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The genetics of sleep disorders in childhood and adolescence

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Abstract

Objective: To review the literature regarding the genetics of sleep disorders in childhood and adolescence.

Sources: Articles published in the past 5 years were searched on MEDLINE using the keywords sleep and genetics. Abstracts were then analyzed. Classical articles with the first description of genes were also included.

Summary of the findings: We often find familial recurrence in many sleep disorders. However, gene loci were discovered for only a few of them. We describe sleep disorders transmitted by genetic heritance and also those in that, although a gene was not found, familial recurrence is high.

Conclusion: Although most of the sleep disorders do not have by now an identified molecular basis, modern techniques are being increasingly applied to determine the contribution of genes to sleep and its associated disorders. The clinical importance of these discoveries may relate not only to improving diagnostic methods but also as a target for drug development.

J Pediatr (Rio J). 2008;84(4 Suppl):S27-32: Sleep, genetics, narcolepsy, restless leg syndrome, parasomnias, childhood.

Introduction

Sleep disorders are frequently reported during childhood and adolescence and a family history is often present.[1] They are very prevalent and may represent an emerging worldwide epidemy.[2]

The importance of diagnosing and treating sleep disorders in children resides, among other factors, in the findings that sleep and temperament are important factors influencing school achievement.[3]

In contrast to the impressive progress in the molecular genetics of circadian rhythms, so far little is known about the molecular basis of normal sleep.[4-7] Even the function of sleep remains an unanswered question in biology.[5]

Many sleep disorders have familial recurrence but to date research into the molecular genetics of sleep disorders remains surprisingly one of the last active fields.[2]

Genetics studies have been mostly restricted to narcolepsy, restless legs syndrome (RLS) and obstructive sleep apnea.

In the last few years many genes have been associated with many diseases. Mapping these alterations have led to an

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easier identification of affected persons, a better understanding of prognosis and also served as new targets to drug development.

The aim of this article was to review the literature regarding the genetics of sleep disorders in childhood and adolescence to provide a better understanding of these sleep disorders and to guide general pediatricians toward diagnosis and prognosis.

Methods

A literature review was performed on MEDLINE using the keywords sleep and genetics in combination and after an isolated search for the keywords narcolepsy, sleep apnea, and RLS. The abstracts were analyzed and articles containing information regarding pediatric age range were included. Classical articles with the first description of genes and relevant papers on specific genetic analysis were also included.

Results

Narcolepsy

Narcolepsy is a chronic sleep disorder that occurs with a slight predominance in males, from childhood to the fifth decade (with a peak on the second decade). It is characterized by a tetrad of symptoms related to the occurrence of rapid eye movement sleep (REM sleep) at inappropriate times. Excessive daytime sleepiness, cataplexy (abrupt and reversible decrease in or loss of muscle tone, without loss of consciousness, most frequently elicited by emotions such as laughter, anger or surprise), sleep paralysis (terrifying experience that occurs when falling asleep or on awakening, where patients find themselves suddenly unable to move, speak or breath deeply) and hypnagogic/ hypnopompic hallucinations (vivid dreaming that can be difficult to distinguish from reality, auditory, visual or cenesthopathic hallucinations that occur at sleep onset an can be either diurnal or nocturnal).[8,9]

Familial occurrence of narcolepsy – cataplexy was first reported in 1877, by Westphal.[8] However, the first observation that narcolepsy is associated with human leukocyte antigen (HLA) DR2 was reported in Japan 100 years later.[8] More than 85% of all narcoleptics with definite cataplexy share a mutation (an HLA allele) on chromosome 6, HLA DQB1*0602 alone or in combination with HLA DR15. Later, in 1999, a second gene, orexin (hypocretin), located on chromosome 12, was related to narcolepsy in a dog model.[8] Hypocretins/ orexins are novel hypothalamic neuropeptides involved in energy homeostasis and neuroendocrine functions.[10] Deficiency of hypocretin-ligand is found in many narcoleptic patients with cataplexy.[11,12] As hypocretin usually participates in the maintenance of wakefulness, the loss of neurons that release this peptide might allow REM sleep occurring at any time and determine cataplectic attacks.[9] These findings give new insights on the pathophysiology of narcolepsy: a specific genetic background (the HLA mutation in chromosome 6) might increase the susceptibility of hypocretin containing brain neurons to immune attack. The current most likely hypothesis for narcolepsy is an autoimmune process targeting hypocretin neurons in response to unknown environmental factors.[9-11,13,14] In this perspective, neurologists and pediatricians should be aware that the early treatment with immunoglobulins in children/adolescents with recently diagnosed narcolepsy could arrest the progression of the disease and even limit or avoid chronic treatment with amphetamines or wake promoting agents (modafinil) or antidepressants.[15]

Downregulation of gene Mx2 in white blood cells of narcoleptic patients and expression of gene NLC1-A in a specific region on chromosome 21 (21q22.3) have been recently proposed as novel genetic factors related to narcolepsy.[16,17] However, DQB1*0602 remains the best HLA marker across all ethnic groups.[8,18]

Advanced sleep phase syndrome and delayed sleep phase syndrome

Sleep is regulated by a homeostatic process that determines its need and by a circadian process that determines its timing.[19] The sleep-wake cycle is under the control of the circadian clock and the first clock gene isolated (Clock, Per) was in a drosophila. Later, homologous counterparts have been found in mammals.[20]

Two sleep circadian disorders had their genes recently discovered.[21] Delayed sleep phase syndrome (DSPS) is characterized by sleep onset and delayed wake times (3-6 hours) relative to the conventional sleep-wake time. The typical patient generally does not sleep before 2 AM and does not wake up before 10-12 AM, although sleep architecture could be considered normal. The patient generally reports being more alert in the evening than in the morning. When he/she is constraint to wake early because of school, it may result in chronically insufficient sleep and excessive daytime sleepiness. It is one of the most frequent complaints in adolescence and is frequently associated with poor school performance.[1,20] Delayed sleep phase is associated with a polymorphism in Per3. Advanced sleep phase syndrome is characterized by habitual and involuntary sleep and wake time earlier than societal means. It is less common than the DSPS and generally occurs out of the pediatric age range.[19] It is produced by a point mutation in a human clock gene (Per2).[21]

Insomnia

Insomnia is defined as a difficulty in initiating and/or maintaining sleep. Insomnia in childhood is generally related to a wide range of external, environmental causes or habits that vary according to age from infancy to adolescence. Its pathophysiology is completely different from adulthood and so should be the clinical approach of the pediatrician.[22] Although this complaint is frequently associated with positive family history, no genes have been found.

Using animal models of sleep deprivation, researchers have identified a gene, Homer1a , whose expression reflects susceptibility to sleep loss.[19] Adult patients homozygous for the clock gene genotype are more predisposed to initial, middle and terminal insomnia. Furthermore, fatal familial insomnia, a lethal disorder that does not occur in childhood, was related to a point mutation in the prion protein gene.[21]

Obstructive sleep apnea

In children many different complaints and syndromes are associated with obstructive sleep apnea (OSA).[23] The presence of subtle sleep alterations, measured by the cyclic alternating pattern (CAP) in children with obstructive apneas, has been previously reported.[24]

The etiology of OSA is multifactorial, consisting of a complex association between anatomic and neuromuscular factors, besides genetic predisposition. In children OSA related to obesity remains a public health problem.[25]

Recent data have indicated that OSA in adults might be influenced by genetic factors regarding obesity and fat distribution, upper airway muscle control, craniofacial morphology (reduction in airway and mandibular size), ventilatory control and sleep. Furthermore, some gene polymorphisms have been identified in this population. However, it is still unknown if the recognized candidates genes are directly causal to phenotype or not.[25-28] Studies in rodents suggested that deficiency of monoaminoxidase A is associated with an increase in sleep apnea and excess of serotonin might contribute to this phenotype.[29]

A recent paper has hypothesized that pediatric OSA would lead to altered gene expression in circulating leukocytes. Results showed that RNA derived from peripheral leukocytes confirms the presence of altered expression of functionally relevant gene clusters in pediatric OSA.[30]

It is known that the severity of OSA accounts for only approximately 40% of the variance in cognitive performance and that genetic determinants of individual susceptibility may contribute to the morbidity of OSA. Recently Gozal et al.[31] have showed that apolipoprotein E (ApoE) epsilon4 allele was present in three out of 199 children without OSA, whereas in those with OSA, APOE epsilon4 was found in 16 out of 146 children ($p < 0.0002$) and this was also correlated with cognitive scores. These results suggested that the APOE epsilon4 allele is not only associated with increased odds of having sleep-disordered breathing, but also with an increased risk for neurocognitive dysfunction.[31] Sleep apnea is a complex disease and the identification of susceptibility genetic loci will increase the ability to assess risk.[29-33] The identification of genes related to the pathogenesis of this syndrome could lead to the development of therapeutic agents that could modify its natural course and prevent cardiovascular and neurocognitive morbidities in children.[28]

Congenital central hypoventilation syndrome

Congenital central hypoventilation syndrome (CCHS) is a rare disorder of respiratory control characterized by hypoventilation during sleep, nonresponsiveness to respiratory stimulants, and unawareness of hypoxia with adequate baseline ventilation during wakefulness. The clinical course varies but symptoms could be recognized, in some cases, in the first days of life (cyanosis, apnea, sudden respiratory failure when asleep). It was previously known as Ondine's curse.[34] It may occur in combination with other syndromes, such as Moebius syndrome and more recently a strong association with Hirschprung's disease and tumors of neural crest origin has been reported.[35,36] The first cases of this association were reported by Haddad et al. in 1978.[37] The term neurocristopathy, which includes this diagnosis, was proposed in 1980.[38] Around 50% of patients with CCHS have Hirschprung's disease, and around 20% have neural crest tumors.[35] This disease results from a mutation (polyalanine repeat expansion) of the homeobox gene (PHOX) 2B or PHOX2B, which is pivotal in the development of most relays of the autonomic nervous system, including all autonomic neural crest derivatives.[39] Incomplete penetrance can occur in families, so the intensity of symptoms may vary. A genetic evaluation is indicated in family members of affected cases to establish reproductive risk and risk of developing alveolar hypoventilation.[40,41]

Sudden infant death syndrome

Sudden infant death syndrome (SIDS) is defined as "the sudden death of an infant under 1 year of age, which remains unexplained after a through case investigation, including performance of a complete autopsy, examination of death scene, and review of clinical history."[42] Behavioral risk factors have been identified and the most prevalent are use of prone position, smoke exposure, soft bedding and overheating. Siblings of SIDS victims are at increased risk for SIDS. However, in familial cases metabolic or genetic disorders as long QT syndrome and inborn errors of metabolism should be excluded.[43-46]

To date no genotypic differences that could be linked to clinically defined phenotypes have been identified. However, several different polymorphisms (sodium and potassium channels, serotonin transporters, in genes involved in autonomic nervous system development, such as PHOX2a, RET, ECE1, TLX3 and EN1, and in cytokine-interleukin 10 - IL10) have been reported when comparing SIDS to controls.[46]

Restless legs syndrome

RLS is a common sleep disorder that is often misdiagnosed in childhood with growing pain.[1] It is characterized by an irresistible urge to move legs generally when falling asleep and an unpleasant sensation in the lower limbs. It is a major cause of sleep disruption. In most patients with RLS periodic limb movements can be detected during sleep.[47-50] However, the role of periodic limb movements in causing sleepiness is

controversial as some recent publications have suggested that they are only markers of respiratory effort-related arousals.[51] Iron depletion has been associated with the pathogenesis of RLS. In a population study recently performed in Iceland a common variant in an intron of BTBD9 on chromosome 6p21.2 was observed as a marker of periodic limb movements that occurred in close association with decreased serum ferritin levels.[52] In a German study significant associations between RLS and intronic variants in the homeobox gene MEIS1, BTBD9, MAP2K5 and the transcription factor LBXCOR1 on chromosomes 2p, 6p and 15q, respectively, were observed. As the gene MEIS1 is implicated in limb development, this finding may raise the possibility that RLS is a developmental disorder.[53]

Parasomnias

Pediatric parasomnias comprise a wide variety of different confounding behaviors during sleep. The American Academy of Sleep Medicine defines parasomnias as "undesirable physical events or experiences that occur during entry into sleep, within sleep or during arousal from sleep." These events encompass abnormal sleep-related movements, behaviors, emotions, perceptions, dreaming and autonomic nervous system functioning.[1]

In this review we will consider only parasomnias of childhood for which a genetic basis has been reported.

Sleepwalking, confusional arousals and night terrors

Sleepwalking, confusional arousals and night terrors are parasomnias that occur during non-rapid eye movement (NREM) sleep and they frequently share positive family history.[1,21] No clear mode of transmission has been identified so far, but a higher concordance among homozygotic twins and an association with an HLA (DQB1*0501) allele in the familial form have been identified.[54] A common genetic predisposition (DQB1*05) between sleep walking and REM sleep behavior disorder has also been reported.[55]

Nocturnal enuresis

Nocturnal enuresis is considered one of the most prevalent and persistent sleep problem in childhood and is defined as two or more incontinent episodes in a month in children between 5 and 6 years of age or one or more episodes after 6 years of age in the absence of physical disorders such as diabetes, seizures or urinary tract infection.[1] Family history is the most consistently supported etiologic variable and it is most often transmitted as an autosomal dominant inheritance, with high penetrance (90%). Four gene loci have been identified (8q, 12q, 12q, 22q11).[56]

Conclusions

Although most of the sleep disorders do not have by now an identified molecular basis, modern techniques are being increasingly applied to determine the contribution of genes to sleep and its associated disorders. The clinical importance of these discoveries may relate not only to improved diagnostic methods but also as target for drug development.

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