Narcolepsy

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Narcolepsy is a chronic sleep disorder, or dyssomnia, characterized by excessive sleepiness and sleep attacks at inappropriate times, such as while at work. People with narcolepsy often experience disturbed nocturnal sleep and an abnormal daytime sleep pattern, which often is confused with insomnia. Narcoleptics, when falling asleep, generally experience the REM stage of sleep within 5 minutes; whereas most people do not experience REM sleep until an hour or so later.[1]

Another one of the many problems that some narcoleptics experience is cataplexy, a sudden muscular weakness brought on by strong emotions (though many people experience cataplexy without having an emotional trigger).[2] It often manifests as muscular weaknesses ranging from a barely perceptible slackening of the facial muscles to the dropping of the jaw or head, weakness at the knees (often referred to as "knee buckling[3]"), or a total collapse. Usually speech is slurred and vision is impaired (double vision, inability to focus), but hearing and awareness remain normal. In some rare cases, an individual's body becomes paralyzed and muscles become stiff. Some narcolepsy affected persons also experience heightened senses of taste and smell.

Narcolepsy is a neurological sleep disorder. It is not caused by mental illness or psychological problems. It is most likely affected by a number of genetic mutations and abnormalities that affect specific biologic factors in the brain, combined with an environmental trigger during the brain's development, such as a virus.[4]

The term *narcolepsy* derives from the French word *narcolepsie* created by the French physician Jean-Baptiste-Édouard Gélineau by combining the Greek νάρκη (*narkē*, "numbness" or "stupor"),[5][6] and λῆψις (*lepsis*), "attack" or "seizure".[7]

Signs and symptoms

The main characteristic of narcolepsy is Excessive Daytime Sleepiness (EDS), even after adequate night time sleep. A person with narcolepsy is likely to become drowsy or fall asleep or just be very tired throughout the day, often at inappropriate times and places. Daytime naps may occur with little warning and may be physically irresistible. These naps can occur several times a day. They are typically refreshing, but only for a few hours. Drowsiness may persist for prolonged periods of time. In addition, night-time sleep may be fragmented with frequent awakenings.

The classic symptoms of the disorder, often referred to as the "tetrad of narcolepsy," are cataplexy, sleep paralysis, hypnagogic hallucinations, and excessive daytime sleepiness.[8] Other symptoms include automatic behaviors.[9][10] These symptoms may not occur in all patients. Cataplexy is an episodic condition featuring loss of muscle function, ranging from slight weakness (such as limpness at the neck or knees, sagging

facial muscles, or inability to speak clearly) to complete body collapse. Episodes may be triggered by sudden emotional reactions such as laughter, anger, surprise, or fear, and may last from a few seconds to several minutes. The person remains conscious throughout the episode. In some cases, cataplexy may resemble epileptic seizures.[11] Sleep paralysis is the temporary inability to talk or move when waking (or less often, when falling asleep). It may last a few seconds to minutes. This is often frightening but is not dangerous. Hypnagogic hallucinations are vivid, often frightening, dreamlike experiences that occur while dozing, falling asleep and/or while awakening.

Automatic behavior means that a person continues to function (talking, putting things away, etc.) during sleep episodes, but awakens with no memory of performing such activities. It is estimated that up to 40 percent of people with narcolepsy experience automatic behavior during sleep episodes. Sleep paralysis and hypnagogic hallucinations also occur in people who do not have narcolepsy, but more frequently in people who are suffering from extreme lack of sleep. Cataplexy is generally considered to be unique to narcolepsy and is analogous to sleep paralysis in that the usually protective paralysis mechanism occurring during sleep is inappropriately activated. The opposite of this situation (failure to activate this protective paralysis) occurs in rapid eye movement behavior disorder.

In most cases, the first symptom of narcolepsy to appear is excessive and overwhelming daytime sleepiness. The other symptoms may begin alone or in combination months or years after the onset of the daytime naps. There are wide variations in the development, severity, and order of appearance of cataplexy, sleep paralysis, and hypnagogic hallucinations in individuals. Only about 20 to 25 percent of people with narcolepsy experience all four symptoms. The excessive daytime sleepiness generally persists throughout life, but sleep paralysis and hypnagogic hallucinations may not. A rare subset of narcoleptics also experience heightened senses of taste and smell supertaster, phenomenon.[*citation needed*]

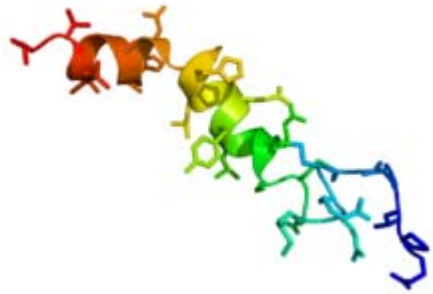
Although these are the common symptoms of narcolepsy, many people with narcolepsy also suffer from insomnia for extended periods of time. The symptoms of narcolepsy, especially the excessive daytime sleepiness and cataplexy, often become severe enough to cause serious problems in a person's social, personal, and professional life. Normally, when an individual is awake, brain waves show a regular rhythm. When a person first falls asleep, the brain waves become slower and less regular. This sleep state is called non-rapid eye movement (NREM) sleep. After about an hour and a half of NREM sleep, the brain waves begin to show a more active pattern again. This sleep state, called REM sleep (rapid eye movement sleep), is when most remembered dreaming occurs. Associated with the EEG-observed waves during REM sleep, muscle atonia is present (called REM atonia).

In narcolepsy, the order and length of NREM and REM sleep periods are disturbed, with REM sleep occurring at sleep onset instead of after a period of NREM sleep. Thus, narcolepsy is a disorder in which REM sleep appears at an abnormal time. Also, some of the aspects of REM sleep that normally occur only during sleep—lack of muscular

control, sleep paralysis, and vivid dreams—occur at other times in people with narcolepsy. For example, the lack of muscular control can occur during wakefulness in a cataplexy episode; it is said that there is intrusion of REM atonia during wakefulness. Sleep paralysis and vivid dreams can occur while falling asleep or waking up. Simply put, the brain does not pass through the normal stages of dozing and deep sleep but goes directly into (and out of) rapid eye movement (REM) sleep.

This has several consequences. Night time sleep does not include as much deep sleep, so the brain tries to "catch up" during the day, hence EDS. People with narcolepsy may visibly fall asleep at unpredicted moments (such motions as head bobbing are common). People with narcolepsy fall quickly into what appears to be very deep sleep, and they wake up suddenly and can be disoriented when they do (dizziness is a common occurrence). They have very vivid dreams, which they often remember in great detail. People with narcolepsy may dream even when they only fall asleep for a few seconds.

Causes



A depiction of the neuropeptide **Orexin-A**. People with narcolepsy often have a reduced number of neurons that produce this protein.

Although the cause of narcolepsy was not determined for many years after its discovery, scientists had discovered conditions that seemed to be associated with an increase in an individual's risk of having the disorder. Specifically, there appeared to be a strong link between narcoleptic individuals and certain genetic conditions. One factor that seemed to predispose an individual to narcolepsy involved an area of Chromosome 6 known as the HLA complex.[12] There appeared to be a correlation between narcoleptic individuals and certain variations in HLA genes, although it was not required for the condition to occur. Certain variations in the HLA complex were thought to increase the risk of an auto-immune response to protein-producing neurons in the brain. The protein produced, called hypocretin or orexin, is responsible for controlling appetite and sleep patterns.[13] Individuals with narcolepsy often have reduced numbers of these protein-producing neurons in their brains.[13] In 2009 the autoimmune hypothesis was supported by research carried out at Stanford University School of Medicine.[14][15]

The neural control of normal sleep states and the relationship to narcolepsy are only partially understood. In humans, narcoleptic sleep is characterized by a tendency to go

abruptly from a waking state to REM sleep with little or no intervening non-REM sleep. The changes in the motor and proprioceptive systems during REM sleep have been studied in both human and animal models. During normal REM sleep, spinal and brainstem alpha motor neuron depolarization produces almost complete atonia of skeletal muscles via an inhibitory descending reticulospinal pathway. Acetylcholine may be one of the neurotransmitters involved in this pathway. In narcolepsy, the reflex inhibition of the motor system seen in cataplexy has features normally seen only in normal REM sleep[1].

In 2004 researchers in Australia induced narcolepsy-like symptoms in mice by injecting them with antibodies from narcoleptic humans. The research has been published in the Lancet providing strong evidence suggesting that some cases of narcolepsy might be caused by autoimmune disease.[16] Narcolepsy is strongly associated with HLA-DQB1*0602 genotype.[17] There is also an association with HLA-DR2 and HLA-DQ1. This may represent linkage disequilibrium. Despite the experimental evidence in human narcolepsy that there may be an inherited basis for at least some forms of narcolepsy, the mode of inheritance remains unknown. Some cases are associated with genetic diseases such as Niemann-Pick disease[18] or Prader-Willi syndrome.[19]

Currently a link between GlaxoSmithKline's swine flu vaccine Pandemrix and childhood narcolepsy is being investigated due to increased prevalence of narcolepsy in Irish, Finnish and Swedish children after vaccinations. Finland's National Institute of Health and Welfare is recommending that Pandemrix vaccinations are suspended pending further investigation into 15 reported cases of recently vaccinated children developing narcolepsy.[20][21] In Finland in mid-November 2010, 37 cases of children's narcolepsy had been reported as suspected adverse events of Pandemrix. This can be compared to the normal average of 3 cases of children's narcolepsy per year.[22] In Sweden, *Läkemedelsverket* (Medical products agency) did a case inventory study during 2009□2010. They found that "the incidence of narcolepsy with cataplexy in children/adolescents in the Swedish population increased during the pandemic and vaccination period, with a rapid decline in incidence during the post pandemic period." Their conclusion is that these results "provide strengthened evidence that vaccination with Pandemrix during the pandemic period was associated with an increase in the risk for narcolepsy with cataplexy in children/adolescents 19 years and younger."[23]

More recently, studies done in China and published in Nature Reviews: Neurology have indicated that influenza infection, and H1N1 in particular, can trigger narcolepsy onset.[24]

Diagnosis

Diagnosis is relatively easy when all the symptoms of narcolepsy are present, but if the sleep attacks are isolated and cataplexy is mild or absent, diagnosis is more difficult. It is also possible for cataplexy to occur in isolation.[*citation needed*] Three tests that are commonly used in diagnosing narcolepsy are the polysomnogram, the multiple sleep latency test (MSLT), and administration of the Epworth Sleepiness Scale. These tests are usually

performed by a sleep specialist. The polysomnogram involves continuous recording of sleep brain waves and a number of nerve and muscle functions during nighttime sleep. When tested, people with narcolepsy fall asleep rapidly, enter REM sleep early, and may awaken often during the night. The polysomnogram also helps to detect other possible sleep disorders that could cause daytime sleepiness.

The Epworth Sleepiness Scale is a brief questionnaire that is administered to determine the likelihood of the presence of a sleep disorder, including narcolepsy.

For the multiple sleep latency test, a person is given a chance to sleep every 2 hours during normal wake times. Observations are made of the time taken to reach various stages of sleep (sleep onset latency). This test measures the degree of daytime sleepiness and also detects how soon REM sleep begins. Again, people with narcolepsy fall asleep rapidly and enter REM sleep early. Occasionally, a multiple sleep latency test can result in a false-negative for a narcoleptic.[25]

Recent research has also revealed the possibility of measuring hypocretin levels in a patient's cerebrospinal fluid to diagnose narcolepsy[26], with abnormally low levels serving as a strong indicator of the disorder. This test can be useful when MSLT results are inconclusive or difficult to interpret.[27] However, the test requires patients to undergo a spinal tap to actually extract the cerebrospinal fluid.

Treatment

Patients with narcolepsy can be substantially helped, but not cured.[28] Treatment is tailored to the individual, based on symptoms and therapeutic response. The time required to achieve optimal control of symptoms is highly variable, and may take several months or longer. Medication adjustments are frequently necessary, and complete control of symptoms is seldom possible. While oral medications are the mainstay of formal narcolepsy treatment, lifestyle changes are also important.

The main treatment of excessive daytime sleepiness in narcolepsy is central nervous system stimulants such as methylphenidate, amphetamine, methamphetamine, modafinil (Provigil), a new stimulant with a different pharmacologic mechanism, and/or armodafinil (Nuvigil). In Fall 2007 an alert for severe adverse skin reactions to modafinil was issued by the FDA.[29] Other medications used are codeine[30] and selegiline.[31] Another drug that is used is atomoxetine[32] (Strattera), a non-stimulant and norepinephrine reuptake inhibitor (NRI), that has little or no abuse potential. In many cases, planned regular short naps can reduce the need for pharmacological treatment of the EDS but only improve symptoms for a short duration. A 120 minute nap provided benefit for 3 hours in patient alertness where as a 15 minute provided no benefit.[33]

Cataplexy and other REM-sleep symptoms are frequently treated with tricyclic antidepressants such as clomipramine, imipramine, or protriptyline, as well as other drugs that suppress REM sleep. Venlafaxine (branded as Effexor XR by Wyeth Pharmaceuticals), an antidepressant which blocks the reuptake of serotonin and

norepinephrine, has shown usefulness in managing symptoms of cataplexy,[34] however, it has notable side-effects including sleep disruption.[*citation needed*]

Another treatment option for narcolepsy is Xyrem (sodium oxybate) oral solution. Xyrem is a prescription medication manufactured by Jazz Pharmaceuticals, and is approved by the U.S. Food and Drug Administration (FDA) for the treatment of cataplexy associated with narcolepsy[35] and Excessive Daytime Sleepiness (EDS) associated with narcolepsy.[36] The American Academy of Sleep Medicine (AASM) recently recognized Xyrem as a standard of care for the treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy in its Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin.[37]

Using stimulants to mask daytime sleepiness does not address the actual cause of the problem. Stimulants may provide some assistance with daytime activity, but the underlying cause will remain and potentially worsen over time due to the stimulant itself becoming an obstruction to delta wave sleep periods. Lifestyle changes involving reduced stress, more exercise (especially for overweight persons experiencing EDS caused by sleep apnea and snoring) and less stimulant intake (such as coffee and nicotine) are likely to be ideal forms of assistive treatment. Some people with narcolepsy have a nocturnal body clock and are helped by selecting an occupation that properly coincides with their body's natural sleep cycle (such as sleeping in the day and working at night). This allows sufferers to avoid the need to force themselves into the more common 9 to 5 schedule that their body is unable to maintain, and avoids the need to take stimulants to remain active during the times when their bodies are inclined to rest.

In addition to drug therapy, an important part of treatment is scheduling short naps (10 to 15 minutes) two to three times per day to help control excessive daytime sleepiness and help the person stay as alert as possible.[*citation needed*] Daytime naps are not a replacement for nighttime sleep, especially if a person's body is natively inclined towards a nocturnal life cycle. Ongoing communication between the health care provider, patient, and the patient's family members is important for optimal management of narcolepsy.

Finally, a recent study reported that transplantation of hypocretin neurons into the pontine reticular formation in rats is feasible, indicating the development of alternative therapeutic strategies in addition to pharmacological interventions.[38]

Epidemiology

In the United States, it is estimated that this condition afflicts as many as 200,000 Americans,[39] but fewer than 50,000 are diagnosed. It is as widespread as Parkinson's disease or multiple sclerosis and more prevalent than cystic fibrosis, but it is less well known. Narcolepsy is often mistaken for depression, epilepsy, or the side effects of medications. It can also be mistaken for poor sleeping habits, recreational drug use, or laziness. Narcolepsy can occur in both men and women at any age, although its symptoms are usually first noticed in teenagers or young adults. There is strong evidence

that narcolepsy may run in families; around 10 percent of people diagnosed with narcolepsy with cataplexy have a close relative with this neurological disorder.[1]

Narcolepsy has its typical onset in adolescence and young adulthood. There is an average 15-year delay between onset and correct diagnosis which may contribute substantially to the disabling features of the disorder. Cognitive, educational, occupational, and psychosocial problems associated with the excessive daytime sleepiness of narcolepsy have been documented. For these to occur in the crucial teen years when education, development of self-image, and development of occupational choice are taking place is especially devastating. While cognitive impairment does occur, it may only be a reflection of the excessive daytime somnolence.[*citation needed*]

The prevalence of narcolepsy is about 1 per 2,000 persons.[39] It is a reason for patient visits to sleep disorder centers, and with its onset in adolescence, it is also a major cause of learning difficulty and absenteeism from school. Normal teenagers often already experience excessive daytime sleepiness because of a maturational increase in physiological sleep tendency accentuated by multiple educational and social pressures; this may be disabling with the addition of narcolepsy symptoms in susceptible teenagers. In clinical practice, the differentiation between narcolepsy and other conditions characterized by excessive somnolence may be difficult. Treatment options are currently limited. There is a paucity in the literature of controlled double-blind studies of possible effective drugs or other forms of therapy. Mechanisms of action of some of the few available therapeutic agents have been explored but detailed studies of mechanisms of action are needed before new classes of therapeutic agents can be developed. Narcolepsy is an underdiagnosed condition in the general population. This is partly because its severity varies from obvious to barely noticeable. Some people with narcolepsy do not suffer from loss of muscle control. Others may only feel sleepy in the evenings.

Society and culture

Depictions of the disorder in fiction and pop culture can range greatly in the accuracy of how they portray the symptoms. Narcolepsy is often depicted in an exaggerated fashion in comedy films or TV shows. Also in the movie *Rat Race*, one of the main characters (Enrico Pollini, played by Rowan Atkinson) has narcolepsy.

The Little Sleep, a detective novel by Paul Tremblay, portrayed the main character, Mark G., as having narcolepsy. The character deals with daily, even hourly frustrations due to the general cognitive fog, not being able to trust his own memory and even not being able to drive. Mark shares the frustration felt by many with narcolepsy, that his disease is not taken seriously and that he is "the punch line in a joke".