

## MORNING REPORT

## Tired of Feeling Sleepy

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**A**n otherwise healthy 25-year-old woman presents to her primary care physician concerned that she is tired all the time, “dragging through the day.” She first had trouble staying awake at school around age 14 and has experienced worsening of her symptoms since then. She occasionally nods off while driving and often falls asleep during work breaks. Her medical history only includes seasonal allergies, and she takes an oral contraceptive. She works as a research assistant, denies smoking or illicit drug use, and rarely consumes alcohol. Nobody in her family experiences similar symptoms. Her Epworth Sleepiness Scale score is 17/24.

*Feeling “tired” can be interpreted various ways, making it important to distinguish fatigue from sleepiness during initial evaluation. While fatigue can result from prolonged physical or mental exertion, excessive daytime sleepiness (EDS) refers to the tendency to fall asleep; fatigue can improve with short work breaks or rest without sleep, whereas sedentary conditions often exacerbate true EDS.<sup>1</sup> A commonly used subjective sleepiness measurement tool is the Epworth Sleepiness Scale (ESS). This self-administered questionnaire records sleepiness on a scale from 0 to 24, with a score greater than 10 representing sleepiness and a score greater than 15 suggesting pathological sleepiness.<sup>2</sup> Given the patient’s history and the results of her ESS, she appears to be pathologically sleepy.*

*The differential diagnosis for EDS is quite broad. Common non-sleep disorder etiologies include medication effects, hypothyroidism, and mood disorders such as depression. Illicit drug use should also be considered. Basic laboratory work-up (e.g.*

*chemistries, complete blood count [CBC], thyroid function tests [TFTs], and urine toxicology screen [Utox]) along with a depression screen can rule out many of these diagnoses. In addition to laboratory testing, a detailed sleep history should be obtained to evaluate for sleep disorders leading to EDS such as:*

- *Disorders of sleep quantity: sleep deprivation (“insufficient sleep syndrome,” poor sleep hygiene)*
- *Disorders of sleep quality: sleep apnea, restless leg syndrome (RLS)*
- *Disorders of circadian rhythm: advanced sleep phase, delayed sleep phase, jet lag*
- *Primary disorders of hypersomnolence: narcolepsy, idiopathic hypersomnia*

The patient sleeps between about 8:30 pm and 6:30 am nightly; she has a similar sleep schedule on both weekdays and weekends. There are frequent, temporarily refreshing two-hour daytime naps on weekends. Our patient reports no recent travel. She does not snore and never awakens choking or gasping. The patient denies nighttime lower extremity dysesthesias (aches, pains, crawling sensations) as can be seen in RLS. Her depression screen is negative. On physical examination, her vital signs include a pulse of 76 beats/minute, blood pressure of 120/68 mmHg, and BMI of 21.5 kg/m<sup>2</sup>. There are no signs of macroglossia (enlarged tongue), retro/micrognathia (recessed/small mandible), enlarged tonsils, or low-lying soft palate to suggest that the upper airway could obstruct during sleep. The rest of her examination, including neurologic assessment, is also normal.

Her chemistry panel, CBC, thyroid function tests, and urine toxicology screen are all within normal limits. The patient reports ongoing sleepiness and anxiety over what could be wrong with her.

*Since the most common sleep and non-sleep-related disorders are unlikely to be contributing to our patient’s symptoms, there is now increased likelihood of a primary hypersomnolence disorder such as narcolepsy or idiopathic hypersomnia.*

*Narcolepsy is a lifelong condition that often develops in adolescence and early adulthood. It is characterized by an inability to maintain wakefulness due to abnormal intrusions of rapid eye movement (REM) sleep (or features of REM sleep). REM sleep is an active stage of sleep where brain activity is similar to that of wakefulness or very light non-REM sleep; there is also an active paralysis of all skeletal muscles (known as REM muscle atonia) with the exception of the ocular muscles, the cricothyroid muscles, and the stapedius muscle. The patient should be queried for features comprising its classic tetrad (not all need be present for a diagnosis of narcolepsy):<sup>3</sup>*

1. *EDS*
2. *Cataplexy (sudden bilateral loss of skeletal muscle tone often elicited by strong emotion)*
3. *Hypnagogic hallucinations (sensory experiences upon transitioning between wakefulness and sleep that appear real)*
4. *Sleep paralysis (sensation of complete skeletal muscle paralysis when transitioning between sleep and wakefulness)*

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EDS in the setting of cataplexy is considered pathognomonic for narcolepsy. However, cataplexy may not be seen at all or may occur several years after the onset of significant sleepiness. The other REM-related phenomena may be seen in idiopathic forms of hypersomnia or, more commonly, in patients with significant acute or chronic sleep deprivation. Prevalence of narcolepsy among individuals of European ancestry (such as our patient) is 0.02% to 0.05%, although prevalence rates up to 0.16% have been reported in East Asian populations; possession of the human leukocyte antigen (HLA) DQB1\*0602 predisposes patients to the loss of hypothalamic hypocretin neurons seen in some cases of narcolepsy.<sup>4</sup> Idiopathic hypersomnia, in comparison, is characterized by EDS despite adequate or, more commonly, significantly increased sleep amounts. REM sleep-related phenomena (items 2-4 above) are less commonly seen than in narcolepsy, and post-awakening confusion (“sleep drunkenness”) is common in this population.

On obtaining a more detailed history, the patient states that when laughing intensely or suddenly angered, her jaw feels weak and her body feels “heavy” as if she might “crumble.” Additionally, she describes monthly episodes where she awakens from a dream completely paralyzed for almost one minute. Less frequently, she has awakened from sleep to observe a “ghost” or “life-sized action figure” standing near her bed. The patient was referred to sleep medicine for further evaluation of possible narcolepsy.

The patient’s weakness with strong emotion is suggestive of cataplexy. Although pathognomonic for

narcolepsy, cataplexy can be difficult to assess; a cataplectic episode need not involve complete physical collapse but may include more subtle features such as jaw dropping and head nodding.

With a strong suspicion for narcolepsy, a Multiple Sleep Latency Test (MSLT) should be obtained. The MSLT complements the subjective ESS as an objective measure of pathological sleepiness and is considered the gold standard used to diagnose narcolepsy.<sup>5</sup>

After undergoing in-laboratory overnight polysomnography (PSG), which demonstrated normal sleep quality and quantity in the absence of sleep-disordered breathing, the patient remained in the sleep laboratory through the next afternoon. She was given five opportunities to nap and fell asleep each time after an average of 6.9 minutes (a mean sleep onset latency of less than 8 minutes is consistent with narcolepsy). Additionally, REM sleep was observed on two naps within 15 minutes of falling asleep. The presence of two sleep-onset REM periods (SOREMPs) is reasonably

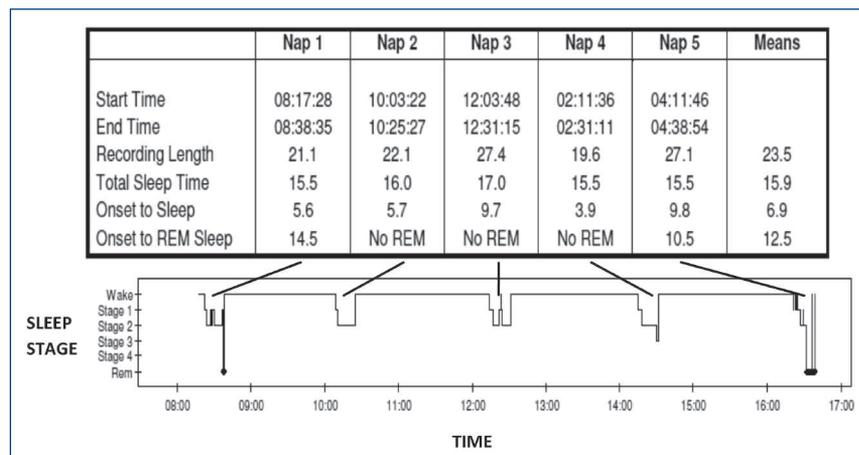
specific for the diagnosis of narcolepsy (Figure 1).<sup>6</sup>

The patient was diagnosed as having narcolepsy with cataplexy, and modafinil was prescribed. She has experienced considerable improvement in her EDS without noticeable side effects. There has been no change in her cataplexy.

Medical treatment of narcolepsy is symptomatic. Current first-line therapy for narcolepsy-associated EDS includes wakefulness-promoting agents such as modafinil and armodafinil.<sup>7</sup> Common side effects when starting these medications—nausea and headache—typically resolve within days. Our patient’s oral contraceptive could be less effective while taking either of these medications due to their possible induction of drug metabolizing enzyme CYP3A4; she should be encouraged to use barrier contraception while on modafinil or armodafinil. Patients should stop these medications immediately at the first sign of drug-related rash due to a slight risk of Steven-Johnson Syndrome. Stimulants such as amphetamine, dextroam-

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**Figure 1. Patient’s MSLT Report**



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phetamine, and methylphenidate remain effective treatments but carry more burdensome side effects (anxiety and tachycardia as well as hypertension and stroke in older individuals). When present, cataplexy does not respond to stimulant therapy and requires additional specific therapy. Cataplexy can typically be managed easily with REM suppressing medications. Historically, tricyclic antidepressants were used, but selective serotonin uptake inhibitors (SSRIs) are now considered first-line therapy for cataplexy. Patients with refractory cataplexy, daytime sleepiness, and nighttime sleep fragmentation (which can develop in patients with long-standing narcolepsy of more than five years) may benefit from sodium oxybate, which requires specialized patient training and use of a single national pharmacy.<sup>7</sup>

In addition to taking medication, patients with narcolepsy should get at least eight to nine hours of sleep nightly. They should also pay strict attention to proper sleep hygiene (sleeping in a darkened cool room, eliminating bright light within one hour of bedtime, avoiding caffeine six to eight hours before bedtime). Two regularly scheduled 15-minute naps daily are recommended to patients with residual EDS. Furthermore, our patient should not drive until her sleepiness is adequately controlled.<sup>7</sup> Safer driving practices, such as strategic caffeine consump-

tion before driving, pulling over to take a 15-minute nap at the earliest signs of sleepiness, and limiting driving distances without breaks, should also be adhered to strictly. Patients with narcolepsy qualify for benefits under the Americans with Disabilities Act<sup>®</sup> and may be entitled to accommodations including longer time for task completion and longer breaks that allow for 20 to 30 minute naps. Long term, patients with narcolepsy should be queried for development of cataplexy and nighttime sleep fragmentation, which may require additional specific pharmacologic therapy.

### Learning Points

- The ESS is a reliable tool for differentiating between fatigue and sleepiness, which is important when formulating an appropriate differential diagnosis and work-up plan.
- Narcolepsy's classic tetrad includes EDS, cataplexy, hypnagogic hallucinations, and sleep paralysis, though many patients with the disorder do not manifest all of them initially.
- Wakefulness-promoting agents, such as modafinil and armodafinil, have been shown to manage narcolepsy-associated EDS effectively, especially in conjunction with sufficient sleep time and proper sleep hygiene practices.

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