CLINICAL VIGNETTE

A Case of Excessive Daytime Sleepiness

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Case Presentation

An 18-year-old college student presents to sleep clinic for evaluation of worsening excessive daytime sleepiness. Patient reports he sleeps for about 8-9 hours nightly, but wakes up feeling unrefreshed. He reports sleep paralysis about once per week. During the daytime, he often gets an irrepressible need for sleep. He often dozes off in class. He has not dozed off driving. He reports that his grades have recently suffered, whereas he used to get A's in class, now he is getting B's and C's. He thinks this is related to excessive daytime sleepiness making it difficult to stay awake in class and study during the daytime. He denies snoring, witnessed apneas, or morning headaches. He has no medical problems, and takes no medication. He denies family history of sleep apnea, narcolepsy, depression, anxiety. His labs and vital signs are within normal limits. He is referred to undergo a polysomnogram (PSG) and multiple sleep latency test (MSLT) to evaluate for narcolepsy. PSG showed good sleep efficiency, and no evidence of obstructive sleep apnea. MSLT showed sleep onset latency of 3.2 minutes, and 3 sleep onset REM (SOREM) periods, diagnosing narcolepsy.

Discussion

Introduction***:*** Narcolepsy is a clinical syndrome characterized by excessive daytime sleepiness, and symptoms related to the abnormal regulation of wakefulness and sleep.[1] Characteristic to this disorder is a short rapid eye movement (REM) latency, and frequent intrusion of REM sleep into wakefulness. Narcolepsy can be divided into narcolepsy with cataplexy (narcolepsy type 1) and narcolepsy without cataplexy (narcolepsy type 2).[2-4]

Epidemiology***:*** The prevalence of narcolepsy is estimated to be 25 to 50 per 100,000 people, with an incidence of 0.74 per 100,000 person years.[4] Narcolepsy typically presents in late teenage years and early twenties, and may have a second peak in middle-age. It is equally common in men and women.[5]

Etiology***:*** Loss of hypocretin signaling, genetic factors, brain lesions, and environmental factors that induce an autoimmune response, may all contribute to the development of narcolepsy.

Hypocretin: Narcolepsy results from a deficiency in hypocretin (hypocretin-1 and hypocretin-2). Loss of hypocretin is caused by the destruction of hypocretin-producing cells in the posterolateral hypothalamus. Hypocretin is released during wakefulness, and it is believed to stabilize wakefulness, prevent inappropriate transitions into REM and non-REM sleep (NREM), and prevent intrusion of REM into wakefulness.[6] Loss of hypocretin may allow REM-related phenomena, for example, cataplexy, hypnagogic hallucinations, and sleep paralysis, to intrude into wakefulness. Patients with narcolepsy type 1 (narcolepsy with cataplexy) have CSF hypocretin-1 deficiency. They have a significant reduction in the number of hypothalamic neurons producing hypocretin, resulting in little or no hypocretin-1 in their spinal fluid.[7] The cause of narcolepsy type 2 is less clear as these patients have normal CSF hypocretin-1 levels.[8] Narcolepsy type 2 may result from less extensive loss of hypocretin neurons, impaired hypocretin receptor signaling, or a distinct mechanism.[9] Twenty percent of narcolepsy type 2 patients have low CSF hypocretin-1 levels, and about half of these patients may later develop cataplexy, suggesting disease progression.[10]

Genetics: Nearly all patients with narcolepsy and cataplexy have low CSF hypocretin-1 and are positive for the human leukocyte antigen (HLA) DQB1*0602 (and DR2 or DRB1*1501).[11] Low CSF hypocretin is very rare in a patient negative for HLADQB1*0602. Additionally, it is estimated that about 45% of type 2 narcoleptics are HLADQB1*0602 positive, and are hypocretin deficient, but have not yet manifested cataplexy. However, the presence of this antigen alone is not diagnostic of narcolepsy as about 25% of the normal Caucasian population is positive for this antigen.[1] While a genetic predisposition for narcolepsy seems to exist, environmental factors may play a larger role. Twin studies show that if one member of identical twins has narcolepsy, the chance the other twin will develop narcolepsy is only 30%.[12]

Autoimmune hypothesis: Researchers have hypothesized that a genetic predisposition coupled with an autoimmune process (infection or vaccine) that selectively kills hypocretin neurons, results in the development of hypocretin-deficient narcolepsy.[13] As the onset of narcolepsy is highest in the spring, a winter infection, possibly streptococcal pharyngitis, may be a trigger.[14] A 2009 study found elevated anti-streptococcal antibodies in patients with recent narcolepsy onset, lending support to this theory.[15] In 2009 individuals in several European countries developed narcolepsy type 1 soon after receiving Pandemrix, an AS03-adjuvanted 2009 H1N1 influenza vaccine. Risk of narcolepsy after Pandemrix was greatest in individuals with DQB1*0602.[16] The autoimmune hypothesis remains contro-

versial however,[17] as neuroimaging studies have found no consistent abnormalities.[18]

Secondary narcolepsy: Rarely, lesions in the posterior hypothalamus and midbrain can cause narcolepsy. This is hypothesized due to injury to hypocretin neurons and their projections.[19]

Clinical features***:*** Narcolepsy is a disorder whereby elements of sleep intrude into wakefulness and elements of wakefulness intrude into sleep. Core symptoms of narcolepsy include excessive daytime sleepiness, cataplexy, sleep related hallucinations, and sleep paralysis.

Excessive daytime sleepiness: This is present in virtually 100% of patients. Duration of > 3months is required, and is defined as an irrepressible need for sleep or unintended lapses into drowsiness or sleep.[1]

Cataplexy: This is the only symptom specific for narcolepsy, but it is present in only 60 – 70% of narcoleptics. It is defined as, more than one episode of brief (<2minutes), bilaterally symmetrical sudden loss of muscle tone and deep tendon reflexes, with retained consciousness.[2] Cataplexy is usually precipitated by strong emotions, usually positive. Cataplexy usually occurs within a few years of the onset of sleepiness.

Sleep related hallucinations: These are vivid, bizarre images associated with sleep onset (hypnogogic) or offset (hypnopompic). Patients commonly describe a stranger or animal, and are often aware the images are not real.

Sleep paralysis: This occurs upon awakening, whereby patient is awake but can't move for several seconds.

Diagnostic evaluation***:*** If a patient with chronic daytime sleepiness is suspected of narcolepsy, a PSG and MSLT should be performed. Medications that may affect sleep and alertness should be withdrawn for 2 weeks (or five half-life intervals) prior to testing.[1] In the two weeks prior to the MSLT, the patient should have a normal sleep schedule and adequate sleep (>7 hours per night). Ideally actigraphy + sleep log should document adequate sleep in the week prior to MSLT.

Polysomnogram: The sleep study is done the night prior to MSLT to ensure adequate sleep and rule out another sleep disorder, such as sleep apnea, that may cause abnormal MSLT findings or sleepiness.

Multiple sleep latency test (MSLT): This is a daytime study that begins about 1 hour after conclusion of nocturnal polysomnogram. The patient is placed in a dark quiet room and asked to take five 20 minute naps, at two hour intervals. Healthy subjects usually fall asleep in 10 to 15 minutes, but people with narcolepsy often fall asleep in less than 8 minutes.[20] The naps of narcoleptics often include REM sleep additionally.[21] The criteria for a positive MSLT are, a mean sleep onset latency of ≤ 8 minutes, and 2 or more sleep onset REM (SOREM, REM that occurs within 15minutes of sleep onset). MSLT is not 100% sensitive for narcolepsy and false negatives may occur 7 to 30% of the time.[22] A repeat MSLT may be needed if there is high clinical suspicion. The MSLT may be associated with false positives, in patients with OSA and insufficient sleep.[23]

Diagnostic criteria[2]***:***

Narcolepsy ICSD-3 Diagnostic Criteria	
Narcolepsy Type 1 (with cataplexy) Criteria (A + B1 or A + B2) must be met	**Narcolepsy Type 2 (without cataplexy)** Criteria A – E must be met
A. Daily events of irrepressible need to sleep, occurring for at least 3 months B. Presence of one or both of following: 1. Cataplexy *and* a mean sleep latency of ≤ 8 **AND** 2 or more sleep onset REM periods (SOREM) on MSLT. 2. Cerebrospinal fluid (CSF) hypocretin-1 concentration, measure by immunoreactivity is either ≤ 110 picogram per milliliter (pg/ml) or <1/3 of mean value in normal subjects	A. Daily events of irrepressible need to sleep, occurring for at least 3 months B. Mean sleep latency of ≤ 8 **AND** 2 or more sleep onset REM periods (SOREM) on MSLT. C. Absent cataplexy D. *Either* CSF hypocretin-1 concentration has not been measured *or* CSF hypocretin-1 concentration measured by immunoreactivity is either >110 pg/ml or > 1/3 mean value in normal subjects E. Hypersomnolence and / or MSLT findings are not better explained by alternate causes such as insufficient sleep, OSA, delayed sleep phase disorder, medications / substances, or their withdrawal

Treatment***:*** Treatment of narcolepsy addresses daytime sleepiness and cataplexy. All patients with narcolepsy have daytime sleepiness. While conservative management with scheduled napping may be effective for some, most patients require wake promoting medications.

Modafinil and Armodafinil are dopamine agonists that are FDA approved for treatment of sleepiness in narcoleptics. These medications have limited abuse potential and are preferred as first line therapy. Solriamfetol is a new selective dopamine and norepinephrine reuptake inhibitor with wake-promoting effects

that has been recently FDA approved for the treatment of sleepiness in narcoleptics. Pitolisant is an oral histamine H3 receptor recently approved for treatment of daytime sleepiness in adults with narcolepsy. Stimulants such as Methylphenidate and Amphetamines may also be used to treat excessive daytime sleepiness, but these have an increased risk for abuse, tolerance, and rebound of symptoms.

Sodium Oxybate (Xyrem) is the only medication FDA approved for treatment of both sleepiness and cataplexy in patients with narcolepsy.[24] It is the sodium salt of gamma hydroxybutyrate (GHB) and a metabolite of gamma amino butyric acid (GABA). It may act through GABA-B receptors, but its precise mechanism of action in patients with narcolepsy is unknown.[25] Sodium oxybate is given as a liquid at bedtime, with a second dose 2.5 to 4 hours later; the second dose is necessary owing to its short half-life. Over-dosage can result in respiratory depression, coma, and death.[26] Coadministration with central nervous system depressants such as alcohol, benzodiazepines, and opioids increase risk for respiratory depression and death. Gamma hydroxybutyrate gained notoriety as a "date rape" drug and has potential for abuse, so access to it is very restricted in the United States.

NARCOLEPSY TREATMENTS	
EXCESSIVE DAYTIME SLEEPINESS	**CATAPLEXY**
Scheduled Naps **Alerting Agents:** 1. Modafinil 2. Armodafinil 3. Solriamfetol 4. Pitolisant **Stimulants:** 1. Methylphenidate 2. Dextroamphetamine 3. Dextroamphetamine salts **Other treatments:** 1. Sodium Oxybate	Sodium Oxybate

Case Outcome:

Patient was started on Modafinil for treatment of excessive daytime sleepiness. He continued to have daytime sleepiness, so Sodium Oxybate one dose at bedtime and second dose four hours later, was added to his regimen. Sodium Oxybate dose was uptitrated to 3mg twice nightly. Nighttime Sodium Oxybate plus Modafinil during the day, resolved his excessive daytime sleepiness and sleep paralysis. His grades at school improved.

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