Idiopathic Hypersomnia

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Venkata M. Mukkavilli

History

Patient is a 24-year-old female, who is a first year medical student was referred by primary care physician for excessive sleepiness, and suspected narcolepsy.

She started experiencing excessive daytime sleepiness in senior year high school and has gotten worse over the past 6 months. She managed without much difficulty in college by attending afternoon classes. Her problems started in med school as she struggles to wake up in the morning and often has difficulty staying awake in classes. She was found napping in the class many times and is lagging in her grades.

Her normal sleep schedule is from 9 PM to 7 AM and extends sleep on weekends. She sleeps around 10–11 h and takes a nap for 30–60 mins on weekdays. On weekends and holidays, she sleeps for 12–14 h at night and takes 1–2 naps during the day. She falls asleep very easily, sleeps well through the night and never feels refreshed in the morning or after taking a nap. Extending sleep on weekends did not improve her excessive daytime sleepiness. She drinks 2 cups of coffee in the morning and 3–4 energy drinks throughout the day to stay alert. Coffee and energy drinks were helpful in the past but doesn't work anymore to keep her alert during the day.

She denied hypnogogic, hypnopompic hallucinations, and cataplexy. She reports experiencing sleep paralysis once 2–3 years ago. She snores rarely, but denied witnessed apneas. She denied restless leg symptoms and parasomnias.

She has history of seasonal allergies and takes fexofenadine in spring for 2–3 months, and is currently taking birth control pills. She also reports history of depression 5 years ago lasting for 6 months after a breakup and received counseling.

V. M. Mukkavilli (✉)
Department of Psychiatry, UT southwestern medical center, Dallas, TX, USA

Parkland Health System, Dallas, TX, USA
e-mail: Venkata.Mukkavilli@utsouthwestern.edu

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She was not prescribed any antidepressant medications. She denied symptoms of depression or anxiety at present. She also denied recreational drug use. She drinks alcohol socially. Patient reports her maternal grand mother was also a long sleeper like her but never sought any treatment.

Physical Examination

Vitals: BMI = 27.2. BP = 112/76 mmHg, Pulse = 74.

Patient appeared sleepy and tired otherwise her general physical examination was completely normal.

Laboratory Tests

Complete blood count, serum chemistry panel, thyroid functions, Vitamin B12 and Vitamin D were within normal range. Urine drug screen on the morning of the MSLT was negative.

Actigraphy and Sleep Log

Reviewed patient's smart watch sleep data and sleep log. It revealed average sleep was 10.5 h on weekdays and 12.3 h on weekends, two weeks prior to the sleep study.

Epworth sleepiness score: 17/24.

Polysomnogram and MSLT

Diagnostic PSG: Polysomnogram revealed sleep latency of 7.5 mins, total sleep time was 432 mins and sleep efficiency of 92.7%. Sleep architecture showed increased REM sleep. Apnea hypopnea index was 1.2. Periodic limb movement index was zero. Details of the PSG and attended nap study/MSLT is shown in Table 8.1, and Fig. 8.1. MSLT revealed mean Sleep latency of 3.6 mins in five naps and no SOREMs. Details of the attended nap study/MSLT is shown in Table 8.2, and Fig. 8.2.

Question What diagnostic criteria differentiates idiopathic hypersomnia from narcolepsy in this patient with mean sleep latency of 3.6 minutes?

Answer options:

(a) Sleep efficiency of > 87%
(b) REM latency of 25 minutes in PSG
(c) Total sleep time > 360 min
(d) Absence of sleep onset REM periods

Table 8.1 Results of PSG in a tabular form (This figure is original and has never been published online or in print)

Time at light out	21.24
Time at light on	06.04
Total recording time	520 mins
Total sleep time	482 mins
Sleep efficiency	92.7%
Sleep latency	7.5 mins
REM latency	25.5 mins.
WASO	23 mins.
Stage N1	4.8%
Stage N2	51.8%
Stage N3	2.1%
Stage REM	41.3%
AHI	1.2/h
Periodic limb movement index	0/h
Arousal index	3.1/h

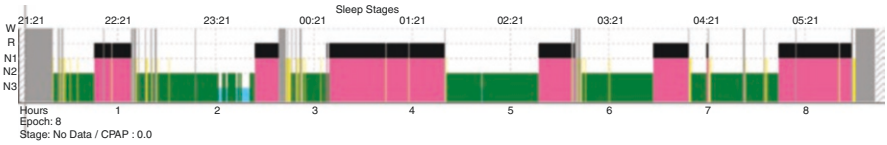
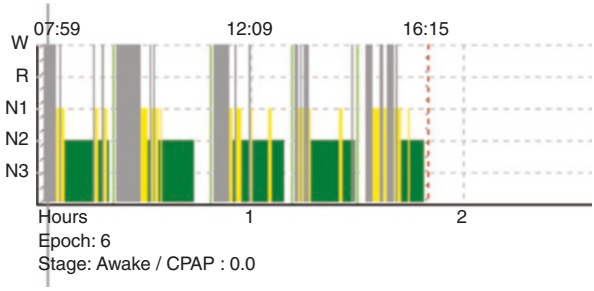


Fig. 8.1 Hypnogram of overnight PSG (This figure is original and has never been published online or in print)

Table 8.2 Results of MSLT (This figure is original and has never been published online or in print)

Naps	Nap 1	Nap 2	Nap 3	Nap 4	Nap 5
Recording time (minutes)	20.5	20	19.5	18.5	17
Total sleep time (minutes)	13.5	14	14	13	11.5
Sleep latency (minutes)	3.5	7	4.5	1	2
Onset to REM sleep	No REM	No REM	No REM	No REM	No REM

Fig. 8.2 Hypnogram of MSLT showing sleep onset in the 5 naps. Yellow indicates stage N1 sleep, green indicates N2 sleep, gray indicates wake stage. (This figure is original and has never been published online or in print)



Diagnosis and Treatment

Clinical history, physical examination and sleep study is suggestive of idiopathic hypersomnia. Patient was recommended both behavioral approaches including sleep hygiene, strategic naps, and pharmacological treatment. She was started on Modafinil 100 mg by mouth daily and subsequently increased to twice daily at 7 AM and 1 PM in 6 weeks. Also, counseled patient about drug-drug interaction with birth control pills, voiding the effectiveness of birth control pills, and advised to use alternate methods of contraception.

Differential Diagnoses

Hypersomnia due to sleep apnea.
Major depression.
Hypersomnia due to medications.
Hypersomnia due to substance use.
Narcolepsy type 1 or 2.

Discussion

Sleepiness is a core feature of multiple disorders and no validated biomarkers that is diagnostic of IH, a careful history and diagnostic testing can distinguish IH from other possible disorders.

The possible diagnosis is idiopathic hypersomnia due to excessive daytime sleepiness, irrepressible need to sleep and daytime lapses into sleep, absence of cataplexy, and her MSLT shows no sleep onset REM periods (Table 8.2, Fig. 8.2). Her mean sleep latency is 3.6 mins and average total sleep time in 24 h is more than 11 h. Other supportive symptoms of IH are severe and prolonged sleep inertia (sleep drunkenness), unrefreshing naps, high sleep efficiency (>90%).

The ICD 3 diagnostic criteria for idiopathic hypersomnia are periods of irresistible need to sleep on daytime lapses into sleep coding for at least 3 months, absence of cataplexy, and MSLT shows less than 2 sleep onset REM periods. Either mean sleep latency less than or equal to 8 mins, or total 24 sleep time is more than 660 mins on a 24-h PSG, or monitored by wrist actigraphy in association with a sleep log. Rule out insufficient sleep syndrome, another sleep disorder, other medical or psychiatric disorder or use of drugs and medications.

The age of onset varies but it is frequently present between the age of 10 and 30 years. The prevalence of IH in general population is approximately 50 per million people. Females may be affected more frequently than men. There are no consistent findings showing association between HLA markers for diagnosis of IH[2]. Cerebrospinal fluid hypocretin-1 levels are normal in IH. A recent meta-analysis of 10 studies on nocturnal sleep in IH patient showed decreased slow wave sleep and increased REM sleep compared to controls.

Narcolepsy type 1 and type 2. The distinction between IH and Narcolepsy type I are fairly distinct. Narcolepsy type 1 (NT1) patients have cataplexy, fragmented nocturnal sleep, and generally short naps are refreshing. In contrast, the distinction between IH and Narcolepsy type 2 (NT2) is more difficult. Sleep paralysis and sleep related hallucinations are commonly seen in patient with NT2 but they are also seen in a quarter of IH patients. Genetic testing HLA DQB1*0602 is not positive in all patients with NT2 unlike in Narcolepsy type 1. The differentiation between IH and Narcolepsy type 2 entirely rests on the presence or absence of 2 sleep-onset REM periods (SOREMs) [1].

Distinguishing between circadian rhythm disorder, delayed sleep phase syndrome (DSPS) and IH is difficult as DSPS patients will frequently present with the combination of daytime sleepiness and sleep drunkenness, which are seen in Idiopathic hypersomnia. Insufficient sleep syndrome can also present with daytime sleepiness, irritability, attention deficit and fatigue but it improves with prolonged sleep time unlike in IH[3]. History, sleep log and actigraphy are very important in distinguishing these disorders from IH. IH can be sometime confused with chronic fatigue syndrome but patients with chronic fatigue syndrome generally complain fatigue rather than excessive daytime sleepiness and doesn't resolve with sleep or rest.

Hypersomnia due to medications and substances occurs because of current medications like sedative/hypnotics, muscle relaxants, opioids, antidepressants, antiallergy, antiepilepsy drugs, and other centrally acting medications or substance use or withdrawal of caffeine, nicotine. Commonly used substances causing excessive sleepiness include marijuana, barbiturates, benzodiazepines, gamma hydroxybutyrate, opiates, and alcohol. It can be distinguished from IH with a careful history and toxicology screen. Similarly, hypersomnolence due to medical condition and neurological conditions is generally apparent from history and physical examinations.

One of the most challenging differential diagnoses is hypersomnolence associated with psychiatric disorders. ICSD 3 does not assign causality in the diagnosis because of uncertainty about the nature of the relationship. A judgement about whether the main diagnosis is IH or primary psychiatric should be ascertained. Patient did have a history of depressive illness in the past, but she clearly denied depressive symptoms. Also, in depression patients may have excessive daytime sleepiness but generally sleep varies from day-to-day and it is often associated with poor sleep at night.

Treatment of Idiopathic Hypersomnia

Treatment of idiopathic hypersomnia includes both nonpharmacologic and pharmacologic treatment. Nonpharmacologic treatment includes behavioral approaches and sleep hygiene but generally these are unhelpful. Different medications have been tried in idiopathic hypersomnia patients, including, stimulants antidepressants, sodium oxybate, clarithromycin, flumazenil, clonidine, levodopa, bromocriptine,

selegiline and amantadine. Overall, two thirds of the patient reported symptoms improvement with modafinil or amphetamine. Around one third of the patient's reported spontaneous remission of symptoms.

Outcome of the Case

Patient responded to modafinil treatment and Epworth score in 3 months follow up was 10/24 showing significant improvement.

Take Home Pearls

1. Idiopathic hypersomnia is a diagnosis of exclusion and requires exclusion of other causes of hypersomnolence in addition to sleep log, actigraphy, sleep study.
2. Modafinil is the first line drug for treatment of Idiopathic hypersomnia.
3. Modafinil will decrease the level or effect of hormonal contraceptives (estrogen) by hepatic/intestinal enzyme CYP3A4 metabolism. Health care professionals should discuss with patient about drug-drug interaction and advise to use other contraceptive methods while taking modafinil and for 2 months after stopping modafinil.
4. Spontaneous improvement in EDS may occur in up to one-third of patients.

Correct Answer
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Reference

1. Trotti LM. Idiopathic Hypersomnia. Sleep Med Clin. 2017;12(3):331–44. https://doi.org/10.1016/j.jsmc.2017.03.009. Epub 2017 Jun 16. PMID: 28778232; PMCID: PMC5558858