

# Narcolepsy

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## Abstract

*Narcolepsy is a disorder of the regulation of consciousness and sleep characterized by excessive diurnal somnolence, sudden onset of attacks of cataplexy during full consciousness, hallucinations and sleep paralysis. The frequency is estimated to be 0.05% of the general population. The age of narcolepsy onset varies widely, with symptoms appearing as of the first years of life until about 50 years of age. The diurnal somnolence associated with attacks of cataplexy is sufficient to diagnose the disease. For atypical or incomplete forms, complementary examinations are required. EEG recordings during sleep completed the following day with repeated tests of falling asleep. Impairment in the orexin system caused by genetic and autoimmune mechanisms may trigger narcolepsy. HLA typing detects the DR15 DQB1\*0602 gene in the quasi-totality of narcoleptic subjects. Treatment for excessive diurnal somnolence and sleep attacks relies on naps distributed throughout the day and modafinil or methylphenidate. The treatment of cataplexy attacks calls upon tricyclic antidepressants or non anti-cholinergic agents. Narcolepsy can be severely debilitating and is often attenuated by these therapeutic agents that control the symptoms without curing the disease.*

## Key-words

Narcolepsy, sleep disorder, diurnal somnolence, cataplexy, hallucinations, marker HLA DR15 DQB1, modafinil, methylphenidate

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## Name of the disease

- Narcolepsy
- Gélineau's syndrome

## Excluded diseases

- Syndrome of sleep apnea
- [Idiopathic hypersomnia](#)
- Psychiatric hypersomnia

## Definition

Described in 1877 by Westphal, then in 1880 by Gélineau, narcolepsy is a disorder of the regulation of consciousness and sleep characterized by excessive diurnal somnolence, sudden onset of attacks of cataplexy during full consciousness, hallucinations and sleep paralysis.

**Frequency**

The frequency is estimated to be 0.05% of the general population. The prevalence is not known with certitude.

**Clinical description**

The age of narcolepsy onset varies widely, with symptoms appearing as of the first years of life until about 50 years of age, but with two peaks for age at diagnosis, the first between 15 and 20 years and the second smaller one around 37 years.

A tetrad of clinical symptoms enables the diagnosis: 1) excessive diurnal somnolence giving rise to quasi-uncontrollable, daily sleep attack; 2) attacks of cataplexy or sudden loss of muscle tone occurring during full consciousness, often in association with sudden emotional reactions, either generalized paralysis or weakness localized to the arms or the jaw; 3) hypnagogic (at the onset of sleep) or hypnopompic (the drowsy state following sleep) phenomena, particularly vivid auditory, visual or even kinesthetic illusions or hallucinations, which do not correspond to reality. These hallucinations are not recognized as real by the subject, although they are sometimes vivacious and frightening; 4) sleep paralysis also occurs just when falling asleep or awakening and the subject who wants to move finds that he/she is unable to do so.

To these four cardinal signs are added, nocturnal dyssomnia with repeated awakenings, nightmares or parasomnias (behavioral disorders of 'paradoxal' rapid eye movement (REM) sleep, for example). Diurnal somnolence is usually the first sign to appear.

**Diagnosis**

The diurnal somnolence associated with attacks of cataplexy is sufficient to diagnose the disease. For atypical or incomplete forms, complementary examinations are required. EEG recordings during sleep completed the following day with repeated tests of falling asleep (see below).

The EEG recording enables: 1) assessment of the mode of falling asleep 'slow' or non-rapid eye movement (NREM) sleep or REM sleep; 2) to evaluate the extent of dyssomnia; 3) to eliminate another pathology (sleep apnea syndrome or increased resistance of the upper airways, periodic movements of the legs).

Repeated tests of falling asleep consist of asking the subject to go to bed in a calm, dark room, and trying to let 'himself go' and fall asleep 5 times during the day at 2-hour intervals. The highly somnolent individual falls asleep during almost all the tests within the space of 8 minutes, and the narcoleptic immediately enters REM sleep at least twice. Immediate entry into

REM sleep is the most characteristic sign of the disease.

HLA typing can be done to confirm that the patient belongs to the group 'at risk', the 20–25% of the general population who are carriers of the HLA.DR15 DQB1\*0602 gene.

The time lapse between the first signs and the diagnosis of the disease has diminished, from 10 to 3 years, over the last few years.

**Evolution and repercussions of the disease**

The progression of the disease is difficult to generalize. Sleep attacks and excessive diurnal somnolence persist throughout the individual's life but can be attenuated at retirement age. Cataplexy attacks can disappear or subjects can learn to handle better the emotions that precipitate them.

Narcolepsy is responsible for a familial, social and professional handicap whose extent reflects the severity of the disease. In children, school-related problems are usually severe. Narcolepsy can be the cause of work or traffic accidents. French legislation (law of 7 May 1997) requires that the disease be declared to the commission emitting driver's licenses, which are accorded unless effective treatment is demonstrated.

**Etiology**

The symptoms of the disease can be explained by a disorder of the regulation of consciousness and sleep. During consciousness, abnormal episodes of REM sleep occur. Cataplexy attacks and sleep paralysis correspond to the development, during consciousness, of episodes of muscular atonia, specific to REM sleep. The hallucinations reflect a dreamlike activity that arises when the individual is not completely asleep.

**Animal model**

Dogs can have a disease that closely resembles human narcolepsy. It has been demonstrated that dog narcolepsy is transmitted by autosomal dominant inheritance and that it is due to a mutation of the gene coding for the hypocretin (orexin) 2 receptor (Lin *et al.*, 1999). Orexin is a hypothalamic neuropeptide that reacts with specific receptors.

**Mechanisms of the disease in humans**

The orexin system is also implicated in human narcolepsy: orexin is undetectable in the cerebrospinal fluid of narcoleptic individuals (Nashino *et al.*, 2000) and the number of hypothalamic orexin neurons is markedly diminished in narcoleptic subjects at autopsy (Thannickal *et al.*, 2000). Genetic and autoimmune mechanisms might be implicated in this loss of orexin cells in humans. The risk of developing narcolepsy is higher in children of

narcoleptic but remains low. HLA typing detects the DR15 DQB1\*0602 gene in the quasi-totality of narcoleptic subjects (Matsuki *et al.*, 1992; Mignot *et al.*, 1997). However, this haplotype is also found in 20–25% of the general population individuals.

### Management and treatment

First, regular hours for sleep and sufficient time asleep are necessary.

Treatment for excessive diurnal somnolence and sleep attacks relies on naps distributed throughout the day and a drug, Modiodal® (modafinil), which is well tolerated and effective in 75% of the subjects, creating neither addiction nor dependence. Ritalin® (methylphenidate) can be used in the treatment of narcolepsy patients who insufficiently react to modafinil.

The treatment of cataplexy attacks calls upon tricyclic antidepressants, such as Anafranil® (clomipramine) or non anti-cholinergic agents, like Vivalan® (viloxazine), Prozac® (fluoxetine) or Floxytral® (fluvoxamine).

Narcolepsy can be severely debilitating and is often attenuated by these therapeutic agents that control the symptoms without curing the disease.

### Unresolved questions

The relationship between the HLA system and orexin remains to be discovered.

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