is one of the most popular, yet the scientific basis for its use is among the weakest. This competitive H1 histamine receptor blocker has multiple effects on the central and peripheral nervous systems including sedative and hypnotic, as well as antiallergic, antiemetic, and antitussive properties. It is rapidly absorbed from the gastrointestinal (GI) tract with peak levels within 2 h; the drug affects a wide range of physiologic functions including arousal, cognition, and memory through interactions with H1 receptors in the posterior hypothalamus. Diphenhydramine

has been evaluated in both adults and children, and it produces a decrease in sleep latency and the number of awakenings with an average duration of effect lasting 4–6 h. Dose is generally up to 1 mg/kg with a maximum of 50 mg. When it was studied in infants aged 6–15 months whose parents reported frequent night awakenings, the trial had to be stopped early because it was ineffective: only 1 of 22 children on active drug improved compared with 3 of 22 who received placebo [18]. Even when apparently effective, use of this drug often leads to tolerance, with need for increasing doses and consequent increase in side effects [19]. Safety issues with this popular over-the-counter approach are often not discussed, but overdoses are not uncommon. Anticholinergic side effects include blurred vision, dry mouth, constipation, urinary retention, tachycardia, pupillary dilatation, constipation and urinary retention, dystonia, and confusion. More severe adverse reactions can include stupor, anxiety, and visual hallucinations with rare cardiac rhythm disorders and seizures. There have even been rare lethal consequences, including one report from accidental overdosage [20].

Hydroxyzine

This piperazine antihistamine is a prescription drug which exerts its sedative effects like diphenhydramine through H1 receptor blocking properties with minimal effects on sleep architecture. Although there are multiple reports on the use of the drug for anxiety disorders, there are no direct studies that address its use for sleep promotion. However, it has been compared with chloral hydrate (see below) as a sedative for use in procedures such as EEG [21]. These authors, based in Turkey where both drugs are still commonly employed routinely as sedatives, demonstrated that both drugs worked equally well in promoting rapid sleep onset. General dosing recommendation for use as a hypnotic or anxiolytic is 0.5–1 mg/kg/dose.

Chloral Hydrate

While chloral hydrate has lost its popularity in the United States as a sedative and hypnotic, it is still widely available around the world. In the past, its apparently benign safety profile with significant sleep promotion and little respiratory or cardiovascular toxicity made it one of the most common medications for insomnia given to children. It is rapidly absorbed from the GI tract and converted to trichloroethanol which is a powerful central nervous system (CNS) depressant with a half-life of 8–12 h in children and adults and significantly longer in infants and children. Even though typical therapeutic doses of 20–50 mg/kg/dose usually have little adverse effect, children with obstructive apnea, white matter disease, and brain stem disorders are at particular risk for respiratory compromise. Overdoses can lead to respiratory depression, stupor, and coma as well as cardiovascular instability [22].

Clonidine

The only FDA-approved indication for this alpha-2-adrenergic agonist for developmental disabilities is ADHD in children, and it is approved only in an extended-release preparation. Notwithstanding this bureaucratic limitation, clonidine was still the second most commonly used medication for treating sleep difficulties (after antihistamines) according to a large survey of 800 pediatricians in four states across the United States [23]. A recent review of the use of clonidine in the pediatric population focused on its use in children with various developmental disabilities [24]. Furthermore, clonidine was the most widely used medication to treat insomnia according to a survey of child and adolescent psychiatrists [25].

Clonidine was first marketed for the control of hypertension, and it is still occasionally used for that purpose. From its first use, it manifested the common side effect of sedation, and early studies demonstrated that it was associated with relatively normal sleep architecture except for REM suppression. Its serum half-life is long (6–24 h), but its peak effects for sleep generally last only 2–4 h. Side effects include hypotension, bradycardia, and anticholinergic properties such as dry mouth. Sudden discontinuation can lead to rebound hypertension and REM rebound. Most clinicians start with 0.05 mg at any age and increase in 0.05 mg increments, although there is no clear recommended hypnotic dose. A small case series gives examples of the value of clonidine in children with a variety of developmental disorders [26]. The drug has also been studied in children with autism with two-thirds of patients having a positive response at 0.1 mg in an open-label retrospective review [27].

The frequent coexistence of sleep problems in children with ADHD led to its off-label popularity as a treatment, as well as the finding that adrenergic drugs showed efficacy in treatment of ADHD long before regulatory approval of an extended-release clonidine for this indication [28]. Caution is advised in this population because there have been reports of serious cardiovascular side effects when clonidine is co-administered with stimulants [29, 30].

Benzodiazepines

There is a long history of various benzodiazepines being used for adults and children with insomnia and parasomnias. The reputed mechanism is through activation of GABA-A receptors which can lead both to drowsiness and reduced

anxiety. Despite decreased arousability, people taking benzodiazepines show a reduction in deep non-REM (stage N3 or slow wave) sleep. The two most commonly prescribed benzodiazepines for children are clonazepam and diazepam, both of which are among those in this class with the longest half-lives. Clonazepam is a far more effective chronic antiepileptic medication than diazepam, and it can be used for both seizure control and sleep promotion. Both drugs can be effective in treating non-REM parasomnias, including night terrors and sleepwalking. Other benzodiazepines are rarely used, mostly because of extremely long half-lives (flunazepam) or, conversely, such short half-lives that rebound arousals in the middle of the night are common (temazepam, estazolam, and triazolam). Among the concerns about using this class of drugs is the effect of muscle relaxation in children with obstructive and central sleep apnea. This class of medications should be avoided in children with sleep-disordered breathing because they blunt the arousal response to hypoxemia and can thus worsen apnea.

Non-benzodiazepine Hypnotics

There have been few studies of the use of non-benzodiazepine hypnotics in children, none of which are approved for use in individuals below 18 years old. They are widely used for insomnia in adults and not infrequently prescribed off-label to children. These drugs include zolpidem (Ambien), eszopiclone (Lunesta), and zaleplon (Sonata). This class of drugs is an improvement on benzodiazepine hypnotics because they allow normal sleep architecture and have a lower incidence of rebound effects when abruptly stopped. Still, they are not intended for nightly use lasting more than a few days. All of these drugs have a similarly rapid onset of action with significantly shortened sleep latency, but zaleplon has the shortest half-life (1 h) and typically only helps sleep-onset insomnia. Even zolpidem, with a half-life of 2.5 h, may allow for continued arousals at night, but an extended-release preparation is now available which can provide all-night coverage. Since many children with insomnia have sleep-onset difficulties only, it may be clinically acceptable to add a brief course of a non-benzodiazepine hypnotic to a behavioral regimen for an adolescent with a condition like delayed sleep-phase syndrome; however, this is more likely to run the risk of morning sedation or of rebound insomnia when the drug is stopped. Since there is evidence that tolerance to the drug does not occur even after 6 months of nightly exposure, eszopiclone has been FDA approved for long-term use in adults [31].

There is limited pharmacokinetic information about the use of zolpidem in children ranging in age from 2 to 18 years which showed efficacy and tolerability. Based on a single pediatric pharmacokinetic study, the recommended pediatric dose is 0.25 mg/kg with a maximum dose of 20 mg [32]. A placebo-controlled double-blind study of children with insomnia and ADHD found no effect: there was no improvement in sleep latency between the active compound and placebo, but there were more complaints of dizziness, headache, and hallucinations with zolpidem [33]. Eszopiclone has a longer half-life of 6 h, but there are no studies that describe its safety or efficacy in children.

Sedating Antidepressants

Trazodone (Desyrel) and mirtazapine (Remeron) are occasionally used to achieve sleep. Both are atypical antidepressants which are often sedating even at doses lower than typically used for the FDA-indicated symptom, but neither is approved for any purpose in children or adolescents. Trazodone is a serotonin 5-HT_2 receptor antagonist that promotes sleep by inhibiting uptake of serotonin and blocking histamine receptors. Mirtazapine is a histamine H1-receptor antagonist which reduces sleep latency and increases sleep duration without significant effects on REM. Both can lead to daytime sedation. The common side effects of trazodone are dizziness, vision changes, constipation, and dry mouth; rare complications can include exacerbation of seizures, cardiac arrhythmias, hypotension, and priapism. The most common side effect of mirtazapine is weight gain. Dizziness, constipation, and dry mouth are also frequently seen.

Other antidepressants including paroxetine (Paxil), amitriptyline (Elavil), and imipramine (Tofranil) may also have sedating properties. Although paroxetine is among the most sedating of the SSRIs, it should be avoided in children and adolescents because of the risk of suicidality. The use of antidepressants for sleep difficulties complicating mood disorders requires careful consideration of the type of sleep problem from insomnia to daytime sleepiness or co-existing primary sleep disorder such as obstructive apnea or PLMS. It is not uncommon for sleep difficulties to respond to effective treatment of the primary mood disorder, and at other times treating the sleep problem can significantly improve mood symptoms. In addition to mood disorders, these medications are commonly used for migraine prophylaxis (amitriptyline) and uncommonly for ADHD (imipramine).

Neuroleptics

The use of atypical neuroleptics including risperidone and aripiprazole has been approved to treat aggression in children with autism. Randomized controlled trials noted adverse events including drowsiness and somnolence, and in fact, these were the most commonly noted side effects occurring in twice as many subjects in the risperidone arm compared to placebo (24% vs 12%) in one pivotal study [34]. Typical and atypical antipsychotic drugs are also used off-label for similar behavioral problems in children with other

developmental disabilities. Since there is often a calming effect in addition to sedation in some that allows children to settle more effectively, some clinicians have tried these drugs to help with sleep in children. However, there is no evidence on safety or efficacy in the neurologically typical child and only anecdotal information about its effect on sleep in autism. Risperidone has been shown to increase non-REM sleep (both N2 and N3) and to suppress REM sleep [35]. While these medications may help children to fall asleep and the known effects on sleep architecture are favorable, their routine use is strongly discouraged since there is little on the safety and tolerability for short-term use as well as the long-term risks for gynecomastia, tardive dyskinesia, and other unknown consequences. It is also important to recognize the risk of weight gain with this class of medication which could significantly worsen any underlying sleep apnea.

Herbal Supplements

There is widespread usage of complementary sleep aids which are generally believed to have an acceptable safety profile, but none have been studied in children, and the data are generally weak in adults. A review of the available evidence for the sleep-promoting qualities of herbal supplements was carried out by the American Academy of Sleep Medicine in 2004. Although there were few randomized placebo-controlled studies, rigorous scientific data supporting safety and benefit were lacking for the majority of nutritional supplements. Available studies were limited by small studies with inadequate design, no objective measurements, and lack of statistical analysis [36]. There was no evidence for chamomile or St. John's wort. Limited, conflicting studies showed possible value for the short-term use of valerian. This plant derivative was studied in children with intellectual disability in a randomized double-blind, placebo-controlled fashion, with positive results, but the total n was only 5 [37]. The AASM review cited the significant potential risks associated with Jamaican dogwood, kava kava, alcohol, and L-tryptophan. Although L-tryptophan was quite popular at one point, it is no longer available following cases of eosinophilic myalgia syndrome attributed to contamination during the manufacturing process. Proponents of complementary and alternative medications have recommended herbal supplements such as lavender applied as aromatherapy, but they have never been systematically studied [38].

Treatment of Excessive Daytime Sleepiness

As important as the caveat about not treating insomnia with a pharmacologic approach before comprehensive investigation of the causes and initial behavioral management, it is even more urgent applied to daytime somnolence in the patient population with developmental disabilities. One should never treat a symptom like sleepiness with medication until it is clear whether the child is getting adequate amount and quality of nocturnal sleep, whether there is a sedating medication, or if the child is sleepy as a consequence of post-ictal lethargy or unrecognized seizures. Daydreaming or emotional withdrawal from the environment can be interpreted as sleepiness. Physically limited children may be so under-stimulated at times as to fall asleep during the day, a problem that can be further compounded by misinterpretation since they may not sleep well at night resulting from their total daily sleep requirement being partially met by daytime sleep such that their nighttime sleep is fragmented. Perhaps the most common cause beyond inadequate amount of nocturnal sleep – an epidemic problem affecting more than half of US adolescents and a third of younger children – one must consider primary sleep disturbances such as obstructive apnea and periodic limb movement disorder [39]. Only after all of these are first addressed is it reasonable to consider if medications may be necessary to supplement behavioral approaches, such as with narcolepsy. Please see also Chapter 8 for additional discussion, especially as regards treatment of narcolepsy.

Modafinil

This non-stimulant alerting agent has become the first-line approach for excessive daytime sleepiness associated with narcolepsy because of its safety and side effect profile [40]. Its mechanism of action appears to be different from methylphenidate or amphetamines, and it is hypothesized that it works on hypothalamic wake-promoting centers. Well-controlled trials in adults with narcolepsy have demonstrated improvements in wakefulness and objective measures of sleepiness in narcoleptic individuals. The half-life of 10–12 h allows for once- or twice-daily administration (usually morning and noon) at doses of 200–400 mg. Experience has demonstrated very low abuse potential or rebound increase in sleepiness. While still off-label in children, there are reports in children with narcolepsy demonstrating effectiveness [41]. Armodafinil, the R-enantiomer of the parent compound, has a longer half-life and can enhance wakefulness with a single daily administration at doses of 150–250 mg daily.

Stimulants

Methylphenidate and amphetamine preparations have largely been supplanted by modafinil for the treatment of daytime sleepiness in narcolepsy due to its better safety profile. The non-stimulant results in much less irritability, anxiety, tachycardia, increased blood pressure, appetite suppression, and nocturnal sleep disturbance. However, many of these negative

attributes were described when the only available preparations were short-acting. Longer-acting, smoother delivery systems such as various proprietary extended-release forms of methylphenidate (e.g., Concerta, Daytrana, and Quillivant XR), dexmethylphenidate (e.g., Focalin XR), and lisdexamfetamine dimesylate (e.g., Vyvanse) can generally provide the same degree of wakefulness as modafinil with minimal side effects. Pharmacologic treatment in general is well outlined in a review from the American Academy of Sleep Medicine [42].

Kleine-Levin Syndrome

In discussing neurologic disorders producing daytime somnolence, it is important to highlight this rare sleep disorder which primarily affects adolescents. It is characterized by episodes of severe hypersomnia, cognitive impairment, apathy, and psychiatric disturbance. Most have specific feelings of derealization and eating disturbances with a large minority expressing hypersexuality, compulsions, and depressed mood. Treatment has been mainly symptomatic with stimulants, neuroleptics, or antidepressants, but these rarely help. Only lithium had a higher reported response rate for preventing relapses in one very large review [43]. In a more recent review, carbamazepine, valproate, and other anti-epileptic drugs were still favored by many clinicians [44].

Treatment of Restless Leg Syndrome and Periodic Limb Movement in Sleep

The distinction between restless legs syndrome (RLS) and periodic movements in sleep (PLMS) is discussed elsewhere in Chapter 10, but it should be noted that the distinction is often difficult in children, who are typically unable to describe the subjective discomfort that defines RLS. It is common to rely on evidence of associated PLMS to support suspicion of RLS in children. Either or both related conditions can disturb consolidated night sleep and lead to daytime sleep deprivation that can cause sleepiness; they can also mimic or contribute to symptoms of ADHD.

Medications Used to Treat RLS and PLMS

Iron Supplementation

Iron depletion as defined by low serum ferritin can lead to both RLS and PLMS. The mechanism appears to be the local deficiency of iron necessary as a cofactor for tyrosine hydroxylase, the first step in dopamine synthesis. It took time for this to be appreciated, since there is a wide range of serum ferritin levels in the unaffected population, but clinical improvement is often seen in symptomatic individuals whose ferritin is less than 50 mcg/ml – even those who are normocythemic – when given iron supplementation [45, 46]. The usual dose is 3 mg/kg/day of elemental iron divided twice daily in non-anemic individuals with a goal to bring serum ferritin up to 50 mcg/ml [47].

The relationship between developmental disabilities and sleep problems may have subtler and poorly understood connections. For example, children with autism often have restricted diets and gastrointestinal symptoms in addition to sleep onset as well as sleep maintenance insomnia. Whether due to narrow food choices or malabsorption, children with these problems would be at risk for iron deficiency. Although anemia is uncommon in this population, at least one group has looked at ferritin levels and found a remarkable incidence of insufficient dietary iron intake, particularly in preschool children, with extremely low ferritin levels (mean 15.7 mcg/L) at baseline. Treatment over 8 weeks increased mean ferritin levels significantly and improved restless sleep [48]. Unfortunately, the methodology was limited, and did not include objective measures to monitor PLMS by polysomnography, and it is unclear whether sleep questionnaires could adequately identify the presence of restless legs or periodic limb movements in this population. The study was limited in scope, both in sample size, duration of treatment (inadequate to bring ferritin levels above 50), and objective outcome measures, but it is very provocative and suggests further lines of research.

Selective Dopamine Agonists

Drugs such as pramipexole (Mirapex), ropinirole (Requip), and pergolide (Permax) have become the standard treatment for adults with RLS and PLMS. They are more powerful and require lower doses than direct dopamine precursors such as L-dopa. Well-designed studies have only been carried out in adults, and there is little evidence base in children and adolescents beyond case reports. If these drugs are used, it makes sense to follow the guidelines for adults, start with the lowest possible dose, and make gradual changes no more than weekly in order to find the lowest effective dose and avoid unnecessary side effects. As with other treatments for sleep disorders, there are no FDA-approved medications for pediatrics. However, experience has been summarized in a recent comprehensive review article [46].

Treatment of Parasomnias

Parasomnias, discussed in detail in Chapter 7, are abrupt events that disrupt the sleep-wake interface – either during entry into sleep, within sleep, or during arousal from sleep. They can be frightening both to children and caregivers and may be confused with other paroxysmal phenomena includ-

ing seizures and panic attacks. While most common in preschool aged children, they tend to occur infrequently, and it is unusual to have more than one event per night or on a daily basis. It is believed that there is a genetic predisposition which allows activation of subcortical central pattern generators to respond to external (e.g., ambient noise) or internal (e.g., reflux, fever, epilepsy, PLMS, apnea) stimuli, leading to the instability of the arousal mechanisms resulting in behaviors from somniloquy to full pavor nocturnus or night terrors. Children with developmental disabilities may have many reasons for immaturity of their sleep-wake system in addition to being prone to the very disorders just listed that can trigger disruption and parasomnias. Since parents are already concerned about their children's neurodevelopmental status, it is not hard to imagine why they might leap to the conclusion that such nocturnal arousals have a more serious basis such as seizure. According to one study, disruptive parasomnias in children should trigger an evaluation for a precipitating cause. In a large case series of 84 children with sleep terrors, 58% had sleep-disordered breathing, and partial arousals disappeared with treatment [49]. The pathophysiology and differential diagnosis of parasomnias are discussed in more detail elsewhere. This section will only discuss the treatment of non-REM parasomnias, which are the most common. It should be noted that all pharmacologic approaches to parasomnias are off-label since there are no approved agents for any of these disorders.

Treatment of infrequent sleep disruption caused by sleepwalking, confusional arousals, and sleep terrors obviously requires understanding, support, and environmental protection to avoid injury. However, infrequent events typically do not need to be treated. Parents are usually reassured that events can be minimized by avoiding sleep deprivation with a regular schedule including adequate nap time and by the fact that most toddlers will outgrow their tendency to experience parasomnias. In cases where parasomnias are frequent or atypical events or additional reassurance is needed, full polysomnography with 16-channel EEG is recommended to clarify the (unlikely) differential which includes seizure disorder, apnea, or PLMS.

Medications Commonly Used to Treat Non-REM Parasomnias

Benzodiazepines

There have not been any formal studies of benzodiazepines or other medication treatments in non-REM parasomnias, but expert consensus suggests pharmacologic treatment if no specific treatable triggers can be found and the events are problematic. This includes low-dose benzodiazepines at bedtime, such as clonazepam at doses ranging 0.125–0.5 mg. Potential side effects such as drooling and paradoxical hyperactivity may be particularly troublesome for children with neurodevelopmental disabilities [50].

The mechanism of action is believed to be based on benzodiazepines' GABAergic effect. This can improve the situation by reducing the depth of N3 sleep from which non-REM parasomnias arise and by decreasing arousability. It is important to first be sure that one is not missing a secondary form of parasomnia due to obstructive sleep apnea, since decreasing arousability could lead to longer events with more profound desaturations. It is also important to choose medications with optimum durations of action, since a drug with too long of a half-life can lead to morning sedation or irritability and a drug with too short of a half-life can delay undesired events until later in the night without actually eliminating them. Clonazepam probably has the best track record [51]. Its time-to-peak action is 1–3 h, which coincides with the usual timing of non-REM parasomnias, and duration of action is typically 6–8 h in children and up to 12 h in adults, even though the half-life of the drug is typically longer than 24 h. In recent years, clonazepam has become more convenient, with oral dissolving tablets in sizes ranging from as small as 0.125 mg to as large as 2 mg. Some clinicians find comparable efficacy with diazepam in doses from 2.5 to 10 mg. It is often too long acting for adolescents, but more rapid metabolism in younger children makes it a reasonable option without causing a hangover effect. Although not available as a dissolvable tablet, it has the advantage of being available as a suspension for children unable to swallow pills.

Other Medications

There are case reports of other drugs being effective for non-REM parasomnias. Paroxetine was effective in an adult with a 30-year history of night terrors, although most pediatric clinicians would avoid this drug in children due to its higher rate of suicidal ideation compared to other SSRIs [52]. Another isolated case report described remarkable improvement with trazadone in a 7-year-old child with sleep terrors [53].

Chronobiologic Disorders

Although these neurologic disorders will be discussed in Chapter 9, it is worth mentioning the challenges presented by children with congenital blindness and Smith-Magenis syndrome. The former may not be able to form a sleep-wake cycle due to lack of input to the hypothalamic centers. The latter was already briefly discussed in the section on melatonin treatment due to its inverted pattern of melatonin secretion leading to a characteristic circadian sleep disorder in addition to dysmorphic features, developmental delays, and behavioral difficulties. The disrupted sleep pat-

tern can be so severe that it is what first brings children with Smith-Magenis syndrome to medical attention [14].

Treatment with nightly melatonin with a morning beta-adrenergic blocker, when necessary, has proven to be effective to control sleep schedule in many children, with beneficial secondary effects on behavior as well [54]. Melatonin was given in doses up to 15 mg at night, and acebutolol 10 mg/kg was given in the morning. This led to more organized, stable sleep architecture with improved N3 and REM sleep percentages as well as elimination of daytime naps, marked reduction in tantrums, and generally improved behavior. Other specific disorders with melatonin secretion abnormalities have also been studied: for example, Angelman syndrome has been shown to have low-peak melatonin levels in addition to a phase delay in nocturnal melatonin release [55].

Conclusions

While sleep disorders in children with neurological disorders are even more common than in the general population, there is still a lack of comfort with their management voiced by many pediatricians, neurologists, and developmental specialists. This is partly due to the minimal training in sleep medicine many receive during training. In addition, many well-meaning clinicians are intimidated by the dearth of well-designed trials to demonstrate safety and efficacy leading to the lack of FDA approval of drugs for children. Reliance on adult data and anecdotal experience are often inadequate. Without a clear evidence base and the absence of FDA-approved medications for specific sleep disorders in children, it is no wonder that pediatric generalists and specialists are reluctant to recommend drugs and unsurprising that parents and caregivers wind up using over-the-counter preparations and complementary-alternative approaches that have even less scientific credibility. However, as a society, we are coupled with the twin epidemics of obesity (leading to increased prevalence of sleep-disordered breathing) and inadequate sleep (attributed to factors from lifestyle choices to school hours and excessive light exposure at night). Therefore, it is incumbent on all involved in the care of children to advocate for improved knowledge of sleep as well as more effective treatments.

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Exercise, Weight, and Sleep

30

Andrea Heyman

Case Vignette

Henry is an 11 year 6 month old boy with a history of sleep disturbance, autism spectrum disorder (ASD), mixed receptive-expressive language disorder, ADHD, and anxiety disorder. He has difficulty falling asleep and becomes anxious when he can't fall asleep. He does not use electronics around bedtime. Generally, he falls asleep between 10 PM and 12:30 AM, although sometimes he stays up until 2 AM. He stares at the ceiling, frustrated because he can't fall asleep. Even after falling asleep, Henry wakes in the middle of the night and has difficulty falling back to sleep. He always falls asleep in the car and also during reading class at school before midday. He has had snoring and no witnessed apneas. There is no history of parasomnias. Henry does not exercise regularly and spends most of his free time playing video games or on his tablet. His diet is very limited: he prefers fast food and convenience foods, and he won't eat vegetables. He drinks sweetened beverages such as soda and juice daily. His most recent growth parameters are as follows:

Weight (kg)	%ile	Z score	Height (cm)	%ile	Z score	BMI	%ile	Z score
80.1	>99	2.76	162.5	98.0	2.16	30.3	99.0	2.3

Evidence Base

Exercise

The Physical Activity Guidelines for Americans indicate that youth should have 60 minutes of physical activity a day, most days of the week [1]. Participation in play, sports, and recreation helps build and maintain healthy bones, muscles, and joints [2]. Regular physical activity benefits youth physiologically and psychosocially, improving bone density, muscle tissue, and maintenance of body weight and also reducing depression and social isolation [3].

Studies show that children and adolescents with intellectual disabilities have lower levels of physical fitness when compared with their typical peers [4–6]. Others indicate that children with ASD fail to meet the recommended amount of moderate-to-vigorous physical activity [7, 8]. This decrease in activity may be due to cognitive, physical, or social limitations [9]. Weak social and communication skills can impede participation in various physical activities [4]. Parents of children with ASD report barriers to physical activity participation: their child may require too much supervision; adult coaches lack skills needed to include their child; their child has few friends; and other children exclude their child [10]. Some communities offer fitness programs specially tailored to children with special needs; however, many communities do not have the resources to offer such programing [11], while others do not have the resources to match demand. Despite efforts to improve physical activity accessibility for this population, children with disabilities have lower levels of cardiorespiratory fitness and muscular endurance, and higher rates of obesity, than their typically developing peers [12]. Must et al. emphasize the need for physical activity programs designed to meet the needs of children with neurodevelopmental disabilities [13]. Until these needs are met, children with neurodevelopmental disabilities may continue to experience decreased physical fitness measures, potentially increasing their risk of developing cardiovascular disease in the future.

A. Heyman
Nutrition, Kennedy Krieger Institute, Baltimore, MD, USA
e-mail: Heyman@kennedykrieger.org

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Case Vignette

Henry's parents have tried signing him up for several team sports like soccer, baseball, and lacrosse over the years, but these did not go well. Henry had a hard time grasping the rules of the game. Socially, he did not interact or fit in with his teammates and he needed more supervision than was available in order to participate in programs [14]. Over time, Henry's parents gave up and allowed him to pursue his preferred, sedentary activities such that he does not engage in regular physical activity.

Exercise and Sleep

A strong relationship between exercise and sleep in adults has been documented. Studies show an association between self-reported exercise and better sleep in adults [15–18]. Positive effects of exercise on sleep such as shorter sleep-onset time and more total sleep time have been found in older adults with mild sleep problems [19, 20]. Wang and Youngstedt found that sleep quality in older women improved the night following an aerobic exercise session [21]. Among children, researchers have found that intense daytime physical activity might promote good sleep quality in typically developing 6–10 year olds [22]. Likewise, typically developing children who are more physically active tend to have healthier, more consistent sleep patterns than those who exercise minimally [22]. This relationship carries over to the limited information available about children with neurodevelopmental disabilities, showing that preschool children with ASD benefit from a high level of morning and afternoon physical activity with earlier sleep onset [23].

Regular physical activity has been found to reduce the risk of developing any type of sleep disorder in adult men and women [17]. Exercise training in adults can reduce the severity of obstructive sleep apnea even with minimal changes in body weight [24]. In a cross-sectional study, Peppard and Young also found decreased apneic events with increased physical activity even after adjusting for body mass index [25]. Exercise training also reduces daytime sleepiness and improves sleep efficiency in adults with obstructive sleep apnea [17].

As noted elsewhere in this book, children with ASD frequently experience sleep disruption [26]. Wachob and Lorenzi found that activity levels were significantly related to sleep patterns in children ages 9–16 with ASD: more physically active children had better sleep quality [27].

Not only can physical activity result in better sleep, but good sleep promotes better physical activity as seen from studies on sleep timing. Evans et al. found that typically developing children with obstructive sleep apnea have limited ability to perform exercise due to reduced cardiac output and oxygen consumption at peak exercise capacity independent of their weight status [28]. Also, lack of sleep impairs a person's ability to exercise and increases the risk of exercise-induced injuries [16].

Sleep timing and circadian rhythms may also impact exercise. Typically developing children who wake up later in the day are found to be less active [29]. Similar results have been found in adults with intellectual disabilities: Mikulovic et al. found that adults with intellectual disability who woke up early are more physically active than those who wake up late and those who wake up later tend to participate in more sedentary activities throughout the day [30]. Likewise, adolescents with intellectual disabilities who wake up early were more active than those who wake up late [31].

Research has shown that children with ASD spend significantly more time in sedentary activities – particularly those involving screens such as television, movies and video games –compared to typically developing children [10, 14, 32, 33]. The American Academy of Pediatrics suggests that children less than 2 years of age not use any screen media and preschoolers 2–5 years limit screen media to less than 1 h daily [34]. Yet children with ASD have spent 62% more time watching television and more hours per day playing video games than their typically developing siblings [32]. Also, the age at which children begin their television viewing is earlier in children with ASD compared to typically developing children [33]. Furthermore, children with ASD or ADHD with access to bedroom media spend less time sleeping each night [35].

There are several potential mechanisms by which exercise can promote sleep. First, exercise reduces anxiety [36]. Anxiety is a common factor in reduced sleep among children; therefore, minimizing anxiety through exercise may result in improved sleep. Sleep usually begins when the core temperature changes and body heat loss is maximal. Regular exercise promotes an increase in body temperature. As body temperature returns to normal, the resulting downregulation is associated with sleepiness [37]. Depression reduces sleep in adults; exercise may improve sleep in adults with depression [20].

The effects of exercise on sleep in children with neurodevelopmental disabilities have not been extensively studied. Nevertheless, patients like Henry could benefit significantly from regular exercise. For example, regular daily exercise may reduce the anxiety he experiences when trying to fall asleep or by increasing his sleepiness at bedtime by promoting a reduction in core temperature. Exercise for children can include participating in physical education class, participating in dance class or sports team practice, playing at recess, and active play at home or outdoors. Henry's family should look for opportunities to incorporate more physical activity into his daily routine. They can assign Henry active daily chores such as taking out the garbage, sweeping the kitchen floor, or walking the dog. Also, Henry can walk around the block to and from the bus stop on school days. Adding small

increments of physical activity throughout Henry's day can form healthy habits on which he can build. With time and encouragement, these small increments can grow to longer periods of physical activity.

Obesity Prevalence

The prevalence of childhood obesity, a significant public health concern, has tripled in the past three decades [38]. Data from the 2011 to 2014 National Health and Nutrition Examination Survey, a nationally representative sample, indicates that 17.0% of children in the United States are obese [38]. Data from the 2011 National Survey of Children's Health suggest that 28.9% of children with intellectual disability between the ages 10 and 17 were obese [39]. Other literature documents that children with neurodevelopmental disabilities are disproportionately affected by obesity [39–42]. Findings from 2009 to 2010 NHANES data show no significant change in obesity prevalence since 2003–2004 [43]. In short, there has been no significant improvement in childhood obesity prevalence in the past decade.

Weight and Sleep

The relationship between weight and sleep has been an area of active study in adults and typically developing children but less so in children with neurodevelopmental disabilities. A recent review of multiple longitudinal studies with adults noted that all found an association between short sleep duration and increased weight [44]. Many studies have described a relationship between short sleep duration and obesity in youth [44–47]. Iglayreger et al. created a composite cardiometabolic risk score and found sleep duration inversely predicts cardiometabolic risk, even after controlling for physical activity, in obese adolescents [48]. However, studies with adolescents show mixed results, most likely due to variations in methodology. A recent study found an association between short sleep and adiposity for both 10-year-old boys and girls [49]; however, a longitudinal study of 9–11-year-olds found an association between short sleep and BMI only in girls [50].

Some studies indicate that the time at which a child goes to bed is a better predictor of obesity than sleep duration [28, 51, 52], and late bedtimes were associated with adiposity independent of sleep duration [52, 53]. Vanhelst et al. documented that certain patterns of sleep behavior were more closely associated with overweight and obesity in adolescents with intellectual disability. Subjects were categorized into four sleep patterns: early bed/early rise, early bed/late rise, late bed/late rise, and late bed/early rise. Subjects in either of the late-bed groups were more likely to be overweight or obese [30]. Late bedtime seems to be a unique contributor to obesity risk.

Recent research suggests a bidirectional relationship between childhood obesity and sleep dysfunction. Obesity is a risk factor for developing obstructive sleep apnea. An obese child is four to five times more likely to develop obstructive sleep apnea than a nonobese child [54]. Conversely, typically developing children with sleep-disordered breathing have increased odds of becoming overweight [55]. In addition, children are more likely to develop obesity if they sleep less than 9 h per night [56].

The Centers for Disease Control and Prevention (CDC) defines childhood obesity as those whose body mass index percentile is at or above the 95th percentile relative to children the same age and gender [57]. Henry's growth parameters indicate that he is obese. Gradual weight loss is appropriate and should be achieved by modifying his diet and exercise habits. His parents have worked with a nutritionist in the past; but did not agree with some of the specific recommendations. For example, the nutritionist recommended that Henry eliminate all sweetened beverages from his diet and his parents felt this was unrealistic for a child. They stopped working with the nutritionist after one visit and only followed the provided recommendations for 2 weeks before returning to previous habits.

Several mechanisms may underlie the sleep-obesity association. Hunger and satiety hormones, ghrelin and leptin, are affected by sleep deprivation [58]. Ghrelin, a peptide hormone, is secreted primarily in the stomach. When the stomach is empty, ghrelin is secreted, triggering hunger and appetite. When the stomach stretches, ghrelin secretion stops, decreasing feelings of hunger. Ghrelin's receptor, the ghrelin/growth hormone secretagogue receptor, is found in the same cells as the receptor for leptin, also a peptide hormone, which functions to inhibit hunger. Therefore, leptin levels are suppressed prior to eating and elevated after eating (Fig. 30.1). Both hormones are affected by alterations in sleep. Sleep deprivation drives leptin levels down, resulting in decreased satisfaction after eating. Lack of sleep also causes ghrelin levels to rise, resulting in increased appetite.

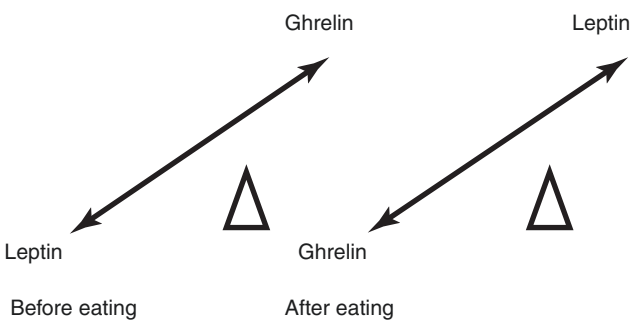

Fig. 30.1 The relationship between ghrelin and leptin

Simply put, inadequate sleep affects an individual's appetite regulatory system, increasing appetite and leading to overeating and weight gain. A fair amount of research examines the effects of sleep on leptin levels in children [59, 60]. When compared with children who sleep less, children who sleep more report decreased caloric intake and lower fasting leptin levels. These children also weigh less [59].

It is possible that children with neurodevelopmental disabilities increase their overall energy intake with sleep deprivation through increased total calorie consumption. Such a relationship has been found in adults [60–63]. Lack of sleep is associated with decreased physical activity resulting from fatigue and lack of energy to exercise. In addition, Golley found that typically developing children who went to bed late and woke up late ate fewer fruits, vegetables, and dairy and more "empty-calorie" snack foods independent of sleep duration [52]. In a study of Australian children with ADHD, parents reported increased sleep disturbance in children who had a higher intake of carbohydrates, fats, and sugar [64]. Long-term consumption of poorer diet quality can promote weight gain. In addition, children with neurodevelopmental disabilities often eat a less varied diet with calorie dense foods which may affect weight [65, 66]. Also, sleep deprivation is associated with a slight decrease in thermoregulation due to a reduction in core body temperature results. Over time, this slight decrease in calorie expenditure may result in weight gain.

Psychotropic medications are often used to treat children with neurodevelopmental disabilities. These medications can alter appetite, change food preferences, induce fluid retention, and change hormone production [67]. The atypical antipsychotics, in particular, are associated with weight gain, which can be substantial.

Physical activity and weight are important factors affecting sleep in children with neurodevelopmental disabilities. All three variables have reciprocal relationships, each potentially affecting the other. Henry has risk factors which attribute to his lack of sleep. He is physically active far less than the 60 daily minutes prescribed in the Physical Activity Guidelines for Americans. In addition, he is obese. Henry's lack of sleep may in turn hamper his ability to exercise and may contribute to excess weight gain. Physical activity and weight are two important behavioral factors which are modifiable and could offer a non-pharmacologic means to treat sleep disorders in children with neurodevelopmental disabilities.

Many children with neurodevelopmental disabilities and sleep disorders stand to benefit from modifying behavior in order to achieve a healthy weight and to improve exercise habits. Childhood weight management programs aim to improve weight and physical activity and have been developed for typically developing children who are obese. However, few centers have developed weight management programs specifically for children with neurodevelopmental disabilities. A 10-week school-based program was developed for children with intellectual disabilities or autism in Australia. Evaluation of its participants indicate improvements in a 6-min walk test – a standard measure to measure endurance and walking speed – and a decrease in candy and chocolate consumption [4]. The Wake Forest School of Medicine, in conjunction with the Brenner FIT Program, provided a multidisciplinary intervention for children with obesity and found those with cognitive disabilities demonstrated greater decreases in BMI z-score when compared to their obese typically developing peers who also received the intervention [68]. Z-scores indicate the number of standard deviations from the mean value. In this case, measuring changes in z-score values can indicate shifts in BMI percentile toward the mean even without actual changes in BMI percentile. These programs utilized the unique strengths of each individual patient and family unit.

In creating a weight management program for children with neurodevelopmental disabilities, it is important to incorporate the expertise of several disciplines including specialists in nutrition, exercise, and behavior. These professionals should be experienced in working with children with neurodevelopmental disabilities in order to address their unique needs. A participant in the group may need on-the-spot modifications to any exercise or educational lesson, which an experienced professional can provide. An ideal weight management program should provide initial weekly sessions for 2–3 months [4]. This frequency of intervention provides a base for children to establish new exercise and eating habits. The exercise, nutrition, and behavior specialists coordinate sessions to build strength, endurance, and nutrition knowledge. For example, the nutrition professional may create a nutrition lesson plan that incorporates multiple learning modalities such as visual, auditory, tactile, and kinesthetic. The behavior specialist may then work with parents to help address barriers to maintaining healthy eating and exercise habits at home. Incentives such as trips to the park or a new jump rope may be used to motivate children to meet their goals. After the period of weekly sessions, group participants should be followed at regular intervals to ensure they are maintaining healthy habits. A successful program will demonstrate positive changes in endurance and strength measures as well as changes in eating habits.

Case Vignette: Recommendations and Treatment

It has been 2 years since Henry's family took him to a nutritionist. His sleep, weight, and inactivity continue to be an issue. The sleep specialist recommended behavior modification efforts again and working with a

nutritionist who specializes in weight management for children with disabilities. That initial nutrition clinic interview revealed that Henry drinks soda and juice daily. He eats no vegetables. His family relies on fast food and convenience food items often. He uses a tablet most of his time away from school, and he does not engage in regular physical activity. After assessing his diet, the nutritionist had several recommendations in mind; however, during the interview, Henry's mother made several comments indicating she did not yet appreciate the importance of changing Henry's eating and exercise habits. Knowing that weight loss efforts are more successful for children when parents are committed to making similar healthy lifestyle changes [70–72], the nutritionist decided to implement some motivational interviewing techniques. Motivational interviewing is a method that aims to engage intrinsic motivation within a client, in this case a parent, in order to change behavior. Motivational interviewing is a patient-centered style which guides people to explore their ambivalence about changing behavior. The nutritionist asked Henry's mother "What do you think will happen to Henry if he does not change his eating patterns?" and also "Why do you think the sleep specialist is concerned about Henry's weight?" After discussing responses to these questions, Henry's mother was able to identify three key healthy changes to eating with which she agreed: (1) decrease Henry's sweetened beverage consumption to 0.5 cup juice per day, (2) provide fruit at breakfast, and (3) have Henry eat three bites of vegetable at dinner. His mother endorsed that she believed making these changes was reasonable and could potentially be helpful for Henry.

In 2015, the American Academy of Pediatrics' most recent guidelines for treating overweight or obese children were released [72]. This publication provided comprehensive guidelines for the treatment of childhood obesity. Among the recommendations were guidelines for dietary, physical activity, and sedentary activity behavior designed to help reduce childhood obesity. Evidence supports recommendations which include the following: limiting sweetened beverage consumption; encouraging adequate consumption of fruits and vegetables; limiting screen time; eating breakfast daily; encouraging healthy choices while eating out, especially at fast-food restaurants; encouraging family meals; limiting food portion sizes; and encouraging at least 60 min of physical activity daily [72]. These recommendations do not specifically address individual needs of children with neurodevelopmental disabilities; however, it is appropriate for providers to use these target behaviors as a guide when creating treatment plans. The primary goal of obesity treatment is to improve a child's health in the long term through establishing healthy lifestyle habits.

Target behaviors for patients and families to adopt to prevent excessive weight gain [73]
Encourage consumption of diets with recommended quantities of fruits and vegetables
Limit television and other screen time
Eat breakfast daily
Limit eating out at restaurants, particularly fast-food restaurants
Encourage family meals
Limit portion size
Encourage adequate daily physical activity
Limit consumption of sugar-sweetened beverages

Treating a child who has developed obesity is very challenging. Therefore, targeting primary obesity prevention within the family, school, and community environments is critical. Parents should offer regularly scheduled, balanced, varied meals and snacks for their children while limiting empty-calorie foods, high-fat meats, and dairy products. Parents should also promote physical activity and active play and limit screen time and sedentary activities. Schools should provide a healthy food environment, which limits using food as a reward and parties that serve primarily sweets.

Case Vignette: Follow-Up

At follow-up, Henry had maintained his weight from his previous visit. This was deemed successful since Henry had been gaining 1–2 kg monthly for the previous 8 months. His mother shared her challenges and successes in making healthy behavior changes. She found she was able to limit Henry's juice and soda consumption when they ate at home but not when they ate out. Henry was successful with eating fruit at breakfast. She reported that initially Henry was reluctant to eat three bites of vegetables at dinner. However, both parents have been consistent in requiring this of Henry. Although Henry does not enjoy eating vegetables, he is indeed eating three bites without complaint. Mostly his mother felt positive and was motivated to make further efforts to support weight loss for Henry. A short-term weight loss goal was discussed and established for Henry based on recommendations provided by the American Academy of Pediatrics' guidelines in treating overweight or obese children (Table 30.1). At this visit, the nutritionist recommended Henry be evaluated by a physical therapist to help develop a home exercise program.

Table 30.1 Weight goals for children with obesity, with and without health risks

2–5 years	5th–84th percentile or 85th–94th percentile with no health risks	Weight velocity maintenance
	85th–94th percentile with health risks	Weight maintenance or slow weight gain
	95th percentile	Weight maintenance (weight loss of up to 1 lb/mo may be acceptable if BMI is 21 or 22 kg/m^2
6–11 years	5th–84th percentile or 85th–94th percentile with no health risks	Weight velocity maintenance
	85th–94th percentile with health risks	Weight maintenance
	95th–99th percentile	Gradual weight loss (1 lb/mo or 0.5 kg/mo)
	99th percentile	Weight loss (maximum is 2 lb/wk)
12–18 years	5th–84th percentile or 85th–94th percentile with no health risks	Weight velocity maintenance; after linear growth is complete, weight maintenance
	85th–94th percentile with health risks	Weight maintenance or gradual weight loss
	95th–99th percentile	Weight loss (maximum is 2 lb/wk)
	99th percentile	Weight loss (maximum is 2 lb/wk

Data from Ref. [74]

Maintaining regular exercise and a healthy weight is beneficial for the overall health of children with neurodevelopmental disabilities and may improve sleep irregularities. Yet as discussed earlier in this chapter, meeting these recommendations poses many challenges for children with neurodevelopmental disabilities. Physicians may prescribe exercise to children; however, there are several factors to consider when creating a formal prescription for physical activity in children with neurodevelopmental disabilities [74]. First, it is important to obtain current health and fitness status to identify any reasons to restrict or modify activity. This also provides a baseline for tracking improvement. Next, physicians should maintain regular follow-up visits to monitor health and fitness progress and identify potential problems such as musculoskeletal issues.

Listed below are some useful tips to help incorporate physical activity into children's routines. Additionally, some communities have recreation programs geared for children with neurodevelopmental disabilities. Those communities without specialized programs should evaluate creating opportunities for physical activity for this population, such as sports programming.

Incorporating physical activity into daily routines
Help your kids participate in a variety of age-appropriate activities For preschoolers, play duck, duck goose, follow the leader, or freeze dance Older children may enjoy yoga, martial arts, or dance class Keep a variety of sports equipment on hand such as balls, hula hoops, or jump ropes
Establish a regular schedule for physical activity Schedule physical activity on a calendar or set reminders on phone to remind your child it is time to get active Play outside for 15 min before going inside the house after school 10 min push-ups, sit-ups, etc. before dinner
Incorporate activity into daily routines Take the stairs instead of the elevator Walk to school or walk around the block after being dropped off by school bus
Embrace a healthier lifestyle yourself, so you'll be a positive role model for your family Eat vegetables Try new foods Drink water instead of soda
Keep it fun, so you can count on your kids to come back for more

Case Vignette

When Henry returned to the nutritionist for his third visit, he had already seen the physical therapist that had helped his family develop an appropriate physical activity plan. They found that several short periods of exercise throughout the day were most effective for Henry. These 5–10-min exercise sessions were added as part of his family's daily routine. By this visit Henry had lost 4 lbs over the previous 3 months, and his mother felt confident they could continue their new healthy lifestyle behaviors. Henry will continue to be followed every 3 months to ensure ongoing progress.

Further Research and Future Directions

The relationship between sleep duration, sleep timing, physical activity, and weight should be established in children with neurodevelopmental disabilities. Weight and physical activity are factors which can be modified by behavioral interventions. If the relationships between weight, physical activity, and sleep are clarified among children with neurodevelopmental disabilities, medical providers could have non-invasive interventions to promote for treatment of sleep disorders in this population. Further research may be able to establish specific physical activity type and duration

recommendations to promote improved sleep onset and duration while limiting wakefulness. Similarly, best practices in treating obese children with neurodevelopmental disabilities should be established. Understanding specific techniques or teaching modalities which convey nutrition messages and motivate adherence to healthy eating habits can be helpful in promoting healthy weight in children with neurodevelopmental disabilities. Clarifying these relationships would help establish standards of practice for practitioners working with children with neurodevelopmental disabilities and sleep disorders.

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Melatonin

31

Roberta M. Leu

Introduction

Melatonin is an endogenous neurohormone. It was first isolated from the pineal gland by Lerner et al. in 1958 [1]. While the majority of melatonin circulating in the blood is produced by the pineal gland, there is evidence that it is also made in other body sites including the skin, lymphocytes, bone marrow, thymus, platelets, retina, and gastrointestinal tract [2, 3]. Melatonin production is regulated by light-dark cycles which set the circadian rhythm of the suprachiasmatic nuclei (SCN) via the retinohypothalamic tract [4, 5]. Melatonin synthesis is activated during darkness and suppressed by light. In darkness, norepinephrine is secreted and acts on beta-adrenergic receptors in pinealocytes, resulting in an increase in cyclic adenosine monophosphate (cAMP), the transcription of arylalkylamine *N*-acetyltransferase (AANAT), the rate-limiting enzyme in melatonin synthesis, and thus melatonin production [6]. In a person with a normal circadian rhythm, the secretion of melatonin begins 2 h before routine sleep onset (the dim light melatonin onset or DLMO), is elevated during the night, and is minimal during the day. On the biochemical level, synthesis of melatonin occurs in a four-step reaction beginning with tryptophan, which is converted into 5-hydroxytryptophan, then serotonin, followed by N-acetylserotonin, and finally melatonin (N-acetyl-5-methoxytryptamine) [2] (Fig. 31.1).

Melatonin has been found to have anxiolytic, antioxidant, free radical-scavenging, anti-inflammatory, antiproliferative, circadian entrainment, and hypnotic properties [2, 7, 8]. Its sedative effect comes from the binding of melatonin to the MT1 receptor, while circadian phase shifting effects come from binding of melatonin to the MT2 receptor [9]. The first report in the literature of melatonin being used for sleep in a child was in 1991 when Palm et al. entrained the circadian rhythm of a 9-year-old boy with intellectual disability who was blind and had a free-running circadian rhythm [10].

Pharmacokinetics of Melatonin

Melatonin is lipophilic [2]. It rapidly enters cells and crosses the blood-brain barrier [2]. Oral melatonin at doses of 2 and 4 mg has poor absolute bioavailability (only 15% of the dose makes it into the systemic circulation) thought to be due to poor oral absorption and/or large first-pass metabolism [8]. Normal physiologic levels of melatonin range from 60 to 300 pg/mL [11]. Administration of 0.3 mg of melatonin 2–4 h prior to habitual bedtime results in normal physiologic levels of melatonin [12]. Melatonin's onset of action is fast with a T_{max} of 30–60 min [13]. It has a short half-life of 30–60 min [2]. Immediate release oral melatonin maintains plasma melatonin levels above normal physiologic levels for 3–4 h while slow release oral melatonin maintains such levels for 5–7 h after ingestion [14]. Melatonin is metabolized in the liver by the cytochrome P450 enzyme CYP1A2 into 6-hydroxymelatonin [15]. It is then conjugated with sulfate into 6-sulphatoxymelatonin and excreted in the urine [15]. There is some evidence that prepubertal children metabolize melatonin faster than adults do and thus may require a higher dose of melatonin [4, 16].

Treating with Exogenous Melatonin

In the United States, supplemental melatonin is widely available over the counter (OTC) in multiple formulations (it is not available over the counter in many European countries such as the United Kingdom). These include immediate release tablets, slow release tablets, dual layer immediate and slow release tablets, dissolvable tablets, capsules,

R. M. Leu
Pulmonary, Allergy/Immunology, Cystic Fibrosis and Sleep Division, Emory University/Children's Healthcare of Atlanta, Atlanta, GA, USA

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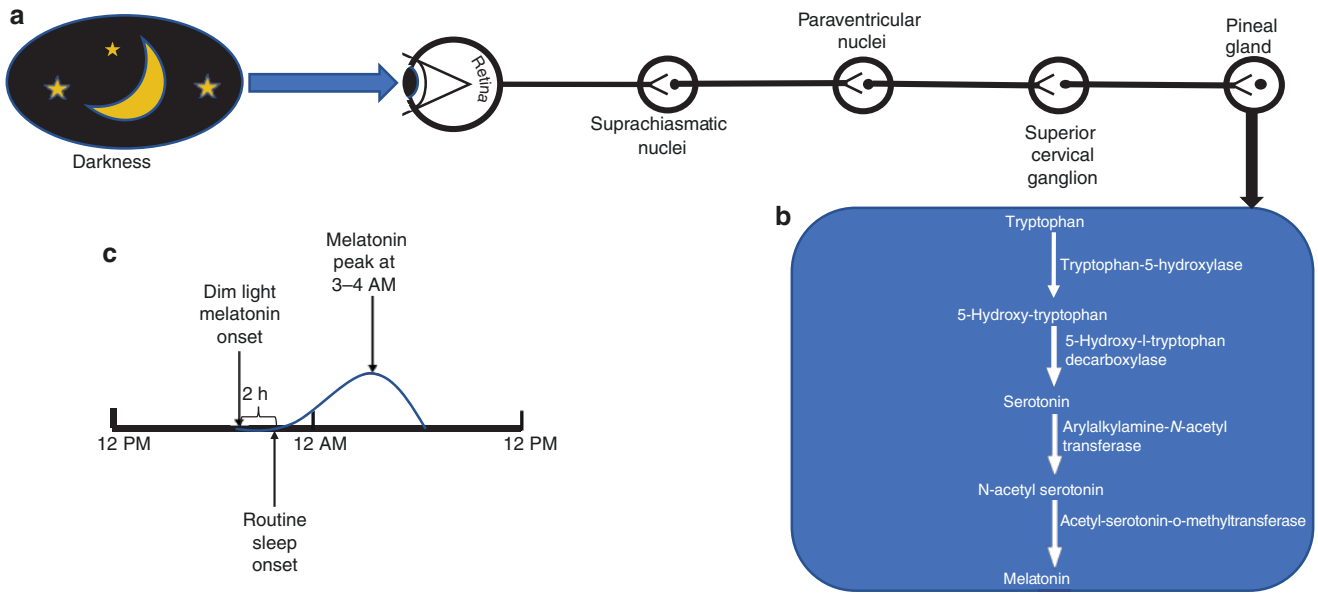

Fig. 31.1 Melatonin physiology. (**a**) Melatonin production is suppressed by light and stimulated by darkness. Nerve fibers travel from the retina through the retinohypothalamic tract to the suprachiasmatic nucleus (i.e., the "biologic clock") in the hypothalamus. They continue through the paraventricular nuclei down to the superior cervical ganglion in the cervical spinal cord and back up to the pineal gland. (**b**) In the pineal gland, melatonin synthesis involves a four-step conversion process beginning with tryptophan. (**c**) An example of melatonin's circadian pattern. Two hours before routine sleep onset, melatonin production increases in the pineal gland, marking the dim light melatonin onset (DLMO). Melatonin secretion peaks in the middle of the night and declines by morning

lozenges, liquids, sprays, dissolving strips, and gummies that may be taken orally. Some of the dissolvable tablets, liquids, and sprays are labeled to be taken sublingually for rapid absorption and to bypass first-pass metabolism for rapid onset. Crushed tablets dissolved in water and liquid melatonin may be administered per gastrostomy tube. If mixed into solution, melatonin will remain stable for up to 6 h at room temperature [17]. Body creams, lotions, and a transdermal patches are also available. Melatonin is typically sold in the following strengths: 0.3 mg (or 300 mcg), 0.5 mg, 1 mg, 1.5 mg, 2.5 mg, 3 mg, 5 mg, 10 mg, and 20 mg.

The burgeoning of melatonin formulations has likely been enabled by the categorization of melatonin as a dietary supplement in the United States as opposed to a medication. It is thus not subject to the rigorous Food and Drug Administration regulations to which prescription medications are held. This has opened up the market to melatonin products containing many other herbal supplements (e.g., valerian root, chamomile flower powder, magnesium, gamma-aminobutyric acid, vitamin B-6) that are also not tightly regulated. Consequently, there have been concerns for impurities and the accuracy of the melatonin strength on product labels. In June of 2007, the Food and Drug Administration issued a ruling requiring "current good manufacturing practices," giving companies until June 2010 to put into place quality control procedures that eliminate contaminants and impurities and allow for accurate strength labeling. However, a 2017 study from Canada showed that melatonin content varied by −83% to +478% compared to the dose reported on the label [18]. This variability was not unique to specific formulations or brands, and in fact, lot to lot variability in a brand could be as high as 465% [18]. Of their 30 samples, 26% were found to contain serotonin, which at inappropriate doses can have harmful side effects [18]. To mitigate this issue, families may opt for "pharmaceutical grade" melatonin which can be acquired online [19]. Most melatonin available OTC in the United States is synthetic in order to avoid potential virus transmission from animal products [20]. Manufacturers are required to label their melatonin source if it is from a plant or animal [21]. It can otherwise be assumed that the melatonin is synthetically derived [21], but if there is any question or concern, it would be best to call the manufacturer for verification.

Dosing

There are no universal guidelines on dosing of melatonin. When melatonin is used to advance one's circadian rhythm, it is most effective if given at the lower dose of 0.5 mg 5 h before the DLMO [22, 23]. Pediatric studies aiming to correct sleep onset and sleep maintenance issues have generally used doses of 2.5 mg up to 10 mg [2, 24]. In Jan et al.'s study, infants and toddlers were started on 2.5 mg of melatonin while older children were started on 5 mg [24]. An 11-month

prospective, naturalistic, observational study of melatonin use in children with intellectual disability, ADHD, or autism who had not responded to behavioral interventions for sleep started subjects on a dose of 2.5 mg 30 min before bedtime [25]. If a subject showed no response to melatonin, then the dose was increased at 4-week intervals to a maximum dose of 10 mg. The researchers found that increasing the melatonin dose above 6 mg only benefitted a small percentage of children (9% of their study population). However, doses as high as 12 mg have been used in other studies [26, 27]. Even melatonin at very high doses does not result in uncontrollable sedation [6], but clinically, it is better to maintain a patient's dose in the conventionally used ranges discussed above.

There is considerable interindividual variation in response to melatonin. The optimal dose of melatonin has not been found to be related to age or weight [28]. Thus there is not a standard mg per kg dosing recommendation for melatonin. Ways of predicting a clinically effective dose in a patient have not been identified. The therapeutic dose is essentially determined by clinical responsiveness; thus, follow-up with the prescribing provider is recommended [29]. Studies tend to show that melatonin is more useful for sleep induction as opposed to sleep maintenance [24]. For a sedating effect to help induce sleep, melatonin may be given 30–60 min before desired bedtime [15]. Typically, response to melatonin for sleep induction is experienced within days of starting it [4]. In an open-label, dose-escalation study of melatonin use in children with autism spectrum disorders, response to melatonin was typically seen within the first week of use [28].

Over time, some people find that melatonin's sedating effect "no longer works" for them. It is natural to assume that one has developed a tolerance to melatonin and to respond by increasing the melatonin dose. However, Braam et al. found that an increased melatonin dose did not improve responsiveness, and thus did not believe that tolerance was the issue [15]. A prospective long-term study of children on melatonin (mean duration of use over 4.3 years) did not show loss of melatonin efficacy over time, suggesting that responders do not typically develop a tolerance to melatonin [29]. Additionally, in a study of 107 children with an autism spectrum disorder, 7 children had initial improvement in their sleep with melatonin, but the problem returned after 3–12 months of use even though they increased the melatonin dose [30]. Interestingly, Braam et al. found that melatonin clearance tests on subjects who stopped responding to melatonin suggested that these subjects were slow metabolizers of melatonin [15]. They theorized that being a slow melatonin metabolizer results in the accumulation of melatonin and that high levels of melatonin resulted in a loss of circadian rhythmicity, rendering the exogenous melatonin ineffective. Furthermore, those subjects who stopped responding to melatonin improved after their melatonin dose was lowered. A follow-up study showed that slow metabolizers of melatonin were likely due to certain single nucleotide polymorphisms in the *CYP1A2* gene [31]. In the general population, about 12–14% of individuals have a slow melatonin metabolizer phenotype [31].

Once a good sleep schedule has been established for at least 6 weeks, providers can consider stopping the melatonin [32]. Chemical dependence, withdrawal, and abuse have not been observed for melatonin [33]; thus a slow tapering schedule is not necessary. However, providers may consider a taper to see what a patient's ability to sleep without melatonin is. There are some children who have such poor neuromodulation of their sleep that they need to be on melatonin throughout their lifetime in order to sleep.

Safety of Melatonin

Melatonin use appears to be fairly benign [2, 34]. An acute toxicity study of melatonin in rats and mice showed that the median lethal oral dose ($LD_{50\ oral}$) was very high at 1250 mg/kg for the mouse and >3200 mg/kg for the rat (researchers essentially could not find the $LD_{50\ oral}$ for the rat) [35]. This study also found that the sedative effect of melatonin occurred at doses far lower than doses necessary to cause neurotoxicity. In a randomized, double-blind study of adult men on 10 mg of melatonin versus placebo for 28 days, there were no significant changes in measures including complete blood count, comprehensive metabolic panel, cholesterol levels, urinalysis, T3, T4, thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), cortisol, and melatonin [36]. In girls with Rett syndrome, blood work including a complete blood count, chemistry, and liver function tests prior to melatonin (doses of 2.5 up to 10 mg were used) use and after a 4-week treatment period on melatonin did not show any adverse effects [11]. Miyamoto et al. followed complete blood counts, urinalyses, serum chemistries, LH, FSH, prolactin, and estradiol in two children with Rett syndrome on melatonin [37]. Over 2 years, no adverse effects were observed. In Malow et al.'s 14-week trial of melatonin in 24 children with an autism spectrum disorder, there were no changes in complete blood count, metabolic panels including liver and renal function, adrenocorticotropic hormone (ACTH), cortisol, estrogen, testosterone, FSH, LH, or prolactin [28].

There are a few long-term studies of chronic melatonin usage in children. The use of supplemental melatonin in children began fairly recently, starting in the early 1990s [10]. In 1996, Jan et al. reported no adverse consequences of taking melatonin over the course of 4 years in a group of 100 subjects [24]. They ranged in age from 3 months to 21 years and had taken melatonin in the dose range of 2.5–10 mg [24]. A prospective study on 41 subjects who had used melatonin

over a mean duration of 4.3 years did not find any safety concerns [29]. Questionnaire-based follow-up of melatonin use in 94 children with ADHD over 3.7 years showed that only 1/5 of subjects had adverse events; however, most complaints were mild, and the study did not distinguish whether these adverse events were from melatonin use or other medications (such as stimulants) that subjects could have been taking [33].

Side Effects of Melatonin

Side effects of melatonin are relatively mild and, when compared to placebo in studies, tend to occur at similar rates [4, 38]. Symptoms that have been reported more commonly include headaches, dizziness, nausea, diarrhea, enuresis, rash, hypothermia, tiredness, fogginess, and daytime sleepiness [4, 21, 39]. These side effects may resolve after initial treatment and generally do not result in the patient discontinuing the melatonin [39]. In this author's unpublished clinical experience, an increase in sleep terrors is sometimes seen with onset of melatonin use. Sleep terrors typically occur out of N3 sleep. It is possible that this initial increase in sleep terrors is because more N3 sleep has been seen in the context of higher melatonin levels [3].

Melatonin has been found to have some properties that have not been reported as significant side effects, but they are worth noting and being mindful of. For example, it has been observed to inhibit platelet aggregation [4]. Melatonin has also been found to lower blood pressure [40]. It can potentially have an adverse effect on mood [4, 11]. Whether or not melatonin exacerbates asthma in patients with nocturnal asthma is controversial [41]. Nocturnal asthma is believed to have a circadian pattern with increased airway inflammation at night [41]. It has been postulated that melatonin is pro-inflammatory, mediating this nocturnal airway inflammation [41]. A randomized, double-blind, placebo-controlled study of melatonin (dose of 3 mg) use in women with mild to moderate asthma for 4 weeks did not find any difference in asthma symptoms compared to placebo [42]. What this study did find was that melatonin improved sleep in subjects with asthma. In a randomized, double-blind, placebo-controlled study of 22 children with an autism spectrum disorder on a 3-month treatment period of melatonin, no asthma attacks were reported [38]. While further investigation is necessary, melatonin can still be considered as a sleep aid in patients with asthma [41] as long as the prescribing provider is aware of this potential side effect and thus knows to monitor and stop the melatonin if asthma exacerbations indeed increase on melatonin.

There has been a question of whether or not melatonin use affects pubertal development. Waldhauser and Steger looked at melatonin levels in 280 subjects and found that levels were low in early infancy, increased to their highest levels around 1–3 years of age, and dropped by about 75% until young adulthood at which time they remained stable [43]. This led to theories that in the prepubertal years, higher melatonin levels inhibit pubertal development and that a decline in melatonin results in the onset of puberty [4, 44]. Clinical data has not supported the theory that exogenous melatonin affects pubertal development (e.g., stopping exogenous melatonin has not resulted in precocious puberty, and long-term use of exogenous melatonin has not resulted in the delay of pubertal development). A Dutch study looked at long-term exogenous melatonin use in prepubertal children [45]. The mean duration of exogenous melatonin use was 3.1 years, and the mean dose of melatonin used was 2.7 mg (minimum dose of 0.3 mg and maximum dose of 10 mg). Of 59 children included in the study, Tanner stage information was available on 46 of the children. The authors concluded that long-term exogenous melatonin use did not affect the timing of pubertal development in their study population.

Drug Interaction

Drugs that affect norepinephrine levels or its action can affect melatonin secretion. For example, beta-blockers and alpha-2 agonists decrease melatonin production [6]. Tricyclic antidepressants that inhibit norepinephrine reuptake increase melatonin production [6]. Fluvoxamine and cimetidine can inhibit CYP1A2 and thus increase melatonin concentrations [21]. On the other hand, melatonin can inhibit CYP1A2 and CYP3A; thus medications metabolized by these enzymes can be increased in concentration if used with melatonin [21]. As discussed above, melatonin has the potential to decrease blood pressure. This should be taken into consideration when melatonin is used in conjunction with antihypertensives [21].

Case Vignette

Sarah was a 4-year-old girl with autism who was nonverbal and had been a "good sleeper" in infancy. When she was 2 years of age, she began to take longer to settle to sleep. Her parents had a firm bedtime routine that ended at 8 PM in her room with her being placed in her crib in the dark to sleep. On the baby monitor, they could see that she remained awake for hours playing in her crib or engaging in self-stimulatory behaviors, typically falling asleep at 12 AM. She woke at 6 AM for the day and did not take naps during the day. Melatonin was initiated at 1 mg given 30 min before bedtime. Her parents felt that it made her calmer, but

did not help her fall asleep. The melatonin dose was thus increased and eventually titrated up to 3 mg given 30 min before bedtime, and she was able to fall asleep with this dosage by 9 PM. While she was only getting 9 h of sleep per night, her parents felt that this was a great improvement and continued her on this regimen. One month after achieving this improved sleep schedule, Sarah returned to clinic. Her parents reported that she was no longer responding to the melatonin. The melatonin dose was decreased to 0.5 mg 30 min before bedtime. On this dose, she was again able to fall asleep by 9 PM. On follow-up at 3 and 6 months, she continued to do well on the lowered melatonin dose.

Use of Melatonin in Special Populations

Available data on melatonin use for sleep problems in specific groups of neurodevelopmental disorders is reviewed in the remainder of this chapter. Due to the rarity of many of the diagnoses or challenges in study recruitment, many of the studies were small, including the gold standard randomized, double-blind, placebo-controlled studies.

Autism

The estimated prevalence of sleep problems in children with an autism spectrum disorder (ASD) is 44–83% with falling asleep and/or maintaining sleep being the most common issue [46]. The etiology of these difficulties sleeping is unclear. Multiple factors may affect sleep in children with autism including sleep fragmentation from seizures, side effects of medications taken for comorbid conditions, difficulty transitioning from one activity to another, anxiety, hyperarousal, and environmental conditions that affect the influence of zeitgebers or environmental cues that entrain the circadian rhythm (e.g., light exposure). Melatonin has drawn significant interest in the arena of autism research, originally for the biomedical model that melatonin hypersecretion could lead to autism [47]. However, the current focus is on melatonin and sleep and the potential that aberrations in melatonin could contribute to their sleep difficulties.

Compared to controls, children with ASD have been documented to have lower nocturnal melatonin levels [48–51]. The primary metabolite of melatonin, 6-sulphatoxymelatonin (6-SM), has also been found to have lower diurnal and nocturnal excretion rates in children with ASD compared to typically developing controls [52]. Additionally, polymorphisms in the acetylserotonin methyltransferase (*ASMT)* gene have been associated with decreased *ASMT* transcripts and activity (ASMT is the last enzyme in the melatonin synthesis pathway) [50]. However, studies documenting these low endogenous melatonin levels have not examined subjective or objective sleep measurements in these patients. In a study of 23 children (aged 4–10 years) with well-characterized ASD, 9 of whom had none or mild sleep concerns and 15 of whom had moderate to severe sleep issues, low nocturnal 6-SM levels were observed [3]. Interestingly, the low nocturnal 6-SM levels did not correlate with any subscales on the Children's Sleep Habits Questionnaire that suggested difficulty sleeping (e.g., the Bedtime Resistance, Sleep Onset Delay, Sleep Duration or Sleep Anxiety subscales) [3]. Also, a pharmacokinetic study of endogenous and exogenous melatonin in nine children (aged 3–10 years) with confirmed diagnoses of ASD and a history of sleep onset insomnia showed that pretreatment endogenous melatonin levels were not abnormal [53]. Despite their normal endogenous melatonin profiles, these children still had improvement in their sleep on supplemental melatonin. It is possible that the discrepancy between melatonin levels occurred because one measured melatonin in platelets while another measured melatonin in serum and others measured urinary 6-SM levels. It is possible that a subset of children with ASD have low melatonin levels. It is also possible that the low melatonin and low nocturnal 6-SM levels have some other significance in ASD. A study found that specific single nucleotide polymorphisms (SNPs) in *ASMT* and *CYP1A2* caused decreased ASMT expression (by virtue of which one would expect decreased melatonin) and decreased CYP1A2 enzyme activity, respectively, and that both were associated with sleep onset delay in children with ASD [54]. Perhaps the method by which melatonin helps children with ASD sleep is more convoluted than simple repletion of deficient melatonin levels. On the other hand, it could be as simple as melatonin exerting its hypnotic property.

Melatonin is commonly recommended by physicians for individuals with ASD. In an analysis of three survey studies, the overall prevalence of physicians making this recommendation was 32.4% [55]. Melatonin has largely been found to be helpful in managing difficulty with sleep onset for children with ASD. While starting melatonin can completely resolve insomnia in a child with ASD, it is also common for it to improve but not fully resolve. In Andersen et al.'s study of 107 children with ASD aged 2–18 years on a maximum dose of 6 mg of melatonin, only 25% reported full resolution of sleep issues while 60% reported that melatonin helped, but had not fully fixed the sleep problem [30].

Some studies have shown that night wakings in their study population improved [53, 56], but this is not typical for melatonin. Interestingly, in a study by Goldman et al., a child who routinely woke up at 2 AM stopped doing so on melatonin, even though pharmacokinetic profiles of her melatonin levels showed that on 1 mg of supplemental melatonin, her

melatonin level had fallen to the same level as her endogenous melatonin level by 2 AM and that on 3 mg of supplemental melatonin, her melatonin level had fallen to her endogenous level by 5 AM [53].

A few randomized, double-blind, placebo-controlled crossover studies of melatonin for sleep problems in children with ASD have been done [27, 38, 56, 57]. While 3 of these studies were small, with sample sizes ranging from 11 to 22 [38, 56, 57], one multicenter trial had a sample size of 146 [27]. In these studies, children ranged in age from 2 to 16 years [27, 38, 56, 57]. Doses of melatonin used in these studies ranged from 0.5 to 12 mg [27, 38, 56, 57]. Treatment periods ranged from 2 weeks to 3 months [27, 38, 56, 57]. Sleep data was typically obtained from sleep diaries/charts and questionnaires with two of the studies including actigraphy as an objective sleep measure [27, 38, 56, 57]. These studies showed that the children tended to fall asleep earlier and faster and had longer total sleep times [27, 38, 56, 57]. With the exception of one of the studies, night wakings were not improved [27, 38, 56, 57]. Two of the studies specifically had study populations that had failed behavioral intervention for their severe difficulty sleeping [27, 38]. A further meta-analysis included three of the above-described randomized, double-blind, placebo-controlled crossover studies and two additional studies not described above, because they included children with other neurodevelopmental disabilities; however, the meta-analysis only included individuals with ASD [55]. This meta-analysis found that compared to baseline sleep, total sleep duration improved by 73 min; compared to placebo, total sleep duration in children taking melatonin improved by 44 min; compared to baseline, use of melatonin improved sleep onset latency by 66 min; and compared to placebo, sleep onset latency improved by 39 min [55]. In addition to the five studies used in the meta-analysis, Rossignol et al. also reviewed 13 additional uncontrolled trials of exogenous melatonin use [55]. Of the 18 total studies, 7 reported no side effects, and in the remaining studies, side effects were either transient or mild [55].

Although there are children with ASD and severe sleep problems that do not respond to behavioral management, physicians should always include behavioral interventions as part of their management. Cortesi et al. studied 160 children with ASD aged 4–10 years [58]. Their study was designed to have three treatment arms: (1) controlled release melatonin, (2) four sessions of cognitive behavioral therapy, and (3) a combination of controlled release melatonin and cognitive behavioral therapy. These treatment arms were compared to a placebo group. All treatment arms showed improvement in their sleep, but the combination of controlled release melatonin and cognitive behavioral therapy showed the most improvement with the most treatment responders and fewest dropouts.

ADHD

As many as 50% of children with attention-deficit/hyperactivity disorder (ADHD) have a sleep problem [59]. Sleep problems in children with ADHD include bedtime resistance, prolonged sleep onset, fragmented sleep, being tired in the morning, daytime sleepiness, restless legs syndrome, periodic limb movement disorder, and sleep disordered breathing [59, 60]. While issues with sleep onset are easy to blame on stimulant medication side effects, it is apparent that these issues can exist even in the absence of these medications. In children without ADHD who are medication-free, the prevalence of sleep onset insomnia is estimated to be 28% [33]. It is hard to know whether poor sleep begets ADHD or vice versa.

Melatonin has been shown to help with the sleep of children with ADHD and sleep onset insomnia. Van der Heijden et al. conducted a randomized, double-blind, placebo-controlled trial of 3 or 6 mg of melatonin (depending on weight) versus placebo in 105 medication-free children (aged 6–12 years) with ADHD [61]. DLMO advanced by a mean of 44 min on melatonin, and sleep onset advanced by about 27 min. Total sleep time increased by 20 min.

Being on a stimulant medication does not necessarily prevent melatonin from helping with a child's sleep. Weiss et al. conducted a randomized, double-blind, placebo-controlled crossover trial of melatonin in 27 children with ADHD on stimulant medication aged 6–14 years whose sleep problems had not improved with sleep hygiene methods [62]. With 5 mg of melatonin given 20 min before bedtime, their sleep onset latency was found to decrease from a mean of 62 min down to 46 min. Further improvement in sleep onset latency was observed in those who continued melatonin in the 90 days post-trial.

Hoebert et al. found that melatonin was effective in improving sleep in children with ADHD and insomnia in 88% and that stopping the melatonin resulted in the return of sleep onset insomnia in 92% (subjects were to stop it for 1 week every year to see if it was still needed) [33]. Parents reported the additional benefit of improved mood and behavior [33].

Down Syndrome

The prevalence of sleep problems in children with Down syndrome is as high as 76% [63]. Research studying the use of melatonin specifically to treat their sleep problems has not been reported in the literature. A comparison of 24-h urinary 6-hydroxymelatonin sulfate levels in subjects with and without Down syndrome showed no significant differences between groups; thus they appear to exhibit normal diurnal and nocturnal melatonin secretion patterns [64]. Interestingly,

research on long-term use of melatonin in Down syndrome has focused on its potential neuroprotective properties that could thus reduce cognitive decline [65].

Angelman Syndrome

Angelman syndrome results from loss of maternal genetic material in the 15q11–13 chromosomal region [66]. The most common maternal genetic deletion in this region that results in Angelman syndrome involves the *UBE3A* gene [67]. Sleep problems are common in this population with a prevalence rate of 50–90% [67]. Sleep problems in children with Angelman syndrome include difficulty settling at bedtime, night wakings, and circadian rhythm disorders [66, 67]. These sleep issues can become remarkably worse in the 2–6-year-old age range [67].

Two small studies have shown that melatonin can be helpful in sleep onset and maintenance problems in children with Angelman syndrome. Zhdanova et al. monitored 7 days of baseline sleep in 13 children with Angelman aged 2–10 years, then on 0.3 mg of melatonin 30–60 min before habitual bedtime for 5 days [68]. The total sleep time improved in these children as did their melatonin levels. During the baseline period, peak serum melatonin levels ranged from 19 to 177 pg/mL. The use of exogenous melatonin elevated peak serum melatonin levels to 128–2800 pg/mL. Braam et al. conducted a randomized placebo-controlled study on eight children with Angelman and chronic idiopathic insomnia [66]. Their baseline sleep pattern was observed for 1 week, and then the subjects received melatonin (2.5 mg at 6 PM in children <6 years and 5 mg at 7 PM in children ≥6 years of age) or placebo for 4 weeks [66]. Caregiver report of sleep parameters (recorded on sleep diaries) showed that sleep latency decreased by 32 min, sleep onset occurred 28 min earlier than usual, and total sleep time improved by an average of 56 min [66]. Number of nights with wakings decreased from 3.1 nights per week to 1.56 nights per week [66]. Salivary melatonin levels were higher after taking exogenous melatonin [66]. In this study, caregivers reported that they were satisfied with the improvement in their child's sleep, that their child was easier to manage during the day, and that children were less sleepy and more attentive [66].

Melatonin may also benefit children with Angelman syndrome who have a circadian rhythm sleep disorder (CRSD). Takeasu et al. examined CSRD and serum melatonin patterns in 15 Angelman subjects [67]. Eight of them had a CRSD. Six of these subjects took 1 mg of melatonin between 6 PM and 7 PM for 3 months. This intervention improved sleep in the subjects who had a free-running circadian rhythm and irregular sleep/wake rhythm, increasing total nocturnal sleep time by more than 80%. Melatonin did not improve the sleep of the two subjects who had delayed sleep phase type. While the expected negative correlation between age and melatonin level was observed in controls, it was not observed in those with Angelman syndrome. Instead, serum melatonin levels were found to be lower in children with Angelman than controls throughout the night, suggesting that their melatonin levels are low well before puberty. Interestingly, the *UBE3A* gene involved in the etiology of Angelman syndrome is an ubiquitin ligase which affects control of proteins involved in circadian regulation [67]. Reduction in the expression of *UBE3A* may result in the circadian rhythm disorders seen in Angelman. In fact, a drosophila model of Angelman syndrome consisting of a *UBE3A* mutation exhibits a free-running circadian rhythm [69].

Rett Syndrome

More than 80% of children with Rett syndrome have problems with their sleep, and these issues tend to be lifelong [11]. These problems include irregular sleep/wake schedule, night wakings, and decreased total sleep time [11]. In a study by McArthur et al., 1 week of actigraphy data to look at baseline sleep/wake patterns showed a mean sleep onset latency of 42 min and about 15 awakenings per night [11]. The severity of sleep problems have not been found to correlate with the child's age or stage of Rett syndrome [11]. Nor have conventionally used medications been found to consistently improve the sleep of children with Rett syndrome [11]. Melatonin has also been inconsistent in helping with the sleep of children with Rett syndrome.

Miyamoto et al. treated one child with Rett syndrome who had a free-running circadian rhythm and another who had fragmented sleep with screaming at night with 5 mg of melatonin [37]. Melatonin helped the child with the free-running circadian rhythm more so than the child who had night wakings. Additionally, the child with night wakings continued to have early morning awakenings which did not respond to increasing the melatonin dose. In both subjects, the progress that was made on the melatonin was lost when the melatonin was stopped. The subjects were reinitiated on 3 mg of melatonin each night, and their sleep problems improved again.

McArthur et al. conducted a double-blind placebo-controlled crossover trial of melatonin in nine girls with Rett syndrome with a mean age of 10.1 years [11]. Melatonin dosages were determined by weight (2.5 mg for 15–25 kg subjects, 5 mg for 25–30 kg subjects, 7.5 mg for 35–45 kg subjects, and 10 mg for >45 kg subjects). For the first 3 weeks of melatonin treatment, actigraphy data showed that subjects had improved sleep onset latencies compared to placebo (about 32 min on placebo vs. 19 min on melatonin). In the fourth week of melatonin treatment, this benefit was not

observed. They postulated that this was because melatonin had worked by advancing the subjects' circadian rhythms. Melatonin did not appear to improve sleep in all of the subjects; however, the total sleep time and sleep efficiencies improved in the subjects who had the worst sleep. While it may still be useful to trial a subject with Rett syndrome and sleep problems on melatonin, it is possible that the cause of sleep issues in Rett syndrome is unrelated to melatonin pathology.

Between the two studies described above, the only side effect reported was from one parent who reported that their child had "severe mood swings" during a 4-week trial of melatonin [11].

Tuberous Sclerosis

Severe sleep problems are common in tuberous sclerosis. In a survey study of caregivers, 60% reported that their child with tuberous sclerosis had difficulty settling to sleep, and 62% reported that their child had night wakings [34]. The etiology of the severe sleep problems is unknown. It is likely that it is multifactorial in nature with factors including challenging behavior, learning difficulties, sleep disruption from epilepsy, and side effects of anti-epileptic medications [34, 70, 71]. Sleep problems in children with tuberous sclerosis do not seem to respond to conventionally used behavior techniques or sedatives [34, 70]. On the contrary, these sedatives tend to increase their hyperactivity [70].

Trials of melatonin using 5–10 mg doses have shown mild benefit to children with tuberous sclerosis and problems sleeping. Melatonin was shown to improve total sleep time [34, 70, 71], but not number of night wakings [71]. In a comparison of 5 mg vs. 10 mg dosing of melatonin, children on 10 mg of melatonin fell asleep an average of 10 min faster than children on 5 mg of melatonin [71]. However, the higher dose of melatonin did not bring any added benefit to total sleep time or number of night wakings. No adverse side effects from the melatonin were reported.

Melatonin secretion patterns appear to be normal in children with tuberous sclerosis [70]. The sleep benefit that patients with tuberous sclerosis see after taking melatonin is suspected to be from melatonin's sedating property [34, 70].

Epilepsy

The topic of melatonin and epilepsy is complex as there is the potential that melatonin has many different roles in this population. Melatonin has been studied in children with epilepsy as a hypnotic to improve sleep. It has been observed to have a possible *pro*-convulsant effect. There has also been much interest in melatonin for its possible *anti*convulsant effect.

Poor sleep is common in children with epilepsy. Both seizures and anti-epileptics have the potential to cause sleep problems in children with epilepsy. Seizures can result in sleep fragmentation, increased wake time after sleep onset, and a change in their circadian rhythm [71, 72]. Anti-epileptic medications can affect melatonin levels and, thus, sleep. For example, valproic acid has been shown to decrease melatonin levels in healthy young adults [11]. Phenobarbital delays the rate-limiting step of melatonin synthesis and induces the enzyme that breaks melatonin down [11].

Small studies have investigated whether melatonin helps improve sleep in children with epilepsy. Uberos et al. looked at melatonin usage in ten children with severe epileptic disorders including West syndrome, Lennox syndrome, progressive myoclonic epilepsy, epileptic encephalopathy from hypoxic ischemic encephalopathy, and epilepsy from cytomegalovirus [72]. Their sleep diagnoses included irregular sleep/wake pattern, advanced sleep phase syndrome, and delayed sleep phase syndrome. Subjects were given placebo for 1 week and then 3 mg of melatonin 30 min before bedtime for 3 months. Actigraphy data showed that subjects receiving melatonin had an improved sleep latency, increased total sleep time, and improved sleep efficiency. Coppola et al. performed a randomized, double-blind, placebo-controlled, crossover trial to look at the efficacy of melatonin in improving sleep in 25 subjects with intellectual disability aged 3.6–26 years, some of whom had epilepsy [26]. Subjects were randomized to fast release oral melatonin or placebo. They were started on 3 mg of melatonin and titrated by 3 mg/week up to a maximum dose of 9 mg if needed. Melatonin was observed to improve sleep latency, but did not improve nocturnal awakenings or total duration of daytime sleep. In Elkhayat's study of children with epilepsy, 1.5 mg of oral melatonin was given 30 min before bedtime for 3 months [73]. On melatonin, there was improvement in bedtime resistance, sleep duration, sleep latency, frequency of nocturnal awakenings, sleepwalking, and daytime sleepiness.

Sheldon conducted a study on six children aged 9 months to 18 years with multiple neurological deficits including a history of epilepsy, which was present in five of the six subjects, and severe sleep problems [74]. The intention was to see if 5 mg of melatonin given at bedtime improved sleep in these subjects. When treated with melatonin, five out of six subjects had improvement in sleep onset latency, sleep maintenance, and total sleep time. Although sleep improved, four of the subjects also had either an increase in their seizure activity or onset of a new type of seizure activity. After melatonin was discontinued, the seizure frequency or type of seizure reverted back to what it was prior to melatonin treatment. Three of the subjects were rechallenged with 1 mg of melatonin, and the change in seizure frequency or seizure type recurred, only to again stop with discontinuation of the melatonin.

On the other hand, there are other studies showing no effect of melatonin on seizures. In a study by Carr et al., 19 of 41 children had a seizure disorder, but chronic use of melatonin did not result in more seizures, and there were no subjects with new seizures [29]. In Hancock's study, five subjects had seizures, and there was no change in seizure frequency compared with baseline before melatonin use [71].

While Sheldon's study showed a potential pro-convulsant effect of melatonin, there is also data to suggest that melatonin can have an anticonvulsant effect. In Mongolian gerbils, pinealectomy resulted in onset of seizure activity [75]. However, treating pinealectomized Mongolian gerbils with melatonin resulted in a decline in seizure activity [76]. Additionally, when rats received intraventricular injection of anti-melatonin antibody, epileptiform activity was seen [77]. This data suggests that melatonin exerts an anticonvulsant effect. There are multiple potential ways in which melatonin could do this. It is possible that melatonin simply improves sleep quality and thus increases central motor seizure inhibition. Melatonin has been found to enhance GABAergic inhibitory neurotransmission [2], an important mechanism of action for many anti-epileptic drugs [78]. Interestingly, melatonin levels have been found to increase during seizures, suggesting that melatonin may be an endogenous anticonvulsant [78].

Studies have shown mixed results on how well melatonin helps to control seizures. Studies by Elkhayat et al. and Coppola et al. showed mixed effects of melatonin on seizures. Elkhayat et al. conducted a study on 23 children with intractable epilepsy, giving them 1.5 mg of melatonin 30 min before bedtime [73]. Over the 3-month treatment period, 87% had decreased frequency and/or severity of their seizures. However, in 13% of subjects, seizures worsened and melatonin was discontinued. Side effects reported in this study included headache, rash, and abdominal pain, but none of the side effects were significant enough for subjects to stop the melatonin. In Coppola et al.'s study, 11 of the subjects did not have seizures at study onset [26]. In two of them, seizures started after initiating melatonin treatment. Discontinuing melatonin resulted in the seizures stopping. Seven of the subjects had uncontrolled seizures at the start of the study. One of these became seizure-free, two had some improvement, two had worsening of seizures, and two were unchanged. Studies by Goldberg-Stern et al. and Uberos et al. showed general improvement in seizures while on melatonin. Goldberg-Stern et al. conducted a double-blind, randomized, placebo-controlled, crossover pilot trial including ten subjects [79]. The melatonin dose during the melatonin treatment period was 10 mg at bedtime. On placebo, the mean number of diurnal seizures was 7.75. On melatonin, the mean number of diurnal seizures was 4.6. Mean number of partial seizures was found to decrease from 8.31 on placebo down to 5.26 on melatonin. The researchers did not find significant changes in the frequency of generalized or nocturnal seizures, maximal number of seizures per day, or seizure duration. Their subjects did not experience worsening of their seizures and did not report any significant side effects. Uberos et al. showed decreased frequency of seizures [72]. Some studies have found no change in seizures while on melatonin. In a study of melatonin use in 107 children with autism, Andersen et al. did not find new onset seizure, nor did those children with a history of seizures have any increase in seizures [30]. Wright's study of 22 children with ASD did not show seizures [38]. Gringras et al. found that the 16 children with a history of epilepsy who were enrolled in their study did not have worsening of seizure control or the emergence of a new type of seizure [27].

Fragile X Syndrome

Sleep problems are reported to occur in up to 77% of children with fragile X syndrome [57]. Compared to controls, boys with fragile X syndrome have greater variability in total sleep time, mean sleep onset latency, and sleep termination times [80]. Boys with fragile X syndrome have more frequent night wakings, and the night wakings are much longer than they are in control groups [80]. Their issues do not appear to be due to insufficient melatonin production. Instead, boys with fragile X syndrome have been found to have greater nocturnal melatonin production compared to controls [80]. Despite this, they have still been observed to have improved sleep when given supplemental melatonin. In a 4-week randomized, double-blind, placebo-controlled, crossover trial of 3 mg of melatonin that included children with ASD and fragile X syndrome, participants were found to have an increase in mean sleep duration, decrease in mean sleep onset latency, and earlier sleep onset time compared to placebo [57].

Concussion and Traumatic Brain Injury

Depending on the location of a person's brain injury, a person can have resulting insomnia or hypersomnia [81]. Insomnia occurs in an estimated 40–65% of patients with minor traumatic brain injury (TBI) [82]. Polysomnography and actigraphy data in adolescents 3 years after minor head injury showed decreased sleep despite no other apparent clinical sequelae from the injury [83]. Multiple factors contribute to the insomnia including pain, emotional trauma, and damage to neural structures that regulate sleep/wake rhythms [81]. TBI patients have been found to have lower levels of melatonin production [84]. An evaluation of tentorial length and angle in TBI patients with sleep/wake disturbances

showed that they had longer and flatter orientations of the tentorium compared to those without sleep problems [85]. The result is that the edge of the tentorium would be closer to the pineal gland and thus increase the likelihood that upon traumatic impact to the brain, the pineal gland could be injured [85].

In a study by Ayalon et al., 42 patients with insomnia complaints and a history of TBI underwent sleep evaluation [82]. The cause of their insomnia was diagnosed as a circadian rhythm disorder in 36% of subjects. Of them, eight had a delayed sleep phase pattern, and seven had an irregular sleep/wake pattern.

A randomized, double-blind, controlled, crossover trial comparing 5 mg of melatonin and 25 mg of amitriptyline to improve sleep in TBI patients showed no significant difference between the two when it came to sleep latency and total sleep time [86]. Once effect size was accounted for, patients on melatonin were found to have improved daytime alertness.

Other properties of melatonin, such as its anxiolytic, sedative, and anticonvulsant effects, can be useful after TBI since these patients can be agitated and have convulsions after head trauma [7]. While there are promising reasons to consider melatonin for treating sleep problems in TBI, there is an overall lack of evidence for this purpose and thus need for further studies [87].

Future Directions

While studies have shown that melatonin improves the sleep of children with neurodevelopmental disorders, further research examining appropriate dosing for age and or weight is essential. Controlled studies could also examine if there is optimal dosing specific to certain neurodevelopmental disorders. Most importantly, considering that melatonin is a neurohormone and that most doses available over the counter are supraphysiologic, further research into the effects of long-term use through childhood are needed. Research to answer how young is too young to start melatonin is necessary. Lastly, as more extended release formulations of melatonin become available, further controlled studies can clarify whether they confer any additional benefit or harm compared to instant release melatonin.

Conclusion

Melatonin seems to have positive effects on sleep in children with a variety of neurodevelopmental disorders. It typically shortens the length of time it takes for a child to fall asleep and increases total sleep time at night. Effect on night wakings is variable. While short-term use has been observed to have minimal side effects, long-term effects of initiating exogenous melatonin use in childhood are unknown.

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Occupational Therapy and Sleep

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Theresa Zakorchemny and Mary Lashno

Case Vignette

Owen was a 4-year-old boy referred to occupational therapy due to poor participation in daily tasks because of issues related to sensory processing. Referral information indicated that Owen moved constantly, ran laps around the house, and had difficulty sitting still. Other concerns included poor motor coordination and appearing "clumsy," seeming overwhelmed in noisy settings, and sleeping poorly. The occupational therapist met with Owen and his mother to find out more about his daily routines, habits, interests, and environment. Owen lived with his parents and newborn sibling. Owen's mother herself had sensory processing issues that were not addressed when she was younger. She was very motivated to help Owen with his struggles. Owen was doing well academically and successfully managed his routine during the school day. A primary area of concern for Owen and his parents was his poor sleep.

What is occupational therapy (OT)? The practice of OT began in the early 1900s in psychiatric hospitals along with the rise of moral treatment approaches. Occupational therapists (OTs) were first referred to as occupational nurses and then later in the 1940s as reconstruction aides with the treatment of physical and mental injuries of soldiers returning from war [1]. OTs have always worked with the framework of using occupational tasks to maximize a patient's function. Occupational tasks include everyday life activities (self-care tasks, work-related tasks, leisure tasks) in different environments. After the rehabilitation movement of the 1950s and 1960s, OTs began to work with individuals with developmental disabilities, including children. Along with changes that took place within the healthcare field, the 1980s and 1990s brought a movement toward quality of life, with OTs involved in education, prevention, screening, and health maintenance [2]. Occupational therapists have maintained the belief that through occupational tasks, each person has the capacity to advocate and achieve their own better state of well-being. Occupational therapy is provided in a variety of settings, including hospitals, long-term care facilities, hospices, adult outpatient clinics, homes and community settings, schools, residential settings, and pediatric outpatient clinics.

According to the American Occupational Therapy Association [3], the main goal of occupational therapy for an individual is "achieving health, well-being, and participation in life through the engagement in occupation." Occupations include activity of daily living, or ADL (self-care, productivity or work, and leisure activity), and instrumental ADL (IADL; such as household tasks, money management). In 2002 the AOTA practice framework categorized sleep as an ADL. In 2014 it further categorized sleep as an independent performance task with the additional statement "restful and adequate sleep provides the foundation for optimal occupational performance, participation, and engagement in daily life" [3]. Studies in the occupational therapy literature specifically related to sleep are lacking, as found by Lindy Weaver [4] following an examination of studies between 2006 and 2013 that researched the effectiveness of work, ADL, education, and sleep interventions for people with autism spectrum disorder. A total of 23 studies were found through databases of journal articles and reviews, with 9 related to work intervention, 11 to ADL and IADL, and 3 related to education. There were no studies found in the OT literature related to sleep intervention for children with autism [4].

T. Zakorchemny · M. Lashno (✉)
Occupational Therapy, Kennedy Krieger Institute, Baltimore, MD, USA
e-mail: lashno@kennedykrieger.org

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This chapter will focus on the role of occupational therapy in addressing sleep disorders in the pediatric population, particularly in children with poor sensory processing, attention-deficit/hyperactivity disorder, autism, and developmental delays. To support the occupational therapist's role in working with children and families experiencing sleep disturbance, the Model of Human Occupation (MOHO) will be used as the underlying framework to guide therapy intervention. Sensory processing disorders will be defined and studies reviewed that suggest a relationship between sleep and sensory processing. Finally, treatment approaches using occupational therapy principles will be discussed. Since to date there are few research studies addressing specific treatment strategies, many of the techniques are considered anecdotal and are based on clinical experience as well as supporting literature in the occupational therapy domain of practice.

Andrew Green and Cary Brown recently published *An Occupational Therapist's Guide to Sleep and Sleep Problems* in 2015. This book provides occupational therapists with knowledge about sleep, sleep disorders, sleep cycles, and pharmaceutical and non-pharmaceutical approaches to sleep problems. The framework suggested to address sleep is the Model of Human Occupation (MOHO), developed by Gary Kielhofner [7], since it encompasses a holistic view of treatment, taking into account not just the individual but the individual's environment and the complex interrelationships between both [5]. MOHO supports four basic concepts that must be considered when evaluating and developing a treatment plan for an individual: volition, habituation, performance capacity, and environment [5]. Before reviewing these concepts in greater detail, consider the complexity of supporting the needs of a child with a sleep problem. The child is part of a much larger system that includes the parent(s), sibling(s), extended family, and community/social relationships. A child relies heavily on the belief system of the parents and family and, as such, does not have control over his/her daily routines, particularly during the early years [5]. It is the role of the child to accommodate to and carry out the routines that the parents set and the role of the parent to teach and guide the child to successfully carry out the routines. When working with children, OTs must be attentive about parental needs and values and provide education to support parental understanding of the child's performance capacity.

The concept of volition can also be understood as motivation [6]. The OT needs to take into account what both the child and the family value or consider important. In terms of volition or motivation, the drive to make change in one's routines or habits may be influenced by their interests and how they perceive their own performance. A parent, for example, may perceive their adolescent's late night sleep routine as disruptive to the adolescent's school performance. The adolescent, on the other hand, may not feel it to be disruptive and may feel that he/she can simply take a nap after school, "no big deal." The young child who falls asleep at 8 PM every night but wakes and goes into a parent's bed at midnight is not likely to perceive this as problematic, whereas the parent may perceive this as quite problematic, with attempts to stop the behavior being met with distress by the child.

The concept of habituation refers to the learned or automatic routines one has as part of his/her occupational task [7]. Most people will develop habits that support their performance needs and life roles [7]. In the task of sleep, OTs assess and determine life roles of the child and family in order to support the family's situation and circumstances rather than focus only on the child's impairment. Habits related to sleep patterns can be considered adaptive if they lead to restorative sleep and are not disruptive to life roles. For example, a young girl insists on having her favorite stuffed animal and will only go to bed if it is available to her. This habit is fairly common and not necessarily disruptive to the family as a whole. However, should the family be on vacation and the stuffed animal accidentally left at an airport 2 h away and the child starts screaming because she needs her stuffed animal to sleep, this quickly becomes a maladaptive habit. A child with a regulated sensory system may cry and become upset, though typically can be consoled with a backup plan, or an extra hug, knowing that the stuffed animal is safe in the lost and found at the airport. A child with a poorly regulated sensory system, however, does not have the capacity to be consoled, and the "lost" animal is the "final straw" in a sensory-loaded day. Habits can be considered maladaptive if they disrupt life roles and continue to impede sleep. Habituation and volition come into play here as the OT helps the family to identify maladaptive versus adaptive habits and thus promotes prioritization and motivation in making change.

Performance capacity is the individual's ability to perform or execute the occupational task [7]. As cited in Reynolds and Lane [8], neurological connections that provide a foundation for learning and behavior are formed early in life. Sleep is a state of activity that serves to promote neural integration. Poor quality of sleep can result in maladaptive behaviors of inattention, poor cognitive performance, and impaired motor coordination [8]. The OT is trained to identify a child's performance capacity using standardized and non-standardized measurements of the child's motor coordination, sensory processing, musculoskeletal and neurological function, and cognitive abilities, including memory and problem-solving. For the occupational task of sleep, the OT can evaluate underlying sensory processing issues that may disrupt a child's sleep patterns. The OT will also assess for any indication of musculoskeletal or chronic pain problems that can be disruptive to sleep. Parental and adolescent questionnaires that are designed to tap into a child's sensory

processing patterns are used. The child is observed while performing a series of motor actions (upper body/lower body/combined) and asked to assume antigravity postures (airplane posture in prone, body tuck in supine) in order to clinically observe his/her sensory-motor coordination and praxis (motor praxis) functions. Certain performance skills or difficulty of skills within a specific cluster may indicate difficulty with processing and integrating sensory and motor information.

In evaluating the environment of the child as it pertains to sleep, the OT must be aware that the child for the most part is not able to change his or her environment without direct support from the parent or caregiver. When considering the environment and its impact on the child's sleep, the culture of the family needs to be considered. In some families, for example, co-sleeping may be valued and supported by extended family. The idea of a child having his/her own bedroom is not valued universally [5]. OTs will ask about the visual environment for sleeping (i.e., lighting), the tactile environment (clothing and bedding), and the auditory environment (noise levels) to determine if there may be environmental barriers to the child's sleep based on the child's sensory profile or performance capacity.

Case Vignette, Continued

Through a discussion with Owen and his mother, we learned that Owen preferred his family to help him with dressing and feeding tasks at home; although with playful encouragement, he participated in these tasks. Owen liked to negotiate for what he wants. He was easily upset with any changes to his routine. Owen enjoyed imaginative play and outside activity that he initiated. He did not like heights or any type of play where he was inverted.

In terms of nighttime routines, Owen's family started the bedtime routine at 7 PM: this included bath, reading books, and "lights out" by 8:00 PM. Owen did not usually fall asleep until 10:30 or 11:00 PM. Once put to bed, he summoned his parents every 5–10 min for water, bathroom, or goodnight kisses. He was always restless and insisted on using a pacifier, although this did not contribute to him falling asleep. His family tried various options including a night light, music, and even putting him to bed a little later, but nothing seemed to change his sleep routine. He was awake by 6:00 AM. His poor sleep routine began to impact his mood and overall family harmony. With the birth of the new baby, additional 1:1 time to address Owen's needs decreased.

In the case study with Owen, we look at volition in terms of the parental motivation to facilitate change and the child's motivation to participate in change. We see that parental motivation is high, with Owen's mother understanding his sensory processing difficulties through her own personal sensory experiences, and with having a newborn child in the home. Achieving restorative sleep is highly valued by both parents. In comparison, Owen's motivation is somewhat high in that he shares a desire to sleep better. However, he is not comfortable with changes to his routine, so it will be important to further assess his performance capacity to determine his sensory processing patterns as well as his ability to participate in recommended activity. Habituation refers to his already established routines that are maladaptive in terms of achieving a consistent bedtime routine that allows a full night's sleep.

In a study that questioned 256 occupational therapists on their use of MOHO in their practice [9], more than 80% of OTs indicated they use MOHO in their practice at least some of the time. OTs working with individuals with sensory impairments identified using MOHO principles 85.1% of the time. Using principles of volition, habituation, performance capacity, and environment supports enhances the OT's ability to relate to the child and family and to prioritize needs in order to promote optimal outcome in occupational task performance, in this case sleep.

Several studies were reviewed that looked at the relationship of sensory processing patterns and sleep problems in typical children [10–12] and atypically developing children [8, 12–14]. Sensory processing is the neurological process of our nervous system to take information from our body or the environment, organize it in the brain, and determine the correct behavioral or physiological response to the various types of input [15]. Ayres [16], who first began to study sensory integration in young children, stated "the effectiveness of a child's response to sensory input is dependent upon the accuracy of the sensory feedback during the response." For the purpose of this chapter addressing OT and sleep, the following sensory concepts or terms will be used. *Sensory domain* is the specific sensory area that is being studied or addressed. Sensory domains most discussed in OT literature are auditory, tactile, proprioception, visual, taste/olfactory, and movement. *Sensory filtering or gating* refers to our ability to determine the sensory information that is essential to complete a task and/or ignore what is not needed at that specific time. For example, when falling asleep, a child under blankets in bed does not typically hyper-focus on nonessential stimuli, such as the feel of the loose thread on the blanket or the constant sounds around them such as the heating unit or rustling of leaves outside the window. Davies and Gavin [17] researched electroencephalographic measures (EEG) in 20 children identified as having sensory processing disorders

and 25 children without identified disorders. The children with sensory processing disorders showed less sensory gating than typically developing peers. In terms of sensory gating, they researched the brain's ability to suppress repeated or irrelevant stimuli. This particular study focused on the auditory domain of sensory processing. Results suggest that identification or diagnosis of sensory processing disorder (in auditory domain) can be supported with brain-based activity measurements such as EEG and event-related potential (ERP) brain-based activity. Milner [18] demonstrated impairments in sensory gating in poor sleepers during pre-sleep wakefulness in a study of adults with insomnia, again using auditory stimuli. It was suggested from this that people with insomnia have difficulty disengaging from the sensory environment [18] and thus sleep is difficult.

Sensory registration is the ability to notice input, so responses are influenced by a convergence of equally reliable sensory information [19]. Davies and Gavin [17] investigated sensory registration as evaluating the consistency of brain responses to sensory stimuli. Registering sensory information in an organized manner allows us to notice and interpret sensory information in a meaningful way in order to engage in the designated activity. For instance, a child typically is able to perceive body language of parents when bedtime approaches and interpret sensory information gained from the routine habits performed at bedtime (e.g., bathing, putting on pajamas, reading a story) to begin to settle into the calm arousal state necessary for sleeping. A child who does not register sensory information in an organized manner misses sensory information from his environment needed for an adaptive response. Davies and Gavin [17] found that sensory registration of simple auditory stimuli is less organized in children with sensory processing disorders. This may further suggest that these children would likely not be able to organize more complex sensory stimuli to engage in an adaptive manner in the functional task that is sleep.

Other research projects have studied electrodermal responses and functional behaviors in children with sensory processing disorders and found that children with sensory processing disorders respond differently physiologically to sensory stimuli than do children without identified sensory processing disorders [20, 21]. Studies such as these have further identified a pattern of sensory processing disorder based on a child's neurological threshold for registering, processing, and organizing incoming sensory information. Schoen et al. [21] described three sensory patterns in a child with a *sensory modulation disorder*. Defining these subtypes will provide a foundation for discussion of treatment strategies.

The first subtype is that of a sensory processing disorder involving *over-responsivity* to sensory input. A child with this subtype of sensory processing will avoid situations where sensory input, particularly unpredictable sensory input, can occur. He or she can demonstrate an extreme response to what most view as non-threatening stimuli. This can be seen in a child who reacts with an extreme emotional response or even in an aggressive manner to non-threatening tactile input, such as a tap on the shoulder or a stray hair brushing the skin. This child avoids sensory input such as loud sounds, clothing tags, or particular textures of clothing or foods. The second subtype is a sensory processing disorder involving *under-responsivity* to sensory input. This child ignores or does not register the sensory stimuli and may appear as passive, not interested or engaged in task, and lethargic, tired, or "lazy." The third subtype is termed *sensory seeker* and craves sensory input, with the outward behavior of appearing always "on the go" and moving constantly. The child is often touching things and jumping, "crashing," or running. These children often have difficulty during the day settling to take naps.

Children with sensory processing disorders often display a combination of these subtypes and may appear over-responsive or under-responsive, depending on the types of sensory input. For example, a child may be highly or overly sensitive to environment sounds (e.g., vacuum, hair dryer, sirens) and physically feel the need to escape those stimuli. The same child may move constantly throughout the day with very few periods when he is able to sit still. A young toddler who has a sensory seeking profile may refuse naps and constantly climb, run, or jump throughout the day. When the time comes to settle in for the night, the same child may also have a sensory over-responsivity profile and have difficulty filtering nonessential stimuli in order to achieve a calm state for sleep. The child may move about in bed, be annoyed by the feel of the sheets, or be irritated by the intermittent sound of crickets outside the window. He may be hyperaroused if his bath was just before bed, due to distress with the sensations of water on the face and hair washing.

Vasak and others [10] sought to identify information about the relationship between sensory processing patterns and sleep problems in typically developing infants and toddlers. This retrospective clinical chart review studied infants and toddlers seen in a Canadian community setting by an OT specializing in pediatric sleep problems. A total of 177 charts were reviewed. As is common in OT practice, to gain perspective on the children's sensory processing patterns, parents were given the Infant Toddler Sensory Profile (ITSP) [22]. The ITSP evaluates the child's sensory processing in four quadrants: registration, sensation seeking, sensory sen-

sitivity, and sensory avoiding. They were also given the BISQ (Brief Infant Sleep Questionnaire) [23]. An increased number of symptoms indicating sensory processing disorder in one or more sensory quadrants were found in 55% of the children. Increased sensory sensitivity was found to be the most common sensory processing pattern of infants and toddlers with sleep problems. These children required more time to fall asleep once they were put to bed than did children with typical sensory scores. Also, Shochat and colleagues [11] looked at sensory processing patterns of 56 school children through parental questionnaires on sleep habits, behavior, and sensory processing. In their study the relationship between sleep and behavior decreased when controlling for sensory processing. Sensory seeking and tactile sensitivity were significant predictors for behavior. Further, sensory sensitivity (in the tactile domain) was a significant predictor of sleep problems. Through findings of correlations between subcategories of sensory processing (tactile sensitivity, sensory seeking, auditory filtering, and movement sensitivity), it was suggested that sensory processing abilities and different sensory profiles affect both a child's nighttime sleep behavior and daytime wake behavior.

Fjeldsted and Hanlon [13] participated in a pilot study to assess the relationship of sleep and sensory processing in children with fetal alcohol syndrome. Data was collected on 20 children using the BISQ and the ITSP. Results also correlated sensory avoiding patterns (over-responsivity) with more wakefulness at night.

Reynolds and Lane [8] investigated the correlation of sensory sensitivity and sleep problems with preliminary data for children with ASD and typically developing children. In this study, sensory processing patterns were studied in 55 children 6–12 years, 27 with ASD and 28 without either an ASD or an identified sensory processing disorder. Among children with ASD, those with sensory avoiding patterns on the sensory profile had more problems with sleep. Among typically developing children, those with sensory sensitivity and sensory seeking patterns on the sensory profile had more problems with sleep. Sensory avoiding and sensory sensitivity are low neurological threshold patterns or over-responsivity patterns. These studies support the need for further research of sensory processing patterns and specific sensory domains that correlate with sleep problems in children with autism, ADHD, and developmental delays. Referring back to using MOHO as a framework, the identification of performance capacity (i.e., sensory/neuronal thresholds) will aid in identifying appropriate treatment intervention strategies.

Once the occupational therapist has established the principal roles, habits, and routines of the child and has an understanding of the child's sensory processing patterns, the treatment plan can be developed.

Case Vignette, Continued

Owen's mother completed a Sensory Profile questionnaire and the BEARS sleep screening tool [24]. The BEARS is a mnemonic for questions about bedtime problems, excessive daytime sleepiness, awakenings during the night, regularity of duration of sleep, and snoring. Owen's sensory profile demonstrated that compared to peers, his sensory processing in areas of hearing, touch, and body awareness was two standard deviations below the mean. Balance and motion, as well as planning and ideas, scored in the typical range. Parents noted on the BEARS that he has problems going to bed and falling asleep and that he does not take naps during the day. Owen demonstrated awareness of his fears related to sounds (toilets flushing) and heights. While completing tabletop activities, he was observed to fidget almost all the time. He had difficulty persisting with a challenging task, such as fastening buttons. Low sensory registration was evident by reported high pain tolerance. He did not always know the position of his body in relation to gravity and space; he sometimes tripped over or bumped into obstacles or sat too close to the edge of his chair and fell off. He moved about "all the time," though was not organized in his movement. Owen's overall impaired ability to regulate incoming sensory information manifested both in significant avoidance (food textures, tactile materials such as sand, paint, markers, and settling to sleep) and also in becoming easily overwhelmed (running around the room, decreased safety awareness).

Owen was observed as he participated in different movement activities. He strongly disliked any inverted position, such as wheelbarrow walking. He avoided sitting on a therapy ball with support, as he was afraid to fall. With frequent encouragement, he was able to sit in front of the OT on a large rectangular swing while moved in small degrees back and forth.

Ongoing OT was recommended for Owen to improve his ability to participate in self-care skills and per parent request to improve his participation in sleep.

With the identification of sleep as its own occupational performance task, occupational therapists can use knowledge of sleep physiology and sleep disorders and use evidence-based practice to evaluate and address the functional implications of poor sleep patterns and sleep disorders on occupational performance and participation [25]. An occupational therapist who works with children who have sleep disorders will also explore their sleep's impact on the family as a whole.

Cognitive or behavior therapy interventions as well as sensory strategies or "sensory tools" to address sensory avoiding, sensory sensitivity, or sensory seeking patterns impacting sleep are utilized. Vasek et al. [10] suggested that addressing the levels of stimulation/activity during the day and environmental factors (e.g., noise, light levels, sleep location, temperature, and tactile aspects of bedding/clothing) should be considered in addressing sleep problems in children with sensory needs. Fjeldsted and Hanlon-Dearman [13] suggested that embedding a sensory diet in the child's daily routine can help improve sleep. A sensory diet is the utilization of sensory "tools" from the different sensory domains – tactile, proprioceptive, visual, auditory, taste/olfactory, and movement – within the child's day to provide regular opportunities to meet the child's sensory needs. The goal of a sensory diet is to help the child organize his/her responses to stimuli necessary for an adaptive response (as opposed to a maladaptive one) while participating in occupational tasks at home, school, and community. The use of sensory tools when waking should be considered, such as considering the temperature and texture of breakfast, providing movement breaks within the day, and offering "heavy work" activities that provide proprioceptive input throughout the day [13]. Critical times during the day when the child appears to be having difficulty with transitions, such as going from a preferred class (art) to a non-preferred class (math) or transitioning from home to school, are particular times to consider sensory tools to help the child successfully transition. OTs look at helping the child to maintain a balance of sensory and motor activity throughout the day in order to meet his or her individual sensory needs. The impact on sleep may be smoother transitions to bed, more cooperative napping for young toddlers, calmer evening states as are needed to wind down for sleep, and more wakefulness in the morning.

O'Connell and Vannan [14] studied and reported findings of a specific program implemented in Australia through the Early Childhood Services, termed Sleepwise approach. The progress of 23 children over a year's time was monitored, with the program including three educational workshops for families over the course of a year. Information about children's sleep patterns was gathered over a 2-week period of time through sleep diaries kept by parents and a detailed home-based sleep interview. Sensory strategies used addressed the child's ability to self-soothe to sleep. Visual tools and sleep stories were used to cue or prompt the sleep-wake rhythm. It was found that 8 weeks was the average time necessary before differences in sleep patterns were identified. Goals specific to the child's sleep were developed based on improving sleep and increasing function in the home, not necessarily on achieving "optimal" or "ideal" sleep. Of the 13 families involved in this study, 57% reported positive outcomes. The communication strategy of sleep stories was used successfully with 65% of the children. In terms of sensory tools, the use of a security object was found helpful for 48% of the subjects; second to that was music at 26% and weighted quilt/pillows at 21%. The behavioral strategy found to be used most successfully was gradual ignoring (60%) of maladaptive or disruptive behaviors to sleep.

OTs have long incorporated the use of touch-pressure input (a firm hug or firm touch) as one of many sensory tools for addressing sensory seeking patterns as well as sensory sensitivity patterns in children, adolescents, and adults. Temple Grandin [26] defined the term deep pressure stimulation as a form of touch pressure applied to the body and providing the feeling of a firm hug, holding, swaddling, or massage. To provide a child with continuous touch-pressure input, specific items such as a weighted blanket, weighted vest, or weighted lap pad have been used as part of a child's sensory diet. A 2001 study by Fertel-Daly et al. [27] compared a group of five students at baseline while wearing a weighted vest for 2 h and after removal of the weighted vest. Moderate improvements were found in students while wearing the weighted vest for increased focus and decreased distractions. However, there was no significant difference observed in these behaviors following removal of the vests. Mullen and others [28] researched the safety and therapeutic effects of deep pressure stimulation using a weighted blanket with 32 non-disabled adults, working in an acute inpatient mental health clinic. With the use of the weighted blanket, 33% of the respondents showed a decrease in electrodermal activity while using the weighted blanket. Lowered subjective anxiety after use was reported by 63% of the subjects, and the use of the weighted blanket as a calming modality was suggested by 78% of the subjects. This study, however, is significantly limited due to the use of a heterogeneous, nonhospitalized volunteer sample of adults. Determining the weight of the blanket or the weighted vest is typically determined by generalizing other studies of guidelines established for backpacks, or 5–10% of the body weight [28]. Weighted blankets were used on the volunteers in the previously discussed study for 5 min, in contrast to the weighted vests in the study by Fertel-Daly et al., which were worn for 2 h [27]. Determining a duration of wear for the weighted vest during the day and the benefit of the weighted blanket for nighttime sleep is anecdotal and often based on individual preferences and exploration as part of the clinical process.

There are numerous sensory tools or strategies that are often recommended as part of a sensory diet. Tools that provide touch-pressure input are often used for children with over-responsivity and under-responsivity sensory patterns. Touch pressure has been used for calming and relaxation purposes. For stress reduction purposes, the use of progressive muscle relaxation involves proprioceptive input as the person contracts individual muscle groups. It is often an

automatic response for someone who is hurt to quickly grab and squeeze the area that was acutely injured, such as when stubbing a toe or banging a knee on a table, in order to provide touch-pressure input to the injured area. A literature search for studies that assess specific touch-pressure tools, including weighted or pressure vests, revealed few; these were limited to companies selling sensory products to parents of children with autism or related disorders collecting subjective data about the vests using primarily parental report. For a child with poor organization of movement resulting in difficulties settling at night, numerous touch-pressure "tools" can be tried. Grandin [26] noted that what may work for one child does not necessarily work for another child. The following is a list of possible calming proprioceptive activities [15], though is not all inclusive, and often additional activities are identified by the parent and child through facilitated discussion with the occupational therapist:

Vibrating pillows or toys (with supervision and monitoring for tolerance)
Deep pressure rubs to the back, head, arms, and legs
Rubbing lotion on the arms, legs, or back (consider pre-warming the lotion)
Being snuggled up in a beanbag chair or wrapped in blankets; covering the body (not head) with a heavy quilt or under a weighted blanket
"Hot dog" or "taco" game where the child is wrapped in a blanket or sleeping bag and deep pressure is provided to his/her back while singing a simple rhythmic song
Wedging beanbags around the child's body
Pairing touch-pressure activity with slow vestibular input such as gentle linear back and forth movement or slow rolling back and forth on floor while wrapped in a blanket

Case Vignette, Continued

Owen attended weekly OT sessions with treatment focusing on sensory strategies to help him regulate incoming sensory information. Over several months, he began to make solid gains in tolerating both tactile and movement activities. It was felt that the use of sensory strategies might help improve his sleeping. These were decided in collaboration with family. Some of the recommendations included the following:

Heavy work activity to provide the body with deep touch pressure (proprioception), processed in the brain as calming and organizing. During his OT visits, it was often observed that with the introduction of any stressful new task, Owen was more successful if "heavy work" activities were incorporated into it. An example would be jumping and "crashing" play with introduction of moldable clay (tactile).

Owen's mother was instructed to continue to have Owen take his bath in the evenings, and following that sensory input (of the warm water), to set up a bedtime circuit routine that included some jumping on a small trampoline and some exercises (jumping jacks, running from one part of room to another to put dirty clothes in hamper and toys away). Owen also moved back and forth to the bookshelf to pick out books for bedtime. This provided Owen with organized movement experience.

Owen likes stuffed animals, and he was encouraged to pick out a few to accompany him to bed. He was also provided some time to quietly play with his toys in bed after lights out.

Owen has a double bed, and his family purchased a large body pillow that they tucked around him, making sure the pillow was tucked firmly against his body.

A pacifier was available to Owen overnight but also a sippy cup with water, and he was encouraged to start to take sips of water instead of accessing the pacifier.

Owen preferred the lights out and no music for a dark and quiet room; his mother did note that this tended to "amp him up" rather than calm him down.

Owen was provided with four coupons that he had to give to his family each time he requested an extra goodnight kiss; he could use all four coupons but was required to go to sleep after they were used up.

As noted previously, in addition to addressing sensory needs of the child, OTs have the opportunity through weekly therapy sessions to educate parents and caregivers on sleep terminology, misconceptions, and expectations [25]. This in turn provides the family with knowledge to improve volition and interest to alter or adjust the child's sleep routine. Achieving adequate sleep is necessary for optimal participation in everyday activity, both for the child and also for parents. The time spent between the OT and the child and family is typically 1.5–2 h for the initial evaluation visit and 1 h per week thereafter. Information gathered through these visits can be vital if shared with other members of the team, for instance, the physician, psychiatrist, and possibly social worker, to develop a holistic plan that meets the economic, social, physical, environmental and cultural needs of the family to achieve maximal gains and improved overall function.

Case Vignette: Outcome

Owen's mother tried these techniques over a 2-week timespan. She reported that the "heavy work" circuit before going to bed seemed to be working out well along with choosing his stuffed animals to play with after the lights were out. She reported that he was also doing well being tucked in with the large pillow. He was also positioning his stuffed animals very close to his body and wrapping the blanket tightly around himself and the animals. Owen's mother was pleased, as he was now going to sleep by 9:00 PM and sleeping through the night. He occasionally took the pacifier, but his mother noted less pacifier use and more sips of water from the sippy cup. Owen continued to wake at 6 AM. Although he was not achieving an optimal 11–12 h of sleep, he was achieving 9 h of sleep, a significant improvement for him.

Conclusion

Addressing sleep problems in children with developmental disorders, autism, ADHD, and sensory processing disorders is within the scope of occupational therapy [25]. Occupational therapists often address sensory processing issues with the child and family throughout the day, though as indicated by clinical reviews have not focused on sleep as a separate occupational performance task. With the change made in the 2014 OT framework, rest and sleep is now recognized an occupational performance task independent of ADL, work, play, and leisure. Occupational therapists can gain knowledge about normal and abnormal sleep patterns in order to establish a baseline for goal attainment. For many families who have to manage a child with sensory processing issues and sleep problems, achieving improved sleep patterns, not necessarily optimal sleep, is an acceptable and desirable outcome. This chapter discussed the Model of Human Occupation as a framework from which to base the approach and treatment of sleep problems in children with various developmental and sensory disorders. This model presents a holistic approach that takes into account not only the child's performance capacity (including sensory processing patterns) but also the motivational level of the child/parent/family and the habits or routines established within the home environment. Studies reviewed in this chapter suggest a relationship between sensory processing and poor sleep in both typical and atypically developing children. Poor sensory gating has been found, at least in the auditory domain, for children with sensory processing disorders. Over-responsive and sensory avoiding patterns appear to correlate with sleep problems in children with autism, ADHD, and developmental delays. Additional studies using medical technology are needed to provide evidence of differing brain activity in children with sensory processing disorder compared to typically developing children or children with autism and ADHD. With sleep now as an independent occupational performance task, studies can be further narrowed in focus on sleep, with the support of other disciplines including behavior therapy.

Occupational therapists can help to identify a child's sensory processing patterns. These sensory processing patterns can be maladaptive and lead to learned behaviors and rigid patterns (avoidance or seeking) and influence a child's participation in everyday activity, including sleep. Underlying psychological skills such as the developing coping skills, improving frustration tolerance, and engaging in appropriate problem-solving for improved family dynamics also needs to be addressed through intervention. The complexity of sleep as it impacts on the home and family unit requires a multidisciplinary approach. Occupational therapists can help to "put the puzzle together" by identifying underlying sensory processing patterns that can be changed in order to help the child balance day and evening routines for a better night's sleep.

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Behavioral Intervention for Procedural Desensitization for Polysomnography

33

Valerie Paasch, Lucy R. Leibowitz, and Keith J. Slifer

Case Vignette

Marco was a 6-year-old boy with isodicentric chromosome 15, a chromosomal abnormality which causes developmental delays, and a history of sleep disturbance. Marco was born full term following an uncomplicated pregnancy. Early developmental milestones, including speech, were delayed. Marco was able to speak several words with prompting, but did so inconsistently, so a communication board was used to assist with functional communication. Marco's mother described his receptive language as being significantly stronger than his expressive language skills. With respect to motor skills, Marco was able to ambulate independently but had coordination difficulties. His medical record also indicated low muscle tone.

Marco's sleep disturbance started around age three when he began having difficulties initiating and maintaining sleep without parental presence. Marco was prescribed clonidine, which helped with initiating sleep. However, Marco's mother endorsed mild snoring as well as frequent night awakenings of unexplained cause. A previous electroencephalogram (EEG) did not show any seizure activity. An overnight polysomnogram (PSG) was attempted at age 3, but could not be completed due to Marco removing the monitoring equipment (i.e., leads and electrodes, nasal cannula, pulse oximetry).

The family was interested in attempting another PSG with full electroencephalogram (EEG) in order to evaluate for obstructive sleep apnea (OSA) and nighttime seizure activity as contributing to his nighttime arousals. Given his history of inability to tolerate an overnight sleep study, Marco was referred by his neurologist in a pediatric sleep clinic at an urban pediatric hospital to an outpatient pediatric psychology clinic for behavioral training in preparation for his sleep study.

V. Paasch (✉)
Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Department of Behavioral Psychology, Kennedy Krieger Institute, Baltimore, MD, USA
e-mail: paasch@kennedykrieger.org

L. R. Leibowitz
Department of Behavioral Psychology, Kennedy Krieger Institute, Baltimore, MD, USA

K. J. Slifer
Department of Behavioral Psychology, Kennedy Krieger Institute, Baltimore, MD, USA

Department of Psychiatry and Behavioral Sciences and the Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Introduction

Children with medical conditions and neurodevelopmental disabilities (NDD) may be more likely than their typically developing peers to have sleep problems [1, 2] and seizure activity [3]. Sleep-disordered breathing such as obstructive sleep apnea (OSA) can occur at higher rates in children with medical conditions or NDD. Specifically, rates of sleep-disordered breathing and OSA are higher in children with Down syndrome [4], Prader-Willi syndrome [5], uncontrolled epilepsy [6], attention-deficit/hyperactivity disorder (ADHD)

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[7], and cerebral palsy [8]. Another type of sleep disorder, periodic limb movements during sleep (PLMS), can be associated with ADHD [7], Williams syndrome [9], intellectual disability [10], and Angelman syndrome [11].

Untreated sleep problems can have a variety of negative effects on a child. Untreated OSA and sleep-disordered breathing can negatively impact a child's cardiovascular functioning or lead to failure to thrive [4, 12], in addition to adversely affecting a child's alertness, attention, and academic performance [4, 13] and behavioral and emotional regulation [13]. Untreated periodic limb movement disorder (PLMD) can be associated with disrupted sleep, poor attention, and related behavior problems [14]. Untreated seizure activity can impact cognitive functioning [15] and lead to overall regression of skills [16] in the child.

Given the potential negative consequences of leaving sleep concerns untreated, assessment, diagnosis, and intervention are imperative. Guidelines dictate that a PSG be ordered to assess suspected OSA or sleep-disordered breathing [17, 18] and suspected PLMD [18, 19]. PSG may provide supportive data for diagnosis of restless leg syndrome [18, 19]. It can be indicated in the evaluation of parasomnias with atypical presentations, associated injury, or symptoms of a comorbid sleep disorder and sleep-related epilepsy [19]. Laboratory-based PSG is generally recommended for evaluation of children with suspected sleep-disordered breathing [20]. As a result of their high prevalence of seizure activity, sleep disturbance, and sleep-disordered breathing, children with NDD may be more likely than their typically developing peers to require PSG.

Conducting lab-based studies is expensive and can be difficult with children with NDD due to their challenges with comprehension and behavior [21]. Specifically, children with NDD may have language impairments and higher rates of disruptive behavior [22], anxiety [23], and tactile defensiveness [24], all of which can complicate a child's ability to tolerate the equipment and sensors required for a PSG. Behavioral challenges can contribute to difficulties applying equipment, including outright equipment refusals, preventing all recommended assessment materials from being applied to the child [21]. The omission of equipment on this basis (i.e., a nasal cannula that could not be tolerated) unfortunately limits the data obtained and hence the utility of findings [21, 25] and may prevent the referral concern from being fully assessed and appropriately treated. When this happens, the study may have to be reattempted at a future date.

The completion of a lab-based PSG places significant demands on a child. PSG involves the child spending the night in an unfamiliar location, typically in an outpatient medical facility or even a hospital. In order to complete the procedure, the child must remain seated and cooperative for a lengthy period of time, while a technician, who may or may not have experience working with children, applies the equipment. This requires the child to allow an unfamiliar adult to approach, remain in close proximity to, and touch him repeatedly as numerous sensors are applied to his head, face, chest, abdomen, and legs. The child must also tolerate exposure to a variety of sticky and grainy textures as the skin is cleaned and sensors are attached. Once applied, equipment must be tolerated and cannot be removed until the following day, an additional challenge for the child. The chance of intentional or accidental equipment removal increases when a child displays hyperactivity, impulsivity, anxiety, avoidance, and aggression. Although the child's caregiver is present throughout the night, the sleep environment and sleeping arrangements differ from his home environment. As a result of equipment placement, a child's sleeping position may be altered (i.e., needing to sleep on his back instead of his usual stomach position), and he may wake overnight when equipment is reapplied or repositioned. Finally, a child's typical routine may be further impacted if he is awakened earlier than usual in an effort to begin equipment removal.

Most parents of children with and without developmental delay indicate their experience with PSG is satisfactory [26]. In most cases, the presence of a developmental delay or medical condition does not significantly impact typicality of sleep during PSG [26]; however, sleep in the laboratory is more likely to be atypical in young children [26, 27]. Pain associated with PSG was rarely reported [26], although anecdotally many report the nasal cannula can be challenging to tolerate.

Evidence Base for Procedural Preparation

Children with NDD may have more difficulty tolerating medical procedures. Additionally, prior negative experience with medical treatment can result in increased distress, making a child more anxious and less cooperative with a current procedure [28]. Therefore, children with NDD or complicating medical conditions may be more likely to be sedated to enhance cooperation with procedures in general [29]. While sedation is generally safe and effective [29], there are cautions to its use. Sedation is not immediate and may not be effective for all children [30]. It can also be associated with unwanted or dangerous side effects, such decreased oxygen saturation, vomiting, and altered EEG findings [31–33], and its use is not recommended in the context of PSG. The use of restraint to enhance cooperation is not acceptable at many outpatient facilities and can be traumatic for the parent and child. Restraint can be unsafe for the child, parent, and technician and may cause the child to develop anxiety that then generalizes to other health-care settings and procedures [34, 35]. Similarly, efforts to wait to apply equipment after the child is asleep often contribute to distress and equipment removal when the child inevitably wakes [36]. Because of

these potential negative outcomes, it is preferred that equipment is applied while the child is awake, without the use of sedation or restraint.

The simple act of providing age-appropriate sensory and procedural information can be a beneficial intervention for children [37]. For example, receiving adequate information about a medical procedure may increase child cooperation [25, 38] and decrease distress and anxiety [39, 40]. When health-care providers are the ones giving information, it eliminates parental stress about needing to know exactly what information to provide to their child about the procedure [41]. Access to information can also reduce parental anxiety, allowing caregivers to feel they can better support their child during the procedure [41].

Previous research has demonstrated the effective use of behavioral intervention to increase compliance with medical procedures in both typically developing children and those with intellectual and developmental disabilities. These studies have used specific behavior analysis-based intervention strategies that require some preliminary definitions, which are provided below:

- *Positive reinforcement* refers to providing a preferred item or activity (reinforcer) contingent on a target behavior being displayed (e.g., appropriate sitting). Reinforcement is provided to increase the likelihood that the target behavior will be displayed in the future. *Differential reinforcement* involves providing a reinforcer in response to behavior one wishes to increase (e.g., appropriate sitting), but not in response to behavior one intends to decrease (e.g., aggression).
- *Negative reinforcement* involves removing an aversive or non-preferred item or activity contingent on a target behavior, thereby increasing the future probability that the behavior will occur. *Escape extinction* refers to blocking the patient's escape from a feared or non-preferred stimulus (e.g., medical equipment) in order to weaken avoidance behavior that has been maintained by negative reinforcement. In behavioral studies targeting cooperation with medical procedures, escape extinction that has been used to teach the child that attempts to remove medical equipment would not be successful; that is, they would not produce negative reinforcement or result in complete avoidance of the procedure. For example, if the child attempts to avoid or disrupt contact with medical material, the therapist physically interrupts the attempted avoidance and redirects the child to an alternative behavior that is incompatible with escape but compatible with the medical procedure (i.e., "hold your toy" while handing the object to the child or "clap your hands" during a song).
- *Counterconditioning* involves modifying negative arousal such as anxiety by using carefully planned, gradual exposure to a feared stimulus (e.g., medical equipment) while simultaneously engaging the patient in a distracting, relaxing, or otherwise pleasurable activity (e.g., preferred toy or video). Anxiety is counterconditioned as the child begins to associate the enjoyable activity (toy) with the previously feared activity (medical equipment).
- *Shaping* refers to using differential positive reinforcement to strengthen successive approximations of a target behavior. Over time, differential reinforcement of progressively more acceptable behavior, along with withholding reinforcement when unacceptable behavior occurs, teaches the child to behave more appropriately for the situation (e.g., cooperating with the procedures required for a successful PSG).

In the literature, interventions have ranged from providing procedural information/pictures to mock procedures to more comprehensive behavioral treatment packages including reinforcement, counterconditioning, and escape extinction. Behavioral intervention has been documented to help typically developing children cope and comply with physical exam [28], dental exam [42], endoscopy [38], magnetic resonance imaging (MRI) [43, 44], venipuncture [45–47], cancer treatment [48–51], positive airway pressure (PAP) [52], EEG [53], and burn care [54].

Behavioral intervention has also been documented to help children with NDD tolerate medical procedures without restraint or sedation. For example, procedural preparation helped children with NDD tolerate physical examination [55], PAP [52, 56], needle sticks [57, 58], MRI [59], PSG [60, 61], and EEG [62, 63].

A specific protocol for EEG desensitization was developed by Slifer et al. [62]. Seven children with NDD were referred for behavioral intervention due to a previous failed EEG attempt or concern that the child would not be able to successfully complete the procedure. An individualized task analysis was created for each child, and items to promote distraction and counterconditioning were identified. Differential reinforcement, escape extinction, counterconditioning, and shaping were used during the desensitization process to promote cooperation during mock EEG training sessions. Following intervention, all children were able to tolerate the EEG without the use of sedation or restraint. The Slifer et al. [62] protocol was then utilized with 17 children with Smith-Lemli-Opitz syndrome (SLOS) who needed to complete overnight EEG [62]. Mock EEG training sessions were 1 h in length and occurred immediately prior to the actual procedure. Strategies from the training session were then generalized to the actual procedure. Following the 1-h preparation session, 15 participants tolerated placement of all 21 EEG leads, while the remaining two participants tolerated placement of nine leads (resulting in collection of limited data).

Preliminary evidence from modifications to Slifer et al. [62] EEG desensitization protocol have shown that these behavioral techniques can also help children with and without NDD tolerate PSG [60, 61]. Paasch and colleagues [61] outline a behavioral protocol to assist with PSG desensitization [61]. Case examples provide a detailed illustration of the individualized behavioral strategies that led to successful PSG completion for three children with NDD. In a second study by this author, children were referred for PSG desensitization following a failed PSG or concern that a child's anxiety, behavior, or sensory sensitivity would impact their ability to successfully complete the study. Twenty-three children completed desensitization, which included behavioral interventions such as visual task analysis, redirection, distraction, contingent reinforcement, differential attention, shaping and stimulus fading, escape extinction, home practice, and a tour of the sleep laboratory. After an average of 3.95 sessions, 19 children successfully completed PSG without the use of sedation or restraint. Change in referral concern (i.e., sleep study no longer medically warranted for three participants) and family barriers (one participant) prevented the others from attempting the study after completing behavioral training for PSG.

If formal desensitization and behavioral training is not needed, behavioral recommendations can still be used to increase a child's tolerance of PSG. For example, it is recommended that the caregiver be present for the entirety of the procedure, and the technician should have experience working with children [17]. The child and caregiver should also receive guidance about the procedure and be oriented to the lab in advance, which may include a trial application of some equipment [17]. Additionally, implementation of behavioral strategies in the lab, such as distraction or reinforcement for cooperation, may help a child better tolerate his study [36]. Finally, taking a family-centered approach that includes the parent, pre-procedure preparation (i.e., speaking with family prior to study), environmental management, developmentally appropriate explanations, and options to support child coping can improve the child's experience during a PSG [64].

Management

Outpatient behavioral training sessions to increase PSG compliance consist of 30–60 min sessions with a behavioral therapist and involve active participation from caregivers. At our institution, the first interview with parents is often completed in an outpatient behavioral psychology clinic in order to obtain information about the child's history and previous experience with a PSG, EEG, or other medical diagnostic procedures. This includes an assessment of barriers that have previously made or are anticipated to make tolerance of an overnight PSG challenging. In the first session, the child's preferred items are identified by caregivers in order to gather information about potential play items or activities that may be used for distraction, counterconditioning, and positive reinforcement to increase motivation.

Table 33.1 Sample task analysis

	Tolerated?	Escape, avoidance, or distress?
Step	Yes/no	E, A, D
Sit on the bed or chair	–	–
Put two electrodes on the left leg	–	–
Put two electrodes on the right leg	–	–
Place one respiratory belt around the chest	–	–
Place one respiratory belt around the waist	–	–
Put electrode on the chest	–	–
Allow the face and head to be touched	–	–
Measure head circumference	–	–
Measure head ear to ear	–	–
Measure head front to back	–	–
Use facial scrub (or simulate by rubbing the face and scalp with Q-tip)	–	–
Put one electrode on the forehead with tape or adhesive paste	–	–
Put two electrodes on the cheeks with tape or adhesive paste	–	–
Put one electrode on the chin with tape or adhesive paste	–	–
Place electrodes on the head with clips or adhesive paste	–	–
Wrap the head in gauze	–	–
Place pulse oximeter on the finger	–	–
Place nasal cannula	–	–
Lie down or remain seated once all equipment is applied	–	–

Following the initial session, behavioral desensitization sessions involve following a task analysis that breaks the PSG into its component steps (Table 33.1 and Fig. 33.1). This allows for step-by-step exposure during a mock PSG and documentation of child tolerance and distress behavior during each step. A visual task analysis with pictures may be used to communicate to the child what will occur in each step of the PSG. Depending on the child's age and level of functioning, the visual task analysis may be used to assist with predictability (i.e., letting the child know what step will follow) and/or reinforcement (i.e., placing a sticker or stamp once each step is completed).

A kit of real and mock PSG equipment is used during behavioral training (Fig. 33.2). The steps of the PSG are often approximated as necessary during the gradual exposure for desensitization (i.e., first using hairclips to resemble EEG leads). Therapists provide education to caregivers regarding the use of differential reinforcement (i.e., ignoring,

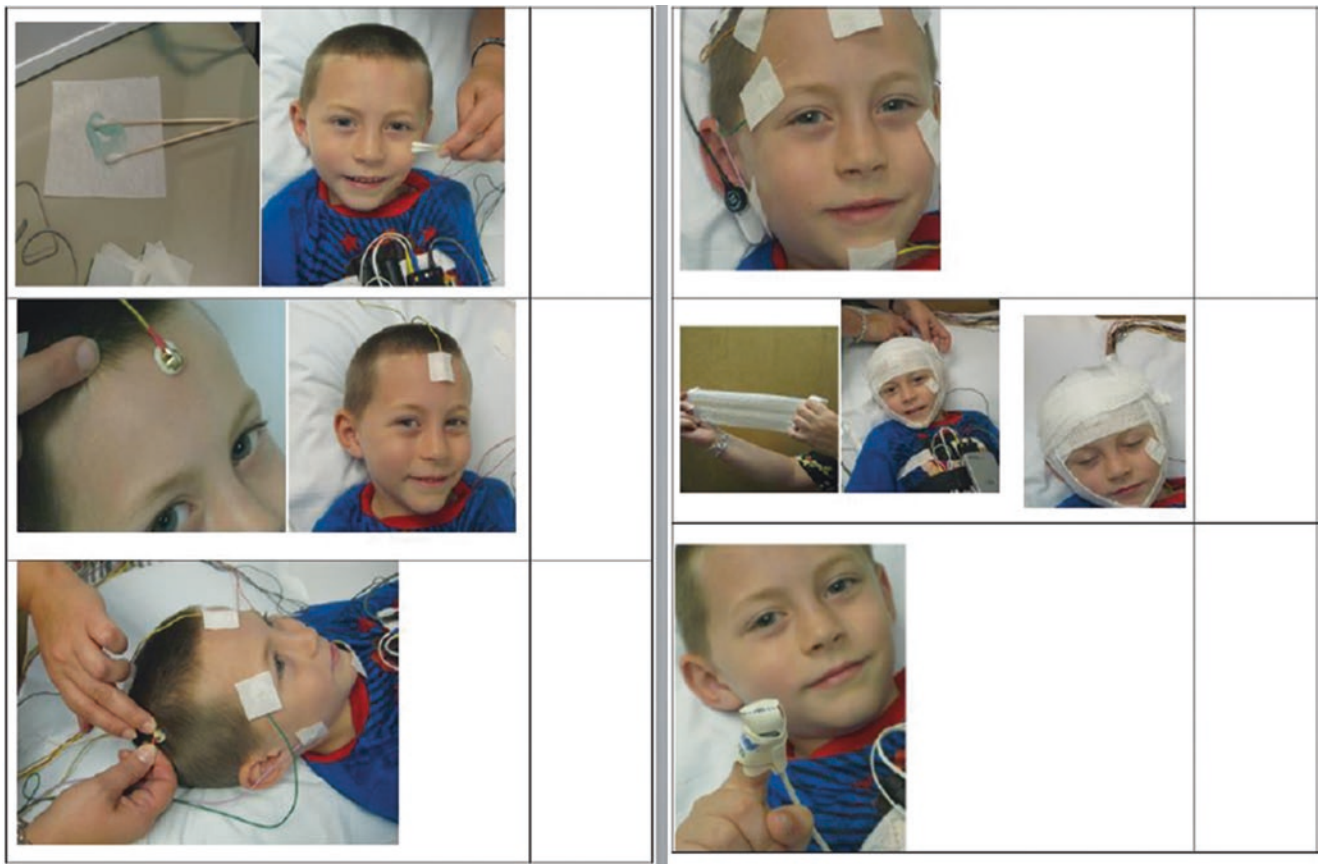

Fig. 33.1 Sample visual task analysis used in PSG preparation

Fig. 33.2 A sample PSG preparation kit used in behavioral desensitization

redirecting, and blocking escape behavior and reinforcing cooperation, and tolerance of materials). Behavioral strategies include gradual exposure, use of a consistent routine during desensitization sessions, modeling coping behavior, providing differential reinforcement, and using counterconditioning (i.e., providing access to preferred activities, using relaxation strategies and distraction during exposure to PSG equipment and routine).

Specific behavioral strategies used in behavioral training include stimulus fading, allowing for gradual exposure to materials, which may be approximated as necessary. To implement response shaping, approximations of cooperative

behavior during each step in the task analysis (e.g., initially sitting on a chair with the equipment on the table, then sitting in a chair with the equipment in the child's lap, then sitting in a chair with one piece of equipment applied, etc.) are positively reinforced through access to preferred items and activities (i.e., tangible stimuli or social praise). The length of time of exposure is gradually increased as sessions progress and tolerance improves. Escape extinction is also important during these steps so that children learn that trials end based on an external cue (i.e., timer or eventual completion of the sleep study), rather than in response to the child's level of distress or attempts to remove equipment. Stimulus fading may also be used with respect to approximating the location where materials are placed (i.e., placing an electrode in a less sensitive location such as the hand before placing it on the face).

Another strategy consistently used in behavioral desensitization sessions is vicarious learning or modeling, which shows the child materials placed on another individual (i.e., caregiver) who experiences no distress and demonstrates successful coping, before the child is asked to explore and tolerate the materials directly. This allows a child to experience milder levels of distress while watching someone else exposed to PSG sensors and equipment, thereby helping to extinguish some of the child's anticipatory anxiety.

At-home practice may be recommended to assist with generalizing cooperation and coping skills and to supplement practice time outside of session. This can include home-based review of the visual task analysis or continuing to practice with PSG materials as prescribed by the therapist to continue exposure and decrease sensitivity and anxiety.

Marco's Course of Treatment

Services were provided by a behavioral therapist with a master's degree, under the supervision of a licensed clinical psychologist. Marco's family attended sessions in the outpatient pediatric psychology clinic at an urban pediatric hospital for children with NDD. Sessions were conducted on a weekly or twice-weekly basis. In the first outpatient session, the therapist interviewed Marco's mother in order to gather information about his preferred foods, activities, and social reinforcers. Initial compliance training was completed during this initial session, which consisted of the therapist providing Marco with an instruction and then following his compliance with positive reinforcement. After this initial compliance training, Marco was able to sit on an exam bed and appeared to respond positively to social praise.

In the first desensitization session, contingent positive reinforcement was introduced, as Marco's mother provided access to a favorite video during periods that he remained calm. The therapist modeled briefly removing the video when Marco displayed distress (i.e., whining, crying). Timers were also used to track how long Marco tolerated materials. Marco tolerated five trials of increasing length, ranging from 1 sec to 5 min, in which the therapist's hands were placed on Marco's head, approximating the sensation of EEG leads being attached. Marco subsequently tolerated 5 min of a hair clip in his hair to approximate lead placement, followed by 5 min of an electrode on his leg and scalp, respectively. During this session, he displayed varying levels of distress, including crying. He did not attempt to pull off equipment; therefore, no blocking was required. Social praise was provided during and following each trial.

In the second desensitization study, Marco's mother continued providing contingent reinforcement in the form of access to a preferred video. Marco also held a preferred toy to further reduce the likelihood of him pulling at any equipment. The therapist was able to proceed through the steps of the sleep study task analysis continuously. Marco tolerated the respiratory impedance plethysmography belt around his waist; pulse oximeter on his finger; an electrode on the forehead, scalp, and each leg; the gauze wrapped around his head; and the nasal cannula under his nose. Marco tolerated sitting on the exam bed with all materials for 30 min. Marco scratched his nose when the nasal cannula was applied, but did not attempt to remove it or any other equipment. No blocking was required. Marco's mother and the therapist continued providing attention and praise throughout the trial. Marco presented with mostly neutral and calm affect throughout the session. He displayed minimal agitation throughout the session, but this did not appear to be associated with application of sleep study materials. Marco was easily soothed by positive verbal reinforcement, physical reinforcement (high fives from the therapist and hugs from his mother), and contingent access to his preferred videos.

In the third desensitization session, Marco was able to enter the room and sit on the exam bed with his mother with no outward distress. He was provided with a preferred toy which he held for the majority of the session. The therapist was again able to proceed through the sleep study task analysis continuously. Marco was able to tolerate sitting on the bed with the various materials in place for 30 min. During this session, Marco and his mother also visited the sleep laboratory in order to assist with generalization. Marco displayed moderate distress upon entering the laboratory but responded well to being provided contingent access to his preferred video while he sat on the unfamiliar exam bed. During this session, minimal distress (i.e., vocalizations) was observed in response to electrodes being placed on his skin, and moderate distress was observed (i.e., crying and holding his mother) when the electrodes were removed. Marco was easily soothed by positive verbal and physical reinforcement (i.e., hugs, praise, high fives) and contingent access to his preferred videos.

In the fourth and final desensitization session, another therapist participated and helped apply sensors in order to assist with generalization to working with unfamiliar adults, specifically the technician who would apply them for the actual PSG. Marco had no difficulties entering the sleep study laboratory and sitting on the bed with his mother. He continued to respond well to high fives as well as distraction and contingent reinforcement. Marco was also provided with a preferred toy which he held for the majority of the session. Marco was able to tolerate the application of all sleep study materials. His muscle tone appeared to increase when electrodes were applied, but he did not attempt to remove any materials, and no blocking was necessary. After all materials were applied, Marco was able to continue sitting on the bed while maintaining physical contact with his mother and watching a preferred video.

Figure 33.3 depicts Marco's progress with behavioral desensitization. Distress behaviors include vocalizations (i.e., moaning, whining, crying, other verbalizations to indicate distress or refusal), physical aggression (i.e., hitting, kicking, throwing objects), escape (i.e., attempts to escape room or remove materials), and other signs of physical discomfort (i.e., grimacing, increases in tone). Behavioral distress was coded on a scale from 0 to 3 to indicate the severity of discomfort with materials in session across the abovementioned domains. Ratings of no distress were coded as "0" to indicate behaviors were not present. Behaviors that occurred minimally at lower levels (i.e., moaning, whining, fidgeting with materials, and slight increases in muscle tone) were rated as a "1." Ratings of "2" include behaviors (i.e., vocalizations, attempts to escape, and physical discomfort) that moderately impacted the ability to apply materials. Ratings of "3" include any physical aggression or extremely heightened vocalizations or physical discomfort such that it severely impacted equipment application.

With respect to Marco's level of distress throughout his five sessions (initial evaluation and four subsequent desensitization sessions), Marco displayed no distress ("0") in the initial evaluation, mild distress in the form of whining and mildly increased muscle tone ("1") in the second and fourth desensitization sessions, and moderate distress ("2"), including crying, in the first and third desensitization sessions. Marco did not display severe distress ("3") in any of the sessions, as no aggressive behavior requiring blocking occurred.

Following desensitization and training, Marco successfully completed his overnight PSG with full EEG, which indicated normal findings with respect to breathing during sleep but abnormal findings with respect to the presence of a seizure disorder of focal origin. Following assessment and diagnosis, appropriate treatment was provided by Marco's neurologist.

Areas of Uncertainty and Future Directions

The procedures detailed in this chapter are based on general principles of behavior, as well as strategies and procedures that have broad support in the behavior analysis, behavior therapy, and pediatric psychology literature. The specific procedural preparation techniques include simulated (mock) medical procedures, stimulus fading for gradual exposure, distraction, counterconditioning, response shaping using differential positive reinforcement, and escape extinction. All of these techniques have substantial empirical validation in other clinical and medical contexts. The case example presented in this chapter illustrates a behavioral intervention that can be used to assist children with NDD in coping and cooperating with PSG without sedation or restraint.

Like many children seen in our practice, Marco successfully completed the behavioral desensitization and training

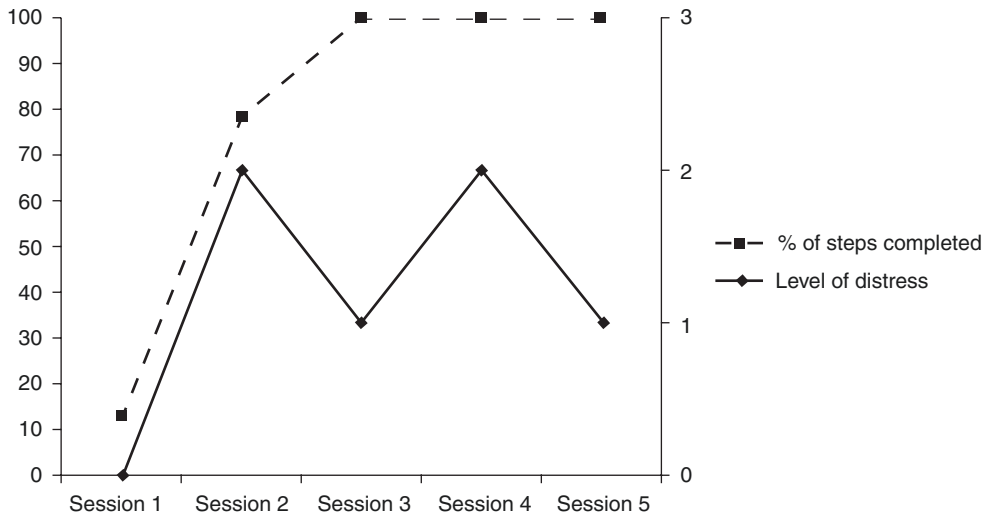

Fig. 33.3 Clinical outcome data for "Marco" depicting progress with behavioral desensitization. The dotted line represents the percentage of task analysis steps completed by Marco in each therapy session. The solid line represents Marco's level of observable distress, on a scale of 0–3, during each session

in a relatively short amount of time, after which he successfully completed a PSG without sedation or restraint. However, one must question the extent to which Marco's case is typical or atypical. In many ways, Marco is a typical case in that he benefited from the structure and predictability provided by a task analysis, counterconditioning associated with pairing a preferred item with procedure preparation, and reinforcement associated with task cooperation. In other respects, he is atypical, in that he did not engage in significant escape behaviors or require blocking of attempts to remove the equipment. In our experience, many children with NDD do require escape extinction. While escape prevention can be initially frustrating to children, if done in the context of a procedure preparation package that includes distraction and positive reinforcement, it is generally well-tolerated after some initial distress. The success of this procedure, however, is dependent on the extent to which parents and caregivers are willing to allow their child with NDD to experience some mild to moderate distress (i.e., anxiety, yelling), which is often comparable to the distress experienced by the child when frustrated or anxious in everyday life. Most parents and caregivers who help their children with NDD cope with the demands of home, school, and community life are indeed familiar with this behavior.

We have accumulated many cases like Marco's in which we have obtained similarly successful results following behavioral preparation for PSG. We aimed here to describe these procedures in enough detail for others to replicate our approach for the benefit of their patients. This case example has the many limitations that come with a descriptive case example. While this example and our presentation of the procedures involved are clinically informative, we have not demonstrated experimentally that our intervention was necessary or definitely responsible for Marco's subsequent success with PSG. We also do not know if all of the included intervention components are necessary to achieve a successful PSG. Controlled single-subject experiments and randomized clinical trials are needed to refine our protocol into one that is efficient. Ideally a protocol would be sufficiently manualized for broad replication, including only essential components, yet allowing for individualization to accommodate the idiosyncrasies of a wide variety of individuals with NDD. Future experiments should include video-recorded or live direct observation during all conditions including the actual PSG, in order to provide objective, reliable, and valid data to support the effects of this behavioral intervention. We do not know the extent to which caregivers are able to implement procedures learned in the behavioral training during the actual PSG, so additional assessment in this domain should be a future goal.

Based on the growing literature on behavioral interventions to increase child cooperation and coping during a multitude of challenging and sometimes aversive medical procedures, we are optimistic that our protocol, or a more efficient revision of it, will be empirically validated and become a common practice at pediatric medical settings serving youth with NDD. While we are optimistic about the generalizable benefits of this behavioral intervention, we do not as yet know to what extent success during the actual PSG is dependent on the skills of the technicians conducting the PSG at specialized pediatric facilities. It is very likely that systematic behavioral training for the technicians and cumulated practical experience in working with individuals with neurodevelopmental disabilities is needed for success. For immediate clinical application, systematic behavioral assessment and ongoing observational data during all training sessions are important. With session-by-session outcome data, behavioral interventions can be individualized to the unique challenges and needs of the patient to maximize the chances of success.

General Guidelines

- Children with NDD are more likely than typically developing children to require PSG.
- Conducting PSG with children with NDD is possible, and they may benefit from, or even require, behavioral training in order to cooperate successfully.
- Behavioral intervention can be used to desensitize the child to PSG equipment and to teach cooperation and coping with PSG procedures to avoid the use of restraint.
- Providers should assess whether it is likely that a child will be able to successfully tolerate PSG (Table 33.2). If it is suspected that the child will not, the child should be referred as soon as possible to a behaviorally trained pediatric psychologist or behavior therapist for desensitization and training.
- If formal desensitization and behavioral training are not thought to be needed, the parent or caregiver should be present and engaged during the procedure, and the technician should have experience working with children.
- Whenever possible, the child and caregiver should receive information about this procedure, be oriented in advance to the sleep laboratory, and be allowed trial application of some equipment.
- Developmentally appropriate language should be used when interacting with the child.
- The child's preferred items or activities should be assessed, made available during PSG, and provided as reinforcement contingent on cooperation and tolerance.
- A preferred activity for distraction should be provided during sensor attachment and equipment application.

Table 33.2 Questions to ask when considering whether a child would benefit from procedure preparation

Previous medical procedures	Behavior	Sensory
Has the child previously completed PSG or EEG? Was he able to tolerate the procedure? If not, why not?	Is the child hyperactive? If so, will he be able to remain still for setup? Are there activities that can keep him still?	Does the child have sensory sensitivities? Is he sensitive to touch? Is he sensitive to certain (i.e., grainy, sticky) textures?
Is he typically anxious in medical settings or with medical procedures? Is the child going to be anxious when he sees the medical equipment? Has there been anything effective for minimizing this anxiety in the past?	Is the child aggressive? Is it likely that he will try to hit or bite? Does he engage in self-injurious behaviors?	Does the child have sensory sensitivities on certain parts of his body? Can he tolerate someone touching his head/face? Can he tolerate wearing things (like a hat) on his head?
Do you feel like the child can successfully complete PSG? Do you think the child would benefit from additional preparation for the procedure?	Does the child follow directions? Will he listen if told not to touch or remove items? Can he generally cooperate with a physical exam or having vitals taken?	–
Can the child complete medical procedures without sedation or restraint?	Would the caregiver benefit from learning additional strategies to help manage the child in the lab?	–

- It may be helpful to have the child hold a preferred toy or activity-related material as a behavior that is incompatible with removing sensors.

Guidelines for Behavioral Therapists

- Training can be conducted in 30–60 min sessions using mock or actual PSG equipment and materials.
- The initial session should focus on assessing barriers to cooperation (e.g., anxiety, hyperactivity, tactile defensiveness, escape-avoidance behavior), and preferred activities and items to use for distraction and differential reinforcement.
- Desensitization and training should follow a consistent gradual exposure format by following a task analysis of the behaviors or steps required for successful coping and cooperation.
- A visual task analysis may be helpful to communicate to the child what will occur during PSG and establish predictability and routine for exposure, prompts, and systematic use of differential reinforcement.
- Modeling of cooperative behavior by the therapist, caregiver, or other individuals can help the child learn the PSG setup routine and see that it does not cause discomfort or distress.
- Use stimulus fading to gradually expose the child to potentially feared stimuli and unfamiliar or non-preferred sensations while fading along dimensions of physical proximity and duration of exposure.
- Differentially reinforce successive approximations of child cooperation and tolerance of sensors, equipment, and procedural demands (e.g., limited movement, remaining in one location, following directions).
- Gently interrupt and physically block escape-avoidance behavior such as pulling off sensors, leaving the procedure area, or using a hand to cover the spot where a sensor is to be placed while redirecting child's attention to a preferred distracting activity.
- Use an auditory or visual timer to communicate the duration of exposure and signal when the caregiver (not the child) may remove the sensors/equipment.
- Assign time-limited home practice with specific materials that the child has been able to tolerate in session in order to strengthen learning and generalize treatment benefits to locations outside of the behavioral clinic.

Conclusions and Recommendations

Each child is different, and in our experience, individualization of intervention increases the probability of success. For example, the items and activities that will be most effective for distraction and positive reinforcement vary greatly from child to child and, in children with NDD, are often quite specific and idiosyncratic. Selecting the right distractor and reinforcement for a given child can dramatically improve the child's motivation to cope, cooperate, and divert attention away from equipment and sensors. While we cannot guarantee that the behavioral procedures presented in this chapter will be effective in every case, we know from our own practices that with the right distraction and reinforcement during appropriate desensitization and training, the vast majority of youth, even those with severe NDD, can learn to successfully tolerate PSG studies.

We recommend whenever possible for children with NDD that a brief assessment by a behaviorally trained pediatric psychologist be conducted to consider what level of behavioral intervention might be required before the child is ready

for a PSG to be scheduled. Behaviorally trained pediatric psychologists can provide outpatient desensitization and training and work with the family and medical caregivers to transfer the benefits of procedural preparation to the laboratory where the PSG will be conducted.

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Behavioral Intervention for Positive Airway Pressure (CPAP/BPAP) Desensitization

34

Keith J. Slifer, Margaret A. Tunney, and Valerie Paasch

Case Vignette

Kenneth was a 3-year-old boy with a genetic condition associated with a range of manifestations including skeletal abnormalities, endocrine abnormalities, developmental delay, and obesity. He was born at 39 weeks' gestation. He had significant respiratory distress shortly after birth and spent several days in the neonatal intensive care unit (NICU) during which time an abnormal heart valve was discovered and he was hospitalized during infancy. Developmentally, Kenneth had limited verbal communication and used only a few simple words consistently. He was ambulatory but had fine motor delays. Moderate obstructive and mild central sleep apneas were revealed on a sleep study at 3 months of age. Continuous positive airway pressure (CPAP) was prescribed but not worn due to Kenneth's inability to tolerate placement of his mask.

Kenneth's bedtime ranged from 8:00 pm to 10:00 pm with 20-min sleep onset latency. He initiated sleep in his own bed but often relocated to his caregiver's bed in the middle of the night. In the morning, he woke around 5:00 am and napped between 4:00 pm and 6:00 pm. Given his inability to tolerate CPAP, Kenneth was referred by his pediatric pulmonologist for CPAP desensitization in an outpatient pediatric psychology clinic at an urban pediatric hospital.

Introduction

Sleep-disordered breathing (SDB), such as obstructive sleep apnea (OSA) [1–5], is more common in children with medical conditions and neurodevelopmental disabilities (NDD). SDB and OSA can lead to disrupted sleep and adversely impact a child's health and daily functioning. Untreated SDB and OSA can impair cardiovascular function and may lead to failure to thrive [1, 6] and difficulties with alertness, attention, and school performance [1, 7]. SDB and OSA that go untreated can also disrupt behavioral and emotional control [7].

Treating OSA in children typically begins with surgery to remove tonsils and adenoids that may be impinging on the child's airway. However, when surgery is not possible or appropriate, or has not adequately treated OSA, positive airway pressure (PAP) is often the next recommended treatment. PAP requires the child to wear an interface, either a mask (attached to headgear consisting of Velcro straps) over the nose and/or mouth or nasal pillows that are securely inserted a little way into the nose. In either case, the interface is connected to the tubing that delivers air at a continuous pressure (CPAP) or bi-level pressure that varies between

K. J. Slifer
Department of Psychiatry and Behavioral Sciences and the Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Department of Behavioral Psychology, Kennedy Krieger Institute, Baltimore, MD, USA

M. A. Tunney
Department of Behavioral Psychology, Kennedy Krieger Institute, Baltimore, MD, USA

V. Paasch (✉)
Department of Behavioral Psychology, Kennedy Krieger Institute, Baltimore, MD, USA

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: paasch@kennedykrieger.org

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inhalation and exhalation (BPAP). When successful, this airway pressure is adequate to inflate and keep open the airway to prevent obstructive events. Most PAP machines have a "ramp" feature, set to gradually increase the pressure to therapeutic levels, which is intended to improve tolerance and adherence.

Understandably, PAP adherence can be difficult for children, and their adherence is often suboptimal [8, 9]. PAP requires the child to cope with equipment on his head and face, and even potentially in his nose (nasal pillows), creating unfamiliar and uncomfortable pressure sensations. This is complicated further if the mask is pushed out of alignment as the child changes positions during sleep. Perhaps the most challenging aspect of PAP is that the child must tolerate the sensation of air being delivered under pressure to their nose or mouth, causing additional unfamiliar and initially uncomfortable sensations. The child must learn to acclimate to these sensations, as well as the noise of the PAP machine, and ultimately must be able to initiate and maintain sleep while experiencing these sensations. Prior research has shown that older age and use of a full-face mask decreased CPAP compliance rates [10].

PAP treatment can be challenging for anyone but may be especially difficult for a child with NDD. Children with NDD may have higher rates of disruptive behavior [11], anxiety [12], and tactile defensiveness [13], all of which can complicate their ability to tolerate PAP. They also may have a higher prevalence of facial abnormalities, which can impact proper PAP interface fit. When the fit is poor, the air may blow into the eyes or face, or may shift during sleep, causing discomfort and impacting adherence. While children with NDD are capable of learning to tolerate PAP, they may take a longer time to acclimate to it [10].

Evidence Base for Behavioral Desensitization for PAP Tolerance

Children with NDD may have more difficulty tolerating medical procedures or equipment. Previous research has demonstrated the effective use of behavioral intervention to increase compliance with medical procedures in both typically developing children and those with NDD. Please see the "Behavioral Intervention for Procedural Desensitization" chapter in this book for a more extensive review on the empirical support for procedural preparation in children.

These prior desensitization studies have utilized behavioral-based terminology and interventions, which are briefly defined below:

- *Positive reinforcement*: providing a preferred item or activity (reinforcer) contingent on a desired behavior, such as sitting quietly. Reinforcement is given to increase the chance that the target behavior will be performed in the future. *Differential reinforcement* involves providing a reinforcer in response to behavior one hopes to increase (e.g., sitting quietly), but not in response to behavior one hopes to decrease (e.g., yelling).
- *Negative reinforcement*: removing an aversive or non-preferred item or activity contingent on a desired behavior. This increases the probability that the desired behavior will occur in the future.
- *Escape extinction*: blocking the child's escape from a feared or non-preferred stimulus (e.g., PAP interface) in order to decrease escape behavior that has been maintained by negative reinforcement. Escape extinction is used to teach the child that attempts to remove medical equipment will not be successful; that is, they will not result in escape from the equipment.
- *Counterconditioning*: decreasing negative arousal, such as fear, by using carefully chosen, gradual exposure to the feared stimulus (in this case, medical equipment) while simultaneously engaging the child in a distracting, relaxing, or otherwise pleasurable activity – often a preferred toy or, during daytime rehearsal, a video. The child's anxiety is counterconditioned as he begins to associate the pleasurable activity (toy) with the activity (attaching medical equipment) that previously provoked anxiety.
- *Stimulus fading*: gradually changing some aspect of the physical environment along dimensions of size, shape, color, intensity, proximity to an individual, duration of exposure, etc. while keeping all other environmental variables constant. The goal is to make the change so gradually that it is not noticed by the individual, or if noticed, that it does not change behavior.
- *Shaping*: using differential positive reinforcement to strengthen or "shape" successive approximations of a target behavior. Over time, differential reinforcement of progressively more desirable behaviors, along with withdrawal of reinforcement when unacceptable behavior occurs, teaches the child to behave more appropriately for the situation or procedure, in this case, by cooperating with the steps required for successful PAP usage.

For over a decade, behavioral psychologists have been teaching pediatric patients to cooperate with and adhere to PAP therapy for treatment of OSA and related disorders [10, 14–16]. A 2003 study by Koontz, Slifer, Cataldo, and Marcus [15] involved 20 children with and without NDD who had been diagnosed with OSA and prescribed PAP. Participants either received (1) a 1.5-h behavioral consultation with recommendations; (2) consultation, recommendations, and ongoing behavior therapy (average of three sessions); or (3) consultation, recommendations, and recommendation for ongoing behavior therapy, which was declined by the family. Post-intervention, 75% of those receiving the consultation or

the consultation + behavior therapy interventions successfully tolerated PAP and improved their overall usage, as compared to 0% of the group that was offered but declined additional behavioral intervention. Additionally, physicians and caregivers gave high satisfaction ratings regarding the intervention. The results indicated that the children who achieved the greatest increases in mean hours per night of PAP adherence (e.g., >5 h per night) were those reported to have higher levels of estimated cognitive functioning. This initial study was based on a nonexperimental analysis of retrospective clinic data; therefore, a second study was conducted by Slifer and colleagues [16] using repeated-measure, single-participant experimental design.

This second study by Slifer and colleagues used desensitization with four preschoolers aged 3–5 years who had developmental delays and one or more serious health impairments: obesity, heart problems, diabetes, asthma, lung abnormalities, or prior surgery [16]. The children were identified for behavioral intervention because of their distress reactions to the PAP mask and airflow during initial attempts to conduct a PAP titration during polysomnogram (PSG) or to initiate PAP therapy following PSG. Intervention was conducted in inpatient (three participants) or outpatient (one participant) settings and included distraction, counterconditioning, gradual exposure, differential reinforcement, escape extinction, and caregiver training. Behavioral assessment and intervention was conducted using behavioral rehearsal during sessions in which the PAP equipment, mask, and airflow were presented one step at a time.

Before beginning behavioral intervention, each child's mask and equipment were assessed by a nurse or respiratory therapist to determine if the child's mask fit properly. Pressure marks on the skin, air leaks into the eyes, or other discomforts were addressed with interventions including a petite-size gel mask, warm air humidification, use of a "ramp" setting to gradually increase pressure, or other modification to improve the child's physical comfort. Each child was observed during one or two PAP placement attempts. Initial adherence data were recorded and in addition, the child's favorite activities were assessed for potential use to relax, distract, and motivate the child.

A prospective, repeated-measure, nonconcurrent, multiple-baseline experimental design was used to evaluate the behavioral protocol's effectiveness. Prior to behavioral training, none of the children were consistently wearing the PAP equipment. After behavior therapy and caregiver training, all of the children successfully tolerated PAP and increased their hours of use to between 7 and 10 h per night.

Taken in combination, the studies described above provide preliminary empirical support for the usefulness of behavior analysis and therapy in decreasing anxiety, behavioral distress, and escape/avoidance behavior while systematically increasing cooperation and adherence in children with and without NDD having OSA. The combination of task analysis (which will be described in detail later in this chapter), distraction, graduated exposure, counterconditioning, shaping compliance through differential reinforcement, and escape extinction appeared to be effective for increasing child cooperation with and adherence to PAP.

Given the preliminary empirical support for behavioral interventions to improve pediatric PAP adherence, Harford and colleagues developed a systematic program for pediatric patients aged 0–21 with and without NDD [17]. Their program was conducted by specialists and trainees in both clinical psychology and respiratory therapy. Patients were typically seen for their initial appointment following diagnosis of OSA. During this initial appointment, education was provided to the child and caregiver regarding OSA and PAP, a mask fitting was conducted, the child was exposed to and briefly desensitized to the equipment (which continued in additional sessions as needed), and additional strengths and barriers that potentially affect adherence were assessed. The child continued to be seen every 2 weeks for individualized treatment and downloads of PAP adherence data until adherence reached 4 h a night for more than 80% of nights, followed by monthly appointments until adherence was demonstrated for 3 months. Then, patients were reintegrated into the sleep disorders clinic and medically monitored on a regular basis. Preliminary data analysis showed that 5 of the 12 patients following the protocol had greater than 75% PAP usage at their most recent appointment. Barriers to improvement with the PAP protocol included being lost to follow up, depressive symptoms, sensory problems, and lack of caregiver acceptance of PAP. Variable results were found for children with NDD following this protocol. More research is needed on the critical strategies and procedures that are necessary for successful PAP desensitization, as well as on barriers to adherence and creative strategies for overcoming those barriers.

Management

Behavioral training sessions to increase PAP compliance can be conducted on an outpatient or inpatient basis depending on medical status and the urgency for establishing adherence. In either setting, desensitization sessions of 30–60 min with a behavior therapist are typically the most a child can tolerate initially. Parents and other caregivers should be actively involved in the sessions as deemed strategically appropriate by the behavior therapist.

Even though PAP is prescribed for nighttime and naptime use, behavioral training and desensitization *should always occur when the child is awake* in order for the child to receive the full benefit of counterconditioning and to integrate PAP *as an activity that is associated with falling asleep*. This is an

important requirement that caregivers often try to skip over. It must be emphasized that children, whose PAP equipment is placed after they fall asleep and have never learned to fall asleep with the equipment on will almost invariably awaken, become distressed by the unfamiliar sensations, and remove the equipment. This can lead the child to avoid going to bed and to become fearful of going to sleep, causing or exacerbating difficulties with sleep initiation and reinitiation after partial nighttime arousals. Attempting to deceive the child by putting the equipment on after falling asleep is almost never successful in the long run.

The first interview with parents focuses on obtaining information about the child's history and previous experience with PAP and other medical diagnostic procedures. In this first session, the child's preferred items and activities should be assessed in order to identify options that may be used for distraction, counterconditioning, and positive reinforcement. The child's own PAP equipment is used during behavioral treatment. This equipment will have been prescribed by the physician and should have been fitted during a pulmonary clinic visit or a visit from a home healthcare provider/durable medical equipment company.

After the initial session, behavioral desensitization sessions follow a task analysis that breaks the PAP into its component steps. Using a task analysis allows for predictable, step-by-step exposure during PAP desensitization trials, in addition to documenting child tolerance and distress behavior during each step. The task analysis may be broken down into written descriptions or picture representation (Fig. 34.1) based on the child's developmental level and preferences.

Sample PAP Task Analysis

1. Sit on the bed and engage in enjoyable activity.
2. Place mask (not attached to the hose or cap/headgear) on the face for 5 s.
3. Place mask (not attached to the hose or cap/headgear) on the face for 10 s.
4. Place mask (not attached to the hose or cap/headgear) on the face for 1 min.
5. Loosely attach one side of the mask to the cap/headgear.
6. Loosely attach other side of mask to the cap/headgear.
7. On one side of mask, tighten cap/headgear to proper position.
8. On second side of mask, tighten cap/headgear to proper position.
9. Turn on machine/air.
10. Attach tubing to machine.
11. Attach tubing to mask (with pressure turned on) for 3 s.
12. Attach tubing to mask (with pressure turned on) for 5 s.
13. Attach tubing to mask (with pressure turned on) for 10 s.
14. Attach tubing to mask (with pressure turned on) for 1 min.
15. Attach tubing to mask (with pressure turned on) for 5 min.
16. Attach tubing to mask (with pressure turned on) for 10 min.
17. Attach tubing to mask (with pressure turned on) for 15 min.

One advantage of the visual task analysis is that in addition to making the procedure more predictable for the child, it can be used to assist with providing reinforcement (i.e., placing a sticker or stamp once each step is completed, then receiving a prize, or accessing a preferred stimulus or activity after completing all steps included in the session). Additionally, with systematic performance data, the therapist and caregivers can quantify progress that may not be apparent in any individual exposure trial or therapy session. This helps to maintain optimism and motivation to persist with desensitization efforts when progress seems slow.

A key component of this behavioral intervention is counterconditioning sessions to reduce the child's anxiety through gradual exposure to the medical supplies, equipment, and physical sensations the child will experience. This exposure can be conducted while the child is enjoying a distracting, preferred activity, as the activity may keep the child in a relaxed state that overrides or, at least, competes with feelings of anxiety. Once the child visibly relaxes and enjoys the activity, gradual exposure can be conducted by slowly moving the equipment (PAP mask or machine) closer to the child. The duration of contact with the equipment and its sensations (i.e., pressure of the mask or nasal pillow, smell of supplemental oxygen if used and plastic tubing, sound of the PAP machine, air pressure through the mask and into the nose) should be slowly increased, and any cooperative behaviors should be differentially reinforced.

Vicarious learning or modeling can be another helpful strategy. This involves placing the materials on a doll, stuffed animal, or other individual (i.e., caregiver or therapist) and allows the child to become familiarized with the equipment. Caregivers and therapists are able to show the child that equipment is safe, in addition to modeling successful coping, before the child is prompted to wear the equipment. This allows a child to be gradually exposed to the PAP equipment on someone else (and to possibly experience mild distress in doing so), which helps begin to extinguish the child's anticipatory anxiety.

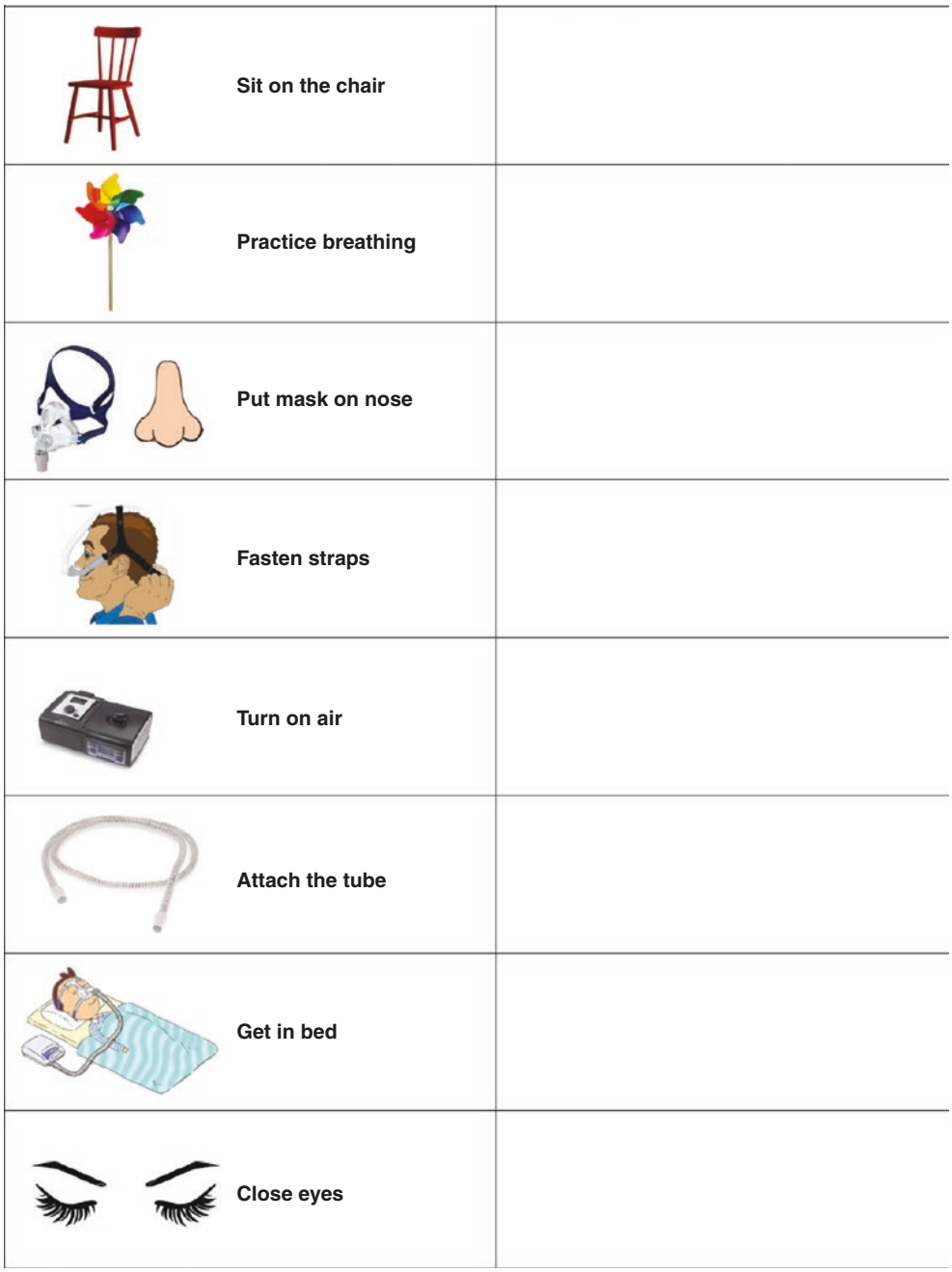

Fig. 34.1 Sample visual task analysis for PAP

Another strategy used in behavioral training for PAP is to allow for gradual exposure to materials (stimulus fading). In addition, in a process referred to as behavioral "shaping," approximations of cooperative behavior are positively reinforced through access to preferred items and activities (i.e., tangible stimuli, videos, games, and social praise). Approximations may begin with reinforcement for sitting in a chair with PAP equipment on a table nearby when prompted, then sitting in a chair with the equipment in the child's lap, then sitting in a chair with one piece of equipment applied, and so forth. In this way, stimulus fading is used for approximating the placement of the mask and the intensity of airflow. The length of time of exposure also is gradually increased as tolerance and cooperation improve.

Escape extinction is implemented as needed by interrupting the child's attempts to pull, remove, or push away the equipment. If equipment is successfully removed by the child, it should be quickly replaced. Blocking escape behavior ensures that the child cannot escape or avoid PAP-related sensations and increases the chances they will begin forming positive associations with PAP resulting from distraction, relaxation, and positive reinforcement (counterconditioning). Additionally, escape extinction teaches children that trials end based on an external cue, such as a timer alerting or a discrete play activity being completed, rather than in response to distress or attempts to remove equipment.

In addition to direct skill implementation with the child, therapists also provide education to caregivers regarding

differential reinforcement of cooperation and tolerance of the PAP-related stimuli and sensations while ignoring, redirecting, and blocking escape behavior. Parent training during which caregivers rehearse how to respond to child distress and escape behaviors is important for skill generalization to the home environment.

When the child is able to comfortably tolerate each step of the task analysis, training efforts subsequently focus on increasing the time of exposure to the equipment and sensations. For PAP adherence, the child also must learn to fall asleep wearing the mask or nasal pillow with air pressure at the prescribed level. To promote generalization from the medical setting to the home environment, parents should be assisted with developing a consistent bedtime routine that includes PAP placement. For example, the routine should begin about 30 min before bedtime and should include calming, soothing activities paired with placing the PAP mask and lying down in bed to go to sleep. Direct caregiver training on the intervention procedures should be provided by modeling developmentally appropriate instructions, use of distraction, differential positive reinforcement, and escape extinction as described above. Verbal and written instructions, therapist demonstrations, in vivo behavioral rehearsal with the child, and provision of corrective verbal feedback can be used to train caregivers to generalize these skills to home. When possible, it is helpful to coordinate desensitization appointments with the child's naptime in order to rehearse the bedtime routine and mask placement at a time when the child is likely to fall asleep.

At-home practice may be recommended to assist with generalizing PAP cooperation and coping skills to a different setting. This additional practice can include home-based review of the visual task analysis or practice with PAP materials. This at-home rehearsal allows the child to continue PAP exposure, thereby further decreasing sensitivity and anxiety to the equipment, in addition to giving caregivers the opportunity to identify problems and seek recommendations related to PAP usage at home. As discussed earlier in this chapter, *the ultimate goal is for the child to routinely fall asleep at home with PAP on and air pressure at the prescribed setting. By establishing the association between wearing PAP and falling asleep, caregivers enhance the child's ability to reinitiate sleep with the PAP on during night wakings and partial arousals*.

Case Vignette: Kenneth's Course of Treatment

Kenneth and his grandparents attended an initial evaluation session in an outpatient pediatric psychology clinic at an urban pediatric hospital for children with NDD. In the first session, the therapist obtained behavioral observations and conducted an interview. When presented with a task demand by his grandparent, Kenneth exhibited both disruptive and self-injurious behavior: he whined, flipped a small chair, and hit himself in the face. Undesirable behaviors stopped following removal of task demand and provision of access to preferred items. Information regarding sleep and tolerance of CPAP was obtained. In the 1 year prior to evaluation, grandparents reported that Kenneth tolerated CPAP mask placement for a maximum of 1 min using distraction with preferred activities. Screaming, crying, turning his head, and pushing the mask away were reported during attempted mask placement.

Due to geographic barriers, the family was unable to commute for weekly outpatient sessions. Kenneth was referred for an inpatient admission at a pediatric neurorehabilitation unit for intensive CPAP desensitization. During evaluation, the grandparents reported an average baseline CPAP tolerance of 2 s which could only be achieved with maximum physical assistance. Distress and behavioral dysregulation as evidenced by crying, hitting, kicking, screaming, and hitting himself in the face and head was reported upon presentation of the mask. Similar distress was also reported during use of inhalers and nasal sprays. In addition to CPAP intolerance, general behavioral difficulties noted included disruptive behaviors (e.g., whining, yelling, crying), self-injurious behaviors (e.g., head banging, hitting self in the face and head), and aggression (e.g., kicking, biting, hitting, pinching, throwing objects). Triggers included frustration when denied access to preferred items, soiled diapers, and prompts to complete non-preferred task demands.

Initially, treatment sessions were conducted twice daily for approximately 1 h per session. Kenneth remained seated in his crib during sessions. During the first day of treatment, sessions consisted of 30 trials of 1–5 s duration. His home CPAP equipment was used. The mask was initially disassembled and the pieces were presented separately. Each trial consisted of a task demand paired with a countdown presented both verbally and visually (i.e., fingers on hand, visual timer). Following successful completion of each trial, positive reinforcement in the form of social praise and access to his preferred item, an electronic tablet, was provided. Task demands were systematically increased across trials and included looking at the mask, placing his hand on the mask, and placing the nosepiece on his lower arm, mid-arm, shoulder, top of his forehead, and then nose. Kenneth started to anticipate the steps, demonstrating learning by counting with the therapist using his fingers and pointing to reinforcing stimuli. No crying, physical aggression, or self-injurious behaviors were observed.

On the second day of treatment, trials increased in length up to 15 s with intervention initially remaining consistent. On subsequent trials, positive reinforcement was provided contingent on continued adherence with task demand (i.e., tablet provided during each trial), increasing in length up to 60 s. A visual and verbal countdown was used during the final 5 s of each trial. Task demands were systematically increased to include placement of the mask headgear, first with one strap loosely secured, then two straps loosely secured, and finally all straps secured. Upon achievement of all straps secured, the timer was removed, and trials were continued until Kenneth exhibited verbal distress (e.g., whining) or touched the mask, after which he was prompted to place his hands on his lap and wait for completion of a 5-s countdown. At the end of the countdown, both the mask and access to the preferred item were removed. Once the mask was replaced, access to preferred item was restored. In this way adherence with the mask was consistently paired with access to preferred activities. Kenneth increased tolerance of the mask to 30 min in seven trials. No crying, physical aggression, or self-injurious behaviors were exhibited. He was observed to point his nose toward the therapist and use sign language for "please" to initiate mask placement in an effort to obtain access to his preferred item. For the remainder of sessions throughout admission, when he caught sight of the therapist, Kenneth would sit in the middle of his bed and put a pillow on his lap to prepare for trials in anticipation of the tablet, which was typically placed on his pillow.

During the initial session on the third day of treatment, the therapist collaborated with the respiratory therapist (RT) to evaluate the fit of Kenneth's mask in relation to the facial anomalies associated with Kenneth's genetic condition. Due to his history of distress, he never had a proper mask fitting. Upon evaluation by RT, his mask was determined to fit poorly, and a new pediatric mask was provided. Shaping trials increasing in length of time were conducted until tolerance of placement was achieved at which time RT evaluated the fit of the mask. This new mask was also determined to be inadequate so a third pediatric mask was provided. Additional shaping trials were conducted until adequate fit and tolerance were achieved on the sixth day of treatment. No physical aggression or self-injurious behaviors were observed. Two instances of brief distress behavior in the form of crying were observed but resolved with a change to a different preferred activity. Through the shaping trials and differential reinforcement, Kenneth learned that his mask must be kept on in the proper position to gain access to his preferred activity. Because of this, he learned to adjust his mask placement to ensure it was properly placed. When distracted, Kenneth occasionally touched his mask, but in response to a gentle "hands down" verbal prompt, he immediately put his hands on his lap and did not become distressed.

Upon achieving tolerance for mask placement during daytime trials, initiation of mask placement was conducted prior to naptime, and a naptime routine was established (e.g., sit on bed, place mask, provide access to brief video on tablet, prompt to lie down, transition tablet to lullaby music, turn tablet screen away, and maintain audio). Kenneth consistently fell asleep with his mask placed at naptime. After two consistent days of sleep initiation with the mask placed at naptime, it was then also placed prior to overnight sleep initiation. The tablet was faded out and replaced with activities more conducive to sleep: a bedtime story and lullaby music.

Beginning on treatment day 7, daytime trials focused on introduction of air pressure. This began with CPAP pressure set to the lowest possible setting, with approximately 6 in. between the tubing attached to Kenneth's mask and the tubing attached to his CPAP machine. The distance between the tubing was systematically decreased until tubing was fully connected together. During the initial four trials of full connection, distress behavior decreased with each trial as Kenneth habituated to the CPAP, and no attempts at escape were made. No crying was observed during the remainder of trials. RT remained present during sessions conducted with air pressure and collaborated throughout treatment.

Throughout the remainder of his admission, the therapist provided intervention on approximately 10 additional days. Intervention included daytime trials to increase tolerance of air pressure while systematically increasing CPAP pressures to reach the prescribed pressure target. CPAP mask with prescribed pressure delivered was placed prior to sleep initiation at both naptime and bedtime. The therapist trained caregivers and multiple RTs to complete Kenneth's naptime and bedtime routine with CPAP placement to generalize to other providers and fade the presence of the behavior therapist. Finally, modifications were made to naptime and bedtime routines to increase efficiency with CPAP placement and decrease breaks between steps. During overnight sleep, some grabbing and pulling behaviors were observed. Blocking was provided to maintain CPAP placement and to promote sleep maintenance and habituation to CPAP. Overnight tolerance of CPAP at time of discharge was approximately 8 h.

Areas of Uncertainty and Future Directions

The procedures detailed in this chapter are based on general principles of behavior and procedures that have broad support in the behavior analysis, behavior therapy, and pediatric psychology literature. Use of simulated (mock) medical procedures, stimulus fading for gradual exposure, distraction, counterconditioning, response shaping using differential positive reinforcement, and escape extinction all have substantial empirical validation in other clinical contexts.

Escape extinction can be initially frustrating to children, but if it is implemented within a multicomponent intervention that includes positive features such as distraction and reinforcement, it tends to be well-tolerated after some initial distress. To be successful, this procedure requires parents and caregivers to allow their child with NDD to experience some mild to moderate distress, as evidenced by crying, pulling away, or shouting. This level of distress is comparable to what a child may experience when frustrated by behavioral demands to participate in non-preferred activities of daily life, such as personal hygiene care, school demands, or bedtime. Children with NDD are routinely exposed to some level of frustration and distress at home, school, and in the community.

More research is needed to test experimentally which of the specific intervention procedures described here are necessary to achieve PAP tolerance and adherence. Controlled single-subject experiments and randomized clinical trials are needed to further refine these interventions. As research accumulates PAP desensitization may be sufficiently manualized for broad application using only essential components, while allowing for individualization for specific individuals with NDD.

Successful PAP desensitization may require the specialized skills of an advanced behavioral therapist working at a specialized pediatric facility. However, with additional training and accumulated practical experience working with individuals with NDD, respiratory therapists, nurses, child life therapists, or other healthcare professionals may be able to successfully desensitize children with NDD to PAP. Ongoing recorded or written data from the training sessions would be helpful. With session-by-session outcome data, behavioral interventions can be individualized to the unique challenges and needs of the specific patient to maximize the chances of success.

Providing the types of behavioral services described in this chapter can be difficult with very young children and with children and youth of any age who have NDD. Also, children with severe anxiety or general behavior problems occurring across settings require an extra degree of behavioral expertise from those who work with them. For children with NDD, the process of therapy can look chaotic at times to the casual observer due to the child's distress behavior and attempts to escape a non-preferred and confusing situation. With more severe NDD, learning may be slower and require more frequent but briefer training trials. Some children may learn more quickly if the training is conducted in brief trials in one setting and then the child is allowed to escape for a contingent break after he or she was cooperative during a training trial. In these situations, the availability of colleagues for backup and "extra hands" may be needed. Specialized environments and resources may be required to keep children safe when escape extinction results in severe tantrums.

Children with NDD may be highly sensitive to routine changes, tactile stimulation, and unexpected noises. However, the behavioral interventions described above can be successful despite these sensitivities but may require more time, resources, planning, problem-solving, and access to the patient and family. Sometimes, when PAP is urgently needed, admission to a pediatric inpatient unit that has intensive medical and behavioral resources available could be considered in places where these resources are available. These types of facilities are most often available at university-affiliated hospitals with special services for individuals with medical, neurodevelopmental, and behavioral disorders. These programs may be referred to as "Behavioral Medicine" programs and may be embedded in departments of pediatrics or psychiatry at major medical institutions.

Finally, professionals attempting to do behavioral desensitization with children and youth with NDD should be conscious of their own capabilities, limitations, and resources before attempting to intervene with individuals with complex neurodevelopmental, behavioral, or psychiatric needs.

PAP Desensitization Summary

1. Children with NDD are more likely than typically developing children to require PAP.
2. Children with NDD are often able to tolerate PAP but may require behavioral training in order to successfully tolerate it.
3. Behavioral intervention can be used to desensitize the child to PAP and to teach cooperation and coping so that distress is minimized and procedural tolerance is acquired.
4. Providers should consider the likelihood that a specific child will be able to successfully tolerate PAP without behavioral intervention, and if tolerance seems unlikely, the child should be referred as soon as possible to a behaviorally trained pediatric psychologist or behavior therapist for desensitization.
5. The initial session should focus on assessing barriers to cooperation (e.g., anxiety, hyperactivity, tactile defensiveness, escape-avoidance behavior) and identify

preferred activities and items to use for distraction and differential reinforcement.

6. The PAP mask and components should initially be introduced during the daytime so distress, tolerance, and progress can be closely monitored while gradually teaching tolerance using behavioral strategies (e.g., distraction, blocking, differential reinforcement) that may be difficult for parents to consistently implement if attempted at home overnight before the child is sufficiently desensitized.
7. The desired outcome is that the child develops a strong association between wearing the PAP and falling asleep so that it will be possible to reinitiate sleep with it on during nighttime partial arousals or night waking.
8. A preferred activity for distraction should be provided during initial introduction of the PAP mask, machine, and airflow pressure.
9. It may be helpful to have the child engage in an activity that is incompatible with removing the mask (e.g., holding a toy or playing a game on the computer tablet).
10. For most children training can be conducted in 30–60 min sessions using their prescribed PAP equipment and materials.
11. Desensitization and training should follow a consistent gradual exposure format by following a task analysis of the behaviors or steps required for successful coping and cooperation.
12. A visual task analysis is helpful to communicate to the child what will happen during PAP and to establish a predictable routine for prompts, exposure, and differential reinforcement.
13. Modeling cooperative behavior can help the child learn the PAP routine and see that it does not cause discomfort or distress.
14. Use stimulus fading to gradually expose the child to the unfamiliar or non-preferred stimuli and sensations involved in PAP while shaping physical proximity and time of exposure.
15. Differentially reinforce successive approximations of cooperation and tolerance of equipment, procedural demands, and sensations using praise and contingent access to preferred items and activities.
16. Gently physically interrupt and prevent escape-avoidance behavior such as pulling off the mask, leaving the area, and hiding one's face while redirecting the child's attention to a preferred distracting activity.
17. Use a timer to communicate the duration of exposure, and signal when the caregiver, not the child, will remove the equipment.
18. Assign time-limited home practice with the specific materials and routine that the child has been able to tolerate in session in order to strengthen learning and transfer treatment outside of the behavioral clinic.

Conclusions and Recommendations

Each child is different and individualization of intervention increases the probability of success. The specific items and activities that will be most effective for distraction and positive reinforcement are idiosyncratic. Selecting the right distractor and reinforcement can dramatically improve the child's motivation to cope, cooperate, and divert attention away from PAP equipment. The behavioral procedures presented in this chapter may not be effective in every case, but with the right distraction and reinforcement during appropriate desensitization and training, the vast majority of youth with NDD can learn to successfully tolerate PAP.

Whenever possible, children with NDD should be referred to a behaviorally trained pediatric psychologist to assess the level of behavioral intervention likely to be required before the child is ready for PAP therapy. Behaviorally trained pediatric psychologists can work with the child, family, and medical caregivers to desensitize the child to PAP and establish environmental modifications and routines necessary to achieve PAP adherence.

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