PRIMEVIEW

NARCOLEPSY

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Narcolepsy is a chronic sleep disorder that is characterized by excessive daytime sleepiness. The disorder can be subdivided into two subtypes: narcolepsy type 1 (NT1; also known as narcolepsy with cataplexy) and narcolepsy type 2 (NT2; also known as narcolepsy without cataplexy).

EPIDEMIOLOGY

The main genetic risk factor for narcolepsy is the *HLA-DQB1*06:02* allele, which is found in 86–98% of patients with NT1. Other genetic risk factors include polymorphisms in several immune-related genes, such as those encoding the T cell receptor, pro-cathepsin H and chemokine receptors. Environmental risk factors for NT1 include certain formulations of the H1N1 influenza vaccination, influenza virus infection and streptococcal infection.

The global prevalence of narcolepsy is 25–50 cases per 100,000 individuals, which probably reflects a combination of NT1 and NT2 subtypes

DIAGNOSIS

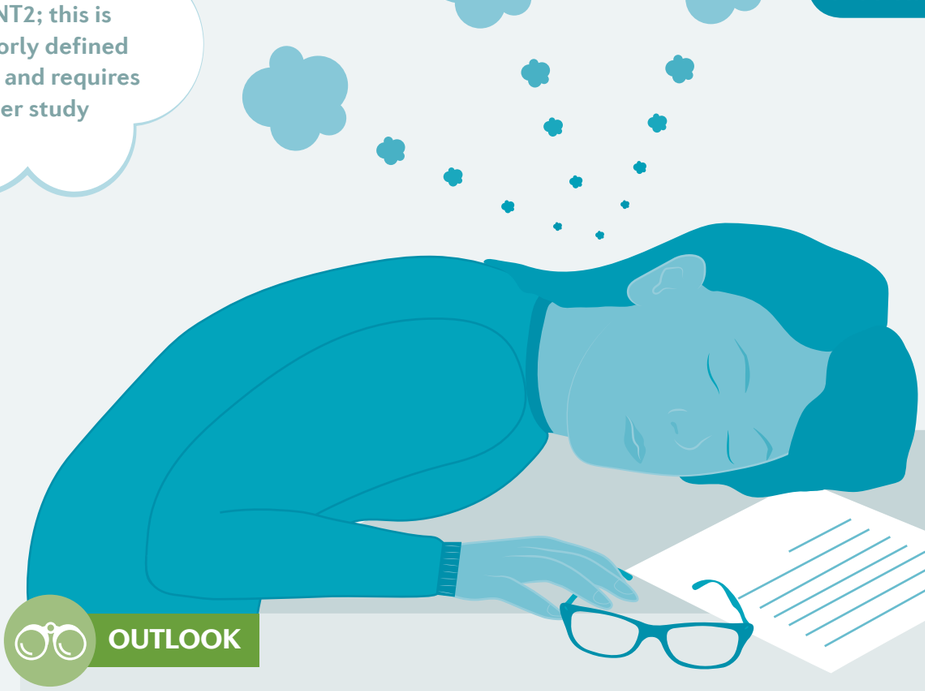
The core symptoms of narcolepsy include excessive daytime sleepiness, disrupted night-time sleep, hypnagogic hallucinations (that is, hallucinations when the individual is falling asleep) and sleep paralysis

Patients with NT1 also develop cataplexy — a loss of muscle tone during wakefulness that is usually evoked by strong emotions

Diagnosis requires sleep questionnaires, polysomnography (a comprehensive recording of the patient during sleep) and the multiple sleep latency test (which is used to quantify daytime sleepiness)

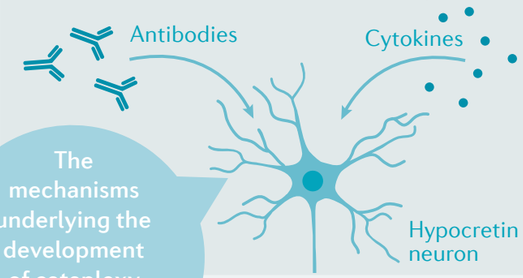
These objective electrophysiological tests are used to assess the transition into REM states and the durations of the different sleep periods, to better understand the patient's condition

Compared with NT1, less is known about NT2; this is still a poorly defined condition and requires further study



MECHANISMS

The selective loss of hypocretin neurons in the lateral hypothalamus is speculated to underlie the development of NT1. Hypocretin neurons act as a stabilizing input to inhibitory connections between brain areas that promote wakefulness and those that promote sleep. Thus, loss of these neurons could lead to uncontrolled transitions between sleep and wakefulness, resulting in the sleep disturbances that are observed in patients. The mechanism underlying the loss of hypocretin neurons is unknown, but the most likely hypothesis is that the loss of neurons is mediated by an autoimmune response. Supporting evidence for this includes the selective neuronal loss, the identification of autoreactive T cells in patients with narcolepsy and the strong association between polymorphisms in immune-related genes and NT1. However, no direct evidence has been reported.



The mechanisms underlying the development of cataplexy are poorly understood

QUALITY OF LIFE

Patients with narcolepsy have deficits in alertness and attention, which are enhanced when patients have to concentrate on demanding, monotonous and prolonged tasks. Several comorbidities are found in patients with narcolepsy, including psychiatric conditions, other sleep disorders (such as sleep apnoea and restless legs syndrome) and metabolic diseases.

Narcolepsy might increase the risk of car accidents

MANAGEMENT

Stimulants (such as modafinil and armodafinil) are the first-line treatments for excessive daytime sleepiness in patients with narcolepsy. Sodium oxybate is the only treatment that can improve all of the core narcolepsy symptoms, including excessive daytime sleepiness, disrupted night-time sleep and, in patients with NT1, cataplexy.

Pitolisant, a histamine receptor antagonist, has been approved for the treatment of narcolepsy by the European Medicines Agency

Non-pharmacological management of narcolepsy includes scheduled daytime naps and night-time sleep

OUTLOOK

Despite a substantial improvement in our understanding of the pathophysiology, diagnosis and treatment of narcolepsy over the past decade, further questions remain. Although the autoimmune-mediated loss of hypocretin neurons is likely in patients with NT1, more studies are required to provide direct evidence in support of this hypothesis.

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