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Review Article

Sleep in children with autistic spectrum disorder

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ABSTRACT

Children and adolescents with autistic spectrum disorders (ASD) suffer from sleep problems, particularly insomnia, at a higher rate than typically developing children, ranging from 40% to 80%. Sleep problems in ASD might occur as a result of complex interactions between biological, psychological, social/environmental, and family factors, including child rearing practices that are not conducive to good sleep. Interestingly, children with a history of developmental regression have a more disturbed sleep pattern than children without regression. Even though regulation of sleep in children with ASD is still poorly understood, circadian abnormalities in autism might be the result of genetic abnormalities related to melatonin synthesis and melatonin's role in modulating synaptic transmission. Recently a bifurcation of the sleep/wake cycle with increased sensitivity to external noise and short sleep duration causing irregular sleep onset and wake up times has been suggested. Identifying and treating sleep disorders may result not only in improved sleep, but also impact favorably on daytime behavior and family functioning. Several studies have also demonstrated effectiveness of behavioral interventions for sleep onset and maintenance problems in these populations. When behavioral interventions are not effective or lead only to a partial response, pharmacological treatment options should be considered. Studies of melatonin use in children with ASD provide evidence for its effectiveness and safety in the long run. The clinician assessing a child with an ASD should screen carefully for sleep disorders and make referrals as indicated.

1. Introduction

Autism spectrum disorders (ASD) are life-long neurodevelopmental disorders that affect all areas of child development, characterized by markedly abnormal or impaired social interaction and communication, restricted interests, and stereotypical behaviors [1]. Numerous research studies indicate that children with ASD experience more sleep problems than the general population. The main objective of this review is to present research data on the sleep problems in children with ASD with emphasis on their prevalence, clinical characteristics, sleep architecture, potential etiology, influence on daytime behavior, assessment and treatment.

2. Prevalence of sleep problems in ASD

Sleep problems are highly prevalent in children with ASD ranging from 40% to 80% [2–12]. A recent study showed that sleep problems rank as one of the most common concurrent clinical disorders among children with ASD [13]. Since the majority of research studies include children with ASD and intellectual deficits, the prevalence rates of sleep problems need to be evaluated in the context of comorbid intellectual disability. Some reports revealed an increased proportion of severely developmentally delayed children with ASD who had sleep problems [14,15]. Given this association between intellectual deficits and sleep problems, attempts have been made to control for mental retardation as a confounding variable. In a study of highly functioning children with ASD, sleep problems appeared to be relatively specific to children with ASD compared to both typically developing children and children with intellectual disabilities without autism [16]. Based on parental reports, Krakowiak and colleagues [17] found that 53% of children (2–5 years of age) with ASD had at least one frequently experienced sleep problem compared to 46% of children with non-ASD developmental delays and 32% of typically developing (TD) children.

These studies and others demonstrate that children with ASD are particularly vulnerable to sleep difficulties [16–20]. However, the majority of these studies are based on parental reports. A recent study, using a multimethod approach, found that pre-school children with autism and developmentally delayed children without autism showed more sleep problems as reported by their

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parents than TD children, but these problems were not directly supported by more objective actigraphic data. Moreover, they found that parents of children with ASD slightly over reported sleep problems. Thus, the authors suggested that objective and subjective measures of sleep problems in pre-school-age children may produce different results [21].

Sleep problems often last for many years and sometimes continue into adulthood [22,23]. In one study, 63% of children with ASD and sleep problems experienced persistence of sleep difficulties over time [24]. However, Goodlin-Jones and colleagues recently used objective and subjective measures to assess sleep in preschool children with autism, children with developmental delays only, and typically developing children; objectively measured sleep problems were rarely persistent over a 6-month period of time [25].

3. Clinical characteristics of sleep in children with ASD

Sleep onset and maintenance problems resulting in reduced sleep duration are the most common concerns expressed by the parents of children with ASD. Several studies have reported settling problems with some children with ASD taking more than an hour to fall asleep [10,17,26]. According to parental reports, night wakings also commonly occur in children with ASD. Periods of nocturnal awakening lasting for up to 2–3 h have been reported when the child may simply laugh, talk, scream, or get up and play with toys or various objects in the room [9,15,26,27]. As noted by Richdale and Schreck [20], these night wakings are typical of children with autism. Studies utilizing actigraphy largely confirm increased sleep latency, frequent night waking, and shorter sleep duration [21,24,28]. It is worth noting that sleep onset and night-waking problems are often associated with poor sleep hygiene or maladaptive sleep associations [24]. Thus, as in the general population, behavioral insomnia is frequently experienced by children with ASD.

Although some sleep problems may have a strong behavioral component, circadian rhythm disturbances have also been reported in children with ASD [24]. Irregular sleep–wake patterns, free running sleep/wake rhythms, sleep onset delay and early morning awakening have been reported in children with autism [29–31]. Infants with autism tend to show early waking in the morning or later sleep onset in the evening [29]. Inanuma [32] reported significant day to day variability in sleep onset or waking times in children with ASD, especially in those less than 4 years of age.

Regulation of sleep in children with ASD is still poorly understood. In their recent study, Matsuura and colleagues [33] suggested a bifurcation of the sleep/wake cycle with increased sensitivity to external noise and short sleep duration causing irregular sleep onset and wake up times. The authors speculated that children with ASD have an altered balance between homeostatic and circadian forces leading to a heightened sensitivity of the sleep/wake cycle to environmental stimuli. They also concluded that sleep regulation tended to improve with age. The latter conclusion is supported by a study showing that more than 70% of children with ASD experience delays in circadian rhythm development by at least 5 months compared to typically developing children [31]. Interestingly, in a recent study comparing the sleep patterns and problems of pre-school age children with carefully diagnosed autism, developmental delay and TD, Goodlin-Jones and colleagues [21] found that children with autism sleep for shorter periods of time during a 24-h day. This suggests that sleep patterns in children with autism are organized differently than other children.

Moreover, seasonal changes in sleep patterns have been described among children with ASD. In one case, the sleep problems of an adolescent male with autism decreased from January to June and disappeared by July and August. His sleep disturbances recurred in October and were sustained through November and December [30]. In a recent study by Giannotti and colleagues [15], more than 10% of children with autism had sleep problems that varied by season. Sleep problems rapidly increased during the fall and spring, particularly in those individuals with a history of developmental regression.

Studies investigating variables potentially related to sleep problems (age, IQ, severity of autistic symptoms) in children with autism have yielded mixed results. Regarding the relationship between IQ and sleep problems, Richdale and Prior [18] reported more frequent sleep problems in children with moderate to severe intellectual disability compared to autistic children with mild degrees of disability. Another study reported only more night wakings [34] in children with mental retardation compared to children with autism and no retardation. In contrast, the majority of studies suggested that sleep problems can occur at all IQ levels, including in those who do not have mental retardation [2,16,17,35,36]. Regarding the relationship between age and sleep problems in children with autism, several studies have found increasing age to be associated with decreasing sleep problems [8,17,18]. In contrast, Honomichl [6] found that school aged children were reported to present more sleep problems than preschoolers. However, other studies reported no significant relationship between age and sleep problems in children with ASD [24,34–36]. Finally, regarding the association between sleep problems and severity of autistic symptomatology, some studies have reported a significant positive association between autism severity and parent reported sleep problems [27,36,37]. These findings suggest that sleep problems are part of the autism symptom complex and increase with increasing autism severity.

In considering prevalence and clinical characteristics of sleep problems in ASD, it should be noted that the majority of studies have been carried out on heterogeneous samples including children of various ages, intellectual levels, and types of autistic spectrum disorders. There have not been detailed analyses of associations between sleep patterns and particular medical conditions, which may themselves alter sleep or their treatments. Few studies have been carried out on more homogeneous groups.

4. Sleep architecture in children with ASD

Several PSG studies have confirmed the presence of disrupted sleep architecture in children with ASD [14,38–41]. PSG abnormalities include increased REM density [39], reduction of REM sleep, and an increase of undifferentiated sleep with a clear abundance of spindle activity not only during stage 2 sleep but also during SWS and REM sleep [38]. Longer sleep latency, increased night wakings, lower sleep efficiency, increased stage 1 sleep and decreased SWS as well as decreased density of spindle activity [41] have been described in children with ASD. One study indicated reduced total sleep time and shorter REM latency [14]. In this study, Miano and colleagues investigated sleep NREM microstructure in children with ASD and intellectual disability using cyclic alternating pattern (CAP) analysis [14,42]. They found a lower CAP rate associated with SWS sleep suggesting a subtle alteration of the arousal level during NREM. Whether these microstructural alterations of sleep relate to autism or intellectual disability is not known. A recent PSG investigation found that among children with autism, those with a history of autistic regression had longer sleep latency, less sleep efficiency, increased wake after sleep onset and longer REM latency than those without regression. Moreover, children with autistic regression showed lower CAP rates and A1 index during light sleep than children without history of regression and than TD children [43]. In contrast, a PSG study of a selected group of children with autism and sleep problems but without mental

retardation found lower sleep efficiency, prolonged sleep latency, decreased REM sleep and increased stages 3 and 4 sleep compared to children with ASD without sleep problems and typically developing children [10]. Interestingly, a PSG study on sleep architecture and NREM alteration found that children with Asperger syndrome showed lower CAP rates in stages 1 and 2, but not in SWS, and an increased percentage of A1 and decreased percentage of A2 compared with TD children. Moreover, with respect to children with ASD, Asperger subjects showed an increased CAP rate in SWS and decreased rate in sleep stage 2 suggesting that these different microstructural alterations of sleep might be related to the degree of mental ability [44].

Inconsistent results on sleep architecture in ASD can be explained by the wide range of patient population and methodology used across different studies. Future research in this area should emphasize more stringent diagnostic and selection criteria for subjects and more unified definitions of sleep disorders.

5. Pathophysiological mechanisms of sleep disorders in ASD

Richdale and Schreck [20] proposed that sleep problems in ASD might occur as a result of complex interactions between biological, psychological, social/environmental and family factors, including child rearing practices that are not conducive to good sleep. Any one or combination of these factors might contribute to sleep problems in children with ASD.

6. Neurobiological abnormalities

Intrinsic biological or genetic abnormalities that alter neuronal pathways in the brain might contribute to sleep problems in ASD. Most autistic children exhibit abnormal EEG and sleep/wake patterns, suggesting that the balance of excitation–inhibition is disrupted. Proposed hypotheses of sleep dysregulation in autism include abnormalities in the hypothalamic–pituitary–adrenal axis regulating circadian rhythms and alteration in hormone/neurotransmitter (melatonin/serotonin) production [9].

Several neurotransmitter systems, including gamma-aminobutyric acid (GABA), serotonin and melatonin, are implicated in promoting sleep and establishing a regular sleep/wake cycle. Aberration in these systems may be responsible for sleep disturbance in ASD [45]. Failure to develop a circadian cycle due to failure to entrain to the day/night cycle has been suggested in ASD [46]. This implicates involvement of five HT neurons among ascending brainstem monoaminergic neurons that modulate development of the circadian sleep/wake cycle [47].

The preoptic area of the hypothalamus is a major sleep-promoting system that uses GABA as a neurotransmitter. Sleep-active neurons in the preoptic area project to brainstem regions that contain neurons involved in arousal from sleep; inhibiting these regions in turn promotes sleep. These regions include pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT), locus coeruleus, and dorsal raphe [48]. In autism, GABAergic interneurons migration and maturation could be affected [45]. A region of genetic susceptibility has been identified on chromosome 15q that contains GABA-related genes [49]. The expression of the autism susceptibility genes may affect sleep regulation by interfering with the normal inhibitory function of GABA via the preoptic area neurons. Therefore, the reduction of sleep time might be a consequence of dysfunction of the brainstem aminergic pathways [39].

7. Circadian abnormalities

Bourgeron [50] suggested that clock genes associated with low melatonin may be involved in abnormal circadian timing in autism. He hypothesized that circadian abnormalities in autism might be the result of genetic abnormalities related to melatonin synthesis and melatonin's role in modulating synaptic transmission. An association between clock gene polymorphisms and autism has been reported [51]. These findings support the hypothesis of circadian abnormalities underlying sleep disturbances in autism.

At least four independent studies have demonstrated abnormal melatonin regulation in individuals with ASD compared with controls, including elevated daytime melatonin and significantly lower nocturnal melatonin [47,52–54]. Among those, one study shows significantly lower excretion rates of urinary 6-sulphatoxymelatonin (the major metabolite of melatonin) in children and adolescents with autism compared to age-and-gender matched controls, with more marked differences in pre-pubertal subjects [47]. Interestingly, the low level of melatonin correlated with severity of autistic symptomatology. In a more recent study, Melke [55] found abnormal melatonin levels in the unaffected parents of children with autism, suggesting a possible genetic origin. In this study, the melatonin deficit was associated with low *ASMT* activity. The *ASMT* gene, located on pseudo-autosomal region 1 of the sex chromosomes and deleted in several individuals with ASD, encodes the last enzyme involved in melatonin synthesis, indicating that variations in this gene could explain the melatonin deficit.

Abnormalities in serotonin synthesis have been demonstrated in children with ASD, including an increased synthesis and asymmetry in serotonin production [56,57]. Recently, Makkonen [58] found reduced serotonin transporter binding capacity in children with ASD. It has been hypothesized that a primary deficit of melatonin synthesis could indirectly lead to accumulation of upstream substrates (*N*-acetylserotonin) and serotonin. Thus, a single defect within the melatonin synthesis pathway could lead to both low melatonin and high serotonin levels in autism [50]. Taken together, these data indicate that the deficit in melatonin may cause abnormal sleep/wake cycles in individuals with ASD. Given these low melatonin levels, exogenous melatonin administration may be therapeutic.

8. Psychological or behavioral factors

Children with ASD have a high rate of psychiatric comorbidities that may interfere with the regulation of sleep. Anxiety disorders, mood disorders, and attention-deficit/hyperactivity disorder frequently occur in patients with ASD [59], resulting in complicated presentations of sleep disturbances [8,9,37,60].

Behavioral sleep disorders such as bedtime resistance, sleep-onset association and limit-setting types of behavioral insomnia are common among children with ASD and can be successfully addressed with behavioral interventions [61]. Maladaptive bedtime routines may lead to settling difficulties at bedtime with inconsistent sleep onset time. The adherence to positive and consistent bedtime routines is associated with a reduction in sleep problems in children with ASD [61,62].

Children's sleep problems can significantly impact the quality of sleep of other family members. Sleep problems were reported by almost 70% of 210 Hong Kong families with a young child with ASD. Parental stress predicted the severity of sleep problems in these children [63]. Sleep maintenance difficulties in children with ASD have a significant impact on parental sleep [64]. A recent study by Meltzer [65] reported poorer sleep quality and shorter total sleep time among parents of children with autism compared to parents of typically developing children.

9. Developmental regression and sleep problems

In a minority of patients, symptoms of autism become apparent after a period of normal or mildly delayed development followed

by the loss of previously acquired skills [66,67]. Autistic regression typically occurs between 1 and 3 years of age, with a peak at around 24 months. This regression occurs in about 15–40% of children with autism [66–70]. Even though the mechanisms underlying autistic regression are still unknown, it has been postulated that rapid synaptic growth and pruning during the second year of life is impaired in autism due to genetic influences [71] resulting in a particular developmental phenotype.

Interestingly, Giannotti and co-authors found that over 50% of children with autism had at least one sleep problem, with a peak onset during the second year of life which coincides with the time of autistic regression [72]. This temporal overlap might be coincidental, but could also be interpreted as the expression of a biologically determined mechanism which influences a particular developmental trajectory during a critical phase of child development. More recent data from parental surveys and nocturnal polysomnography suggest that children with ASD and a history of regression have a more disturbed sleep pattern than children without regression [15]. It is noteworthy that approximately one-third of children with autism develop epilepsy [73] with prevalence estimates between 12% and 39% [74,75]. Epileptiform EEG abnormalities in children with autism have been reported to range between 8% and 15% [68] and 60% [76,77]. Although epilepsy cannot be considered a causal factor, in some cases it arises in the context of abnormal brain systems or networks which seems to be implicated in the autistic disorder as well.

The coexistence of disrupted sleep patterns and significantly higher presence of epilepsy in regressed children suggests a disruption of neuronal circuitry, which might be a reflection of the underlying pathology. In addition, seizures and sleep problems could possibly be caused by the underlying pathological process and have a compounding effect on the evolving neurocognitive dysfunction in autism. Although the biological basis and possible casual relationships of these associations remain unknown, this may point to different subgroups of patients with autism.

10. Impact of sleep problems on daytime behavior in children with ASD

An important reason, if not the most important, for intervening when children with ASD have sleep problems is to improve daytime functioning. Parents of poorly sleeping children with ASD routinely report worse daytime behavior following nights of fragmented or insufficient sleep. Although several studies have pointed out the negative effect of sleep disorders on daytime behavior in children with intellectual disabilities [22,78–80], few studies have evaluated the effect of sleep disorders exclusively in autism. Schreck and colleagues [27] demonstrated that short sleep duration was associated with social skills deficits, stereotypic behavior, and increased overall autism scores. Children with autism described by their parents as ‘‘poor sleepers” as opposed to ‘‘good sleepers,” had more difficulties with reciprocal social interaction on the Autism Diagnostic Observation Schedule and higher scores related to affective problems on the Child Behavior Checklist [10]. In a case report, a girl with ASD and obstructive sleep apnea showed improvement in daytime behaviors measured before and after treatment with adenotonsillectomy [81]. Her ability to interact socially improved as did her ability to focus and she demonstrated less repetitive behavior and auditory sensitivity.

11. Non-pharmacological treatment

Sleep hygiene and behavioral therapy have been shown to be effective interventions for both typically developing children and for children with ASD. Several studies have demonstrated effectiveness of behavioral interventions for sleep onset and maintenance problems in children with ASD [61,62]. Richdale and Wiggs [82] have written a comprehensive review of behavioral interventions in children with developmental disabilities and autism. Basic principles of sleep hygiene include the selection of an appropriate bedtime, establishment of a positive consistent bedtime routine, minimizing television watching and playing computer or video games, and reducing emotional/behavioral stimulation at night. It is equally important to establish a consistent bedtime and wake time to promote a regular sleep/wake cycle.

Children with ASD frequently have hypersensitivity to environmental stimuli, including noises or tactile sensitivity to bedclothes or blankets. Addressing sensory hypersensitivity especially associated with the sleep environment may help improve quality of sleep. For example, parents have reported weighted blankets being helpful in children with tactile sensitivities. However, there are no evidence-based research studies supporting their consistent use for children with ASD. A parental survey conducted by Williams and colleagues [83] indicated that wrapping a child with ASD in a blanket helped with sleep onset.

As a general rule the sleep environment should provide the child with the most comfortable temperature, preferred texture of the pajamas and bedding, and optimal control of noise and light. Some children may benefit from white noise machines or other soothing sounds during sleep.

Other behavioral interventions like graduated extinction, scheduled nocturnal awakenings, and bedroom passes can be utilized to set appropriate behavioral limits at bedtime and to promote the development of more adaptive self-soothing skills [84]. Limiting naps may help to improve sleep continuity and reduce sleep onset latency in children who tend to nap extensively during the day. Light therapy is effective in advancing or delaying the sleep phase in patients with circadian sleep disorders and can be considered for children with ASD who present with circadian rhythms dysfunction.

12. Pharmacological treatment

When behavioral interventions are not effective or lead only to a partial response, pharmacological treatment options should be considered in as an adjuvant to ongoing behavioral therapy for sleep disorders. When considering pharmacological options, it is important to realize that there are no medications approved by the Food and Drug Administration (FDA) for the treatment of pediatric insomnia. Selection of a sleep-promoting agent should be based on the individual patient’s characteristics, pharmacological properties of the drug, previous history of child’s response to sedative/hypnotics, psychiatric and medical comorbidities and drug–drug interactions.

Melatonin has been more extensively studied in children with insomnia than any other sleep-promoting medication. Initial research in children with neurodevelopmental disorders demonstrated reductions in sleep latency and improvements in total sleep time and sleep efficiency when melatonin was administered close to bedtime [85–88]. A more recent large retrospective study that included over 100 children with ASD documented minimal adverse effects from melatonin with improved quality of sleep in 85% of participants [89]. Melatonin was shown to be effective in a dose range from 3 to 6 mg in children with ASD [90–92]. Controlled-release melatonin was found to be superior to behavioral intervention in a controlled study of children with ASD using actigraphy. Melatonin in this study was highly effective in reducing sleep onset latency, night-to-night variability in bedtime, waking after sleep onset, and in increasing sleep duration [92]. There is evidence to support use of extended release formulations of melatonin for

sleep maintenance insomnia in children [93]. Although, the studies of melatonin use in children with ASD provide evidence for its effectiveness and safety they frequently lack controls and are small in sample sizes.

There is limited research on the use of prescription medications with sedative properties for children with autism. One study demonstrated the effectiveness of niaprazine, a histamine H1-receptor antagonist with sedative properties which is available in Europe, to treat insomnia in this population [94]. For more detailed information on the pharmacological treatment of pediatric insomnia, please refer to a recent review by Owens [95].

Successful pharmacological treatment of comorbid psychiatric disorders like ADHD, mood and/or anxiety disorders as well as neurological conditions like epilepsy and movement disorders may help to alleviate symptoms of insomnia and markedly improve outcome.

13. Conclusion

Children and adolescents with an ASD are at substantial risk for experiencing sleep problems, particularly insomnia. The clinician assessing a child with an ASD should screen carefully for sleep disorders and make referrals as indicated. Identifying and treating sleep disorders may result not only in improved sleep, but also impact favorably on daytime behavior and family functioning. Fortunately, there are a variety of treatments available, including behavioral interventions and pharmacotherapy. It is imperative to establish standards of care for the evaluation and treatment of sleep disorders in this population. Additionally, clinical trials targeting insomnia are needed using interventions such as behavioral, pharmacological, and light therapy.

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