

STUCK IN THE MSLT -- CHALLENGES IN DIAGNOSING AND TREATING THE OTHER CENTRAL DISORDERS OF HYPERSOMNOLENCE

Lynn Marie Trotti, MD, MSc
Emory University School of Medicine
Atlanta, GA

Diagnostic Challenges

Diagnosis criteria for the major central disorders of hypersomnolence are specified in the International Classification of Sleep Disorders (1) and are summarized in the table.

	Narcolepsy type 1	Narcolepsy type 2	Idiopathic Hypersomnia	Kleine-Levin syndrome
Excessive Daytime Sleepiness	At least 3 months	At least 3 months	At least 3 months	<i>Episodic</i> bouts of long sleep and sleepiness, lasting 2 days to 5 weeks, accompanied by cognitive, perceptual, feeding, or behavioral change
Cataplexy	Typically present ¹	Absent	Absent	Absent
MSLT mean sleep latency	< 8 minutes ¹	< 8 minutes	< 8 minutes	Not required for diagnosis
Number of SOREMS	≥2 ¹	≥2	0-1	Not required for diagnosis
Cerebrospinal fluid hypocretin	If measured, ≤110 pg/mL	If measured, > 110 pg/mL	If measured, > 110 pg/mL	
24 hour measured sleep time (or actigraphic equivalent over 7 days)	Not required for diagnosis	Not required for diagnosis	>660 minutes can be used in lieu of typical MSLT findings	Not required for diagnosis but very long during spells

¹ Not required if cerebrospinal fluid hypocretin level is < 110 pg/mL or < 1/3 of control values. Abbreviations: MSLT = multiple sleep latency test; SOREM = sleep onset REM period (i.e., REM onset within the first 15 minutes after sleep onset, including both the initial sleep onset during nocturnal PSG and the 5 nap opportunities of the MSLT)

As is apparent from the above, there are several features that are particularly valuable in distinguishing several of these disorders. For patients suspected of having narcolepsy type 1, the presence of typical cataplexy is very specific for this diagnosis. Measurement of cerebrospinal fluid hypocretin provides unequivocal confirmation of this diagnosis, although commercial testing of hypocretin is not presently available. In patients with Kleine-Levin syndrome, the history of profound sleepiness and associated features, with relatively normal inter-ictal periods, makes the diagnosis on clinical grounds alone, without the requirement for electro-physiologic testing.

However, for narcolepsy type 2 and idiopathic hypersomnia (IH), diagnosis rests heavily on electrophysiologic testing, especially the multiple sleep latency test (MSLT). In this test, which is performed during the day immediately following an in-laboratory polysomnogram, patients are asked to lie down, close their eyes, and try to fall asleep at two hour intervals, five times throughout the day. The speed with which they are able to fall asleep on command (i.e., a measure of their “sleepability”) is averaged across the five nap opportunities to yield a mean sleep latency. Each nap that contains at least one epoch of REM sleep within 15 minutes of sleep onset is counted as a sleep-onset REM period (SOREM). Clinical characteristics of narcolepsy type 2 and idiopathic hypersomnia are very similar (2), enough so that patients with narcolepsy type 2 and those

with idiopathic hypersomnia without habitual sleep durations > 10 hours are reliably sorted into the same cluster based on symptoms using cluster analysis (3). As a result, the only feature that distinguishes these two disorders is one (or more) sleep onset REM periods (SOREM) on MSLT.

Unfortunately, the test-retest reliability of the MSLT, including SOREMs, is relatively poor in patients with central disorders of hypersomnolence other than narcolepsy type 1. In patients with type 1 narcolepsy, test-retest reliability is very good (4). In the other disorders, this is not the case, with diagnosis changing upon clinical repeat testing in half of patients (5). A similarly poor retest reliability is seen in population controls undergoing repeat MSLTs, with kappas for various MSLT features of only 0.1-0.3 (6).

Population-based MSLT studies have also shed light on the specificity problem of the MSLT. A mean sleep latency of less than 8 minutes is seen in 22% of multiple sleep latency tests performed in the general public (including repeat testing) (6). Multiple (at least two) SOREMs are also not uncommonly seen in the general population, occurring in 3.9-7% of MSLTs (6, 7). In the population, predictors of short mean sleep latency are short habitual sleep time and obstructive sleep apnea (6). Predictors of multiple SOREMs are short mean sleep latency, shift work, and male gender (6, 7).

MSLT sensitivity for disease may also have important limitations. Among 105 consecutive patients being evaluated for problematic sleepiness lasting at least three months who met all criteria for IH other than MSLT, 58 (55%) had an MSLT mean sleep latency more than 8 minutes; 28 of these 58 met criteria IH using total sleep time of over 660 minutes, leaving 30/105 undiagnosed (8). While it is difficult, in the absence of a gold standard other than the MSLT, to know whether these 29% of patients represent false positives or an accurate classification of disease vs non-diseased, a similar pattern has been seen by other groups. Out of 100 consecutive and very carefully phenotyped patients reporting excessive daytime sleepiness (in whom insufficient sleep, mood disorders, and non-hypersomnia sleep disorders had all been carefully excluded), 33 did not meet MSLT criteria for any hypersomnolence disorder due to a mean sleep latency more than 8 minutes (9). These patients with "subjective EDS" were similar to IH patients on measures of day and night sleep (excluding mean sleep latency), although were less likely to be positive for HLA DQB1*0602, leading the authors to speculate that the MSLT was truly misclassifying people who had clinically significant disease.

Once diagnosis is established, several treatment challenges arise. First, there are currently no medications approved by the US FDA that are labelled for the treatment of IH. In the case of insurance companies that only cover medications for their FDA-approved uses, this severely limits treatment options for IH patients. Direct reference to the two published, placebo-controlled, randomized controlled trials of modafinil including patients with idiopathic hypersomnia (10, 11) have been helpful in insurance appeals in some cases. In the study by Philip et al, 13 patients with narcolepsy and 14 with IH were treated with modafinil 200 mg twice a day in a crossover design, and demonstrated significant improvement versus placebo in ability to remain awake on maintenance of wakefulness test and in reduction in inappropriate line crossings on an on-road driving test (10). In the study by Mayer et al, idiopathic hypersomnia patients on modafinil 200 mg per day demonstrated significant improvement on Epworth Sleepiness Scale scores compared to those on placebo; MWT latencies were improved compared to baseline but not significantly different than placebo (11).

Second, even when medications are covered by insurers, they are not always effective. In clinical series, only 2/3rds of IH patients treated with modafinil remain on this medication with a good clinical response (12-15). Clinical response rates to amphetamines are lower (13, 14). In aggregate, approximately ¼ of patients with idiopathic hypersomnia are unable to achieve satisfactory symptom control with standard medications. Alternative treatments have been preliminarily investigated by several groups. Based on the presence of a positive allosteric modulator of GABA-A receptors within the spinal fluid of patients with hypocretin-normal hypersomnolence disorders (idiopathic hypersomnia, narcolepsy without cataplexy, subjective EDS), use of two negative modulators/antagonists of GABA-A receptors has been proposed. These include clarithromycin, a macrolide antibiotic for which a cross-over, randomized, controlled trial including patients with IH has demonstrated improvement in multiple subjective measures of sleepiness (16), and compounded flumazenil, which in a large patient series has demonstrated improvement in otherwise treatment-refractory sleepiness in a substantial minority of patients (17). Others have advocated the use of low dose (25 mcg) levothyroxine for patients with IH with long habitual sleep times, with reported benefits on sleepiness and sleep duration in a small patient series (18). Sodium oxybate has been used for the treatment of medication-refractory IH, with a response rate similar to that seen in narcolepsy, despite the use of significantly lower doses of medications and once-a-night dosing among patients with IH (19). The same group has also used pitolisant, a histaminergic medication that has recently been shown to help with both sleepiness and cataplexy in patients with narcolepsy (20, 21), for treatment-refractory IH patients and demonstrated an approximately 35% clinical response rate (22). This medication is not presently approved for use for any indication in the United States. Very recently, a small trial of transcranial direct current stimulation in treatment-naïve IH patients demonstrated improvement in sleepiness compared to baseline in 7 of 8 patients (23).

References

1. International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
2. Khan Z, Trotti LM. Central Disorders of Hypersomnolence: Focus on the Narcolepsies and Idiopathic Hypersomnia. *Chest*. 2015;148(1):262-73.
3. Sonka K, Susta M, M. B. Narcolepsy with and without cataplexy, idiopathic hypersomnia with and without long sleep time: a cluster analysis. *Sleep Medicine*. 2015; epub ahead of print.
4. Folkerts M, Rosenthal L, Roehrs T, Krstevska S, Murlidhar A, Zorick F, Wittig R, Roth T. The reliability of the diagnostic features in patients with narcolepsy. *Biol Psychiatry*. 1996;40(3):208-14.
5. Trotti LM, Staab BA, Rye DB. Test-retest reliability of the multiple sleep latency test in narcolepsy without cataplexy and idiopathic hypersomnia. *J Clin Sleep Med*. 2013;9(8):789-95.
6. Goldbart A, Peppard P, Finn L, Ruoff CM, Barnet J, Young T, Mignot E. Narcolepsy and predictors of positive MSLTs in the Wisconsin Sleep Cohort. *Sleep*. 2014;37(6):1043-51.
7. Singh M, Drake CL, Roth T. The prevalence of multiple sleep-onset REM periods in a population-based sample. *Sleep*. 2006;29(7):890-5.
8. Vernet C, Arnulf I. Idiopathic hypersomnia with and without long sleep time: a controlled series of 75 patients. *Sleep*. 2009;32(6):753-9.
9. Pizza F, Moghadam KK, Vandi S, Detto S, Poli F, Mignot E, Ferri R, Plazzi G. Daytime continuous polysomnography predicts MSLT results in hypersomnias of central origin. *J Sleep Res*. 2013;22(1):32-40.
10. Philip P, Chauffon C, Taillard J, Capelli A, Coste O, Leger D, Moore N, Sagaspe P. Modafinil improves real driving performance in patients with hypersomnia: a randomized double-blind placebo-controlled crossover clinical trial. *Sleep*. 2014;37(3):483-7.
11. Mayer G, Benes H, Young P, Bitterlich M, Rodenbeck A. Modafinil in the treatment of idiopathic hypersomnia without long sleep time—a randomized, double-blind, placebo-controlled study. *J Sleep Res*. 2015;24(1):74-81.
12. Lavault S, Dauvilliers Y, Drouot X, Leu-Semenescu S, Golmard JL, Lecendreux M, Franco P, Arnulf I. Benefit and risk of modafinil in idiopathic hypersomnia vs. narcolepsy with cataplexy. *Sleep Med*. 2011;12(6):550-6.
13. Ali M, Auger RR, Slocumb NL, Morgenthaler T. Idiopathic hypersomnia: clinical features and response to treatment. *J Clin Sleep Med*. 2009;5(6):562-8.
14. Anderson KN, Pilsworth S, Sharples LD, Smith IE, Shneerson JM. Idiopathic hypersomnia: a study of 77 cases. *Sleep*. 2007;30(10):1274-81.
15. Bastuji H, Jouvet M. Successful treatment of idiopathic hypersomnia and narcolepsy with modafinil. *Progress in neuro-psychopharmacology & biological psychiatry*. 1988;12(5):695-700.
16. Trotti LM, Saini P, Bliwise DL, Freeman AA, Jenkins A, Rye DB. Clarithromycin in gamma-aminobutyric acid-Related hypersomnolence: A randomized, crossover trial. *Ann Neurol*. 2015;78(3):454-65.
17. Trotti LM, Saini P, Koola C, LaBarbera V, Bliwise DL, Rye DB. Flumazenil for the Treatment of Refractory Hypersomnolence: Clinical Experience with 153 Patients. *J Clin Sleep Med*. 2016;12(10):1389-94.
18. Shinno H, Ishikawa I, Yamanaka M, Usui A, Danjo S, Inami Y, Horiguchi J, Nakamura Y. Effect of levothyroxine on prolonged nocturnal sleep time and excessive daytime somnolence in patients with idiopathic hypersomnia. *Sleep Med*. 2011;12(6):578-83.
19. Leu-Semenescu S, Louis P, Arnulf I. Benefits and risk of sodium oxybate in idiopathic hypersomnia versus narcolepsy type 1: a chart review. *Sleep Med*. 2016;17:38-44.
20. Dauvilliers Y, Bassetti C, Lammers GJ, Arnulf I, Mayer G, Rodenbeck A, Lehert P, Ding C-L, Lecomte J-M, Schwartz J-C. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. *The Lancet Neurology*. 2013;12(11):1068-75.
21. Szakacs Z, Dauvilliers Y, Mikhaylov V, Poverennova I, Krylov S, Jankovic S, Sonka K, Lehert P, Lecomte I, Lecomte JM, Schwartz JC, group H-Cs. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2017.
22. Leu-Semenescu S, Nittur N, Golmard J-L, Arnulf I. Effects of pitolisant, a histamine H3 inverse agonist, in drug-resistant idiopathic and symptomatic hypersomnia: a chart review. *Sleep medicine*. 2014.
23. Galbiati A, Abutalebi J, Iannaccone S, Borsa VM, Musteata S, Zucconi M, Giora E, Ferini-Strambi L. The effects of Transcranial Direct Current Stimulation (tDCS) on Idiopathic Hypersomnia: a pilot study. *Archives italiennes de biologie*. 2016;154(1):1-5.