MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES
RESEARCH REVIEWS *10: 122–125 (2004)*

SLEEP DISORDERS, EPILEPSY, AND AUTISM

Beth A. Malow*

Vanderbilt Sleep Disorders Center, Vanderbilt University School of Medicine, Nashville, Tennessee

The purpose of this review article is to describe the clinical data linking autism with sleep and epilepsy and to discuss the impact of treating sleep disorders in children with autism either with or without coexisting epileptic seizures. Studies are presented to support the view that sleep is abnormal in individuals with autistic spectrum disorders. Epilepsy and sleep have reciprocal relationships, with sleep facilitating seizures and seizures adversely affecting sleep architecture. The hypothesis put forth is that identifying and treating sleep disorders, which are potentially caused by or contributed to by autism, may impact favorably on seizure control and on daytime behavior. The article concludes with some practical suggestions for the evaluation and treatment of sleep disorders in this population of children with autism.
MRDD Research Reviews 2004;10:122–125.

Key Words: autism; sleep; epilepsy; polysomnography; REM sleep; melatonin

INTRODUCTION

Autism describes a spectrum of neurobehavioral developmental disorders characterized by deficits in social interaction and communication, with repetitive behavior patterns and a limited repertoire of interests. A variety of neurobiological abnormalities have been described in autism, including alterations in neurotransmitters and hormones involved in sleep regulation. Serotonin, through its modulation of brainstem cholinergic neurons, plays a critical role in suppressing REM sleep and promoting arousal [Horner et al., 1997]. Serotonin synthesis is decreased in children with autism compared to nonautistic children [Chugani et al., 1999]. Melatonin, produced by the pineal gland, is a key regulator of circadian rhythms and decreases during sleep in children [Kulman et al., 2000] and young adults [Nir et al., 1995] with autism. Therefore, given autism's potential neurobiological underpinnings, sleep may be affected in this disorder. The following section presents the evidence for sleep abnormalities in autism. These studies are pioneering, still limited by small numbers of subjects and the heterogeneity of the subjects studied.

EVIDENCE FOR ABNORMAL SLEEP IN AUTISM SPECTRUM DISORDERS

Questionnaire Studies

The majority of published studies on this topic have used questionnaires to survey parents of children with autism about their child's sleep and compared these reports to those of parents with nonautistic children. Responses to such questionnaires have emphasized abnormalities in the circadian pattern (e.g., sleep onset and waking do not occur at expected times) and in sleep continuity (e.g., sleep is fragmented by arousals or awakenings). For example, parents of autistic children have reported that their children have prolonged sleep onset times and sleep latency, manifested by going to sleep at a later bedtime and taking longer to fall asleep [Richdale and Prior, 1995]. They have also reported early morning wake time and frequent arousals during the sleep period. These parental observations of altered circadian patterns are supported by a study of 89 autistic children in Japan in whom sleep logs were kept for 28 days during summer vacation. The majority of subjects showed late sleep onset and early awakening. One subject developed a non-24-hr sleep–wake syndrome [Takase et al., 1998]. Actigraphy (a procedure in which a monitor is attached to a subject's wrist to monitor rest/activity patterns), however, has not borne out these observations on altered circadian patterns and sleep continuity with the exception of an early morning arousal time [Hering et al., 1999]. This discrepancy between parental observations and actigraphy has been attributed to parental oversensitivity to sleep disturbances in their children. Actigraphy, however, has its limitations in that it measures movement during the night rather than physiological sleep and cannot substitute for the gold standard of polysomnography.

Just as abnormalities in motor and speech development are commonplace in autism, abnormalities in the development of sleep–wake cycles have also been noted [Segawa, 1992]. Only a minority (approximately 32%) of 85 autistic subjects showed a clear day and night difference in sleep time by 5 months of age, with the majority exhibiting a delay (relative to normal controls) in this differentiation, even into early childhood.

In one study surveying parents of 100 children (ages 2–11 years) with pervasive developmental disorders, 54% reported a sleep problem in their child, which was substantiated upon administration of the Children's Sleep Habits Questionnaire (CSHQ) [Honomichl et al., 2002]. Of interest, regardless of parental perception of problematic sleep, all children exhibited longer sleep-onset times and greater fragmentation of sleep, as documented by sleep diaries, than reported for age-matched controls. The group with sleep problems had longer awakenings, longer sleep latency, and shorter total sleep time than those without sleep problems, and older children (ages 6–11) had

Grant sponsor: Vanderbilt University Interdisciplinary Discovery Grant and NINDS KO2 NS02099
*Correspondence to: Beth A. Malow, MD, MS, Department of Neurology, 2100 Pierce Avenue, Nashville, TN 37212. E-mail: beth.malow@vanderbilt.edu
Received 23 June 2004; Accepted 25 June 2004
Published online in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/mrdd.20023

more sleep difficulties. In an independent study of 55 children on the autistic spectrum, compared to those with mental retardation or other developmental handicaps or to normal controls, a greater percentage of parents of children with autism indicated that their child had a sleep problem as compared to parents of children without autism [Schreck and Mulick, 2000]. In addition, children with autism, as compared to the other groups, were more likely to have nightmare-type disturbances, environmental disturbances (complaining of an uncomfortable room), sleep apnea and bruxism, and disoriented awakening.

Polysomnography (PSG)

There have been relatively few reports of PSG-based sleep studies in children with autism. Overall, these have focused on abnormalities in REM sleep, including immaturity in the organization of eye movements into discrete bursts [Tanguay et al., 1976], increased muscle twitches during REM sleep [Elia et al., 2000], and undifferentiated sleep in which features of non-REM and REM sleep are intermixed [Diomedi et al., 1999]. The prolonged sleep times, early wake times, and frequent interruptions in sleep noted in the survey literature have not been commented on in these PSG studies. A provocative case series reported sleep disorders in a group of 11 patients with autism (diagnosed by DSM-IV criteria) in whom parents complained that their child's sleep was "disrupted with frequent awakenings; with 'bad days' often following poor sleep at night" [Thirumalai et al., 2002]. Diagnoses included obstructive sleep apnea (OSA, 3 patients), periodic limb movements of sleep (1 patient), and a seizure disorder (1 patient). The most striking finding was that 5 of 11 patients had REM sleep behavior disorders (RBD). Normally during REM sleep there is muscular "paralysis"; however, in RBD patients do not exhibit muscle atonia and are free to "act out their dreams." RBD is diagnosed by the occurrence, on PSG, of persistence of chin muscle tone and the appearance of excessive limb muscle tone during REM sleep, even in the absence of overt behaviors. This disorder typically affects elderly males with neurodegenerative disorders such as Parkinson's disease, and its animal model correlate involves lesions of the pontine tegmentum [Schenck and Mahowald, 1990]. In humans with a form of Parkinsonism called "multiple system atrophy," REM sleep behavior disorder has been linked to degeneration of dopaminergic neurons in the substantia nigra, a subcortical region involved in motor control [Gilman et al., 2003]. This finding, in light of increased phasic muscle activity in REM sleep in mentally retarded subjects with autism [Diomedi et al., 1999], raises the possibility that neurostructural or neurochemical abnormalities involving the brainstem or subcortical regions (that have downstream effects on the brainstem) may be associated with autism. However, one shortcoming of this case series was that medications were not specified. Tricyclic antidepressants and the selective serotonin reuptake inhibitors (SSRIs) may provoke REM sleep behavior disorder [Mahowald and Schenck, 2000]. If a medication-free cohort also exhibits abnormalities consistent with REM sleep behavior disorder, these findings may represent a major advance in our understanding of the mechanistic underpinnings of autism.

Regardless of parental perception of problematic sleep, all autistic children exhibited longer sleep onset times and greater fragmentation of sleep than age-matched controls, as documented by sleep diaries.

Melatonin

Secreted by the pineal gland, melatonin is a key regulator of the circadian cycle. Abnormalities in the circadian secretion of melatonin, as well as lower mean concentrations of the hormone, have been documented in blood samples from children [Kulman et al., 2000] and young adults [Nir et al., 1995] with autism. In a case report of a 14-year-old autistic male with severe mental retardation, 6 mg of melatonin given at 11 PM prolonged night sleep and improved sleep–wake rhythm [Hayashi, 2000]. The timing of the melatonin dose was important; if the melatonin was given at 9 PM, the patient experienced early morning waking and fragmented sleep. Melatonin has been used in other developmental disabilities in addition to autism, and the knowledge gained from these studies may be applicable to patients with autism. Low-dose melatonin (0.3 mg) given to 13 Angelman syndrome children, 0.5 to 1 hr before bedtime, improved sleep duration and decreased motor activity during the total sleep period [Zhdanova et al., 1999]. One double-blind study of the effects of melatonin on sleep in multihandicapped children found an improvement in sleep in some but not all children [Jan et al., 1994]. Another double-blind study treated seven tuberous sclerosis patients and found that melatonin prolonged total sleep time [O'Callaghan et al., 1999]. An editorial urged that those caring for those with autism not to neglect behavioral interventions when considering melatonin treatment [Lord, 1998]. Indeed, one study described the successful treatment of sleep problems in a 5-year-old boy with autism using behavioral approaches, including training sessions for the parents in implementing a bedtime routine, extinction, and positive reinforcement for complying with the program [Weiskop et al., 2001]. Extinction refers to the often difficult task of teaching parents to ignore crying and, if children leave their room, to return them calmly—without eye contact, talking, or yelling. The net result is that the child learns to fall asleep, and return to sleep if awakened, on his or her own.

The above studies have paved the way for investigations of sleep and autism. In future studies, careful attention should be paid to (1) ensuring that a definitive diagnosis of autism is established with state-of-the-art measures, (2) limiting the heterogeneity of the group studied (inclusion of those with mental retardation, medication-treated children, and those with epilepsy may confound the findings), (3) combining PSG studies with parental reports and relating parental concerns (e.g., frequent awakenings) to the PSG findings, and (4) performing double-blind studies whenever possible if a pharmacological intervention is under consideration.

EPILEPSY IN AUTISTIC SPECTRUM DISORDERS AND THE IMPACT OF SLEEP DISORDERS

The relationship of epilepsy to autism is discussed thoroughly in other articles within this issue. This section focuses on the sleep–epilepsy relationship. Sleep state can influence epilepsy and, in turn, epilepsy may affect sleep.

A variety of epileptic syndromes, particularly types of frontal lobe epilepsy, are characterized by seizures that occur

exclusively or predominantly during non-rapid eye movement (NREM) sleep [Malow, 1996]. Interictal epileptiform discharges (IEDs) are sharp waves or spikes that occur in an EEG between seizures. At the cellular level, they represent the summation of large numbers of excitatory postsynaptic potentials (EPSPs). Similarly to seizures, they are activated during NREM sleep and suppressed during REM sleep. The impact of sleep-related seizures and IEDs on learning and memory and on daytime behavior remains uncertain and is an area for future investigation [Binnie, 2003].

Sleep deprivation probably has seizure-provoking effects, especially in association with physical or emotional stress [Frucht et al., 2000]. Chronic sleep deprivation may be caused by sleep disorders that fragment (disrupt) sleep, such as obstructive sleep apnea (OSA). In OSA, pauses in breathing arouse the patient from sleep due to a protective response, with the net result being sleep fragmentation. Studies of treating OSA in children with epilepsy have shown an improvement in seizure control [Koh et al., 2000; Malow et al., 2003; Tirosh et al., 1995]. Other sleep disorders, including insomnia, may also lead to lack of sleep and potentially worsen seizure control. Therefore, paying attention to sleep in the child with autism and seizures, and implementing appropriate treatment strategies (see Evaluation and Treatment below), may result in improved seizure control.

Epileptic seizures may themselves affect sleep, with this influence not limited to the time of onset of the seizure. Temporal lobe complex partial seizures decrease REM sleep, particularly when occurring during sleep but also when they occur on the day before sleep onset [Bazil et al., 2000]. These changes may result from a disruption in circadian rhythms or hormonal influences resulting from the seizures.

EVALUATION AND TREATMENT OF SLEEP DISORDERS IN AUTISM

Daytime functioning and quality of life in children with autism, with or without epilepsy, may be affected by sleep disorders. In normally developing children as well as those with autism, sleep problems have been correlated with family or parental distress and with problematic daytime behavior. [Patzold et al., 1998]. In a cohort of more than 3000 five-year-old children, those with sleep-disordered breathing were more likely to have daytime sleepiness and problem behaviors, including hyperactivity, inattention, and aggressiveness [Gottlieb et al., 2003]. Therefore, it is plausible that treatment of sleep disorders may impact favorably on daytime behaviors in autism and reduce stress in parents and other caregivers.

Table 1. Strategies for Improving Sleep in Children with Autism

Take a sleep history to identify treatable sleep disorders and consider polysomnography when appropriate
Behavioral treatments
Sleep Hygiene: e.g., avoidance of caffeine, engaging in regular exercise, having a bedtime routine
Sleep Restriction
Extinction (training children to fall asleep on their own)
Light Therapy
Pharmacological treatments
Antiepileptic drugs
Antidepressants
Other medications (e.g., clonidine)
Melatonin

Recommendations are as follows (Table 1):

1. Take a sleep history to identify treatable disorders such as inadequate sleep hygiene or sleep-related breathing disorders. Ask parents about bedtime, wake time, awakenings during the night, the presence of snoring or excessive leg movements, and daytime sleepiness. Polysomnography is generally not performed for insomnia but is done when the concern of a sleep-related breathing disorder exists. Polysomnography is also useful when there is a concern of nocturnal seizures contributing to sleep problems or daytime sleepiness. A multiple sleep latency test, performed the morning after polysomnography, is done when narcolepsy is a consideration or to obtain an objective assessment of daytime sleepiness. Despite parental concerns that their children with developmental delays will be unable to cooperate with testing, polysomnography is often informative. A sleep center with a child-friendly environment and experienced technologists (who are versed at putting on electrodes after a child has fallen asleep if necessary) is often key to the success of such a study. In addition, having the child and family visit the sleep center prior to the study to alleviate anxieties, and instructing the family to avoid sleep deprivation or overactivity the day of the study, are also useful maneuvers. In children diagnosed with obstructive sleep apnea, the first line of therapy is often to remove tonsils and adenoids if not previously removed. If they have already been removed, the child may be a candidate for continuous positive airway pressure (CPAP), which overcomes the upper airway obstruction with pressurized air delivered through a mask. Desensitization of patients to CPAP is important in this population and can be done successfully, often in conjunction with a respiratory therapist. Parental support and encouragement is critical for success.

2. Educate parents to pay attention to basic principles of sleep hygiene, including a regular and consistent bedtime, a structured bedtime routine, avoidance of caffeine, regular exercise, and avoidance of conditioned associations that interfere with sleep (e.g., watching television in bed). Teaching parents the challenging task of letting their children fall asleep on their own (at bedtime or upon awakening in the night) requires patience but will pay off for them and their children in the long-term. Restriction of daytime sleep may also be effective in promoting more consolidated sleep at night. All of these interventions will result in a better night's sleep and the alleviation of emotional stress for the family as well as the child.

3. There are a wide range of options for pharmacological treatment, best used in conjunction with the behavioral techniques noted above. A helpful principle for prescribing medications for sleep is to consider the overlapping neurological systems that are affected. Epilepsy, depression, or both may coexist with autism in the child with sleep concerns. Wherever possible, prescribe a medication for the coexisting condition that also assists with sleep, while avoiding those that cause insomnia. For example, in children with coexisting epilepsy, the antiepileptic regimen can be adjusted to administer a bedtime dose of medication that provides sedation and promotes sleep. AED options include carbamazepine, levatiracetam, gabapentin, or topiramate, which are usually dosed two or three times a day but can be adjusted so that a higher dose is given 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. Many of these antiepileptic medications also have beneficial effects on mood and are used in children without epilepsy who have

coexisting depression or anxiety. These medications can also stabilize bipolar types of mood swings and intermittent explosive symptoms. Specific antidepressants that promote sleep include the tricyclic antidepressants (including amitriptylline, imipramine, and nortryptilline) and mirtazapine (which tend to be highly sedating), trazadone (highly sedating and should be avoided in males who cannot communicate reliably because of the risk of priapism), and citalopram and nefazadone (mildly sedating). Bupropion, venlafaxine, fluoxetine, and sertraline are relatively stimulating and should be avoided in those patients with insomnia and reserved for those with daytime sleepiness without insomnia. Other medications that promote sleep include clonidine, diphenhydramine, and benzodiazepines. With all medications, it is important to start with low doses and increase gradually to avoid adverse effects.

4. As reviewed in this chapter, melatonin has been implicated as abnormal in autism. Supplemental melatonin has been advocated as a sleep-promoting agent as well as a treatment for "resetting" the circadian clock in those with autism who have sleep-onset delay and early-morning awakenings. The safety and efficacy of melatonin has not been established inasmuch as it is not a Food and Drug Administration-approved drug. There are several concerns about the use of melatonin in the autistic population, including a lowering of the seizure threshold, the lack of consistency in dosing or in the purity of preparation, and the tendency for parents to administer it more haphazardly given its perception as a nutritional supplement rather than a potent medication. Nonetheless, melatonin may be effective, particularly in those children with persistent alterations in the sleep–wake cycle. It should be started using a small doses (0.5 to 1 mg) approximately 1 hour before bedtime. Higher doses of up to 5–10 mg have been used in refractory cases without adverse effects.

5. Light therapy may also be useful for children with circadian rhythm abnormalities in combination with chronotherapy, where the sleep–wake cycle is delayed over the course of several days until the desired bedtime is reached. Light of 1000 lux administered for 1–3 hr in the morning is recommended and is safe, although no definitive studies have been performed in autism. Bright light administered in the morning "resets" the circadian clock and facilitates an earlier bedtime. There are several commercial light boxes available. An alternative to purchasing a commercial light box is for the patient to be exposed to bright light each morning. Attention to behavioral problems is essential, as adherence to a strict bedtime and wake time routine is necessary to prevent the return of a delayed bedtime. Close follow-up is recommended in children receiving light therapy to prevent relapse. ■

ACKNOWLEDGMENT

Dr. Susan McGrew of Vanderbilt University reviewed the pharmacological treatment section of this article and made helpful suggestions

REFERENCES

Bazil CW, Castro LH, Walczak TS. 2000. Reduction of rapid eye movement sleep by diurnal and nocturnal seizures in temporal lobe epilepsy. Arch Neurol 57:363–368.

Binnie CD. 2003. Cognitive impairment during epileptiform discharges: Is it ever justifiable to treat the EEG? Lancet Neurol 2:725–730.

Chugani DC, Muzik O, Behen M, Rothermel R, Janisse JJ, Lee J, et al. 1999. Developmental changes in brain serotonin synthesis capacity in autistic and nonautistic children. Ann Neurol 45:287–295.

Diomedi M, Curatolo P, Scalise A, Placidi F, Caretto F, Gigli GL. 1999. Sleep abnormalities in mentally retarded autistic subjects: Down's syndrome with mental retardation and normal subjects. Brain Dev 21:548–553.

Elia M, Ferri R, Musumeci SA, Del Gracco S, Bottitta M, Scuderi C, et al. 2000. Sleep in subjects with autistic disorder: A neurophysiological and psychological study. Brain Dev 22:88–92.

Frucht MM, Quigg M, Schwaner C, Fountain NB. 2000. Distribution of seizure precipitants among epilepsy syndromes. Epilepsia 41:1534–1539.

Gilman S, Koeppe RA, Chervin RD, Consens FB, Little R, An H, et al. 2003. REM sleep behavior disorder is related to striatal monoaminergic deficit in MSA. Neurology 61:29–34.

Gottlieb DJ, Vezina RM, Chase C. 2003. Symptoms of sleep-disordered breathing in 5-year-old children are associated with sleepiness and problem behaviors. Pediatrics 112:870–877.

Hayashi E. 2000. Effects of melatonin on sleep-wake rhythm: The sleep diary of an autistic male. Psychiat Clin Neurosci 54:383–384.

Hering E, Epstein R, Elroy S, Iancu DR, Zelnik N. 1999. Sleep patterns in autistic children. J Autism Dev Disord 29:143–147.

Honomichl RD, Goodlin-Jones BL, Burnham M, Gaylor E, Anders TF. 2002. Sleep patterns of children with pervasive developmental disorders. J Autism Dev Disord 32:553–561.

Horner RL, Sanford LD, Annis D, Pack AI, Morrison AR. 1997. Serotonin at the laterodorsal tegmental nucleus suppresses rapid-eye-movement sleep in freely behaving rats. J Neurosci 17:7541–7552.

Jan JE, Esperzedl H, Appleton RE. 1994. The treatment of sleep disorders with melatonin. Dev Med Child Neurol 36:97–107.

Koh S, Ward SL, Lin M, Chen LS. 2000. Sleep apnea treatment improves seizure control in children with neurodevelopmental disorders. Pediatr Neurol 22:36–39.

Kulman G, Lissoni P, Rovelli F, Roselli MG, Brivio F, Sequeri P. 2000. Evidence of pineal endocrine hypofunction in autistic children. Neuroendocrinol Lett 21:31–34.

Lord C. 1998. What is melatonin? J Autism Dev Disord 28:345–346.

Mahowald M, Schenck C. 2000. REM sleep parasomnias. In: Kryger M, Roth T, Dement W, editors. Principles and practice of sleep medicine. Philadelphia: Saunders. p 724–741.

Malow BA. 1996. Sleep and epilepsy. In: Aldrich MS, editor. Neurologic clinics—Sleep disorders II. Philadelphia: Saunders. p 765–789.

Malow BA, Weatherwax KJ, Chervin RD, Hoban TF, Marzec ML, Martin C, et al. 2003. Identification and treatment of obstructive sleep apnea in adults and children with epilepsy: A prospective pilot study. Sleep Med 4:509–515.

Nir I, Meir D, Zilber N, Knobler H, Hadjez J, Lerner Y. 1995. Brief report: circadian melatonin, thyroid-stimulating hormone, prolactin, and cortisol levels in serum of young adults with autism. J Autism Dev Disord 25: 641–654.

O'Callaghan FJK, Clarke AA, Hancock E, Hunt A, Osborne JP. 1999. Use of melatonin to treat sleep disorders in tuberous sclerosis. Dev Med Child Neurol 41:123–126.

Patzold LM, Richdale AL, Tonge BJ. 1998. An investigation into sleep characteristics of children with autism and Asperger's Disorder. J Paediatr Child Health 34:528–533.

Richdale AL, Prior MR. 1995. The sleep/wake rhythm in children with autism. Eur Child Adolesc Psychiat 4:175–186.

Schenck C, Mahowald M. 1990. Polysomnographic, neurologic, psychiatric, and clinical outcome report on 70 consecutive cases with the REM sleep behavior disorder (RBD): Sustained clonazepam efficacy in 89.5% of 57 treated patients. Clev Clin J Med 57:S10–S24.

Schreck KA, Mulick JA. 2000. Parental report of sleep problems in children with autism. J Autism Dev Disord 30:127–135.

Segawa M. 1992. Neurology: as a window on brainstem dysfunction. In: Naruse H, Ornitz EM, editors. Neurobiology of infantile autism. New York: Elsevier.

Takase M, Taira M, Sasaki H. 1998. Sleep–wake rhythm of autistic children. Psychiat Clin Neurosci 52:181–182.

Tanguay PE, Ornitz EM, Forsythe AB, Ritvo ER. 1976. Rapid eye movement (REM) activity in normal and autistic children during REM sleep. J Autism Child Schizophr 6:275–288.

Thirumalai SS, Shubin RA, Robinson R. 2002. Rapid eye movement sleep behavior disorder in children with autism. J Child Neurol 17: 173–178.

Tirosh E, Tal Y, Jaffe M. 1995. CPAP treatment of obstructive sleep apnea and neurodevelopmental deficits. Acta Paediatr 84:791–794.

Weiskop S, Matthews J, Richdale A. 2001. Treatment of sleep problems in a 5-year-old boy with autism using behavioural principles. Autism 5:209–221.

Zhdanova IV, Wurtman RJ, Wagstaff J. 1999. Effects of a low dose of melatonin on sleep in children with Angelman syndrome. Disabil Rehabil Endocrinol Metabl 12:57–67.