



SLEEP DISORDER: HYPERSOMNIA

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Abstract: Hypersomnia is a persistent complaint of excessive daytime sleep or drowsiness that interferes with the patient's daily activities. It may impair work performance and may be involved in workplace or driving accidents. Hypersomnia syndromes have been known for over a century, beginning with narcolepsy. The effective treatment is carrying out with stimulant and antiepileptic drugs. NT1 is not only affect sleep-wake but also emotional, motor, metabolic, psychiatric, cognitive, and autonomic functions. Recurrent hypersomnia causes substantial disruptions in social and family life, and there is no known prognosis. Stimulants are used to treat recurring hypersomnia episodes. Prophylactic therapies such as valproate, carbamazepine, or lithium carbonate, or estrogenic ovulatory inhibitors may be effective. Treatment for narcolepsy and idiopathic hypersomnia can be either non pharmacological or pharmacological. Non pharmacological treatment generally includes patient counseling and follow up to excess disease stage. Also in non-pharmacological treatment patient were suggested to take low carbohydrate diet and to perform exercise as it make person active.

Index Terms -Sleep disorder, Hypersomnia, Narcolepsy, Treatment

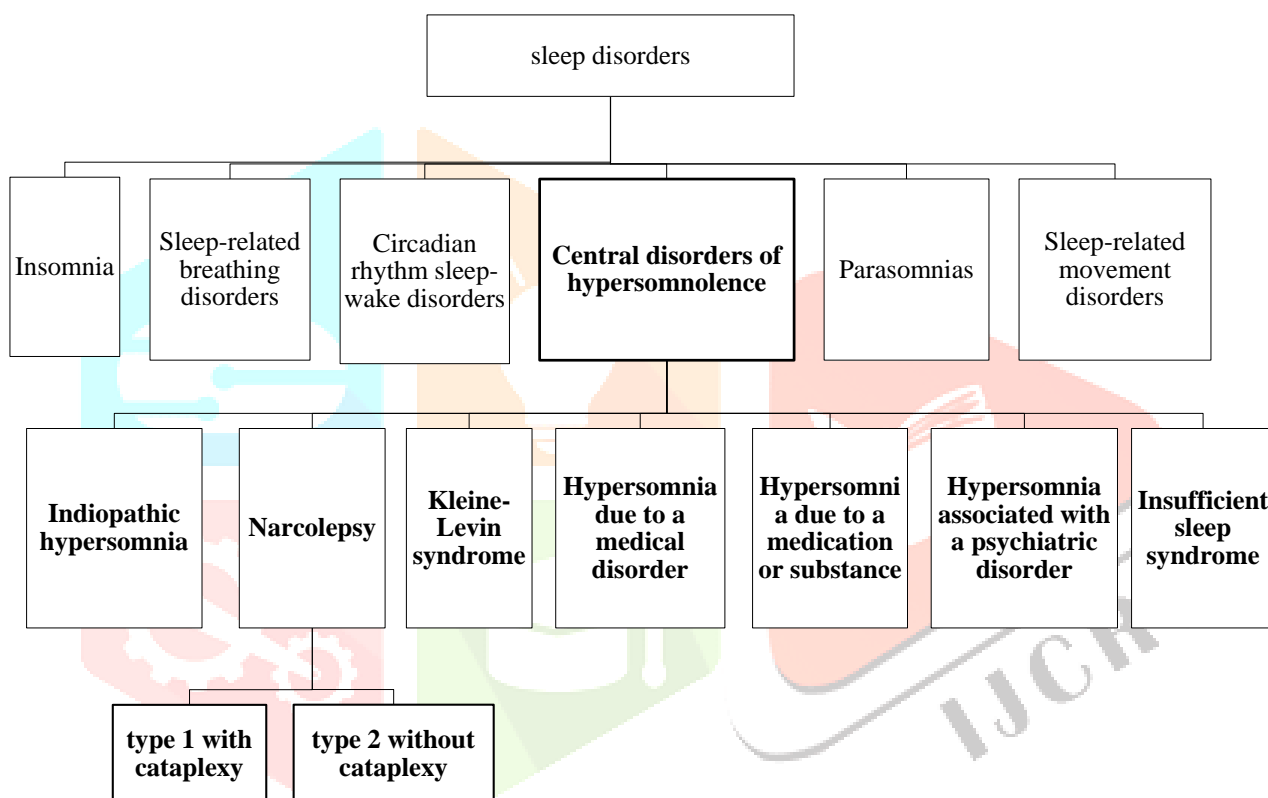
I. INTRODUCTION

Sleep is very important component for survival and also to maintain the mammalian homeostasis. And destruction in normal sleep leads to various sleep disorders like insomnia, narcolepsy, sleep apnea, hypersomnia^[1]. Destruction in sleep can leads to either increase (sleepiness) or decrease (sleeplessness) in sleep time. Example of increasing or prolong sleep time i.e. sleepiness is hypersomnia, narcolepsy^[2] etc. and similarly example of decrease in sleep time i.e. sleeplessness or wakefulness is insomnia^[3]. So the sleep disorder in which destruction in sleep pattern leads to prolonged night time sleep or excessive daytime sleep or both is called as Hypersomnia. There are many mechanisms and chemicals which are responsible for a normal sleep and imbalance between such mechanisms and chemicals cause Hypersomnia. The most noticeable sign of hypersomnia is a persistent complaint of excessive daytime sleep or drowsiness that interferes with the patient's daily activities. It may impair work performance and may be involved in workplace or driving accidents in our mechanised cultures. Although hypersomnia syndromes have been known for over a century, beginning with narcolepsy¹, modern sleep medicine has only recently focused on the health and economic consequences of falling asleep at any time. Hypersomnia disorders are affecting a growing percentage of the 15% to 30% of adults who have sleep issues. Hypersomnia affects 4% to 6% of the general population, with a higher frequency in men due to sleep apnea disorders, which are the most common cause of excessive daytime sleepiness. Sleep medicine has profited from the influence of hypersomnia in recent years, and it is now fully developed in industrialized countries. Although a lack of nighttime sleep is the most obvious cause, extreme tiredness can be caused by a variety of factors, resulting in an arbitrary classification. In this review, we propose categorizing hypersomnia disorders under many areas. The clinical classification of hypersomnia syndromes will be discussed first, followed by a discussion of the methodological tools available to investigate sleep and wakefulness: narcolepsy, idiopathic hypersomnia, recurrent hypersomnia, insufficient sleep syndrome, medication and toxin-dependent sleepiness, hypersomnia associated with psychiatric disorders, hypersomnia associated with neurological disorders, posttraumatic hypersomnia, infection and hypersomnia, hypersomnia^[4].

II. HISTORY:

Hypersomnia is not a new concept; it was first narrated about a century before as Narcolepsy, primary sleep disorder by Gelineau in 1880. Then Adie^[5] came up with new term catelepsy, loss of emotion. Later in 1928 Wilson^[6] introduce several narcolepsies. After that between 1930 to 1960 several researches are carry out on these several narcolepsies and shows the existence of several narcolepsies which includes idiopathic sleep disorder, sleep paralysis, cataplexy, hypnagogic hallucination^[7,8]. Then during 1960-1963, Rapid Eye Movement (REM) was linked with narcolepsies as critical biological marker of narcolepsies^[9,10]. Then the concept of idiopathic hypersomnia is came up after observing some patients with nonstructural hypersomnia by Bedrich Roth and colleagues^[11]. Although initially narcolepsy and idiopathic hypersomnia is considered as different concept but later some evidences showing similarity between these two terms were discovered. Similarity in clinical feature of these two disorders were observed^[12].

III. Classification of sleep disorders^[13]:



3.1 Narcolepsy ^[14]:

Narcolepsy is chronic neurological disorder that causes a selective loss or dysfunction of some neurons of the lateral hypothalamus. Excessive daytime sleepiness and cataplexy are common symptoms of Narcolepsy type 1 (NT1). In addition to this some sleep-wake symptoms also includes like hallucinations, sleep paralysis and disturbed sleep. The effective treatment is carrying out with stimulant and anticataplectic drugs. NT1 is not only affect sleep-wake but also emotional, motor, metabolic, psychiatric, cognitive, and autonomic functions. Narcolepsy type 2 (NT2) is includes Excessive sleepiness without cataplexy.

3.2 Idiopathic hypersomnia^[15]:

Idiopathic hypersomnia (IH) is a chronic neurological disorder that results in daytime sleepiness, frequently accompanied by long nocturnal or daytime sleep, unrefreshing sleep, and difficulty in awakening, cognitive dysfunction, and autonomic symptoms. The cause of IH is currently unknown, although the strong family history of similar symptoms suggested a genetic predisposition. Autonomic, inflammatory, and immune system dysfunction have all been suggested, and patients with IH have been discovered to have an endogenous GABA-A receptor modulator in their cerebrospinal fluid. IH is diagnosed through a detailed clinical history, with special attention paid to other illnesses with comparable symptomatology,

as well as objective testing such as actigraphy, multiple sleep latency testing and polysomnography. IH symptoms are primarily addressed with off-label usage of narcolepsy medicines because there are no FDA-approved therapies. Modafinil is the first-line treatment, with two randomised, controlled trials in IH patients supporting it. A significant proportion of IH patients are resistant or intolerant to traditional treatments, necessitating new treatment regimens involving newer medicines. Patients with this difficult chronic disease may still have poor quality of life and safety despite current treatment options.

3.3 Kleine-Levin syndrome^[16]:

Kleine–Levin syndrome (KLS) manifests recurrent attacks of unexplained sleepiness accompanied by aberrant behavior. Most patients according to publications in English and French were young Caucasians. Asians were rarely reported either due to decreased awareness, misdiagnosis and/or due to different ethnic–environmental factors. It is quite possible that increased awareness of the syndrome may have led to the detection of the expected number of KLS patients in Taiwan. Increased awareness played a major role in our experience in Israel where we diagnosed more than 40 patients and reported 34 of them in detail.

3.4 Recurrent hypersomnia:

Recurrent hypersomnia is marked by periods of excessive sleep that persist anywhere from a few days to many weeks. Patients can sleep for at least 18 hours each day and only get up to eat and urinate. Weeks or months pass between episodes, during which time normal sleep habits are regained. Overeating, sexual disinhibition, and other mental disorders may occur in conjunction with excessive sleep. Kleine-Levin syndrome, which affects teenage boys with the HLA DQB1*0201* type, represents this polysymptomatic form. In relation to menstruation, the syndrome could potentially be idiopathic. It could also be a result of neurological or psychological issues, or a viral illness that occurred weeks ago. Recurrent hypersomnia must be distinguished from obstructive sleep apnea syndrome, narcolepsy, and periodic limb movement disorder in differential diagnosis. EEG and polysomnographic recordings, as well as brain imaging, may be used to confirm hypersomnia and rule out epilepsy and organic pathology. Idiopathic recurrent hypersomnia's origin is unknown, but most symptoms can be attributed to hypothalamic dysfunction. Recurrent hypersomnia causes substantial disruptions in social and family life, and there is no known prognosis. In most cases, the progression through life is positive, with symptoms gradually disappearing. Stimulants are used to treat recurring hypersomnia episodes, notwithstanding their ineffectiveness. In the case of menstruation-related problems, prophylactic therapies such as valproate, carbamazepine, or lithium carbonate, or estrogenic ovulatory inhibitors, may be effective.

IV. Symptoms:

In comparison to the controls, daytime naps are more frequent and last longer. Short naps revitalise the controls, but not the patients in 75% of cases. The alertness of both controls and patients is influenced by the same external conditions during the day (e.g., higher on a sunny day than on a grey day), but the patients feel more sedated in darkness, in a calm setting, when listening to music or conversing, whether alone or not. Hyperactivity aids them in resisting tiredness more than the controls. In comparison to the controls, patients spend more time in the evening and are more alert in the evening than they are in the morning. The patients can only concentrate for one hour (versus almost four consecutive hours in controls). They complain of attention and memory problems, as well as misplacing stuff on a regular basis. The majority of them have cold extremities and are nearsighted. Excessive sleeping Hypersomnia is a Greek word that means "extra sleep," which encapsulates one of the disease's key characteristics. It's unfortunate that the term hypersomnia has come to imply a variety of illnesses that are connected with excessive daytime sleepiness but not with an actual lack of sleep (Billiard, 1994). The sleep excess in idiopathic hypersomnia is best expressed in unrestricted situations, such as on weekends, holidays, and in the sleep laboratory, with an average of three additional hours slept. One may notice in this study that the sleep time obtained during long-term monitoring in the sleep laboratory is very similar to the usual sleep time during holidays and on weekends in the patients, suggesting it is not a completely artificial measure, disconnected from true life. Controls also sleep longer in these conditions, only an extra hour here, but even more in epidemiological surveys. Hypersomniacs and controls sleep less during

the working days, suggesting that an actimetry, or a sleep agenda, in these forced life conditions is poorly sensitive, except if one pays attention to large sleep differences between working days (more than 7 h) and weekend days (more than 10–12 h). In addition, the sleep debt caused by the constraint of working is probably much higher in hypersomniacs. Controls can sleep a maximum of 10–13 h in a row (versus 10–20 h in hypersomniacs), suggesting that being able to sleep occasionally more than 13 h in a row (without previous sleep debt) is specific to hypersomniacs. Notably, the patients and the controls reported the same amount of sleep when they were 10 years old and the same frequency of a long-sleeper phenotype in one or both parents. These results suggest that the disease is acquired and does not result from an additional sleep load on an already sleepy phenotype. Sleep drunkenness Sleep drunkenness is another symptom of hypersomnia and constitutes an important disability in the daily life of the patients. Seventy-eight percent of the patients had difficulties with morning awakening, and one-third had sleep drunkenness, paralleling the percentages (21 and 52%) reported in other series. However, this last symptom is highly specific, as clearcut sleep drunkenness is not found in controls. Compared with hypersomniacs without any sleep drunkenness, those with sleep drunkenness are more frequently evening types on the Horne–Ostberg score. In this article, hypersomniacs are more frequently evening types than controls, and more alert in the evening than in the morning. These data suggest that they have a delayed shift in their circadian rhythm and a longer circadian period. To support this hypothesis, one had to perform a Subjective symptoms in idiopathic hypersomnia continuous measure of the body core temperature and the melatonin secretion (ideally during a constant routine to avoid the masking effect of a long sleep on the temperature) in these two groups. In our series, the patients with sleep drunkenness did not have a longer sleep time. The fact that sleep drunkenness is not correlated with sleep duration argues against an extreme form of sleep inertia (a normal period of hypovigilance and impaired cognitive and behavioural performances following awakening from naps, increasing with the duration of the earlier sleep in healthy subjects). The same observation can be made for naps, as not only long but also short naps (which had to limit the sleep inertia) are felt as nonrefreshing by 75% of hypersomniacs.

Eventually, one may imagine that forced awakening during slow-wave sleep at the end of the night would promote disorientation, diminished mentation and blunted responses to questions. In our study, however, slow-wave sleep is equally frequent at the end of the night in the patients with and without sleep drunkenness, suggesting that the presence of late slow-wave sleep is not causing the sleep drunkenness. However, this conclusion is limited by the fact that we do not inquire about sleep drunkenness the very morning of night 2, but as a general, frequent symptom. Notably, Roth et al. (1972) observed that sleep drunkenness is infrequent in the settings of the sleep laboratory, possibly as a consequence of a lighter, more fragmented sleep before awakening. The methods that make awakening in the morning easier are different in the patients and controls. Of interest, the habit of waking up at a certain time and the presence of a bright, sunny light are quite efficient in the controls but not in the hypersomniacs. The regulation of sleep termination has been thought to be embedded in a daily circadian rhythm, controlling in parallel the release of pituitary and adrenal hormones. A routine, predicted time of sleep offset is preceded by a gradual increase of adrenocorticotrophin 90–180 min before the final awakening (Born et al., 1999). Whether hypersomniacs have delayed pituitary hormone secretion in the morning (with a cortisol phase delay as observed by Nevsimalova et al., 2000 in 15 hypersomniacs) or have become resistant to these strong internal circadian signals is partly unknown. In this study, the intervention of someone helps them to wake up, but makes them quite dependent on others. Notably, a human voice calling someone by his first name is better processed by the sleeping brain than a sound during non-REM and REM sleep (Bastuji et al., 2002). A subject can not only call but also touch and even shake the sleeping hypersomniac, leading to a multimodal arousal. As a practical consequence, one may advise hypersomniacs to live in a student community or with a family (a parent or a caregiver) with someone responsible for waking them up. Daytime alertness Although patients insist on differentiating between sleepiness (as estimated by their ability to fall asleep in passive conditions, e.g. using the MSLT or the Epworth score) and tiredness/decreased alertness, we could not find stimuli that preferentially affect the sleepiness rather than the tiredness/alertness, they always go in the same direction. Billiard (1994) previously noticed that most patients with idiopathic hypersomnia never feel fully awake during the daytime, even if they can resist sleep easier than narcoleptics.

During the daytime, alertness is modulated by the same external conditions (e.g. higher during a sunny day than a grey or rainy day or than when exposed to artificial lighting, regardless of whether it is neon, halogen or incandescent lighting) in the controls and patients, but the patients feel more sedated than the controls in darkness. Bright light (e.g. 8– 10 000 lux, closer to sunlight) has already been demonstrated to increase alertness in workers but we are not aware of studies showing an alertness change reported during a grey or rainy day, so one may encourage hypersomniacs to use sun-like bright lights when working. Noises and loud environments are perceived as sedative by the controls and hypersomniacs, possibly because of the increase load to focus ones attention. In contrast, a quiet environment, music and conversation help the controls (but not the hypersomniacs) to feel alert and focused. However, being with friends (and not with strangers) is perceived as stimulating in the hypersomniacs, even if it is to a lesser degree than the controls. Taken together, it seems that hypersomnia narrows the spectrum of conditions associated with full alertness, given that the patients feel tired in the presence of over-stimulating conditions (a loud environment, strangers and flashing light), and feel sleepy in under-stimulating conditions (darkness, left alone or listening to a conversation). Basically, it appears in this study that the patients would feel all right only during holidays, in a nice landscape with sun and friends. One may wonder if they use, in this case, the motivation/mood system to stay awake rather than the usual arousal systems. In addition, being hyperactive helps hypersomniacs to resist sleepiness more than controls. They use this term to describe both any increased motor activity (such as standing up rather than sitting, walking while learning or speaking continuously) and doing several tasks at the same time (such as writing while listening). Hyperactivity is a symptom of attention deficit/hyperactivity disorder. In this case, excessive motor activity can be viewed as a strategy to stay awake and alert, while decreased attention could be the consequence of the hypoarousal (Lecendreau et al., 2000). We suspect that the hypersomniacs use the motor arousal to supplement their cognitive arousal, and the stress of multi-tasks to increase their level of alertness by fighting monotony. As a consequence, they could get more tired. Hence, we wonder if the feeling of tiredness that the patients described as different from sleepiness is a general lack of mental energy, as a consequence of using multi-modal systems to fight sleepiness. Cognitive and somatic symptoms A deficit of attention has been previously described in patients with idiopathic hypersomnia. European Sleep Research Society, Executive dysfunction is a consequence of many disorders with excessive daytime sleepiness, including narcolepsy, sleep apnoea syndrome and sleep deprivation; it had to be improved using stimulants. We could not find any previous report of defective memory in idiopathic hypersomnia. Whether the patients have a long-term memory deficit (i.e. in absence of attention and working memory deficit) is unlikely, but had to be formally assessed. In the present study, the patients notably reported that they could not sustain attention for more than 1 h, versus almost 4 h in the controls. This limited mental endurance suggests that patients with idiopathic hypersomnia have a cognitive fatigability, as it was described in patients with chronic fatigue syndrome ; this aspect could be tested on sustained attention tests.

Automatic behaviours are found both in patients and in controls, but the severity is different. Telling something inappropriate in a conversation and making a mistake during a usual activity are more frequently experienced by patients than by healthy controls (except if they are sleep deprived). Hence, one may interview patients about the frequency of these behaviours. When the patients mix two different activities during routine tasks, they seem only partly able to shift from an action (bringing the garbage to the cellar) to another action (going to the dentist). As this sort of shifting (and focusing) is seen as a frontal lobe function, it suggests that their automatic programs are no longer driven by the frontal lobe.

Although they are not monitored, they do not seem to be drowsy or in stage one during these behaviours. Rather, they are unfocused. The automatic behaviours can be partly responsible for the memory problems reported by the patients. For example, a patient lost her glasses for 3 months because she had put them into a videotape case. She spontaneously reports this incident as a memory problem. Some somatic problems regarding the autonomic nervous system (Raynaud-like syndrome, migraine and orthostatic syncope) have already been described in hypersomnia. In this study, some functional equivalents (cold extremities and fainting) are indeed more frequent in hypersomniacs than in controls, while there is no more headache in the patient group. In addition, half of the hypersomniacs are near-sighted, 38% are allergic and 25% have problems regulating their temperature. The mechanism of these symptoms is unknown, they could contribute to the burden of the disease. The symptoms reported in this article are subjective, which constitutes a limitation of this work. There is no formal testing of the cognitive status by a neuropsychologist, no measure of supine hypotension, no systematic sight

assessment in the controls, so that a bias towards over-reporting in patients is still possible. The questionnaire is, however, the same for any subject, whether hypersomniac or not. On the contrary, we try to catch the somatic problems of the patients, which are by definition subjective.

V. Diagnosis^[17]:

Diagnosis is starts with simple step of interaction with patient. And further diagnosis is carry out by maintaining sleep diary which includes duration of sleep, number of sleep episodes and its chronology. Dairy is ended with subjective quality questionnaires (Stanford sleepiness and Epworth sleepiness scale).

Next level of diagnosis is by using polysomnographic techniques like Electroencephalogram (EEG), electrocardiogram (ECG), electromyogram (EMG), electro-oculogram (EOG), leg movement or respiratory parameter. This diagnosis is carry out in both nocturnal sleep and in daytime sleep.

Most common diagnosis test is Multiple Sleep Latency Test (MSLT). In this test Rapid Eye Movement (REM) sleep latency or REM latency is checked. REM latency less than 8min is indicates Excessive day time sleepiness (normal is between 10-15 min).

Many other test are also use for diagnosis of IH like psychomotor test, oxford sleep resistance test etc.

VI. Treatment:

Treatment vary with diagnosis because diagnosis gives clear idea about what type of treatment should require for patient i.e. either non pharmacological or pharmacological.

6.1 Non-pharmacological treatment^[18]:

Non pharmacological treatment has its own importance in case of narcolepsy and idiopathic hypersomnia. It generally includes patient counseling and follow up to excess disease stage. Also in non-pharmacological treatment patient were suggested to take self-care and to observe your sleep schedule. Also they were suggested to take low carbohydrate diet and to perform exercise as it make person active.

6.2 Pharmacological treatment:

Not every patient shows positive response toward non-pharmacological treatment, for such patients pharmacological treatment i.e. drug treatment is given in addition to non-pharmacological treatment.

Table no. 1: Treatment for Hypersomnia

Drug	Description
Modafinil^[19]	Most studied and used drug for treatment of hypersomnia. It inhibits the dopamine transport as a result dopamine concentration is increases in extracellular site.
GABA-A receptor antagonist	They inhibits the GABA receptor.
Flumazenil^[20]	Flumazenil is benzodiazepine antagonist. It can be given subcutaneously.
Clarithromycin^[21]	It shows improvement in daytime sleepiness. It can be also used in other hypersomnolence other than IH

Methylphenidate ^[22]	It inhibites reuptake of dopamine. And used in treatment of idiopathic hypersomnia.
Sodium oxybate ^[23]	It is used to treat Narcolepsy as well as Idiopathic hypersomnia (IH requires lower dose than narcolepsy)
Solriamfetol ^[24]	It is a dopamine and norepinephrine reuptake inhibitor. It used in treatment of Excessive Daytime Sleepiness with Narcolepsy
Pitolisant ^[25]	It blocks presynaptic H3 histamine reuptake and increases the histamine release in the brain in patients with idiopathic hypersomnia as well as symptomatic hypersomnia
Methylcobalamin (Vitamin B12) ^[26]	It can be used in case of recurrent hypersomnia

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