DIAGNOSIS AND TREATMENT OF THE NARCOLEPSY SYNDROME

Analysis of Seventy-Five Case Records

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THE narcolepsy syndrome is known also as *Gélineau's disease, the Gélineau-Redlich syndrome, paroxysmal sleep,* and *sleep epilepsy.* Because of the comparative rarity of the disease and our lack of understanding of the term *narcolepsy,* we recently had difficulty in diagnosing several cases of the syndrome. This report undertakes to clarify the meaning of the term, to discuss the entity, and to report an analysis of 75 case records of narcoleptics treated at the Cleveland Clinic in the last nine years.

In the past it has been alleged that the sleep of the narcoleptic is paroxysmal in onset.[1] *Hypersomnolence* has frequently been used to describe the condition in which the patient is persistently drowsy without having actual sleeping spells, or in which he falls asleep perhaps only once a day while engaged in some activity. Yoss and Daly[2] recently defined narcolepsy as consisting of four components: (1) narcolepsy proper — "excessive and persistent sleepiness"; (2) cataplexy — muscular weakness induced by emotion; (3) sleep paralysis — transient, benign loss of muscle tone at the beginning or end of sleep; (4) hypnagogic hallucinations — usually vivid auditory or visual hallucinations or illusions occurring during day or night drowsiness, usually with sleep paralysis. We are essentially in agreement with their definition. In our 75 patients, excessive and persistent sleepiness occurred alone or in combination with other symptoms. *Figure 1* illustrates the incidence of the four components of the narcolepsy syndrome in our patients. (1) Narcolepsy (excessive sleepiness) was present in all 75 patients. (2) Cataplectic attacks in combination with other symptoms occurred in 51 patients. (3) Narcolepsy occurred alone in 24 patients. (4) Sleep paralysis with other symptoms was present in 10 patients. (5) Hypnagogic hallucinations with other symptoms occurred in 4 patients. (6) The full tetrad was present in 3 patients.

There were 47 men and 28 women in the series, from 20 to 70 years of age. Three patients stated that some other member of the family had symptoms of the narcolepsy syndrome.

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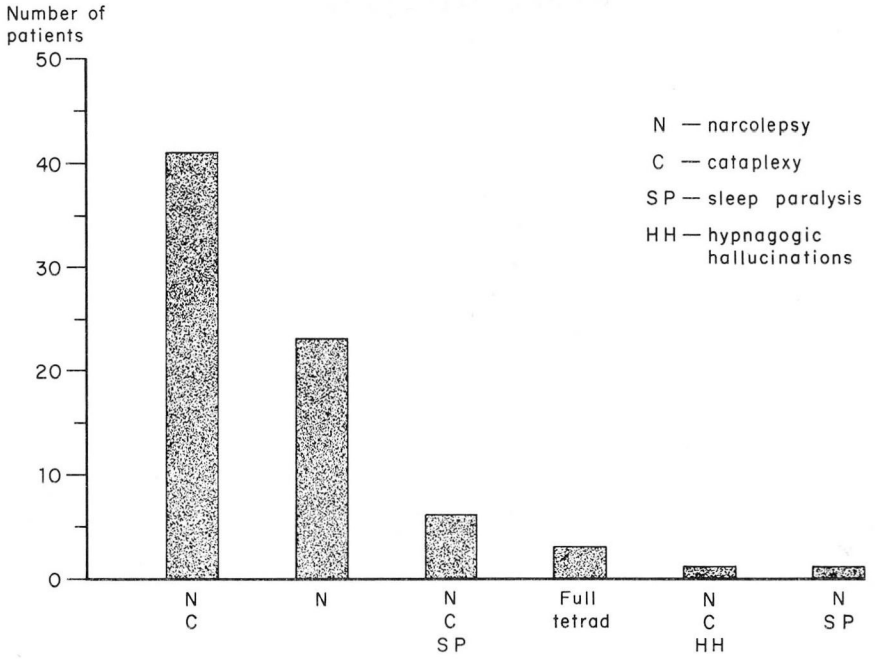

Fig. 1.

Analysis of 75 Case Records

Narcolepsy. The pathognomonic symptom of the syndrome is narcolepsy or excessive and persistent sleepiness. It emerges gradually; however, onset occurred by or before the second decade in 36 patients, and by the third decade in 54 patients *(Fig. 2).* The abnormal sleepiness may be classified on the basis of severity: (1) Constant drowsiness with ability to resist sleep but only at the expense of further drowsiness. (2) Mild sleepiness, rather persistent drowsiness with only rare episodes of sleep. (3) Moderate sleepiness, in which episodes of sleep overtake the person during the usual normal working hours and activities, such as driving, reading, sitting, watching a television program, or at the theater. The patients who fell asleep while driving cars usually were warned in time to stop for a short nap and were not fatigued, although several had serious accidents. (4) Severe sleepiness, episodes of sleep which overtake the person while he is eating, during conversation, while walking, or during situations that usually excite wakefulness, such as watching a baseball game or taking dictation. In 56 patients, onset of sleep occurred during physical activity. In patients with no history of onset of sleep during activity, cataplexy was present.

Patients with narcolepsy apparently suffer from a persistent, though fluctuating impairment of wakefulness; when this impairment is severe there are episodes

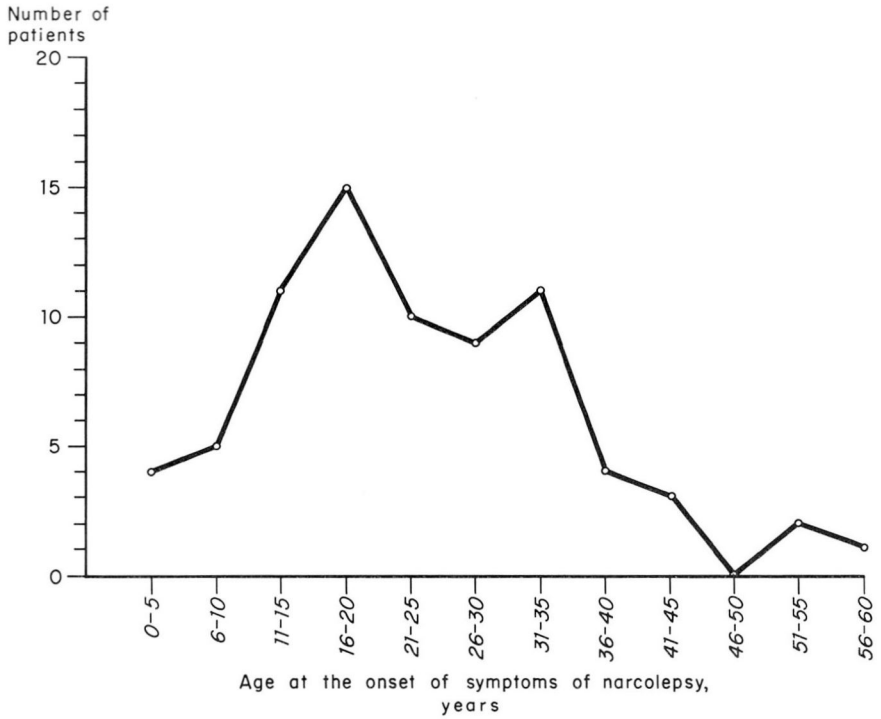

Fig. 2.

of great drowsiness or sleep. Only seven patients either were fatigable or felt constantly tired. Sleep came from no apparent cause and occurred at any time and under any circumstance, but most patients were subject to frequent episodes of sleep that were aggravated by conditions that bring on physiologic sleep, of which complete physical relaxation was the most frequent, although monotonous occupation was a frequent conditioning factor.

The onset of acute episodes of sleep ranged in rapidity from a drifting into sleep without warning (though rarely), to a gradual drowsiness that would herald sleep. The duration of the episodes ranged from a few seconds to several hours, but averaged from 10 to 20 minutes. Short episodes usually recurred during the day. Patients generally felt refreshed on waking. The period of night sleep was from 6 to 12 hours with an average of 8 hours of restful sleep. For nine patients night sleep was disturbed by nightmares, partial insomnia, or restlessness at some time during the course of narcolepsy. Three patients reported that sleep talking and somnambulism occurred.

Cataplexy. Cataplexy consists of muscular weakness induced by emotion; it occurred in 50 patients. The act of laughing induced cataplexy in 33 patients. The emotions of anger or surprise were also apt to induce an attack. Muscular

paresis ranged from a subjective sensation of weakness in one group of muscles to complete paralysis causing the patient to sink to the ground without losing consciousness. Only 16 patients fell to the ground and, in general, before most episodes the patients had sufficient warning and could break the fall by grasping some object. The duration of the attack rarely was longer than one minute. Cataplexy occurred as the first symptom in four patients. Narcolepsy and cataplexy generally were simultaneous in onset; however, in one patient episodes of cataplexy first occurred 16 years after the onset of narcolepsy.

Sleep paralysis. Sleep paralysis is a transient, benign loss of muscle tone at the beginning or the end of sleep and usually is associated with a distressingly clear consciousness. Ten patients experienced episodes of paralysis when drowsing off into sleep, or when waking from sleep but while still drowsy. The number of attacks was equally divided, as to correlation with time of sleep — during the day or night, or upon waking in the morning. The paralyses had the same clinical characteristic as cataplexy, usually lasted less than one minute, but in one patient paralysis remained for more than one hour. Paralysis usually was complete, although a few patients were able to open their eyes and one patient was able to utter a few words. The paralysis was flaccid, but frequently the patients described the sensation as that of feeling "stiff." Recovery was spontaneous or induced. Often a light touch from someone else was all that was needed to disrupt the attack; at times vigorous shaking was necessary.

Hypnagogic hallucinations. Hypnagogic hallucinations occurred in four patients, and were associated with either night or day drowsiness. The hallucinations usually occurred with sleep paralysis while going to sleep. They consisted of vivid visual and auditory experiences that were pleasant as often as unpleasant. Some patients re-experienced scenes from "horror movies." One patient remembered hearing her sister say, "Keep smoking and you will stay awake." One patient was overcome by sleep from the sounds of a bell coming closer and closer to him.

Diagnosis

The sole basis for diagnosis is the patient's history, that is, the presence of an excessive and persistent sleepiness. It varies from persistent drowsiness with ability to fight off sleep resulting in more drowsiness, through irresistible single daily attacks of sleep, to frequent episodes of irresistible sleep even while active.

Three other features help in the diagnosis: (1) cataplexy's being associated with narcolepsy in two thirds of the cases and consisting of attacks of muscular paresis rarely lasting longer than one minute and with clear consciousness; (2) sleep paralysis consisting of transient, benign attacks of total absence of voluntary movement at the beginning or end of sleep and usually of short duration; (3) hypnagogic hallucinations consisting of vivid auditory or visual hallucinations, or illusions occurring during day or night drowsiness usually with sleep paralysis.

In three fourths of the patients, sleep came on when they were active, and if the patients did not have narcolepsy associated with activity, they had unmistakable cataplexy.

Differential Diagnosis

Sources of errors. If some of the tetrad of symptoms is absent, or the physician fails to assign significance to the excessive sleepiness, or the patient is unable to describe his abnormality clearly enough to arouse suspicion in the physician's mind, the diagnosis of narcolepsy may be missed.

Anxiety tension states with fatigue. The most common erroneous diagnosis encountered in our series was that of neurotic fatigue. Only eight patients with narcolepsy had associated muscular and physical exhaustion that typifies the neurotic fatigue state. Patients with narcolepsy often sleep from 10 to 15 minutes and awake refreshed, in contrast to the neurotic who naps from two to three hours without obtaining relief of his fatigue. On careful questioning, patients with anxiety and fatigue will state that drowsiness is not present nor are periods of uncontrolled sleep; but some say they need extra sleep because of insomnia at night. When a patient says: "I'm always tired," or "I have no pep or energy," it behooves the physician to determine whether or not the patient has excessive or persistent sleepiness.

Hypothyroidism. The majority of patients with narcolepsy did not state that they had excessive sleepiness, but rather that they had "no pep," or were "tired all the time." These descriptive phrases may inadvertently mask the fact that they mean that they have "excessive sleepiness." When there is doubt as to the meaning, a determination of the basal metabolic rate will aid the clinician. A low rate may substantiate a tentative diagnosis of hypothyroidism. However, such values are not truly accurate, since the patient has not maintained a state of relaxed alertness. The lowered oxygen consumption results from the reduced oxygen requirement associated with the somnolent state and not from a true decrease in the basal metabolic rate. Objective measurements of thyroid function, in narcoleptics, such as the determinations of the protein-bound iodine or the thyroid uptake of radioiodine, have revealed that narcoleptics do not present chemical evidence of hypothyroidism.[2] No patient in our series showed improvement on treatment with thyroid extract.

Obesity. It has been emphasized that obesity as an accompaniment of narcolepsy is additional evidence of an endocrine disorder. In our patients the incidence of obesity in women was no greater than in women in the general population. However, of the 47 men, 15 were 20 per cent or more overweight, and increase in appetite or a gain in weight was not associated with the onset of the disease.

Epilepsy. A diagnosis of epilepsy was under consideration when the patient stated that he *suddenly* fell asleep or blacked out, or when the cataplectic spells were considered akinetic seizures.[3] By careful questioning it was found that all

narcoleptic patients were drowsy preceding their sleeping spells, and were not suddenly overcome with sleep. The patient who mentions blackouts, appears to be a normal person who sleeps with quiet respirations and can be easily aroused by external stimuli. It is not a paroxysmal epileptic unconsciousness from which the patient cannot be aroused. Cataplectic attacks were related to emotional stimuli, and the patients were clearly conscious.

Double vision. Several patients in our series had double vision, thereby arousing suspicions of the presence of myasthenia gravis. Diplopia occurred only with extreme drowsiness. Yoss and Daly[2] stated that patients who had double vision had a relatively high degree of exophoria. The ability to maintain fusion is reduced during drowsiness, thus resulting in latent ocular imbalance and double vision.

Physical and neurologic examination. The results of the examinations were within the normal range and did not aid in establishing the diagnosis of narcolepsy. Lumbar punctures showed no essential abnormalities of the pressure or of the composition of the cerebrospinal fluid. The skull and chest appeared to be essentially normal as shown on roentgenograms. Results of hematologic studies, glucose tolerance tests, blood calcium and phosphorus estimations, serologic tests, and fasting blood sugar values were within normal limits.

Electroencephalograms. Electroencephalograms were recorded for 42 patients, 9 of whom were in the group who had cataplexy, and 33 who had only narcolepsy. Of the 33 patients with narcolepsy, 31 had well-developed background alpha activity except for two patients whose records were obtained mainly while they were asleep. Of the two exceptions, one patient had a background of from 7 to 8 cps. of activity, though well-developed, and the other had a good alpha activity upon hyperventilation for three minutes. According to these records of narcolepsy, 32 patients had what was considered to be excessive amounts of theta slow activity on overbreathing for three minutes. Three of these had both resting and hyperventilation excess in theta slow activity. Of the nine records in the cataplexy group, four showed the presence of excessive slow activity on the resting record or during hyperventilation; the other five records showed that slow activity was normal.

Drowsiness was not studied separately because it could not be dissociated from that caused by the normally used sedatives before recording electroencephalograms. Data in seven records of the narcolepsy group were normal in all respects except for brief runs of moderate amplitude theta activity during the normal background. This was further observed in two of the nine patients in the cataplexy group, both of whom had otherwise normal records. From these observations it is suggested that the electroencephalographic pattern, though not pathognomonic for these conditions, is helpful in that there may be evidence of excessive, slow activity on rest or hyperventilation in about half the patients. In the negative evaluation it would be useful in excluding other neurologic abnormalities from prime consideration even though the diagnosis is made on purely clinical evidence.

Course and Treatment

In our patients, after one episode of narcolepsy the excessive sleepiness persisted relatively unchanged for the duration of the follow-up. Remissions of a few months' duration at the onset were rare. The treatment of narcolepsy is symptomatic and employs the use of agrypnotic drugs. Good results were obtained from dextroamphetamine sulfate,* *d*-Desoxyephedrine hydrochloride,† or amphetamine sulfate.‡ Methylphenidate hydrochloride§ was administered to only a few patients. When a satisfactory regimen was established, 56 of the patients reported excellent relief of excessive sleepiness. Cataplexy was not consistently relieved by agrypnotic drugs, but the attacks were generally reduced in frequency and severity. The reason for this improvement is not clear. Sleep paralysis and hypnagogic hallucinations were not affected by the use of agrypnotic drugs.

Comment

Narcolepsy occurs in patients who are otherwise healthy. Preponderance among men was reported by Daniels;[4] our series is in agreement. However, Yoss and Daly[5] believe that the higher incidence in men than in women may be because men are more apt to seek treatment for the disability because of social economic pressures. In no patient with narcolepsy did signs of epilepsy or organic disease develop, to which the attacks could be attributed. Narcolepsy was not associated with tumors in the brain stem or hypothalamic area; nor did it occur after viral encephalitis, or trauma to the head with prolonged unconsciousness. Although sleep disorders may follow these later diseases, they are distinct from narcolepsy,[6-8] which is an entity in itself. Bradley and Elkes,[9] after a detailed study on the effects of certain drugs on the electric activity of the brain, stated that a slight variation in the local titer of a neurohumoral agent in the midline areas of the reticular formation may profoundly affect the excitability of large neuron pools at great distance. They believe that changes in function may depend on the rate of liberation, diffusion, and destruction of locally produced neurohumoral agents.

The ultimate cause of narcolepsy is not known. How the depression of wakefulness is brought about is in the realm of speculation; it appears to be a state of depression of the reticular activating system, possibly from a neurohumoral deficiency.

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**Dexedrine; Smith, Kline & French Laboratories.*
†Desoxyn, Abbott Laboratories.
‡Benzedrine; Smith, Kline & French Laboratories.
§Ritalin, CIBA Pharmaceutical Products Inc.

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