Narcolepsy

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Narcolepsy afflicts more than 200,000 Americans. In most cases the first symptom of the disease, excessive daytime sleepiness, develops during childhood or adolescence. This initial presentation is followed by cataplexy or other auxiliary symptoms several years later. Not infrequently, many years pass before the proper diagnosis of narcolepsy is made. Narcolepsy is a chronic lifelong disease without periods of remission. Excessive daytime sleepiness, inappropriate sleep attacks, and the pathognomonic symptom of cataplexy, are diagnostic of narcolepsy. Confirmation of the disease is made by a multiple sleep latency test. Although still not being used for diagnostic purposes, the association between narcolepsy and the human leukocyte group A (HLA) antigen DR2 is the strongest so far described for any disease. With the help of psychosocial support, therapeutic naps, and medications, the patient with narcolepsy may be able to lead a normal life. Methylphenidate and imipramine are the two most widely used drugs for the treatment of daytime somnolence and cataplexy, respectively.

Key words. Sleep, REM; narcolepsy; hallucination; cataplexy; sleep disorders.
J Fam Pract 1993; 36:207-213.

The awareness of sleep disorders has greatly increased during the past two decades.[1–6] Sleep apnea and narcolepsy are the two most frequently encountered causes of excessive daytime somnolence in sleep disorder centers. Sleep apnea is a potentially life-threatening disorder with many complications including cardiac arrhythmias and systemic and pulmonary hypertension leading to right-sided heart failure.[7,8] On the other hand, narcolepsy is a chronic, nonfatal, but often debilitating disease, causing difficulty throughout life: problems at work, broken marriages, low self-esteem, psychological and emotional disturbances, and industrial and automobile accidents.[9–11]

Gelineu first used the term *narcolepsy* in 1880, and Yoss and Daly described the tetrad of narcolepsy, cataplexy, hypnagogic hallucinations, and sleep paralysis in 1957.[12] Narcolepsy is now characterized by dysfunction of rapid eye movement (REM) sleep.[13,14] In narcolepsy, REM sleep occurs suddenly during the awake state. The neurophysiologic mechanisms of REM sleep cause the symptoms of narcolepsy.[15–19]

Submitted, revised, April 1, 1992.

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 ISSN 0094-3509

Prevalence

Narcolepsy is not a rare disease. In one survey, physicians reported narcolepsy in 0.5% of their adult patients.[20] Several large studies have reported an incidence of 1 per 1000 with both sexes affected equally.[21–23] It has been estimated that 100,000 to 200,000 people in the United States have narcolepsy.

Clinical Features

Narcolepsy can be diagnosed clinically by its typical symptoms (Table 1). The two primary symptoms are excessive daytime sleepiness, with irresistible sleep attacks, and cataplexy. Auxiliary symptoms occur in 70% to 80% of patients with narcolepsy, the most important being hypnagogic hallucinations, sleep paralysis, disrupted nocturnal sleep, and automatic behavior. Those patients exhibiting no auxiliary symptoms are considered to have so-called independent narcolepsy.[24–26] In one study of 170 patients, all had daytime hypersomnolence, 10% experienced daytime sleepiness alone, 20% to 25% had daytime sleepiness and one auxiliary symptom, and 50% had daytime sleepiness and all three auxiliary symptoms.[27]

The major symptoms of narcolepsy are caused by an inappropriate intrusion of REM sleep into a person's waking hours. The sleep attacks are complete REM sleep

Table 1. Common Symptoms of Narcolepsy

Symptoms	Patients Affected, %
Excessive daytime somnolence	100
Disturbed sleep	90
Cataplexy	80
Hypnagogic hallucinations	70
Sleep paralysis	60
Automatic behavior	50

episodes. The muscle weakness of cataplexy and sleep paralysis appear to be identical to the muscle inhibition occurring during REM sleep, and the hallucinations are dreamlike experiences during partial wakefulness.[28]

The sleep attacks appear as clinically normal sleep, are characteristically brief, but may last from a few seconds to 30 minutes, and are usually refreshing.[29,30] The attacks are often precipitated by passive recreation such as reading or watching television, which may induce sleepiness even in normal people. Patients with narcolepsy, however, may experience attacks in situations considered to be stimulating such as playing games or during conversation. The patients can be easily awakened from these sleep episodes by auditory or tactile stimulation. A refractory period of alertness of 1 to 4 hours follows each attack.

Cataplexy, the pathognomonic symptom of narcolepsy, is present in 80% of patients. Cataplexy is a sudden brief loss of muscle control usually precipitated by strong emotions such as laughter, surprise, elation, or anger, although in rare instances it may occur without an identifiable cause.[6] Many narcoleptics develop a flat affect in an attempt to suppress the emotions that trigger cataplectic attacks.[30] Thus, many narcoleptics find it difficult to interact normally in social situations. Cataplexy generally involves only the voluntary muscles, usually sparing extraocular and respiratory muscles. Patients typically remain fully conscious during the attack and have complete recall of the episodes.

Twenty-five percent to 50% of patients with narcolepsy exhibit sleep paralysis and hypnagogic hallucinations that occur during the transition periods between sleeping and waking.[31] Hypnagogic hallucinations are vivid, usually frightening experiences occurring at the onset of sleep. These episodes usually incorporate elements of the patient's environment; therefore, they are labeled hallucinations rather than dreams. The hallucinations are usually visual or auditory but may be tactile and are often quite complex. With sleep paralysis, there is a temporary loss of muscle tone and an inability to move. If both occur simultaneously, patients are unable to move or cry out in response to the hallucinatory danger; however, either type of episode may be interrupted if the patient is touched.

About 50% of narcoleptic patients have automatic behavior with complete retrograde amnesia.[32] There may be brief lapses in the middle of conversation or during more complex behavior such as walking, driving, or continuing routine work for a period of time. The lapses most often occur during the late afternoon and evening.

Patients with narcolepsy fall asleep easily but usually report frequent nighttime awakenings. The total wake time and number of awakenings during sleep increase linearly with age. Sleep efficiency, a measurement of the time a patient actually sleeps while in bed, is decreased early in life and shows a more rapid decline compared with that of the general population.[27] The incidence of periodic leg movements during nocturnal sleep is also higher than in the general population. Approximately 80% of narcoleptic patients have periodic hunger pangs and cravings for sweet foods, and these symptoms may awaken them during the night.[15]

Blurred vision was reported as the third most common complaint among one group of narcoleptic patients seen by ophthalmologists. Intermittent diplopia also occurs in these patients.[33–36]

Approximately one half of the patients with narcolepsy have memory problems, particularly loss of recent memory.[37,38] It is hypothesized that "microsleep" occurring during the daytime interferes with perception and acquisition of information.[39] Objective evaluations have shown that narcoleptics do have more difficulty in maintaining attention, although the results of tests of concentration and memory are not significantly different from those of controls.[40] However, normal results on concentration and memory tests have been attributed to the use of stimulants by an estimated 77% of narcolepsy patients.

Onset of Symptoms

Although narcolepsy may occur at any age, onset commonly occurs during the second decade of life.[27,41,42] The highest incidence is among people 15 to 25 years of age. Excessive daytime sleepiness and sleep attacks are the initial symptoms of narcolepsy, with auxiliary symptoms generally appearing several years after the onset of sleep attacks. A gap of over 40 years has been reported between the onset of daytime sleepiness and the first attack of cataplexy.[43]

Table 2. Diagnostic Tests for Narcolepsy

Multiple Sleep Latency Test (MSLT)
Variants of MSLT
Single 45-minute test
Two 1-hour tests
Maintenance-of-wakefulness test
Evoked potential
Pupillometry

Laboratory Diagnosis

History and physical examination are helpful in establishing the clinical diagnosis of narcolepsy and ruling out related disorders.[44,45] A nocturnal polysomnogram is usually done initially to document the adequacy of sleep and for evaluation of sleep apneas, which are more common causes of daytime somnolence.

A number of laboratory tests have been used in confirming the diagnosis of narcolepsy (Table 2). The Multiple Sleep Latency Test (MSLT) is the primary test used for diagnosis.[46–48] This test assesses two major components of narcolepsy: hypersomnolence and REM-onset sleep. Usually, five 20-minute nap periods, each separated by 2 hours, are monitored. Hypersomnolence is established if the patient falls asleep within 5 minutes. In normal people, sleep latency (the time required to fall asleep) is usually more than 10 minutes; and REM, which usually begins 75 to 90 minutes after going to sleep, does not occur during these short nap periods. If the mean sleep latency is less than 5 minutes (ie, patients fall asleep quickly) and REM sleep is seen in two of the five nap studies (ie, patients go quickly into REM sleep), a diagnosis of narcolepsy is strongly suggested. Sleep-onset REM periods, though characteristic of narcolepsy, have been described in other diseases. These periods occur quite frequently in patients with sleep apnea, in patients experiencing drug withdrawal, and in normal subjects with irregular sleep schedules.

Many variants of the standard MSLT have been suggested. The degree of excessive daytime somnolence can be assessed by a single 45-minute recording to determine the latencies of various sleep stages.[49] This test establishes the degree of hypersomnolence, but does not differentiate from other disorders that can cause hypersomnolence. The use of two 1-hour polysomnographic recordings has been suggested as an alternative diagnostic test.[50] Abnormally short sleep latency or REM onset of less than 10 minutes on either of the two recordings has both high diagnostic sensitivity (84%) and high specificity (80%). Another variant of MSLT is the maintenance-of-wakefulness test, measuring the patient's ability to remain awake in a quiet room.[51] This test has been used to evaluate the efficacy of various drugs in maintaining wakefulness. Browman et al[52] evaluated the MSLT and the maintenance-of-wakefulness test by continuous 48-hour polysomnographic recordings, and found that both tests differentiated narcolepsy patients from controls.

Broughton et al[53] have suggested using auditory evoked potentials for the evaluation of sleepiness. This test may be helpful in evaluating pharmacologic agents; however, in a follow-up study,[54] Broughton found evoked potentials to be less sensitive and less accurate than MSLT.

Pupillometry measures the ability of the subjects to remain alert in the dark.[55] The pupillary diameter is measured by an infrared pupillograph. The alert, well-rested person has pupils of larger diameter that vary little in size during a 15-minute tracing. In patients with hypersomnolence, the pupils show progressive constriction. Pupillometry is relatively inexpensive and less time consuming than MSLT; however, it has not been standardized in normal subjects nor compared with other tests for accuracy. In a recent study, pupil size showed a significantly greater number of spontaneous oscillations per minute in narcoleptics compared with controls; however, a variety of methodological and statistical shortcomings remain with pupillometric tests.[56]

Narcolepsy and HLA-DR2

Recently a strong association between narcolepsy and the HLA antigens has been demonstrated. The HLA region is located on the short arm of human chromosome 6. The association between narcolepsy and HLA-DR2 and HLA-DW1 antigens is the strongest association so far described for any disease.[57] Reports from Japan, France, and England show a near 100% association between narcolepsy and the major histocompatibility complex class II gene product, HLA-DR2.[58–63] Other studies show the association ranging from 90% to 98%.[64,65] About one third of the normal healthy individuals are also positive for HLA-DR2; therefore the specificity of this test is low. Because of the low specificity, tissue typing is not helpful in making the diagnosis. Because of this high sensitivity, a negative test practically rules out the diagnosis of narcolepsy. Narcolepsy with negative HLA-DR2 has been described[66–67]; however, the possibility exists that the patient with negative HLA-DR2 may actually have some other disease.

Individuals with HLA-DR2 are at a higher risk of developing narcolepsy than the general population.[65] Identification of a specific submolecular fraction or epit-

ome of the whole DR2 molecule might permit more accurate confirmation of the diagnosis than polysomnography, and prenatal diagnosis of narcolepsy by amniocentesis might be possible in the future.[9]

Differential Diagnosis

Inadequate sleep is a common cause of excessive daytime sleepiness. Other than narcolepsy, the principal causes of excessive daytime sleepiness are sleep apnea syndromes, narcolepsy with sleep apnea, idiopathic CNS hypersomnolence, and periodic movements in sleep. Other considerations are hypothyroidism, hypoglycemia, abuse of sedative drugs, metabolic encephalopathy, encephalitis, and brain tumor. Occasionally, narcolepsy is confused with petit mal or psychomotor seizures, depending on whether cataplexy or automatic behavior is exhibited. At times patients have been considered schizophrenic because of bizarre mentation and visual or auditory hallucinations at the onset of sleep. Kleine-Levin syndrome and hypersomnia linked to menstruation are two rare causes to keep in mind when evaluating a confusing case of hypersomnia.[68,69] Occasionally, because of certain common features, multiple sclerosis may be labeled falsely as narcolepsy, or vice versa.[70]

Treatment

The aim of treating a narcoleptic patient is to relieve the symptoms that interfere with day-to-day functioning and to reassure the patient and family. With the help of psychosocial counseling, therapeutic naps, and medication, the patient may be able to perform at an optimal level.

Narcolepsy is frequently misunderstood.[31,38] Parents, teachers, spouses, and coworkers often assign motivational causes, further dampening patient self-esteem. It must be explained to the patient and his or her family members, friends, and coworkers that narcolepsy is a physical illness which the patient cannot voluntarily control. Family and group therapy may be valuable in helping patients accept the illness and establish reasonable expectations.

For milder cases of narcolepsy, a schedule of several short naps during the day will improve alertness considerably and reduce daytime sleepiness. Increasing the length of the nap produces no increase in alertness.[71]

The objective of pharmacologic treatment of narcolepsy is to alleviate the two most troublesome symptoms, sleep attacks and cataplexy. Although cataplexy is present in 80% of patients with narcolepsy, often only one symptom, either sleep attacks or cataplexy, interferes with overall functioning. Hypersomnolence is treated with CNS stimulants (eg, methylphenidate), and cataplexy is treated with REM-suppressing antidepressants (eg, imipramine) (Table 3).[72,73] Despite recent advances in drug therapy of narcolepsy, methylphenidate and imipramine are still the most widely used and effective drugs.

Table 3. Drug Therapy for Narcolepsy

Drug	Usual 24-Hour Dose
For hypersomnolence	
Methylphenidate	10–60 mg
Dextroamphetamine	10–60 mg
Pemoline	18.75–112.5 mg
Mazindol	1–6 mg
Propranolol	40–120 mg
For cataplexy	
Imipramine	25–100 mg
Protriptyline	5–60 mg
Clomipramine	10–100 mg
Desipramine	25–100 mg
Fluoxetine	20–60 mg
Gammahydroxybutyrate	5–7 g
Viloxazine	50–100 mg

Methylphenidate at a dose of 20 mg/day (range 5 to 60 mg) is the drug of choice for hypersomnolence because of its prompt action and low incidence of side effects.[74,75] Late afternoon or evening doses should be avoided so as not to interfere with nighttime sleep. Other stimulants frequently in use are pemoline and dextroamphetamine.[28] Pemoline has behavioral effects similar to those of methylphenidate. Because of its 12-hour half-life, pemoline (18.75 to 112.5 mg) may be given once daily. It has a slower onset of action, and both its degree of stimulation and its side effects seem to be lower than those of methylphenidate and amphetamines. Occasionally pemoline initially worsens sleepiness for several hours after ingestion. Tolerance to pemoline usually does not develop.[76] Dextroamphetamine (10 to 60 mg daily) is often used and preferred by some. Drug dependence, amphetamine psychosis,[31] and even paradoxical sleepiness[6] can occur, but many patients can take stimulants without significant side effects.

Mitler et al[75] recently reported on the comparative efficacy of methylphenidate, pemoline, and protriptyline in patients with narcolepsy. Methylphenidate improved wakefulness but pemoline did not; however, pemoline improved performance ability more reliably than methylphenidate. Protriptyline improved neither wakefulness nor performance. Propranolol, a β-adrenergic blocker, has been reported to be effective in treating daytime hypersomnolence and sleep attacks, but tolerance develops rapidly.[77] Anecdotal reports suggest that codeine improves daytime hypersomnolence.[78]

The most common treatment for cataplexy is the tricyclic antidepressant imipramine. Antidepressants probably act by suppressing REM sleep. The effect of imipramine on REM sleep and on cataplexy is immediate and requires a lower dose than when it is used as an antidepressant.[6] Tricyclics with sedating properties such as imipramine should be given in the evening so as not to interact with the effect of stimulant medications. Usually 50 to 75 mg of imipramine can effectively control cataplexy, sleep paralysis, and hypnagogic hallucinations. Protriptyline (10 to 20 mg at night) has been reported to control both cataplexy and sleep attacks.[79] Protriptyline has become popular because of its effectiveness in treating cataplexy; and because it does not cause drowsiness, it can be given during the daytime. It is usually better tolerated than stimulant drugs by the elderly.[80] Anticholinergic side effects such as dry mouth, anorexia, sweating, hypotension, tachycardia, blurred vision, and sexual dysfunction can occur with the use of tricyclic compounds. When tricyclics are suddenly withdrawn, there can be a marked increase in cataplexy.

When cataplexy and sleepiness are both severe, analeptics and antidepressants may be combined, but careful titration and monitoring is mandatory in view of serious side effects.[31] Methylphenidate can potentiate the effect of tricyclics by interfering with hepatic metabolism.

Among the newer treatments for narcolepsy, the most promising is gamma hydroxybutyrate (GHB), which occurs naturally in the hypothalamus and basal ganglia of the brain. It is effective in treating symptoms of cataplexy but also has some beneficial effect on daytime alertness.[81,82] A recent study shows that GHB taken at night in conjunction with low doses of stimulants during the day rapidly alleviates the symptoms of narcolepsy in most patients.[83] Nighttime sleep disruption is improved by GHB as it consolidates sleep by increasing slow-wave sleep and reduces nocturnal awakenings.[84] The improved quality of nighttime sleep appears to reduce other REM-related manifestations of narcolepsy.

Viloxazine hydrochloride, derived from propranolol, has been shown to inhibit REM sleep, cataplexy, sleep attacks, and other auxiliary symptoms, but does not increase alertness.[85] It seems to be better tolerated in elderly patients. Mazindol, a new anorectic, seems to be effective in reducing excessive daytime sleepiness, and perhaps cataplexy.[86,87]

Conclusions

Narcolepsy should be suspected in all patients with chronic daytime hypersomnolence, particularly if cataplexy or other auxiliary symptoms are present. If an irregular sleep-wake cycle or drug use is not the cause of the somnolence, then the main possibilities remaining are sleep apnea and narcolepsy. Since narcolepsy is a lifelong disease and the treatment often includes stimulant medications, the diagnosis must be firmly established before starting drug therapy. The initial diagnostic test is usually a nocturnal polysomnogram to rule out sleep apnea. The reference standard in making a diagnosis of narcolepsy at the present time is the MSLT. HLA typing alone cannot be relied upon because of the high prevalence of DR2 in the general population. Therapeutic naps and medications can usually control the symptoms of narcolepsy. Many times additional effort is required to educate the family, employers, and coworkers about the disease and the therapy.

Acknowledgments

The authors are grateful to Dr W.A. Speir for helpful review of the manuscript and to Kay McCoy for expert secretarial assistance.

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