Idiopathic Hypersomnia

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KEYWORDS

• Idiopathic hypersomnia • Narcolepsy • Excessive daytime sleepiness • Multiple sleep latency test • Sleep drunkenness

KEY POINTS

- Idiopathic hypersomnia (IH) is thought to be a rare disorder, but population-based estimates of prevalence are limited. Symptoms of IH are not uncommon.
- The differential diagnosis includes insufficient sleep time, circadian rhythm disorders, narcolepsy without cataplexy, hypersomnolence associated with psychiatric disease and medical conditions.
- Current diagnostic schema for IH diagnosis are imperfect, such that some patients do not meet criteria but still have problematic sleepiness.
- First-line treatment is generally modafinil, which is supported by 2 randomized, controlled trials showing efficacy. Psychostimulants are often used for IH treatment, although data supporting their use are sparse.
- Medication-refractory symptoms or medication intolerance prevents control of symptoms in one-quarter of IH patients; alternate treatment options are available, including clarithromycin.

INTRODUCTION

Idiopathic hypersomnia (IH) is a chronic neurologic disorder that manifests as pathologic daytime sleepiness with or without prolonged sleep durations. Population-based estimates of the frequency of IH are difficult to obtain, given the requirements for electrophysiologic testing and ruling out of other disorders that may cause similar symptoms. Clinic-based estimates of IH prevalence are limited by differing referral patterns and biases, such that estimates of the relative frequency of IH to narcolepsy with cataplexy vary substantially, anywhere from 1:10 to greater than 1:1.[1–5] As such, the true prevalence of IH is unknown. Using a questionnaire-based algorithm, Ohayon and colleagues[6] have demonstrated that the symptom of excessive sleepiness, associated with irresistible daytime naps, multiple naps in the same day, nonrestorative nocturnal sleep of at least 9 hours, or difficulty waking after sleep, is present in 0.5% of the population. Although presumably not all of these individuals would meet diagnostic criteria for IH, it is clear that the symptoms of IH are not uncommon.

As the name "idiopathic" hypersomnia implies, the pathophysiology of IH is presently unknown. Hypocretin deficiency, known to cause narcolepsy type 1, is not present in patients with IH.[7] Cerebrospinal fluid from patients with IH, and several other central disorders of hypersomnolence, has been shown to enhance activity at gamma-aminobutyric acid (GABA)-A receptors in vitro, in excess of that of cerebrospinal fluid from controls.[8] Although this enhancement of GABAergic transmission has not been shown to be causal to sleepiness or long sleep durations in patients with IH, biological plausibility is demonstrated by the known GABAergic mechanisms of sleep onset

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and maintenance, as well as the prominent role of GABA-A receptor agonists and modulators in the production of pharmacologic sleep and anesthesia.[9–12] Further, symptoms of IH are reversible in some patients with use of GABA-receptor antagonists or negative allosteric modulators (see Treatment Resistance).[8,13,14]

A family history of excessive sleepiness, IH, or another central disorder of hypersomnolence is seen in 34% to 38% of IH patients,[4,15,16] with parent–child transmission suggested by the finding that 12.5% of IH patients have at least 1 parent who routinely sleeps more than 9.5 hours per night.[17] Taken together, these reports suggest a genetic contribution to IH. However, the strong association between narcolepsy type 1 and HLA DQB1*0602 is not observed in patients with IH, in whom the rate of positivity for this allele ranges from 8% to 27%, depending on the population, and approximates the rate in controls.[4,18–20] An immune system dysregulation, unique from that implicated in narcolepsy type 1, might be present in patients with IH, as suggested by their significantly increased rates of comorbid inflammatory or allergic disorders[17,21] and altered immunoglobulin G profile compared with controls.[22] Disruption of autonomic nervous system functioning, with a shift toward increased vagal tone, has been noted in patients with IH compared with controls, possibly contributing to some of the vegetative symptoms (faintness, orthostatic hypotension, Raynaud syndrome) that are commonly observed in IH patients.[17,23,24]

Classically, sleep efficiency is greater than 90% in patients with IH,[4,16,18,24,25] although some studies have reported mean values in the high 80s.[15,19] The tendency for high sleep efficiency is somewhat at odds with the recently proposed hypothesis that patients with IH have fragmented sleep, as evidenced by more sleep stage changes, more N1 sleep, and more awakenings per hour than either controls or patients with narcolepsy type 1.[26] Abnormalities in slow wave sleep percentage have been proposed but inconsistently observed.[1,4,16,18,19,25,26] A single, small study has suggested an increase in spindle activity in IH patients compared with those with narcolepsy (type unspecified).[27]

PATIENT EVALUATION OVERVIEW

Core Diagnostic Features of Idiopathic Hypersomnia

Daytime sleepiness, defined as an irresistible need to sleep or episode of daytime sleep, is the core diagnostic feature of IH. Current diagnostic criteria in the *International Classification of Sleep Disorders* (ICSD), third edition,[24] require a combination of sleepiness for least 3 months, not better explained by another disorder or substance, and specific polysomnographic or actigraphic criteria (**Box 1**).

Ancillary Symptoms of Idiopathic Hypersomnia

Several ancillary features are commonly seen in people with IH.

Long sleep duration

Earlier editions of the ICSD explicitly defined a subset of IH defined by long sleep times (ie, >10 hours for the main sleep period). Although current criteria do not distinguish those with long sleep from those without, long sleep times can be used to confirm an IH diagnosis.[24]

Prolonged and unrefreshing naps

Similar to long sleep at night, naps during the day tend to be of long duration in patients with IH.[4,15,24] Patients with IH often find naps to be unrefreshing.[4,15–18,24] The clinical consequence of this is that, unlike in patients with narcolepsy

Box 1
Idiopathic hypersomnia diagnostic criteria

All of the following criteria must be met

1. Daily daytime sleepiness, defined as an "irrepressible need to sleep" or daytime sleep, that has been present at least 3 months
2. No cataplexy
3. No MSLT evidence for narcolepsy (ie, <2 sleep-onset REM periods on the overnight PSG and daytime MSLT considered together)
4. Electrophysiologic evidence of hypersomnolence, defined as either (or both) of:
   a. Mean sleep latency on MSLT of at least 8 minutes
   b. At least 11 hours of sleep per 24 hours, documented on a single 24-hour PSG or averaged across at least 7 days of actigraphic monitoring during ad lib sleep
5. Insufficient sleep is ruled out (including immediately before 24-hour PSG, if performed)
6. No other disorder or substance use better explains the symptoms

Abbreviations: MSLT, multiple sleep latency test; PSG, polysomnogram; REM, rapid eye movement.

Data from International classification of sleep disorders. 3rd edition. Darien (IL): American Academy of Sleep Medicine; 2014.