Narcolepsy and Cataplexy

Narcolepsy is a chronic neurological condition producing disruption to the normal sleep pattern. This produces excessive sleepiness. Narcolepsy may occur with or without cataplexy. Cataplexy is a sudden loss of muscle tone and power in response to strong emotion - it always and only occurs as part of narcolepsy.[1]

The term 'narcolepsy' was first used by Gelineau in 1880 to describe a pathological state of daytime sleepiness and is a term derived from the Greek 'seized by somnolence'.[2]

Epidemiology[3]

- Prevalence is estimated as 25 per 100,000 in Caucasian populations.[4]
- Age of onset is typically around adolescence. A smaller number of cases presents at around 35 years.
- Less than 5% of narcolepsy with cataplexy occurs in children. One study found that it was often linked to complex movement disorders.[5][6] It is possible that incidence statistics would increase if diagnostic features were recognised at an earlier age.[6]
- There is a male predominance.
- First-degree relatives are at increased risk of narcolepsy compared with the general population.

Aetiology[1]

The precise cause is unknown; both environmental and genetic factors may play a part:

- The peptide hypocretin (orexin) may be involved. This is derived from the hypothalamus and is thought to be involved in sleep/wake cycles, food intake and pleasure-seeking behaviour. Narcolepsy may be caused by the loss of a relatively few neurons that are responsible for producing the neuropeptide hypocretin in the CNS. Possibly, immunological mechanisms may lead to loss of hypocretin.
- Narcolepsy is associated with a specific HLA allele, DQB1*0602.
- Most cases are sporadic but a familial form occurs in a small proportion of narcolepsy patients.
- Possible triggers include head trauma, infection and change in sleep habits.
- A sudden increase in narcolepsy in children was seen in Finland and other European countries in 2010. This was linked to two pandemic 2009-10 H1N1 influenza vaccines. Analysis of the cases has found that genetic predisposition to narcolepsy explains some of the variability noted in different countries although the mechanism is not completely understood.[7]

Physiology[1]

- Patients with narcolepsy usually have a total sleep time similar to that of non-narcoleptic patients but their sleep is fragmented, with night-time sleep loss and daytime naps.
- Dysregulation of rapid eye movement (REM) sleep may be part of the mechanism; people with narcolepsy may enter REM sleep more quickly than those without narcolepsy. Cataplexy, sleep paralysis and hypnagogic hallucinations may be due to REM sleep intruding into wakefulness.[8]

Presentation[1]

There is a tetrad of classic symptoms: excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations and sleep paralysis. However, many patients do not have all these features. EDS and cataplexy are the key diagnostic symptoms.
Patients have persistent sleepiness, which may be irresistible. They may nap during normal activities such as eating and talking. Excessive fatigue is a common complaint and is described by those affected as being a different symptom to sleepiness.\[^9\]

Automatism occurs in many narcolepsy patients - when affected by severe sleepiness, they may have episodes in which they appear to be awake but lack full awareness and may behave inappropriately at such times.

EDS symptoms can severely disrupt daily life.

Autonomic symptoms have been reported in narcoleptic patients and include pupillary abnormalities, fainting spells, erectile dysfunction, night sweats, gastric problems, low body temperature, systemic hypotension, dry mouth, heart palpitations, headache and extremities dysthermia.\[^10\]

**Cataplexy**

Cataplexy is defined as a sudden loss of voluntary muscle tone, with preserved consciousness, triggered by emotion.\[^4\] The emotional stimulus may be, for example, laughter, pleasure, anger or excitement. The attacks can last just a few seconds or many minutes. Cataplexy is pathognomonic for narcolepsy and is present in around 70% of narcolepsy patients.\[^11\]

Features of a cataplexy attack:

- Severity can vary - eg, from a barely susceptible slackening of the facial muscles, dropping of the jaw or the entire head, to weakness at the knees or collapse on to the floor. In severe attacks, all voluntary muscles except the diaphragm may be affected.
- Slurred speech and visual symptoms such as blurred vision or diplopia may be experienced.
- Hearing, awareness and consciousness are intact.
- Frequency varies, from several attacks per day to less than one per year.\[^4\]
- The weakness is usually bilateral but one case report describes unilateral attacks.\[^12\]

**Sleep paralysis**

- This may occur as the patient is falling asleep or awakening.
- Patients are aware but are, briefly, unable to move or open their eyes.
- It affects approximately one third of narcolepsy patients.
- It may be alarming and associated with a sensation of inability to breathe (although diaphragmatic breathing usually continues through the episodes).

**Hypnagogic hallucinations**

- These occur at the onset of sleep (hypnagogic) or on awakening (hypnopompic).
- They are often visual but may be auditory, tactile or multisensory.

**Assessment**

**History**

A thorough history is important, with particular reference to:

- Normal sleep pattern.
- Sleepiness in unusual situations.\[^13\] For example, using the Epworth Sleepiness Scale.\[^14\]
- Other medical conditions, employment, alcohol or drugs, medication and family history.
- A careful description of symptoms/attacks (if considering cataplexy, sleep paralysis or hallucinations).
- Partial weakness - specifically ask patients about partial weakness (eg, mild facial or jaw weakness), which they may not report.

**Investigations\[^15\]**

- The Epworth Sleepiness Scale is helpful for quantifying daytime sleepiness.\[^13\]
- Sleep studies - overnight polysomnogram followed by multiple sleep latency test (MSLT). The MSLT is an objective test of sleepiness.
- Electroencephalogram (EEG).
• Brain MRI to exclude other causes - eg, space-occupying lesions.
• Whilst biomarkers such as low CSF hypocretin and the presence of the HLA-DQB1*0602 allele are thought to be sensitive tests in cataplexy patients, their usefulness for narcolepsy without cataplexy is uncertain.[16]

Diagnosis

Diagnosis is clinical, based on a thorough history, analysis of sleep patterns and (if necessary) exclusion of other causes.

The diagnosis in children remains challenging.[17]

Diagnostic criteria[4]

For narcolepsy with cataplexy:

• Excessive daytime sleepiness, almost daily for ≥3 months.
• Cataplexy, defined as sudden, transient episodes of loss of muscle tone, triggered by emotions.
• If possible, confirm the diagnosis by nocturnal polysomnography followed by an MSLT - see 'Investigations', above. Alternatively, confirm by CSF hypocretin-1 levels ≤110 pg/mL, or one third of mean control values.
• The hypersomnia is not better explained by another condition (sleep disorder, medical or neurological condition, mental disorder, substance misuse or medication).

For narcolepsy without cataplexy:

• Excessive daytime sleepiness, almost daily for ≥3 months.
• The diagnosis must be confirmed by nocturnal polysomnography followed by an MSLT - see 'Investigations', above.
• The hypersomnia is not better explained by another condition (sleep disorder, medical or neurological condition, mental disorder, substance misuse or medication).
• Typical cataplexy not present, though atypical or uncertain episodes may be reported.

Differential diagnosis

There is a wide differential diagnosis:

• Excessive daytime sleepiness - alternative causes are sleep deprivation, obstructive sleep apnoea, drugs/toxins and various other causes of hypersomnia.
• Automatism - may mimic partial complex seizures.
• Cataplexy - may mimic drop attacks, syncope, seizures/epilepsy, transient ischaemic attack, periodic paralysis (channelopathies), psychiatric disorder, or cataplectic-like episodes (the latter can occur in healthy people).
• Sleep paralysis - can be an isolated, physiological occurrence; other causes are periodic paralysis, familial sleep paralysis or upper brain stroke.
• Hypnagogic hallucinations - may mimic psychosis, sleep onset rumination, or temporo-occipital brain lesions.

Management[4, 11]

Fitness to drive[18]

Patients must cease driving on diagnosis and inform the DVLA. Driving is allowed once satisfactory control of symptoms has been achieved, or with a satisfactory objective assessment of maintained wakefulness. For Group 2, licences may be issued subject to specialist assessment and a satisfactory objective assessment of maintained wakefulness.
Referral

Patients with suspected cataplexy/narcolepsy should be referred to a sleep disorder service. Once diagnosed, management should be under a clinician with experience of narcolepsy management.\[13\]

Non-drug treatment

For EDS

- Good sleep hygiene - a strict sleep schedule providing 7-8 hours' of night-time sleep.
- Strategic daytime naps - scheduled naps can reduce EDS.
- Regular exercise may improve energy and sleep patterns.
- Education of family, friends and colleagues, who need to understand that the urge to sleep can be irresistible.

For cataplexy

- Support and information for the patient and their family, as full-blown cataplectic attacks can be frightening.
- Family members can learn to recognise the onset of attacks, to help prevent falls and injuries.
- There is no known cure - treatment aims to control symptoms. Therefore, drug treatment should be avoided if cataplexy is not causing a significant problem for the patient.

Drug treatment\[19\]

The drugs used to manage narcolepsy in adults have also been found effective in children, at appropriate reduced dosage.\[20\]

Drug treatment of EDS and other sleep symptoms\[21\]

- Stimulants (amphetamines and methylphenidate) have been used for decades but with significant side-effects.
- One study found that patients with narcolepsy treated with drugs had improved executive functions (cognitive functions that regulate, control and manage mental processes such as planning, working memory, attention and problem solving).\[22\]
- Modafinil:
  - Its sole indication (currently) is for narcolepsy, to treat EDS. It may also help cataplexy symptoms.
  - Caution was advised in a 2011 Medicines and Healthcare products Regulatory Agency (MHRA) notice (see box, below).
- Antidepressants (tricyclic or selective serotonin reuptake inhibitors (SSRIs)) may improve symptoms of sleep paralysis or hypnagogic hallucinations.
- Benzodiazepines (short-acting) are sometimes used to consolidate night-time sleep, in refractory cases.

European guidelines of 2006 suggest the following strategy for drug treatment of EDS:\[4\]

- First-line is modafinil (but note subsequent MHRA warnings, below).
- Second-line is methylphenidate.
- Third-line (in severe cases) is modafinil combined with sodium oxybate.

Modafinil - MHRA warnings\[23\]

- Avoid use if <18 years, uncontrolled hypertension or cardiac arrhythmias, pregnant/breast-feeding. Caution if there is history of psychosis, depression, or mania, alcohol or substance abuse.
- Stop treatment if there are serious skin or hypersensitivity reactions or psychiatric disorders such as suicidal ideation.
- Monitoring during treatment - baseline electrocardiogram pre-treatment; monitor blood pressure and heart rate/rhythm; stop treatment if these are abnormal.
Drug treatment of cataplexy

NB: if anticataplectic drugs are stopped abruptly, rebound cataplexy can occur - including (rarely) status cataplecticus (see ‘Complications’, below). Drug treatment options are:

- Sodium oxybate (a sodium salt of gamma-hydroxybutyrate (GHB)); European guidelines suggest this as first-line treatment. Most patients improve within a few days of starting the drug but the full response may take three months.

- Antidepressants:
  - Tricyclic antidepressants, particularly clomipramine. Low doses (eg, 10-20 mg daily of clomipramine) can be very effective, so start at a low dose.
  - SSRIs - probably less active against cataplexy but they have fewer adverse effects.
  - Newer antidepressants such as venlafaxine and reboxetine have been used, although there are fewer clinical data regarding their effectiveness with cataplexy. One report suggests that there is a difference in effectiveness between the different formulations of venlafaxine, with the extended-release formulation being less effective for cataplexy. Although clinical consensus is that antidepressants can be helpful for cataplexy, the evidence base is lacking.

- Selegilene is another possible treatment for both EDS and cataplexy but its use is limited by potential drug and diet interactions and there is little clinical experience with its use in this scenario.

Complications

- Problems related to tiredness - eg, poor concentration and memory.
- Interference with life and work - daytime sleepiness and cataplexy attacks may affect employment, driving, social/personal relationships and general well-being.
- Falls or injuries during cataplexy attacks.
- Status cataplecticus - can occur if anticataplectic medication is stopped abruptly. Patients may have frequent or prolonged cataplexy attacks, which can be frightening.
- Patients who have narcolepsy with cataplexy have been found to be more impulsive and more prone to binge eating than patients without cataplexy and controls. There is a high risk of obesity and metabolic syndrome.

Prognosis

- Symptoms are usually lifelong but may be improved with treatment or after retirement.
- Cataplexy may sometimes disappear over time, either spontaneously or with treatment. Again, it may improve after retirement.
- One study found that the earlier the diagnosis, the better the socio-economic outcome and general perception of health.

Research

Possible future treatments might involve:

- Immunological therapies - eg, intravenous immunoglobulin, immunosuppression.
- Histamine H3-receptor agonists.
- Hypocretin-based therapies - hypocretin agonists, hypocretin cell transplantation, gene therapy.
- Nicotine.

Further reading & references

- Horsley W; Sodium oxybate in the management of narcolepsy with cataplexy, North East Treatment Advisory Group, December 2009
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