Narcolepsy

Description/Etiology

Narcolepsy, a chronic neurologic disorder caused by a brain malfunction in regulating sleep-wake cycles, is characterized by a variable combination of cataplexy (i.e., a condition brought on by intense emotions in which the person briefly loses muscle control while remaining totally conscious), excessive daytime sleepiness (EDS), sleep paralysis, hypnagogic (i.e., as one is falling asleep) hallucinations and hypnopompic (i.e., drowsy state as one is falling asleep) hallucinations, and disturbed nocturnal sleep. Patients with narcolepsy can feel sleep-deprived and experience unwanted “sleep attacks” several times a day, after which they awaken and feel refreshed. Narcolepsy has a major effect on the patient’s functional status and quality of life; episodes of cataplexy and paralysis can be extremely frightening, and episodes of cataplexy with complete loss of muscle tone can cause severe injury.

There are two types of narcolepsy: type 1 (T1N) and type 2 (T2N). The types distinguished by the presence (in T1N) or absence (in T2N) of cataplexy. T2N is further categorized into two groups based on the number of sleep onset rapid eye movement (REM) periods (SOREMPs): patients with two or more SOREMPs have “regular” T2N, and those with one or no SOREMPs have idiopathic hypersomnia.

Although the exact etiology of narcolepsy is unclear, T1N is thought to be related to the selective loss of cells that secrete the neurotransmitters hypocretin-1 and hypocretin-2 (also called orexin A and orexin B) in the lateral hypothalamus. Levels of hypocretin-1, which normally stimulates arousal and helps regulate sleep, can be measured in the cerebrospinal fluid (CSF) and are low to undetectable in patients with T1N. Patients with T2N have normal levels of hypocretin, suggesting that a different cause might be responsible for T2N. Diagnosis is made based on clinical evaluation and results of sleep studies. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), the following criteria must be met to formally diagnose narcolepsy: lapsing into sleep at least three times a week during the past 3 months and having either several episodes of cataplexy each month, hypocretin deficiency, or REM sleep of ≤ 15 minutes. There is often a delay in accurate diagnosis, perhaps for several years, and it may be initially misdiagnosed as a primary psychotic illness (e.g., schizophrenia, bipolar disorder), depression, epilepsy, or adverse medication effects. Differential diagnosis includes normal changes in sleep cycles, sleep deprivation, and other primary or secondary sleep disorders, as well as medical disorders (e.g., encephalopathy) or substance use disorder.

Narcolepsy cannot be cured but is treatable. Treatment typically consists of a combination of drug therapy and education regarding lifestyle modifications that minimize EDS events and effects.

Facts and Figures

Narcolepsy affects approximately 1 in 3000 people. In the United States, 0.02–0.18% of the adult population is affected, while it affects 0.02% of adults worldwide. The reported prevalence varies geographically and is 0.002% in Israeli Jews and Arabs, 0.005% in the Irish general population, 0.02% of whites in the Czech Republic, 0.026% of whites in Finland, 0.04% of whites in the United Kingdom, 0.05% of whites in France, and 0.18% in Japan. Narcolepsy equally affects both men and women. Onset of narcolepsy is typically...
in children, adolescents, and young adults; the two peaks of onset are at 15–25 years of age and 30–35 years of age. Between 30% and 50% of patients with narcolepsy experience cataplexy. Patients with narcolepsy are involved in motor vehicle accidents at 10 times the rate of the general public.

**Risk Factors**

Although the exact etiology of narcolepsy is not fully understood, narcolepsy results from a number of causes, including electrophysiological factors, genetics, changes in neurotransmitters, and environmental influences. The human leukocyte antigen (HLA) subtype DQB1*0602 is closely associated with narcolepsy. Ninety-five percent of patients with TN1 and 96% of those with hypocretin deficiency carry the HLA-DQB1*0602 allele. The antigen forms a heterodimer with another closely related HLA antigen subtype, DQA1*0102 allele, and can act as an antigen presenter to T-cell receptors, resulting in a hampered immune response as well as narcolepsy susceptibility. The deficiencies in orexin and hypocretin seen in T1N are due to the loss of neurons that produce these. Narcolepsy has a strong familial association; risk for persons with a first-degree relative with the disorder is as high as 40%. Tumors, vascular malformations, and strokes can cause narcolepsy. It is found in genetic disorders such as Niemann-Pick disease type C, Prader-Willi syndrome, and paraneoplastic syndromes.

**Signs and Symptoms/Clinical Presentation**

› **Physical indicators:** Cataplexy, complete or partial paralysis, and slurred speech
› **Cognitive indicators:** EDS, hypnagogic hallucinations, and abnormalities in concentration, attention, memory, and performance

**Assessment**

› **Patient History**
  • Assess risk factors, history of drug use, and patient/family medical history

› **Physical Findings of Particular Interest**
  • Atonia, which is a REM-related impairment of voluntary movement that can otherwise occur during the regular dream state, can be present

› **Laboratory Tests**
  • Genetic testing can confirm the presence of HLA-DQB1*0602 allele
  • CSF analysis is performed to measure hypocretin-1 levels
    – In patients with narcolepsy who have cataplexy, CSF levels of hypocretin-1 are usually low to undetectable at < 110 pg/mL
  • Urinalysis and serum chemistry testing can be performed to assess for underlying medical conditions, if suspected
  • Drug testing can be performed to assess for use of substances that can cause hypnagogic hallucinations

› **Other Diagnostic Tests/Studies**
  • Polysomnography (PSG) can be performed to evaluate sleep cycles and stages with the use of EEG, EMG, and direct observation to monitor eye movement, respiratory rate, BP, oxygen saturation, and heart rhythm during sleep
  • The Multiple Sleep Latency Test (MSLT) will measure the time it takes to fall asleep and to go into deep sleep
  • The Stanford Narcolepsy Questionnaire, the Pediatric Sleepiness Scale, and the Epworth Sleepiness Scale can be administered to assess the extent of narcolepsy signs and symptoms

**Treatment Goals**

› **Promote Symptom Resolution and Reduce Risk for Complications**
  • Assess vital signs and all physiologic systems and review results of laboratory/other diagnostic tests; contact the treating clinician with information regarding abnormalities and treat, as ordered
  • Follow facility protocols for fall prevention and to maintain patient safety (e.g., airway, circulation, and prevention of injury)
  • Administer prescribed medications and monitor treatment efficacy and for adverse effects; prescribed drug therapy often includes
    – stimulant-like agents (e.g., modafinil, armodafinil) or stimulants (e.g., dextroamphetamine, dextroamphetamine/amphetamine, methylphenidate) for treatment of EDS
    – REM-suppressing agents (e.g., tricyclic antidepressants [e.g., atomoxetine, protriptyline], selective serotonin reuptake inhibitors [SSRIs; e.g., FLUoxetine, venlafaxine]) and sodium oxybate for cataplexy
Prescribed medications and management guidelines are typically the same for T1N and T2N, except for cataplexy management.

Provide Emotional Support and Educate About Strategies to Control Manifestations

- Assess patient/family anxiety level and for knowledge deficits regarding narcolepsy; provide emotional support, educate, and encourage discussion regarding the condition, diagnostic procedures, potential complications of narcolepsy, treatment risks and benefits, and individualized prognosis
- Advise the patient to eat lightly before important activities to help reduce the risk of an attack after meals, and to schedule regular naps to reduce daytime cataplectic episodes
- Educate regarding good sleep hygiene techniques, including the possibility of taking regularly scheduled naps during the day and establishing a regular bedtime
- Educate regarding avoiding caffeinated drinks to improve the quality of nighttime sleep and smoking cessation because nicotine can worsen narcolepsy and cataplexy
- Encourage wearing a medical alert bracelet that indicates the nature of narcolepsy to help receive appropriate care in case of a cataplectic incident

Food for Thought

- Although it is commonly believed that persons with narcolepsy spend a much greater proportion of their time sleeping than the general population, most persons with narcolepsy actually get about the same amount of sleep as the general population because they are frequently awake at night
- The Americans with Disabilities Act mandates employers of those with narcolepsy to provide reasonable/necessary accommodations
- Pitolisant is a selective histamine H3 receptor inverse agonist that blocks histamine autoreceptors, boosting the activity of histaminergic neurons in the brain and increasing release of various neurotransmitters, including dopamine, acetylcholine, and noradrenaline. Researchers in a randomized controlled trial involving 106 adult patients in nine European countries found that pitolisant reduced cataplexy and EDS compared to placebo. Adverse effects included headache, irritability, anxiety, and nausea (which was severe in one case) (Szakacs et al., 2017)
  - Pitolisant received marketing approval by the European Medicines Agency in March 2016 and was launched in the United Kingdom in September 2016
  - An expanded access program began in the US in February 2018 to provide access to pitolisant while the drug’s manufacturer prepares and submits documentation for FDA approval

Red Flags

- Stimulants can cause dizziness, blurred vision, and restlessness and can mask signs and symptoms of extreme fatigue; stimulants should not be taken when driving or other activity is planned
- Modafinil can reduce the efficacy of oral contraceptives, and cyclosporine
- Amphetamines are habit-forming, and rapid discontinuation can cause severe withdrawal signs and symptoms

What Do I Need to Tell the Patient/Patient’s Family?

- Provide written information, if available, and resources (e.g., Narcolepsy Network, https://narcolepsynetwork.org/) to support verbal education
- Emphasize the potential for injury and the necessity of initiating strategies to maintain safety
- Educate regarding the prescribed medication regimen and the importance of adherence
- Encourage the patient to keep a sleep log for 2–3 weeks to monitor EDS and track usual sleep patterns (e.g., sleep deprivation, irregular sleep/wake pattern, interrupted sleep), and encourage recording simultaneous alcohol consumption and drug use
- An exercise program for children may be helpful; schedule adjustments, as well as accommodations such as frequent breaks or naps, may be necessary for school-age children to enhance alertness
- Vocational counseling is important for patients and parents to avoid problematic professions/vocations (e.g., driving)

References


