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TRAINEES' FORUM

A simple approach to central disorders of hypersomnolence

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Abstract

Sleep is an essential part of a healthy life which is vital to maintain bodily functions in a well-balanced state. Nevertheless, excessive sleepiness can disturb the overall physical and mental health of an individual. Though daytime hypersomnolence has a myriad of causes, central disorders of hypersomnolence deserve special attention. When evaluating a patient with daytime hypersomnolence, its presence must be confirmed with an accepted screening tool. A detailed history, examination and laboratory work up is necessary to exclude common medical, neurological and psychiatric illnesses which are common causes of hypersomnolence.

This review mainly focuses on central causes of hypersomnolence such as insufficient sleep syndrome, narcolepsy, idiopathic hypersomnolence syndrome and Kleine-Levin syndrome. Polysomnogram and multiple sleep latency tests are cornerstone investigations in evaluating these conditions. Despite these central disorders of hypersomnolence being lifelong chronic illnesses, promising pharmacological therapies as well as non-pharmacological measures are available for the alleviation of troublesome symptoms.

KEYWORDS
Sleep disorders, narcolepsy, Idiopathic hypersomnolence syndrome

Introduction to sleep and hypersomnolence

Sleep is an essential component of life, which maintains body physiology in a well-balanced state. Even though it is thought to be a passive and inactive state of the brain, sleep is an active state of anabolism during which vital bodily functions like promotion of growth and boosting of immunity take place.[1]

Consciousness is defined as a state of wakefulness together with awareness. As opposed to an unconscious person who is in a coma or dead, sleep is a reversible and a transient state of impaired conscious awareness about the external world. It is a natural and physiological periodic phenomenon.[2]

Normal sleep

In order to understand abnormal sleep, it is vital to learn about "normal" sleep. A normal 8-hour sleep consists of 5-6 cycles of sleep. Each cycle consists of several stages of sleep. Using the electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG) characteristics, these sleep stages are identified as rapid eye movement sleep (REM) and non-rapid eye movement sleep (NREM). NREM sleep is divided in to N1, N2 and N3 states. N1 NREM sleep is a lighter stage of sleep where one is easily arousable with less intense stimuli. N3 sleep denotes a deeper stage of sleep, where larger stimuli are needed to wake up. In addition to going through these stages, one will also cycle from NREM to REM sleep from time to time.

REM sleep accounts for 20-25% of total sleep where the EEG shows low amplitude beta, desynchronized theta and short runs of alpha activity. REM sleep has two phases known as tonic and phasic. The tonic phase is persistent through the entire REM period with atonia of all skeletal muscles except for diaphragm and extraocular muscles. There is depression of reflexes as well. The phasic stage superimposes on the tonic stage intermittently and it is characterized by bursts of rapid eye movements, myoclonic jerks of limbs and face, fluctuations in blood pressure, irregularities in breathing and heart rate and middle ear muscle activity. REM sleep is associated with vivid dreams. Towards the later part of the sleep, duration of REM sleep progressively lengthens and becomes the predominant stage of sleep. Generally, there is a latency of 50-190 minutes for REM sleep to appear after the onset of sleep.

NREM sleep accounts for 75-80% of total sleep. N1 is short (3-8%), while N2 (45-55%) and N3 (15-23%) are longer. Each substage is identified by the characteristic EEG wave forms.

The N1 stage which is first to appear after falling asleep has some alpha rhythm as in wakefulness but with a 50% reduction. This is intermixed with slow theta and beta waves. The N2 sleep stage encompasses sleep spindles, K complexes and vertical sharp waves. N3, being the deepest stage of sleep, has slow theta and delta waves ranging from 20-100% for an epoch.

Initial evaluation of a patient with hypersomnolence

Hypersomnolence refers to an irrepressible urge to sleep or episodes of daytime sleep.[3] As opposed to "fatigue", where there is lack of energy without excessive sleepiness, hypersomnolence implies an increased tendency to fall asleep.[4] In central hypersomnolence disorders, excessive daytime sleepiness (EDS) occurs in the absence of disrupted nocturnal sleep or a circadian rhythm disorder. The International Classification of Sleep Disorders (ICSD), 3rd edition has described eight central causes of hypersomnolence as mentioned in Table 1.[3,4] This review mainly focuses on central causes of hypersomnolence.

TABLE 1 Central causes of hypersomnolence (ICSD – International classification of sleep disorders[3])

Central causes of hypersomnolence
Narcolepsy type 1
Narcolepsy type 2
Idiopathic hypersomnolence syndrome
Kleine-Levin syndrome
Hypersomnia due to medical disorder
Hypersomnia due to medication or substance
Hypersomnia due to psychiatric disorder
Insufficient sleep syndrome

At the outset, EDS must be confirmed with an accepted screening tool. The Epworth sleepiness scale is an accepted scoring system (Table 2) where a score > 10 confirms EDS.[5]

TABLE 2 Epworth sleepiness scale[5]

Feature	Chance of dozing			
Sitting and reading	0	1	2	3
Watching TV	0	1	2	3
Sitting inactive in a public place (e.g., a theatre or a meeting)	0	1	2	3
As a passenger in a car for an hour without a break	0	1	2	3
Lying down to rest in the afternoon when circumstances permit	0	1	2	3
Sitting and talking to someone	0	1	2	3
In a car, while stopped for a few minutes in traffic	0	1	2	3
Sitting quietly after lunch or alcohol	0	1	2	3

No chance of dozing =0. Slight chance of dozing =1. Moderate chance of dozing =2. High chance of dozing =3

The quality and quantity of nocturnal sleep must be assessed, to exclude disrupted and low-quality sleep and circadian rhythm disorders, which in itself may be the cause for hypersomnolence in the day time. In the absence of such, central causes of hypersomnolence can be pondered upon.[6] A myriad of medical, neurological and psychiatric illnesses can cause EDS and a detailed history, examination and targeted laboratory tests should be carried out to narrow down the diagnosis. Certain neurological disorders, such as stroke, multiple sclerosis, Parkinson disease, Alzheimer disease, epilepsy and migraine can give rise to disabling hypersomnia. Both medications and recreational drugs can produce sleep disorders.

Groups of medications that can cause hypersomnia are mentioned below (Box 1).[7]

Box 1. Medications causing hypersomnolence

- Antidepressants (serotonin reuptake inhibitors)
- Antipsychotics
- Antiparkinson drugs (i.e., levodopa)
- Opiates
- Antihistamines (1st generation H1 receptor antagonists)
- Cardiovascular drugs (e.g., beta blockers, centrally acting alpha blockers, spironolactone)
- Muscle relaxants (e.g., baclofen)
- Antiemetics (e.g., metoclopramide, ondansetron, prochlorperazine)
- Analgesics (e.g., tramadol, nonsteroidal anti-inflammatory drugs)

Of the central causes of EDS, **insufficient sleep syndrome** must be singled out, owing to its increasing prevalence worldwide, resulting in not only excessive sleepiness but also posing a major threat to overall health.[8] Insufficient sleep syndrome is caused by curtailed nocturnal sleep time and it is usually amenable to an adequate, undisrupted sleep at night.[4]

According to ICSD-3, there are three persistent central hypersomnolence disorders, which are not associated with any medical illness or substance use. They are narcolepsy type 1, narcolepsy type 2 and idiopathic hypersomnolence syndrome.[4] A comparison of these three conditions with regards to their clinical features, investigation findings and diagnostic criteria has been made in Table 3.

Narcolepsy type 1 is a lifelong, central disorder of hypersomnolence, with a bimodal distribution with two peaks at 15 years and 35 years of age. Pathogenesis is related to deficiency of the neuropeptide orexin (hypocretin), due to the lack of orexin producing neurons in the hypothalamus. Orexin is vital for regulation of the sleep-wake cycle. Low levels of orexin in CSF (less than 110 pg/ml) in a patient with EDS, confirms the diagnosis of narcolepsy type 1.

Human leucocyte antigen (HLA) DQB1*06:02 is positive in 95% of patients with narcolepsy. Since it is also present in 30% of the normal population, it has a negative predictive value.[1,7] An increasing incidence of narcolepsy was reported during the 2009-2010 H1N1 pandemic, especially from China, where the pathophysiology was thought to be immune mediated loss of orexin producing neurons in the hypothalamus, due to H1N1 viral infection.[9] Cases of hypersomnolence following COVID-19 vaccination have been reported, though a plausible direct link between the two has not been established.[10,11]

Core clinical features of narcolepsy apart from EDS are cataplexy, sleep paralysis, hypnogogic and hypnopompic hallucinations.

In cataplexy there is sudden loss of tone of the voluntary muscles causing drop attacks with preserved consciousness. It is due to the intrusion of REM sleep into wakefulness. It is unique to narcolepsy type 1 and closely linked to low levels of orexin and HLA DQB1*06:02 positivity.[1,7] Sleep paralysis occurs at sleep-wake transitions, where the patient is unable to make voluntary movements while being fully awake and alert. Since it is a terrifying experience, it is sometimes accompanied by vivid hallucinations.[6] Visual followed by auditory and tactile hallucinations can occur when falling asleep or waking up. These features, though common to narcolepsy, occur in other hypersomnolence disorders as well.

Narcolepsy type 2 is a less severe form than narcolepsy type 1, of which the pathophysiology is not well elucidated. Orexin levels in the CSF is in the normal range and cataplexy does not occur in this condition.[1]

Idiopathic hypersomnolence syndrome (IHS) entails long sleep hours, only to wake up unrefreshed with pronounced sleep fatigue. Unlike narcolepsy, these patients do not benefit from short day time naps and cataplexy is never a feature. Autonomic fluctuations are well described. Since this condition has reportedly occurred following Guillain-Barre syndrome and viral infections, an immune mediated pathogenesis is postulated.[12]

Kleine-Levin syndrome is a distinct disease entity from the rest of the central disorders of hypersomnia. It occurs in episodes, each lasting a few days to several weeks wherein the patient sleeps for long durations, usually >18 hours per day. In addition, psychiatric manifestations like hyperphagia, hypersexuality, derealization and apathy are also present in the disease.[1]

TABLE 3 Summary of the clinical features, investigation findings and diagnostic criteria in three central hypersomnolence disorders (EDS: excessive daytime sleepiness, REM: rapid eye movement, CSF: cerebrospinal fluid)

Feature	Narcolepsy type 1	Narcolepsy type 2	Idiopathic Hypersomnolence syndrome
Day time hypersomnolence	Present	Present	Present
Cataplexy	Present	Absent	Absent
Sleep paralysis	Present	Less common	Very uncommon
Hallucinations	Present	Less common	Very uncommon
Low nocturnal sleep efficacy	Present	Less than type 1	Present
Sleep fatigue	Rare	Commoner than in type 1	Present
Mean Sleep Latency Time (MSLT)	< 8 mins	<8 mins	< 8 mins
Number of sleep onset REM periods (SOREMs)	2 or more	2 or more	None or one
CSF orexin levels	Low	Normal	Normal
Diagnostic criteria	EDS + Cataplexy + typical MSLT results OR EDS + low Hypocretin	EDS + typical MSLT results	EDS + typical MSLT results OR >11 hours sleep on polysomnography OR >11 hours sleep on 7-day actigraphy -Other causes excluded.

Investigating a patient with central hypersomnolence

While methods are available to assess a patient in the outpatient setting, laboratory-based studies are imperative in confirming the diagnosis.

The home sleep apnoea test monitors the saturation of a patient throughout a set time thereby aiding the diagnosis of obstructive sleep apnea (OSA). A **sleep diary** maintained over a 2-week period is instrumental in describing the sleep related behavior of the individual. **Ambulatory actigraphy** is performed using an electronic device attached to the wrist to monitor the level of activity throughout the day, to quantify the amount and adequacy of sleep over a 7-day period. This is used mostly for the assessment of insomnias and IHS.[6]

As for the laboratory-based investigations, polysomnography immediately followed by multiple sleep latency test (MSLT) on the following day provide diagnostic information for narcolepsy and other disorders of hypersomnolence.

Polysomnography is performed over a duration of 6 hours (minimum) and 11 hours (maximum). It continuously monitors the respiratory effort, arterial oxygen saturation, air flow, eye movements (by electrooculogram) cardiac rhythm (by electrocardiogram) and limb movements (by electromyogram). It is facilitated by simultaneous audiovisual recordings enhancing its diagnostic utility. In addition to providing diagnostic information on sleep related breathing disorders, movement disorders and parasomnias, it also provides details pertaining to REM sleep latency and sleep architecture. MSLT

must be preceded by polysomnography to exclude a disrupted sleep, which may give a false positive result in the MSLT.[6,13]

Multiple sleep latency test (MSLT) is the validated investigation to diagnose narcolepsy. It is an objective assessment of tendency to fall asleep. It is done on the day following a polysomnogram after excluding nocturnal disrupted sleep due to other causes like OSA. A sleep log over the preceding two weeks will also be instrumental to assess the sleep schedule of the candidate. Medications or psychoactive substances which can increase or reduce sleep latency, and those which can lengthen REM latency (e.g., serotonin selective reuptake inhibitors) must be discontinued before the test. Though MSLT can diagnose narcolepsy and differentiate narcolepsy from IHS, it is not suitable for the evaluation of OSA, circadian rhythm disorders or EDS due to medical or neurological conditions. The patient is given five nap opportunities at two-hour intervals. At each nap the following measures are taken[6]:

i. Sleep latency – Time to fall asleep after closing the eyes in the nap opportunity
ii. Sleep onset REM periods (SOREMs) – number of nap opportunities, where REM sleep latency was less than 15 minutes

Narcolepsy is diagnosed when cataplexy is combined with mean sleep latency less than 8 minutes, with two or more SOREMs. IHS is characterized by a mean sleep latency < 8 minutes with one or no SOREMs. Patients with IHS have long duration of sleep, typically more than 11 hours which is the cut off for extended polysomnography.[6,14]

In the **Maintenance of Wakefulness Test (MWT)** the patient is asked to stay awake for 40 minutes, in four testing opportunities. Although it is not routinely used for the initial evaluation of EDS, it comes in handy in assessing the response to treatment of hypersomnolence, especially in the research setting.[14]

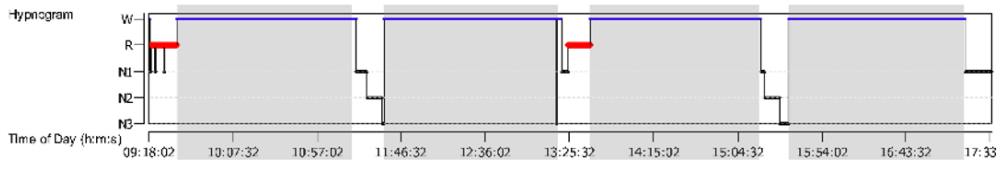
Management of central disorders of hypersomnolence

Most of the hypersomnolence syndromes are lifelong disorders with only symptomatic management available to improve quality of life. Hypersomnolence due to neurological and medical disorders are amenable to some extent by treating the underlying ailment. Paying attention to the drug prescriptions of the patient is vital to minimize medications which can induce EDS.

Non pharmacological treatment encloses scheduled day time naps and regular undisrupted nocturnal sleeps. This is effective for patients with narcolepsy with disabling EDS who respond poorly to stimulant medications.[15,16] This strategy is not applicable to patients with IHS and it may even aggravate sleep fatigue. Narcolepsy patients must be screened for coexistent factors aggravating EDS, e.g., OSA, medical disorders and drugs etc., and any such factors should be eliminated. Choosing an occupation with active routines with adequate rest at night will also be helpful.[17] Caffeine is also found to be helpful in maintaining alertness in patients with narcolepsy.[18]

Nap Summary

	Nap 1	Nap 2	Nap 3	Nap 4	Nap 5	Average
Lights Off	09:18:10 AM	11:18:11 AM	01:19:35 PM	03:18:28 PM	05:18:09 PM	-
Lights On	09:34:23 AM	11:35:56 AM	01:37:24 PM	03:34:42 PM	05:34:12 PM	-
Time In Bed	16.2	17.8	17.8	16.2	16.1	16.8
Sleep Time	15.9	15.9	16.4	16.2	15.2	15.9
Sleep Efficiency	97.8%	89.7%	92.0%	99.7%	94.6%	94.6%
Sleep Onset	09:18:31 AM	11:20:01 AM	01:21:01 PM	03:18:31 PM	05:19:01 PM	-
Sleep Latency	0.3	1.8	1.4	0.1	0.9	0.9
REM Onset	09:19:01 AM	-	01:25:01 PM	-	-	-
REM Sleep Onset Latency	0.5	-	4.0	-	-	2.3



Comments

Mean sleep latency is reduced. There are two REM sleep onset periods. These changes are suggestive of Narcolepsy, if provided PSG is normal.
There is nocturnal sleep disturbance with abnormal PSG in this patient. Hence the above changes should be considered secondary

FIGURE 1 **Multiple sleep latency test (MSLT) of a patient with narcolepsy type 1.**
REM: Rapid eye movement, PSG: polysomnogram

Pharmacological therapy

Despite being an enduring illness, pharmacological agents are effective in alleviating the troublesome symptoms of narcolepsy. They can relieve EDS and cataplexy while improving daytime alertness. These agents are approved by the FDA for both narcolepsy type 1 and 2 in general.

Modafinil/Armodafinil

Modafinil exerts its action by enhancement of dopaminergic neurotransmission and it has an effect on the glutaminergic and orexin systems, provoking wakefulness. This is the FDA approved drug of choice for the treatment of narcolepsy type 1 and 2. It can also be used to treat IHS, off label. Randomized controlled trials have proven its efficacy and its ability to significantly improve Epworth sleepiness scale scores and daytime wakefulness with an excellent safety profile. It is not effective for cataplexy.[19,20]

The adult daily dose is 100-400 mg given in a single or two divided doses. Despite being a well-tolerated drug, it may cause side effects such as Stevens-Johnson syndrome, angioedema, psychosis, mania, hallucinations, insomnia, anxiety and it reduces the effectiveness of oral contraceptives.[1,21]

Sodium oxybate

This is the sodium salt of γ-hydroxybutyrate. Being the only FDA approved drug to treat cataplexy, it also improves other symptoms of narcolepsy like EDS, reduced sleep efficacy and REM sleep related disorders like sleep paralysis.[22] In 2021, FDA approved sodium oxybate for the treatment of IHS. This alleviates disabling sleep fatigue and EDS while promoting wakefulness.[23] It is recommended to be taken at bedtime since it promotes sleep consolidation and deep sleep. The side effect profile though rare, includes CNS and respiratory depression, psychosis, abuse, suicidal thoughts and seizures.

Solriamfetol

This is a dopamine and nor-dopamine reuptake inhibitor which was FDA approved for the treatment of EDS in narcolepsy and OSA. It can be used off label to treat IHS. It has a potential for abuse.[1]

Pitolisant

This is a H3 receptor blocker which increases wakefulness by promoting CNS histaminergic transmission. Though it is FDA approved only for the treatment of EDS of narcolepsy, recent trials have revealed its weak anti-cataplexy effect as well.[24] Pitolisant can cause QT prolongation and reduce the effectiveness of hormonal birth control pills.[1]

Psychostimulants

Methylphenidate and amphetamines inhibit the reuptake of monoamines such as dopamine, serotonin and norepinephrine thereby promoting alertness. Owing to their cardiovascular and neuropsychiatric adverse effects and propensity to addiction and abuse, these drugs are prescribed with great caution and the patient should be followed up regularly.[1,17]

Treatment of cataplexy

In addition to sodium oxybate and pitolisant, REM sleep suppressants such as serotonin-norepinephrine reuptake inhibitors have a place for treatment of cataplexy. Venlafaxine, fluoxetine and sertraline are backed by anecdotal evidence rather than controlled trials.[1,17]

Driving in narcolepsy

In the absence of a set of guidelines or regulation, decisions regarding driving must be individualized to patients depending on their clinical profile and control of symptoms by pharmacotherapy. While narcolepsy patients can drive, it must be a shared decision between the patient and the clinician. Tests like maintenance of wakefulness test (MWT) are useful in assessing alertness, but does not guarantee 100% safety for driving. There are some country-specific guidelines available. Patients with narcolepsy are prohibited from driving heavy vehicles and some guidelines allow driving for only those who have a stable clinical profile while being on medications. Taking stimulant medicine before driving, taking breaks during long rides, not driving after a meal or at night and having an accompanying colleague etc., can make driving even safer for these patients.[16]

CONCLUSION

Although sleep is a vital aspect of a healthy life, hypersomnolence can be disabling and counterproductive. A thorough understanding of normal sleep is imperative to fathom pathological sleep. Specific investigations in the outpatient setting and the laboratory such as polysomnography and the multiple sleep latency test are extremely important in the diagnosis, particularly for narcolepsy. Despite being chronic lifelong conditions, promising pharmacotherapies and behavioural modifications are available to alleviate disabling symptoms related to central disorders of hypersomnolence.

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