

INVITED REVIEW

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SLEEP AND GASTROINTESTINAL DISTURBANCES IN AUTISM SPECTRUM DISORDER IN CHILDREN

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Abstract

Autism spectrum disorder (ASD), a neurodevelopmental disorder with a prevalence of 1 in 68 children, commonly presents with comorbid conditions which include sleep disorders. Sleep disorders reported in ASD include, among others, increased bedtime resistance, insomnia, parasomnia, sleep disordered breathing, morning rise problems, and daytime sleepiness. Polysomnography studies show that children with ASD have altered sleep architecture including shorter total sleep time and longer sleep latency than typically developing peers. Sleep-related problems have been shown to affect overall autism scores, social skills deficits, stereotypic behavior, and cognitive performance. Additionally, problematic sleep in children with ASD has been associated with higher levels of parental stress. Underlying causes specifically related to sleep disorders are not fully known. Gastrointestinal (GI) disorders are commonly associated with sleep problems in these patients. Children with ASD and GI symptoms have been found to have a higher prevalence of sleep disturbances compared with typically developing peers who do not have GI symptoms. Treatment approaches to children with sleep disorders are varied and range from lifestyle modifications and behavioral interventions to drug therapies and surgical interventions. Physicians should take into account GI disorders as possible underlying causes of sleep-related problems in children with ASD. Therapeutic interventions should begin with less invasive methods before progressing to more invasive options such as pharmacotherapy and should be based on medical indications in order to provide effective care while minimizing potential adverse health effects. Evidence-based studies concerning GI and sleep disorders in children with ASD are limited and further studies are warranted.

Key words: autism spectrum disorder, gastroesophageal reflux, gastrointestinal diseases, insomnia, pharmacotherapy, sleep disorders

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is characterized by persistent deficits in social communication, social interaction and restricted repetitive and stereotyped behavior, interests, and activities [1]. Attention on ASD has been rapidly increasing due to the fact that for the past 40 years its prevalence has been steadily rising worldwide with about 1 in 68 children being identified with ASD in the United States according to estimates from the CDC's Autism and Developmental Disabilities Monitoring Network [2]. This rise in incidence is not fully understood and may be the result of several factors including an increased awareness of the condition by both parents and professionals, better diagnostic and assessment methods and/or screening tests, modifications to previous definitions and criteria of diagnosis, and a possible increase in the condition itself.

SLEEP DISORDERS IN AUTISM

Sleep disorders are among the many comorbid conditions present in ASDs [3]. Sleep problems in children with ASD are commonly reported. Fifty-three percent of young children with ASD may have at least one sleep problem [4]. Self-administered child sleep questionnaires completed by parents show that possibly even up to 86% of these children have at least one sleep problem almost every day [5]. A study by Liu et al. on sleep problems in children with ASD showed that 54% had problems with bedtime resistance, 56% with insomnia, 53% with parasomnias, 25% with sleep disordered breathing, 45% with morning rise problems, and 31% with daytime sleepiness [5]. Krakowiak et al. found that the most common sleep complaints among children with ASDs were related to shortened sleep time, nighttime awakening, bedtime resistance, and sleep initiation [4]. In addition, Miano

et al. showed that parents of children with ASD reported a higher prevalence of disorders of maintaining sleep, enuresis, and repetitive behavior when falling asleep. Moreover, the authors observed altered sleep architecture and cyclic alternating patterns in polysomnography studies [6]. A recent meta-analysis by Elrod and Hood found that children with ASD in general had shorter total sleep time, longer sleep latency, and lower sleep efficiency than typically developing peers [7].

Sleep is an essential part of a healthy lifestyle being linked with many physiological processes such as wound healing, immune system functioning, metabolite clearance of the brain, ontogenesis, memory processes, and others [8-11]. The importance of sleep is especially highlighted by the lack or impairment thereof. A lack of sleep or decreased quality of sleep have been reported in numerous studies to be associated with multiple adverse health effects such as arterial hypertension, diabetes/impaired glucose metabolism, obesity, depression, as well as impaired neurobehavioral performance [12, 13].

Studies on abnormal sleep in pediatric populations have shown that children differ from adults in their response to restrictions in sleep. Acute sleep restrictions have been found to cause decreases in all stages of sleep (except slow-wave sleep), reductions in sleep-onset latency and rapid eye movement (REM) latency, and reductions of wakefulness during the sleep period. Significant increases in daytime sleepiness following sleep restriction seem to persist into the morning. Children seem to be more severely affected by sleep restriction than adults. Results of polysomnography studies are comparable to adults, but children do not show recovery rebound of slow-wave sleep and REM sleep [13]. Sleep problems or restriction in pediatric populations have been associated with emotions, impulsivity, school performance, and executive functioning tasks, among others [14].

Sleep problems may significantly influence the cause and/or exacerbate the core disease of ASD if left untreated. A study by Schreck et al. found that fewer hours of sleep per night predicted overall autism scores and social skills deficits. Similarly, stereotypic behavior was predicted by fewer hours of sleep per night and screaming during the night. Increased sensitivity to environmental stimuli in the bedroom and screaming at night predicted communication problems [15]. Most recently, a study by Tessier et al. noted that children with ASD had lower sleep spindle density which had a significant correlation with cognitive performance [16]. Sleep problems not only affect the child's health and behavior but as well as the parent's (and quite possibly other family members). Problematic sleep in children with ASD has been associated with higher levels of parental stress which in turn may have an effect on subsequent care of the child [17, 18].

Unfortunately, sleep problems are commonly underdiagnosed, underappreciated, undertreated. The road to diagnosing sleep problems is equally problematic and filled with roadblocks. For one, the very nature of ASD greatly increases the difficulty of a diagnostic approach. Verbal communication with children affected by ASD can range from difficult to nearly impossible. Unlike normally developing children, they cannot simply state what they

are feeling or going through. Because of this, clinicians as well as parents have to be aware of other clues that may point to underlying causes of these sleep problems.

SLEEP PROBLEMS AND ALIMENTARY TRACT AILMENTS IN ASD

An important point to consider is that sleep problems may be exacerbated by, or even be the result of, other comorbid conditions. Other comorbid disorders in children with ASD are quite prevalent. In a population of over 160 children with ASD, Liu et al. observed attention deficit hyperactivity disorder (31%), epilepsy (11%), asthma (17%), allergies (50%), and gastrointestinal (GI) symptoms (21% with vomiting, reflux, spit-ups, 17% with chronic diarrhea, 18% with chronic constipation, 18% with abdominal pain, and 14% with intestinal bloating) [5].

Alimentary tract symptoms and disorders have been progressively taking the spotlight in terms of comorbid conditions in patients with ASDs in recent years. As we proposed in our recent paper, GI disorders and ASD coincidence may be an example of an overlap syndrome [19]. A common pathogenic background of both disorders may be composed of many pathways including genetic factors, immune abnormalities, enzyme insufficiencies, and genetic and metabolic activity of the microbiome and dietary metabolites which may contribute to brain dysfunction and neuroinflammation [20, 21]. Although the mechanism of these sleep disturbances is difficult to ascertain, nighttime awakening with pain or abdominal discomfort is common with gastroesophageal reflux and reflux esophagitis in children. Autistic children with GI symptoms have been found to have a higher prevalence of sleep disturbances, compared with those in the general population who do not have GI symptoms and with their siblings [22-24]. Furthermore, GI symptoms have been significantly correlated with insomnia and parasomnias [5]. More recently, a prospective study by Geier et al. showed that even up to 48% of children with ASD may present with GI disturbances [25]. Interestingly, individuals with comorbid psychiatric disorders, which are also common in individuals with ASD, had poorer rated health, as well as more frequent GI problems and sleep problems [26]. However, certain studies show that children with ASDs may not necessarily differ from typically developing children in sleep disturbances. Schreck and Mulick found that overall sleep duration was similar between ASD and normal children in a population of 5-12 year-olds and Polimeni et al. noted that hours of sleep per night were likewise similar between ASD and normal children [27, 28].

POSSIBLE THERAPEUTIC APPROACHES

Treatment approaches to children with sleep disorders are varied and range from behavioral interventions to drug therapies. Parent-based education and behavioral interventions are usually the first-line therapy unless symptoms are severe [29]. Behavioral parent training has been shown to significantly improve sleep problems versus comparison groups based on primary sleep outcomes of parental reports [30]. A study by Malow et al. showed that

Table I. Possible pharmacological interventions in children with autism spectrum disorder and sleep disorders.

Example drug	Drug class	Principal role	Reference(s)
Melatonin	Indoleamine derivative	Improvement of sleep-wake rhythm and sleep latency	[33, 34]
Ubiquinol	Coenzyme Q10 derivative	Modulation of neuronal activity through decreasing oxidative stress	[35]
Clonidine	α_2 -Adrenergic receptor agonist	Improvement of sleep initiation latency and nighttime awakening	[37]
Atomoxetine	Norepinephrine reuptake inhibitor	Symptom reduction in hyperactivity, self-stimulation	[38]
Fluoxetine	Selective serotonin reuptake inhibitor	Reduction of repetitive behaviors and irritability	[39]
Aripiprazole Risperidone	Neuroleptic	Reduction of challenging and repetitive behaviors	[36, 40]

parent-based education was beneficial in reducing sleep problems associated with mean sleep onset latency and sleep onset delay [31]. Decreasing bedroom media access may also prove to be very beneficial. Bedroom access to a television or a computer was more strongly associated with reduced sleep among boys with ASD compared with typically developing children. In addition to bedroom access, the amount of time spent playing video games was associated with less sleep also among boys with ASD [32].

Table I presents specific drug therapies [33-40]. They include melatonin (which has hypnotic and chronobiotic properties) and its derivatives as candidates for physiological sleep induction in disorders of insomnia and circadian rhythm sleep. Melatonin and its agonists are potentially effective and safe drugs in the treatment of comorbid insomnia with accompanying beneficial effects in a variety of neurological, psychiatric, cardiovascular and metabolic disorders [33, 34]. Ubiquinol supportive therapy has been shown in a study by Gvozdjakova et al. to improve sleep symptoms in 34% of children with ASD, but also improved communication with parents (in 12%), verbal communication (in 21%), playing games (in 42%), and food rejection (in 17%) [35]. Other pharmacological approaches include α_2 -adrenergic receptor agonists, such as clonidine, selective norepinephrine reuptake inhibitors, such as atomoxetine, selective serotonin reuptake inhibitors, such as fluoxetine, or neuroleptics, such as aripiprazole and risperidone [36-40]. Although these therapeutic choices have been shown to have positive results, these treatments may also bring with them adverse effects including weight gain, sedation, symptoms of restless legs, sleepiness, or even insomnia itself.

Taking into account that GI problems may be responsible for a great deal of sleep problems, one should consider that treatment focused on these conditions may bring relief or at least improvement in sleep problems symptoms [41]. Lifestyle modifications, including smaller but more frequent meals or elevated head position during sleep should be considered as possible first-line treatments. Other approaches that should be taken into account

whenever a child with ASD presents with sleep problems include, but are not limited to, proton pump inhibitors for gastroesophageal reflux or diet elimination/substitution therapies in food allergy such as cow milk protein allergy, lactose intolerance or celiac disease [41, 42]. Naturally, of paramount importance is adhering to medical indications for introducing these treatments by way of proper diagnostic tests.

CONCLUSIONS

Concisely, neurodevelopmental disorders such as ASD commonly present with comorbid disorders including sleep-related problems. Underlying causes specifically related to sleep disorders are not fully known. Furthermore, GI disorders are commonly associated with sleep problems and a patient history and physical examination should always include a GI aspect. Treatment approaches should begin with less invasive methods before progressing to options such as pharmacological interventions. Lastly, physicians should be open to discuss all available approaches in order to provide maximal care, as well as to minimize potential adverse health effects.

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Conflicts of interest

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