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Narcolepsy and Cataplexy – a practical approach to diagnosis
and managing the impact of this chronic condition on
children and their families

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Abstract

Narcolepsy is a neurological condition affecting the regulation of normal sleep/wake cycles leading to excessive daytime sleepiness (EDS). Attacks of muscle weakness often precipitated by strong emotions (cataplexy), sleep paralysis and hypnagogic hallucinations all represent intrusion of REM sleep into wakefulness.

Narcolepsy is caused by destruction of hypocretin producing cells due to an autoimmune process often by an infective trigger. Hypocretin is found in the hypothalamus and plays a role in stabilisation of the transition between wake and sleep states.

A comprehensive history to exclude other causes of EDS, including poor sleep habits, is essential. Primary sleep related conditions such as sleep apnoea should be excluded. Investigations for confirmation of the diagnosis include Actigraphy, Polysomnography (PSG), Multiple Sleep Latency Testing (MSLT) and CSF analysis.

The symptoms of this debilitating condition can have a huge impact on a child's life and are often vastly underestimated. The impact of EDS on cognitive function is an important factor in difficulties at school, mood, quality of life and future career opportunities.

Drug management is usually initiated and monitored by a specialist centre. Sleep hygiene and planned naps can optimise daytime performance. Advances in understanding the pathophysiology have led to trials of novel treatment approaches. Pharmacological and non-pharmacological interventions require further systematic evaluation, especially in young children.

Keywords

Narcolepsy, Excessive daytime sleepiness, Cataplexy, Hypocretin, Multiple Sleep Latency Test, Cognitive function

In this review we aim to provide both an overview of the diagnosis and recent advances in the management of narcolepsy and cataplexy, and an insight into the impact that this condition has on children and their families.

Definition

Narcolepsy is a lifelong incurable neurological condition affecting the regulation of normal sleep/wake cycles. Excessive daytime sleepiness (EDS) and attacks of muscle weakness which are often precipitated by strong emotions (cataplexy) are hallmarks of the disorder. Dysregulation of sleep/wake can lead to fragmented night-time sleep in association with hypnagogic and hypnopompic hallucinations, vivid nightmares and sleep paralysis.

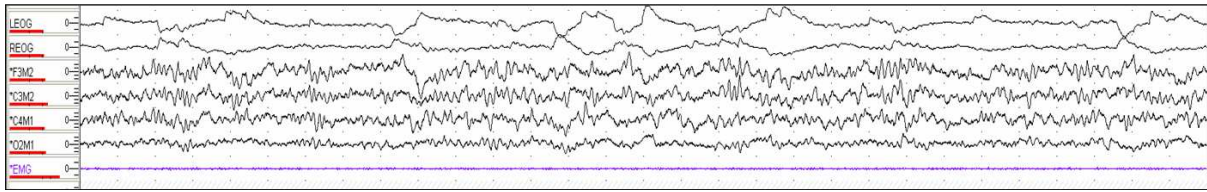
Prevalence

The prevalence of narcolepsy is estimated to be 20-50 per 100,000 population, around a quarter of the prevalence of multiple sclerosis. Historically, the prevalence was underestimated, with early studies reporting a median delay of 10 years between symptom onset and diagnosis. With increased understanding and recognition of the condition this is improving. The disorder most commonly starts in the teens but around 8% present before the age of 5 years. A family history is uncommon but occurs in 1-2% of first degree relatives. A cohort of children presented with florid symptoms and unusual presentations of cataplexy following the swine-flu vaccine in the winter epidemic of 2010-11, bringing the condition to media attention.

Pathophysiology

Normal sleep architecture, or the “hypnogram” is a pattern of sleep stages which is well-defined and characteristically involves transitioning through the lighter stages of sleep (stage N1 and stage N2), followed by the deeper slow wave sleep (stage N3), then a return to stage N2 followed by a period of rapid eye movement (REM) sleep (figure 1). This pattern makes up a sleep cycle. There are 4 to 5 sleep cycles across a night with slow wave sleep predominating in the first part of the night and the REM sleep becoming more prevalent in the second half of the night. REM sleep is associated with muscle atonia and is usually when dreams may be experienced. These processes are regulated from the brainstem, thalamus and basal forebrain by neurotransmitters including noradrenaline, serotonin, acetylcholine, histamine and the recently discovered hypocretins.

Figure 1. 30 second Epoch of REM sleep



The first convincing written reports of narcolepsy-cataplexy were reported in Germany in the 1870s and in 1930, the posterior hypothalamus was recognised as a critical region for the promotion of wakefulness. The early postwar period was fraught with psychoanalytical explanations for narcolepsy-cataplexy but Vogel, in 1960, was the first to report REM sleep at sleep onset in a narcoleptic patient. People with narcolepsy enter REM sleep more quickly than usual during nocturnal sleep, and cataplexy, sleep paralysis and hypnagogic hallucinations all represent intrusion of REM sleep into wakefulness.

In the 1980s, a search for potential narcolepsy genes revealed that the tissue type HLA-DQB1*0602 is present in 95% people with both narcolepsy and cataplexy and 40% people with narcolepsy without cataplexy, suggesting that an autoimmune process may have a role in the disorder. However, the frequency of the gene in the general population of 18-35% indicated that other factors had to be involved to produce narcolepsy.

The most recent breakthrough in the 1990s was the discovery of a peptide neurotransmitter found in the hypothalamus. The peptide was discovered simultaneously by two independent research groups, one of which named it "orexin" (as it stimulated appetite in rats) and the other "hypocretin" (as it was found in the hypothalamus and resembled secretin). The peptide plays a role in stabilisation of the transition between wake and sleep states. Reduced concentrations of hypocretin in the cerebrospinal fluid (CSF) in humans with narcolepsy and cataplexy suggest that the condition is caused by a deficiency in hypocretin production and that hypocretin producing cells may be destroyed by an autoimmune process in HLA-associated narcolepsy.

Triggers to this autoimmune process are often infections. Antibodies to the primary trigger are formed which share similar properties to hypocretin producing cells in the hypothalamus, resulting in destruction of the hypocretin cells. Implicated organisms include group A strep and viruses such as H1N1 influenza. In 2010 and 2011, reports from Scandinavia emerged describing a causal link between the H1N1 pandemrix vaccine and cases of narcolepsy in children. A retrospective analysis confirmed a link in the UK also. The mechanism by which this occurred has yet to be confirmed but

may have arisen due to the immunogenic adjuvant AS03, a chemical mixed with the vaccine to deliberately heighten the body's immune stimulation or to a homogeneity between the H1N1 influenza nucleoprotein and the hypocretin receptor.

Making a diagnosis of narcolepsy

Excessive Daytime Sleepiness (EDS)

An accurate history is the key to the diagnosis of EDS. A background level of sleepiness is characteristically present, with episodic urges to sleep, exacerbated by monotonous situations and often in inappropriate places, for example during a meal or at school. Care must be taken to distinguish between sleepiness (the urge to fall asleep) and fatigue (weariness and muscle aches). A number of tools for measuring sleepiness are available but the Epworth Sleepiness Scale is a helpful instrument for quantifying daytime sleepiness.

A comprehensive history to exclude other causes of EDS is essential. The most common cause is sleep disturbance and insufficient nocturnal sleep caused by poor sleep habits. Primary sleep related conditions such as obstructive sleep apnoea and periodic limb movement disorder, circadian rhythm disorders, medical conditions leading to sleep disturbance (e.g. gastro-oesophageal reflux disease, nocturnal cough/discomfort), mood disorders and current medications should also be considered. A sleep diary is useful in highlighting whether there is a true excess in sleep need or a disordered nocturnal sleep pattern resulting in EDS.

Cataplexy

Symptoms of cataplexy range from jaw dropping, to weakness at the knees, to total collapse. At disease onset, the cataplexy symptoms may be more subtle, with drooping of the eyelids or lolling of the tongue. These subtle features described as "cataplectic facies" may delay the correct diagnosis by pointing to other differential diagnoses such as myasthenia. Cataplexy is usually triggered by strong emotions such as laughter, anger and surprise and may last between a few seconds and several minutes. The loss of muscle tone is bilateral and the child retains awareness throughout the episode. Home videos of these episodes may aid in confirmation of the diagnosis.

REM intrusion

Disrupted nocturnal sleep is frequently associated with vivid nightmares due to REM intrusion. Hypnagogic/hypnopompic hallucinations (vivid, dream-like experiences at the start/end of sleep), occur in 39-50% children with narcolepsy and are often emotionally disturbing and difficult to

distinguish from reality. More unusual symptoms associated with narcolepsy include sleep paralysis (inability to move for a minute or two at the beginning or end of sleep due to persisting REM atonia), confusional arousals and automatic behaviour (the continued error prone performance of a task at a time of mounting sleepiness).

Obesity

Narcolepsy can be associated with precocious puberty, and obesity and is a feature in up to 84% of children with narcolepsy, despite lower calorie intake, often manifesting prior to diagnosis. The mechanism of weight gain is not clear but may be related to abnormal hypocretin and leptin levels leading to impaired energy metabolism. Parents may report an increase in snacking which can be difficult to control and leads to further confrontation with their child.

Referral to a sleep centre and shared care

If the history suggests a true EDS need with no underlying cause for nocturnal sleep disturbance and/or intermittent muscle weakness in response to emotional triggers, a referral to a specialist sleep centre is recommended for confirmation of the diagnosis. After diagnosis, a review at least annually by a specialist familiar with the condition and evolving treatments is a proposed model of care.

Diagnostic Investigations

Investigations recommended for confirmation of the diagnosis of narcolepsy and cataplexy are as follows:

- Actigraphy and sleep diary
- Polysomnography (PSG) and Multiple Sleep Latency Testing (MSLT)
- CSF and blood analysis

Actigraphy and sleep diary

Actigraphy is a quantitative method of recording motor activity during sleep and wake and is a useful screening method to exclude sleep pattern disorders. A two week period of actigraphy with a sleep diary is recommended as part of the diagnostic process to exclude other primary sleep disorders and sleep hygiene problems.

Overnight polysomnography

Polysomnography is a multi-channel physiological test to monitor sleep patterns, breathing, gas exchange parameters and leg movements during sleep. Polysomnography can be used to rule out

primary sleep disorders and can also provide evidence to support a diagnosis of narcolepsy. Such supportive evidence to aid the clinician's interpretation of results includes: a short sleep onset latency, a shortened REM sleep 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. Most of these features are not part of the International Classification of Sleep Disorders (ICSD) diagnostic criteria for narcolepsy, and can occur in many other sleep disorders, however it is worth noting their presence in the overall report.

Multiple sleep latency test

Two of the classical features of narcolepsy are EDS and falling asleep quickly into REM sleep. These features can be measured using an objective daytime test known as the Multiple Sleep Latency Test (MSLT). During this test, the patient is given 4 or 5 equally spaced opportunities to 'try and fall asleep' in the daytime. During each of these nap opportunities three main measurements are taken:

[1] Sleep onset latency (SOL) - the time it takes to fall asleep.

[2] The presence or absence of REM sleep during each nap, known as the frequency of sleep onset REM periods (SOREMPs).

[3] The REM latency (REMSOL) - the time taken to fall asleep into REM sleep if present.

Performing an MSLT requires specialist sleep or neurology facilities where an overnight polysomnography sleep study and a daytime MSLT test can be undertaken. Paediatric practice parameters for the use of Full Polysomnography and the MSLT were published in 2012. This review concluded that the MSLT was technically feasible and could provide meaningful results in typically developing children aged 5 years and older. The International Classification of sleep disorders states that the diagnostic criteria for narcolepsy from an MSLT test are a mean sleep onset latency ≤ 8 minutes and either one SOREMP on overnight PSG plus one SOREMP on the MSLT; or 2 or more SOREMPs on the MSLT.

CSF and blood analysis

CSF analysis of hypocretin is used to confirm narcolepsy, particularly if the MSLT is not possible or shows inconclusive results. Cerebrospinal fluid hypocretin-1 deficiency <110 pg/mL or less than one-third of the normative values with the same standardized assay is stated in the ICSD as one of the diagnostic criteria for narcolepsy with cataplexy.

HLA blood analysis for HLA-DQB1*0602 is poorly sensitive in confirming a diagnosis of narcolepsy but very specific in excluding a diagnosis if negative.

Impact

The symptoms of narcolepsy and cataplexy can have a huge impact on all aspects of life and are often vastly underestimated due to a misunderstanding of the condition. The sleep fragmentation experienced by many children resulting in extreme daytime tiredness can take its toll on mood and quality of life and impact on friendships, educational attainment and planning for the future. Career prospects, ability to drive and future relationships are all teenage concerns that are worsened by having narcolepsy. Frequent or vivid nightmares or hallucinations can be frightening with difficulty separating reality from dreams. Children may involuntarily display their symptoms in front of their peers at school and will learn quickly to control behaviours by avoiding triggers such as laughter. The need for a lunchtime nap and outbursts of anger result in “feeling different”, social isolation and confrontations.

A parent of a child affected by narcolepsy and cataplexy writes:

A parent's perspective:

“... my husband and I googled away, reading as long as we could stand until it was impossible to bear the sadness any longer, we cried, grieving for what our son had lost, meanwhile he just got worse, on a cocktail of drugs that didn't seem to assist, making him ill.

He has tried to commit suicide several times, opening car doors at speed, or simply trying to throw himself from upstairs windows. Eventually we were able to get CAMHS (Child & Adolescent Mental Health Services) involved, we still grieve and family therapy is now open to us.

This is a nightmare you'd not wish on your worst enemy, but to date, with the best help available we are attempting to empower our son so that narcolepsy is a small part of him and doesn't define him.

Cognitive function in school-age children with narcolepsy

Individuals with narcolepsy have recently highlighted in “*The Voice of the patient*” narcolepsy report that although the characteristic symptoms have the most significant effect on their daily life, it is the impact of the disorder on cognitive function that matters most. EDS is reported to cause

impairments in decision-making, concentration and learning. It is particularly important to understand the impact of narcolepsy on cognitive function in school-age children so that the children are provided with the most effective support to enable them to achieve their full potential.

A systematic review of cognitive function and psychosocial well-being in school-age children with narcolepsy found that this group are at particular risk of cognitive impairment in at least one domain (e.g. decision making, verbal IQ, performance IQ), however a consistent pattern of impairment was not found across the studies. The most commonly reported problems were persistent sleepiness, lack of alertness and lack of concentration which are likely to impact on cognitive function and may be the underlying cause of the high levels of academic failure reported in the children.

The difficulties of coping with this condition are highlighted in this account from a teenager with narcolepsy and cataplexy:

A teenager's perspective:

"Narcolepsy goes beyond the regular human experience of being tired. You've all experienced long shifts and jetlag, wanting nothing more than to just sleep. Imagine living every day like that; never recovering and still having to get on with everyday life. Long term sleep deprivation impacts every aspect of your life, threatening not only your physical and mental health but your relationships with family and friends.

The effect Narcolepsy has on my daily life is incomprehensible; every day I am faced with the challenge of simply staying awake, scheduling in regular naps, remembering to take medication at the right time and dealing with cataplexy; which expresses itself in many forms. My cataplexy occurs with emotions and tiredness, manifesting itself in the form of buckling knees, the dropping of the head and neck, being unable to control my tongue and simply not being able to walk and talk. But, like any chronic disorder, Narcolepsy is unique to the individual. Many other challenges include memory loss, brain fog, automatic behaviour and hallucinations.

Narcolepsy not only stops me doing the things I want to do, but prevents me from doing the things I need to do, such as eating and brushing my teeth. Frustratingly it doesn't affect your intelligence, but it does affect your future due to society's ignorance. Having Narcolepsy has made me grow up a lot faster and altered my outlook on life; appreciating the smaller things a lot more, especially a good night's sleep. With the support of the family and school, the right medication and an empathetic, understanding consultant, it is possible to succeed with narcolepsy. "

Management

Management is pharmacological and non-pharmacological. Drug management is usually initiated and monitored by a specialist centre following diagnosis, however lifestyle management and support is essential and can be best provided by local clinicians with whom the patient is familiar. The specialist centre should take a multidisciplinary team (MDT) approach with input from experts in narcolepsy who can liaise with school, local clinicians and GPs, local pharmacy and the family. Specialist teams frequently comprise: clinicians, nurses, pharmacist, physiologist, psychologist and a transition arrangement to an adult narcolepsy service. Attention to sleep hygiene and planned naps can be used to optimise daytime performance. Relevant and accurate information should be made available to the patient, relatives and schools, as well as medical professionals unfamiliar with the condition. Information and support provided by the charity Narcolepsy UK (www.narcolepsy.org.uk) is extremely useful and recommended highly by most families. Weight management is important in preventing complications of obesity. Children should be encouraged to take part in sports activities and an exercise program may have a stimulating effect.

Driving

In the United Kingdom, people with narcolepsy are required by law to inform the Driver and Vehicle Licensing Authority (DVLA) about the diagnosis and are generally advised to refrain from driving until the DVLA has reached a decision on their case. Holders of ordinary group 1 licences will be permitted to drive once “satisfactory control of symptoms” is achieved; people with narcolepsy are generally considered unfit to hold group 2 (heavy goods vehicle and bus) licences, although exceptions can be made.

School

This account has been written by a teenager with narcolepsy who has recently experienced the rigours of GCSE exams whilst coping with severe narcolepsy symptoms:

Coping Strategies for School

“In order to help maintain their concentration and to stay awake, they may fidget, drink lots of water or squeeze a stress ball. Going for a short walk around school and keeping the classroom cool can also help. Narcolepsy and Cataplexy often lowers children’s self-esteem, meaning that they usually shy away and get left out of group work, so it’s important for teachers to be inclusive, encourage participation and to organise groups themselves.

Scheduled naps during the day can have a significant positive impact on narcoleptics’ wakefulness, it is therefore imperative that the school have a safe, quiet area for these, and allow napping during lessons. Being woken up by the teacher in the middle of a lesson can be really embarrassing and distressing for the child, so having their friend next to them wake them up quietly after 10-15 minutes is better.

If a child falls asleep in a lesson, they can often miss important points and work, which can lead to them falling behind the rest of the class. To avoid this, teachers could print off the PowerPoint for the coming lesson and give it discretely to the child at the start of the lesson or email the PowerPoint so the child can refer to it later if they need to. Allowing them to photocopy a friend’s notes if they miss work (rather than copy up) can save a lot of time, which could be used to do homework, extra-curricular activities or even have a nap.

Exams are a crucial part of school, and narcolepsy can cause a child’s performance to suffer in them. Certain arrangements must therefore be put in place for both internal and external exams. These arrangements could include; extra time, rest breaks for naps, late or early starts and for the child to take the exam in a separate room. This is easier for internal exams because the school organises these, but for external exams you or the school must apply and provide evidence. For internal exams it may be possible for the school to rearrange the exam timetable to suit when the child is most awake. In order to retain concentration and to help the child to stay awake and alert they should take the exam in a cool/air-conditioned room, with lots of natural light.”

Drug Treatment

Drug treatments of narcolepsy and cataplexy are traditionally divided into those that treat EDS and those that improve cataplexy. For many patients this will be lifelong treatment. A detailed description of the pharmacological profile of each compound was reviewed by Mignot in 2012.

First-line medications for treatment of excessive daytime sleepiness are methylphenidate preparations and modafinil. Clinical consensus varies and there is currently an absence of head-to-head randomised controlled trials to evidence choices. Combination treatment can be effective and reduce drug-induced adverse effects.

Methylphenidate acts by blocking monoamine uptake. An initial dose of 5-10mg in the morning is titrated against effect and often a second dose added at lunchtime. Immediate and sustained release preparations are used in isolation or in combination. The mechanism of action of Modafinil is unclear but probably involves relatively selective dopamine reuptake inhibition. Clinical experience suggests that modafinil is an effective and safe treatment, however there are no studies of its use in childhood narcolepsy. The MHRA advises against prescribing in children under 18 years due to the potential to cause severe Stevens-Johnson skin reactions and psychiatric complications. Second-line treatments include amphetamines and atomoxetine.

Treatment of cataplexy is with antidepressant medications which suppress REM sleep. Venlafaxine (serotonin and norepinephrine reuptake inhibitor), fluoxetine (selective serotonin reuptake inhibitor) as well as clomipramine (tricyclic antidepressant) are all effective.

More recently, sodium oxybate (brand name Xyrem®) has been proposed as third-line treatment. Sodium oxybate is derived from the neurotransmitter GABA, acts via GABA-B or specific GHB receptors and suppresses dopaminergic release. Trials have shown its efficacy in treating narcolepsy and cataplexy in adults, resulting in consolidation of nocturnal sleep, reduction in daytime sleepiness and often significantly improving cataplexy. It is linked to frequent side effects such as nausea, headache, bed wetting, confusion and new onset parasomnias and must be prescribed with caution in children with obstructive sleep apnoea. However, it is the only drug available for use in narcolepsy that simultaneously treats sleepiness, cataplexy and fragmented sleep. . Published case series evidence suggests it is also effective in post-pubertal children (combined n=23), however, it is not licensed for use in children. Sodium oxybate should only be initiated following an MDT discussion, which should include psychological assessment where the child is deemed to be at higher risk of harm.

Future Research

The advances in understanding the pathophysiology of narcolepsy in recent years has led to novel approaches to narcolepsy treatment. Immunomodulation has been proposed as a potential therapeutic option; however, trials have had mixed results and none has reversed the disease process. Recent results suggest a T-cell rather than B-cell/antibody mediation. Medications targeting T-cells (e.g., alpha-4 integrin inhibitors blocking T cell entry to the brain, such as natalizumab) may therefore have more beneficial effects.

A trial of hypocretin replacement therapy using intranasal administration of hypocretin-1 is currently under evaluation. Central administration of hypocretin-1 reverses narcolepsy in animal models, but unfortunately the hypocretin peptide does not cross the blood brain barrier. Studies are needed to fully evaluate this therapy, including its potential for use in the paediatric population.

A randomized, double-blind clinical trial of pitolisant, an H3 receptor inverse agonist has shown promising results in adults and adolescents. Further stimulant options including caffeine, benzodiazepines and baclofen have been used on a case by case basis but have not been evaluated in formal trials.

In general both pharmacological and non-pharmacological interventions, including exercise and cognitive behavioural therapies require systematic evaluation, especially in young children. In addition, further education of the medical profession and the public is needed to minimise the impact of this debilitating condition and ultimately to improve prognosis and outcomes for children and adolescents presenting with narcolepsy with cataplexy.

PRACTICE POINTS

- Narcolepsy and cataplexy and their impact on the lives of children remain under-recognised
- Fragmentation of nocturnal sleep contributes to excessive daytime sleepiness
- Cataplexy can present as facial or eyelid drooping or tongue lolling
- Sleep hygiene, diet management and exercise programmes are important aspects of management

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Conflict of interest statement

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