

Narcolepsy, idiopathic hypersomnolence and related conditions

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Narcolepsy with cataplexy is primarily a disorder of excessive daytime sleepiness (EDS) and episodic collapse. Despite a quality of life impact similar to Parkinson's disease (PD)¹ and significant individual and societal costs² it is often overlooked. A UK survey found median time from first symptom to diagnosis to be 10.5 years.³ The delay in diagnosis may be because it is uncommon (European prevalence 0.047%⁴), but is no doubt exacerbated by a paucity of sleep medicine training (median 5 min in UK medical undergraduate curricula⁵). Narcolepsy has a variety of presentations which may be wrongly attributed to more familiar disorders or lifestyle and there is an overlap with normality. EDS is reported by up to 10% of the general population⁶ and objective measures of sleepiness do not reliably differentiate narcoleptics and normal subjects.⁷ It is important for the acute care physician to be aware of the features of, and means for, diagnosing narcolepsy so that opportunities to treat this disabling condition are not missed.

Diagnosis

Anyone reporting EDS warrants a detailed sleep history. It is important to tease out an increased propensity to fall asleep from other symptoms reported as tiredness, particularly physical and emotional fatigue. The Epworth Sleepiness Scale can be a useful measure.⁸ Explanations for perceived sleepiness, including lifestyle, mood disorders, other medical conditions and medication, should be explored (Table 1). People with narcolepsy typically need brief, refreshing

naps; if these are not possible, they can have irresistible sleep episodes ('sleep attacks'). The identification of other factors such as sleep disordered breathing (SDB) contributing to sleepiness should not discourage the pursuit of a diagnosis of narcolepsy if features are compelling because sleep disorders can coexist.⁹

Cataplexy

Cataplexy is emotionally triggered muscle weakness and, with EDS, is essential to the diagnosis of classical narcolepsy.^{9–11} Symptoms usually develop months or years after EDS but, because sleepiness can be overlooked, cataplexy is sometimes the presenting complaint. It should be considered when patients present with apparent absence episodes, unexplained collapse or episodic clumsiness. Prolonged or intractable episodes (status catalepticus) may be mistaken for seizures,

coma or malingering. The weakness of cataplexy is typically bilateral and can involve the legs ('weak at the knees'), hands, face, neck or shoulder girdle. Frequency can range from rarely to several times a day. Ptosis may give the impression of unconsciousness and distract from the correct diagnosis but, apart from occasional evolution into sleep, awareness is preserved.

The differential diagnosis of cataplexy includes periodic paralysis, myasthenia gravis, atonic seizures and vertebrobasilar insufficiency.¹⁰ The absence of cataplexy can represent disease-in-evolution or so-called 'monosymptomatic narcolepsy'⁹ but other diagnoses should be considered.

Other narcoleptic symptoms

The other symptoms of the 'narcoleptic tetrad' involve different facets of rapid eye movement (REM) sleep invading wakefulness:

- sleep paralysis (persistent motor atonia)
- hypnagogic/hypnopompic hallucinations (dream-like experiences during sleep-wake transitions).

Table 1. Causes of excessive daytime sleepiness.

Insufficient sleep	<ul style="list-style-type: none"> • Time • Quality (alcohol, caffeine) • Both (noise, temperature)
Other disorder	<ul style="list-style-type: none"> • Pain • Nocturia • Dyspnoea • Cough
Medications	<ul style="list-style-type: none"> • Daytime sedation • Nocturnal sleep disruption (diuretics, steroids, statins)
Anxiety/depression	
Circadian rhythm disorder	<ul style="list-style-type: none"> • Advanced sleep phase syndrome • Delayed sleep phase syndrome • Shift work disorder • Jet lag
Sleep-disordered breathing	<ul style="list-style-type: none"> • Obstructive sleep apnoea • Central sleep apnoea • Hypoventilation
Narcolepsy	
Restless legs syndrome/periodic limb movement during sleep	
Idiopathic hypersomnia	
Recurrent hypersomnia	

Automatism, poor nocturnal sleep and dream enactment (REM sleep behaviour disorder) can also occur.^{9–11}

Although not inevitable in, or exclusive to, narcolepsy, when accompanying cataplexy and sleep attacks, it is understandable how lack of familiarity with these features can result in narcolepsy being mistaken for seizures, psychiatric disorders or malingering.

Physical examination

The physical examination is usually normal. Cataplexy has characteristic features, including areflexia and facial twitching, but episodes usually occur only in relaxed, intimate settings and so are rarely seen in clinic.¹¹ Unless the diagnosis can be confidently made on clinical features alone, suspected narcolepsy and other unexplained cases of EDS should undergo specific investigation.⁹

Pathophysiology

The discovery of the neurotransmitter orexin (hypocretin) has refined the pathophysiological description of narcolepsy as a condition of sleep-wake instability.¹² Orexin stabilises wake and sleep states through widespread subcortical neuronal projections from the lateral hypothalamus (Fig 1). Cerebrospinal fluid (CSF) and brain studies have established that most people with narcolepsy and cataplexy have orexin deficiency.^{14–16}

Up to 2% of narcoleptics have symptomatic first-degree relatives but most cases are sporadic.¹⁷ Global research has yielded only one case of human narcolepsy caused by a prepro-orexin gene mutation¹⁵ but wider genetic studies continue. There is a strong human leukocyte antigen (HLA) association. The DQB1*0602 haplotype is found in 88–98% of patients with non-familial cataplexy.¹⁸ The newly discovered association of narcolepsy with a T cell receptor polymorphism and demonstration of elevated antistreptococcal antibodies in recent-onset cases support the hypothesis of a genetically determined

autoimmune condition triggered by infection.^{19,20}

Investigation

Nocturnal polysomnography

The investigation of choice for unexplained EDS is nocturnal polysomnography (PSG). Electroencephalogram, chin electromyogram and electro-oculogram enable the staging of wakefulness, REM and non-REM sleep. Respiratory and leg monitoring allow screening for SDB and periodic limb movement. Features suggestive of narcolepsy include rapid sleep onset and premature entry into REM sleep (Fig 2).

Multiple sleep latency test

Diurnal sleep drive is measured by the multiple sleep latency test (MSLT).

Subjects undergo PSG-monitored nap opportunities at two-hourly intervals.⁷ Mean sleep latency is usually less than eight minutes in narcolepsy (most narcoleptics fall asleep within 5 min)⁷ and multiple REM sleep episodes occur (Fig 3). International guidelines mandate a combination of these two criteria but sensitivity is only around 80% in classical cases and they are not entirely specific.^{9,21,22}

Other investigations

HLA testing has only limited utility as it is positive in up to 38% of non-narcoleptics.¹⁸ A negative test with a classical history may cause pause for thought. CSF orexin assay may be useful when PSG and MSLT are unavailable, but the test is invasive and less discriminatory in cases without cataplexy.^{9,14}

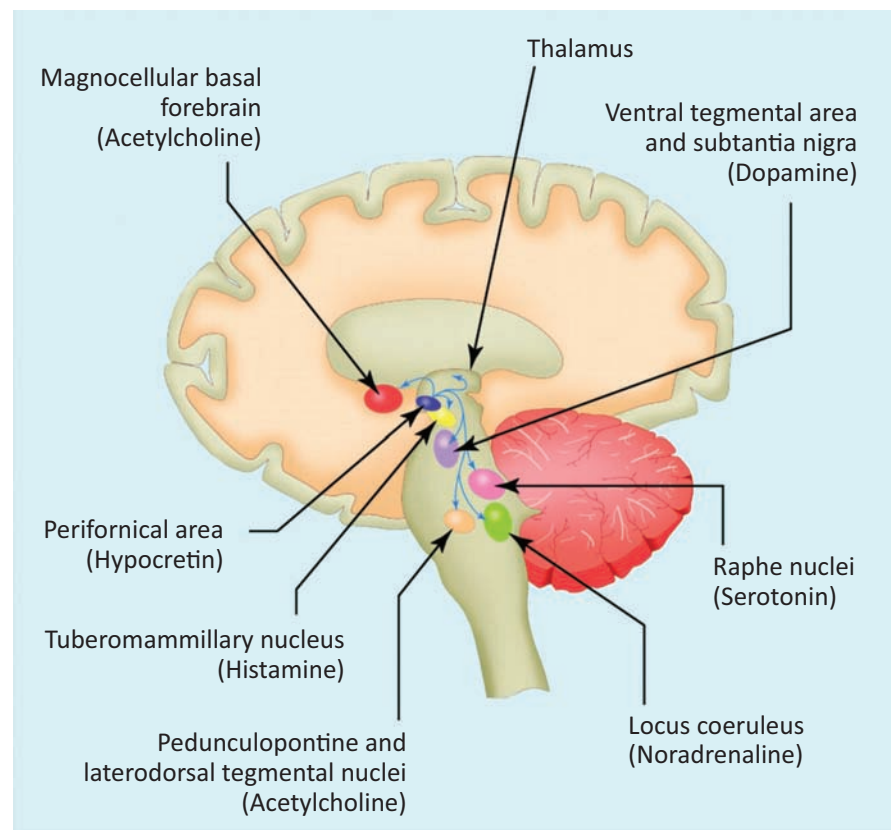


Fig 1. Hypocretin (orexin) system. The sleep-wake cycle is governed by a complex, multilevel neuronal system in the brainstem, thalamus, hypothalamus and basal forebrain. Hypocretin-producing neurons in the hypothalamus stabilise the activity of other key neuronal groups involved in the control of sleep and waking. These nuclei and their principal neurotransmitters are shown here in highly schematic fashion. Reproduced with permission from BMJ Publishing Group Ltd.¹³

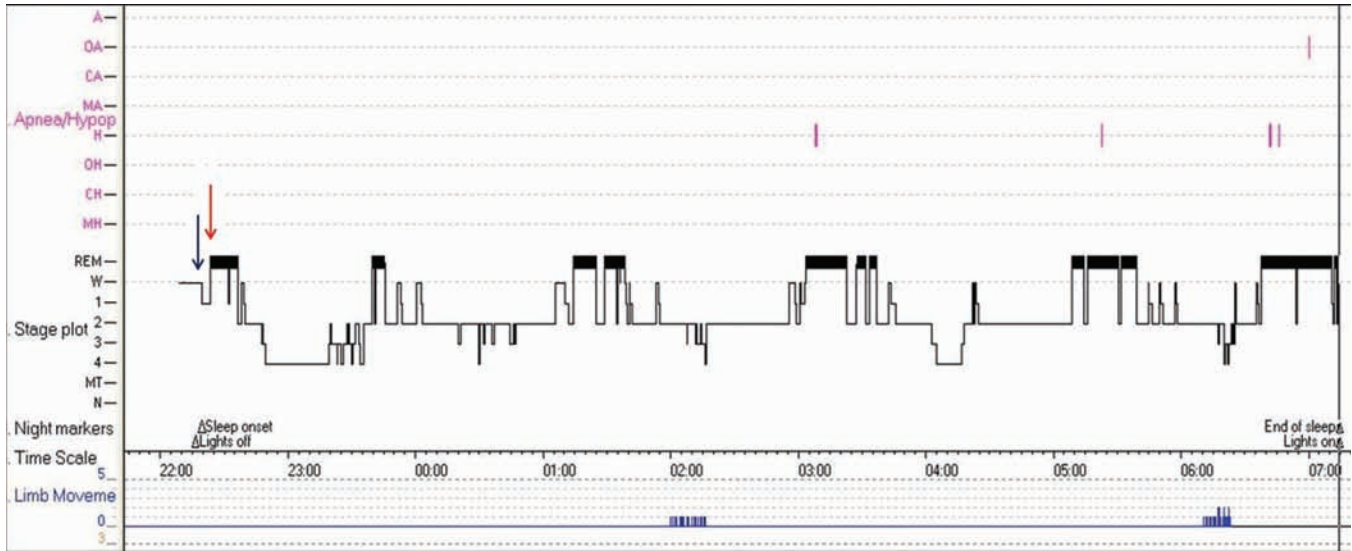


Fig 2. Polysomnogram summary (hypnogram) from patient with narcolepsy. There is rapid sleep onset (blue arrow) and early rapid eye movement (REM) sleep (red arrow). There are clinically insignificant numbers of apnoeas (purple marks) and periodic limb movements (bottom trace in blue) which do not explain sleepiness in this case.

Secondary narcolepsy and other hypersomnias

Rarely, other medical disorders present with narcoleptic features. Those featuring cataplexy include:

- hypothalamic lesions
- paraneoplastic encephalitis
- Niemann-Pick type C disease
- Coffin-Lowry syndrome.

In the absence of abnormalities on neurological examination there is no justification for neurological imaging. Narcolepsy-like sleepiness has been reported in:

- head trauma
- myotonic dystrophy
- Prader-Willi syndrome
- PD
- multisystem atrophy.

To fulfil diagnostic criteria, patients should have the characteristic MSLT features with SDB excluded or controlled.⁹

Recurrent hypersomnias are rare and little understood. Kleine-Levin syndrome is the best characterised, with recurrent episodes of hypersomnolence, often first in adolescence, which may last several days and be interspersed with asymptomatic intervals of

weeks to years. Cognitive and behavioural abnormalities, classically binge-eating and hypersexuality, are variably associated. A prolonged 24-hour sleep time may be demonstrated if PSG is achieved during an episode.⁹ Lithium may be useful, but evidence for its effectiveness is limited.²³

In patients with unexplained EDS, idiopathic central nervous system hypersomnolence (ICNSH) should be considered. This diagnosis has been inconsistently described and ascribed.²⁴ The new International Classification of Sleep Disorders has attempted to address this inconsistency with diagnostic criteria⁹ but, in the absence of any known

aetiology or diagnostic test, these are arbitrary. There is typically difficulty waking up in the morning (sleep inertia) and EDS. Naps are more prolonged than in narcolepsy and usually unrefreshing. If nocturnal sleep duration allows time for the performance of MSLT after PSG, the mean sleep latency should be under eight minutes without associated multiple REM sleep episodes.⁹

Management

Lifestyle

Optimal sleep hygiene is important for any disorder with EDS. Nocturnal sleep should be sufficient and regular and the

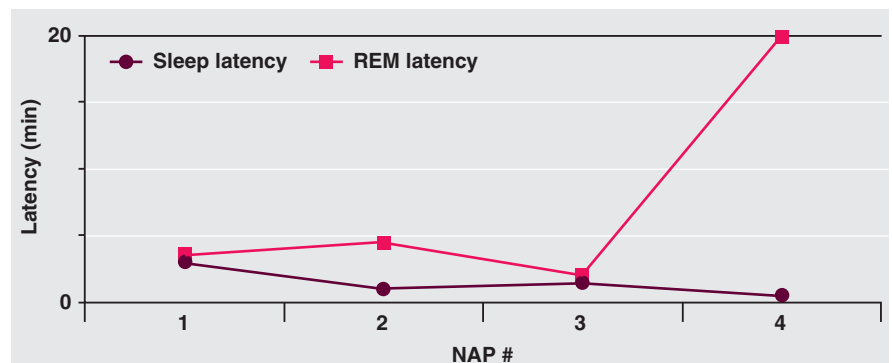


Fig 3. Characteristic narcoleptic multiple sleep latency test result showing evolution of latencies. The subject slept on each of four opportunities offered through the day. The mean sleep latency is only 1.5 min and rapid eye movement (REM) sleep is seen in three of the naps.

environment conducive to sleep. Alcohol and caffeine intake should be moderated. Brief naps are often useful in narcolepsy but rarely in ICNSH. Patients should be advised of the need to report their diagnosis to the driving authorities and not to drive until EDS is controlled.

Wakefulness-promoting therapy

Drug treatment for hypersomnolence is similar for narcolepsy and ICNSH, although the evidence base is stronger for narcolepsy.

Modafinil is recommended as first-line treatment for narcolepsy.²³ Tolerance and dependency are not reported. Side effects are usually mild and rarely lead to discontinuation. Modafinil is used in ICNSH, although it may not be as effective as in narcolepsy; this use is not licensed in the UK.^{23,25} It may be an option in hypersomnia associated with PD and myotonic dystrophy.²³

Dexamfetamine. Dexamfetamine (5–60 mg/day), methylphenidate (5–100 mg/day) and other stimulants have long been used to treat narcolepsy and ICNSH. They can be very effective, although there is potential for tolerance and dependency. Sympathomimetic side effects are recognised and higher doses have been associated with psychosis.²⁴ Risk-benefit data are scanty and these drugs are usually second-line therapy.²³

Anticatataplectics

If cataplexy requires treatment, the REM sleep-suppressing tricyclic antidepressants and selective serotonin reuptake inhibitors have an established but poorly evidenced role. They can also be useful in sleep paralysis and hallucinations. Alternatives include venlafaxine and reboxetine.²³ Rebound cataplexy can occur with drug withdrawal.

Sodium oxybate

Sodium oxybate is effective in narcolepsy and cataplexy²³ although its mode of action is not clear. It is a profound sedative, promoting deep non-REM (slow wave) sleep. Its rapid onset of action and short half-life require it to be taken at night in divided doses. These are titrated up over several weeks until symptoms are controlled, maximum dose reached (9 g) or side effects preclude further increase. Full benefit takes longer to manifest. There is no tolerance, dependency or withdrawal syndrome. Often used first-line in the USA, its expense means it is reserved for refractory cases in the UK where funding requires individual case approval.

Conclusions

It is important to consider the possibility of narcolepsy and other non-respiratory disorders in patients with EDS. Accurate

and timely diagnosis should be the norm. Symptoms can be disabling and costly but effective treatment is available.

Conflict of interests

TQ has received sponsorship from UCB Pharma Ltd and a travel bursary from Cephalon UK to attend sleep medical conferences. IES has received a speaker's fee from Cephalon UK and sponsorship from UCB Pharma Ltd to attend a sleep medical conference.

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Key points

Narcolepsy is under-recognised and should be considered in cases of unexplained daytime sleepiness or collapse

Narcolepsy has significant adverse effects on quality of life and socioeconomic impacts

Accurate diagnosis requires careful consideration of clinical and electrophysiological features

Effective drug treatments are available

Exclusion of classical narcolepsy should prompt the consideration of monosymptomatic or secondary narcolepsy, and idiopathic hypersomnolence because treatment can still be effective

KEY WORDS: cataplexy, collapse, excessive sleepiness, idiopathic hypersomnolence, narcolepsy

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Obstructive sleep apnoea: relevance to non-sleep clinicians

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Obstructive sleep apnoea (OSA) is a common condition which greatly impacts on quality of life and is associated with reduced life expectancy. Most diagnosed cases are managed by respiratory physicians. There is established, well-evidenced guidance on treatment, especially with continuous positive airway pressure (CPAP).¹ However, given an incidence of at least 2% in the adult population, it is inevitable that clinicians from a range of specialties will see patients with OSA of whom up to 80% will be undiagnosed. Such patients may present in extremis in the emergency room or as outpatients with symptoms that mimic those of another disorder or with a comorbid condition that predisposes to OSA. It is also important to have an understanding of prescribing for patients with OSA, including the risks of sedation.

This article reviews areas of overlap with non-cardiological specialties. An accompanying article discusses the cardiovascular associations of sleep apnoea syndromes. (pp 275–8).

Symptoms

Most people with OSA are males in mid-life and around 70% are obese. It is, however, important not to assume all patients fit this stereotype. A more complete risk profile is given in Table 1.² The most frequently reported symptoms are daytime sleepiness and unrefreshing sleep with poor concentration. Low mood and marital disharmony are also commonly present.³ These symptoms reduce quality of life but may be misinterpreted as due to fatigue or depression. In women in particular the primary complaint may be one of feeling tired all the time with no energy, rather than falling asleep uncontrollably in the daytime. Headache especially on waking has been thought to be a symptom of OSA and may be present when severe OSA leads to ventilatory failure with CO₂ retention, but headache alone is not

Table 1. The STOP BANG scoring system. This validated score can be used as a quick screen for obstructive sleep apnoea (OSA) risk, particularly in judging presurgical risk and the need to refer for diagnostic respiratory studies. Reproduced with permission from Wolters Kluwer.²

Symptom	Question
S Snoring	Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?
T Tiredness	Do you often feel tired, fatigued or sleepy during the daytime?
O Observed apnoea	Has anyone observed you stop breathing during your sleep?
P Pressure	Do you have or are you being treated for high blood pressure?
B BMI >35 kg/m ²	
A Age >50 years	
N Neck circumference >40 cm	
G Male gender	

High risk of OSA: ≥3 questions answered yes.
 Low risk of OSA <3 questions answered yes.
 BMI = body mass index.