

Paediatric sleep medicine

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The sleep of infants and children has unique features that slowly evolve into the adult characteristics of sleep. There are developmental changes in sleep patterns, sleep state and sleep architecture.

This review is an attempt to highlight the various development changes and address the spectrum of sleep disturbances they encounter.

Newborns sleep approximately 70% of a 24 hour cycle. The average newborn will sleep approximately 16 hours per day but there is individual variation (range 14 – 18 hours). Newborns sleep for approximately 3-4 hours at a time and are awake for approximately 1-2 hours. Sleep occurs randomly during the day and night. The amount of time spent in sleep decreases as infants mature. The total sleep time gradually declines over the first 60 months of life. The total sleep time decreases from an average of 14.2 hours at age 6 months to an average of 11.4 hours by age 60 months to 8.1 hours per night at 16 years. Iglowstein et al¹ demonstrated that sleep becomes consolidated in the nighttime and daytime sleep (naps) declines substantially by age 12 months and then more gradually over the next 3 years.

Sleep Architecture

The EEG of quiet sleep evolves from tracé discontinue to trace, alternant and into the mature NREM sleep by age 6 months post term. Other features of quiet sleep (NREM)

include absence of eye movements, sustained muscle tone and few body movements. Regular breathing and heart rate patterns are noted in this state. After birth the quiet sleep pattern tracé alternant is gradually replaced by increasing numbers of delta waves.

Immature sleep spindles are detected by age 4 weeks and evolve rapidly to the mature form by 8 weeks. K-complexes are detected between 4 – 6 months and by age 6 months NREM can be differentiated into the four adult stages.

Sleep onset in the newborn is often through active-REM sleep. Active sleep can be detected by 32 weeks PCA. The EEG is characterized by a low voltage mixed frequency pattern. There are rapid eye movements, low muscle tone and variability of heart and respiratory rate. The respiratory pattern can be variable with paradoxical respiratory efforts, increased central apneas and periodic breathing. Paradoxical efforts can persist to age 3 years. Intermittent body movements and jerks of the extremities as well as facial grimaces and twitches are noted.

Quiet-NREM sleep and active-REM sleep cycle throughout the night. The length of the cycle gradually increases with age. The cycle length of a newborn is approximately 50 minutes and gradually increases to the adult cycle length of 90 minutes by school age.

In the newborn, the sleep/wake episodes occur randomly throughout a 24 hour period.

Circadian rhythms evolve over the first months of life so that core body temperature develops a circadian rhythm by the age of 1 month and secretion of hormones such as melatonin and cortisol have a circadian pattern by approximately 3 months. Sleep gradually becomes more consolidated so that many infants sleep through the night by 6 months of age².

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Two prominent age-related changes in sleep architecture are a decrease in the amount of slow wave sleep (stages 3 and 4) and an increase in the number of awakenings per night. Time spent in REM sleep also decreases with age. Using actigraphic measures of sleep, a monotonic decrease in the number of naps per day and in the number of minutes spent asleep during the day in the first 5 years of life is seen. Night time sleep remained constant over this time frame, indicating that decreases in total sleep time were due to the change in daytime sleep³.

Sudden infant death syndrome and apparent life threatening event

SIDS is the sudden death of any infant under one year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history⁴. In contrast to SIDS, where the baby has expired, infants may present with an apparent life-threatening event (ALTE).

Guilleminault et al⁵ demonstrated a higher rate of obstructive events in infants felt to be at risk for SIDS than in age matched controls. A decreased arousal response may also play a role in the pathophysiology of SIDS. Also suggested is an altered autonomic control in SIDS victims, with a trend towards more homeostasis and less heart rate variability. Development of SIDS in relation to the prone position in certain studies has demonstrated a relative risk of 8.8 compared with other positions.

Congenital central hypoventilation syndrome: Children with CCHS have negligible responses to hypercarbia and hypoxemia, even when awake minute ventilation is inadequate⁶. They lack a perception of dyspnea but maintain conscious control of breathing. Thus, they may be at risk for hypercarbia and hypoxemia during exercise. Several studies have implicated mutations in the PHOX2b gene on chromosome 4p12.

Sleep disorders in children

Sleep problems are common in children and range from minor disruptions of sleep to significant disorders requiring intervention. Sleep related breathing disorders frequently go unrecognized in children despite readily apparent symptoms and potentially severe consequences. Narcolepsy typically starts in the second decade of life but can present in preschool children. Parasomnias are extremely common

and may become pathological either in terms of frequency or severity. Insufficient sleep is extremely common in children. This is probably due to a variety of factors including a tendency to phase delay, early start times for schools and sports, competing behaviors at bedtime (television, internet), caffeine use, and a failure to account for increased sleep need in children.

After 3 months, problems with night waking or difficulty settling may emerge. Piercing screams during sleep, normal in infants, may be considered a sign of night terrors (2-3%) in toddlers. With the development of language, reports of nightmares (10-50%) become possible. Sleepwalking (5%) may emerge with the onset of walking during the day, reaching a peak of occurrence at age 8 to 12 years. As noted above, enuresis may occur at about the same age.

Parasomnia: The word *para* in Greek means alongside of, while *somnus* in Latin means sleep, thus the word parasomnia means events that accompany sleep. Parasomnias are undesirable physical events or experiences that occur during entry into sleep, within sleep or during arousals from sleep.

There is a strong familial pattern for parasomnias, especially sleepwalking. When both parents have a history of sleepwalking, up to 60% of children are also sleepwalkers. Twin studies suggest that genetic factors play a role in 65% of cases.

Several sleep disorders are prominent in teenagers. The most common sleep problem, however, is insufficient sleep 10% (higher in teens – up to 33%) This is attributed to conflict between the circadian timing of sleep and societal constraints. Due to changes in the circadian system, delayed sleep phase disorder (7% teens) is more likely to occur in teenagers than in any other age group.

The incidence of narcolepsy peaks in the second decade, although cases with onset as early as 3 years of age have been reported.

Behavioral insomnia of childhood

Sleep-onset association type

The child begins to associate sleep-onset with circumstances that are highly problematic or demanding of the caregiver. In the absence of the associated conditions, sleep-onset is significantly delayed or sleep is otherwise disrupted. Nighttime awakenings require caregiver intervention for the child to return to sleep.

Children who are used to falling asleep while being held,

rocked, or patted, or using a pacifier may be unable to fall asleep on their own until those associations are re-established. If circumstances at waking are different from those present at sleep onset, there may be difficulty returning to sleep. The child may cry or otherwise demand attention until the associated bedtime conditions are repeated

Limit-setting type

Children are refusing to go to bed at an appropriate time or refusing to return to bed following a nighttime awakening. The caregiver demonstrates insufficient or inappropriate limit setting to establish appropriate sleeping behavior in the child. This can lead to frequent "curtain calls". Causes of inadequate or inconsistent limit setting are varied and are sometimes complex. They may reflect lack of knowledge of the importance of limit setting or of limit setting techniques, absent motivation, guilt, environmental or medical constraints, cultural factors, or underlying psychosocial problems. Proper intervention must take all of these into account. Parents must decide what the pre-sleep routine will be and enforce the limits.

Obstructive sleep apnea

Pediatric OSA is a common disorder which is most likely under-diagnosed. Up to 20% of normal children snore intermittently and 7% to 10% of children are habitual or regular snorers. Current best estimates suggest that 1% to 3% of preschool children have significant disease. The age distribution of OSA corresponds to the peak period of lymphoid hyperplasia and adenotonsillar hypertrophy in children, which may be a contributing factor for pediatric OSA. Unlike adults, gender distribution in children, at least during the prepubertal years, is approximately equal.

Obstruction can occur from narrowing at any portion of the upper airway, for example choanal atresia, adenotonsillar tissue hypertrophy or micrognathia.

Risk factors in children for OSA are a reflection of the interaction between upper airway narrowing or obstruction and floppiness of the upper airway. The most common risk factor for pediatric OSA is usually a combination of adenoidal and tonsillar hypertrophy.

Children with craniofacial anomalies that cause upper airway narrowing, including retrognathia, mid-face hypoplasia, and maxillary and mandibular hypoplasia, are also at increased risk for OSA, including children with congenital syndromes, such as Pierre Robin, Treacher-Collins

and achondroplasia.

Children and adolescents with Down syndrome⁹ have a number of potential risk factors for OSAS, including relative mid-face hypoplasia, generalized hypotonia, macroglossia, obesity.

Symptomatology

Young children with sleep fragmentation are more likely to manifest daytime sleepiness behaviorally, through increased activity, aggression, poor concentration, and irritability rather than to complain of feeling "sleepy." Children with OSAS may have difficulty awakening in the morning despite having what appears to be adequate time in bed. Morning headaches may be a result of hypercapnia or hypoxia. Children with upper airway obstruction may have mouth breathing, halitosis, nasal congestion, and rhinorrhea, as well as hyponasal voice.

The clinical consequences of untreated pediatric OSA can be categorized into effects on growth, neurocognitive morbidity and cardiovascular consequences¹⁰. In contrast to adults who are frequently overweight, children with OSAS may fail to thrive secondary to increased work of breathing. The neurocognitive morbidity, generally arises from alterations in gas exchange and/or sleep fragmentation. The hypoxemia and/or hypercarbia associated with apnea and/or obstructive hypoventilation may lead to pulmonary and/or systemic hypertension.

The guidelines recommend screening all children for snoring and specialty referral of complex high-risk patients, while those in cardio-respiratory failure requiring urgent evaluation¹¹. Polysomnography is recommended as the gold standard for discriminating between primary snoring and OSA. There is a role for abbreviated nap studies in the pediatric population. Adenotonsillectomy is recommended as the first-line treatment for most children and continuous positive airway pressure an option for those who are not candidates for surgery or do not respond to surgery.

Enuresis

Persistent bedwetting more than twice a month past the age of five years

Primary enuresis: Patient has never been dry on a regular basis

Secondary enuresis: Patient becomes enuretic after being dry for at least six months

Children with enuresis seem to have a functionally small bladder capacity. This may be a correlate rather than a cause of enuresis. The treatment modalities of retention and bladder stretching in children result in little or no increase in bladder capacity in most children. Dysfunctional detrusor activity, sometimes referred to as neurogenic bladder, has been proposed as both an organic and functional cause of enuresis. Although some children do have abnormal muscular responses during voiding, these abnormalities are usually associated with daytime symptoms and abnormal urine analysis. Enuresis is not associated with depth of sleep as defined by sleep stage; however, children with enuresis may have a higher arousal threshold than controls.

Disorders such as sleep apnea may also be associated with nocturnal episodes of enuresis.

After age five years, resolution occurs at a rate of 15% per year until the adult incidence of 1% is reached. It is more prevalent in males than females. In families where both parents were enuretic, 77% of the children have enuresis; 44% of children had enuresis if one parent was enuretic.

Pediatric Restless legs syndrome

A history of leg discomfort in child's own words that begins with inactivity, is relieved by movement and is typically present in the evening or at night is consistent with diagnosis of pediatric RLS. The presence of a family history of RLS with either a parent or sibling with definite RLS and the finding of periodic limb movements of 5 or more per hour of sleep on polysomnography are also consistent with a diagnosis of pediatric RLS¹³.

Night-Walkers" Survey: among 138 adults with RLS (mean age 60 years), 18% reported symptoms having begun before age of 10 years and 25% reported symptoms began before age 20 years.

A structured sleep environment and a strictly-followed sleep schedule will assist in reducing sleep deprivation, improve sleep quality and reduce need for medications. Limit setting is often a problem and may require professional guidance to accomplish; limit setting will also help reduce sleep deprivation. Iron deficiency, if present, should be treated promptly and has been shown to improve symptoms. Clonazepam is a benzodiazepine is sometimes used in the treatment of RLS in children. Dopaminergic agents are also reported to be effective.

Delayed sleep phase syndrome (DSPS)

Patients with DSPS report difficulty falling asleep and difficulty awakening at the times required by school or work schedules. When responsibilities no longer dictate an early sleep schedule (e.g., summer vacation), the patient has no difficulty sleeping and waking. The preferred scheduling of the major sleep episode is delayed.

The desire to go to bed later and to sleep till late in the morning is related to a shift in internal biological clock, as represented by the delay in the timing of the circadian melatonin rhythm (dashed line). This delay in circadian timing is associated with and may be the primary cause of sleep onset insomnia (i.e., patients attempt to go to sleep at a biological time when the circadian clock is promoting wakefulness) and morning sleepiness (i.e., patients awaken at a biological time when the circadian clock is promoting sleep). The phase delay in circadian timing maybe related to biological (circadian physiology) and behavioral (e.g., social activities, increased light exposure in the evening, earlier school start times) changes that occur during adolescence.⁸

DSPS combined with early school start times is thought to contribute to poor school performance and reduced sleep during the week³. Inadequate sleep in adolescents is reported to contribute to increase risk of automobile accidents and increased use of caffeine, nicotine and alcohol.

Three main therapies for delayed sleep phase have been described: chronotherapy, or progressive delay of sleep onset; bright light therapy, using strategically timed light pulses to phase shift the sleep cycle; and melatonin, used either as a phase shifting agent or as a hypnotic.

Depression in adolescents

Between 2% and 8% of adolescents suffer from major depression with a lifetime prevalence rate in adolescents being as high as 15%-20%. Depressive disorders are associated with poor psychosocial outcomes, comorbid psychiatric and medical conditions, substance abuse and a high risk of suicide – one of the leading causes of death in this age group. Sixty six percent of depressed children suffer from insomnia. Ten percent of depressed adolescents continue to experience insomnia after remission and 25% of depressed adolescents complain of hypersomnia.

Narcolepsy

The predisposition to narcolepsy is not only genetic in origin — other factors can contribute to the development of narcolepsy. Case series indicate that only 25% to 30% of monozygotic twins are concordant for narcolepsy. Therefore, environmental factors must be implicated in triggering this disorder on top of a specific genetic predisposition.

Several environmental factors have been postulated. For example, an unknown antigen such as a virus could bind with the HLA molecule HLA DQB1*0602 triggering an immune response. Due to similarities with host structures this would then induce an autoimmune response.

Other possible factors include changes in neuroanatomy or neurochemical pathways due to head trauma or toxin exposure. Sleep deprivation or changes in the sleep/wake cycle have been reported to precipitate narcolepsy. However, the specificity of environmental factors has not been established.

Finally, it is important to note the effect of development on the occurrence of the disorder. Narcolepsy frequently starts around adolescence suggesting a precipitating role of the hormonal changes around puberty. Ageing can affect symptom severity. Many narcoleptics experience improvement in cataplexy with aging.

Hypocretins-1 and -2 are produced exclusively by a well-defined group of neurons localized in the lateral hypothalamus. The neurons project to the olfactory bulb, cerebral cortex, thalamus, hypothalamus and brainstem, particularly the locus coeruleus, raphe nucleus and to cholinergic nuclei and cholinceptive site (such as pontine reticular formation), thought to be important for the sleep regulation. The large majority (85-90%) of patients with narcolepsy-cataplexy have low or undetectable hypocretin-1 ligand in their cerebrospinal fluid.⁴⁴ This hypocretin deficiency is tightly associated with the occurrence of cataplexy and HLA-DQ1*0602¹⁴.

Low CSF hypocretin 1 levels are very specific for narcolepsy when compared to other sleep or neurological disorders.

Narcolepsy affects 0.03% to 0.1% of the general population. 1% to 2% of first degree relatives have narcolepsy-cataplexy.

Symptomatology

By definition, all narcoleptics have excessive daytime sleepiness. Hypnagogic hallucinations and sleep paralysis

occurred in 40% to 60% of patients and fragmented sleep in about 50%. The clinical presentation of narcolepsy in children, particularly before the age of puberty, is often different from the adult presentation and requires special awareness. Symptoms are most often detected in the classroom where the sleepiness associated with narcolepsy may present as an unrecognized or misdiagnosed learning disability or as attention deficit disorder. Muscle weakness episodes representing cataplexy may be mislabeled as psychogenic in origin.

Finally, narcolepsy may be secondary to other neurologic disorders such as Niemann-Pick disease type C and diencephalic tumors. Narcolepsy symptoms may mimic or be misinterpreted as other conditions, e.g., depression, psychosis, attention deficit disorder, syncope. They may also be unrecognized and attributed to just being lazy, sleepy, clumsy, shy, a loner, and a daydreamer. Symptoms may develop slowly, usually beginning with excessive sleepiness, which can precede cataplexy by one to many years, with cataplexy sometimes beginning simultaneously or on rare occasions prior to excessive sleepiness

Anic-Labat et al found that 85.1% of narcoleptics had clear-cut cataplexy. All patients with cataplexy were diagnosed with narcolepsy. Of the other 920 subjects, 29 had “doubtful” cataplexy.

The diagnosis of narcolepsy begins with a thorough sleep history with careful attention to sleep timing and routines. The medical and psychiatric history should also be reviewed. Sleep logs, to document two to three weeks of the sleep wake schedule, are often helpful. The sleep laboratory evaluation includes both poly-somnography and Multiple Sleep Latency Test. Case specific evaluations may include measurement of hypocretin levels in cerebrospinal fluid, directed radiologic or hematologic work up. If indicated, a drug screen may be necessary. Psychological testing may provide useful information regarding alternative diagnostic considerations (e.g. depression), or about the neuropsychological manifestations of narcolepsy in the individual patient.

Treatment

The treatment of narcolepsy includes education (about narcolepsy and good sleep hygiene) and support: behavioral and pharmacologic components. The education and support components are critical in this lifelong disorder. These efforts should include the patient, family, school and coaches. All involved parties should focus on realistic goals and performance standards. School and career counseling are needed. Driving precautions are critical, and in some states

notification of the Motor Vehicle Bureau may be required in some states. Patients should be closely monitored for high risk behaviors including, boxing, swimming, drinking, driving, and drug use. Close attention to possible depression is warranted.

The pharmacologic treatment generally involves the use of stimulant medications to decrease sleepiness. Methylphenidate, a non-amphetamine stimulant, has been the most widely used medication. The medication is titrated as twice or three times daily dosing, and a sustained release formulation is available once the necessary dose has been established. Modafinil, a non-amphetamine wake-promoting medication that is commonly used for the treatment of narcolepsy and daytime sleepiness in adults, has not been approved for treatment of narcolepsy in children under age 16, but is approved for the treatment of ADHD in that population. Amphetamines, typically dextroamphetamine, are used if other stimulants are inadequate or they have unacceptable side effects. There is growing evidence that sodium oxybate also decreases daytime sleepiness. Further pharmacologic adjustments may be necessary for patients with significant auxiliary REM manifestations, (cataplexy, sleep paralysis and hypnagogic hallucinations). Only sodium oxybate 3 - 9 gm (divided dose at bedtime and repeated 3 - 4 hours later, has been approved by the FDA for treating cataplexy in narcolepsy patients 18 and older.

Conclusion

In summary, we should arise to address the vast spectrum of sleep disturbances that arise and affect one of the most vulnerable section of our population.

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