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Narcolepsy with cataplexy can occur in the absence of a positive Multiple Sleep Latency Test

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Case

J. W. presented as a 20-year-old college student with a 3-year history of progressive daytime sleepiness. In high school, she started to fall asleep in both her morning and afternoon classes and took a nap when she returned home from school. Despite her frequent napping, she maintained good grades and graduated high school with honors. However, she was now performing poorly in college because she had trouble staying awake to study for tests or to complete papers. She "only wanted to sleep." She didn't want to go out with friends or even go to class for that matter. As she was having so much difficulty in college and seemed to "withdraw" from her usual activities, her primary care provider suspected clinical depression and placed her on paroxetine.

However, J. W. did not improve. She saw a sleep medicine specialist, Dr. P., but she did not report hypnogogic hallucinations or sleep paralysis. However, she did report a more recent "funny and weird" feeling with profound laughter. Interestingly, this feeling only occurred when she laughed with this one particular friend. She never fell to the ground or "felt weak" per se. She always "grabbed" her friend though, when she laughed, which seemed odd to her. Otherwise, J. W. was healthy, had a normal exam, and was no longer taking the paroxetine. With a suspicion of narcolepsy without cataplexy (as Dr. P. did not feel that her "funny feeling" represented cataplexy), Dr. P. pursued a polysomnogram (PSG) followed by a Multiple Sleep Latency Test (MSLT). A negative urine toxicology screen was obtained at the time of the sleep laboratory testing. On the PSG, J. W. fell asleep quickly with a sleep onset latency of 2.5 minutes. Latency to rapid eye movement (REM) sleep was 58 minutes, with 23% of total sleep spent in REM sleep. Sleep architecture appeared fragmented without a clear ultradian non-REM/REM pattern. The longest consolidated REM sleep period was 18 minutes. Neither sleep apnea, nor any other disorder that could explain non-restorative sleep was identified. The 5-nap MSLT on the following day revealed a mean sleep onset latency of 9.6 minutes (Nap 1: 8.5 min; Nap 2: 6.5 min; Nap 3: 5.5 min; Nap 4: 9.5 min; and Nap 5: 18.0 min). A single sleep-onset REM period (SOREMP) was noted in Nap 3 (Figure 11.1). However, the suggestion that REM sleep was imminent – appearance of a REM sleep-consistent electroencephalogram (EEG), with saw-tooth waves – was noted on two separate occasions in Nap 2. The technician notes were unremarkable except for "the patient looked anxious" and was "pacing back and forth" in the room after Nap 3. With these findings of a mean sleep onset latency of 9.6 minutes and 1 SOREMP, the test was interpreted as negative for narcolepsy, but more specifically was interpreted as negative for excessive daytime sleepiness. And because of the reported negative MSLT findings, and in spite of the PSG findings of a shortened sleep onset latency, slightly decreased REM-sleep latency, and prominent sleep fragmentation,

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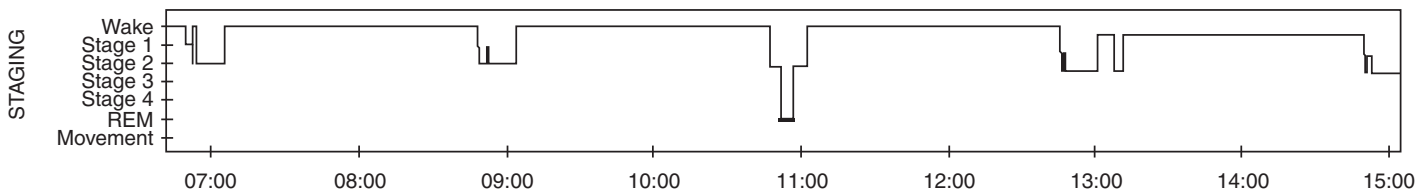

Figure 11.1 Hypnogram from this patient's initial Multiple Sleep Latency Test (MSLT). A hypnogram summarizes the sleep stages attained during a sleep study. In this case, only the third nap showed rapid eye movement (REM) sleep. Appearance of REM sleep within 15 minutes of sleep onset, during a 20-minute MSLT nap opportunity, qualifies the nap as a sleep-onset REM period (SOREMP). However, two or more SOREMPs on an MSLT are required to confirm a diagnosis of narcolepsy without cataplexy. (Note, this hypnogram shows an older convention in which non-REM sleep was scored as stage 1, 2, 3, and 4. Current standards divide non-REM sleep into stages N1, N2, and N3, which includes former stages 3 and 4.)

Dr. P. suspected generalized anxiety disorder and placed J. W. on alprazolam and buspirone. Her symptoms worsened and her mother insisted J. W. obtain a second opinion, which led her to Dr. E. about 1 year after originally seeing Dr. P.

Dr. E. obtained a similar history, but questioned J. W. further regarding her "funny feeling" with laughter. Not only did she feel "funny" but she described a feeling like her "face was melting" and that it was hard for her to form words when she was laughing so hard. Even though the feeling only lasted seconds, it occurred repetitively at times during the laughing spell. Dr. E. was convinced her symptoms represented cataplexy. Dr. E. thus diagnosed J. W. with narcolepsy with cataplexy, and although he didn't believe that repeat testing was absolutely required, he sought to confirm his suspicion with a repeat PSG followed by MSLT. This PSG revealed a shortened sleep onset latency with a REM-sleep latency of 26 minutes. The 4-nap MSLT uncovered a notably short mean sleep onset latency of 2.4 minutes, with 4 out of 4 SOREMPs. Narcolepsy with cataplexy was confirmed.

What went wrong?

For more than a year after initially presenting to a sleep medicine physician, J. W. remained misdiagnosed as a non-narcoleptic. Even her daytime sleepiness was questioned and labeled as depression and anxiety despite clinical evidence to the contrary. Unfortunately, the missed diagnosis of narcolepsy or the delay in diagnosis is common, with some authors reporting excessively long intervals from the time of initial symptom presentation to the time of ultimate diagnosis.[1] Often times, one lacks the confidence to make the diagnosis of narcolepsy, or the diagnosis of excessive sleepiness for that matter, based on clinical evidence alone, and instead one relies too heavily on laboratory data. In this particular case, the initial MSLT findings did not confirm the presence of narcolepsy without cataplexy (as originally considered by Dr. P.) based on International Classification of Sleep Disorders (ICSD-2)[2] criteria, so the diagnosis was erroneously abandoned.

Or was the initial MSLT incorrectly interpreted, especially in conjunction with the PSG the previous night, which revealed fragmented sleep with shortened sleep onset and REM-sleep latencies? What if Dr. P. eliminated the results of the last nap, due to concern about a "last nap effect" that can prevent sleep when younger patients are "anxious" for their imminent opportunity to finally leave the laboratory?

With Nap-5 eliminated, the mean sleep onset latency would have been 7.5 minutes, within the range of pathologic sleepiness ($<$ 8 min) based on ICSD-2 criteria.[2] Even if one accounts for the "last nap effect" and the re-calculated mean sleep onset latency, how does one address the single SOREMP? One published study found 2 or more SOREMPs on the initial MSLT – a required criterion for the diagnosis of narcolepsy in the absence of cataplexy – in only 83.5% of narcoleptics with cataplexy.[2,3] In a later study, those findings were confirmed with only 74% of narcoleptics yielding 2 or more SOREMPs.[4] The MSLT results differ from one testing date to another, and the test–retest reliability for the number of SOREMPs on an MSLT can be poor. One study explored the diagnostic utility of repeat MSLTs in patients with clinical features of narcolepsy and normal PSG. Mean sleep latency data were gathered between 2004 and 2009 for 125 patients; of these, 10 patients with repeat MSLT data were identified for the study. The results showed that 2 patients among the 10 met narcolepsy criteria on the second MSLT, despite not having met these criteria during the first MSLT. Both patients showed no substantive difference between the two testing periods in terms of preceding night sleep quality. Additionally, only 50% of patients met sleepiness criteria during the first MSLT; with repeat MSLT the number rose to 90%. The authors note that the increase in narcolepsy diagnosis was based on a decrease in the average sleep latency in the second study, not necessarily an increase in SOREMPs.[5]

Further, in an abstract entitled, "The Multiple Sleep Latency Test is not infallible," Jahnke and Aldrich[6] reviewed sleep evaluations of 13 patients with non-diagnostic initial MSLTs that were significantly different from subsequent MSLT results. The authors described multiple cases in which insufficient sleep

obscured narcolepsy. One patient, at the age of 15, developed excessive daytime sleepiness, along with sleep paralysis and hypnagogic hallucinations. At age 20, nocturnal REM sleep latency was 51.5 minutes, with an MSLT that showed a mean sleep latency of 4.6 minutes, and no SOREMPs. After a month of increased nocturnal sleep, the mean sleep latency on a repeat MSLT was still short at 5.1 minutes, and the test now showed 5 SOREMPs.[6]

Many narcoleptics have a negative MSLT initially, and since the sensitivity for identification of two or more SOREMPs in patients with narcolepsy is not 100%, the current standard of practice is to repeat an MSLT test if narcolepsy remains suspect.[7] Thus, one should not rely solely on a single MSLT to discount the diagnosis of narcolepsy if the clinical suspicion is high.

Additional clues

The nighttime PSG also can be a valuable tool in the diagnosis of narcolepsy, especially if the MSLT result is suspect. One study found that the positive predictive value for narcolepsy of a SOREMP at the onset of a nighttime PSG **exceeds** that of the occurrence of SOREMPs on an MSLT.[4] As much as sleep intrudes into wakefulness in narcoleptics, an altered and fragmented sleep pattern with wakefulness often intrudes into sleep. The mechanism of disrupted or fragmented sleep in narcolepsy may differ from one patient to the next, and may be due to REM-intrusion phenomena such as nightmares or even REM-sleep behavior disorder. Non-REM parasomnias such as sleepwalking and confusional arousals are also more prevalent in patients with narcolepsy. Although important, "fragmented sleep" as part of the narcolepsy diagnostic criteria is often overlooked and under-recognized.

Laboratory tests including HLA genotyping or hypocretin-1 (also known as orexin A) analysis from cerebrospinal fluid can also be utilized. The HLA-DQB1*06:02 allele is strongly associated with narcolepsy and has a clinical sensitivity of 85–95% depending on ethnicity. In Caucasians, $>$ 99% of affected narcoleptics with cataplexy have the HLA-DQB1*06:02 allele; however, the specificity is low as 15–25% of unaffected Caucasians have the HLA-DQB1*06:02 allele. Similarly, low cerebrospinal fluid hypocretin-1 levels can be found in a number of neurologic conditions other than narcolepsy, and the finding has a relatively low specificity, but it is most predictive of narcolepsy with cataplexy when the HLA-DQB1*06:02 allele is also present. Bourgin et al.[8] reaffirm the notion that "determination of CSF hypocretin-1 concentration to diagnose narcolepsy might be most useful in ambulatory patients with cataplexy but with a normal MSLT result, or if the MSLT is not interpretable, conclusive, or feasible." As 98% of patients with hypocretin-1 deficiency are positive for HLA-DQB1*06:02 allele, they also suggest HLA typing before lumbar puncture is performed. Unfortunately, however, hypocretin testing is not yet commercially available in many areas, including the United States.

Lastly, the clinical history is perhaps the most important and valuable tool in the diagnosis of narcolepsy with cataplexy. J. W. fits the typical profile of a young, otherwise healthy patient with the onset of hypersomnolence in the second decade of life and the ultimate development of cataplexy. Although she did not feel "weak" with her episodes, nor buckle her knees and fall to the ground, she clearly manifested limited cataplectic attacks that involved the head, neck, and face. A study of 40 young cataplectic patients (age range 13–23 years) reported that sagging of the jaw, inclined head, drooping of the shoulders, and transient buckling of the knees were the most common presentations.[9] J. W. was never asked whether her "funny feelings" had resolved when she was taking paroxetine, a serotonin uptake inhibitor and known treatment for cataplexy.

Any symptom associated with laughter or strong emotion should be explored in great detail when narcolepsy is suspected. More extensive questioning by Dr. P. might have uncovered the facial weakness later identified by Dr. E. In essence, one can make the diagnosis of narcolepsy with cataplexy based on the clinical history, and not rely solely on the MSLT results. The interpretation of the MSLT, when performed, should be made in conjunction with the PSG and within the context of the patient history. With that

in mind, narcolepsy with cataplexy can be diagnosed in the absence of a positive MSLT.

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