Sleep in Children with Autism Spectrum Disorders

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The amount of research conducted on sleep in children and adolescents has increased dramatically over the past decade due to the recognition that many children have significant sleep problems leading to daytime dysfunction. Approximately one third of typically developing children have sleep difficulties at some point, and a similar percentage of adolescents have impaired or insufficient sleep leading to daytime impairments. Sleep problems are known to occur at even greater rates in children with special needs, such as those with developmental disabilities, psychiatric conditions, and medical illnesses. The recognition that interventions can improve sleep and may result in better daytime functioning has fueled a growing interest in more fully characterizing the sleep problems in children with special needs. This article presents a discussion of the sleep problems experienced by children with one particular group of developmental disorders—the autism spectrum disorders.

Introduction

Disrupted sleep and subsequent daytime sleepiness negatively impact behavior in typically developing children, which often manifests as hyperactivity, inattention, and aggression [1–3]. Moreover, disrupted sleep in children may lead to multiple behavioral problems that affect the individual and the family [4]. Given that the neurobiology of sleep and autism spectrum disorders (ASD) overlap, children with ASD are especially prone to sleep disorders. Disrupted sleep and daytime sleepiness may exacerbate core symptoms and behaviors of those with ASD and the frequently associated behaviors of aggression and hyperactivity.

Neurobiology of Sleep as Related to ASD

γ-Aminobutyric acid (GABA) and melatonin, a neurotransmitter and hormone implicated in promoting sleep and establishing a regular sleep-wake cycle, are affected by ASD (Table 1). Aberrations in the systems that regulate these substances may be inherent in ASD, thereby resulting in sleep disturbances. GABA is an important neurotransmitter in the preoptic area of the hypothalamus, a major sleep-promoting system. Brainstem regions, including the pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT), the locus coeruleus, and the dorsal raphe, contain neurons involved in arousal from sleep [5]. Neurons projecting from the preoptic area of the hypothalamus inhibit these brainstem regions, thus promoting sleep. In autism, GABAergic interneurons appear disrupted, and a genetic susceptibility region has been identified on chromosome 15q that contains GABA-related genes [6,7]. The expression of these autism susceptibility genes may affect sleep by interfering with the normal inhibitory function of GABA via the preoptic area neurons.

The circadian system is also involved in the regulation of the sleep and wake cycle. The internal body clock in the suprachiasmatic nucleus (SCN) receives information regarding the environmental light/dark cycle via the retinohypothalamic tract. Melatonin is released by the pineal gland in response to signals from the SCN and inhibited by light [8]. As reviewed in the following text, abnormalities in melatonin production have been documented in patients with ASD.

Prevalence of Sleep Problems in Children with ASD

Between 44% and 83% of children with ASD have sleep problems, particularly sleep initiation and maintenance difficulties [9–11]. Additionally, children with ASD suffer from irregular sleep-wake patterns, early morning awakenings, and poor sleep routines [12,13]. Because most studies have examined children with classic autism, most of whom also have intellectual deficits, these prevalence rates need to be evaluated in the context of the prevalence of sleep problems in patients with intellectual deficits. Attempts have been made to control for the confounding

Table 1. Causes of sleep disturbance in children with autism spectrum disorders

Neurobiologic: abnormalities in GABA or melatonin
Behavioral: inadequate sleep hygiene, sleep-onset association type, limit-setting type
Coexisting neurologic disorder (eg, epilepsy)
Coexisting medical disorder (eg, gastrointestinal reflux disease)
Coexisting psychiatric disorder (eg, anxiety)
Medications (eg, corticosteroids, bronchodilators)
Obstructive sleep apnea
Parasomnias (non-REM arousal disorders, REM sleep behavior disorder, rhythmic movement disorder)
Periodic limb movements of sleep

GABA—γ-aminobutyric acid; REM—rapid eye movement.

variable of intellectual deficits, and it appears that ASD is an independent risk factor for sleep problems [11,14]. A recent study examined parental perception of sleep problems of children with ASD and normal intelligence compared with age-matched controls. Sleep problems in the ASD group occurred at a significantly higher rate than the comparison group and were more severe [15].

Because, by definition, children with Asperger's syndrome do not have intellectual deficits, a number of studies have looked at the prevalence of sleep problems in this population to help determine if ASD is an independent risk factor for sleep problems. One study compared the sleep of 50 children with Asperger's syndrome with the sleep of 43 controls using a sleep questionnaire. Average sleep duration was significantly shorter and sleep latency (time to fall asleep) was significantly longer in the Asperger's syndrome group [16]. These findings were supported by investigations comparing the quality of sleep as measured by parental surveys of children with autism, children with Asperger's syndrome, and typically developing controls [17,18]. Polimeni et al. [17] documented that approximately 73% of children with autism and Asperger's syndrome had sleep problems compared with 50% of typically developing children. Allik et al. [18] studied 8- to 12-year-old children with Asperger's syndrome or high functioning autism and showed that difficulties initiating sleep and daytime sleepiness were more commonly reported by parents of children with ASD than parents of typically developing controls. The insomnia reported by parents corresponded to objective findings obtained with actigraphy. Problematic insomnia reported by parents has been substantiated by a recent study using polysomnography. Malow et al. [19•] evaluated the sleep of children with ASD and age-matched controls, dividing the ASD group into "good sleepers" and "poor sleepers" based on parental responses on the Children's Sleep Habits Questionnaire. "Poor sleepers" (as rated by parents) showed prolonged sleep latency and decreased sleep efficiency on overnight polysomnography compared with ASD "good sleepers" and the typically developing controls. Taken together, these studies suggest that the primary sleep problem in ASD is insomnia.

Proposed Etiologies of Sleep Problems in Children with ASD

Circadian rhythm dysfunction may contribute to the insomnia observed in patients with ASD [20–22]. The circadian master clock, housed in the SCN of the hypothalamus, determines the timing of melatonin production. Several studies have demonstrated abnormal melatonin regulation in individuals with ASD compared with controls, including elevated daytime melatonin and significantly lower nocturnal melatonin [20–22,23•]. Although these studies support abnormalities in circadian rhythm physiology in patients with ASD, they have several limitations. Most importantly, these studies have focused on the amplitude, or amount, of melatonin production and not on the phase of melatonin production relative to sleep. Moreover, the numbers of patients in these studies are small, the presence and nature of their sleep problems are not well defined, and ASD phenotypes are not well characterized. Also, the methodology across studies is not consistent, making comparison of results less reliable.

As with children who are developing typically, children with ASD are prone to have behavioral insomnia of childhood, such as sleep-onset association type or limit-setting type, inadequate sleep hygiene, or a combination of factors [24]. In some cases, these behavioral issues may be the underlying cause of insomnia, although it is likely that behavioral issues are compounded by neurobiologically determined insomnia.

Psychiatric symptoms may interfere with sleep initiation. Children with ASD often have difficulties regulating emotions, especially anxiety. Anxiety resulting in insomnia may manifest in the evening as preparations are made for transitioning to sleep. Children with ASD are at increased risk of developing clinical depression, a condition often associated with insomnia. Medical conditions such as gastrointestinal reflux can contribute to awakening at night, and neurologic conditions such as epilepsy may impact negatively on sleep [25]. Insomnia may also result from a variety of medications used to treat coexisting conditions. Examples include corticosteroids and asthma medications, stimulants for attention-deficit hyperactivity disorder, serotonin reuptake inhibitors for depression, and antiepileptic drugs for epilepsy or mood stabilization.

Beside these etiologies, only a few case series suggest other sleep pathologies in patients with ASD. One case series utilizing polysomnograms demonstrated increased rapid eye movement (REM) sleep without atonia [26]. This finding is seen in patients with REM sleep behavior disorder (RBD). In this case series, patients with REM sleep without atonia were treated with clonazepam, leading to an improvement in their sleep and daytime behavior. One limitation of this study was

that medication use was not specified in the participants; many medications, including the serotonin reuptake inhibitors used in children with autism, can contribute to RBD [27]. A larger study of polysomnograms in children with ASD who were medication free did not identify REM sleep without atonia [19•], although one child in this series was noted to have obstructive sleep apnea (OSA), with improvement in sleep and daytime behavior after adenotonsillectomy [28]. Another study using polysomnograms reported that three of eight patients with Asperger's syndrome had an increased number of periodic limb movements [29]. The clinical significance of periodic limb movements recorded on polysomnogram in the absence of restless legs syndrome or other symptoms is uncertain. Research to date has not demonstrated an increased risk in this population for OSA outside of other known risk factors [15,19•,30].

Assessment of Sleep Problems in Children with ASD

Given the high prevalence rate of sleep disturbances, all children with ASD should be screened for sleep problems by either a questionnaire or clinical evaluation. There are a number of published sleep questionnaires designed for use in children, including the Pediatric Sleep Questionnaire [31] and the Children's Sleep Habits Questionnaire [32]. If sleep disturbances are discovered in the screening process, they should be addressed in the treatment plan. Treatment for some children and adolescents may only require sleep hygiene interventions or changes in the sleep environment. Other children and adolescents may require more detailed behavioral intervention. If symptoms or signs of sleep-disordered breathing are discovered, the individual should be referred to a sleep specialist because overnight polysomnography may be indicated. Although ASD in and of itself does not appear to be an independent risk factor of obstructive sleep apnea, there will be children with ASD who have other risk factors, including adenotonsillar hypertrophy, obesity, and craniofacial abnormalities such as micrognathia. If restless legs syndrome or excessive movements while asleep are suspected, a referral to a sleep specialist is warranted. The most common sleep problem in this population will be insomnia. Behavioral interventions should be offered to all children with ASD and insomnia, but they may not be adequate to address the problem in some children. In those children, pharmacotherapy may be indicated. If the clinician assessing the child with ASD and severe insomnia is not comfortable implementing behavioral measures or prescribing medications for insomnia, referral to a sleep specialist should be made.

Treatment

Insomnia

The diagnosis and treatment of an underlying sleep, medical, or psychiatric condition contributing to insomnia is often done in conjunction with consultants, with confirmatory ancillary tests as needed. In the case of coexisting epilepsy, the child's seizures must be appropriately treated, as even daytime seizures can affect sleep the following night [33]. Whenever possible, a medication that will dually promote sleep and treat a coexisting medical, neurologic, or psychiatric disorder should be used. To help promote sleep, the physician should adjust the dose, timing, or specific medications that the child is already taking.

Once other causes of insomnia in ASD are excluded (or treated), behavioral therapy should be initiated (Table 2). Typically developing children suffering with insomnia benefit from behavioral treatments [34]. Several small studies of children with developmental disorders, including ASD, suggest the utility of behavioral interventions in this population [4,35]. A cornerstone to the behavioral treatment of insomnia in ASD is identifying maladaptive sleep habits and educating parents in the basic principles of sleep hygiene. These include selection of an appropriate bedtime and wake time, establishment of a bedtime routine, and encouraging non-reinforcing interactions with the child during night wakings.

Exogenous melatonin has shown promise in promoting sleep, although controlled studies of its efficacy and tolerability are limited. Its relative availability (does not require a prescription), low expense, and favorable safety profile make it an attractive choice for promoting sleep in children with ASD. Although melatonin is considered a nutritional supplement, is not approved by the US Food and Drug Administration (FDA), and has not been rigorously tested for safety, efficacy, or purity of preparation, no serious long-term adverse effects have been seen with this widely used supplement.

Several small studies of melatonin in children with neurodevelopmental disabilities and ASD demonstrate favorable results. Reductions in sleep latency (ie, time to fall asleep) and improvements in total sleep time and sleep efficiency (ie, time asleep divided by time in bed and expressed as a percentage), with minimal or no adverse effects, have been observed in studies of children with neurodevelopmental disorders given supplemental melatonin [36–39]. Epileptic seizures did not occur in children who had been seizure free, and seizures did not increase in those with epilepsy in these studies. Only one study of five children with refractory seizures reported increased epileptic seizures during melatonin treatment [40]. A large retrospective study of more than 100 children with ASD treated with melatonin documented minimal adverse effects, with improved sleep in 85% of children treated [41].

Two trials of supplemental melatonin have been performed exclusively in children with ASD. One open-label trial administered 3 mg of immediate-release melatonin 30 minutes prior to bedtime for 2 weeks in 15 children with Asperger's syndrome [16]. All children had severe sleep problems and none were taking psychotropic medications. Sleep latency, as measured by actigraphy,

Table 2. Treatment of sleep disorders in children with autism spectrum disorders

Insomnia
Behavioral therapies, including attention to daytime habits, bedtime routine, and interactions with caregivers during night wakings
Supplemental melatonin
Light therapy
Other pharmacologic therapy, whenever possible targeted to treat coexisting medical, neurologic, and psychiatric comorbidities
Obstructive sleep apnea
Adenotonsillectomy
Weight loss
Continuous positive airway pressure
Non-REM arousal disorders: clonazepam and home safety measures
Rhythmic movement disorder: clonazepam and protective headgear
REM behavior disorder: clonazepam (first line), dopaminergic agents, melatonin, and home safety measures
Periodic limb movements of sleep: dopaminergic agents (first line), clonazepam, gabapentin, pregabalin

REM—rapid eye movement.

significantly decreased during treatment. Improvement in daytime behavior also occurred. Two children experienced mild tiredness and difficulty awakening, and two also had headaches. A second open-label study of combined immediate- and controlled-release melatonin (3–6 mg) in children with autism showed improvement in sleep diaries and questionnaires in all patients [42]. One month after melatonin was discontinued, most of the children returned to pretreatment sleep scores.

Because melatonin's half-life is less than 1 hour, it is recommended that melatonin be given 30 minutes prior to the desired time of sleep onset. In addition to causing sedation, melatonin also has a chronobiotic (phase-shifting) effect. Therefore, melatonin may be more effective in treating delayed sleep phase syndrome when given several hours before bedtime at physiologic doses (less than 500 μg). Doses of 1 to 3 mg are more sedating and more commonly used when a hypnotic effect is desired. Dosage is usually started at 1 mg and titrated by 1 mg every 1 to 2 weeks up to 3 mg if needed. Occasionally, doses of 6 mg or higher are needed. Because it is available over the counter and not regulated by the FDA, it is important to instruct parents to read the label carefully and avoid choosing a brand with other active ingredients (eg, diphenhydramine). Oral melatonin is rapidly metabolized, and extended-release melatonin (also available over the counter) may be helpful for the child with sleep maintenance difficulties [43]. Once a sleep cycle is established for 6 weeks or more, the melatonin may be discontinued, although long-term use appears safe and may be necessary.

Apart from melatonin, there is a wide range of options for pharmacologic treatment, which is best used in conjunction with behavioral techniques and tailored to the cause of the individual child's sleep problem. With all medications, it is important to start with low doses and increase gradually, monitoring carefully for adverse effects, because children with autism may be sensitive to certain classes of medications and unable to communicate side effects. It is important to keep in mind that there are no FDA-approved medications for pediatric insomnia.

A helpful principle for prescribing sleep medications in children with ASD is to consider the overlapping neurologic and psychiatric systems that are affected. Wherever possible, prescribe a medication that also assists with the coexisting condition. In children with coexisting epilepsy, antiepileptics with sedating properties can be used. The antiepileptic regimen can be adjusted to administer a bedtime dose of medication that provides sedation and promotes sleep. Options include carbamazepine, gabapentin, or topiramate, which are usually dosed two or three times a day but can be adjusted to give a higher dose at bedtime. Valproic acid comes in an extended-release form that can be given once a day, at bedtime. Lamotrigine tends to be more stimulating and may interfere with sleep, but may be an excellent choice in children with daytime sleepiness.

Children with insomnia associated with extreme mood irritability, aggression, or self-injurious behavior may benefit from treatment with atypical neuroleptics. Risperidone has recently been approved by the FDA for treating severe irritability and aggression in children with autism. In a child with these difficulties and insomnia, risperidone could be initiated at bedtime; if multiple daily doses are needed, the dosage can be adjusted to give the higher dose at bedtime.

In the anxious or depressed child, specific antidepressants that promote sleep may be considered. These include the highly sedating drugs mirtazapine and trazodone, the mildly sedating serotonin reuptake inhibitor fluvoxamine,

and the tricyclic antidepressants. (Due to risk of priapism, male patients who cannot reliably communicate should not be prescribed trazodone.) The serotonin reuptake inhibitors or tricyclic antidepressants may also be useful for children with obsessional thoughts that interfere with sleep onset. Clonidine is also useful for sleep initiation problems in the child who is mildly anxious or over-aroused at night. Benzodiazepines such as clonazepam are another option.

Light therapy may be useful for children with circadian rhythm abnormalities, such as delayed sleep phase syndrome. Bright light administered in the morning "resets" the circadian clock and facilitates an earlier bedtime [44]. There are several commercial light boxes that emit ultraviolet-free light. An alternative to purchasing a commercial light box is for the patient to get exposed to bright light each morning. Although no definitive studies have been performed on patients with autism, light of 2500 lux administered for 30 minutes to 2 hours in the morning is recommended and is safe, based on experience from the pediatric seasonal affective disorder literature [45]. The dosage may be increased to 10,000 lux as needed. Lower doses may require longer treatment times. Cautions include the small risk of precipitating a manic episode in coexisting or unrecognized bipolar disorder or the risk of a photosensitivity reaction (usually precipitated by ultraviolet light exposure) [46,47]. If a child has a photosensitizing condition or is taking photosensitizing medications, the risk–benefit ratio should be carefully weighed and a non–ultraviolet-emitting light source should be used. Close follow-up with adherence to sleep hygiene measures is necessary to prevent relapse.

Other sleep disorders

Although many sleep disorders can present in childhood, parasomnias and obstructive sleep apnea are common disorders that have unique relevance for children with ASD. Parasomnias can be confused with other conditions prevalent in ASD, such as epileptic seizures or repetitive and stereotyped behaviors. Parasomnias need to be distinguished from epileptic seizures in this population, given the increased prevalence of epilepsy in autism [48]. The parasomnias include the non-REM arousal disorders, rhythmic movement disorder, and RBD. Nocturnal events can usually be distinguished by history, although video-electroencephalogram-polysomnography in a sleep center is occasionally warranted.

The non-REM arousal disorders consist of a spectrum of events (sleepwalking, sleep terrors, confusional arousals) arising from non-REM sleep. Clonazepam is often effective for treatment of non-REM arousal disorders; tricyclic antidepressants given at night can also be useful. In rhythmic movement disorder, children exhibit repetitive, stereotyped, and rhythmic motor behaviors that occur predominantly during drowsiness and transition to sleep. These behaviors typically include body rolling, body rocking, head rolling, and head banging. Injuries can occur. Episodes usually occur at sleep onset but can occur at any time during the night. Although common in infants (59%) and small children (prevalence of 5% at 5 years), when rhythmic movement disorder persists to older childhood, ASD, mental retardation, or related disorders are usually present, and these children may have similar behaviors during the day [49]. Treatment should be initiated when the potential for injury is present. Clonazepam is the recommended choice, although it is not universally effective. Individuals suffering with RBD "act out their dreams" due to an interruption of physiologic muscle atonia during REM sleep. RBD disorder often responds to clonazepam, although dopaminergic agents and melatonin have also been tried [50]. In all these parasomnias, attention to safety issues is paramount. Children with these conditions are at risk of leaving the bed or bedroom, placing themselves at risk for injury. Bedside monitors and alarms or bells placed on a door that indicate to parents when a child has left the room may be necessary.

OSA may affect up to 3% of children in the general population and is characterized by loud snoring or noisy breathing (usually worse in the supine position) in association with restless sleep, frequent awakenings, and sweating in sleep. Pauses in respiration are not always evident. Diagnosis is made by overnight polysomnography, with monitoring of respiratory airflow and effort, as well as oxygenation, during sleep. Although the prevalence of OSA in children with ASD is unknown, identifying the presence of this sleep disorder can be very rewarding in caring for a child with ASD because improvements in sleep as well as daytime behavior may occur. Whereas daytime sleepiness is common in adults with OSA due to disrupted sleep at night, children may not appear sleepy and may instead exhibit symptoms of hyperactivity and other problematic behaviors. These behaviors may improve with treatment.

In children who continue to exhibit symptoms of OSA after adenotonsillectomy, a repeat polysomnogram is warranted. Children with obesity or craniofacial abnormalities may not respond fully to adenotonsillectomy. These children may be good candidates for treatment with continuous positive airway pressure (CPAP). In CPAP therapy, a steady stream of air pressure administered through the nasal passages into the back of the throat keeps the airway open. Although it may appear that children with ASD would have great difficulty adjusting to a CPAP mask due to tactile sensitivities, success can be achieved by providing a combination of parent education and CPAP desensitization. A variety of CPAP interfaces, including nasal interfaces that do not involve a mask, are available for children.

Impact on Daytime Behavior of Treating Sleep Disorders in Children with ASD

Children with ASD may show improvement in daytime behavior and functioning if comorbid sleep disorders are diagnosed and treated. Although definitive studies have

not been conducted in typically developing children, associations between sleep apnea and disruptive daytime behavior are well documented, with improvement in problem behaviors seen after adenotonsillectomy [51–53]. Short sleep duration has been associated with stereotypic behavior, higher overall autism scores, and social skill deficits in children with ASD [54]. A relationship likely exists among sleep problems, repetitive behaviors, and craving for sameness in children with autism, although this relation may be moderated by their level of cognitive ability [55]. In a case report of a girl with ASD and OSA, treatment with adenotonsillectomy improved daytime behavior [28]. Although she retained her autism diagnosis on the Autism Diagnostic Observation Schedule, her performance on this test improved in a variety of domains, including social interaction and the ability to focus. She also showed improvement on the Child Behavior Checklist, a questionnaire completed by parents.

Conclusions

Children with ASD frequently have significant sleep problems, most commonly insomnia. Fortunately, there are a variety of treatments available, including behavioral interventions and pharmacotherapy. When establishing a treatment plan, it is imperative to understand the underlying etiology of the sleep problem, which in many cases is multifactorial. Identifying and treating sleep disorders may result not only in improved sleep, but also impact favorably on daytime behavior and family functioning.

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