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Title:

Paediatric Narcolepsy: A Review of Diagnosis and Management

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Abstract

Narcolepsy is a chronic disabling neurological sleep disorder that requires lifelong treatment. We have outlined the clinical features of narcolepsy, the assessment and diagnosis process and have summarised the existing treatment options for children and adolescents with narcolepsy. In the future, the approach to management of paediatric narcolepsy should ideally be in a multidisciplinary setting, involving specialists in sleep medicine, sleep physiology, neurologists and psychologists/psychiatrists. A multidisciplinary approach will help to manage the potential impact of narcolepsy on children and adolescents who are in a stage of their life that is critical to their physical, emotional and social development and their academic attainment.

Key words: Child, Adolescent, Narcolepsy, Cataplexy, Sleep, Psychological well-being

What is known about this topic

- Narcolepsy is a disabling neurological sleep disorder that requires lifelong treatment.

What this study adds

- Concise review of current knowledge, including defining clinical characteristics, diagnostic procedure and the need for a multidisciplinary approach to management.

Introduction

Narcolepsy is a chronic and disabling neurological sleep disorder characterised by excessive daytime sleepiness (EDS) and attacks of muscle weakness which are often precipitated by strong emotions (cataplexy). The estimated prevalence of narcolepsy with cataplexy in adults is 25 to 50 cases per 100,000 people (1). It is a condition that has traditionally been thought of as a disorder of adulthood (2) however, contrary to this assumption, more than 50% of individuals with narcolepsy report experiencing the onset of symptoms before the age of 18 years (3), typically during adolescence. The prevalence of narcolepsy in children and adolescents is yet to be determined (4, 5). It has been estimated that delays between the onset of symptoms and the diagnosis of narcolepsy can range from 10-15 years (6). Individuals with narcolepsy vary in their presentation and this can lead to the misinterpretation of symptoms and misdiagnosis.

The pathophysiology of narcolepsy

The exact cause of narcolepsy is unclear (7), however it is generally considered to arise from a combination of genetic and environmental factors (8). The presence of the human leucocyte antigen (HLA) DQB1*0602 is a primary susceptibility factor for the condition (9) and additional environmental factors have been identified that are commonly reported to precede the onset of symptoms. These include major psychological stress, streptococcal infection, seasonal influenza, a sudden change in sleep patterns and head trauma (10).

Hypocretin (also known as orexin) is a neurotransmitter that plays a role in stabilising the transition between sleep and wake states, by promoting wakefulness and suppressing rapid eye movement (REM) sleep (11). The loss of hypocretin cells in the hypothalamus is reported to cause the onset of narcolepsy symptoms (12). The prevailing hypothesis is that narcolepsy is an autoimmune condition and can be caused by autoimmune response (12).

It has been suggested that H1N1 influenza has a causal link with narcolepsy and an association with the ASO3 adjuvanted pandemic A/H1N1 2009 influenza vaccine (Pandemrix) was documented (3, 12, 13) leading to an estimated 1000 cases globally during the H1N1 (swine flu) Pandemic in 2009 and 2010 (7, 14). This vaccine is no longer in use and no association exists with other vaccines currently in use.

Clinical features of narcolepsy

The International Classification of Sleep Disorders-Third Edition (ICSD-3) (15) distinguishes between two types of narcolepsy; narcolepsy type 1 and narcolepsy type 2. Type 1 narcolepsy is also known as 'narcolepsy-cataplexy' because individuals have deficiency of the neuropeptide hypocretin or experience cataplexy. Type 2 narcolepsy is also known as 'narcolepsy without cataplexy' as individuals do not experience cataplexy and the relationship with cerebrospinal levels of hypocretin is less definite than in type 1 narcolepsy. It is also important to note the difference between 'primary/idiopathic' narcolepsy and 'secondary/symptomatic' narcolepsy-cataplexy. Primary narcolepsy is caused by the loss of hypocretin, whereas secondary narcolepsy develops as result of other medical conditions (e.g. structural brain lesions) (5).

The full array of narcolepsy symptoms are rarely present in childhood and variations in the development of each symptom are possible.

Excessive daytime sleepiness

Excessive daytime sleepiness (EDS) is the most commonly reported first symptom of narcolepsy. Particularly in cases of childhood narcolepsy, it can be difficult for clinicians to distinguish between the normal requirement for daytime naps during childhood and excessive need for sleep. In addition, in cases of suspected adolescent narcolepsy, the distinction between sleepiness due to chronic sleep deprivation and poor sleep habits and sleepiness caused by narcolepsy can be challenging and is a significant contributing factor to the 10 year mean delay in diagnosis of narcolepsy. The ICSD-3 states that for a diagnosis of narcolepsy the individual must have daily periods of irrepressible need to sleep or daytime lapses into sleep, occurring for at least 3 months (15).

Cataplexy

Cataplexy is another predominant symptom of narcolepsy experienced by approximately 60-75% of children diagnosed. Cataplexy may not be present initially, but can develop weeks to years after the onset of EDS (16). The best predictor of the development of cataplexy is hypocretin deficiency (15). A cataplexy attack involves a sudden, temporary loss of muscular control and can be triggered by a range of different emotions (usual triggers are laughter, anger or surprise) (6). Attacks are usually short in duration and progress from the facial region down to the lower limbs, which can lead to full-body collapse. Breathing and eye

movements are unaffected and the individual remains aware during the episode (11). Cataplexy represents the intrusion of REM sleep atonia during wakefulness.

Sleep fragmentation

Children with narcolepsy experience disturbed overnight sleep due to their condition affecting the regulation of sleep-wake states (16). This can lead to frequent night time awakenings (6) which results in fragmented sleep.

Abnormal REM sleep phenomena

Narcolepsy is also characterised by abnormal REM sleep phenomena. Individuals with narcolepsy enter REM sleep more quickly than typically expected during nocturnal sleep and often experience REM sleep at sleep onset. REM sleep early in the night can cause individuals with narcolepsy to experience multisensory hallucinations and sleep paralysis in the transitional period between wakefulness and sleep (17). Vivid auditory or visual hallucinations that occur at sleep onset are known as hypnagogic hallucinations and those that occur during awakening are known as hypnopompic hallucinations. The hallucinations are reported to be so realistic that children can become terrified (18).

Hallucinations are often accompanied by sleep paralysis, which is a temporary inability to move or speak when falling asleep or waking up, possibly with a feeling of being unable to breathe despite respiratory movements being spared (19). The episodes usually last seconds to minutes and end spontaneously. Some children with narcolepsy show excessive movements during REM sleep which is characteristic of REM sleep without atonia disorder.

In keeping with the elevated sleep fragmentation overnight, there are frequent transitions between wake and REM sleep noted in narcolepsy, leading to abnormal REM sleep phenomena occurring throughout the night.

Additional features

The additional features described below are not part of the diagnostic criteria but they are commonly reported in the literature (11, 17, 20).

Automatic behaviour

Automatic behaviour can appear when an individual with narcolepsy is becoming increasingly tired. This often manifests as individuals doing tasks without being able to recall the process of doing them (20). It is important that those around individuals with narcolepsy

can recognise the signs of automatic behaviour and offer support when needed, particularly in situations where the child could be at risk if they are not fully alert.

Obesity

Obesity is common in narcolepsy and tends to happen quickly and suddenly after the onset of other narcolepsy symptoms (11). The mechanism of weight gain is not clear but may be related to abnormal hypocretin levels leading to impaired energy metabolism. Parents frequently report an increase in their child's snacking, in particular in relation to night-time hunger, which could also contribute to weight gain. Excessive daytime sleepiness may lead to a reduction in overall activity due to increased time spent resting or sleeping. National Health Service guidelines recommend that to maintain a basic level of health, young people aged 5 to 18 years need to do at least 60 minutes of moderate to vigorous physical activity every day (21). There is a lack of research that has objectively assessed whether children with narcolepsy are meeting these criteria.

Periodic limb movement disorder

Periodic limb movements are seen frequently in patients with narcolepsy. While these often improve with treatment of other symptoms, it can also be beneficial to treat these in parallel, including optimisation of ferritin stores to 50-80mcg/L.

Mental health

The mental health consequences of narcolepsy can be significant, including co-morbid diagnoses of depression and anxiety (22, 23). The impact is multifactorial, with the chronic effects of sleep disruption and the burden of chronic disease playing a major part, but the hypocretin deficiency itself has also been implicated as a direct pathophysiological factor.

Diagnostic criteria

Diagnosis of childhood narcolepsy is established by clinical evaluation and sleep recordings (6). Diagnostic evaluation includes the use of: parental sleep diaries to provide information about the child's sleep patterns, a device worn on the wrist (called an actigraphy watch) to record the child's movements which indicate overall sleep-wake patterns (4), overnight polysomnography (PSG) to provide detailed physiological information about sleep, and the multiple sleep latency test (MSLT) to objectively measure EDS. Some paediatric sleep

centres perform a blood test to look for the HLA-DQB1* 0602 haplotype and a lumbar puncture to look at levels of hypocretin in the cerebrospinal fluid.

Sleep diaries

Parents may be asked to complete a sleep diary documenting their child's bedtime, wake time and daytime naps for a period of up to two weeks. This is useful for highlighting poor bedtime routines (17) or a disordered nocturnal sleep pattern which may result in excessive daytime sleepiness. The limitations of sleep diaries are that they rely on parents estimating details about their child's sleep patterns and these estimates may be prone to error and be biased by socially desirable responding (24).

Actigraphy

Actigraphy is an objective method of estimating sleep-wake patterns by recording motor activity over an extended period of time in the child's natural environment (4). The small device is normally worn on the child's non-dominant wrist. A two-week period of actigraphy is recommended as part of the diagnosis process. Ideally, actigraphy should be used alongside a sleep and actigraphy wear time diary so that the data can be accurately cleaned (removing periods of non-wear time) and sleep onset latency, sleep efficiency, total minutes in bed, total sleep time, wake after sleep onset, the number of awakenings and average awakening (minutes) can be calculated. It is recommended that this two-week period of actigraphy and sleep diary use is completed prior to an overnight polysomnography recording and a MSLT to rule out sleep-wake phase disorders.

Overnight polysomnography

Polysomnography (PSG) is a multi-channel physiological test to monitor sleep patterns, breathing, gas exchange parameters and leg movements during sleep. The results of an overnight polysomnography recording can be used to provide evidence to support a diagnosis of narcolepsy and to rule out other sleep disorders that may cause excessive daytime sleepiness such as sleep-related breathing disorders. The presence of the following symptoms can support a diagnosis of narcolepsy:

- A short sleep onset latency (SOL) of up to 8 minutes
- A shortened REM sleep onset latency of 15 minutes or less (SOREMP)
- An increase in leg movements overnight and twitches in REM sleep

- An overall fragmentation of the hypnogram with a high level of sleep disturbance (clinicians will assess sleep efficiency, arousal index and % time in each stage of sleep)

Multiple Sleep Latency Test

The Multiple Sleep Latency Test (MSLT) involves daytime PSG recording and is an objective measure of EDS. This test is conducted on the day following an overnight polysomnography recording that has demonstrated adequate overnight sleep of ≥6 hours (adult criteria) to allow valid interpretation of the MSLT data (25). The MSLT is based on 20-minute polysomnography recordings repeated every 2 hours (four or five times a day) starting about 2 hours after morning awakening. The individual is asked to try and fall asleep at each of these time points. The ICSD-3 (15) states that the MSLT should show a mean sleep latency of 8 minutes or less and more than two sleep onset REM periods (SOREMPs) for a diagnosis of narcolepsy. Sleep Centres in the UK may conduct urine drug screening in adolescents to rule out recreational drug use which may contribute to EDS.

There are no paediatric criteria for interpreting the minimum sleep duration on PSG prior to an MSLT or paediatric MSLT criteria therefore, to date, adult criteria are relied upon. However, interpretation of these adult guidelines can be improved by the diagnostic tests being performed by experienced sleep physiologists alongside clinicians who are regularly involved in paediatric narcolepsy diagnosis and test interpretation.

Human leukocyte antigen typing

Human leukocyte antigen (HLA) typing may be used as a diagnostic tool to test for the presence of the HLA-DQB1*0602 haplotype. A blood test with a positive result adds more diagnostic probability of narcolepsy (5), however the results must be interpreted with caution as the HLA DBQB1*0602 is also present in 18-35% of the general population (5).

Cerebrospinal fluid hypocretin 1 level

The most valuable diagnostic marker for narcolepsy type 1 is an undetectable hypocretin-1 level (or a level lower than 110 pg/mL) in the cerebral spinal fluid (CSF), which is measured using a lumbar puncture. As this procedure is invasive, it is usually used as a second line investigation in sleep centres where MSLT is available.

Treatment

There is currently no cure for narcolepsy but medications are available to treat the symptoms of the disorder. There are no specific treatments for children with narcolepsy, however the medications used to manage narcolepsy in adults have also been shown to be effective in children. Children diagnosed with narcolepsy are normally recommended a treatment plan that combines pharmacological therapy and non-pharmacological interventions.

Non-pharmacological treatments

Families are advised about good sleep routine and habits and the significant importance of keeping regular sleep wake patterns. Patients are encouraged to exercise during the day with the aim of promoting wakefulness, reducing the risk of obesity and improving the quality of their sleep at night. Scheduled brief naps are also recommended as a first-line therapy prior to commencing pharmacological therapy. Scheduled naps are particularly important in adolescents with narcolepsy, at a time when their circadian rhythm is shifting. Families are educated about the triggers of cataplexy and the nature of the episodes so that they can learn to support the child during a cataplexy attack and help to eliminate potential triggers where ever possible. Accurate information about narcolepsy should be provided so patients can share this with their relatives, school and other medical professionals involved in their care who are unfamiliar with narcolepsy (20). If available, nurses may be able to visit schools to provide information about how they can support the child's medication and nap schedule. Some specialist sleep centres in the UK hold family support groups to enable children to meet others with the same diagnosis which is important as narcolepsy is a rare disease. Importantly, in some cases, children may require additional support from Child & Adolescent Mental Health Services to cope with the psychological consequences of living with this chronic disorder and early intervention is crucial.

Pharmacological treatments

Medications for narcolepsy are traditionally divided into those that treat EDS and those that improve cataplexy.

Treatments for excessive daytime sleepiness

The aim of treating EDS is to restore a normal or sufficient level of alertness and function (26). There are various treatment options for EDS including:

- Central nervous system stimulants (e.g. Methylphenidate, Dexamphetamine)
- Wake promoting agents (e.g. Modafinil)

- Nocturnal sleep promoting agent-Sodium oxybate (also treats cataplexy)

In addition, there are newer medications for treating EDS such as Pitolisant (Wakix®) and Solriamfetol.

Side effects for these medications can include decreased appetite with nausea and weight loss, headaches, dry mouth, anxiety or aggression and cardiovascular effects such as palpitations, tremor and hypertension (27).

The primary function of sodium oxybate is to improve sleep fragmentation. In 2016, NHS England's specialised services announced that they will routinely commission sodium oxybate for symptom control in post-pubertal children with narcolepsy with cataplexy (28). This medication should only be prescribed by a specialist in a tertiary setting. In adults with narcolepsy sodium oxybate has been shown to increase slow wave sleep (SWS) and subsequently improve daytime symptoms. However, this medication is linked to frequent negative side effects such nausea, dizziness, headache and bed wetting (28).

Treatments for cataplexy

Cataplexy is mainly treated with antidepressant medications which suppress REM sleep.

- Tricyclic antidepressants (e.g. Clomipramine)
- Selective serotonin reuptake inhibitors (e.g. Fluoxetine)
- Serotonin and norepinephrine reuptake inhibitors (e.g. Venlafaxine)

Side effects can include nausea and vomiting, sweating and flattening of affect.

Comorbidities

Narcolepsy can be associated with a number of other comorbid medical problems (29), including comorbid sleep disorders such as sleep-related breathing disorders, nightmares and lucid dreaming, sleep walking, REM sleep behaviour disorder, restless legs syndrome and periodic leg movements (30). Narcolepsy in both children and adults is associated with obesity (31). An increased body mass index (BMI) is frequently associated with upper airway obstruction, increasing the likelihood that individuals with narcolepsy could have comorbid obstructive sleep apnoea-hypopnea syndrome (30). The impact of these comorbid conditions can be significant and they must be treated alongside the symptoms of narcolepsy to enable the best possible outcomes.

Mortality

There is very limited literature available on mortality in narcolepsy. Ohayon, Black, Lai, Eller, Guinta, and Bhattacharyya (2014) (32) conducted a retrospective database evaluation (representative of the general United States population) to characterise the mortality rate in narcolepsy. The authors found a statistically significant 1.5 fold increase in all-cause mortality relative to those without narcolepsy for each of the three consecutive study years studied (32). The cause of the increased mortality is currently unknown, however the authors speculate that it may be due to comorbid medical illnesses, rather than narcolepsy having an independent effect on the cause of death. Further research is needed to develop a better understanding of the potential causes of increased mortality to enable better care and introduce preventative measures (32).

Conclusions

Narcolepsy is a disabling condition that requires lifelong treatment. It is important to consider the impact narcolepsy may have on school-age children who are in a stage of their life that is critical to their physical, emotional and social development and their academic attainment. The approach to management of paediatric narcolepsy should ideally be in a multidisciplinary setting, involving specialists in sleep medicine to manage the core symptoms and psychologists to manage the potential impact on mental health and quality of life.

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