SLEEP MEDICINE: A CASE-BASED APPROACH NARCOLEPSY AND HYPERSOMNIA CASES FOR THE GENERAL NEUROLOGIST

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The diagnosis of narcolepsy (types 1 and 2) and idiopathic hypersomnia (IH) requires a combination of clinical evaluation and sleep diagnostics. While sleepiness is characteristic of all three disorders, a key feature of narcolepsy (especially type 1) is "REM dyscontrol". Symptomatically, this is manifest as intrusion of features of REM into wakefulness (i.e., cataplexy, sleep paralysis, and sleep-related hallucinations). Cataplexy is specific for type 1 narcolepsy (and, by definition, diagnosis of either narcolepsy type 2 or idiopathic hypersomnia require the absence of cataplexy). However, sleep paralysis and sleep-related hallucinations are less specific, occurring most commonly in narcolepsy type 1, then narcolepsy type 2, but also present not uncommonly in patients with idiopathic hypersomnia (and, in the case of sleep paralysis, in the general population). On electrodiagnostic testing, REM dyscontrol is manifest as "sleep onset REM periods" (SOREMs). In healthy controls, typical latency to REM sleep following sleep onset is approximately 90 minutes. A SOREM is defined as REM sleep occurring within the first 15 minutes after sleep onset. Although patients with narcolepsy may sometimes transition directly from wakefulness into REM sleep (1), the term SOREM does not imply that this necessarily has happened; the REM sleep can occur following any other stage of sleep, so long as it occurs within 15 minutes of the first epoch of sleep. In prior classifications, only SOREMs during the MSLT were counted toward diagnosis. However, increasing recognition of nocturnal SOREMs (i.e., REM sleep within 15 minutes of the first time a patient falls asleep in a given night) as a marker of narcolepsy type 1 or 2 (2, 3) has led to a change in diagnostic criteria. Currently, the number of SOREMs is summed across the nocturnal PSG and next-day MSLT nap opportunities; if 2 or more SOREMs occur, it supports the diagnosis of narcolepsy, while if 0 or 1 SOREMs occur, it is supportive of idiopathic hypersomnia (assuming other criteria are also met) (4).

Because of the importance of SOREMs in diagnostic testing, neurologists ordering PSG/MSLT should be aware of the effects of medications on REM sleep. The American Academy of Sleep Medicine's guideline for performing the multiple sleep latency test recommends that ***stimulants (and stimulant-like medications) and REM-suppressing medications "ideally" be withdrawn for two weeks prior to the MSLT*** (5). As this is not always clinically appropriate (e.g., in the case of a patient with brittle depression or history of suicidality), providers should be aware of the potential effects of these medications on diagnostic testing and interpret results accordingly. Serotonergic antidepressants, including most tricyclics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors, consistently prolong REM latency and/or decrease percentage of time spent in REM sleep on nocturnal studies (6-8). Other medications that are REM suppressing include: several anti-hypertensives (pindolol and clonidine), several anti-epileptic medications (carbamazepine, clonazepam and other benzodiazepines, phenobarbital, and phenytoin), dopamine agonists, and opiates (9-12). On the other hand, medications with REM promoting effects are also commonly prescribed by neurologists, including gabapentin and cholinesterase inhibitors (10, 11, 13).

Several groups have reported a problem of MSLT sensitivity for the diagnosis of idiopathic hypersomnia. In a group of 105 patients with a clinical syndrome of idiopathic hypersomnia, 56% had a mean sleep latency of greater than 8 minutes (i.e., did not qualify for an IH diagnosis based on MSLT). This effect was much more pronounced for those with long sleep times, in whom the MSLT was normal 71% of the time (14). In a group of consecutive patients suspected of having a central disorder of hypersomnolence, in whom insufficient sleep, mood disorders, and nocturnal sleep disorders had been carefully excluded, 33% had a normal MSLT (i.e., did not qualify for any diagnosis) (15). In recognition of this limitation and the tendency of a group of patients with idiopathic hypersomnia to sleep for long periods of time, the current diagnostic criteria for idiopathic hypersomnia

allow for a measured sleep duration of at least 660 minutes in lieu of mean sleep latency findings; this measured sleep time can either occur during 24 hour polysomnography (although reimbursement issues for this procedure may limit its clinical usefulness) or averaged across at least 7 nights of ambulatory actigraphy during which patients sleep ad lib (4).

Terminology to characterize the two types of narcolepsy has recently shifted from “with cataplexy” and “without cataplexy” to “type 1” and “type 2”. This move importantly emphasizes the difference in pathophysiology between the two disorders. Patients with type 1 either have documented low cerebrospinal fluid hypocretin or are anticipated to have low values if they were to be tested (the latter defined as the group with both typical MSLT findings – mean sleep latency less than 8 minutes and at least 2 SOREMs – AND clear cut cataplexy). Patients with type 2 are either known to have normal hypocretin or are presumed to have normal hypocretin based on the absence of cataplexy. Although cataplexy and hypocretin-deficiency are tightly related, the “type 1/type 2” nomenclature gives precedence to hypocretin over cataplexy, especially important in the case of patients without apparent cataplexy but with measured low hypocretin (who have type 1 narcolepsy by current definition). Narcolepsy type 1 is suspected to result from an auto-immune attack on hypocretin neurons. Support for this auto-immune hypothesis comes from several converging lines of evidence, including: 1) a strong association between HLA-DQB1*0602 and narcolepsy type 1; 2) a genome-wide association study showing association between narcolepsy and a single nucleotide polymorphism within the T-cell receptor alpha locus (16); and 3) an increase in incidence of type 1 narcolepsy among children vaccinated with an adjuvanted H1N1 vaccine in Europe in 2009 (not the version of the vaccine used in the United States) (17). Despite the presumed auto-immune origin of narcolepsy type 1, immune-modulating therapies are not currently recommended for narcolepsy treatment; small case series have suggested at least temporary benefit from intravenous immunoglobulin, but only in those patients with onset of symptoms within the last 9 months (18). The pathophysiology underlying narcolepsy type 2 and idiopathic hypersomnia is unknown.

There are multiple FDA-approved medications for the treatment of sleepiness in patients with narcolepsy. These include wake-promoting agents such as modafinil and armodafinil, the amphetamine stimulants, and sodium oxybate. Modafinil is a racemic mixture of R- and S-enantiomers; armodafinil is only the R-enantiomer. Both of these medications are now available in generic form, and their affordability for patients has improved considerably in recent times. Sodium oxybate is the sodium salt of gamma-hydroxybutyrate and is a GABA-B receptor agonist. Unlike other treatments for excessive daytime sleepiness, it is dosed at bedtime and then again 2.5 to 4 hours later. It is also unique among currently approved treatments for narcolepsy in that it is approved for both sleepiness and cataplexy. Antidepressants, while not FDA approved for any central disorder of hypersomnolence, are commonly used for the treatment of cataplexy and may also be beneficial for sleep paralysis and sleep-related hallucinations (19).

There are currently no FDA-approved treatments for idiopathic hypersomnia, so all treatment of patients with this disorder constitutes off-label use. The most recent practice parameter from the American Academy of Sleep Medicine suggests use of modafinil (19). Since this practice parameter was published, two randomized, controlled trials of modafinil in patients with idiopathic hypersomnia have confirmed its benefit in patients with this disorder (20, 21). The practice parameter also recommended consideration of amphetamine, methamphetamine, dextroamphetamine, and methylphenidate, based on their effectiveness in patients with narcolepsy. In addition to daytime sleepiness, patients with idiopathic hypersomnia frequently experience severe sleep inertia, also known as sleep drunkenness, that manifests as great difficulty awakening in the morning or from a nap (22). Optimal treatment strategies to treat sleep drunkenness are not defined, although patients will sometimes take wake-promoting medications one hour before planned awakening, return to sleep for an hour, then reattempt awakening. In cases where there is no family member to assist with waking to take medications, some patients dose their stimulant medication at bedtime to combat severe sleep inertia the following morning.

The American Academy of Sleep Medicine has published quality measures for the care of patients with narcolepsy (23). These include:

1) Reduce daytime sleepiness (via process measures of assessing sleepiness with a validated scale at every visit and initiation of treatment within 1 month of diagnostic testing)
2) Improve diagnostic accuracy (via process measures of taking a comprehensive sleep history and performing diagnostic testing according to standardized protocols)
3) Reduce adverse events (via process measures of at-least annual follow to assess treatment response, counseling patients regarding medication side effects and drug-drug interactions, and age-appropriate safety measure counseling).

The quality measures highlighted several key medication side effects or interactions (23). Amphetamines carry black box warnings for abuse or dependence, psychosis, and cardiovascular adverse events. Sodium oxybate must be distributed through an FDA Risk Evaluation and Mitigation Strategies (REMS) program, and black box warnings include obtundation, clinically significant respiratory depression, and abuse. Modafinil and armodafinil do not have black box warnings but have important drug-drug interactions, primarily due to their action as strong CYP3A4 inducers. In particular, the combination of oral contraceptive medications and modafinil/armodafinil may result in a decrease in the effectiveness of contraception because of hepatic induction. Women of childbearing potential who are treated with modafinil/armodafinil should be counselled to use alternate or additional non-hormonal contraception. Antidepressants carry black box warnings for suicidality in young people with depression and other psychiatric disorders. The suicidality risk is apparent in patients younger than 24; age 65 and older may be protective. Although the potential risk for suicidality in patients with narcolepsy treated with antidepressants is not well-defined, mood disorders are commonly comorbid to narcolepsy (24), suggesting this risk is clinically relevant in this population.

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