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*without cataplexy probably has a different, as yet unknown, pathogenesis. Once established, narcolepsy is lifelong; spontaneous recovery does not occur. Symptomatic treat- ment—which is essential for school performance, work, driving ability, and quality of life—is with stimulant (e.g. amphetamine) and anticataplectic (e.g. clomipramine) drugs. More recently, sodium oxybate, an anaesthetic, has been used to induce deep sleep over- night, resulting in improvements in all symptoms. Introduction Narcolepsy has been recognized as a distinct condition since the latter part of the 19th century, when the term narcolepsy was first used by Gélineau, and it was clearly distinguished from epilepsy and psychogenic conditions. However, there continue to be substantial delays in diagnosis through a failure to recog- nize its archetypical symptoms. The condition is characterized by dysregulation of the normal sleep-wake cycle with disrupted nocturnal sleep, daytime sleep attacks, and intrusion of rapid eye movement sleep (REM sleep—the main 'dream' sleep) phe- nomena into wakefulness. Aetiology • Narcolepsy in humans is most likely an autoimmune condi- tion that occurs in people with an underlying genetically deter- mined propensity exposed to an environmental trigger (e.g. an infection). Narcolepsy is rarely familial in humans, with a clear Mendelian pattern of inheritance occurring in fewer than 5% of all those af- fected. However, there is evidence that genetic factors do play an important role in aetiology. The lifetime risk for developing nar- colepsy is increased in first-degree relatives of people with narco- lepsy by 10–20-fold and monozygotic twin studies also report high concordance rates of c.30%. There is also a very strong association with the human leukocyte antigen (HLA) haplotype. The strongest association is with the HLA-DQB1*0602 allele that is present in 95% of patients with narcolepsy with cataplexy, and 40% of pa- tients with narcolepsy without cataplexy compared to c.25% of the general population. Our current understanding is that, in most cases, genetic back- ground strongly influences the risk of developing narcolepsy but that environmental factors trigger the condition. About half the patients with narcolepsy recall a major event, usually trauma, infection, stress, or change in sleep pattern preceding the devel- opment of the condition, but this is confounded by recall bias. Nevertheless, there is increasing evidence that there can be an in- fectious trigger. There is an association of narcolepsy with high titres of antistreptolysin O antibodies and with H1N1 influenza infection and vaccination. In rare instances, narcolepsy has been associated with lesions af- fecting the posterior hypothalamus, including those due to tumours, strokes, encephalitis, multiple sclerosis, and neurodegenerative dis- eases. Narcolepsy-type symptoms can develop with rare inherited conditions such as Niemann–Pick type C disease, Norrie disease, Möbius syndrome, and Prader–Willi syndrome.

24.5.2 Narcolepsy 5883 Epidemiology • Narcolepsy is a rare condition that can occur at any age but usu- ally occurs in adolescence. Most people with narcolepsy have cataplexy. Narcolepsy has a prevalence of 25–50/10 000. The prevalence is substantially lower in Israel and substantially higher in Japan. Its overall incidence has been estimated at 0.74 per 100 000 person- years. There is a seasonal variation in the incidence of narcolepsy, with highest incidence in spring and lowest incidence in winter. It can develop at any age, but the peak onset is at 15 years and then a second, smaller peak at 36 years; approximately half the patients have an onset prior to 18 years (Fig. 24.5.2.1). However, there is a mean delay to diagnosis of up to 15 years. Approximately 70% of people with narcolepsy have cataplexy. Pathogenesis/Pathology • Narcolepsy with cataplexy is associated with loss of hypocretin secreting neurons from the hypothalamus. Narcolepsy without cataplexy is likely to have multiple pathophysiologies. Narcolepsy with and without cataplexy are likely to have different pathophysiologies. Narcolepsy with cataplexy is associated with abnormalities of the hypocretin (orexin) neurotransmitter system. This system is critical for

regulating sleep but also plays a part in regulating appetite and metabolism. In dogs, but not in humans, mutations in the hypocretin receptor have been found. However, low or undetectable levels of cerebrospinal fluid hypocretin are found in most patients with narcolepsy with cataplexy. In con- trast, narcolepsy without cataplexy is associated with low-normal hypocretin levels. Post-mortem studies have revealed that there is a reduction in the number of neurons that produce hypocretin in people with narcolepsy with cataplexy (Fig. 24.5.2.1). Together with the observation of a likely autoimmune aetiology and the strong association with HLA type, the present hypothesis is that in most cases, narcolepsy results from autoimmune destruction of hypocretin secreting neurons. In very rare instances (fewer than 5%), narcolepsy may be associated with a genetic abnor- mality affecting hypocretin secretion or its receptors, and in some neurodegenerative conditions the hypocretin neurons seem to be particularly susceptible. The precise mechanisms underlying narcolepsy without cata- plexy (30% of all people with narcolepsy) are unclear, and there might be a range of pathophysiologies. Clinical features • The clinical features of narcolepsy are: excessive daytime somno- lence with sleep attacks, daytime microsleeps (automatic behav-iours), poor and disturbed night-time sleep, and dysregulation of REM sleep phenomena including cataplexy, hypnic hallucin- ations, and sleep paralysis (Table 24.5.2.1). Fig. 24.5.2.1 Distribution of hypocretin cells in perifornical and dorsomedial hypothalamic regions of normal (a, c, e, g) and narcoleptic (b, d, f, h) humans. Calibration bar. = 100 µm in C&D, otherwise calibration bar = 25 µm. Reprinted from Thannickal TC et al. (2000). Reduced number of hypocretin neurons in human narcolepsy. Neuron 27(3), 469–74, copyright © 2000, with permission from Elsevier. Table 24.5.2.1 Symptoms of narcolepsy Symptom Narcolepsy with cataplexy Other hypersomnolent patients(variety of causes) Normal population Sleep paralysis 50% 20% 5% Hallucinations 70% 30% 10% Automatic behaviours 50% 20% 0% Disrupted sleep 70% 70% 25% Violent behaviour in sleep 30% 10% 0% After Sturzenegger C, Bassetti CL. The clinical spectrum of narcolepsy with cataplexy:
a reappraisal. J Sleep Res 2004;13:395–406.

section 24 Neurological disorders 5884 Dysregulation of sleep The main symptom is irresistible sleep attacks during the day, which can occur at inappropriate times (such as during meals or while speaking to people), but usually occur in situations that can make us all sleepy (e.g. car journeys, after lunch, watching television). These sleep attacks usually last seconds up to 20 minutes and result in relief of the feeling of sleepiness. People usually have vivid dreams during these sleep periods and occasionally muddle the dreams with reality (e.g. it is not unusual to believe that there is an intruder in the house). In addition to these naps, people with narcolepsy frequently have microsleeps, in which they may ‘sleep’ for a matter of seconds, re- sulting in short periods of automatic behaviour during daytime, during which people may carry out inappropriate or absent-minded actions (e.g. putting socks in the fridge) or writing/typing nonsense. Microsleeps have been misdiagnosed as absence seizures, but differ clinically in that absences are associated with complete loss of aware- ness and motor arrest. Also, as part of the sleep dysregulation, people with narcolepsy sleep poorly at night, waking frequently. In addition, there is a strong association between narcolepsy and other conditions that can dis- rupt nocturnal sleep, including obstructive sleep apnoea, periodic limb movement of sleep, night terrors/sleep walking (non-REM sleep parasomnia), and dream enactment (REM sleep behavioural disorder). Dysregulation of REM sleep phenomena These consist of cataplexy, sleep paralysis, and hypnic (hypnogogic/ hypnopompic) hallucinations. The latter two symptoms are not un- common in the general population. Cataplexy is almost pathognomonic for narcolepsy and describes episodes of muscle weakness or paralysis.

Cataplexy is precipitated by strong emotion, such as laughter, anger, or surprise, but not by fear. This is an example of REM sleep phenomena intruding into wakefulness, as usually REM sleep at night is accompanied by muscle paralysis (excluding respiratory muscles) in order to prevent dream enactment. Cataplexy ranges in severity. Its less severe form is characterized by transient drooping of eyelids, head nodding, fa- cial jerking, and slurred speech. However, cataplexy may be severe enough to lead to complete collapse. Cataplexy needs to be distin- guished from the physiological 'feeling weak at the knees' that can occur in anyone with anxiety or laughter. Usually cataplectic attacks occur sufficiently slowly, so that people can avoid injury. The epi- sodes are brief, lasting for seconds or minutes, but they may be fol- lowed by a sleep episode or occur recurrently (especially following sudden medication withdrawal). Cataplexy is present in over 70% of people who have narcolepsy and can predate (in c.5%) or, more commonly, follow the onset of other symptoms. Hypnogogic/hypnopompic hallucinations are brief vivid dream- like episodes that occur at sleep onset or immediately before waking respectively, and are often frightening or disturbing in na- ture, and can be muddled with reality. They can also occur during daytime naps. Sleep paralysis is the inability to move on waking from sleep. The episode can last from a few seconds to minutes, but respiratory muscles are unaffected. It is caused by the persistence of REM sleep loss of muscle tone on waking. Sleep paralysis is often associated with hallucinations; usually frightening hallucinations of someone pressing on the chest or choking the person. In addition to the aforementioned symptoms, people with narco- lepsy have increased body mass index (BMI) that may relate to lower metabolic rates. Differential diagnosis Daytime sleepiness can result from anything that disturbs or dis- rupts nocturnal sleep. Commonly this is either behavioural (i.e. people who just do not sleep enough at night) or due to obstructive sleep apnoea or restless leg syndrome/periodic limb movements of sleep (however, these conditions are more common in people with narcolepsy). Usually these conditions result in sleep attacks that are different during the day, such that they are longer, unrefreshing, lack dream sleep, and tend to occur later in the day. Idiopathic hypersomnolence is a rarer condition characterized by normal or excessive nocturnal sleep and then sleep attacks during the day that tend to be longer than those in narcolepsy and not usually associ- ated with dreaming—this condition may need to be differentiated by polysomnography/multiple sleep latency tests (see next). Lastly, psychogenic 'cataplexy' has been described and usually lacks the specific involvement of head and facial muscles early in the attack and presents as sudden collapses. In cases where there is diagnostic doubt, a cerebrospinal fluid hypocretin level can be helpful. Clinical investigations Diagnosis is predominantly clinical with people having the typical constellation of symptoms (Table 24.5.2.1). Cataplexy is a specific symptom, but can be misdiagnosed. Polysomnography (monitoring sleep overnight) is important in excluding other causes of excessive daytime somnolence due to disturbances of night-time sleep. People with narcolepsy typically have early onset sleep (<10 minutes) and early onset REM sleep (<20 minutes). A further test to confirm the diagnosis of narcolepsy is the multiple sleep latency test (MSLT). During this test the patient is allowed to fall asleep 4–5 times at 2- hourly intervals throughout the day and the latency to onset of sleep and REM sleep is measured. Occasionally HLA typing can also be helpful. There is a strong correlation between narcolepsy (with cataplexy) and the HLA HLA-DQB1*06:02 variant, but this subtype is common in the gen- eral population (see earlier) and therefore the positive predictive value is low. Measurement of cerebrospinal fluid hypocretin levels is useful to confirm the diagnosis of narcolepsy with cataplexy when there may be some question about the cataplexy (i.e. uncertainty when that symptom is present). A low cerebrospinal fluid hypocretin is the test with the highest specificity (almost 100%) but is not uni- versally present (especially in people without cataplexy),

but is now used to define the narcolepsy type (Table 24.5.2.2). Treatment At present, there is no cure for narcolepsy and treatment is there- fore symptomatic (Table 24.5.2.3).

24.5.2 Narcolepsy 5885 General management Regular nocturnal sleep habits and attention to sleep hygiene help to minimize daytime somnolence, and one to two planned naps (especially in the afternoon) can be used to optimize daytime performance. Sleepiness Excessive daytime sleepiness is reduced by amphetamine-like stimulants (usually dexamfetamine or methylphenidate), and modafinil (and the R-enantomer, armodafinil). These drugs have very different kinetics, requiring different dosing regimens (Table 24.5.2.3). The use of modafinil is supported by randomized con- trolled trials. Armodafinil may offer some pharmacokinetic ad- vantages over modafinil. Advantages of amphetamine-like drugs include long experience, low cost, a possible action against cata- plexy and higher efficacy; modafinil has the advantage that toler- ance does not develop (which can occur with amphetamines) and a lower rate of side effects. Common side effects of amphetamine- like drugs include irritability and insomnia while modafinil may cause headache, nausea, and rhinitis, and can interact with the oral contraceptive pill. In addition, amphetamines, methylphenidate, and modafinil may cause cardiac arrhythmias and increased blood pressure. Amphetamines are not recommended during pregnancy and the safety of modafinil during pregnancy is unclear. Recently, pitolisant, a histamine H3-receptor inverse agonist, which in- creases histamine release, has been licensed for use in narcolepsy with or without cataplexy. Its stimulant properties are similar to modafinil but it possibly lacks the cardiovascular side-effects. It interacts with the contraceptive pill. However, another advantage is that it has anticataplectic effects. Other stimulants are being developed and are in clinical trials. Overall, approximately 80% have moderate to marked improvement with treatment. Cataplexy Cataplexy can be treated with tricyclic antidepressants (clomipramine) and the selective serotonin uptake inhibitors (flu- oxetine). Other antidepressants, such as venlafaxine, can also be useful. These have not been subjected to randomized control trials. These drugs also treat other narcolepsy symptoms (such as sleep paralysis and hypnic hallucinations). These drugs can result in cardiac side effects, dry mouth, constipation, gastrointestinal upset, low sex drive, and agitation. Selegiline can also be used to treat the cataplexy and excessive daytime sleep, probably because of its central amphetamine-like effect. More recently, sodium oxybate has been shown in randomized control trials to be effective in cata- plexy and also improves daytime somnolence (and other symptoms Table 24.5.2.2 Narcolepsy classification in the International Classification of Sleep Disorders-3 (ICSD-3) Narcolepsy type 1 (with hypocretin deficiency)—both of the following criteria must be met:

1. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep, occurring for at least 3 months.
2. The presence of one or both of the following: a) Cataplexy and a mean sleep latency of at most 8 minutes and 2 or more sleep onset rapid eye movement periods (SOREMPs) on a multiple sleep latency
   test (MSLT) performed according to standard techniques. A SOREMP on the preceding nocturnal polsomnography (i.e. rapid eye movement sleep onset within
   15 minutes of sleep onset) may replace one of the SOREMPs on the MSLT. b) Cerebrospinal fluid hypocretin-1 concentration, measured by immunoreactivity, is either up to 110 picograms/ml or <1/3 of mean values obtained in normal subjects with the same standardized assay. Narcolepsy type 2 (without hypocretin deficiency)—all 5 of the following criteria must be met:

3. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.
4. A mean sleep latency of ≤8 minutes and 2 or more sleep onset REM periods (SOREMPs) on a MSLT performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnography may replace one of the SOREMPs on the MSLT.
5. Cataplexy is absent.
6. Either cerebrospinal fluid hypocretin-1 concentration has not been measured or cerebrospinal fluid hypocretin-1 concentration measured by immunoreactivity is >110 picograms/mL or >1/3 of mean values obtained in normal subjects with the same standardized assay.
7. The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, obstructive sleep apnoea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal. American Academy of Sleep Medicine. Table 24.5.2.3 Pharmacological treatment for narcolepsy Drug Indication Dose/24 hr Comments Oxybate EDS and cataplexy 4.5–9 g Given as divided doses at night (second dose is given 2.5–4 hours after first). Pitolisant EDS and cataplexy 4.5–36 mg Given as a single dose. Interaction with oral contraceptive. Dexamfetamine EDS (cataplexy) 5–60 mg Half-life of about 10 hours. Often needs to be given 2–3 times per day. Methylphenidate EDS (cataplexy) 5–80 mg Very short half-life (2–4 hours) but it is available as a slow release formulation. Modafinil EDS 200–400 mg Half-life 12–18 hours. Can be given once or twice a day. Interaction with oral contraceptive. Clomipramine Cataplexy 10–150 mg Often best given at night. Avoid sudden withdrawal. Fluoxetine Cataplexy 20–60 mg Best given in morning. Avoid sudden withdrawal. Venlafaxine Cataplexy 75–375 mg Often used in refractory cataplexy. Avoid sudden withdrawal. EDS, excessive daytime somnolence.

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