REVIEW ARTICLE

Hypersomnia as a Result of Neurologic Disorders: A Case-based Review

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Introduction

Hypersomnia is defined as the inability to consistently attain and sustain, wakefulness and alertness required to meet demands to accomplish daily living tasks. Hypersomnia can be due to the following mechanisms: (a) failed alertness mechanism leading to sleep attacks, (b) weak alerting systems leading to the requirement of excessive efforts to stay awake or (c) hyperactive sleep-promoting processes leading to excess daytime sleepiness [EDS]. The International Classification of Sleep Disorders-3 [ICSD-3] uses the term "Central Disorders of Hypersomnolence" to refer to these disorders and it includes disorders in which the primary complaint is daytime sleepiness not caused by disturbed nocturnal sleep or misaligned circadian rhythms. EDS is the commonest manifestation of hypersomnia, however, it is neither always present in hypersomnia nor all patients with EDS have hypersomnia. Before considering EDS to be due to hypersomnia, we should rule out disturbed or missed nocturnal sleep. [See Figure 1 and 2]. The common clinical manifestations of hypersomnia include EDS, automatic behavior and (in children, hyperactivity). Table 1 below enlists all other clinical manifestations of Hypersomnia.

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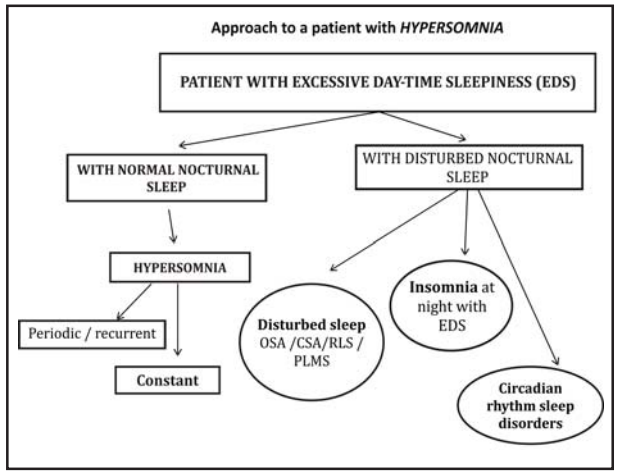

Figure 1: Initial approach to a person presenting with excessive daytime somnolescence:

OSA: Obstructive Sleep Apnoea.
CSA: Central Sleep Apnoea
RLS: Restless Limb Syndrome
PLMS: Periodic Limb Movements in Sleep
EDS: Excessive Daytime Sleepiness.

Hypersomnia due to Neurologic disorders

Hypersomnia due to neurologic disorders can occur pathologically due to reduced sleep length or depth, reduced wakefulness, problems in circadian rhythm, or a combination of either of these. Table 2 below describes the ICSD-3 subtyp Central Disorders of Hypersomnolence.

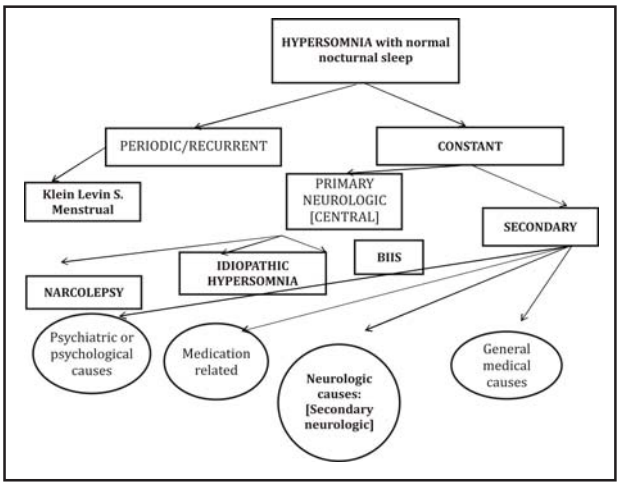

Figure 2: Approach to Hypersomnia with normal nocturnal sleep.

Etiologically, Hypersomnia due to neurologic disorders can be: (a) primary (central Hypersomnia): without any underlying illness but a primary sleep disorder and (b) Secondary: occurring due to an underlying neurologic illness like stroke, trauma, structural lesion or others. Hypersomnia secondary to other neurologic disorders is the cause in up to 90 percent of patients with neurogenic hypersomnia. Only 10 percent of patients have a Primary neurogenic Hypersomnia.

In this review, a case-based approach has been used to review and discuss anapproach to Hypersomnia due to neurologic disorders.

A. Secondary Neurogenic Hypersomnia

CASE 1

A 26-year-old female presented with the complaints of EDS for the last 3 months with undisturbed nocturnal sleep and complaint of polydipsia. She had no complaints of excessive hallucinations, cataplexy, headache, seizures, hyperphagia, hypersexuality, mood/ behavioral disorder or any drug therapy. She was alert and oriented to time, place and person with no focal deficits. The Epworth Sleepiness Scale score [ESS] was 20. The maintenance of wakefulness test showed that while just sitting, she slept within 2-3 minutes. The metabolic parameters were all normal. MRI brain revealed a Sellar ring enhancing lesion which on biopsy was suggestive of a craniopharyngioma.

Hypersomnia secondary to intracranial space occupying lesions

Hypothalamic lesions are an important cause of hypersomnia and the most common are Craniopharyngioma. Most patients have associated headache, vomiting or focal deficits especially in visual field or acuity, but in rare instances, such patients can present initially with hypersomnia only. Sleep is regulated at least partially by the hypothalamic structures, for example, the suprachiasmatic nucleus, regulating melatonin secretion. The secretion of melatonin occurs during the night and it affects sleep patterns. Any disturbance in its secretions results in decreased sleep and EDS as a compensation. Table-3 enlists common examples of structural lesions which can manifest with hypersomnia. A case study demonstrated the development of severe hypersomnia with preserved sleep-wake cycle in patients with the bilateral posterior hypothalamic lesion[3]. The bilateral anterior hypothalamic lesion, however, is associated with disrupted temporal patterns of the sleep-wake cycle in which there were periods of EDS and increased body temperature[4].

CASE 2

A 71-year-old male presented EDS with fatigue for the last 3 weeks with normal nocturnal sleep and no cataplexy. The ESS was 16. The review showed a history of low mood and a history of being hit by a scooter in the market where he fell and was unresponsive for a while. There were no focal deficits on examinations but Mini-Mental State Examination score [MMSE] was 27/30 and Frontal Assessment Battery [FAB] score was 11/18. Metabolic profile was normal. MRI brain revealed a post-traumaticcontusion in the Right Frontal lobe. Thus the patient was diagnosed to have post-traumatic hypersomnia.

Post-traumatic hypersomnia

Hypersomnolence may be observed within 6 to 18 months of head trauma. Its course depends on the location and the extent of the lesions. Injuries to the Fronto-basal,thalamodiencephalic, and hypothalamic region result into hypersomnolence[5]. High-risk patients have a history of coma for 24 hours post-trauma, a head fracture, or require immediate neurosurgical

interventions and were more likely to have scores > 16 points on the ESS and < or = 5 minutes on the Multiple Sleep Latency Test. Head trauma occasionally triggers parasomnias, including sleepwalking, sleep terrors, REM sleep behavior disorder and dissociative disorders. Pain at night was an important factor in EDS6[6].

CASE 3

A 45-year-old hypertensive male, smoker, presented with the history of not waking up in the morning on usual time. He was completely asymptomatic the previous night. Initially, a 0.2 Tesla MRI brain was done which was found to be normal. Metabolic parameters and the cerebrospinal fluid examination were normal. The patient was referred to our center. On examination, the patient was somnolent but was following verbal commands when stimulated and then going back to sleep. A vertical gaze palsy was present. A repeat MRI was done which showed bilateral thalamic infarct suggestive of the artery of Percheron infarction.

Hypersomnia following a Stroke

Around 20-40% of stroke patients present sleep-wake disturbances, mostly with hypersomnia, EDS or insomnia[7]. Sudden onset persistent, severe sleep-wake disturbances are common with bilateral paramedian thalamic, mesencephalic or brainstem infarcts. Strokes in the pontine region result in REM sleep behavior disorder. Patients with dorsal pontine or paramedian thalamic strokes may experience Lhermitte's peduncular hallucinosis, which is characterized by complex, colorful, dream-like visual hallucinations[8]. Multiple sleep latency tests may be inadequate for assessment. Actigraphy on the other side can be helpful to estimate the sleep-wake cycle and sleep/rest needs following astroke[9]. Modafinil is shown to improve patients with a bilateral meso-diencephalic paramedian infarct[10].

CASE 4

A 44-year-old male with young onset Parkinson's disease (PD) for 7 years, taking treatment elsewhere, was admitted for titration of drugs and further treatment. On rounds, he was observed to have EDS with micro-sleep episodes and automatic behavior while routine evaluation of his motor symptoms. On detailed evaluation, the patient had ahistory of disturbed nocturnal sleep. There was the presence of REM sleep behavior disorder, Restless legs syndrome (RLS) and periodic limb movement in sleep. Thus he was diagnosed with EDS secondary to PD. Starting clonazepam (0.5 mg) at night and improving his dopaminergic medicines lead to improvement in symptoms.

Hypersomnia and other sleep disorders in Parkinson's disease

Multiple well-described sleep symptoms and disturbances are recognized in Parkinsonism. Complaints of insomnia, parasomnias, EDS, and sleep onset and maintenance difficulties are common[11]. Multiple studies have shown that medication side effects can result in EDS, though large population studies have also demonstrated EDS in PD patients irrespective of medications[12]. Sleep abnormalities in PD include deficiencies in slow wave sleep, total sleep time, sleep latency, efficiency, and overall architecture and decrease in REM sleep[13]. Sleep fragmentation, altered dream phenomena, and hallucinations also appear to be common in PD patients[14]. Central hypersomnia including a narcolepsy phenotype, with low hypocretin levels measured in the cerebrospinal fluid, is also seen[15].

CASE 5

A 23-year-old male presented with acute fever with a headache for 4-5 days with episodes of projectile vomiting for 2 days and 1 episode of seizure followed by altered sensorium. He would respond to stimulus and verbal commands but on cessation of stimulus would become somnolent again. Nuchal rigidity was present. MRI showed bilateral diencephalic T2 and FLAIR hyperintense signal lesion without post contrast enhancement. A study of the cerebrospinal fluid (CSF) showed lymphocytic pleocytosis with normal glucose and raised protein. Workup for Tuberculosis, Human immuno-virus, Syphilis and fungal results was negative. He had an associated history of dry mouth, eye dryness, and intermittent non-erosive arthritis and his Anti-nuclear antibody profile was positive for Anti-Ro and Anti-La antibodies. Schirmer Eye test confirmed dry eyes and thus he was diagnosed with Sjogren syndrome.

Hypersomnia in inflammatory infectious or non-infectious infiltrative disorders affecting the thalomo-diencephalic region

Table-4 below enlists different possible causes of such inflammatory disorders.

The mechanism of hyper-somnolescence in intracranial infections/ inflammatory disorders is based on hypocretin. Hypocretin originates in lateral neurons of the hypothalamus and regulates normal sleep, appetite, neuroendocrine function, and energy metabolism[16]. Low levels of hypocretin-1 are also found in narcolepsy and disorders like Guillain-Barré syndrome, trauma and brain tumors. This may reflect hypothalamic lesions or dysfunction autoimmune in nature can also cause hypersomnolence[17]. Anti-Ma2 encephalitis has been described to be associated with hypersomnolence[18].

CASE 6

A 34-year-old female presented with a complaint of fatigue, EDS, increased voluntary naps and occasional microsleep episodes which affected household chores for the last 2 years. On examination, the patient had alopecia, bilateral facial weakness, wasted hands with elicitable myotonia suggestive of myotonic dystrophy.

Hypersomnia in neuromuscular diseases

Myotonic dystrophy is characterized by myotonia and muscle weakness. Psychiatric disorder and sleep problems are considered important features of the illness. Hypersomnia occurring in myotonic dystrophy can be due to respiratory involvement but can also present as a CNS feature[19]. EDS is the most common non-muscular symptom occurring in up to 70-80% of adult-onset DM-Type1[20]. It is characterized by persistent sleepiness unaffected by naps and without dream content, occurs in monotonous situations or when attention is not being held[21]. A neuropathological study showed a selective loss of serotoninergic neurons of dorsal raphe nucleus in DM1 patients complaining of EDS[22]. The presence of sleep-onset REM periods (SOREMPs) on the MSLT is a relatively frequent finding in type-1 as well as shortsleep latencies, suggesting a narcoleptic-like phenotype[23]. Modafinil and non-invasive ventilation may improve hypersomnia in patients with neuro-muscular disorders.

B. Intrinsic sleep disorder (Primary neurogenic hypersomnia)

CASE 1

A 23-year-old male presented with complaints of EDS for last 4 months and episodes of falling from the bicycle without reason. Around 2 days back there was an episode of buckling of knees and falling in the college while laughing. The patient had normal 8 hours of nocturnal sleep. There was no history of diplopia, headache, seizure or loss of consciousness. The examination of the patient was unremarkable. The patient had a normal metabolic, EEG and MRI brain. An overnight polysomnography was also normal. On doing multiple sleep latency test sleep onset REM episodes [SOREMs] were found in all 5 naps. The mean sleep onset latency was 2.3 mins. Thus patient was diagnosed to have narcolepsy.

Narcolepsy

Narcolepsy is a disorder of REM sleep and is the classic hypersomnia of central origin. The classic symptoms of narcolepsy include EDS, cataplexy, hypnagogic hallucinations, and sleep paralysis[24]. Narcolepsy can also be present in the absence of cataplexy. Cataplexy is a sudden onset of muscle atonia or hypotonia that is typically provoked by emotion[25].

Traditionally Narcolepsy was sub-classified into "with cataplexy" and "without cataplexy". However, with the establishment of a link between narcolepsy and low hypocretin levels and with the fact that many patients with low CSF hypocretin levels, not manifesting cataplexy initially, in the ICSD-3, Narcolepsy has been subdivided into type-1 and type-2 based presence or absence of either of cataplexy or hypocretin deficiency. Table-5 enlists the diagnostic criteria for Narcolepsy.It is suspected that patients with the HLA marker DQB1*0602 may possess a genetic susceptibility for some event or trigger that causes narcolepsy. These triggers include environmental factors such as infections, head trauma, or even a change in sleeping habits[27]. Hypersomnolence in narcolepsy can benefit with modafinil while cataplexy is managed with the help of tricyclic antidepressants[26].

CASE 2

A 32-year-old female presented with complaints of abrupt onset EDS with no history of cataplexy or history of

drug or substance abuse. CNS examination was unremarkable. The patient had normal metabolic reports and MRI brain. A polysomnography showed sleep of more than 10 hours. Actigraphy showed mean sleep onset latency of 1 min with no SOREMPS. Thus the patient was diagnosed of having idiopathic hypersomnia.

Idiopathic Hypersomnia (IH)

Idiopathic hypersomnia (IH) continues to be a poorly understood entity and is often a diagnosis of exclusion. The cardinal manifestation of IH is EDS despite a normal total sleep time and an absence of sleep-disordered breathing and normal sleep architecture in an overnight sleep study. Table-6 enlists the diagnostic criteria for IH. The cause of IH is speculative, as little is known of its pathophysiology. Abnormal melatonin secretion and a circadian dysfunction have been postulated[29]. The diagnosis of IH is straightforward with the help of MSLT once the other causes are ruled out[30]. Pharmacologic treatment is similar to that of narcolepsy. Stimulants and wake-promoting agents are the mainstays of treatment. Treatment with melatonin as well as levothyroxine has also been tried with some success[31].

CASE 3

A 23-year-old male presented with complaints of recurrent episodes of EDS with binge eating and feelings of excessive and inappropriate sexual arousals. The examination was unremarkable. MRI brain, CSF picture,and metabolic screening were normal. Thus the patient was diagnosed with Klein-Levin syndrome.

Klein-Levin Syndrome (KLS)

KLS is a classic, but rare, cause of recurrent hypersomnia and consists of hyperphagia, hypersomnia, and hypersexuality. Infection or high fever is the most common precipitant. Stress, alcohol use, travel, and sleep deprivation are other precipitants. Patients have normal cognitive functioning with normal alertness between episodes[32]. Table 7 enlists diagnostic criteria of KLS.CT and MRI scans of the brain are always normal[32]. Brain SPECT, however, shows reduced perfusion of the thalamus during an active KLS episode that reverses to normal as the symptoms resolve[33]. Only some patients have demonstrated a response to treatment with valproic acid, lithium, amantadine, or lamotrigine[34].

CASE 4

A 19-year-old college student, presented a history of EDS, sleeping in class, accidents while driving and difficulty in studies. He had habits of sleeping late, playing computer games, having mobile chats, jogging early in the morning. All these complaints used to increase when the patient went home on the weekends. Examination of the patient was unremarkable. All investigations were found to be normal. He was diagnosed to have of Behaviorally Induced Insufficient Sleep Syndrome.

Behaviorally Induced Insufficient Sleep Syndrome

This cause of hypersomnia occurs as a result of sleep deprivation and is most commonly seen among adolescents. It usually does not need an intense investigation because the history of sleep deprivation and of patients catching up on their sleep on weekends makes the diagnosis obvious. If a sleep study is done, it will show a short sleep-onset latency and high sleep efficiency and occasionally, may also reveal SOREMP[29]. Stimulant medications are not recommended since behavioral modifications are sufficient to treat this condition.

C. Hypersomnia as a comorbidity in other neurologic disorders

EDS may also present as a co-morbidity in patients with other neurologic disorders. Patients with epilepsy commonly complain of having EDS. This is considered to be multifactorial in origin, with multiple factors including disturbed nocturnal sleep, nocturnal seizures, comorbid depression or anxiety and effect of anti-epileptic drugs contributing to the problem. Patients also commonly complain EDS with headache disorders like migraines and tension-type headache. However, this is not much studied and documented in the medical literature in detail. Multiple factors involved in its genesis include headaches affecting nocturnal sleep, lifestyle and behavioral issues, circadian rhythm disorders, psychiatric comorbidity and prophylactic medicines for headaches.

Summary

Primary Central sleep disorders generally have a longer history of atleast few months and the diagnostic criteria

require at least 3 months of symptoms.When the symptoms occur acutely, over days or weeks, it is important to rule out secondary neurologic disorders. The approach to a patient with neurological causes of hypersomnia is outlined in Table-8 below.

Table 1: Clinical Manifestations of Hypersomnia

EDS.
Automatic behavior.
Hyperactivity [in children].
Hypersomnia Sensu Stricto [increased sleep need/ behavior in 24 hours]
increased voluntary napping
sleep drunkenness
reduced subjective vigilance
Errors in functions and sudden lapses of vigilance [blackouts]. Hypersomnia would also manifest with reduced level of function and reduced quality of life
the feeling of fatigue
accidents
cognitive disturbances or psychiatric disturbances

Table 2: Types of Central disorders of Hypersomnolence based on ICSD-3

1. Narcolepsy type-1
2. Narcolepsy type-2
3. Idiopathic hypersomnia
4. Kleine–Levin syndrome
5. Hypersomnia due to a medical disorder
6. Hypersomnia due to a medication or substance
7. Hypersomnia associated with a psychiatric disorder
8. Insufficient sleep syndrome
9. Isolated symptoms and normal variants

Table 3: Examples of structural lesions presenting with hypersomnia

Craniopharyngioma with suprasellar extension
Pilocytic astrocytoma of Pituitary
Pituitary adenoma
Brainstem glioma
Subependymoma
Hemispheric tumours [Right Frontal lobe]
Langerhan cell histiocytosis

Table 4: Causes of hypersomnolence in inflammatory diseases are as given below

A. Infections: Acute:Pyogenic / viral / pyogenic Subacute-Chronic: Tuberculous meningitis / Fungal / HIV.
B. Inflammation: Bechet's disease / SLE / Sjogren syndrome.
C. Demyelination:NMO, MS, ADEM
D. Autoimmune encephalitis
E. Paraneoplastic encephalitis

Table 5: Diagnostic criteria for Narcolepsy [based on ICSD-3]

Narcolepsy type-1
A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months
B. The presence of one or both of the following:
1. Cataplexyand a mean sleep latency of ≤8 min and two or more sleep-onset REM periods (SOREMPs) on an MSLT performed according to standard techniques. SOREMP (within 15 min of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT
2. CSF hypocretin-1 concentration, measured by immunoreactivity, is either ≤110 pg/mL or < 1/3 of meanvalues of normal subjects.
Narcolepsy type-2
A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months
B. A mean sleep latency of ≤8 min and two or more sleep-onset REM periods (SOREMPs) are found on a MSLTperformed according to standard techniques. SOREMP (within 15 min of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT
C. Cataplexy is absent
D. Either CSF hypocretin-1 concentration has not been measured or CSF hypocretin-1 concentration measured by immunoreactivity is either >110 pg mL or >1/3 of mean values obtained in normal subjects with the same standardized assay
E. The hypersomnolence and/or MSLT findings are not explained more clearly by other causes such as insufficient sleep, obstructive sleep apnoea, delayed sleep phase disorder or the effect of medication or substances or their withdrawal

Table 6: Diagnostic criteria for idiopathic hypersomnia: (26)

A. The 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. An MSLT performed according to standard techniques shows fewer than two sleep onset REM periods or no sleep onset REM periods if the REM latency on the preceding polysomnogram was ≤15 min
D. The presence of at least one of the following:
1. The MSLT shows a mean sleep latency of d"8 min
2. Total 24-h sleep time is ≥660 min (typically 12–14 h) on 24-h polysomnographic monitoring (performed after correction of chronic sleep deprivation), or by wrist actigraphy in the patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three associations with a sleep log (averaged over at least 7 days with unrestricted sleep)
E. Insufficient sleep syndrome is ruled out
F. The hypersomnolence and/or MSLT findings are not explained more clearly by another sleep disorder, other medical or psychiatric disorder or use of drugs or medications

Table 7: Diagnostic criteria of KLS

The diagnostic criteria for KLS include: (26)
A. Recurrent episodes of EDS last 2 days to 4 weeks.
B. The episodes recur at least once a year.
C. The patient has normal alertness, cognitive functioning, and mental status between attacks.
D. The hypersomnia is not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

Table 8: Central disorders of hypersomnolence

PRIMARY CENTRAL DISORDERS [**> 3 months history**]	**HYPERSOMNIA ASSOCIATED WITH MEDICAL DISORDER** [**Duration shorter**]			
1. Narcolepsy types 1 and 2 2.Idiopathic Hypersomnia 3.Klein-Levin Syndrome 4.Behaviourally Insufficient Sleep Syndrome 5.Post-traumatic hypersomnia	HYPERACUTE Vascular lesions involving the Thalamo-diencephalic region [eg Artery of Percheron infarct]	ACUTE 1.Infection 2. Demyelination: MS, NMO, ADEM. 3.Inflammation: Bechet, SLE, Sjogren 4. Autoimmune 5. Paraneoplastic	SUBACUTE-CHRONIC 1. Chronic meningitis 2. Space occupying lesions	Special Settings Neuro-muscular disorders Neurodegenerative disorders HeadacheEpilepsy

References

1. **Ahmed I,** Harris S, Thorpy M. Differential Diagnosis of Hypersomnias. Sleep Medicine Clinics. 2012;7(2):191-204.
2. **A. Brzezinski,** "Melatonin in humans," New England Journal of Medicine, vol. 336, no. 3, pp. 186–195, 1997.
3. Hypersomnia Associated with Bilateral Posterior Hypothalamic Lesion A Polysomnographic Case Study I. Eisensehra S. Noachtara C. von Schlippenbacha I. Uttnerc J. Kleinea K. Seelosb C. Helmchend
4. **Sallanon M,** Denoyer M, Kitahama K, Aubert C, Gay N, Jouvet M: Long-lasting insomnia induced by preoptic neuron lesions and its transient reversal by muscimol injection into the posterior hypothalamus in the cat. Neuro- science 1989;32:669–683.
5. **Guilleminault C.,** Yuen KM., Gulevich MG., Karadeniz D., Léger D., Philip P. Hypersomnia after head-neck trauma: a methodological dilemma. Neurology. 2000;54:653–659
6. **Schenck CH,** Boyd JL, Mahowald MW. A parasomnia overlap disorder involving sleepwalking, sleep terrors, and REM sleep behavior disorder in 33 polysomnographically confirmed cases. Sleep.1997;20(11):972–81. Epub 1998/02/11
7. **Leppävuori A,** Pohjasvaara T, Vataja R, Kaste M, Erkinjunntti T. Insomnia in ischemic stroke patients. Cerebrovasc Dis 2002;14:90–97.
8. **Bassetti C,** Chervin R. Cerebrovascular diseases. In: Kryger MH, Roth T, Dement WC, editors. Principles and Practice of Sleep Medicine. 3rd edition. Philadelphia: W. B. Saunders; 2000. P. 1072–92
9. **Bassetti C,** Mathis J, Gugger M, Lövblad KO, Hess CW. Hypersomnia following thalamic stroke. Ann Neurol 1996;39:471–80
10. **Autret A,** Lucas B, Mondon K, Hommet C, Corcia P, Saudeau D, et al. Sleep and brain lesions: a critical review of the literature and additional new cases. Neurophysiol Clin 2001;31:356–75.
11. **Bhat V,** Weiner WJ. Parkinson's disease. Diagnosis and the initiation of therapy. Minerva Medica. 96: 145-54.
12. **Adler C,** Thorpy M. Sleep issues in Parkinson's disease. Neurology. 2005;64(Issue 12, Supplement 3):S12-S20.
13. **Comella C.** Sleep Disorders in Parkinson's Disease. Sleep Medicine Clinics. 2008;3(3):325-335.
14. **Pappert E,** Goetz C, Niederman F, Raman R, Leurgans S. Hallucinations, sleep fragmentation, and altered dream phenomena in Parkinson's disease. Mov Disord. 1999;14(1):117-121.
15. **Wienecke M,** Werth E, Poryazova R, et al. Progressive dopamine and hypocretin deficiencies in Parkinson's disease: is there an impact on sleep and wakefulness? J Sleep Res. 2012;21:710–717
16. **Mignot E.** Sleep, sleep disorders and hypocretin (orexin). Sleep Medicine. 2004;5:S2-S8.
17. **Arii J,** Kanbayashi T, Tanabe Y, Sawaishi Y, Kimura S, Watanabe A et al. CSF hypocretin-1 (orexin-A) levels in childhood narcolepsy and neurologic disorders. Neurology. 2004;63(12):2440-2442.
18. **Dalmau J.** Clinical analysis of anti-Ma2-associated encephalitis. Brain. 2004;127(8):1831-1844.
19. Apathy and hypersomnia are common features of myotonic dystrophy J S Rubinsztein, D C Rubinsztein, S Goodburn, A J Holland
20. **D. Hilton-Jones,** "Myotonic dystrophy-forgotten aspects of an often neglected condition," Current Opinion in Neurology, vol. 10, no. 5, pp. 399-401, 1997
21. **J. C. Phemister and J. M. Small,** "Hypersomnia in dystrophia myotonica," Journal of Neurology, Neurosurgery, and Psychiatry, vol. 24, pp. 173–175, 1961.
22. **S. Ono, K.** Takahashi, K. Jinnai et al., "Loss of serotonin-containing neurons in the raphe of patients with myotonic dystrophy: a quantitative immunohistochemical study and relation to hypersomnia,"Neurology, vol. 50, no. 2, pp. 535–538, 1998.
23. **E. Martinez-Rodríguez,** L. Lin, A. Iranzo et al., "Decreased hypocretin-1 (orexin-A) levels in the cerebrospinal fluid of patients with myotonic dystrophy and excessive daytime sleepiness," Sleep, vol. 26, no. 3, pp. 287–290, 2003.
24. **Black JE,** Hirshkowitz M. Modafinil for thetreatment of residual excessive sleepiness in nasal continuous positive airway pressure-treated obstructive sleep apnea/hypopnea syndrome. Sleep 2005;28:464-71.
25. **Billiard M,** Guilleminault C, Dement WC. (A menstruation-linked periodic hypersomnia. Kleine- Levin syndrome or new clinical entity? Neurology 1975;25:436–43.
26. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*.3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
27. **Mignot E.** Genetic and familial aspects of narco- lepsy. Neurology 1998;50(2 Suppl 1):S16–22.
28. **Thannickal TC,** Moore RY, Niehus R, et al. Reduced number of hypocretin neurons in human narcolepsy. Neuron 2000;27:469-74.
29. **Malhotra S,** Kushida C. Primary Hypersomnias of Central Origin. CONTINUUM Lifelong Learning in Neurology. 2013;19:67-85.
30. **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(5):576Y578.
31. **Montplaisir J,** Fantini L. Idiopathic hypersomnia: a diagnostic dilemma. A commentary of ''Idiopathic hypersomnia'' (M. Billiard and Y. Dauvilliers). Sleep Med Rev 2001;5(5):361Y362.
32. **Critchley M,** Hoffman H. The syndrome of periodic somnolence and morbid hunger (Kleine-Levin syndrome). Br Med J 1942;1(4230):137Y139.
33. **Huang YS,** Guilleminault C, Kao PF, Liu FY. SPECT findings in the Kleine-Levin syndrome. Sleep 2005;28(8): 955Y960.
34. **Arnulf I,** Lin L, Gadoth N, et al. Kleine-Levin syndrome: a systematic study of 108 patients. Ann Neurol 2008;63(4):482Y493.