Idiopathic hypersomnia

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Introduction

This article includes discussion of idiopathic hypersomnia, hypersomnia with automatic behavior, hypersomnia with sleep drunkenness, idiopathic central nervous system hypersomnia, idiopathic hypersomnia with long sleep time, and idiopathic hypersomnia without long sleep time. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

This article includes discussion of idiopathic hypersomnia (IH), which is characterized by excessive daytime sleepiness, difficulty awakening (sleep drunkenness), and undisturbed overnight sleep without cataplexy or known cause of excessive sleepiness. Excessive sleepiness (hypersomnolence) of unknown etiology, which cannot be explained by another disorder, would be considered idiopathic hypersomnia. This should be clearly distinguished from other disorders that could present with complaints of excessive daytime sleepiness, such as narcolepsy, behaviorally-induced insufficient sleep, circadian rhythm disturbance, obstructive sleep apnea, or from hypersomnolence secondary to a medical condition or medication. These patients frequently present in adolescence and may have symptoms of autonomic nervous system dysregulation, but they are most often affected because of inability to attend to daytime obligations such as school or work. Because the pathophysiology is unknown, management is limited to symptomatic treatment and education.

Key points

- The main symptom of idiopathic hypersomnia is an irresistible urge to sleep despite adequate, or even excessive, nocturnal sleep, which lasts at least 3 months.
- For idiopathic hypersomnia duration of sleep (with and without long sleep time) is no longer a criterion for subtype distinction.
- Idiopathic hypersomnia can be associated with symptoms of autonomic nervous system dysregulation (orthostatic hypotension, syncope, headache, and Raynaud-type phenomena) and with significant sleep inertia (aka “sleep drunkenness”).
- The diagnosis of idiopathic hypersomnia is based on clinical features along with testing to rule out other causes of excessive daytime sleepiness (nocturnal polysomnography, multiple sleep latency test, and actigraphy).
- The differential diagnosis includes other conditions of excessive daytime sleepiness such as narcolepsy, inadequate total sleep time, sleep disorders that impair sleep quality, circadian rhythm disturbances, or hypersomnolence secondary to medical condition or medication.
- Treatment of idiopathic hypersomnia is primarily symptomatic involving education (sleep hygiene and lifestyle modifications) and wake-promoting agents such as stimulants.

Historical note and terminology

Prior to the use of polysomnographic studies, idiopathic hypersomnia (IH) was usually misdiagnosed as narcolepsy. Dement and colleagues first proposed that a diagnostic category other than narcolepsy should be used for patients who have excessive daytime sleepiness but do not have cataplexy, sleep paralysis, or sleep onset rapid eye movement episodes (Dement et al 1966). Subsequently, various labels were proposed to designate this entity: essential narcolepsy (Berti-Ceroni et al 1967), non-REM sleep narcolepsy (Passouant et al 1968), hypersomnia (Rechtschaffen and Roth 1969), hypersomnia with sleep drunkenness (Roth et al 1972), idiopathic hypersomnia (Roth 1976), idiopathic central nervous system hypersomnia (Anonymous 1979), and again idiopathic hypersomnia (American Sleep Disorders Association 1990). The previous sleep disorders classification parsed idiopathic hypersomnia into 2 categories based on sleep duration. Idiopathic hypersomnia with long sleep time (> 10 hours) entails excessive sleepiness with prolonged, unrefreshing naps lasting up to 3 or 4 hours, major sleep episodes of at least 10 to 14 hours in duration with difficulty waking up or sleep drunkenness, and no cataplexy. Idiopathic hypersomnia without long sleep time (< 10 hours) reflects excessive sleepiness and unintended, unrefreshing naps,

with the major sleep episode lasting less than 10 hours, with difficulty waking up or sleep drunkenness, and no cataplexy (American Academy of Sleep Medicine 2001). The 3rd edition of the International Classification of Sleep Disorders (ICSD-3) no longer dichotomizes idiopathic hypersomnia based on sleep duration, suggesting a belief that this may be a single, heterogenous condition (American Academy of Sleep Medicine 2014) (see Table 1).

Table 1. Criteria for Idiopathic Hypersomnia

Idiopathic hypersomnia diagnostic criteria (must meet criteria A to F)

A. Patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months

B. Cataplexy is absent

C. Multiple sleep latency test (MSLT) shows fewer than 2 sleep onset REM periods or no sleep onset REM periods if the REM latency on the preceding polysomnogram was < or = 15 minutes

D. Presence of at least 1 of the following:

1. MSLT shows a mean sleep latency of < or = 8 minutes

2. Total 24-hour sleep time is > or = 660 minutes on 24-hour polysomnographic monitoring (performed after correction of chronic sleep deprivation), or by wrist actigraphy in association with a sleep log (averaged over at least 7 days with unrestricted sleep)

E. Insufficient sleep syndrome is ruled out

F. Hypersomnolence and/or MSLT findings are not better explained by another sleep disorder, other medical or psychiatric disorder, or use of drugs or medications

Supportive findings

- Severe and prolonged sleep inertia (sleep drunkenness)
- High sleep efficiency (> or =90%) on polysomnogram
- Total 24-hour sleep time required for diagnosis is adapted based on normal changes in sleep duration for development (children, adolescents) and cultural variance.

Source: International Classification of Sleep Disorders, American Academy of Sleep Medicine, 3rd edition (2014).

Clinical manifestations

Presentation and course

The onset of idiopathic hypersomnia is often insidious and occurs in the second decade of life with key feature of near constant daytime sleepiness and complaints that the patient almost never feels alert. Along with this background of excessive sleepiness, patients often have long episodes of daytime sleep, with naps lasting over 1 hour. Compared to the daytime sleep episodes that occur in patients with narcolepsy, those associated with idiopathic hypersomnia tend to be more resistible, longer in duration, and not as refreshing. However, this difference from narcolepsy is not absolute and some patients with idiopathic hypersomnia have irresistible daytime sleep episodes and refreshing naps (Aldrich 1996; Bassetti and Aldrich 1997). The most important clinical distinction is the absence of cataplexy in patients with idiopathic hypersomnia.

Night sleep is typically long and consists of an average of 10 hours or more (up to 19 hours) (Voderholzer et al 1998). The nocturnal sleep is generally undisturbed in contrast to patients with narcolepsy, a condition in which fragmented nocturnal sleep is common (Aldrich 1996). Nocturnal sleep is usually consolidated with sleep efficiencies exceeding 85% and normal distribution of NREM and REM sleep stages. Awakening is often difficult, even with the use of sophisticated alarm clocks, and patients may describe morning disorientation in time and space, slowing of thought and speech, and inappropriate “automatic” behaviors lasting from several minutes to an hour or more, which is a state referred to as “sleep drunkenness”. The presence of sleep drunkenness has been reported in 36% to 52% of patients with idiopathic hypersomnia (Anderson et al 2007; Vernet and Arnulf 2009). Of significance, patients may report hypnagogic hallucinations and sleep paralysis, confirming that these symptoms are not specific to narcolepsy (Aldrich 1996; Bassetti and Aldrich 1997). An interesting association in some patients with idiopathic hypersomnia is the presence of what appears to be autonomic nervous system dysregulation, which includes orthostatic hypotension,

headaches, perceived temperature dysregulation, and Raynaud-type phenomena (American Academy of Sleep Medicine 2014). Like narcolepsy, idiopathic hypersomnia is often associated with depressive symptoms (Dauvilliers et al 2009).

According to a retrospective study, idiopathic hypersomnia has a prevalence of less than 1%, which is just 40% of the clinical prevalence of narcolepsy (Bassetti and Aldrich 1997; Billiard and Dauvilliers 2001; Anderson et al 2007). However, in the absence of systematic studies, the prevalence of idiopathic hypersomnia remains to be determined. Features that distinguished idiopathic hypersomnia from a comparable group of 63 narcoleptics were prolonged and nonrefreshing daytime naps, a positive family history of daytime hypersomnolence, increased slow-wave sleep, and longer sleep latency on the multiple sleep latency test (Anderson et al 2007). Patients with idiopathic hypersomnia have a reduced quality of life as evidenced by trouble maintaining employment and academic schedules and increased risk for divorce (Ozaki et al 2012).

Compared with healthy controls (Vernet and Arnulf 2009), patients with idiopathic hypersomnia have more fatigue, higher anxiety and depression scores, and more frequent hypnagogic hallucinations (24%), sleep paralysis (28%), sleep drunkenness (36%), and unrefreshing naps (46%) than controls. In addition, they depend on others to awaken them, have mental fatigability, and have difficulty maintaining alertness during the day (Vernet et al 2010).

Prognosis and complications

Idiopathic hypersomnia is usually a chronic, persistent disorder (Bassetti and Aldrich 1997). In a retrospective chart review only 11% of patients diagnosed with idiopathic hypersomnia were noted to have spontaneous remission of symptoms over the period of observation (Anderson et al 2007). The complications of idiopathic hypersomnia are mostly related to impairment in daytime functioning due to the excessive sleepiness with significant impact on social, professional, and employment-related activities. The greatest mortality risk with idiopathic hypersomnia remains falling asleep while driving or fatigue-associated driving impairment (Broughton et al 1978; Aldrich 1989; American Academy of Sleep Medicine 2001; American Academy of Sleep Medicine 2014).

Clinical vignette

A 23-year-old woman presented with a 2-year history of excessive daytime sleepiness. She reported that she “never” felt refreshed and had significant difficulty awakening from sleep. This caused difficulty with her ability to finish college. Her usual bedtime was 10 PM, and she was awoken by her mother by 7 AM. If not awoken by her parent, she would sleep until 10 AM or longer. She reported having a regular sleep schedule and no difficulty with sleep onset or sleeping through the night. After she was awoken, she reported feeling excessively sleepy, including feeling “sleep drunk,” which typically lasted 2 to 3 hours. She denied any nightmares, restless legs symptoms, cataplexy, hypnagogic hallucinations, or sleep paralysis. She drank 6 to 8 double espressos in the morning and coffee throughout the day without a favorable effect. The patient was unable to keep a job due to the sleepiness. She had been exposed to hexane and had developed a neuropathy that had been improving. Her family history was unremarkable, and review of systems was normal.

With a weight of 142 pounds and a height of 5 feet 2 inches, her BMI was calculated to be 26 kg/m^2. Her vital signs revealed an arterial blood pressure of 113/64 mmHg, temperature of 98.0° F, pulse of 84 beats per minute, respiration rate of 16/min. On physical exam, she was awake and appropriate without neurologic deficit or other abnormalities noted.

An MRI of the head was unremarkable. Laboratory testing showed normal values for electrolytes, renal, hepatic, and thyroid function tests and hemoglobin A1c. An overnight polysomnogram showed a sleep onset latency of 13 minutes and a REM sleep latency (from the first 30-second epoch scored as sleep) of 43 minutes. The sleep efficiency (total sleep time divided by time in bed) was 92%. She snored lightly and had an apnea-hypopnea-index of 3 per hour. The 5-nap multiple sleep latency test revealed a mean sleep latency of 3.5 minutes without sleep-onset REM periods (SOREMPs) on any of the 5 naps.

She was diagnosed with idiopathic hypersomnia and was started on stimulant medication. Methylphenidate, 10 mg in the morning and 10 mg at lunchtime, improved her excessive daytime sleepiness significantly. Once her excessive daytime sleepiness improved, she was able to complete school and find a new job.

Biological basis

Etiology and pathogenesis

The exact cause of idiopathic hypersomnia remains unknown. There are limited data regarding the neurobiology and pathogenesis/pathophysiology of idiopathic hypersomnia, and there is no existing animal model for more detailed study. Many neurochemical studies regarding the disorder have been inconclusive. In a study comparing patients with idiopathic hypersomnia and narcolepsy type 1, using sleep diary and self report measures, 2 subgroups emerged: 1 with family history and 1 with a postinfectious onset (Bruck and Parkes 1996). These findings suggest the possibility of gene-environment interactions that can contribute to disease in a fashion similar to narcolepsy with hypocretin deficiency.

Neurotransmitters. From a structural perspective, the destruction of noradrenergic neurons of the rostral third of the locus coeruleus complex or of the noradrenergic bundle at the level of the isthmus in the cat leads to hypersomnia with a proportional increase of non-REM sleep and REM sleep, resembling idiopathic hypersomnia (Petitjean and Jouvet 1970). This state is accompanied by a decrease of diencephalic norepinephrine (Petitjean and Jouvet 1970). These findings are concordant with the observations of von Economo during the encephalitis lethargica epidemic, which highlighted that patients suffering from excessive sleepiness often had lesions at the junction of the posterior hypothalamus and midbrain (Von Economo 1930). Additionally, therapeutic measures for idiopathic hypersomnia, such as stimulants and modafinil/armodafinil, which typically act on catecholamine (dopamine, norepinephrine) signaling mechanisms, indicate that there may be some contribution of these neurochemical pathways in the pathogenesis of idiopathic hypersomnia. Other aspects that have been evaluated as possibly contributing to the pathogenesis of idiopathic hypersomnia are histamine signaling, melatonin secretion abnormalities, immunologic and inflammatory processes, somnogens, and genetic factors.

In the 1980s, studies in less well-characterized clinical idiopathic hypersomnia patients found some differences in monoamine metabolites and suggested that idiopathic hypersomnia may have a component of disrupted dopamine signaling. One study found decreased dopamine and indoleacetic acid (tryptophan metabolites) compared to controls in the CSF of patients with narcolepsy and idiopathic hypersomnia (Montplaisir and Poirier 2012).

Histamine has also been suggested as a biomarker in the pathophysiology of idiopathic hypersomnia, though the evidence is inconclusive (Rye 2012). Histamine is a wakefulness producing neurotransmitter. In rats, histamine in the frontal cortex is positively correlated with wakefulness (Chu et al 2004). Additionally, mice that are histamine deficient demonstrate less wakefulness in the early stages of arousal (Parmentier et al 2002), and H1-deficient mice have fewer arousals from sleep. Anti-histamines (H1 antagonists) are well known to increase somnolence across many species including humans. Two studies evaluated CSF histamine in patients with hypersomnia of various origins. One small, uncontrolled study looked at CSF histamine in patients with multiple causes of excessive daytime sleepiness and found an inverse correlation of CSF histamine with a severity of reported sleepiness based on the Epworth Sleepiness Scale (Bassetti et al 2010). Kanbayashi and colleagues found that CSF histamine was reduced (compared to controls) in patients with narcolepsy (type 1 and type 2), as well as idiopathic hypersomnia, but not in patients with obstructive sleep apnea (Kanbayashi et al 2009). However, a larger study looking at histamine, t-methylhistamine, and hypocretin in various conditions that lead to hypersomnia failed to show differences in CSF histamine or t-methylhistamine levels in patients with idiopathic hypersomnia compared to controls (Dauvilliers et al 2012). From a more clinical perspective, histaminergic compounds like pitolisant, an inverse H3 agonist, have been useful in the management of drug resistant conditions associated with hypersomnia, including idiopathic hypersomnia, through their resultant increases in brain histamine levels (Leu-Semenescu et al 2014).

Investigators have reported on a potential 500-to-3000-dalton somnogen that potentiates γ-hydroxybutyrate (GABA) through activity at the at the benzodiazepine site on the α2 subunit of the $GABA_A$ receptor (Rye et al 2012). Blockade of the activity with a benzodiazepine antagonist, flumazenil, has yielded modest results in a small proportion of a cohort of mixed hypersomnia patients (Trotti et al 2016).

Although hypocretin-1 is implicated in narcolepsy type 1, this neurotransmitter does not appear to be pathogenic in idiopathic hypersomnia (Dauvilliers et al 2012).

Inflammatory/cytokines. Some studies indicate that idiopathic hypersomnia may have an immunological or inflammatory component, similar to narcolepsy type 1. Among patients with idiopathic hypersomnia, human leukocyte

antigen-Cw2 was found in 22.2% compared to 5.7% in controls ($p < 0.05$) (Montplaisir and Poirier 2012). Also, HLA-DR5, which is in linkage dysequilibrium with HLA-Cw2, was present in 38.8% of patients versus 14.6% of controls (Montplaisir and Poirier 2012). Further studies, however, did not find any similar association with idiopathic hypersomnia and HLA haplotypes (Bassetti and Aldrich 1997; Billiard et al 1998). However, the poor associations with HLA regions may be explained by the variability of subjects exposed to a triggering factor (eg, infection, as in narcolepsy type 1) (Longstreth et al 2009; Dauvilliers et al 2010), as well as the fact that idiopathic hypersomnia represents a heterogenous population. Nonetheless, additional data that indicate there may be an immunological component are the serum total IgG levels in 28 Japanese patients with idiopathic hypersomnia and long sleep times. Those patients with idiopathic hypersomnia had high IgG3 and IgG4 levels, low IgG2 level, and IgG1/IgG2 imbalance, which was different than healthy individuals (Tanaka and Honda 2010).

Related to the immune-mediated-disease hypothesis is the observation that proinflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNFα) are elevated in disorders associated with excessive daytime sleepiness, such as sleep apnea, narcolepsy, and idiopathic hypersomnia. Although these cytokines are part of the innate immune system, their activity meets the criteria of a somnogen/sleep regulatory substance (Krueger et al 2015). Most notably, sleep deprivation also leads to sleepiness and daytime hypersecretion of IL-6. These findings suggest that IL-6 and TNFα are possible mediators of excessive daytime sleepiness in humans (Vgontzas and Chrousos 2002).

Genetics. A genetic basis for some cases of idiopathic hypersomnia is suggested by several investigations. Early studies indicated that a large minority of patients with idiopathic hypersomnia had a similarly affected first degree relative (Nevsimalova-Bruhova and Roth 1972; Roth and Broughton 1980; Billiard and Besset 1998). Although these data strongly suggest a genetic component, possibly autosomal dominant, the limited number of families studied has not permitted definitive determination of the mode of inheritance. A number of studies have sought to explore the genetic basis of sleep duration using genome-wide association studies. Unfortunately, sample size limitations and phenotype heterogeneity have limited the findings thus far. To date, the largest analysis of genetic contributions to sleep duration has come from a study of individuals in the UK Biobank (http://www.ukbiobank.ac.uk) (Jones et al 2016). The findings confirmed a prior association (Gottlieb et al 2015) with the thyroid-specific transcription factor, *PAX8*, and identified a novel association with a multicascade serine/threonine kinase, *VRK2* (Allebrandt et al 2013). However, the variants associated with the identified genes conferred insubstantial effects on sleep duration (2.6 min per *PAX8* allele and 1.6-2.0 min per *VRK2* associated variant), highlighting the difficulties in identifying the genetic contributors to such multifactorial phenotypes. Future study of extreme, well-phenotyped individuals and multiplex families may reveal more meaningful associations.

Additionally, circadian rhythm gene-expression analyses have revealed some abnormalities in individuals with idiopathic hypersomnia; however, causality has yet to be established. In 2014, a study by Lippert and colleagues evaluated gene expression of certain circadian clock genes in cultured dermal fibroblasts of patients with a diagnosis of idiopathic hypersomnia compared to that in normal healthy controls (Lippert et al 2014). This study revealed statistically significant reductions in the amplitude of the expected oscillation in the transcription of *BMAL1*, *PER1*, and *PER2* (Lippert et al 2014). The authors postulated that the dampening of oscillations of these transcriptional factors in the SCN, which modulate pineal melatonin secretion, may explain the decreased melatonin secretion seen in idiopathic hypersomnia (Teclemariam-Mesbah et al 1999; Nevsimalova et al 2000).

In sum, despite a number of intriguing findings spanning the domains of CNS neurotransmitters, immunology, and genetics, the pathophysiology underlying idiopathic hypersomnia remains nebulous. A number of factors contribute to this elusive disorder, not the least of which include the poor objective characterization of this phenotype with the currently available diagnostic methods (see management section below), the genetic complexity, the unclear risk factors, and environmental exposures.

Epidemiology"

Evaluation of the prevalence of idiopathic hypersomnia in the general population is difficult due to the limited number of patients with this condition and the difficulty of making a definitive diagnosis. For example, after excluding patients with symptoms and medication that might confound a diagnosis in patients with daytime sleepiness, Laffont and colleagues comprehensively evaluated 128 patients (16 to 77 years of age) in whom no clear diagnosis had been established for their daytime sleepiness and found that only 12% (15 patients) fit criteria for idiopathic hypersomnia. Using their own nomenclature they characterized the other subjects as having various disorders such as: mild hypersomnia type 1, hypersomnia associated with HLA type DR2-DQw1, mild hypersomnia type 2, patients with

morning recovery from disrupted sleep, young “long sleepers” with difficulty waking up, poor short sleepers since childhood, and older poor sleepers with late onset of symptoms (Laffont et al 2002).

Despite the limited nature of epidemiological data, the prevalence of idiopathic hypersomnia patients compared to narcoleptic patients provides some indication of overall prevalence. For comparison, improvements in recognition and diagnosis of type 1 narcolepsy have pointed to an estimated prevalence of 0.02% to 0.03% (Mignot 1998). Based on review of a large cohort of over 6000 patients with sleep disorders in the United Kingdom, idiopathic hypersomnia was found to be 40% to 60% as prevalent as narcolepsy, depending upon what MSLT criteria is used (Anderson et al 2007). These findings are lower than those in earlier studies, probably because of improved identification of sleep disorders that were formerly diagnosed as idiopathic hypersomnia. Integrating these findings into a metaanalysis exploring the epidemiology, diagnosis, pathophysiology, and treatment of idiopathic hypersomnia suggested that the prevalence of idiopathic hypersomnia in the adult population is between 1 in 5000 and 1 in 50,000.

Clinically, approximately 10% to 29% of individuals referred to a sleep center for excessive daytime sleepiness ultimately receiving a diagnosis of idiopathic hypersomnia (Sowa 2016; Saini and Rye 2017).

Prevention

Prevention and risk factors are unknown.

Differential diagnosis

Idiopathic hypersomnia is probably 1 of the most frequently misdiagnosed sleep disorders, potentially due to disorders that are less recognized than narcolepsy and obstructive sleep apnea, yet can cause excessive daytime sleepiness. Many other conditions produce such sleepiness and can mimic or coexist with a hypersomnia of central origin. All of these possible confounders need to be considered in the differential diagnosis as possibly causing or contributing to the excessive sleepiness in a patient with hypersomnia of central origin (Morgenthaler et al 2007).

An exploration of the causes of excessive daytime sleepiness (EDS) in 16,583 randomly sampled Pennsylvanians identified 1742 sleepy individuals who were then recruited for laboratory evaluation. Regression analysis revealed that a report of being treated for depression is the most significant risk factor for the complaint of excessive daytime sleepiness (with increasing effects in younger individuals), followed by BMI, age, subjective estimate of typical sleep duration, diabetes, smoking, and finally sleep apnea (Bixler et al 2005). This emphasizes that potentially confounding medical/psychiatric disorders and their treatments (Pagel 2009; Gonçalves and Togeiro 2013) precludes the diagnosis of a primary CNS hypersomnia, such as idiopathic hypersomnia, and their presence must be assessed and corrected (where possible) before a diagnosis can be made (American Psychiatric Association 2013; American Academy of Sleep Medicine 2014). Additionally, primary sleep disorders that affect the quality and quantity of sleep must be ruled out, including: upper airway resistance syndrome (UARS, a milder form of obstructive sleep apnea), other primary CNS hypersomnias (eg, Kleine-Levin syndrome and narcolepsy type 1 or 2), circadian sleep phase disorder, and behaviorally-induced insufficient sleep syndrome.

Hypersomnia due to a medical disorder includes irresistible urge to sleep and excessive daytime sleepiness for at least 3 months due to underlying medical or neurologic condition, and it does not meet criteria for narcolepsy. Associated conditions can include neurodegenerative diseases (eg, Parkinson disease or multiple system atrophy), posttraumatic brain injury, stroke or brain tumors (potentially involving the hypothalamus or midbrain), hypothyroidism, or metabolic derangement (chronic renal insufficiency, hepatic encephalopathy, neuroglycopenia) (Dauvilliers and Buguet 2005; Maestri et al 2010; American Academy of Sleep Medicine 2014). Posttraumatic hypersomnia may closely mimic idiopathic hypersomnia. Hypersomnia usually develops 6 to 18 months after head trauma (Guilleminault et al 1983). Excessive sleepiness may be the first symptom of progressive hydrocephalus in the absence of other features of hydrocephalus. Systemic exertional intolerance disease (formerly known as chronic fatigue syndrome, or myalgic encephalomyelitis, despite a lack of evidence of CNS inflammation) is characterized by persistent or relapsing fatigue that does not resolve with bedrest. It is important to differentiate sleepiness (a propensity for dozing off) from fatigue (a lack of physical energy, or body “tiredness”), in any such patients (Krupp et al 1989). Additionally, there are a number of genetic syndromes that result in hypersomnia including autosomal dominant cerebellar ataxia, deafness, narcolepsy (Winkelmann et al 2012), Moebius syndrome (Parkes 1999; Tyagi and Harrington 2003; Krämer et al 2014), Coffin-Lowry syndrome (Nelson and Hahn 2003), Niemann-Pick disease type C1 (Vankova et al 2003; Oyama et al 2006; Pedroso et al 2012), Norrie disease (Vossler et al 1996; Parkes 1999; Smit et al 2006), myotonic dystrophy

(Martínez-Rodríguez et al 2003), and Prader-Willi syndrome (Parkes 1999; Mignot et al 2002).

Hypersomnia due to medication or substance is based on excessive daytime sleepiness and an irresistible urge to sleep due to substance/sedative use or withdrawal from stimulant medications. Substances or sedating medications can include alcohol, opiates, marijuana, benzodiazepines, non-benzodiazepine hypnotics, barbiturates, anti-epileptic medications, antipsychotic medications, anticholinergics, antihistamines, antidepressants, and/or combination of medications. Beyond the obvious psychotropic sedatives, a plethora of medications have drowsiness listed as a side effect, either through primary or off-target effects (Gonçalves and Togeiro 2013). Withdrawal from or abrupt cessation of stimulants such as amphetamines or caffeine can also lead to symptoms of hypersomnia. This can be distinguished from idiopathic hypersomnia with a careful and detailed history, and polysomnography is generally unnecessary.

Hypersomnia associated with psychiatric disorders (dysthymia and related mood disorders) can be distinguished from idiopathic hypersomnia based upon its onset later in life and findings of low-grade, chronic depression revealed through clinical interviews and psychometric testing. In fact, as noted above, depression conferred the highest risk of excessive daytime sleepiness (OR 6.85, $p < 0.001$) in a large multiple logistic regression model (Bixler et al 2005). The multiple sleep latency test often does not demonstrate a short mean sleep latency in depression associated hypersomnia, and continuous 24-hour polysomnography shows normal daytime wakefulness despite patients having relative motor quiescence. Thus, they may not move but they are awake (Dolenc et al 1996). Treatment of hypersomnia may or may not improve depression scores, indicating that the relationship between mood disorders and hypersomnia is more complex than simple cause and effect (Haba-Rubio 2005), particularly in light of the fact that idiopathic hypersomnia patients will develop depression as a result of diagnostic delays and the psychosocial burden of their disease (Dauvilliers et al 2009; Vernet et al 2010). Thus, a concerted approach focused on treating both disorders is essential.

After addressing the primary medical and psychiatric conditions that may result in sleepiness, the most obvious disorders that contribute to excessive daytime sleepiness are the sleep disorders that impair sleep quality and quantity: sleep-disordered breathing (eg, obstructive sleep apnea), restless legs syndrome, periodic limb movement disorder, and circadian phase disorders (Slater and Steier 2012). A less-commonly-known sleep breathing disorder is the upper airway resistance syndrome (UARS). Subjects with UARS may complain of excessive daytime sleepiness (Guilleminault et al 1993). Polysomnography discloses short alpha EEG arousals lasting 3 to 14 seconds that regularly interrupt snoring periods, which are polysomnographically scored as respiratory-event-related arousals (RERA). UARS is classified within obstructive sleep apnea by the American Academy of Sleep Medicine based on the most recent edition of the International Classification of Sleep Disorders (ICSD) (American Academy of Sleep Medicine 2014). To make this diagnosis in adults, the calculated respiratory disturbance index (RDI) should be greater than 5 events per hour (with AHI less than 5 per hour) (Guilleminault and Los Reyes 2011). Furthermore, circadian misalignment (most commonly problematic in those with delayed sleep phase syndrome) is a diagnostic consideration in patients whose main complaint is extreme difficulty awakening at the desired time and excessive morning sleepiness. However, these patients are not sleepy in the evening and go to bed extremely late in the night (Weitzman et al 1981). The diagnosis can be confirmed with review of sleep diary and actigraphy.

Consideration of other primary CNS hypersomnias must also be given. In particular, type 1 narcolepsy is often differentiated through the presence of the telltale presence of cataplexy, which is a sudden loss of muscle tone in response to (usually positive) emotion (Scammell 2015). Differentiation of idiopathic hypersomnia from the non-hypocretin-deficient, type 2 narcolepsy is far more challenging, and clinical symptoms alone cannot provide a clear differentiation of the disorders (Sonka et al 2015), as they are nonspecific to any of the primary hypersomnias (Saini and Rye 2017). Kleine-Levin syndrome is a rare disorder characterized by recurrent episodes of excessive sleepiness (episodes typically lasting 10 days, but possibly up to a few weeks) associated with cognitive dysfunction, altered perception of the environment, eating disorder (commonly hyperphagia), and/or disinhibited behavior (such as hypersexuality), with onset usually in adolescence, and gradual remission often over many years. Most remarkable is that these patients appear to return to a completely normal baseline in the months between the episodes of hypersomnia, and may suffer from a degree of amnesia or report derealization of the event (American Academy of Sleep Medicine 2014).

Given the current epidemic of sleep deprivation (Centers for Disease Control and Prevention 2015), behaviorally-induced insufficient sleep syndrome must be considered in all individuals presenting with excessive daytime sleepiness, impaired concentration, and lowered energy level. A detailed history of the current sleep schedule is

revealing, and actigraphy can also be useful in establishing a wake-sleep pattern (Roehrs et al 1983).

Finally, normal variations in the amount of sleep needed per night can include adults who require longer sleep times, greater than 10 hours (in 24 hour period). They may be misdiagnosed with idiopathic hypersomnia because of extremely long sleep episodes at night. However, these patients are normally alert once they have slept their needed amount of sleep.

Diagnostic workup

The diagnosis of idiopathic hypersomnia is mainly based upon findings discovered during a clinical history. However, actigraphy, polysomnography, and multiple sleep latency testing (MSLT) are necessary to confirm the diagnosis and to rule out other sleep disorders. The most widely used test is overnight polysomnography, followed by the MSLT. This sequence of sleep studies allows sleep-disordered breathing, narcolepsy, periodic leg movements, and sleep fragmentation to be ruled out as causes of excessive daytime sleepiness.

One of the most common mistakes made performing the PSG-MSLT is to wake the patient up in the morning instead of letting them sleep in as long as they can. This leads an individual who may have a prolonged sleep requirement or a circadian rhythm delay to have shortened sleep latencies and risk a false positive result.

The MSLT was originally devised for the diagnosis of narcolepsy type 1 (Carskadon and Dement 1994), where it is best validated (Folkerts et al 1996). However, outside of narcolepsy type 1, its diagnostic utility is more limited (Mignot et al 2006; Trotti et al 2013). A mean sleep latency cutoff of 8 minutes (less than 8 minutes suggestive of hypersomnia) has poor reliability, as many idiopathic hypersomnia patients have mean sleep latencies of more than 8 minutes (leading to a false negative result) and 22% of the general public have sleep latencies of less than 8 minutes (leading to a false positive result) (Carskadon et al 1986; American Academy of Sleep Medicine 2014). Further, 71% of hypersomniacs with long sleep time were noted to have a normal MSLT (Vernet and Arnulf 2009). Maintenance of wakefulness testing (MWT) has used as a tool to determine treatment response and to assess a patient's ability to remain awake in individuals whose hypersomnia may constitute a safety issue. However, like the MSLT, the MWT suffers from similar problems of reliability and its uses remain controversial (Grossman et al 2004; Littner et al 2005).

With prolonged polysomnographic monitoring, without provoked morning awakening, recordings are performed for up to 24 hours and the subject is asked not to fight sleep. This test will typically show prolonged night sleep and 1 or 2 prolonged naps during daytime. Contrasting with narcolepsy, the architecture of sleep is harmonious with few or no awakenings, normal percentage of NREM sleep stages and REM sleep, and no sleep onset rapid eye movement episode either at night or during daytime. The most recent version of the International Classification of Sleep Disorders has allowed for the usage of prolonged polysomnography in the objective documentation of excessive sleep (> 660 minutes) (American Academy of Sleep Medicine 2014). Alternatively, an average sleep duration of greater than 10 hours on at least 7 days of conventional actigraphy can be used to confirm long sleep durations (American Academy of Sleep Medicine 2014).

HLA typing is not sufficiently specific or sensitive to use for diagnosis of idiopathic hypersomnia. The HLA-DQB1*06:02 allele is highly prevalent (97%) in narcolepsy type 1, but is also found frequently (

Management

Treatment of idiopathic hypersomnia is similar to that of narcolepsy, however, with substantially less evidence to support the various therapies. Further, as there are no FDA-approved treatments for idiopathic hypersomnia, medications are used off-label and, thus, must be used cautiously with clearly expressed and documented patient understanding of the risks and benefits of such usage. Nonmedication treatment can include lifestyle modification, attention to sleep hygiene, and/or scheduled naps (Adenuga and Attarian 2014). Education about the impact of the condition on academic development, work, driving, and social life can assist patients as they attempt to live a normal life.

Modafinil and armodafinil (the R racemate of modafinil) have a benefit/risk profile in idiopathic hypersomnia similar to its effect on narcolepsy type 1 (Bastuji and Jouvet 1988; Lavault et al 2011). Modafinil has been reported to have a modest but significant effect on hypersomnia in children (Ivanenko et al 2003; Anderson et al 2007). With response rates as high as 72% (after accounting for dropouts due to factors such as cost) (Ali et al 2009), the American Academy of Sleep Medicine has concluded that modafinil might be an effective therapy for idiopathic hypersomnia

(Morgenthaler et al 2007).

Other psychostimulant drugs such as dextroamphetamine and methylphenidate are the mainstays of treatment, however, due to their high potential for abuse and undesirable side-effects these medications are often reserved for second-line therapy, with a preference for long-acting agents (Morgenthaler et al 2007). For reasons unclear, these medications do not often result in sustained benefits for idiopathic hypersomnia as they do in narcolepsy. This may result in attempts to achieve better clinical response by exceeding recommended maximum guideline dosages. Exceeding standard dosages often precipitates psychosis, headache, substance misuse, tachyarrhythmia, anorexia, or other significant side effects (Auger et al 2005).

Additional therapies have been employed in treatment-refractory idiopathic hypersomnia patients. Sodium oxybate, an agonist at the γ-hydroxybutyrate and $GABA_B$ receptors that promotes slow-wave sleep, was studied in 46 idiopathic hypersomnia patients, revealing a good response in 65% of the 39 patients that chose to fill the prescription (Leu-Semenescu et al 2016). The antibiotic clarithromycin may be a negative allosteric inhibitor of the $GABA_A$ receptor, which prompted study of its effects in a retrospective chart review and small clinical trial, both of which showed modest benefits (Trotti et al 2014; Trotti et al 2015). Similarly the benzodiazepine receptor agonist, flumazenil, was studied by the same group, with minor benefits in psychomotor vigilance task measures and subjective alertness (Rye et al 2012). An inverse agonist targeting the autoinhibitory H3 histamine receptor, pitolisant, has been studied in idiopathic hypersomnia and narcolepsy with clinically significant improvements in excessive daytime sleepiness (Leu-Semenescu et al 2014; Szakacs et al 2017). Finally, a trial of transcranial direct current stimulation demonstrated an improvement in sleepiness and attention compared to baseline evaluation (Galbiati et al 2016). Hopefully further investigations of these and other therapies will result in the discovery of therapies with sustained efficacy for idiopathic hypersomnia.

Outcomes

Even if treated, most patients with idiopathic hypersomnia suffer from psychosocial impairments in their work and personal lives as well as score lower than healthy individuals on assessments of general health (Dauvilliers et al 2009; Ozaki et al 2012). Nonetheless, outcomes can be favorable with stimulant medication, and are usually based on patient subjective reports. Clinical monitoring of therapeutic response can be performed with the maintenance of wakefulness test (MWT) or actigraphy; however, this is not common unless there is an indication (eg, commercial truck drivers). A few objective tests are employed in research (eg, the sustained attention to response task (Fronczek et al 2006) and the psychomotor vigilance test (Dinges and Powell 1985; Basner and Dinges 2011) and can provide objective outcome measures, though they tend to not correlate with symptom reports/subjective measures (Saini and Rye 2017).

Complications of treatment are medication-specific. In general, the psychostimulants used to treat idiopathic hypersomnia result in side effects through their action on the monoaminergic neurotransmitter systems. Medications that work primarily through reuptake inhibition (eg, modafinil) are generally better tolerated than those that also result in dopamine release or norepinephrine reuptake inhibition at higher doses (eg, amphetamine salts). Postmarketing monitoring revealed a risk for Stevens-Johnson syndrome in modafinil (Cephalon Inc. 2007b), and there is diminished hormonal contraceptive efficacy while taking this medication class (Cephalon Inc. 2007a; Cephalon Inc. 2007b). The traditional psychostimulants (eg, amphetamine salts and methylphenidate) are more sympathomimetic, resulting in a higher risk of toxicity, in addition to the higher risk of abuse (Stiefel and Besag 2010; Leviel 2011; Mignot 2012). Sodium oxybate has a heightened risk of anxiety and depression with suicidal ideation. In addition it carries a high sodium load, suggesting a need for caution in patients with heart failure or renal insufficiency (Jazz Pharmaceuticals 2002; Ortega-Albás et al 2010; Rossetti et al 2010).

Special considerations

Pregnancy

No data are available on the effect of pregnancy on idiopathic hypersomnia or of idiopathic hypersomnia on pregnancy. Attention to FDA pregnancy categories for medications used for treatment is essential as most medications are category C (ie, amphetamines, methylphenidate, modafinil, and armodafinil).

Anesthesia

In patients with idiopathic hypersomnia, stimulant drugs should be discontinued in anticipation of surgery. The effects of anesthesia on idiopathic hypersomnia are unknown.

References cited

Adenuga O, Attarian H. Treatment of disorders of hypersomnolence. Curr Treat Options Neurol 2014;16(9):302. PMID 25080137

Aldrich MS. Automobile accidents in patients with sleep disorders. Sleep 1989;12:487-94. PMID 2595172

Aldrich MS. The clinical spectrum of narcolepsy and idiopathic hypersomnia. Neurology 1996;46:393-401. PMID 8614501

Ali M, Auger RR, Slocumb NL, Morgenthaler TI. Idiopathic hypersomnia: clinical features and response to treatment. J Clin Sleep Med 2009;5(6):562-8. PMID 20465024

Allebrandt KV, Amin N, Müller-Myhsok B, et al. A K(ATP) channel gene effect on sleep duration: from genome-wide association studies to function in Drosophila. Mol Psychiatry 2013;18(1):122-32. PMID 22105623

American Academy of Sleep Medicine. International classification of sleep disorders, revised: diagnostic and coding manual. Neurology. Chicago, IL: American Academy of Sleep Medicine, 2001.

American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Diagnostic and coding manual. Westchester, Illinois: American Academy of Sleep Medicine, 2014.

American Sleep Disorders Association. International classification of sleep disorders: diagnostic and coding manual. Rochester (MN): American Sleep Disorders Association, 1990.

Anderson KN, Pilsworth S, Sharples LD, Smith IE, Shneerson JM. Idiopathic hypersomnia: a study of 77 cases. Sleep 2007;30(10):1274-81. PMID 17969461

Andlauer O, Moore H 4th, Hong SC, et al. Predictors of hypocretin (orexin) deficiency in narcolepsy without cataplexy. Sleep 2012;35(9):1247-55F. PMID 22942503

Anonymous. Diagnostic classification of sleep and arousal disorders. 1979 first edition. Association of Sleep Disorders Centers and the Association for the Psychophysiological Study of Sleep. Sleep 1979;2(1):1-154.

Auger RR, Goodman SH, Silber MH, Krahn LE, Pankratz VS, Slocumb NL. Risks of high-dose stimulants in the treatment of disorders of excessive somnolence: a case-control study. Sleep 2005;28(6):667-72. PMID 16477952

Basner M, Dinges DF. Maximizing sensitivity of the psychomotor vigilance test (PVT) to sleep loss. Sleep 2011;34(5):581-91. PMID 21532951

Bassetti C, Aldrich MS. Idiopathic hypersomnia. A series of 42 patients. Brain 1997;120:1423-35. PMID 9278632

Bassetti CL, Baumann CR, Dauvilliers Y, et al. Cerebrospinal fluid histamine levels are decreased in patients with narcolepsy and excessive daytime sleepiness of other origin. J Sleep Res 2010;19(4):620-3. PMID 20846244

Bastuji H, Jouvet M. Successful treatment of idiopathic hypersomnia and narcolepsy with modafinil. Prog Neuropsychopharmacol Biol Psychiatry 1988;12(5):695-700. PMID 2906157

Berti-Ceroni G, Coccagna G, Gambi D, Lugaresi E. Clinico-polygraphic considerations on essential "slow sleep" narcolepsy [Article in Italian]. Sist Nerv 1967;19:81-9. PMID 4304077

Billiard M, Dauvilliers Y. Idiopathic hypersomnia. Sleep Med Rev 2001;5(5):349-58. PMID 12530998

Billiard M, Merle C, Carlander B, Ondze B, Alvarez D, Besset A. Idiopathic hypersomnia. Psychiatry Clin Neurosci 1998;52:125-9. PMID 9628108

Bixler EO, Vgontzas AN, Lin HM, Calhoun SL, Vela-Bueno A, Kales A. Excessive daytime sleepiness in a general

population sample: the role of sleep apnea, age, obesity, diabetes, and depression. J Clin Endocrinol Metab 2005;90(8):4510-5. PMID 15941867

Broughton R, Nevsimalova S, Roth B. The socioeconomic effects (including work, education, recreation and accidents) of idiopathic hypersomnia. Sleep Res 1978;7:217.

Bruck D, Parkes JD. A comparison of idiopathic hypersomnia and narcolepsy-cataplexy using self report measures and sleep diary data. J Neurol Neurosurg Psychiatry 1996;60:576-8. PMID 8778267

Carskadon MA, Dement WC. Normal sleep and its variations. In: Kyrger M, Roth T, Dement WC, eds. Principles and practice of sleep medicine. Philadelphia: Elsevier Saunders, 1994;1-13.

Research paper (PDF): Respiratory and Cardiac Manifestations of Obstructive Sleep Apnea. Available from: https://www.researchgate.net/publication/5603620_Respiratory_and_Cardiac_Manifestations_of_Obstructive_Sleep_Apnea [accessed Mar 30, 2017].Research paper (PDF): Respiratory and Cardiac Manifestations of Obstructive Sleep Apnea. Available from: https://www.researchgate.net/publication/5603620_Respiratory_and_Cardiac_Manifestations_of_Obstructive_Sleep_Apnea [accessed Mar 30, 2017].

Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. Sleep 1986;9(4):519-24. PMID 3809866

Centers for Disease Control and Prevention. Insufficient sleep is a public health problem 2015. Available at: http://www.cdc.gov/features/dssleep/. Accessed February 14, 2014.

Cephalon Inc. Nuvigil: highlights of prescribing information 2007a. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021875s021lbledt.pdf. Accessed December 2016.

Cephalon Inc. Provigil: highlights of prescribing information 2007b. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020717s037s038lbl.pdf. Accessed December 2016.

Chu M, Huang Z, Qu W, Eguchi N, Yao M, Urade Y. Extracellular histamine level in the frontal cortex is positively correlated with the amount of wakefulness in rats. Neurosci Res 2004;29(4):417-20. PMID 15236867

Dauvilliers Y, Buguet A. Hypersomnia. Dialogues Clin Neurosci 2005;7(4):347-56. PMID 16416710

Dauvilliers Y, Delallee N, Jaussant I, et al. Normal cerebrospinal fluid histamine and tele-methylhistamine levels in hypersomnia conditions. Sleep 2012;35:1359-66. PMID 23024434

Dauvilliers Y, Montplaisir J, Cochen V, et al. Post-H1N1 narcolepsy-cataplexy. Sleep 2010;33(11):1428-30. PMID 21102981

Dauvilliers Y, Paquereau J, Bastuji H, Drouot X, Weil JS, Viot-Blanc V. Psychological health in central hypersomnias: The French Harmony Study. J Neurol Neurosurg Psychiatry 2009;80(6):636-41. PMID 19211597

Dement WC, Rechtschaffen A, Gulevich G. The nature of the narcoleptic sleep attack. Neurology 1966;16:18-33. PMID 5948003

Dinges DF, Powell JW. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. Behav Res Methods, Instruments, Comput 1985;17(6):652-5. Available at: http://link.springer.com/article/10.3758/BF03200977.

Dolenc L, Besset A, Billiard M. Hypersomnia in association with dysthymia in comparison with idiopathic hypersomnia and normal controls. Eur J Physiol 1996;431:R303-4. PMID 8739385

Folkerts M, Rosenthal L, Roehrs T, et al. The reliability of the diagnostic features in patients with narcolepsy. Biol Psychiatry 1996;40(3):208-14. PMID 8830954

Fronczek R, Middelkoop HAM, van Dijk JG, Lammers GJ. Focusing on vigilance instead of sleepiness in the assessment of narcolepsy: high sensitivity of the Sustained Attention to Response Task (SART). Sleep 2006;29(2):187-91. PMID

16494086

Galbiati A, Abutalebi J, Iannaccone S, et al. The effects of transcranial direct current stimulation (tDCS) on idiopathic hypersomnia: a pilot study. Arch Ital Biol 2016;154(1):1-5. PMID 27548094

Gonçalves R, Togeiro S. Drug-induced sleepiness and insomnia: an update. Sleep Sci 2013;6(1):36-43.

Gottlieb DJ, Hek K, Chen TH, et al. Novel loci associated with usual sleep duration: the CHARGE Consortium Genome-Wide Association Study. Mol Psychiatry 2015;20(10):1232-9. PMID 25469926

Grossman A, Barenboim E, Azaria B, Sherer Y, Goldstein L. The maintenance of wakefulness test as a predictor of alertness in aircrew members with idiopathic hypersomnia. Aviat Space Environ Med 2004;75(3):281-3. PMID 15018299

Guilleminault C, Faull KF, Miles L, Van den Hoed J. Posttraumatic excessive daytime sleepiness: a review of 20 patients. Neurology 1983;33:1584-9. PMID 6685831

Guilleminault C, Los Reyes VD. Upper-airway resistance syndrome. Handb Clin Neurol 2011;98:401-9. PMID 21056201

Guilleminault C, Stoohs R, Clerk A, Cetel M, Maistros P. A cause of excessive daytime sleepiness. The upper airway resistance syndrome. Chest 1993;104(3):781-7. PMID 8365289

Haba-Rubio J. Psychiatric aspects of organic sleep disorders. Dialogues Clin Neurosci 2005;7(4):335-46. PMID 16416709

Ivanenko A, Tauman R, Gozal D. Modafinil in the treatment of excessive daytime sleepiness in children. Sleep Med 2003;4(6):579-82. PMID 14607353

Jazz Pharmaceuticals. Xyrem: highlights of prescribing information 2002. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021196s013lbl.pdf.

Jones SE, Tyrrell J, Wood AR, et al. Genome-wide association analyses in 128,266 individuals identifies new morningness and sleep duration loci. PLoS Genet 2016;12(8):e1006125. PMID 27494321

Kanbayashi T, Kodama T, Kondo H, et al. CSF histamine contents in narcolepsy, idiopathic hypersomnia and obstructive sleep apnea syndrome. Sleep 2009;32(2):181-7. PMID 19238805

Krämer S, Goldammer U, Sindern E. Moebius syndrome and narcolepsy [Article in German]. Nervenarzt 2014;85(12):1569-72. PMID 25388761

Krueger JM, Szentirmai E, Kapas L. Biochemistry of sleep function: a paradigm for brain organization of sleep. In: Amlaner C, Fuller P, editors. Basics of sleep guide. 2nd ed. Westchester: Sleep Research Society, 2015:69-74.

Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46(10):1121-3. PMID 2803071

Laffont F, Mallet A, Mayer G, et al. Study of a patient population investigated for excessive daytime sleepiness (EDS). Neurophysiol Clin 2002;32(6):343-51. PMID 12570932

Lavault S, Dauvilliers Y, Drouot X, et al. Benefit and risk of modafinil in idiopathic hypersomnia vs. narcolepsy with cataplexy. Sleep Med 2011;12(6):550-6. PMID 21576035

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. PMID 26847972

Leu-Semenescu S, Nittur N, Golmard JL, Arnulf I. Effects of pitolisant, a histamine H3 reverse agonist, in drug-resistant and symptomatic hypersomnia: a chart review. Sleep Med 2014;15(6):681-7. PMID 24854887

Leviel V. Dopamine release mediated by the dopamine transporter, facts and consequences. J Neurochem 2011;118(4):475-89. PMID 21644994

Lin L, Hungs M, Mignot E. Narcolepsy and the HLA region. J Neuroimmunol 2001;117(1-2):9-20. PMID 11431000

Lippert J, Halfter H, Heidbreder A, et al. Altered dynamic in the circadian oscillation of clock genes in dermal fibroblasts of patients suffering from idiopathic hypersomnia. PLoS One 2014;9(1):e85255. PMID 24454829

Littner MR, Kushida C, Wise M, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. Sleep 2005;28(1):113-21. PMID 15700727

Longstreth WT Jr, Ton TG, Koepsell TD. Narcolepsy and streptococcal infections. Sleep 2009;32(12):1548. PMID 20041589

Maestri M, Monzani F, Bonanni E, et al. Insulinoma presenting as idiopathic hypersomnia. Neurol Sci 2010;31(3):349-52. PMID 20119740

Martínez-Rodríguez JE, Lin L, Iranzo A, et al. Decreased hypocretin-1 (Orexin-A) levels in the cerebrospinal fluid of patients with myotonic dystrophy and excessive daytime sleepiness. Sleep 2003;26(3):287-90. PMID 12749547

Mignot E. Genetic and familial aspects of narcolepsy. Neurology 1998;50(2 Suppl 1):S16-22. PMID 9484418

Mignot E, Lammers GJ, Ripley B, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol 2002;59(10):1553-62. PMID 12374492

Mignot E, Lin L, Finn L, et al. Correlates of sleep-onset REM periods during the Multiple Sleep Latency Test in community adults. Brain 2006;129(6):1609-23. PMID 16597649

Mignot E, Lin L, Rogers W, et al. Complex HLA-DR and -DQ interactions confer risk of narcolepsy-cataplexy in three ethnic groups. Am J Hum Genet 2001;68(3):686-99. PMID 11179016

Mignot EJ. A practical guide to the therapy of narcolepsy and hypersomnia syndromes. Neurotherapeutics 2012;9(4):739-52. PMID 23065655

Montplaisir J, Poirier G. HLA in disorders of excessive daytime sleepiness without cataplexy in Canada. In: Honda Y, Juji T, editors. HLA in Narcolepsy. 1st ed. Heidelberg, Germany: Springer, 2012:186-90.

Morgenthaler TI, Kapur VK, Brown T, et al; Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep 2007;30(12):1705-11. PMID 18246980

Nelson GB, Hahn JS. Stimulus-induced drop episodes in Coffin-Lowry syndrome. Pediatrics 2003;111(3):e197-202. PMID 12612271

Nevsimalova S, Blazejova K, Illernova H, et al. A contribution to the pathophysiology of idiopathic hypersomnia. Suppl Clin Neurophysiol 2000;53:366-70. PMID 12741022

Nevsimalova-Bruhova S, Roth B. Heredo-familial aspects of narcolepsy and hypersomnia. Arch Suisses Neurol Neurochir Psychiat 1972;110:45-54.

Ortega-Albás JJ, López-Bernabé R, García AL, Gómez JR. Suicidal ideation secondary to sodium oxybate. J Neuropsychiatry Clin Neurosci 2010;22(3):352.e26-352.e26. PMID 20686162

Oyama K, Takahashi T, Shoji Y, et al. Niemann-Pick disease type C: cataplexy and hypocretin in cerebrospinal fluid. Tohoku J Exp Med 2006;209(3):263-7. PMID 16778374

Ozaki A, Inoue Y, Hayashida K, et al. Quality of life in patients with narcolepsy with cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia without long sleep time: comparison between patients on psychostimulants, drug-naïve patients and the general Japanese population. Sleep Med 2012;13(2):200-6. PMID 22137109

Pagel JF. Excessive daytime sleepiness. Am Fam Physician 2009;79(5):391-6. PMID 19275068

Parkes JD. Genetic factors in human sleep disorders with special reference to Norrie disease, Prader-Willi syndrome

and Moebius syndrome. J Sleep Res 1999;8 Suppl 1:14-22. PMID 10389102

Parmentier R, Ohtsu H, Djebbara-Hannas Z, Valatx J, Watanabe T, Lin JS. Anatomical, physiological, and pharmacological characteristics of histidine decarboxylase knock-out mice: evidence for the role of brain histamine in behavioral and sleep-wake control. J Neurosci 2002;22(17):7695-711. PMID 12196593

Passouant P, Popoviciu L, Velok G, Baldy-Moulinier M. Etude polygraphique des narcolepsies au cours du nycthémère. Rev Neurol 1968;118:431-41. PMID 5724640

Pedroso JL, Fusão EF, Ladeia-Frota C, et al. Teaching video neuroimages: gelastic cataplexy as the first neurologic manifestation of Niemann-Pick disease type C. Neurology 2012;79(22):e189. PMID 23183285

Petitjean F, Jouvet M. Hypersomnie et augmentation de l'acide 5-hydroxy-indolacétique cérébral par lésion isthmique chez le chat. Comptes rendus des scéances de la Société de Biologie (Paris) 1970;164:2228-93. PMID 4257361

Rechtschaffen A, Roth B. Nocturnal sleep of hypersomniacs. Activ Nerv 1969;11(Suppl):229-33. PMID 4307958

Roehrs T, Zorick E, Sicklesteel R, Wittig R, Roth T. Excessive daytime sleepiness associated with insufficient sleep. Sleep 1983;6:319-25. PMID 6665394

Rossetti AO, Heinzer RC, Tafti M, Buclin T. Rapid occurrence of depression following addition of sodium oxybate to modafinil. Sleep Med 2010;11(5):500-1. PMID 20133191

Roth B. Functional hypersomnia. In: Guilleminault C, Dement WC, Passouant P, editors. Narcolepsy. New York: Spectrum Publ, 1976:333-49.

Roth B, Nevsimalova S, Rechtschaffen A. Hypersomnia with "sleep drunkenness." Arch Gen Psychiatry 1972;26:456-62. PMID 5019884

Rye DB. Inability to replicate cerebrospinal fluid histamine deficits in the primary hypersomnias: a back to the drawing board moment. Sleep 2012;35(10):1315-7. PMID 23024426

Rye DB, Bliwise DL, Parker K, et al. Modulation of vigilance in the primary hypersomnias by endogenous enhancement of GABAA receptors. Sci Transl Med 2012;4(161):161ra151. PMID 23175709

Saini P, Rye DB. Hypersomnia: evaluation, treatment, and social and economic aspects. Sleep Med Clin 2017;12(1):47-60. PMID 28159097

Scammell TE. Narcolepsy. N Engl J Med 2015;373(27):2654-62. PMID 26716917

Slater G, Steier J. Excessive daytime sleepiness in sleep disorders. J Thorac Dis 2012;4(6):608-16. PMID 23205286

Smit LS, Lammers GJ, Catsman-Berrevoets CE. Cataplexy leading to the diagnosis of Niemann-Pick disease type C. Pediatr Neurol 2006;35(1):82-4. PMID 16814094

Sonka K, Susta M, Billiard M. Narcolepsy with and without cataplexy, idiopathic hypersomnia with and without long sleep time: a cluster analysis. Sleep Med 2015;16(2):225-31. PMID 25576137

Sowa NA. Idiopathic hypersomnia and hypersomnolence disorder: a systematic review of the literature. Psychosomatics 2016;57(2):152-64. PMID 26895727

Stiefel G, Besag FM. Cardiovascular effects of methylphenidate, amphetamines and atomoxetine in the treatment of attention-deficit hyperactivity disorder. Drug Saf 2010;33(10):821-42. PMID 20812768

Szakacs Z, Dauvilliers Y, Mikhaylov V, et al. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2017;16(3):200-7. PMID 28129985

Tanaka S, Honda M. IgG abnormality in narcolepsy and idiopathic hypersomnia. PLoS One 2010;5(3):e9555. PMID 20221267

Teclemariam-Mesbah R, Ter Horst GJ, Postema F, Wortel J, Buijs RM. Anatomical demonstration of the suprachiasmatic nucleus-pineal pathway. J Comp Neurol 1999;406(2):171-82. PMID 10096604

Trotti LM, Saini P, Bliwise DL, Freeman AA, Jenkins A, Rye DB. Clarithromycin in γ-aminobutyric acid-Related hypersomnolence: a randomized, crossover trial. Ann Neurol 2015;78(3):454-65. PMID 26094838

Trotti LM, Saini P, Freeman AA, et al. Improvement in daytime sleepiness with clarithromycin in patients with GABA-related hypersomnia: clinical experience. J Psychopharmacol 2014;28(7):697-702. PMID 24306133

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. PMID 27568889

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. PMID 23946709

Tyagi A, Harrington H. Cataplexy in association with Moebius syndrome. J Neurol 2003;250(1):110-1. PMID 12528006

Vankova J, Stepanova I, Jech R, et al. Sleep disturbances and hypocretin deficiency in Niemann-Pick disease type C. Sleep 2003;26(4):427-30. PMID 12841368

Vernet C, Arnulf I. Idiopathic hypersomnia with and without long sleep time: a controlled series of 75 patients. Sleep 2009;32(6):753-9. PMID 19544751

Vernet C, Leu-Semenescu S, Buzare MA, et al. Subjective symptoms in idiopathic hypersomnia: beyond excessive sleepiness. J Sleep Res 2010;19(4):525-34. PMID 20408941

Vgontzas AN, Chrousos GP. Sleep, the hypothalamic-pituitary-adrenal axis, and cytokines: multiple interactions and disturbances in sleep disorders. Endocrinol Metab Clin North Am 2002;31(1):15-36. PMID 12055986

Voderholzer U, Backhaus J, Hornyak M, Hohagen F, Berger M, Riemann D. A 19-h spontaneous sleep period in idiopathic central nervous system hypersomnia. J Sleep Res 1998;7:101-3. PMID 9682181

Von Economo C. Sleep as a problem of localization. J Nerv Ment Dis 1930;71:249-59.

Vossler DG, Wyler AR, Wilkus RJ, Gardner-Walker G, Vlcek BW. Cataplexy and monoamine oxidase deficiency in Norrie disease. Neurology 1996;46(5):1258-61. PMID 8628463

Weitzman ED, Czeisler CA, Coleman RM, Spielman AJ, Zimmerman JC, Dement WC. Delayed sleep phase syndrome: a chronobiological disorder with sleep-onset insomnia. Arch Gen Psychiatry 1981;38:737-46. PMID 7247637

Winkelmann J, Lin L, Schormair B, et al. Mutations in DNMT1 cause autosomal dominant cerebellar ataxia, deafness and narcolepsy. Hum Mol Genet 2012;21(10):2205-10. PMID 22328086

**References especially recommended by the author or editor for general reading.

Former authors

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ICD and OMIM codes

ICD codes

ICD-9:
Hypersomnia, unspecified: 780.54
Idiopathic hypersomnia, with long sleep time: 327.11
Idiopathic hypersomnia, without long sleep time: 327.12

ICD-10:

Hypersomnia: G47.1

Profile

Age range of presentation

13-18 years
19-44 years

Sex preponderance

male=female

Family history

family history may be obtained

Heredity

heredity may be a factor, possibly autosomal dominant

Population groups selectively affected

none selectively affected

Occupation groups selectively affected

none selectively affected

Differential diagnosis list

upper airway resistance syndrome
narcolepsy
mood disorders (eg, depression)
systemic exertional intolerance disease (formerly known as chronic fatigue syndrome or myalgic encephalomyelitis)
hypersomnia occurring after viral, bacterial, or parasitic infection
posttraumatic hypersomnia
posttraumatic brain injury
stroke
brain tumors (potentially involving the hypothalamus or midbrain)
hypothyroidism
metabolic derangement
chronic renal insufficiency
hepatic encephalopathy
neuroglycopenia
tumors that involve the hypothalamus, thalamus, or brainstem
strokes that involve the hypothalamus, thalamus, or brainstem
Parkinson disease
Alzheimer disease
multiple system atrophy
demyelinating disorders
myotonic posttraumatic hypersomnia
hydrocephalus
delayed sleep phase syndrome
behaviorally-induced insufficient sleep syndrome
medical symptoms responsible for fragmented sleep
long sleepers
paraneoplastic encephalitis (eg, Ma-2)
neuromyelitis optica spectrum, with hypothalamic involvement

hypersomnia associated with psychiatric disorders (dysthymia and related mood disorders)
type 1 narcolepsy
non-hypocretin-deficient, type 2 narcolepsy
other primary CNS hypersomnias
behaviorally-induced insufficient sleep syndrome

Other topics to consider

Confusional arousal
Hypersomnolence
Modafinil
Narcolepsy
Obstructive Sleep Apnea
Posttraumatic sleep disturbance
Recurrent hypersomnia
Sleep disorders