



Chronic Hypersomnia

Yves Dauvilliers, MD, PhD^{a,b,*}, Michel Billiard, MD^c

■ Idiopathic hypersomnia

History

Epidemiology

Clinical signs

Polysomnography and other laboratory findings

Pathophysiology

Differential diagnosis

Treatment

■ Hypersomnia caused by medical condition

Posttraumatic hypersomnia

Hypersomnia following infection

■ Nonorganic hypersomnia

■ Summary

■ References

Chronic hypersomnias correspond to numerous etiologies of patients with a complaint of excessive daytime sleepiness. The identification of specific phenotypes of hypersomnia is useful to classify patients into different clinical diagnosis. Idiopathic hypersomnia remains a relatively poorly defined and rare condition, and the final diagnosis rests on the exclusion of other causes of hypersomnias. Although considerable progress has been made in understanding hypersomnias in the last few years with the discovery of the hypocretin system, the pathophysiology of idiopathic hypersomnia is still totally unknown. There is a definite need to further develop sleep laboratory investigations to assess the correct diagnosis. Studies at the genetic and biological levels are needed also to further our understanding of the pathophysiology of IH and to develop specific treatment.

Idiopathic hypersomnia

Idiopathic hypersomnia (IH) is a rare condition of excessive daytime sleepiness. IH remains a rela-

tively poorly defined condition because of the absence of specific symptoms, such as cataplexy or sleep apnea. The recent International Classification of Sleep Disorders (ICSD) classifies IH in two forms: IH with long sleep time and IH without long sleep time [1]. Differential diagnosis is frequent and insufficiently recognized. Pathophysiology is almost totally unknown and more studies are needed to recognize IH as an independent disorder in terms of clinical and biologic processes.

History

IH is a rare condition, 5 to 10 times less frequent than narcolepsy, which has been confused with narcolepsy for a long time. Roth et al [2–4] was the first in the late 1950s to describe this disorder characterized by excessive daytime sleepiness, prolonged nocturnal sleep, sleep drunkenness, and the absence of irresistible sleep episodes and cataplexy. Two clinical forms of IH were distinguished by Roth: the monosymptomatic form characterized by excessive daytime sleepiness only, and the polysymptomatic form characterized by excessive day-

^a Service de Neurologie B, Hôpital Gui-de-Chauliac, 80 Avenue Augustin Fliche, 34295 Montpellier Cedex 5, France

^b INSERM E0361, Hôpital La Colombière, Montpellier, France

^c Faculté de Médecine, Hôpital Gui-de-Chauliac, 80 Avenue Augustin Fliche, 34295 Montpellier Cedex 5, France

* Corresponding author. Service de Neurologie B, Hôpital Gui-de-Chauliac, 80 Avenue Augustin Fliche, 34295 Montpellier Cedex 5, France.

E-mail address: y-dauvilliers@chu-montpellier.fr (Y. Dauvilliers).

time sleepiness, abnormally long nocturnal and diurnal sleep, and sleep drunkenness on awakening. In contrast to narcolepsy, diurnal sleep is not irrepressible and does not restore normal alertness. Nocturnal sleep remains undisturbed but with a delayed morning awakening.

Several terms were used to define this hypersomnia: hypersomnia with sleep drunkenness, essential narcolepsy, non-rapid eye movement (NREM) sleep narcolepsy, idiopathic central nervous system hypersomnia. The term "idiopathic hypersomnia" was finally approved and included in the ICSD in 1990 [5] and defined as "a disorder of presumed central nervous system cause that is associated with a normal or prolonged major sleep episode and excessive sleepiness consisting of prolonged (1–2 hours) sleep episodes of non-REM sleep." A possible overlap between narcolepsy without cataplexy and monosymptomatic IH can exist, however, with similar clinical features between the two conditions [6,7]. Recently, the revised version of the ICSD [1] proposes two forms of IH: IH with long sleep time, which corresponds to the polysymptomatic form; and IH without long sleep time, which corresponds to the monosymptomatic form. Although called "idiopathic," this hypersomnia must not correspond to all diagnosis of hypersomnia that do not have well-defined origin [1,8].

IH is individualized based on clinical features and polysomnography (PSG) followed by a Multiple Sleep Latency Test (MSLT), which confirms the objective hypersomnia. PSG shows a sleep of normal quality with few awakenings, a normal proportion of the different sleep stages, and normal sleep efficiency [1]. Sleep apnea, periodic leg movements, and crescendo (by monitoring of esophageal pressure) must not be present. In that sense, the upper airway resistance syndrome [9], first described in 1993, revealed that many patients with previous IH diagnosis may actually have the upper airway resistance syndrome diagnosis.

Although important advances have been made in the clinical description of IH, no clear biologic or genetic markers are available. The normality of cerebrospinal fluid (CSF) hypocretin-1 level and the absence of association with HLA DQB1*0602 reinforce the possible overlap between patients affected with IH without long sleep time and those affected with narcolepsy without cataplexy [10–13].

Epidemiology

The diagnosis of IH, especially IH without long sleep time, is often overestimated; however, the prevalence of IH in the general population is unknown. The nosologic uncertainty and the rarity of the condition may explain the absence of any epidemio-

logic study. Recent sleep center reports revealed a ratio of one patient with IH for 10 with narcolepsy with cataplexy [6,14].

In contrast to narcolepsy, the age at onset is not always easy to pinpoint because of the insidious development of the condition. In most patients, however, the disease starts before 30 years of age [8,14].

There is no indication of gender predominance. The familial aspect of patients with IH is frequent and known since the first description of the disease [15]. In the authors' experience of 28 well-defined IH cases with long sleep time, 67.85% of patients have at least one relative affected with hypersomnia with a possible autosomal-dominant mode of transmission.

Clinical signs

In both forms of IH with and without long sleep time, patients have a complaint of excessive daytime sleepiness occurring almost daily for at least 3 months. Clinical diagnosis of IH also requires that hypersomnia is not better explained by another sleep disorder, medical or mental disorder, medication use, or substance use disorder [1].

IH with long sleep time is a well-defined clinical entity. Patients tend to complain of constant excessive daytime sleepiness with the Epworth Sleepiness Scale above 11. This daytime sleepiness leads to long (more than 1 hour) and unrefreshing naps, less irresistible than in narcolepsy. The nocturnal sleep is also long (more than 10 hours) and uninterrupted, but does not restore normal alertness. Awakening after nighttime or daytime sleep is difficult. These patients may be confused and unable to react adequately to external stimuli on awakening for up to 1 to 3 hours, a state referred to as "sleep drunkenness" or "sleep inertia." Episodes of automatic behavior can occur during this drowsy state especially in the morning, with frequent amnesia postepisodes [4]. Total sleep time, whenever made possible, mainly during holidays and weekends, is always above 12 hours.

In contrast, patients affected with IH without long sleep time never report "sleep inertia." This condition is characterized by isolated excessive daytime sleepiness. Patients complain of recurrent daytime naps more irresistible and more refreshing than in IH with long sleep time. Nocturnal sleep is normal, sometimes prolonged (more than 6 hours but less than 10 hours) but always refreshing [1]. A clinical overlap between IH without long sleep time and narcolepsy without cataplexy may be hypothesized. The presence of both conditions within the same family has also been reported [6].

Although cataplexy is always absent in IH, sleep paralysis and hypnagogic or hypnopompic halluci-

nations may be present as in other sleep disorders or in the general population. Other symptoms have been reported, such as headache (mainly migraine or tension-type headache), and manifestations of neurovegetative impairment with cold hands and feet, orthostatic hypotension, or syncope. Those symptoms are nonspecific, however, and may be found within same proportion in other sleep disorders and in the general population. Mood changes are also frequently reported in IH, probably as in other chronic sleep disorders impeding quality of life, such as narcolepsy with cataplexy. Mood changes must not reach the point of major depression, however, psychiatric hypersomnia being a main clinical differential diagnosis of IH [16].

Evolution of IH over time is not well known but seems to be stable in severity without any spontaneous disappearance of the symptoms. The psychosocial and professional consequences are similar to those found in narcolepsy [17].

Polysomnography and other laboratory findings

Polysomnography

PSG is required to ascertain the diagnosis and to exclude other etiologies of hypersomnia. PSG demonstrates short sleep latency and a normal sleep of prolonged duration (at least 10 hours) in the case of IH with long sleep time. In IH without long sleep time, PSG shows normal sleep or sleep of slightly prolonged duration, always between 6 and 10 hours [1].

NREM and REM sleep are usually in normal proportions. An increased amount of NREM sleep can be found, however, as is the case for sleep spindles [18,19]. Sleep efficiency is above 90% in the authors' experience and 85% in the new ICSD criteria [1]; microarousal index is less than 10 per hour. The presence of important nighttime sleep disruption cannot fit the diagnosis of IH and PSG needs to exclude other causes of daytime sleepiness. Sleep-onset REM period is not reported in IH. Obstructive sleep apnea (index >5 per hour) and periodic limb movements (index >5 per hour) are exclusion criteria; however, in rare cases of an early onset of IH and their late occurrence the diagnosis of IH is still possible. Systematic monitoring of the esophageal pressure during sleep, to exclude upper airway resistance syndrome that may fragment sleep and induce daytime sleepiness, is still subject to debate. Nevertheless the authors recommend the procedure.

Multiple Sleep Latency Test

The most widely used procedure is an all-night PSG recording followed by a MSLT. MSLT is always necessary to confirm the objective hypersomnia

and to exclude other causes of hypersomnia, especially narcolepsy without cataplexy. A mean sleep latency of less than 8 minutes with less than two sleep onset rapid eye movement period (SOREMPs) is necessary for the positive diagnosis [1]. Mean sleep latency is at 6.2 ± 3 minutes in IH with or without long sleep time, higher than in narcolepsy [1]. MSLT is of limited diagnostic value, however, in IH with long sleep time. The first reason is the usual difficulty to keep the patient awake before the test and between sessions of the test. The second one is the obligation to wake up the patient in the morning to perform MSLT, precluding the recording of the prolonged nighttime sleep, a typical symptom of IH with long sleep time. Regarding these limits, several patients may have normal mean sleep latency on the MSLT, being above 8 but less than 10 minutes [6,8].

Other polysomnographic protocols

Because of the previously listed limits of the PSG-MSLT procedure, a 24-hour continuous PSG on an ad libitum sleep-wake protocol may be proposed [8]. This protocol is of potential interest, especially for the diagnosis of IH with long sleep time, in recording a major sleep episode (more than 10 hours) and at least one daytime sleep episode

Box 1: Sleep-wake Montpellier protocol in idiopathic hypersomnia with long sleep time

Day 1-Night 1-Day 2

Overnight PSG recording (after 16 hours sleep deprived) and MSLT (9 AM, 11 AM, 1 PM, 3 PM, and 5 PM) were performed. After 1 minute of sleep on the MSLT, subjects were awakened in order not to interfere with the homeostatic process. Batteries of neuropsychologic tests (including vigilance and cognitive tests) were performed during Day 2 between each nap. Three cognitive evoked potential recording (auditory P 300) sessions took place on Day 1 at 7 PM and on Day 2 at 7 AM and 11 AM

Night 2-Day 3-Night 3

A 32-hour continuous PSG on an ad libitum sleep-wake protocol is performed. After a 16-hour sleep deprivation (Day 2), a PSG recording is performed during 32 hours in the bed rest protocol from 11 PM to 7 AM 2 days after. Conditions are as follows: sound attenuated; dim light (10 lux); interdiction to get up or to listen to music or radio; possibility to ask for food and drink (without alcohol). The choice of the bed rest condition has been made to increase sleepiness, to decrease wakefulness, and to reduce sleep propensity at the end of the study.

of more than 1 hour duration. Spontaneous sleep periods of up to 19.4 hours have been previously reported in that condition, with normal MSLT latency [20]. That procedure still waits for standardization and validation, however, especially regarding the level of physical activity allowed during the recording. At present the authors perform a

bed rest 32-hour continuous PSG (a bed rest is always on an ad libitum sleep-wake protocol) on an ad libitum sleep-wake protocol to ascertain the diagnosis and to assess abnormalities of the sleep-wake regulation [Box 1, Fig. 1]. Because of financial cost, this protocol is not recommended to ascertain the diagnosis of IH patients.

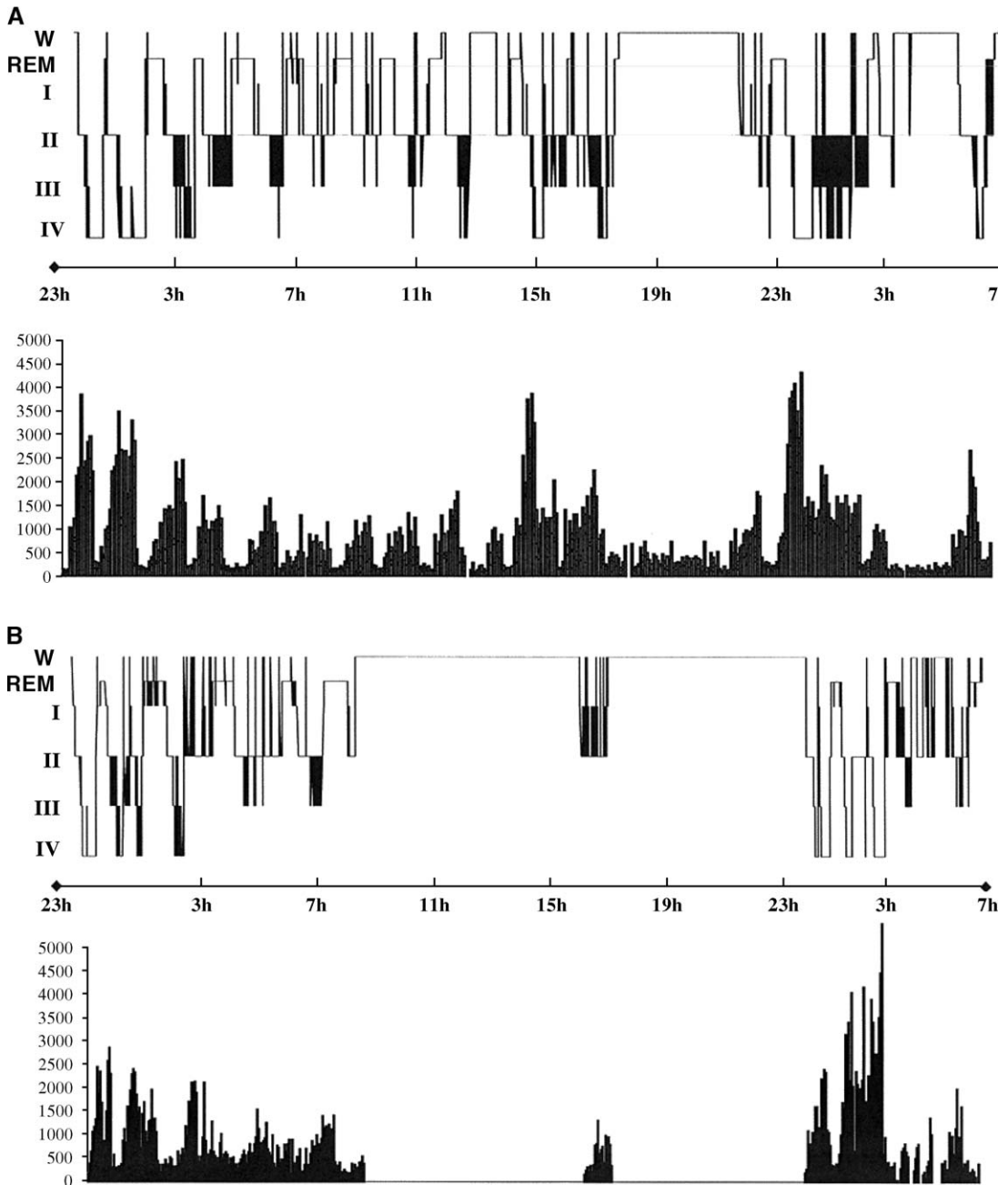


Fig. 1. Hypnogram and slow wave activity (SWA) in a 32-hour bed rest protocol. (A) A 26-year-old woman affected with IH with long sleep time. (B) A 28-year-old control. An increase in total sleep time and in level of SWA was noted, with a slow exponential decay of SWA during the first night when compared with the control. Also noted was a longer duration of the nap during the day in IH patient with an increase in SWA around 3 PM.

Other tests

Several authors recommend ambulatory actigraphy monitoring over several days to demonstrate prolonged nighttime and daytime sleep episodes that are typical of IH with long sleep time [13]. Actigraphy cannot differentiate sleep and wake periods while resting, although this is extremely important for the diagnosis of IH. In addition, as is the case for 24-hour PSG, the actigraphy protocol still needs standardization and validation in IH.

Cognitive evoked potentials (auditory or visual P 300) are also of interest to measure sleep inertia objectively [21–23]. This result is of no practical value, however, in the diagnosis of a single patient. In contrast to narcolepsy, HLA typing is of no help in the positive diagnosis of IH, given the lack of any consistent association with HLA. In addition, CSF hypocretin-1 levels are normal in most cases and especially in all cases of IH with long sleep time [10–12].

Neurologic and psychological evaluations are necessary. They have to be normal to exclude the possibility of hypersomnia associated with neurologic or psychiatric disorders. Finally, brain CT or MRI is of value to rule out an underlying brain lesion.

Pathophysiology

Pathophysiology of IH is almost totally unknown and still speculative. Because of clinical feature differences between the two conditions (IH with and without long sleep time) one may hypothesize a different pathophysiology mechanism. Another hypothesis may be drawn for continuum in the pathophysiology of IH without long sleep time and narcolepsy without cataplexy [12].

There is no available natural model of IH comparable with the narcoleptic dog. The central nervous system changes that lead to the symptoms of IH are unknown, although altered central nervous system monoaminergic activity may be involved. In the cat, destruction of noradrenergic neurons of the rostral third of the locus coeruleus complex or of the norepinephrine bundle at the level of the isthmus leads to hypersomnia with normal NREM and REM cycles, mimicking IH [24]. This state is accompanied by a decrease of diencephalic norepinephrine. In IH subjects, Montplaisir and coworkers [25] found a significant decrease in dopamine and indoleacetic acid (a tryptamine metabolite) in the CSF of both IH and narcoleptics in comparison with controls. In addition, Faull and coworkers [26] found a desynchronization of the dopamine system with the diencephalic norepinephrine and serotonin (5-HT) systems in narcolepsy and a desynchronization of the diencephalic norepinephrine system with the dopamine and 5-HT systems in IH.

In the context of the recently discovered CSF hypocretin-1 deficiency in narcolepsy with cataplexy, CSF hypocretin-1 has been assessed in IH by several groups. None of the investigations done so far, however, has evidenced a clear decreased CSF hypocretin-1 level [10–12]. This is of particular interest in view of the possible relationship between IH and narcolepsy without cataplexy, both characterized by a normal level of CSF hypocretin-1.

Familial aggregation of IH patients is frequent, suggesting a genetic component for IH. The limited number of family studies has not clearly determined any mode of inheritance [6,8,15]. Because of the association of narcolepsy with HLA subtype, immunogenetic studies have also been performed with no consistent result [27,28].

An impaired sleep-wake regulation could be hypothesized in IH with long sleep time. In contrast to narcolepsy, nighttime awakenings are rare, but daytime sleep episodes are also frequent in IH. The difficulty in achieving normal morning or afternoon awakening could be the result of any combination of abnormal homeostatic, circadian, or inertia processes.

From a homeostatic point of view, the difficulty in morning awakening could be related to an abnormal high level of slow wave activity toward the end of the night, caused by either an abnormally slow decay of slow wave activity or by a normal decay of an enhanced level of slow wave activity, as it is the case following sleep deprivation. In the latter case, IH patients could be considered as sleep deprived long sleepers. In contrast with this hypothesis, a recent study by Sforza and coworkers [18] reported a lower level of slow wave activity in IH subjects without any modification of the exponential decay. No behavioral control of wakefulness was performed the day before PSG, however, to enforce the necessary 16-hour sleep deprivation; no wake-up time was indicated and no analysis of sleep spindles and their relation to slow wave activity was reported in this study. Given the inverse relationship between slow wave activity and sleep spindles, another possibility could be an alteration of the time course of activity in the spindle frequency range in IH patients, such as a lesser increase toward the end of the night. A higher sleep spindle density in both cerebral hemispheres at the beginning and at the end of nocturnal sleep has been documented in a few IH patients [19], suggesting a weakened awakening mechanism. These results warrant replication.

A second possibility could be an alteration of the circadian process. In line with this hypothesis, a tendency to a delayed evening melatonin rise and a delayed morning decline has been reported in IH patients, without significant difference with

controls [29,30]. In addition, no body temperature recording has been performed in IH patients to date.

Finally, sleep inertia, the most common feature of IH with long sleep time, could be enhanced in subjects with IH. One study revealed that patients with IH had longer visual P300 latency and smaller amplitude than in normals and narcoleptics. This result was in favor of cognitive dysfunction and not simply of impaired attention [22]. Only one morning P300 was recorded in this study, however, and no distinction between IH with or without long sleep time was available [22]. The authors perform the recording of auditory P300 at three different times (7 PM, 7 AM, and 11 AM) in patients with IH with long sleep time, and show a clear decrease in amplitude especially at 7 AM immediately after provoked awakening [23].

Differential diagnosis

IH is frequently overdiagnosed, especially the form without long sleep time [6,8]. IH is frequently diagnosed in cases of hypersomnia just after excluding narcolepsy and sleep apnea or hypopnea syndrome.

Sleep-deprived long sleepers

A long sleeper sleeps more than the amount of sleep of their normal age group. In the condition of behaviorally induced insufficient sleep, the individual starts suffering from excessive sleepiness in the afternoon, in the evening, or after meals [31]. Patients report that they sleep 5 to 6 hours nightly on week days, and 9 hours during weekends. They have difficulty rising in the morning and sometimes experience sleep drunkenness-like episodes. Work and cognitive performance, and decision making may be impaired. The patient may also complain about increasing levels of fatigue, mood deterioration, muscular pain, gastrointestinal unrest, and visual disturbances. Symptoms disappear on weekends and during the holidays. A detailed history of the subject's current sleep schedule is needed for the diagnosis. The diagnosis is mainly done by interview. In the case of suspected associated pathology, however, such as respiratory disturbances during sleep, PSG may be indicated. In the insufficient sleep syndrome, this recording usually shows good sleep efficiency (>90%) and short sleep latency, indicative of a sleep rebound [31]. It has been suggested that IH with long sleep time may represent the extreme in the distribution of habitual sleep time and that subjects with IH may be long sleepers in a permanent state of sleep deprivation [8]. Subjects with IH with long sleep time do not report any improvement of their exces-

sive daytime sleepiness, however, after prolonged sleeping for days.

Upper airway resistance syndrome

Before ascertaining the diagnosis of IH, sleep-disordered breathing syndromes need to be excluded. Sleep apnea-hypopnea syndrome is easily diagnosed by classical procedures. The upper airway resistance syndrome needs complex investigation. Patients affected are nonobese men or women with a complaint of excessive daytime sleepiness; snoring (especially in men); with frequent fatigue on awakening [9]. Clinical examination often reports a triangular face, a small chin, an arched palate, a class II malocclusion, and a retroposition of the mandible. The diagnosis is ascertained during PSG associated with esophageal pressure monitoring, by the presence of repetitive increase of esophageal pressure that leads to transient arousals without any changes in respiratory disturbance index (index of apnea-hypopnea <5 per hour) and in oxygen saturation [9].

Narcolepsy without cataplexy

This clinical variant of narcolepsy is rare when compared with narcolepsy with cataplexy with a ratio from 1 to 10. In clinical terms, it is almost impossible to differentiate patients affected with IH without long sleep time and those with narcolepsy without cataplexy [6,8]. Associated REM abnormalities, however, such as hypnagogic hallucinations and sleep paralysis, are less frequent and severe in IH patients. The final diagnosis is easy to determine with the MSLT procedure, which demonstrates the presence of two or more SOREMPs only in cases of narcolepsy without cataplexy. The presence of HLA DQB1*0602 or low CSF hypocretin-1 levels also argues in favor of narcolepsy without cataplexy. Most of these patients have normal CSF hypocretin-1 level, however, as in IH patients. A continuum between narcolepsy without cataplexy and IH without long sleep time is also possible in terms of physiopathologic mechanisms [12,13].

Periodic limb movement disorder

This disorder associates a sleep complaint (insomnia or hypersomnia) or daytime fatigue, and polysomnographic demonstration of periodic highly stereotyped limb movements during sleep, exceeding more than five per hour in adults [1]. The periodic highly stereotyped limb movements during sleep must be interpreted in the context of a patient's related complaint with an important overlap between symptomatic and asymptomatic subjects according to the index of periodic highly stereotyped limb movements during sleep.

Hypersomnia caused by medical condition

This includes several different conditions that may mimic IH (see later).

Hypersomnia caused by drug or substance

Hypersomnia secondary to the abuse of sedative-hypnotic drugs or to abrupt cessation of stimulant drugs are easily recognized by clinical interview.

Nonorganic hypersomnia

This condition should be considered as an important differential diagnosis of IH and it is always difficult to rule out hypersomnia associated with depression (see later). Patients may have mood changes that do not qualify for the diagnosis of affective disorders (*Diagnostic and Statistical Manual-IV*). In contrast, patients may have had excessive daytime sleepiness before the appearance of mood changes and clinical manifestations may evolve independently [30].

Pain or other medical symptoms

Pain or other medical symptoms (eg, tumors, migraine, rheumatoid arthritis) responsible for fragmented night sleep may result in excessive daytime sleepiness. A detailed medical history of the patient clarifies the cause of EDS.

Chronic fatigue syndrome

Chronic fatigue syndrome is characterized by persistent or relapsing fatigue that does not resolve with sleep or rest [32]. In addition to fatigue, patients report complaints of myalgia, anxiety, fever, headaches, and cognitive alterations. Chronic fatigue syndrome is not a cause of chronic hypersomnia but a differential diagnosis. Patients have frequent difficulties in clearly distinguishing excessive sleepiness from fatigue. PSG in chronic fatigue syndrome shows reduced sleep efficiency and may document alpha intrusion into sleep electroencephalogram.

Treatment

The lack of understanding of the IH pathophysiology leads to the fact that treatment can only be symptomatic. Treatment does not differ in narcolepsy and IH, and modafinil has become the first-line treatment. Modafinil, 200 to 400 mg per day, seems effective in the management of daytime symptoms [6,8,33]. No double-blind, randomized, controlled study has been performed, however, in IH. Other stimulant drugs including methylphenidate, mazindol, dextroamphetamine, and methamphetamine may be of interest in cases resistant to modafinil. Adverse effects with stimulant drugs include headache, tachycardia, hypertension, irri-

tability, and insomnia. They are less frequent with modafinil than with other stimulants. Real success on daytime sleepiness could be noted with stimulants, but prolonged nighttime sleep and difficulty in morning awakening still persist in IH with long sleep time. Actually, no treatment clearly improves sleep inertia, a consistent complaint of IH patients with long sleep time.

An alternative treatment with melatonin (2 mg of slow release at bedtime) has been proposed in 10 IH patients with long sleep time, with a tendency to a decrease in sleep drunkenness and excessive daytime sleepiness with shorter nocturnal melatonin duration in half of the patients [30]. Several authors have also proposed tricyclic antidepressants, monoamine oxidase inhibitors, or selective serotonin reuptake inhibitors in the management of IH but without clear positive effect, except in cases of mood alteration associated symptoms [6].

Behavioral treatments and sleep hygiene also can be proposed but are of limited effect in IH with long sleep time. Naps are always long and nonrestorative. They are not advisable in these patients.

Hypersomnia caused by medical condition

A variety of neurologic disorders including Parkinson's disease, head trauma, stroke (in the thalamic or mesencephalic levels), encephalitis, and genetic disorders (eg, Niemann-Pick type C disease, Norrie's disease, Prader-Willi syndrome, myotonic dystrophy) may lead to chronic hypersomnia [1] and in some cases may mimic IH. Most of these hypersomnia disorders are discussed elsewhere in this issue. Posttraumatic and postviral hypersomnia, however, are detailed next.

Posttraumatic hypersomnia

Posttraumatic hypersomnia is a common diagnosis of chronic hypersomnia. It occurs mainly in cases of initial coma after head trauma with hypersomnia occurring 6 to 18 months after the trauma. An important study focused on a systematic evaluation of 184 hypersomnia patients with a history of head trauma [34]. Posttraumatic complaint of somnolence was associated with variable degrees of impaired daytime functioning and patients who had been in a coma for 24 hours, who had a head fracture, or who had undergone an immediate neurosurgical procedure had higher scores on the Epworth Sleepiness Scale and decreased sleep latencies on the MSLT. Another study performed on 71 adults with brain injuries revealed that objective hypersomnia was common (47%) in this population, with a relatively high prevalence of sleep apnea-hypopnea syndrome, periodic limb move-

ment disorder, and posttraumatic hypersomnia alone (30%) [35]. Subjects with objectively measured sleepiness were not identified on self-reporting questionnaires, suggesting their inability to perceive their hypersomnolence. No significant differences between hypersomnia and nonhypersomnia groups were present in the Glasgow Coma Scale score and in the length of coma, gender, or time since brain injury. A recent study prospectively assessed CSF hypocretin-1 levels in patients with acute trauma brain injury [36]. Hypocretin-1 deficiency was found in 95% of patients with moderate to severe trauma and in 97% of patients with posttrauma brain CT abnormalities, a result that may reflect hypothalamic damage and lead to hypersomnia. Finally, a head injury in previously asymptomatic individuals may rarely trigger narcolepsy [37].

Hypersomnia following infection

Several patients affected with infectious mononucleosis, Guillain-Barré syndrome, pneumonia, hepatitis, or Whipple's disease may develop, several months after the acute infection, a hypersomnia syndrome that may mimic IH [38,39]. An encephalitic process or an elevation of inflammatory cytokines (tumor necrosis factor- α , interferon- β , and interleukin-1) may play a pathogenic role [40]. In bacterial and viral diseases sleep modifications are coupled with immune reactions with unclear mechanisms. Polysomnographic examinations in infectious diseases are still scarce, except for the Gambian form of human African trypanosomiasis, which is caused by the transmission of trypanosomes by tsetse flies [41].

Nonorganic hypersomnia

This condition, also referred to as "hypersomnia not caused by a substance or known physiologic condition" in the currently revised version of the ICSD [1], includes several different types of hypersomnia with abnormal personality traits, major depressive episode, seasonal affective disorder, or with conversion episode.

The complaint of daytime sleepiness in nonorganic hypersomnia may mimic symptoms in IH patients. In nonorganic hypersomnia, however, symptoms often vary from day to day and are often associated with poor sleep at night [8]. In that sense, insomnia and excessive daytime sleepiness are frequently associated, especially in cases of depression. There are several relationships between sleep difficulties and depression. Chronic insomnia may be a precursor, symptom, residual symptom, or adverse effect of depression or its treatment. Excessive daytime sleepiness may be a precursor,

symptom, or adverse effect of depression [42]. In addition, physicians need to resolve both insomnia and excessive daytime sleepiness because of the risk of depression onset, worsening of depressive symptoms, and relapse of depression after response to antidepressant treatment.

Polysomnographic studies in hypersomnia with mood disorders are rare. In all studies, however, MSLT does not demonstrate shortened mean sleep latency when compared with normal controls [16, 43,44]. In addition, REM sleep is totally absent during daytime naps in depressed patients. A 24-hour continuous PSG revealed a lowered total sleep time, an increased sleep stage 1, and decreased stages 3 and 4 in patients with a complaint of hypersomnia associated with mood disorder in comparison with IH patient [43]. The complaint of hypersomnia in patients associated with mood disorders is rarely objective. The complaint of sleepiness seems to be related to the lack of interest, withdrawal, and decreased energy inherent in the depressed condition, rather than to an increase in sleep propensity or REM sleep propensity. A diagnosis of fatigue seems more likely in that condition, although no objective criteria of fatigue are currently available.

Seasonal affective disorder characterizes the fall and winter recurrence of depressive episodes, with remission of symptoms in spring and summer [45]. Patients with winter depression report hypersomnia, fatigue, loss of energy, carbohydrate craving, appetite, and weight gain. Sleep recordings in seasonal affective disorder patients confirm the presence of hypersomnia and show reduced slow wave sleep during symptomatic episodes. Many hypotheses exist regarding the pathogenic mechanisms of seasonal affective disorder, including circadian phase shifting, abnormal pineal melatonin secretion, and abnormal serotonin synthesis. Light therapy is a natural, noninvasive, effective method of treatment of choice. Light therapy for 14 days every morning seems an effective and interesting treatment in seasonal affective disorder with a significant mood improvement (57%), increased sleep efficiency, decreased sleep latency, decreased slow wave sleep latency, and increased sleep spindles in the first hour of sleep [46]. Light treatment, although a safe and satisfactory treatment for many patients, may be insufficient for more severely ill patients.

Summary

In contrast to narcolepsy, the diagnosis of IH is difficult, still being an exclusion diagnosis of other hypersomnia. IH does not correspond, however, to all patients affected with hypersomnia of unclear

origin. Recent important progress has been made in clarifying the phenotype of IH with two forms in the last revised ICSD: IH with long sleep time and without long sleep time. Although IH with long sleep time is a quite well-characterized clinical entity, IH without long sleep time still needs clarification and new methods of investigation of hypersomnia are needed to make accurate diagnosis of IH. No advance has been made regarding the pathophysiology of both IH conditions. In contrast to narcolepsy with cataplexy, neither HLA typing nor CSF hypocretin-1 measurements have helped in understanding the disease. Much evidence leads to a continuum between IH without long sleep time and narcolepsy without cataplexy with also unclear origin. Further studies at biologic, genetic, neuroanatomic, and pharmacologic levels are highly necessary in IH disorders. Finally, several other causes of chronic hypersomnia exist, mostly insufficiently recognized and with pathophysiology mechanism almost totally unknown.

References

- [1] American Academy of Sleep Medicine. International classification of sleep disorders. 2nd edition. Diagnostic and coding manual. Westchester (IL): American Academy of Sleep Medicine; 2005.
- [2] Roth B. Narkolepsie a hypersomnie s hlediska fysiologie spanku. Praha: Statni Zdravonické Nakladatelství; 1957.
- [3] Rechtschaffen A, Roth B. Nocturnal sleep of hypersomniacs. *Acti Nevr Sup (Praha)* 1969;11: 229–33.
- [4] Roth B, Nevsimalova S, Rechtschaffen A. Hypersomnia with sleep drunkenness. *Arch Gen Psychiatry* 1972;26:456–62.
- [5] ICSD. International classification of sleep disorders: diagnostic and coding manual. Diagnostic Classification Steering Committee. Rochester (MN): American Sleep Disorders Association; 1990.
- [6] Bassetti C, Aldrich MS. Idiopathic hypersomnia: a series of 42 patients. *Brain* 1997;120:1423–35.
- [7] Aldrich MS. The clinical spectrum of narcolepsy and idiopathic hypersomnia. *Neurology* 1996;46: 393–401.
- [8] Billiard M, Dauvilliers Y. Idiopathic hypersomnia. *Sleep Med Rev* 2001;5:349–58.
- [9] Guilleminault C, Stoohs R, Clerk A, et al. A cause of excessive daytime sleepiness: the upper airway resistance syndrome. *Chest* 1993;104:781–7.
- [10] Kanbayashi T, Inoue Y, Chiba S, et al. CSF hypocretin-1 (orexin-A) concentrations in narcolepsy with and without cataplexy and idiopathic hypersomnia. *J Sleep Res* 2002;11:91–3.
- [11] Mignot E, Lammers GJ, Ripley B, et al. The role of cerebrospinal fluid hypocretin in the diagnosis of narcolepsy and other hypersomnias. *Arch Neurol* 2002;59:1553–62.
- [12] Dauvilliers Y, Baumann CR, Carlander B, et al. CSF hypocretin-1 levels in narcolepsy, Kleine-Levin syndrome, and others hypersomnias and neurological conditions. *J Neurol Neurosurg Psychiatry* 2003;74:1667–73.
- [13] Bassetti C, Gugger M, Bischof M, et al. The narcoleptic borderland: a multimodal diagnostic approach including cerebrospinal fluid levels of hypocretin-1 (orexin A). *Sleep Med* 2003;4: 7–12.
- [14] Billiard M, Besset A. Idiopathic hypersomnia. In: Billiard M, editor. *Physiology, investigations and medicine*. New York: Kluwer Academic / Plenum Publishers; 2003. p. 429–35.
- [15] Nevsimalova-Bruhova S, Roth B. Heredofamilial aspects of narcolepsy and hypersomnia. *Schweiz Neurol Neurochir Psychiatry* 1972;110:45–54.
- [16] Billiard M, Dolenc L, Aldaz C, et al. Hypersomnia associated with mood disorders: a new perspective. *J Psychosom Res* 1994;38(Suppl 1): 41–7.
- [17] Broughton R, Nevsimalova S, Roth B. The socio-economic effects (including work, education, recreation and accidents) of idiopathic hypersomnia. *Sleep Res* 1978;7:217.
- [18] Sforza E, Gaudreau H, Petit D, et al. Homeostatic sleep regulation in patients with idiopathic hypersomnia. *Clin Neurophysiol* 2000;111:277–82.
- [19] Bove A, Culebras A, Moore JT, et al. Relationship between sleep spindles and hypersomnia. *Sleep* 1994;17:449–55.
- [20] Voderholzer U, Backhaus J, Hornyak M, et al. 19-h spontaneous sleep period in idiopathic central nervous system hypersomnia. *J Sleep Res* 1998; 7:101–3.
- [21] Bastuji H, Perrin F, Garcia-Larrea L. Event-related potentials during forced awakening: a tool for the study of acute sleep inertia. *J Sleep Res* 2003; 12:189–206.
- [22] Sangal RB, Sangal JM. P300 latency: abnormal in sleep apnea with somnolence and idiopathic hypersomnia, but normal in narcolepsy. *Clin Electroencephalogr* 1995;26:146–53.
- [23] Billiard M, Rondouin G, Espa F, et al. Pathophysiology of idiopathic hypersomnia. *Rev Neurol (Paris)* 2001;157:5S101–6.
- [24] Petitjean F, Jouvet M. Hypersomnie et augmentation de l'acide 5-hydroxy-indolacétique cérébral par lésion isthmique chez le chat. *C R hebdomadaire Acad Sci (Paris)* 1970;164:2288–93.
- [25] Montplaisir J, de Champlain J, Young SN, et al. Narcolepsy and idiopathic hypersomnia: biogenic amines and related compounds in CSF. *Neurology* 1982;32:1299–302.
- [26] Faull KE, Thiemann S, King RJ, et al. Monoamine interactions in narcolepsy and hypersomnia: a preliminary report. *Sleep* 1986;9:246–9.
- [27] Harada S, Matsuki K, Honda Y, et al. Disorders of excessive daytime sleepiness without cataplexy, and their relationship with HLA in Japan. In: Honda Y, Juji T, editors. *HLA in narcolepsy*. Berlin: Springer-Verlag; 1988. p. 172–85.

- [28] Montplaisir J, Poirier G. HLA in disorders of excessive daytime sleepiness without cataplexy in Canada. In: Honda Y, Juji T, editors. HLA in narcolepsy. Berlin: Springer-Verlag; 1988. p. 186–90.
- [29] Nevsimalova S, Blazejova K, Illnerova H, et al. A contribution to pathophysiology of idiopathic hypersomnia. *Clin Neurophysiol* 2000;53:366–70.
- [30] Montplaisir J, Fantini L. Idiopathic hypersomnia: a diagnostic dilemma. *Sleep Med Rev* 2001;5:361–2.
- [31] Roehrs T, Roth T. Chronic insufficient sleep and its recovery. *Sleep Med* 2003;4:5–6.
- [32] Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* 1994;121:953–9.
- [33] Bastuji H, Jouvet M. Successful treatment of idiopathic hypersomnia and narcolepsy with modafinil. *Prog Neuropsychopharmacol Biol Psychiatry* 1988;12:695–700.
- [34] Guilleminault C, Yuen KM, Gulevich MG, et al. Hypersomnia after head-neck trauma: a medico-legal dilemma. *Neurology* 2000;54:653–9.
- [35] Masel BE, Scheibel RS, Kimbark T, et al. Excessive daytime sleepiness in adults with brain injuries. *Arch Phys Med Rehabil* 2001;82:1526–32.
- [36] Baumann CR, Stocker R, Imhof HG, et al. Hypocretin-1 (orexin A) deficiency in acute traumatic brain injury. *Neurology* 2005;65:147–9.
- [37] Lankford DA, Wellman JJ, O'Hara C. Posttraumatic narcolepsy in mild to moderate closed head injury. *Sleep* 1994;17(8 Suppl):S25–8.
- [38] Guilleminault C, Mondini S. Mononucleosis and chronic daytime sleepiness: a long-term follow-up study. *Arch Intern Med* 1986;146:1333–5.
- [39] Voderholzer U, Riemann D, Gann H, et al. Transient total sleep loss in cerebral Whipple's disease: a longitudinal study. *J Sleep Res* 2002;11:321–9.
- [40] Opp MR, Toth LA. Neural-immune interactions in the regulation of sleep. *Front Biosci* 2003;8:768–79.
- [41] Buguet A, Bourdon L, Bouteille B, et al. The duality of sleeping sickness: focusing on sleep. *Sleep Med Rev* 2001;5:139–53.
- [42] Fava M. Daytime sleepiness and insomnia as correlates of depression. *J Clin Psychiatry* 2004;65(Suppl 16):27–32.
- [43] Dolenc L, Besset A, Billiard M. Hypersomnia in association with dysthymia in comparison with idiopathic hypersomnia and normal controls. *Pflugers Arch* 1996;431:303–4.
- [44] Nofzinger EA, Thase ME, Reynolds III CF, et al. Hypersomnia in bipolar depression: a comparison with narcolepsy using the multiple sleep latency test. *Am J Psychiatry* 1991;148:1177–81.
- [45] Rosenthal NE, Sack DA, Gillin JC, et al. Seasonal affective disorder: a description of the syndrome and preliminary findings with light therapy. *Arch Gen Psychiatry* 1984;41:72–80.
- [46] Ibatoullina E, Praschak-Rieder N, Kasper S. Severe atypical symptoms without depression in SAD: effects of bright light therapy. *J Clin Psychiatry* 1997;58:495.