

NARCOLEPSY

By Daniel T. Layish, MD



Narcolepsy is the second most common cause of excessive daytime sleepiness (after obstructive sleep apnea). Narcolepsy is a clinical syndrome characterized by daytime sleepiness as well as cataplexy, hypnagogic hallucinations, and sleep paralysis. Narcolepsy is essentially a disorder of sleep-wake control. It involves both elements of sleep intruding into wakefulness and elements of wakefulness intruding into sleep. Only one-third of narcolepsy patients will have the entire syndrome of hypersomnolence, cataplexy, hypnagogic hallucinations and sleep paralysis. Therefore, narcolepsy needs to be considered even among people who only present with hypersomnolence. Cataplexy is defined as muscle weakness triggered by strong emotion such as laughter. Cataplexy can be dramatic and can sometimes lead to extensive workup to exclude cardiovascular disease or other neurologic processes. However, a careful history should be able to identify a true cataplectic attack. Sleep paralysis typically involves the inability to move for one or two minutes immediately after awakening or just before falling asleep. This phenomenon can occur in otherwise normal individuals (without narcolepsy). Sleep paralysis can be an extremely frightening symptom to a person who has not been educated about its cause and provided with reassurance. In normal REM sleep, skeletal muscle paralysis occurs. Therefore, sleep paralysis would be an example of a REM sleep phenomenon intruding into wakefulness.

Narcolepsy is equally common among men and women. It typically begins during the teens or early 20s, but may occur as early as five years of age or after 40 years of age. Narcolepsy with cataplexy has a prevalence of between 25 and 50 per 100,000 population. Narcolepsy without cataplexy is not as well studied, but is felt to have a similar prevalence. Recent research has shown that narcolepsy results from the loss of certain neuropeptides: orexin-A and orexin-B (also known as hypocretin-1 and hypocretin-2). These neurotransmitters are produced in the lateral hypothalamus. Under normal circumstances, the orexins are released during wakefulness and function to stabilize wakefulness and prevent inappropriate transition into rapid eye movement (REM) sleep. Individuals who have narcolepsy with cataplexy have approximately 90% reduction in the number of hypothalamic neurons producing orexins (with little or no detectable orexin-A in their cerebrospinal fluid). Interestingly, narcolepsy without cataplexy appears to have a different cause because these patients have normal cerebrospinal fluid orexin-A levels.

Genetic factors appear to play a role in narcolepsy. The DQB1*0602 haplotype is present in 95% of narcoleptics with cataplexy. However, environmental factors also play a role. For example, only 25% of affected monozygotic twins are concordant for narcolepsy. One theory is that narcolepsy may be triggered by an autoimmune process, which targets orexin neurons. Interestingly, the onset of narcolepsy is highest in the spring, which may suggest a winter infection. Narcolepsy has also been

associated with lesions of the posterior hypothalamus and mid brain such as tumors and vascular malformations as well as cerebrovascular accidents. This phenomenon is termed secondary narcolepsy.

Patients with narcolepsy actually do NOT sleep more hours than healthy individuals over a 24-hour period. Sleepiness associated with narcolepsy typically improves with naps. Indeed, naps maybe part of the treatment plan for a patient with narcolepsy. Typically, a patient with narcolepsy will have an Epworth Sleepiness Score above 15. An Epworth score above 10 is considered to be abnormal and consistent with excessive daytime sleepiness. The maximum score on the Epworth Sleepiness Scale is 24. Cataplexy develops within three to five years of the onset of sleepiness in 60% of people with narcolepsy. The muscle weakness in cataplexy is often partial affecting the face, neck and knees. Consciousness remains intact during cataplexy.

Hypnagogic hallucinations are vivid and often frightening visual, tactile, or auditory hallucinations that occur as an individual is falling asleep. Again, this dream like state is felt to be an intrusion of a REM phenomenon into wakefulness. Similar hallucinations that occur upon awakening are termed hypnopompic hallucinations. Hypnopompic hallucinations are less common than hypnagogic hallucinations in narcolepsy. Narcoleptics also typically have fragmented sleep with frequent awakenings. It is important to remember that people with narcolepsy have a higher than expected incidence of other sleep disorders such as obstructive sleep apnea, periodic limb movements of sleep, sleep walking, etc. This may reflect a referral bias to some extent. There is also a high prevalence of depression in individuals with narcolepsy.

The diagnosis of narcolepsy involves a careful history and physical exam followed by objective testing. A polysomnogram (sleep study) is important to exclude alternative and/or coexisting causes of chronic daytime sleepiness. This should be followed by a Multiple Sleep Latency Test (MSLT). The MSLT is a series of nap trials. The MSLT will provide a mean sleep latency and also identify episodes of sleep onset REM (SOREM). It is important that stimulant and other psychoactive medications are stopped for approximately one week before testing, and antidepressants should be stopped for at least three weeks before testing to avoid REM rebound effects.

On the sleep study, a patient with narcolepsy typically shows frequent awakenings with mildly reduced sleep efficiency and early onset of REM sleep (REM latency) typically less than 20 minutes. Normal REM latency is between 80-100 minutes after sleep onset. On the MSLT, normal sleep latency is usually 10-15 minutes. Patients with narcolepsy often have a mean sleep latency below eight minutes. Two episodes of sleep onset REM on an MSLT would be strongly suggestive of narcolepsy. The MSLT is

only valid if the sleep study preceding it demonstrates at least six hours of sleep. The MSLT can be falsely negative in 20-30% of cases and should be repeated if the history is strongly suggestive of narcolepsy. Sleep onset REM can occur with other disorders that increase REM sleep pressure such as untreated sleep apnea, insufficient sleep or circadian rhythm disturbances. HLA testing and measurement of Orexin in the cerebrospinal fluid are not used routinely for clinical diagnosis of narcolepsy. More than 99% of DQB1*0602 positive individuals do not have narcolepsy. Hypnagogic hallucinations can occur in many situations besides narcolepsy, including insufficient sleep, sleep apnea, circadian rhythm disorders and anxiety. They can also occur as a rebound phenomenon in patients taking REM suppressing substances (such as antidepressants). In contrast with hallucination seen in psychotic patients, people with hypnagogic hallucinations can usually recognize them as a dream like phenomenon.

NARCOLEPSY TREATMENT

Certain drugs should be avoided in patients with narcolepsy because they can worsen daytime sleepiness. Examples include benzodiazepines, opioids, antipsychotics and alcohol. Prazosin and other alpha-1 antagonist can worsen cataplexy. Sleep deprivation can worsen narcolepsy symptoms, therefore good sleep hygiene should be encouraged. Persistently sleepy patients need to be counseled to avoid potentially dangerous activity such as driving or operating machinery. Pharmacologic therapy may include Modafinil, this medication is well tolerated and illicit use is rare. It is a non-amphetamine (wakefulness promoting agent). A typical starting dose of Modafinil would be 200 mg every morning. Some patients require higher doses, for example, 300 mg or 400 mg in the morning and some patients benefit from divided doses with a second dose in the afternoon. Possible side effects of Modafinil include headache, nausea, dry mouth, anorexia and diarrhea. High doses of Modafinil may increase blood pressure. Modafinil may decrease the effectiveness of oral contraceptives, therefore, woman of childbearing age who take Modafinil need to be advised to use an alternative method of contraception. Another option besides Modafinil is Armodafinil, which is a similar product with a longer half life. Typical dosing would be 150 mg in the morning.

Methylphenidate is felt to be a second line agent because of its sympathomimetic side effects. Amphetamines such as dextroamphetamine and mixed amphetamine salts such as Adderall have also been used in narcolepsy. Antidepressants that suppress REM sleep may be helpful in reducing cataplexy. Sodium oxybate, which is the sodium salt of gamma-Hydroxybutyrate (GHB) is a very good choice for patients who have severe cataplexy. This medication also improves the quality of nighttime sleep and reduces daytime sleepiness. Sodium oxybate is given as a liquid at bedtime with a second dose approximately three hours after bedtime. The second dose is required due to the short half life of sodium oxybate. Combined use of sodium oxybate with alcohol and sedatives or hypnotics is contraindicated due to the potential for respiratory depression. Because of the potential for abuse (GHB has gained notoriety as a "date rape drug") access to sodium oxybate is restricted to a single highly regulated pharmacy.

CONCLUSION:

Narcolepsy is a unique and important sleep disorder which is currently under diagnosed. Increased awareness of this entity should lead to improved ability to provide specific therapy. The study of Narcolepsy teaches us quite a bit about regulation of REM sleep.

Daniel Layish, MD, graduated magna cum laude from Boston University Medical School in 1990. He then completed an Internal Medicine Residency at Barnes Hospital (Washington University) in St. Louis, Missouri and a Pulmonary/Critical Care Fellowship at Duke University in Durham, North Carolina. Since 1997, he has been a member of the Central Florida Pulmonary Group in Orlando. He currently serves as Medical Director of the Intensive Care Unit, Respiratory Therapy and Pulmonary Rehab at Winter Park Memorial Hospital. Dr. Layish may be contacted at 407-841-1100 or by visiting www.cfpulmonary.com. ■

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