The narcoleptic syndrome

The two main clinical features of the narcoleptic syndrome, excessive daytime sleepiness and collapse with laughter or emotion, were recognised by the French neuropsychiatrist Gélineau in 1880. He described a Parisian wine merchant who had many sleep attacks each day and episodic muscle weakness at the sight of a grotesque person, or with the excitement of being dealt a good hand at cards. Four characteristic features of this disorder are now recognised: day sleep attacks, weakness with laughter, sleep paralysis, and so-called "hypnagogic hallucinations". These symptoms can occur in different combinations, and the presence of all is not essential for diagnosis.

The narcoleptic syndrome is life long. Remissions are exceptional but the condition does not affect life span. Excessive daytime sleepiness may slowly worsen and cataplexy improve with increasing age, but this is controversial. The first symptoms usually present at the age of 15 to 25, although cases under 5 have been described. The narcoleptic syndrome results in considerable disability, as great or greater than that caused by epilepsy. Problems at school, work, and in the home are frequent and there is a high road traffic accident rate. Interpersonal problems, separation, and divorce are common.

Prevalence estimates vary from 26 cases per 100 000 in Finland to 590 cases per 100 000 in Japan. There may be a total of 20 000 cases in the United Kingdom. At present many of these go unrecognised. A simple effective screening programme needs to be developed.

Several problems in determining the different causes of excessive daytime sleepiness are due to inexact terminology. In the past the term narcolepsy has been used to cover several different forms of sleepiness. This usage has resulted in occasional diagnostic confusion. Narcolepsy—that is, sleep attack—is not an exact synonym for the narcoleptic syndrome and the term narcolepsy should not be used to refer, for example, to the condition of idiopathic hypersomnia. The term cataplexy has proved difficult to define. Descriptions such as "to strike down with terror", "the hypnotic state in animals while shamming dead", and "stupification", do not match the condition reported by Gélineau and do not stress the importance of the specific trigger factors of muscular weakness that he described. The International Classification of Sleep Disorders more correctly characterises cataplexy by sudden loss of bilateral muscle tone provoked by strong emotion.

The 1990 International Classification of Sleep Disorders defines the essential features of "narcolepsy" as follows:

Narcolepsy is a disorder of unknown aetiology, which is characterised by excessive sleepiness that typically is associated with cataplexy and other REM sleep phenomena such as sleep paralysis and hypnagogic hallucinations.

In this classification sleep paralysis or hypnagogic hallucinations (as well as automatic behaviour and a disrupted major sleep episode) may replace cataplexy for diagnostic purposes. The classification outlines severity criteria (mild, moderate, severe) but not level of diagnostic certainty (possible, probable, definite). In practice, the clinical diagnosis of the narcoleptic syndrome depends on the recognition of the pathological, not physiological, nature of daytime sleepiness and weakness with laughter or intense emotion, as shown by the frequency, severity, and persistence of these symptoms.

Laboratory investigations have been used in the past decade both to establish and to support diagnosis. These include the multiple sleep latency test to show a mean sleep latency of less than seven minutes. Facilitation of rapid eye movement (REM) sleep is shown by the occurrence of two or more sleep onset REM periods in a five nap protocol. Polysomnography will show frequent awakenings and fragmented REM periods during night sleep. Human leucocyte antigen testing shows HLA DR2 positivity in 98% of patients with the narcoleptic syndrome. The most specific marker in Caucasian and black patients is DQB1 0602. These investigations are sometimes considered essential for diagnosis and used as a gold standard to separate the narcoleptic syndrome from other sleep disorders. As with many if not all of the clinical features, however, sleep laboratory findings are non-specific. They may be seen in other conditions, and HLA DR2 is found in 20–30% of normal subjects. In particular, routine electroencephalograms are normal other than showing considerable drowsiness.

The main difficulty in the diagnosis of the narcoleptic syndrome occurs when cataplexy is not present, or when the history of this is equivocal. The gap between the onset of daytime sleepiness and cataplexy is usually short, around two years. In most cases, both symptoms are present at the time of initial presentation. A gap of 40 years between the presentation of daytime sleepiness, and that of cataplexy, has been recorded. Early diagnosis may be impossible here. The accessory symptoms of sleep paralysis and "hypnagogic hallucinations" can be difficult to evaluate and may have little or no diagnostic value (see later). The situation is complicated when features of other sleep-wake disorders such as obstructive sleep
apnoea are present. In our experience, and that of others, this occurs in about 10–15% of elderly male patients with the narcoleptic syndrome. Alternatively, in those cases where only a single symptom is present—and all authors who have studied many "narcoleptic" patients agree that some patients have nothing but sleep attacks—the diagnostic state may be uncertain. The term "monosymptomatic" narcolepsy—that is, excessive daytime sleepiness, or cataplexy, but not both symptoms—has been used to describe a possible forme fruste of the narcoleptic syndrome. This concept may be correct, particularly in cases where excessive daytime sleepiness is accompanied by REM sleep at sleep onset. In practice, however, some degree of diagnostic uncertainty often remains. The problem of diagnosis is highlighted in familial cases. Between 10–25% of patients with both excessive daytime sleepiness and weakness with laughter report a parent, brother, sister, or offspring with one symptom (usually excessive daytime sleepiness) alone. Here it may be difficult to separate normal from pathological findings.

Subjectively reported sleep-wake habits need to be documented and quantified. Several simple methods have been developed, with sleep-wake diaries, sleep logs, and rating scales. These include the Stanford and the Epworth sleepiness scales. Sleep patterns as shown by many of these subjective scales conform quite well with objective measures of sleepiness as shown by the multiple sleep latency test, or with rest-activity cycles as measured by activity monitor recording. Also, in many of these scales, test-retest reliability after more than a year is good. Sleepiness scales can measure different areas such as attack duration, ("How long do your sleep attacks last?"); and attack propensity ("How likely are you to fall asleep while driving?"). The recently developed Ullanlinna narcolepsy scale includes items about sleep latency ("How fast do you usually fall asleep in the evening?"); and sleep attack frequency ("Do you sleep during the day, take naps, do you fall asleep unintentionally during the day?"). Using this scale and combining subjective measures of abnormal sleep tendency with frequency estimates of loss of muscle tone with emotion, patients with the narcoleptic syndrome can be reliably distinguished from normal subjects and those with other forms of excessive daytime sleepiness. The use of a simple cataplexy rating scale, based, for example, on attack propensity ("How likely are you to lose muscle tone or fall down when you laugh?"); as well as on attack characteristics ("Do the muscles around your mouth jerk when you laugh?") may help diagnosis. All these scales are useful in evaluation of treatment.

Excessive daytime sleepiness is found in 0–3–4% of the population. Most of these cases are not due to the narcoleptic syndrome but to more common conditions including chronic sleep deprivation and obstructive sleep apnoea.

The Epworth sleepiness scale grades sleep propensity in eight common situations (sitting reading; watching television; sitting in a public place; as a car passenger; lying down for afternoon rest; sitting talking; sitting after lunch; in a car stopped in traffic). Most patients with the narcoleptic syndrome report a very high propensity to fall asleep in each of these situations, the highest propensity being when lying down for afternoon rest, the lowest in a car stopped in traffic. This distribution corresponds well with the monoony of level of different situation and is similar to that found in normal subjects.

Sleep propensity varies with the time of day. There is a trough of vigilance at afternoon siesta time, and sleep tendency may increase after a heavy meal, particularly one with a high carbohydrate content. This trough is found in narcoleptic patients as well as normal subjects although the overall level of daytime sleepiness, as determined by the Epworth sleepiness scale, is five times greater in the first than the second group. Drowsiness levels are overall slightly higher in patients with the narcoleptic syndrome than those with other causes of excessive daytime sleepiness, including symptomatotic obstructive sleep apnoea and "idiopathic" hypersomnia. Cataplexy is difficult to define and to separate clearly from weakness with laughter. As stressed earlier, a postural atonia rating scale, based on clinical observations about cataplexy, is useful to determine the propensity to loss of muscle tone with sudden intense emotion including anger and surprise as well as laughter. In our experience such a rating scale will differentiate patients with the narcoleptic syndrome from normal subjects and, in the narcoleptic syndrome, the propensity to loss of muscle tone with laughter (high) and noise (low) is opposite to that found in normal subjects. Patients with the narcoleptic syndrome often report that cataplexy is most severe when they are tired, and patients with the highest degree of sleepiness also have the highest propensity to cataplexy.

What is cataplexy? Cataplexy has some resemblance to drop attacks, sudden brief falls that occur without any warning. By contrast with cataplexy, drop attacks are not triggered and are often associated with cardiac or cerebrovascular disease. Other distinctive clinical features include autonomic symptoms and signs, dizziness, or vertigo. These do not occur in cataplexy unless triggered by the emotional stimulus that provokes the attack. As well as a superficial resemblance to drop attacks, cataplexy has some relation with physiological weakness with laughter. The progression of motor atonia and paralysis in cataplexy, starting with weakness of the face, mouth, and neck, spreading to the trunk and limbs, and sometimes ending in a fall, rarely, if ever, however, accompanies laughter in normal subjects. The range of emotional factors that triggers cataplexy is wide, although pleasure is more potent than anger. Some emotional factors, such as anger and fear, commonly result in an increase in muscle tone in normal subjects, but a decrease in the narcoleptic syndrome. The behavioural and physiological correlates of cataplexy are different from those of normal laughter. In cataplexy, behavioural features of REM sleep can be seen. These include phasic muscle jerking around the face and, particularly, around the mouth. This is sometimes accompanied by limb jerking and eye movements. These features are reported by, or can be seen in, 70% of our patients during an attack of cataplexy. In cataplexy, but not in physiological weakness with laughter, atonia may be accompanied by laboratory evidence of REM sleep, occasional dream mentation, and rapid transition to sleep accompanied by abolition of the tendon jerks and evidence of strong postynaptic inhibition of motor neurons as shown electrophysiologically by diminished H reflexes and F responses. We conclude that cataplexy is different not only in degree, but also in nature, from weakness with laughter.

Many patients with the narcoleptic syndrome report that the anticipation of laughter, rather than laughter itself, is the essential factor that provokes cataplexy. Cataplexy may be defined as laughter induced loss of facial and jaw control, spreading to involve the trunk and other body areas, accompanied by muscle jerking around the mouth. These episodes are sometimes portrayed as "jelly" attacks. This description may help patients to identify their somewhat unusual symptoms, and also to differentiate these from epilepsy. Cataplexy is probably
unique to the narcoleptic syndrome although a closely analogous condition has been reported in children with the Prader-Willi syndrome and with Niemann-Pick disease type C. Here the presentation of apparent cataplexy may be subtly different from that in the narcoleptic syndrome, with different trigger factors, and without definite evidence of REM sleep related activity during attacks.9 10

Sleep paralysis, the inability to move during the transition between sleep and wakefulness, is often considered a rare phenomenon that only occurs as part of the narcoleptic syndrome and examples of which in other conditions are not convincing. This notion is false and sleep paralysis has been increasingly recognised to be a common isolated disorder. This may occur after tiredness or irregular sleep, sleep deprivation, or psychological stress. The correct view of sleep paralysis is that the narcoleptic syndrome is only one of very many causes. Sleep paralysis has a wide prevalence rate of between 5% and 62%, often with a strong familial tendency.11

Despite this high prevalence only a few subjects seek medical advice and the condition often goes unreported or unrecognised despite the severe terror associated with some if not most attacks. We have found that occasional sleep paralysis is described by two thirds of patients with excessive daytime sleepiness and cataplexy as compared with 5–10% of patients with symptomatic obstructive sleep apnoea. By contrast, sleep paralysis is very uncommon in idiopathic hypersomnia. Sleep paralysis, cataplexy, and REM sleep have many features in common and it is surprising that, whereas cataplexy may be unique to the narcoleptic syndrome, sleep paralysis occurs in many different circumstances.12

The quintessence of the narcoleptic syndrome is usually one of daytime sleepiness, not night time insomnia. Mitter and his colleagues have, however, stressed the importance of disturbed night sleep, adding this symptom to the key diagnostic features of the syndrome.13 The usual complaints are of light sleep, non-refreshing sleep, and frequent arousals. Indeed it has been claimed that some patients with “narcolepsy” wake over 300 times each night.14 Insomnia is thus a common but much neglected symptom. The time taken to fall asleep at night, however, is only half that of normal subjects. We have found that this short sleep latency is a useful diagnostic feature. Total night sleep time is about 20 to 40 minutes less in patients with the syndrome than in normal subjects, with three to four times more recalled arousals. The complaint of insomnia increases with both disease duration and with age. In some cases it is possible that insomnia is increased by daytime central stimulant drug treatment. A few patients report entirely normal night sleep habits. We have seen an interesting variant of the narcoleptic syndrome where the primary complaint was of night time, not daytime, symptoms, despite the presence of daytime sleepiness and weakness with laughter.

Motor dyscontrol is a characteristic feature of the narcoleptic syndrome with sleep talking, sleep walking, and muscle jerking. All these features are several times more common in patients with the narcoleptic syndrome that in normal subjects. We interpret this finding as a consequence of fragmented night sleep. Interestingly this motor disorder may start in childhood, before the onset of daytime sleepiness or cataplexy.15

The term hypnagogic hallucinations was introduced by Maury to describe a specific form of mental experience, with visual decorative or fanciful patterns, distinct from true dream mentation, and occurring at sleep onset.16 This type of sleep onset experience is uncommon. It is reported occasionally by 5% of normal subjects and, in our experience, by about the same number of patients with the narcoleptic syndrome. By contrast, reports of frequent, egocentric, scene shifting, and often frightening vivid dreams are much more common in patients with the narcoleptic syndrome than in normal subjects. The upper estimate of dream frequency in normal subjects is around three to four times a week, whereas patients with the narcoleptic syndrome may report dreaming 20 or more times each week. Dreams occur both in the day, bordering sleep episodes, and at night. In the narcoleptic syndrome dreams occur at sleep onset and this unusual dream timing, not the dream content, is the important diagnostic determinant, reflecting sleep onset REM activity.

How often is the diagnosis of the narcoleptic syndrome missed? We have noted that diagnosis takes more than five years to achieve in at least one third of patients eventually referred to a sleep disorder clinic. In a survey of 132 patients with definite cataplexy and excessive daytime sleepiness attending the Maudsley Hospital sleep disorders clinic, the period from symptom onset to disease diagnosis was reported as follows: less than one year, 43 (33%); 1–5 years, 42 (33%); 6–10 years, 16 (12%); 11–20 years, 12 (9%); 21–40 years, 16 (12%); 41–60 years, two (2%); and over 60 years, one (1%). Before diagnosis, many of these patients were considered school failures, lazy, bored, or work shy. The effect of this can be devastating for a patient who misses out on work training or university, cannot hold a job, and develops a low level of self esteem. Clinical neurologists in the United Kingdom report an average total practice of between 10 and 20 “narcoleptics”. If most patients of the narcolepsy clinic are reviewed at some stage by a neurologist, only one quarter of the total estimated 20 000 patients in the United Kingdom may be recognised.

How accurate is the diagnosis of the narcoleptic syndrome? At present, the gold standard for diagnosis, as discussed earlier, is based on the presence of characteristic clinical features, supported by specific sleep laboratory findings.

When all the typical features are present, the level of diagnostic accuracy is likely to be high despite the absence of any definite disease marker such as a unique narcolepsy “gene”, or any distinct pathological or biochemical finding. Narcolepsy can be defined, as shown by the many studies confirming Honda’s original finding of the tight association between the narcolepsy syndrome phenotype and HLA DR2.17 This finding would not have been expected had the disease phenotype not been exact.

By contrast with research patients, many, if not most, of the total population of patients with the narcoleptic syndrome do not attend a sleep disorder clinic and do not have laboratory investigations. To study the level of diagnostic accuracy without specialised investigations, we have compared the pattern of disease presentation and severity in three groups of patients presenting with the complaint of excessive daytime sleepiness accompanied by excessive weakness with laughter. These groups comprised those with a definite diagnosis of the narcoleptic syndrome, confirmed by multiple sleep latency testing, polysomnography, and HLA typing, those with a probable diagnosis, as shown by sleep clinic review but without laboratory investigation, and those with a possible diagnosis, in cases presenting before sleep clinic review or investigation. The clinical characteristics were identical in these three groups. We interpret this finding as suggesting that sleep clinic review and laboratory
investigations may not be essential for clinical diagnosis in the presence of unequivocal cataplexy. Such a review is essential in uncertain cases, as well as in research studies.

A diagnosis of the narcoleptic syndrome can be made on clinical grounds alone, without laboratory support in most cases, but despite well defined symptoms, the condition is often missed or wrongly diagnosed. The most characteristic symptom, on which diagnosis primarily depends, is cataplexy, not excessive daytime sleepiness. The syndrome can only be diagnosed with certainty if cataplexy is present. Cataplexy can be defined as "jelly" attacks with laughter provoked loss of muscle tone, often accompanied by facial muscle jerking. The idea of a narcoleptic tetrad, cataplexy and daytime sleepiness accompanied by sleep paralysis and hypnagogic hallucinations, needs revision. Sleep paralysis is common in the narcoleptic syndrome but is found also in many other sleep-wake disorders and is not a diagnostic equivalent of cataplexy. True hypnagogic hallucinations are not a specific feature of the narcoleptic syndrome. Here the complaint is one of very frequent dream recall, with sleep onset dream timing. Additional features include disturbed night sleep, with a short sleep latency, multiple arousals, reduced total night sleep time, and the complaint of insomnia. Motor dyscontrol during night sleep is shown by phasic muscle jerking, sleep talking, and sleep walking. These features may antedate other symptoms. The narcoleptic syndrome is a common and very disabling condition. An effective health screening programme is needed. This could be based on a simple rating scale to allow clinical diagnosis, and aid in the identification of cases that at present are missed. The fundamental requirement of any such scale is the certain recognition of cataplexy.

Treatment of excessive daytime sleepiness in the narcoleptic syndrome depends at present on central stimulant drugs such as dexamphetamine, methyphenidate, and modafinil. These all have limited efficacy, cause frequent sympathomimetic side effects, and can lead to tolerance. Cataplexy usually responds to serotonin reuptake inhibitors including clomipramine and fluoxetine. A combination of two different types of drug may be needed for treatment but can lead to sweating, irritability, increase in appetite and weight, and impaired sexual function. Functional neuroimaging studies indicate that amphetamine causes a major increase in regional blood flow in cortical areas after both visual and auditory stimulation. The advent of new central stimulant drugs such as modafinil, and other novel drugs which inhibit both noradrenaline and serotonin re-uptake should eventually improve the treatment of the narcoleptic syndrome.
The narcoleptic syndrome.

J D Parkes, S J Clift, M J Dahlitz, S Y Chen and G Dunn

*J Neurol Neurosurg Psychiatry* 1995 59: 221-224
doi: 10.1136/jnnp.59.3.221

Updated information and services can be found at:
http://jnnp.bmj.com/content/59/3/221.citation

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/