Sleep Patterns in Autism Spectrum Disorders

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• Autism spectrum disorders • Sleep • Melatonin
• Polysomnogram • Insomnia

Autism spectrum disorders (ASDs) are a group of neurodevelopmental disabilities defined by developmental deficits in 3 domains: communication; social and emotional reciprocity; and stereotyped interests, behavior, and activities.[1] ASDs affect individuals worldwide with a prevalence rate of 60 to 70 per 10,000 as of recent studies.[2,3] The precise neurobiological causes of autism have yet to be elucidated, but genetic factors play an important role.[4,5] In about one-third of the children affected, autism becomes apparent after a period of apparently normal or only relatively delayed development, with a loss of previously acquired abilities.[6,7] The main clinical feature of this phenomenon, which has been defined as ''autistic regression,'' is the loss of spoken language, but social interests and other communicative skills are also generally affected.

Sleep problems are highly prevalent in children with ASD, with rates ranging from 40% to 80%.[8–14] In fact, a recent study found that sleep problems rank as one of the most common concurrent clinical disorders.[15] These sleep problems seem to be relatively specific to children with ASD compared with both typically developing children and children with intellectual disabilities without autism.[16–18] In a recent study using parent reports, Krakowiak and colleagues[19] found that 53% of children (2–5 years of age) with autism had at least 1 frequently experienced sleep problem compared with 46% of children with non-ASD developmental delays and 32% of typically developing children.

Approximately one-third of children with ASD and a history of developmental regression may suffer more sleep problems than those without a history of regression, particularly circadian rhythm sleep disorders. A recent study comparing children with ASD and a history of regression with children with ASD and no regression history

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showed increased rates of circadian rhythm sleep disorders in the former group.[20] In this study using parent report, more than 30% of the children with ASD and a history of regression had delayed sleep phase syndrome while an additional 40% of them had an irregular sleep–wake schedule disorder. These rates compared with 16% of children without developmental regression who had a delayed sleep phase syndrome and 23% who had an irregular sleep–wake schedule disorder. Interestingly, a remarkable temporal overlap between peak age of onset of sleep problems and that of regression has been reported.[21] This observation might be coincidental, but it could also be interpreted as the expression of a biologically determined substrate which influences a particular developmental trajectory in a critical phase of development.

NEUROBIOLOGY OF ASD AND SLEEP

Several neurotransmitter systems involved in promoting sleep and establishing a regular sleep–wake cycle are also affected by ASD. These neurotransmitter systems include gamma-aminobutyric acid (GABA), serotonin, and melatonin. The neurotransmitter GABA is involved in the functioning of the preoptic area of the hypothalamus, an important sleep-promoting region. Neurons in the preoptic area project to brainstem regions involved in arousal from sleep, and inhibiting these regions, in turn, promotes sleep. These brainstem regions include the pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT), the locus coeruleus, and the dorsal raphe.[22] Interneurons using GABA appear disrupted in autism.[23] A genetic susceptibility region for autism has been identified on chromosome *15q* that contains GABA-related genes.[24] Gene expression in this region may affect sleep by interfering with the normal inhibitory function of the GABAergic preoptic area neurons.

Abnormal melatonin regulation has also been shown in individuals with ASD, including elevated daytime melatonin and significantly decreased nocturnal melatonin.[25–27] An interesting study shows significantly lesser excretion rates of urinary 6-sulphatoxymelatonin, the major metabolite of melatonin, in children and adolescents with autism compared with age- and gender-matched controls, with more marked differences in prepubertal subjects.[28] In a more recent study, Melke and colleagues[29] found abnormal melatonin levels in the unaffected parents of children with autism, suggesting a genetic origin. In this study, the melatonin deficit was associated with reduced acetylserotonin methyltransferase (ASMT) activity. ASMT is the last enzyme involved in melatonin synthesis, suggesting that variations in the ASMT gene could be the cause of this deficit. Furthermore, children with ASD have abnormal serotonin production.[30,31] In addition, Makkonen and colleagues[32] recently found reduced serotonin transporter binding capacity in children with ASD.

The abnormalities in GABA, serotonin, and melatonin production in ASD, along with accumulating evidence of clinical sleep and circadian disturbances, provide evidence for involvement of the neurobiological networks regulating sleep in autism. Investigations linking these neurotransmitter abnormalities to the severity of sleep disturbances in ASD have yet to be undertaken. Whether subsets of children with ASD who have clinical abnormalities in their sleep–wake cycle are more likely to exhibit abnormalities in sleep-related neurotransmitters also remains to be determined.

SPECIFIC SLEEP DISORDERS

Insomnia

The most common sleep disorder experienced by children with ASD is insomnia. Pediatric insomnia has been defined as ‘‘repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite age-appropriate time and opportunity for