Narcolepsy With Cataplexy

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Narcolepsy with cataplexy is a serious chronic neuropsychiatric disorder that typically begins at an early age. It has the potential to greatly disrupt social, educational, and vocational development. Because of the nature of its symptoms (e.g., excessive daytime sleepiness), narcolepsy provides insights into the mechanisms regulating human sleep. Its universal symptom of daytime sleepiness probably contributes most substantially to the resulting impaired quality of life that has been documented (1). A specific and intriguing sign of narcolepsy is cataplexy, a transient muscle weakness triggered by emotions. Other classic but nonspecific symptoms include sleep paralysis and hypnagogic hallucinations. Disturbed nocturnal sleep is the most recent addition to the classic symptom complex.

Case Presentation

Mr. A, a 21-year-old college student, came to a sleep disorders center for evaluation of excessive daytime sleepiness. This symptom started at age 11, when he and his family noticed that he seemed to need more sleep than his peers. At age 13, he had daily spells of a sudden inability to move that were consistently triggered by laughter. During these episodes, his head would nod or his knees would buckle, but he would not fall down. These phenomena are consistent with cataplexy. The patient also experienced incidents of inability to move for several minutes after awakening from sleep, which indicated sleep paralysis, and he had nightly dreams that he described as "very real." These vivid dreams featured activities he had been engaged in during the preceding day. When the patient was 14, he had an overnight polysomnogram, which his parents reported gave no explanation for his symptoms. The records of that previous sleep study were unavailable for review.

After high school, the patient's excessive daytime sleepiness and cataplexy persisted. He attended college but struggled academically, with a grade point average of 2.0 on a 4.0-point scale. His description of his sleeping habits indicated an altered sleep-wake pattern. He would typically stay awake until 2:00 or 3:00 a.m. watching television or listening to music. After falling asleep, he often awakened several times during the night.

Although Mr. A had a history of ongoing nicotine dependence, he reported no past history of psychiatric disorders such as major depression or chemical dependency. He had no record of any learning disorder. His medical history and surgical history were significant only for a tonsillectomy.

The patient was attending community college and living at home with his parents. He was socially active and spent considerable time with friends or working out in the gym. He drove a motor vehicle short distances on a daily basis and reported no motor vehicle accidents. He had no known family history of a sleep disorder or a psychiatric disorder.

A mental status examination showed Mr. A to be alert and able to make good eye contact. His speech and language skills were normal. His mood was slightly anxious, and his affect was appropriate. His thought form was unremarkable, and his thought content lacked any delusional thinking or hallucinations. A Mini-Mental State Examination revealed no cognitive impairment.

Diagnostic Evaluation

A sleep evaluation was conducted that consisted of activity monitoring with a portable motion detector on the wrist, overnight polysomnography, and a multiple sleep latency test. Mr. A was not taking any medications at the time of testing. He rated himself as 24 out of 24 on the Epworth Sleepiness Scale (2), a widely used self-report rating of sleepiness. Wrist activity monitoring conducted for 1 week revealed a fairly irregular sleep-wake pattern with a delayed sleep phase and a short total sleep time (mean=5 hours per night). Polysomnography confirmed the absence of sleep-disordered breathing or excessive periodic limb movements. Mr. A had a total sleep time of 430 minutes (7.2 hours) and a normal initial latency of 88 minutes to REM sleep. He did get sufficient sleep during polysomnography to proceed with a multiple sleep latency test the next day. The starting time was adjusted to account for his typically delayed sleep. The multiple sleep latency test showed a markedly short mean initial sleep latency of 30 seconds and the presence of REM sleep during all four naps. A urine drug screen done the same day was negative for any drug of abuse. Testing for the human leukocyte antigen (HLA) revealed the presence of the DQB1*0602 allele. In the context of a delayed sleep phase disorder and insufficient sleep, these data supported the diagnosis of narcolepsy with cataplexy. However, Mr. A declined a lumbar puncture to collect cerebrospinal fluid (CSF) for a measurement of his hypocretin-1 level; narcolepsy has been attributed to low concentrations of this neuropeptide (3).

Treatment

Mr. A was counseled about the importance of adequate sleep hygiene, which involved establishing a consistent schedule and obtaining sufficient sleep time, at least 7 hours. He indicated a willingness to make obtaining adequate sleep a higher priority. Methylphenidate hydrochloride, 10 mg h.s., and time-release methylphenidate hydrochloride, 18 mg h.s., were tried sequentially for a few days. The patient discontinued each sleep aid after a few days because it made him "feel strange." Treatment with modafinil, 100 mg every morning, was better tolerated but only partially effective for his excessive daytime sleepiness. Mr. A did not tolerate higher doses of this

novel agent because it precipitated headache. He was given a prescription for amphetamine-dextroamphetamine, 10 mg every morning, and tolerated a gradual increase in the dose to 50 mg/day. His reported excessive daytime sleepiness was reduced from 23 to 15 on the Epworth Sleepiness Scale.

Not unexpectedly, the patient's cataplectic episodes triggered by laughter continued to occur daily. To target the cataplexy, Mr. A began taking a morning dose of 25 mg of the tricyclic antidepressant imipramine hydrochloride. This medication effectively reduced the frequency of his cataplectic episodes. However, Mr. A did not always take this medication because of its side effects, most notably dry mouth and constipation. He was then given sertraline, 50 mg/day, which he tolerated better and which improved his compliance. His cataplectic attacks decreased from daily events to several episodes a week.

Mr. A also made an effort to improve his sleep schedule. He indicated that he had set a more consistent bedtime closer to midnight than 2:00 a.m. However, he continued to awaken several times each night. The addition of zolpidem tartrate, 5 mg h.s., to his medication regimen helped improve the continuity of his sleep somewhat from midnight to 3:00 a.m. However, he continued to awaken frequently after 3:00 a.m.

Despite trials of multiple medications, Mr. A continued to have unsatisfactory, excessive daytime sleepiness, cataplexy, and poor sleep. His intolerance of various medications limited his treatment options. His partial lack of adherence with the recommended sleep hygiene measures also contributed to his ongoing symptoms. In particular, he had difficulty conforming to the earlier bedtime and developing a more consistent sleep schedule, which is not uncommon for patients attending college. Although he withdrew from several classes, his academic performance remained poor. We then recommended sodium oxybate, a medication approved by the U.S. Food and Drug Administration (FDA) for the treatment of cataplexy, as an adjunct to the amphetamine-dextroamphetamine. Mr. A was given extensive patient education materials about sodium oxybate. Because of the possibility of synergistic effects of sodium oxybate and other hypnotic medications, Mr. A's zolpidem was discontinued. A starting dose of 2.25 g of sodium oxybate was to be taken after Mr. A got into bed, and a second dose was to be taken 3 hours later. With this medication, the quality of Mr. A's sleep improved and he reported feeling more refreshed in the morning. His excessive daytime sleepiness was somewhat reduced, and he gave his sleepiness a rating of 14. The sleep paralysis and hypnagogic hallucinations also resolved, but the cataplexy persisted albeit with decreased frequency.

When the dose of sodium oxybate was increased to 3.00 g twice nightly, his excessive daytime sleepiness and the frequency of his cataplexy continued to improve. However, at this higher dose, he was observed wandering around the house at night but had no recollection of his behavior. In the morning, he would sometimes find objects that he had presumably moved during the night. On one occasion, he wet his bed. The sodium oxybate most likely precipitated his sleepwalking and his single episode of enuresis. Mr. A was advised about how he might modify his sleep environment to reduce the possibility of injury. At follow-up 6 months later, he was continuing to take the same medications.

Discussion

General Background

Narcolepsy is an uncommon but not rare sleep disorder; it occurs in 0.05% of the population (4). Like many psychiatric disorders, it begins at an early age, generally in the second decade of life, and it is a chronic process. Narcolepsy is difficult to diagnose; the typical patient is symptomatic for 10 years before the diagnosis is established (5). Multiple factors contribute to the challenges of diagnosing narcolepsy more quickly. These factors include the extensive differential diagnosis of excessive daytime sleepiness, which includes voluntary sleep restriction, obstructive sleep apnea, circadian rhythm disorders such as delayed sleep phase disorder, chemical dependency, and mood disorders. Another relevant factor is the cost and unavailability of diagnostic sleep studies. For patients who have been taking psychostimulants or antidepressants prescribed for other indications, an adequate washout must be obtained before sleep studies can proceed.

Clinical Manifestations

In addition to the excessive daytime sleepiness associated with narcolepsy, cataplexy occurs in 60% of the patients with narcolepsy; recognizing that these symptoms are possibly due to narcolepsy is often less problematic (4). Nonetheless, cataplexy can be subtle enough to go unrecognized by patients and clinicians alike. The differential diagnosis of cataplexy includes partial complex seizures, syncope, and events related to psychological factors akin to pseudoseizure (6). The preserved consciousness that is invariably associated with cataplexy aids in discriminating these episodes from those with different pathophysiologic mechanisms.

Hypnagogic hallucinations may also occur with narcolepsy, and these are often upsetting for patients. On awakening, a patient may have difficulty determining whether such perceptions are real or part of a dream. Thus, there are published reports of patients with narcolepsy being misdiagnosed with schizophrenia (7). As narcolepsy and schizophrenia have both become better understood, little evidence has been found to support the REM intrusion theory of schizophrenia. Nonetheless, the vivid bizarre dreams of the patient with narcolepsy can be difficult to distinguish clinically from chronic psychotic symptoms (8). These phenomena are characterized by their primarily visual rather than auditory nature and their tendency to occur exclusively during the transition from sleeping to waking. Some patients find these dreams so distressing that they dread falling asleep and often awaken feeling emotionally distressed, which may contribute to their disturbed nocturnal sleep.

Difficulty with sleep maintenance was not included as part of the tetrad of narcolepsy symptoms first described in 1957 by Yoss and Daly (9). Since then, investigators have become more aware of the relatively high prevalence of this symptom (3). The causes of nocturnal awakenings are numerous (e.g., frightening dreams, coexisting obstructive

sleep apnea, parasomnia, periodic limb movements, and alerting side effects of psychostimulant medications). In addition to the fairly recent use of sodium oxybate for maintaining sleep, treatment includes sedating medications from the benzodiazepine and antidepressant classes (10).

Workup and Diagnosis

When unequivocal cataplexy is present, many clinicians agree that narcolepsy can be diagnosed on the basis of the patient's clinical history alone (11). Our patient did indeed have episodes of brief, reversible, bilateral muscle weakness that was provoked exclusively by laughter, which conforms to the classic presentation of narcolepsy. Because these events coexisted with Mr. A's excessive daytime sleepiness, the diagnosis of narcolepsy with cataplexy was highly probable. However, unlike seizures that can be carefully characterized during prolonged neuroepilepsy monitoring, patient-reported cataplexy often occurs outside the clinical setting and thus can rarely be confirmed by clinical observation (12). Clinicians must therefore be alert to the possibility that a patient with drug dependence may simply be fabricating a history of sleep problems to obtain psychostimulants. Because the treatment of narcolepsy warrants the long-term use of many medications that are on the U.S. Drug Enforcement Administration's schedule 2 or 3, most practitioners prefer to base their diagnosis on laboratory testing. HLA testing can support a diagnosis but is certainly not conclusive. The DQB1*0602 allele is found in 30% of the normal population, whereas it is lacking in some well-characterized patients who have narcolepsy with cataplexy (13).

Sleep studies directed toward possible narcolepsy must be carefully planned and must include more than simple polysomnography. As this case illustrates, initial sleep testing is not always diagnostic; the omission of a multiple sleep latency test seriously limited the usefulness of the first evaluation (14). Optimal diagnostic testing includes a means to characterize the patient's sleep-wake patterns over time. Having the patient keep a sleep diary for 1 or 2 weeks, ideally in conjunction with a wrist activity monitor for more objective data, can be invaluable. Our patient was observed to have problematic conditions in both of these areas. His delayed sleep phase led to a careful interview that determined that his excessive daytime sleepiness was not limited to the morning hours, when he was expected to be completing his night's sleep. In this case, the patient and his family confirmed that he was not sleepy for the first hour after awakening but that he was severely sleepy otherwise. Identifying his delayed sleep phase disorder required adjustment of the start time for polysomnography and the multiple sleep latency test to reflect his altered pattern of sleep.

Assessment of this patient's sleep-wake rhythm also revealed that he had chronically insufficient sleep. Sleep deprivation can lead to a false positive result on the multiple sleep latency test, with REM sleep present because sleep debt increases REM pressure (15). However, because disrupted nighttime sleep affects many patients with narcolepsy, it is not feasible to restrict multiple sleep latency tests to patients who obtain 7.5 or more hours of sleep. The best way to control for sleep deprivation is to use polysomnography before the multiple sleep latency test to verify that the patient gets at least 6 hours of sleep at night. To improve the validity of the multiple sleep latency test, it should also be interpreted within the context of the patient's clinical history, which in this case was strongly suggestive of narcolepsy with cataplexy.

The multiple sleep latency test is the pivotal test for the diagnosis of narcolepsy. This daytime sleep study requires the patient to take four or five naps, during which the mean time to sleep onset and the presence of REM sleep are measured. The presence of REM sleep during two or more daytime naps is a currently accepted laboratory marker of narcolepsy. The mechanism behind this abnormally regulated REM sleep appears to be a dysfunctional switching mechanism that leads to the inappropriate intrusion of REM sleep or wakefulness during sleep (16). Cataplexy, sleep paralysis, and hypnagogic hallucinations may all be related to inappropriately regulated REM sleep or absent muscle tone, which is an isolated component of this sleep stage. The exact mechanisms of these phenomena have not been conclusively demonstrated. Considerable evidence points to the insufficiency of a recently described neuropeptide known as hypocretin or orexin. This neuropeptide can be reliably measured in human CSF; however, the test for it has not yet become part of the standard diagnostic testing protocol for narcolepsy with cataplexy (17).

Treatment

Because of the diverse symptoms that can affect patients with narcolepsy, the treatment of this sleep disorder can be complex. Patient education should emphasize the importance of optimal sleep hygiene, including a consistent sleep-wake schedule to facilitate adequate sleep (18). In addition to behavioral interventions, a stimulant is typically used. Modafinil, 200 to 400 mg/day, is a treatment approved by the FDA for excessive daytime sleepiness associated with narcolepsy. It has been shown to be effective in warding off mild to moderate sleepiness (19). Modafinil is generally well tolerated but has several side effects, of which headache is the most common. A psychostimulant, methylphenidate or amphetamine, is often the first-line choice for patients with severely excessive daytime sleepiness (20). Most of these agents have FDA indications for attention deficit hyperactivity disorder but have long been known to work for narcolepsy. The newer formulations that offer extended or continuous release are often especially valuable because they have a longer duration of action. Many patients require treatment only with a stimulating agent. As daytime sleepiness is decreased, cataplectic episodes often become less frequent.

For patients with cataplexy severe enough to warrant targeted treatment, the antidepressant medications have been the mainstay of treatment for years (21). However, no antidepressant has an FDA indication for cataplexy. The noradrenergic compounds, such as imipramine and ven-

lafaxine, are viewed as the most effective treatments for cataplexy. Side effects (e.g., constipation and cardiac conduction delay) may be limiting factors for some patients who use tricyclic agents. One published report of a small pilot study indicated that the selective noradrenergic reuptake inhibitor reboxetine is efficacious (22). Selective serotonin reuptake inhibitors have also been prescribed for cataplexy. Although generally less effective, this class of antidepressant may be an appropriate choice because of its different profile of side effects.

Sodium oxybate received FDA approval in 2002 for its use in the treatment of cataplexy. This novel hypnotic agent has an unknown mechanism of action but is believed to act through the mechanism of γ-aminobutyric acid (GABA). The main clinical finding is a pronounced increase in slow-wave sleep. Thus, GABA appears to consolidate sleep and is associated with a reduction in cataplectic episodes (21). To reduce the chance of injuries resulting from the rapid onset of sleepiness, this liquid medication is taken after the patient has gotten into bed at night. Patients may also experience enuresis because they enter deep sleep. In clinical trials, enuresis was reported for 9% of the patients, but fewer than 1% discontinued the medication for this reason (23). Sleepwalking typically involves the patient engaging in motor activities while only partially awake during slow-wave sleep. With the propensity for sodium oxybate to increase slow-wave sleep, non-REM parasomnia can be induced. In different trials, the prevalence of sleepwalking has been reported as 7% to 32%. However, sleepwalking was identified as the reason for discontinuing sodium oxybate by only 1% of patients (23). Because serious injury is possible during sleepwalking, patients should be advised to assess their sleeping environment carefully. Barriers should be placed to restrict access to hazards, such as staircases, windows, and balconies. The dose of sodium oxybate may need to be reduced or even discontinued in rare cases if a patient appears at risk of serious injury because of non-REM parasomnia. Despite the prospect of sleepwalking and enuresis, the benefits of sodium oxybate can greatly outweigh the risks for patients with an unsatisfactory quality of life after trials of other medications used to treat daytime sleepiness.

Conclusions

Scientific advances clearly document the neurochemical deficiencies in many neuropsychiatric disorders. However, narcolepsy with cataplexy remains difficult to detect and diagnose. The traditional treatment approach typically involves a set of diverse psychoactive medications that target the multiple symptoms of this fascinating sleep disorder.

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