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Topical Review

Narcolepsy in Children: A Diagnostic and Management Approach

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ABSTRACT

OBJECTIVE: To provide a diagnostic and management approach for narcolepsy in children. **METHODS:** Narcolepsy is a chronic disabling disorder characterized by excessive daytime sleepiness, cataplexy, hypnogogic and/or hypnopompic hallucinations, and sleep paralysis. All four features are present in only half of the cases. Excessive daytime sleepiness is the essential feature of narcolepsy at any age and is usually the first symptom to manifest. A combination of excessive daytime sleepiness and definite cataplexy is considered pathognomonic of narcolepsy syndrome. **RESULTS:** New treatment options have become available over the past few years. Early diagnosis and management can significantly improve the quality of life of patients with narcolepsy with cataplexy. **CONCLUSION:** This review summarizes the pathophysiology, clinical features, and management options for children with narcolepsy.

Keywords: narcolepsy, excessive daytime sleepiness, cataplexy, hypocretin

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Introduction

Narcolepsy is primarily a sleep disorder and is one of the most important causes of excessive daytime sleepiness (EDS) in children. Classically, it is characterized by a tetrad of EDS, cataplexy, hypnagogic and hypnopompic hallucinations, and sleep paralysis[1] (see glossary in Box 1). The term "narcolepsy" is derived from two Greek words: *narcos* meaning somnolence and *lepsy* meaning seized.

Narcolepsy is a disabling life-long condition that begins during childhood in more than half of adult patients.[2] The exact prevalence of narcolepsy in the pediatric population is not known; however, the condition is not rare and is probably underestimated because of the high rate of misdiagnosis.[3] A recently published study estimated the pooled incidence rate of narcolepsy in children aged 5-19 years from six European countries to be 0.83 per 100,000 person-years.[4] This study, along with other studies that have recently emerged, linked adjuvanted monovalent H1N1 pandemic flu vaccine with an increased incidence of narcolepsy.[4-8] The European Medicines Agency has now confirmed this association following extensive review of the available literature.[8]

Despite being recognized from as early as the nineteenth century, our understanding of the disorder has only significantly increased over the past two decades. In this review, we present the current knowledge on the topic with a practical overview of the diagnostic and management processes of the pediatric patient with suspected narcolepsy.

Normal pediatric sleep architecture

Sleep has long been recognized as a dynamic process that has different stages. Generally speaking, the wake-sleep cycle has three stages: wakefulness, non–rapid eye movement (NREM) sleep, and REM sleep. NREM sleep typically marks the beginning of sleep,[9] Recently, the American Academy of Sleep Medicine has changed the terminology used to describe the different stages of NREM sleep. Instead of four stages as previously described, NREM sleep is now divided into three stages—N1, N2, and N3—of increasing depth.[10] During the early hours of the night, NREM and REM sleep alternate, but as the night

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Box 1. Glossary of terms used in narcolepsy

Cataplexy: Sudden brief bilateral loss of muscle tone with loss of deep tendon reflexes leading to muscle weakness and or falls. It is commonly triggered by strong emotions such as laughter. Typically, ocular and respiratory muscles are not affected. It is thought to represent rapid eye movement (REM) atonia.
Hypersomnolence: Prolonged periods of sleep that includes daytime and nighttime. Signs include difficulty getting up in the morning, daytime naps that are inappropriate for age, and overwhelming bouts of sleep in inappropriate circumstances.
Hypnagogic: Relating to sleep onset.
Hypnopompic: Relating to partial wakefulness emerging from sleep.
Multiple sleep latency test: An objective method by which the rapidity of going into REM sleep is measured. The test is carried out in a quiet environment during the daytime and the patient is asked to "take a nap." Typically, it consists of five scheduled naps separated by 2-hour breaks.
Polysomnography: A comprehensive nighttime sleep study that measures different physiological parameters such as electroencephalography surface electromyography, electrocardiography, and electrooculography.
Sleep-disordered breathing: This includes a spectrum of disorders that range from simple snoring to obstructive sleep apnea to obstructive hypoventilation. These are commonly associated with excessive daytime sleepiness, inattention, and social difficulties.
Sleep hygiene: A package of measures taken during the daytime and at bedtime to ensure good quality nocturnal sleep.
Sleep paralysis: Transient inability to move any of the body parts during transition from sleep to wakefulness.
Sleep-onset REM period: Beginning of sleep by directly entering into the REM stage.
REM sleep: The stage in the sleep cycle with the highest cerebral activity, whereas the resting muscle tone is at its lowest except for eye movements and respiratory effort. Dreams take place during this phase.

progresses, REM sleep occupies the majority of sleep. The Figure illustrates the typical timing of different sleep stages in a healthy child.

The average duration of sleep per 24 hours progressively decreases from birth until late adolescence. From the age of 3-5 years, daytime napping becomes unusual.[8] Interestingly, many adolescents in mid-puberty seem to have a tendency to need more sleep during the daytime not merely because of sleep hygiene issues, but perhaps because of physiological changes associated with puberty.[9,11,12] Another common cause for increased daytime sleepiness among adolescents is delayed sleep-phase disorder, the prevalence of which was reported to be 3.3% in a recent Norwegian population-based study.[13]

Features of normal REM sleep

About 20%-25% of overnight sleep time in an adult constitutes REM sleep. In contrast, newborn infants spend about 50% of their total sleep time in REM sleep. This percentage gradually decreases in early childhood, and by 10 years of age it becomes similar to that of adults.[14] Upon falling asleep, neonates go to REM sleep immediately and sleep-onset REM starts to change by 3 months of age, at which time NREM and REM sleep cyclic patterns seen in adults begin to appear. During infancy, this cycle duration is much shorter and gradually increases to the normal adult cycle by about 10 years of age.[14] Thereafter, the first REM period occurs about 90 minutes after sleep onset, which is normally predominated by stages 1 and 2 of NREM sleep.

During REM sleep, there is activation of specific brainstem structures that have complex connections.[14] This is mainly in the pontine reticular formation, which leads to tonic inhibition of motor neurones, rapid eye movements, variability of autonomic nervous system, and desynchronization of the electroencephalograph. The limbic cortex is active and hence vivid dreams occur, but because prefrontal cortex and spinal motor neurones are inactive, locomotor execution is not possible.

It is theorized that REM sleep is associated with language development, acquisition of new skills, and memory consolidation.[15]

What causes narcolepsy?

The hypothesis that narcolepsy has an autoimmune basis has been gaining popularity and, although this is likely in narcolepsy type 1, it is not as clear in narcolepsy type 2.

Hypocretin (also known as orexin) is an excitatory neurotransmitter that is primarily secreted from the lateral hypothalamic neurons residing in the posterior hypothalamus. These neurons have extensive excitatory connections with the forebrain and brainstem.[14,16] Hypocretin plays a promoting role in wakefulness and it suppresses REM sleep. The vast majority of narcoleptics with cataplexy and/or with decreased cerebrospinal fluid hypocretin level (type 1) have a significantly decreased number of the hypocretin-secreting neurons in their hypothalamai.[17] Thus any pathologic process that causes destruction of these neurons will ultimately lead to type 1 narcolepsy.

Both genetic and environmental factors seem to play a role in the etiology.[18]

There is increased susceptibility in individuals who possess the human leukocyte antigen (HLA) DQB1*06:02 allele.[19] Several studies have linked the onset of narcolepsy with certain upper respiratory tract infections such as streptococcal infections and pandemic influenza (H1N1).[20] The pathophysiologic processes proposed include molecular mimicry and T-cell cross-activation via the DQB1*06:02.[20]

Anti-Tribbles homolog 2 autoantibodies (anti-TRIB2) were detected in 41% of patients who had narcolepsy with new-onset cataplexy in one study, adding further evidence to the autoimmunity hypothesis.[21]

During the diagnostic evaluation of patients presenting with narcolepsy, an effort should be made to exclude cases