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SLEEP (M THORPY AND M BILLIARD, SECTION EDITORS)

Sleep in Children with Congenital Malformations of the Central Nervous System

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Abstract

Purpose of Review Congenital malformations of the central nervous system may be seen in isolation or in association with syndromes that have multiorgan involvement. Among the potential health challenges these children may face, sleep concerns are frequent and may include chronic insomnia, sleep-related breathing disorders, and circadian rhythm disorders.

Recent Findings In this review, we describe recent research into sleep disorders affecting children with congenital malformations of the CNS including visual impairment, septo-optic dysplasia, agenesis of the corpus callosum, Aicardi syndrome, Chiari malformation, spina bifida, achondroplasia, Joubert syndrome, fetal alcohol spectrum disorders, and congenital Zika syndrome. In many cases, the sleep disturbance can be directly related to observed anatomical differences in the brain (such as in apnea due to Chiari malformation), but in most syndromes, a complete understanding of the underlying pathophysiology connecting the malformation with sleep problem is still being elucidated.

Summary Our review provides a synthesis of available evidence for clinicians who treat this patient population, in whom appropriate diagnosis and management of sleep problems may improve the quality of life for both patient and caregiver.

Keywords Sleep disorders · Corpus callosum · Septo-optic dysplasia · Chiari malformation · Joubert syndrome · Zika · Achondroplasia · Aicardi · Fetal alcohol spectrum disorder

Introduction

Attaining sufficient quantity and quality sleep is integral to optimizing health and wellbeing. Sleep problems in children are very common, with approximately 25% of all children experiencing some type of sleep problem during childhood [1]. These sleep problems not only are a substantial cause of distress within families but can also contribute to a plethora of neurocognitive and other health problems including mood disturbances, deficits in learning, behavioral problems, and obesity [1]. Among children with neurodevelopmental disorders, sleep problems are even more frequent, occurring in the majority of children [2]. Furthermore, their sleep disturbances tend to be more chronic, they may have multiple types of sleep disorders simultaneously, and they are unlikely to resolve without treatment [1].

Over the last two decades, there has been a much needed increase in the study of sleep problems in children with neurodevelopmental disorders. Most review articles focused on children with autism spectrum disorders, Down syndrome, and attention deficit disorder [3]. In this review, we synthesize the evidence regarding sleep disorders in children who have congenital malformations of the central nervous system, including visual impairment, septo-optic dysplasia, agenesis of the corpus callosum, Aicardi syndrome, Chiari malformation, spina bifida, achondroplasia, Joubert syndrome, fetal alcohol spectrum disorders, and congenital Zika syndrome. A summary of findings is presented in Table 1 for convenience. The wide variety and severity of sleep disorders found in children with congenital malformations of the CNS reflects the underlying heterogeneity of disease processes and spectrum of severity.

This article is part of the Topical Collection on *Sleep*

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Table 1 Selected congenital malformations of the CNS and sleep-related features

Disorder	Reported sleep disturbances (see main text for ref)
Disorders of the visual system	
Blindness	Free-running circadian rhythm Greater variability in sleep efficiency and time of sleep onset Abnormal timing of melatonin secretion
Anophthalmia/microphthalmia	Free-running circadian rhythm Extensive daytime sleeping Prolonged early-morning awakenings
Leber congenital amaurosis	Chronic insomnia
Midline disorders	
Septo-optic dysplasia	Arrhythmicity in sleep pattern Sleep fragmentation and poor sleep efficiency Abnormal 24-h melatonin profiles
Agenesis of the corpus callosum	Sleep onset delay Decreased sleep duration Greater bedtime resistance Sleep anxiety Night wakings Parasomnias Sleep-disordered breathing Daytime sleepiness Increased slow-wave sleep and decreased REM sleep More contentless dreams, shorter dreams, more distressful dreams Narcolepsy
Aicardi syndrome	Obstructive sleep apnea
Skull base and hindbrain	
Chiari I malformation	Obstructive sleep apnea Central sleep apnea
Spina bifida	Obstructive sleep apnea Central sleep apnea Sleep-related hypoventilation Poor sleep quality Chronic insomnia Daytime sleepiness
Achondroplasia	Obstructive sleep apnea Sleep-related hypoventilation Central sleep apnea
Joubert syndrome	Central sleep apnea with severe tachypnea followed by apnea
In utero exposures causing multiple brain differences	
Fetal alcohol spectrum disorder	Chronic insomnia Parasomnias Sleep-disordered breathing Sleep fragmentation Abnormal melatonin profiles
Congenital Zika syndrome	Decreased nocturnal sleep time Subjectively poor sleepers

Disorders of the Visual System

The interaction of circadian rhythm and homeostatic sleep drive determines the onset and duration of sleep throughout the 24 h of the day. The homeostatic drive refers to the constant accumulation of sleep debt during wakefulness, i.e., the longer we go without sleep, the larger the sleep debt (and drive to sleep). However, if this were the only force determining our sleep-wake cycle, we would fall asleep intermittently throughout the day in order to pay down or sleep off accumulating sleep debt incrementally. This incremental sleep pattern is seen in animal models in which the suprachiasmatic nucleus has been obliterated [4]. Accordingly, a second force alerts and opposes the increasing homeostatic sleep drive during the day, and this alerting force is the circadian rhythm. The clock-dependent alerting from the circadian rhythm explains

the typical decrease in alertness after lunch (or trough in arousal due to decreasing firing of the ascending arousal system made up of aminergic and cholinergic neurons in the brainstem and deep gray matter) and "second wind" in the later afternoon (due to increase in alerting factor). In the later evening, clock-dependent alerting further decreases and the accumulated sleep debt influences neurons in the ventrolateral preoptic area to fire to initiate and maintain sleep through the night. The transitions between wake and sleep are remarkably rapid and require interactions between reciprocal neuronal circuits in a "flip-flop" switch fashion [5]. The circadian rhythm tends to have a cycle slightly longer than 24 h and therefore requires external cues (zeitgebers) in order to maintain entrainment [6]. While there are many potential signals that can serve as zeitgebers, the most powerful is light. There is growing evidence for possible overlap in the genetic pathways governing circadian rhythms and neuropsychiatric illness [7].

Newborns do not have a clearly defined circadian rhythm at birth [8]. Joseph and colleagues studied the development of circadian rhythm in 35 healthy term infants from 6 to 18 weeks of age [9]. During that time, the investigators monitored temperature, cortisol, and 6-sulfatoxymelatonin (a metabolite of melatonin). Actigraphy was used to measure the infant's sleep activity, and the infants had their circadian gene analyzed by investigating the rhythmic transcript of the gene *Histone 3 family 3b*. Infants showed maturation of cortisol rhythm at 8.2 weeks of age, melatonin rhythm at 9.1 weeks, consolidated nighttime sleep at 9.4 weeks, temperature rhythm (maximum fall in deep body temperature at nighttime) at 10.8 weeks, and a diurnal rhythm in circadian gene expression at 10.9 weeks. The development of a diurnal sleep-wake cycle in infants seems to follow a sequential pattern with cortisol, melatonin, sleep efficiency, and temperature, followed by circadian genes which all cycle over approximately 24 h. The development of this rhythm could be disrupted by structural abnormalities noted in patients with neurodevelopmental issues or even environmental stimuli.

Few studies have evaluated the effect of light on newborns. Tsai and colleagues studied the effect of light on infant circadian entrainment [10]. They evaluated 22 healthy term infants for 7 days with actigraphy and sleep diaries and found that duration of infant bright light exposure was generally low but that more exposure to moderate levels of light and greater circadian rhythm of light exposure were associated with stronger patterns circadian activity. Overall, the results supported the hypothesis that properly timed light exposure is beneficial for infant circadian entrainment. While daytime light exposure may help entrain circadian rhythm, it should be noted that excessive light exposure at night may be associated with circadian disruption and adverse health outcomes [11]. It is also possible that there may be an imprinting effect of nocturnal light exposure that contributes to cancer and anxiety [12, 13].

It has long been recognized that maintaining retinal exposure to light via retinal photoreceptors is essential for establishment of newborn vision. Recognition of congenital cataracts or a developing periorbital hemangioma and quick treatment allows for proper development of vision. Recently, melanopsin and neuropsin located in the intrinsic photosensitive ganglion cells of the retina have been characterized. Circadian entrainment and even pupillary light response require light exposure to occur via the melanopsin-containing cells. Light triggers signaling from the melanopsin cells to the suprachiasmatic nucleus independent of the functioning of the rods and cones to entrain the circadian rhythm [14•]. Normally, the suprachiasmatic nucleus regulates the release of melatonin from the pineal gland such that melatonin is secreted at night during dark; however, light exposure sensed by melanopsin-containing cells can suppress this release of melatonin [15]. Neurodevelopmental abnormalities of the eyes, midline structures such as the suprachiasmatic nucleus or pineal gland, or the optic pathway (optic nerve and radiations) may interfere with the timing and duration of sleep.

Blindness

Given the known importance of light in circadian entrainment, individuals who lack light perception or have visual impairment have an increased risk of sleep difficulties. Classically, totally blind individuals may have free-running circadian rhythm due to the absence of entrainment from light [16, 17]. More recently, Aubin and colleagues examined 30-day actigraphy recordings in 11 blind individuals compared to sighted individuals [18]. Although they did not find group differences when the entire period was averaged, they did find greater variability in sleep efficiency and time of sleep onset, which correlated with severity of clinical sleep disturbances, in blind individuals. Further analysis demonstrated abnormal timing of melatonin consistent with abnormal circadian rhythm, but preservation of cortisol secretion profile; this suggests that melatonin secretion is linked to light exposure but cortisol secretion is less related to light exposure [19]. Finally, they evaluated the sleep structure (architecture) of these individuals via overnight polysomnography [20]. The investigators were able to evaluate sleep architecture differences in the context of circadian phase by measuring melatonin onset, and they found that half of the blind subjects had an abnormal circadian phase while only 18% of the control group had an abnormal circadian phase. Blind individuals that exhibited a normal melatonin timing had the same sleep architecture as the sighted individuals, and blind individuals who exhibited abnormal circadian phase had increased REM sleep latency and wake times. Individuals with blindness and sleep disturbance may benefit from measures that help to entrain the circadian pacemaker, including timed light therapy, melatonin, or newer melatonin receptor agonists such as tasimelteon or ramelteon [17].

Anophthalmia/Microphthalmia

Davitt and colleagues evaluated sleep problems in 13 children with congenital anophthalmia or microphthalmia [21]. Overall, 77% of the families reported that their child had sleep disturbance. The families reported extensive daytime sleeping and prolonged early-morning awakenings. They did find that strict daily schedules were helpful in entraining sleep-wake cycles in these children, which may reflect the effect of non-visual stimuli such as social cues on entraining circadian rhythm. Typically, 50% of blind individuals have non-24 h free-running sleep-wake disorder [22].

Leber Congenital Amaurosis

Leber congenital amaurosis is an inherited abnormality of visual function effecting the outer retina [23]. The outer retina contains rods and cones that contain photopigment, capture light, and transmit that signal. There is a third class of photoreceptive cell called the melanopsin-containing retinal ganglion cell, which are present in the inner retina. The photosensitive melanopsin retinal ganglion cells, not the rods and cones, are primarily responsible for melatonin secretion and entraining circadian rhythm based on visual light input [24•]. When light hits the inner retina, it suppresses melatonin and signals to the brain that it is not yet time for sleep. This signaling process may be impaired in individuals with complete blindness [25•]. Vervloed and colleagues reported a 4-year-old girl with Leber congenital amaurosis who had difficulty with sleep initiation and maintenance, which was successfully treated with a graduated extinction technique [26] suggesting not all sleep problems in children with Leber congenital amaurosis have a physiologic basis and a need for good sleep habits and behavioral interventions exists in these children as well.

Midline Disorders

Septo-optic Dysplasia

Septo-optic dysplasia occurs in approximately 1 of every 10,000 live births [27]. Septo-optic dysplasia (SOD) involves the triad of optic nerve hypoplasia, midline brain differences (absence of the corpus callosum and/or septum pellucidum), and hypopituitarism. Individuals with SOD tend to have poor visual acuity ranging from 20/200 to no light perception, and they may have a range of comorbidities including developmental delay, hydrocephalus, seizures, and additional brain malformations. Given the optic nerve differences and midline brain anomalies, many children with SOD may have sleep challenges. Rivkees reported a 3-year-old child with SOD who exhibited arrhythmicity in sleep pattern with random sleep distributed throughout the day and night. The child responded well to a nighttime dose of melatonin 0.1 mg and began having sleep consolidated at night and less napping during the day [28]. Interestingly, the benefits continued with 6 months of treatment, and when trialed off melatonin, the arrhythmic activity returned. Possible mechanisms for the observed lack of circadian rhythm include midline brain anomalies contributing to abnormal melatonin secretion, inability to correctly process and relay visual stimuli, and/or abnormal function of the suprachiasmatic nucleus. Webb and colleagues further characterized sleep-wake cycles in a cohort of six children with SOD [29•]. All six children were found on actigraphy to have sleep fragmentation with poor sleep efficiency due to frequent and prolonged night awakenings. The investigators also examined 24-h melatonin profiles in these children and found substantial variation in the timing and amount of melatonin produced with no consistent pattern among all children; two children produced almost no melatonin, three children had normal melatonin profiles, and one had increased daytime melatonin secretion. There did not seem to be a correlation between melatonin profiles and sleep-wake cycle as determined by actigraphy. In addition, while one may have expected that the visual impairments in SOD could result in a free-running rhythm of non-24 h, none of the six children exhibited this pattern. While the effects of SOD on the entire pathway from visual perception to suprachiasmatic nucleus to pineal gland are still being elucidated, clearly, clinicians should be vigilant for sleep challenges in children with this disorder.

Agenesis of the Corpus Callosum

The corpus callosum is one of the largest structures in the brain and serves to connect and transfer information between the two cerebral hemispheres. Agenesis of the corpus callosum (ACC) is one of the most frequent congenital brain malformations and occurs in approximately one in 4000 live births [30]. Individuals with ACC may have challenges in general intellectual, academic, executive, social, and behavioral domains [31], as well as altered ability to process socially complex emotions [32]. Children with ACC have a wide spectrum of clinical associated clinical features and comorbidities, likely reflecting the underlying heterogeneity of associated brain malformations and genetic etiologies [33].

Previous research has found that individuals with ACC have a high prevalence of sleep problems. Ingram and Churchill performed a survey of 66 children with ACC and found that overall 78% had clinically significant sleep problems [34•]. Furthermore, compared to typically developing children, children with ACC had greater sleep onset delay, less sleep duration, greater bedtime resistance, sleep anxiety, night wakings, parasomnias, sleep-disordered breathing, and daytime sleepiness. These sleep problems were significantly correlated with overall quality of life regardless of age or gender. Frequent clinically significant sleep problems in

children with ACC were also noted by Badaruddin et al. [35] and Doherty et al. [36]. Interestingly, polysomnographic studies of individuals with ACC have found increased slow-wave sleep, decreased REM sleep, and decreased interhemispheric coherence [37–39]. The corpus callosum may also be involved in dreaming and dream recall, as individuals with ACC tend to have more contentless dreams, shorter dreams, and more distressful dreams [40]. Finally, an individual with ACC was found to have narcolepsy with cataplexy, and the investigators speculated that the lack of a corpus callosum likely suppressed the excitatory function of hypothalamic orexin neurons resulting in narcolepsy [41].

Aicardi Syndrome

Aicardi syndrome was originally described in 1965 and is defined by the triad of agenesis of the corpus callosum, chorioretinal lacunae and infantile spasms [42]. Most children with Aicardi syndrome develop infantile spasms by 3–4 months of age, but only a minority have associated hypsarrhythmia. Many CNS malformations may be present, including callosal agenesis, cortical dysplasia, periventricular heterotopias, asymmetry of cerebral hemispheres, and cystic formations (such as choroid plexus cysts) [42]. Children are typically severely affected, with most having daily seizures and achieving developmental milestones no higher than 12 months [43]. To the best of our knowledge, the only published study of sleep disorders in children with Aicardi syndrome is a case report of a 5-year-old girl who was found to have obstructive sleep apnea and treated with positive airway pressure [44]. It is likely that sleep disorders are under-recognized/studied in this patient population, but timely identification and treatment of sleep-disordered breathing may help to optimize outcomes.

Skull Base and Hindbrain

The foramen magnum is the largest opening at the base of the skull. The medulla oblongata, which carries the tracts, fibers, and pathways between the brain and spinal cord, leaves the brain at the foramen magnum. The meninges, vertebral arteries, meningeal branches of vertebral arteries, and spinal roots of accessory nerves also leave the skull at the level of the foramen magnum. An abnormality at the level of the foramen magnum may affect sleep by disrupting the information transfer out of the brain.

Chiari Malformation

Chiari malformations include malformations of the cerebellum and brainstem. Chiari I malformation consists of abnormal cerebellar tonsils that are displaced > 3–5 mm below the foramen magnum [45], and Chiari II malformation (discussed in the next section) consists of downward displacement of the cerebellum along with spinal myelomeningocele. Chiari I malformations occur in one per 1000–5000 births [46]. Losurdo and colleagues evaluated 53 consecutive children and adolescents who had Chiari I malformation with overnight polysomnography to determine the prevalence of sleep-disordered breathing [47]. Overall, they found that 24% of the children had sleep-disordered breathing with 11% having obstructive sleep apnea, 9% having central sleep apnea, and 3% having both obstructive and central sleep apnea; the presence of sleep-disordered breathing was not associated with degree of herniation. Likewise, Ferre et al. evaluated 70 consecutive patients with Chiari I malformation and found that 50% of patients had a sleep-related breathing disorder with the majority exhibiting a predominantly obstructive component [48•]. As the above studies indicate, Chiari malformation can be associated with either obstructive or central sleep apnea. Compression of the brainstem and respiratory centers is thought to be the mechanism involved in producing central apneas, whereas compression to cranial nerves IX and X may result in decreased upper airway patency and obstruction. In addition, brainstem compression could interfere with the ascending reticular activating system, and episodic airway obstruction may contribute to increased intracranial pressure and the development of syringomyelia [49].

Spina Bifida

Spina bifida (myelomeningocele) is a developmental defect in the spine where a part of the spinal cord and nerve roots protrude in a sac through the spinal defect. Chiari II is the herniation of the cerebellum and medulla into the spinal canal in association with myelomeningocele. Some children with Chiari II and myelomeningocele require decompression of the foramen magnum if they develop symptoms due to brainstem compression [50]. Even after surgical repair of myelomeningocele and Chiari II malformations, over half of children have sleep-disordered breathing [51•]. Furthermore, sleep-disordered breathing is associated with sudden death in young adult patients with myelomeningocele [52]. Shellhaas et al. compared 19 newborns with a repaired myelomeningocele versus 19 control infants with polysomnography and found that infants with repaired myelomeningocele had substantially higher AHIs compared to control patients (34/h vs 19/h), mainly due to more frequent central apneas (10/h vs 4/h) and hypopneas (21/h vs 12/h) rather than obstructive apneas (3/h vs 2.5/h) [53]. Interestingly, the authors found that at the sixth month follow-up, there was no significant association between severity of sleep-related breathing disorder and subsequent developmental delay [53]. Murray et al. used sleep questionnaires, actigraphy, and sleep diaries to assess the sleep of 37 adolescents with spina bifida compared to 37 adolescents without spina bifida [54•].

They found that adolescents with spina bifida experienced poorer sleep quality, reduced sleep, increased insomnia, and increased daytime fatigue compared to the typically developing adolescents. Treatment options for sleep-related breathing disorders in patients with myelomeningocele and Chiari II malformation should be tailored to the individual patient and type of sleep-disordered breathing and include interval follow-up with repeat polysomnography [51•], non-invasive positive airway pressure [55], supplemental oxygen [51•, 53, 55], otolaryngology evaluation [51•], tracheostomy alone [55, 56], tracheostomy with positive airway pressure [55, 56], and neurosurgical evaluation [51•, 56]. Routine screening and evaluation of sleep problems should be performed in individuals with spina bifida.

Achondroplasia

Achondroplasia occurs in approximately 1 in 20,000 newborns [57]. Individuals with achondroplasia have rhizomelic short stature, frontal bossing, midface hypoplasia, narrow thorax, and sometimes foramen magnum stenosis. Children with achondroplasia are at increased risk for obstructive sleep apnea due to craniofacial and airway differences, hypotonia, hypoventilation due to restrictive lung disease, and central sleep apnea due to foramen magnum stenosis [58]. Overall, approximately 42–82% of children with achondroplasia have some form of sleep-related breathing disorder [58]. Adenotonsillectomy has been shown to resolve or reduce the severity of OSA in this population, although many children may still require positive airway pressure for residual disease [59•, 60–63]. Due to the concern for foramen magnum stenosis resulting in central sleep apnea, investigators have evaluated if PSG findings predict cervicomedullary compression. For instance, White and colleagues evaluated 17 individuals with achondroplasia with PSG and MRI [64]. They found evidence of sleep-disordered breathing in all patients with AHIs ranging from 3.5/h to 104.7/h, but there was no correlation between the amount of foramen magnum stenosis and the severity of sleep-disordered breathing based on sleep study. Although the prevalence of sleep-related breathing disorders is high in this population, a recent working group could not come to agreement as to the ideal time to perform a surveillance sleep study in infants with achondroplasia other than "as early as possible" [65]. Given the lack of correlation between PSG findings and foramen magnum stenosis noted above, they did agree that sleep studies should not be used as the sole diagnostic tool to evaluate for foramen magnum stenosis.

Joubert Syndrome

Joubert syndrome is a disorder characterized by a molar tooth sign on head MRI that represents cerebellar vermis hypoplasia [66, 67]. There are several genetic mutations that can result in Joubert, and the prevalence is 1/100,000 births [66, 67]. Infants with Joubert syndrome usually also have hypotonia and developmental delays and may have eye, kidney, or other system involvement. From a respiratory standpoint, these children frequently have an irregular breathing pattern as newborns characterized by severe tachypnea followed by apnea, likely due to effects on respiratory centers in the brainstem. Caffeine or supplemental oxygen may be effective at stabilizing the respiratory pattern [67]. Joubert syndrome is associated with central sleep apnea with respiratory events being periodic in nature and worse during non-REM and has been shown to respond to bilevel positive airway pressure with a backup rate [68]. One self-report survey of patients with Joubert syndrome found snoring in 50% and elevated scores on the pediatric sleep questionnaire suggestive of sleep-related breathing disorder in 43% [69]. Due to the high frequency of sleep-related breathing disorders, the Joubert Syndrome and Related Disorders Foundation recommends a polysomnogram in all children under the age of 12 months, and again if symptoms are present after 12 months of age [70].

In Utero Exposures Causing Multiple Brain Differences

Fetal Alcohol Spectrum Disorder

Fetal alcohol spectrum disorders (FASD) represent one of the most common preventable causes of developmental disability, with an estimated prevalence of 1–5% in the USA [71]. In addition to characteristic facial features, neurocognitive sequelae, and growth problems, children with FASD may have structural brain abnormalities including structural abnormalities of the corpus callous, cerebellum, caudate, hippocampus, and regional differences in cortical thickness and gray matter volume [72].

For decades, the presence of common and persistent sleep difficulties in children with FASD has been recognized [73]. Jan and colleagues provided several general and practical sleep health recommendations for families, including advice regarding sleep environment, preparation for sleep, sleep scheduling, and sleep hygiene for caregivers [74]. Wengel and colleagues found that sensory processing deficits were associated with sleep problems in children with FASD and speculated that children with FASD would benefit from occupational therapy for sensory-based treatment [75]. Chen and colleagues performed a more detailed evaluation of sleep in children with FASD using the Children's Sleep Habits Questionnaire as well as polysomnography (in a subset), and they found that clinically significant sleep problems were present in 85% of children with FASD (primarily related to insomnia) and sleep studies revealed sleep-disordered breathing as well as fragmented sleep with frequent arousals [76•].

Despite their commonality, studies have found health-care professional deficits in the recognition of sleep problems among children with FASD [77]. A larger study by Goril and colleagues found parasomnias and insomnia were the most common sleep disorders in this population, polysomnography demonstrated low sleep efficiency and high sleep fragmentation, and the majority of children had abnormal melatonin profiles suggesting circadian dysregulation [78]. Animal models of FASD have found smaller pontine cholinergic neurons (known to be involved in REM sleep and SWS) and larger hypothalamic orexinergic neurons (which are involved in arousal) [79].

Congenital Zika Syndrome

Zika virus targets neural progenitor cells, and in utero infection is associated with potentially severe neurological sequelae, with neuroimaging findings including intracranial calcifications, ventriculomegaly, decreased brain volume, simplified gyral patterns, dysgenesis of the corpus callosum, hypoplasia of the brainstem and cerebellum, enlarged cisterna magna, and increased extra-axial fluid [80, 81]. Pinato and colleagues examined sleep characteristics of infants and toddlers with congenital Zika syndrome [82•]. They found that children with congenital Zika syndrome had lower total and nocturnal sleep time compared to typically developing children based on responses to the Brief Infant Sleep Questionnaire. In addition, while the typically developing children had less nocturnal wakefulness as they aged, this was not seen in children with Zika. Overall, 34% of the children with congenital Zika syndrome were found to be poor sleepers. To be sure, given their many congenital anomalies (including multiple brain regions, hypotonia, epilepsy, pulmonary disease), these patients are likely at risk for a wide spectrum of sleep disorders and would benefit from careful sleep evaluation.

Conclusion

Neurodevelopmental disorders can cause alterations of sleep. Disorders of the eye can cause changes in light circadian entrainment resulting in a circadian rhythm disorder. Disorders within the brain can interfere with ascending arousal system signaling of neurotransmitters that control our sleep-wake cycle. Disorders of the brainstem can alter the respiratory pattern of breathing during sleep. The study of sleep in individuals with neurodevelopmental disorders and congenital malformations of the CNS will likely advance our understanding of basic sleep physiology and pathophysiology. More importantly, clinicians who maintain a healthy vigilance for sleep problems in this patient population will likely identify opportunities to improve the overall function and health of the patient as well as decrease stress for caregivers.

Compliance with Ethical Standards

Conflict of Interest Jacqueline F. Yates, Matthew M. Troester, and David G. Ingram each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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