Hypersomnias Other Than Narcolepsy: Differential Diagnosis

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Michel Billiard

Introduction

Apart from narcolepsy, there are a number of other forms of hypersomnias. These include some of the sleep-related breathing disorders, mainly obstructive sleep apnea syndrome (OSAS) and, at a lesser degree, central sleep apnea syndrome (CSAS), and the central disorders of hypersomnolence including primary sleep disorders, idiopathic hypersomnia (IH) and Kleine–Levin syndrome (KLS) and various symptomatic hypersomnias, hypersomnia due to a medical disorder, hypersomnia due to a medication or substance, hypersomnia associated with a psychiatric disorder, and insufficient sleep syndrome.

In this chapter, we will first consider how to clinically suspect and confirm excessive somnolence, then suggest a decision tree to orient the differential diagnosis of excessive somnolence and decide on the laboratory investigations to be performed, and finally review the different causes of excessive somnolence apart from narcolepsy.

This review will be based on the recently released International Classification of Sleep Disorders, Third Edition [1].

M. Billiard, MD (✉)
Department of Neurology, Gui de Chauliac Hospital, 80, Avenue Augustin Fliche, 34295 Montpellier Cedex 5, France
e-mail: mbilliard@orange.fr

Definitions

Sleepiness, *somnolence*: the normal biological drive for sleep.

Excessive sleepiness, *hypersomnolence*: a biological drive for sleep whose intensity is such that there is an inability to stay awake and hence a high propensity to fall asleep, even in situations that are inappropriate, interfere with activities of daily living, and can be harmful to the individual. Most commonly excessive sleepiness occurs during the daytime [*excessive daytime sleepiness* (EDS)]. However excessive sleepiness may be present at night in a person whose major sleep episode occurs during the daytime, such as shift worker.

Excessive sleep: prolonged major sleep episode associated with prolonged daytime nap(s).

Hypersomnia: primarily a diagnostic term (e.g., idiopathic hypersomnia, hypersomnia due to medical condition).

Clinical Approach of Excessive Sleepiness

The circumstances of diagnosis are varied: some patients may consult for excessive daytime sleepiness (EDS), either on their own or through an

M. Goswami et al. (eds.), *Narcolepsy*, DOI 10.1007/978-3-319-23739-8_10

Table 10.1 Decision tree

I. The complaint of EDS is directly related to insufficient sleep time	Insufficient sleep syndrome
↓ No	
Use of a medication or substance responsible for sedation, substance abuse, stimulant withdrawal	Hypersomnia due to a medication or substance
II. The complaint of EDS falls into the context of a medical or psychiatric condition EDS associated with a neurologic, infectious or parasitic, endocrine, multisystem, genetic disease	Hypersomnia due to a medical disorder
↓ No	
EDS associated with a psychiatric condition	Hypersomnia associated with a psychiatric condition
III. The complaint of EDS is independent of the above EDS of various degrees associated with some of the following symptoms: loud snoring, breathing pauses during sleep, nycturia, tiredness and/or headache on awakening, cognitive impairment, irritability, depression, reduced libido	Obstructive sleep apnea syndrome
↓ No	
Severe EDS, unwanted episodes of sleep and cataplexy ± hypnagogic hallucinations, sleep paralysis, disturbed nocturnal sleep	Narcolepsy type I
↓ No	
Severe EDS, unwanted episodes of sleep, not associated with cataplexy ± hypnagogic hallucinations, sleep paralysis, and disturbed nocturnal sleep	Narcolepsy type 2
↓ No	
EDS, more continuous and less irresistible than in narcolepsy, long and non-refreshing naps, abnormally long sleep time, difficulty awakening in the morning or at the end of a nap	Idiopathic hypersomnia
↓ No	
Recurrent episodes of excessive sleepiness and sleep duration, each persisting for 2 days to 5 weeks, associated with one of the following: cognitive dysfunction, altered perception, eating disorder, mostly hyperphagia, disinhibited behavior	Kleine–Levin syndrome

accompanying family member. Many complain of fatigue, which turns out to be EDS at the clinical interview. Other patients visit their family doctor for loud snoring, and the interview leads to the discovery of EDS and other symptoms of OSAS. Some others are referred by company doctors due to repeated traffic accidents or poor performance at work. Finally, some patients are found to be abnormally sleepy in the context of somatic or psychiatric disorders.

Once suspected, EDS must be confirmed by a subjective test, most commonly the Epworth Sleepiness Scale (ESS), a scale based on the chance of dozing in eight selected situations [2]. Patients are asked to rate their chance of dozing on a scale of 0–3. The highest possible score is 24 and the normal upper limit is generally considered to be 10.

Gaining a clinical impression should always precede the decision of performing laboratory investigations (Table 10.1). There are several reasons for that. First, the patient should benefit from some information prior to any test. Second, some of these tests are expensive and cannot be scheduled immediately. Thus, they must not be performed systematically. Last, but not least, results of laboratory investigations may be uninformative or even misleading in some cases, like a mean sleep latency of 10 min or more on the multiple sleep latency test (MSLT) in an ostensibly sleepy patient or the presence of sleep-onset REM periods (SOREMPs) in a subject with OSAS or in a subject discontinuing antidepressants before the test.

Laboratory Investigations

Measures of Sleepiness

Multiple Sleep Latency test

This test was developed on the basis of the following principle: the sleepier the subject, the faster he falls asleep. A standard methodology

has been specified by the American Academy of Sleep Medicine [3]. The test consists of five nap opportunities performed at 2-h intervals, starting about 2 h after morning awakening. The test should be conducted during the day following a polysomnographically documented night of adequate sleep, that is, at least 6 h of sleep. All psychotropic medications that can cause sleepiness or suppression of rapid eye movement (REM) sleep should be discontinued 2 weeks before the date of the test. A mean sleep latency of less than 5 min indicates pathological sleepiness, a mean sleep latency from 10 to 20 min is considered as normal, while latencies falling between the normal and the pathological values are considered a gray diagnostic area [4].

Maintenance of Wakefulness Test

The maintenance of wakefulness test (MWT) is a variant of the MSLT, designed to evaluate treatment efficiency in patients with excessive sleepiness. A standard methodology has also been specified by the American Academy of Sleep Medicine [3]. The test consists of four trials performed at 2-h intervals, with the first trial beginning about 2 h after morning awakening. The major difference with the MSLT is in the instruction given to the subject. The subject is asked to attempt to remain awake. He is seated in a comfortable position in bed, as opposed to lying down in the MSLT, with low light behind him (7.5 W, one meter). In contrast to MSLT, drug therapy should not be changed before the test. The recommendation is to use trials of 40 min [5]. Despite the use of the test for many years, there are extremely limited normative data for it. Mean and standard error of the sleep latency for the test show significant changes with age [5].

Measures of Total Sleep Time

Total sleep time can be documented on a 24- or 36-h polysomnography (PSG) or on a 7-day wrist actigraphy performed in a period of unrestricted sleep (e.g., holidays), in association with a sleep log [1].

Measures of Vigilance

These tests are not typically used in clinical practice. However, they may be of interest to test cognitive abilities in patients suffering from sleep-related breathing disorders or disorders of hypersomnolence.

Psychomotor Vigilance Task (PVT)

This test measures the patient's ability to sustain attention by using trials with a duration of about 10 min, in which a handheld, computerized display-and-response unit quantifies response latency to multiple light-emitting diode presentation of a stimulus, to measure deficits in attention and performance [6].

Oxford Sleep Resistance (OSLER) Test

This test consists of four 40-min-long trials during which there are multiple light emission diode presentations. The subject is instructed to respond to each signal with a simple button press. Trials are ended after 40 min or after a failure to respond, which is considered to constitute a failure to maintain wakefulness [7].

Sustained Attention to Response Task (SART)

This test measures the ability to sustain executive control for response inhibition over a given period of time. The SART requires fast responses to random single digits from 1 to 9 (go digit), except for the "3" stimulus (non-go digit) to which participants must not respond [8].

Brain Imaging

Computed tomography (CT) and/or magnetic resonance imaging (MRI) should be performed whenever there is clinical suspicion of an underlying brain lesion.

Psychometric/Psychiatric Evaluation

It should be made in all cases where there is some doubt on the role of the patient's personality in the development of excessive sleepiness.

Various Causes of Hypersomnia

Sleep-Related Breathing Disorders

Obstructive Sleep Apnea Syndrome

This syndrome was first described in 1976 [9]. It is most frequent in 50-year-old males. The prevalence of obstructive sleep apneas accompanied by EDS is 4 % in men and 2 % in women aged 30–60 years in North America [10], although the actual prevalence may be higher.

OSAS is characterized by repeated episodes of complete (apneas) or partial (hypopneas) upper airway obstructions occurring during sleep, associated with a nighttime and daytime symptoms. Nighttime symptoms include apnea/hypopnea episodes terminated by loud snoring, nycturia, fatigue, and sometimes headache on awakening. Daytime symptoms consist of EDS, which can vary from light to severe, irritability, negligence, impaired cognitive functions, depression, loss of libido, and impotence. Interestingly, the frequency of apneas/hypopneas during sleep correlates poorly with the daytime symptom severity.

A body mass index (weight in kg/height in m^2) greater than 30 and a neck circumference greater than 40 cm are frequent although not systematic. Systemic hypertension is frequent. The ear, nose, and throat examination usually reveals a narrow upper airway due to close-set posterior tonsillar pillars, an abnormally long and hypotonic soft palate, a hypertrophic uvula, and macroglossia.

The positive diagnosis rests on PSG or on out of center testing (OCFS) when there is a high pretest probability of moderate-to-severe OSAS. The procedure shows obstructive sleep apneas (cessation of airflow but ongoing respiratory efforts) and/or hypopneas (reduction rather than cessation of airflow with ongoing respiratory effort) and enables quantification of the number of apneas/hypopneas per hour of sleep (apnea or respiratory disorder index). Oxygen saturation typically declines for a variable period of time following the onset of apnea or hypopnea. Obstructive sleep apneas or hypopneas may be accompanied by bradyarrhythmia or tachyarrhythmia.

Of note, some patients do not have apneas or hypopneas but have increasing respiratory efforts resulting in respiratory effort-related arousals (RERAs). This condition is presumed to have the same underlying pathophysiology as obstructive apneas and hypopneas. It is most accurately identified with a quantitative measurement of airflow and esophageal manometry, although it can be inferred when there is obvious inspiratory airflow limitation on a nasal pressure recording. It is considered to be as much as a risk factor for symptoms of unrefreshing sleep and daytime symptoms of OSAS.

The issue of EDS and OSAS is not clear-cut. Although EDS is one of the major complaints in patients with OSAS, not all patients with OSAS complain of EDS. In a large cohort of sleep apnea patients ($n = 2882$), EDS as defined by an ESS > 10 was present only in 57 % of patients [11]. However, there is a frequent tendency in sleep apnea patients to minor the symptom of EDS. This is reflected in the moderate correlation [12, 13] or even the lack of correlation [14] between scores on the ESS and results of the MSLT.

The mechanisms underlying EDS are complex. Arousal responses ranging from autonomic changes to intrusion of alpha activity into sleep may theoretically play a role in EDS. However, there is not much evidence in favor [15]. A poor nocturnal sleep quality has also been advocated. According to Heinzer et al., daytime sleepiness in OSAS patients may be the result of a lack of SWA during the first part of the night [16]. However, greater sleep efficiency has been found in OSA patients with EDS than in those without [11, 17]. Nocturnal hypoxemia is a major determinant of EDS in sleep apnea patients [17], at least in those with severe OSAS [18].

Central Sleep Apnea Syndrome

CSAS is characterized by recurrent cessation of respiration during sleep with the apneas having no associated ventilatory effort. Ventilation and ventilatory effort cease simultaneously, in a repetitive pattern over the course of the night. Prevalence is unknown but probably low. Patients present with symptoms of EDS or frequent nocturnal awakenings or both.

Diagnosis of primary CSAS rests on PSG demonstrating recurrent cessations in ventilatory effort and ventilation during sleep.

CSAS is caused by the instability of the respiratory control system in the transition from wakefulness to sleep and less commonly during stable non-rapid eye movement (NREM) sleep. Central sleep apneas tend to occur in individuals with a high or increased ventilatory responsiveness to CO_2 [19].

Central Disorders of Hypersomnolence

Idiopathic Hypersomnia

Idiopathic hypersomnia (IH) was progressively identified, beginning with the description of sleep drunkenness in 1956 [20] and ending with the publication by Roth in 1976 of a series of 642 personally observed patients including 368 with narcolepsy and 274 with hypersomnia, 191 of whom had hypersomnia with a short cycle (sleep attacks lasting from one to several hours and intervals between the attacks being maximally 1 day), and 22 had hypersomnia with a long cycle (attacks lasting from 1 day to several weeks and intervals between the attacks being from 1 month to several years apart). Within these 191 patients having hypersomnia with a short cycle, Roth distinguished 171 patients with "IH polysymptomatic form," 71 with "IH monosymptomatic form," 5 with neurotic hypersomnia, and 12 with disorders of breathing during sleep [21]. IH polysymptomatic form was characterized by excessive diurnal sleep, prolonged night sleep of a duration of 12–18 h, and great difficulty waking up in the morning, while IH monosymptomatic form was characterized by the most prominent symptom of diurnal sleep of a duration of one to several hours, not as irresistible as in narcolepsy. In 1979, not maintaining the division of idiopathic hypersomnia into two forms, the Diagnostic Classification of Sleep and Arousal Disorders referred to idiopathic CNS hypersomnolence as one of the disorders of excessive somnolence [22], and, in 1990, the first edition of the International Classification of Sleep Disorders (ICSD) referred to IH as one of the intrinsic sleep disorders [23]. In 2005, the second edition of the International Classification of Sleep Disorders (ICSD-2) came back to a division into two forms, namely, IH with and without long sleep time, in which the first form was similar to Roth's polysymptomatic form, while the latter differed by the presence of short refreshing naps [24]. Finally, in March 2014, the third edition of the International Classification of Sleep Disorders was released, and in the absence of specific symptoms in IH with and without long sleep time, the division into two forms was abandoned, waiting for consistent biologic markers [1].

Due to uncertainty on the nosological limits of IH, no prevalence study has ever been conducted. However, ratios of IH to narcolepsy in cohorts of patients published by different sleep disorders centers are available. These ratios range from 9.2 % [25] to 47.2 % [21], corresponding to estimated prevalences of 0.0048–0.095 %, if one accepts a prevalence of around 0.045 % for narcolepsy [26]. The onset of the condition is most often during adolescence or young adulthood. According to some cohorts, there is a higher prevalence of IH in women than in men.

A familial background has been found in up to 40 % of IH patients in a former study [27], but more rigorous studies are warranted.

EDS is the key manifestation of IH and is generally considered more continuous and less irresistible than in narcolepsy. Naps are few, long, and non-refreshing in half to three quarters of patients [1]. Night sleep is abnormally long in at least a third of patients [1]. Awakening in the morning or at the end of naps may be difficult or present as "sleep drunkenness": severe morning inertia consisting of difficulty in coming to complete wakefulness, accompanied by confusion, disorientation, poor motor coordination, slowness, and repeated returns to sleep [28]. Headache, orthostatic hypotension, and cold hands and feet are sometimes present. In addition, subjective symptoms such as being more alert in the evening than in the morning, difficulty focusing more than 1 hour, complaint of attention and memory deficits, mental fatigability, and hyperactivity helping to resist sleepiness have been reported [29]. Altogether, the phenotype of

idiopathic hypersomnia is not unitary, hence the successive suggestions of nosological separation of the condition into two or three forms.

In addition to the above clinical features, the diagnosis of IH requires laboratory investigations. PSG followed by MSLT is mandatory [1]. PSG generally demonstrates a normal architecture of sleep. Episodes of obstructive sleep apneas should theoretically be fewer than 5 h^{-1} and respiratory RERAs fewer than 10. If not, a short-term continuous positive airway pressure (CPAP) trial should be performed, and if there is no change in sleepiness, the diagnosis of IH is confirmed.

A MSLT performed according to standard techniques shows fewer than two SOREMPs or no SOREMP if the REM latency on the preceding PSG is less or equal to 15 min. Finally, one of the following should be present: either a mean sleep latency of <8 min on the MSLT or a total 24-h sleep time >660 min documented on a 24-h PSG or on a 7-day wrist actigraphy performed in a period of unrestricted sleep (e.g., holidays) in association with a sleep log, to account for the fact that mean sleep latency is frequently normal in idiopathic hypersomnia [30, 31].

In addition, psychiatric evaluation should be performed in subjects suspected of having a psychiatric disorder and neuroimaging in case of neurological signs.

Once established, IH is usually stable and long lasting, although cases of spontaneous disappearance have been reported [30, 32, 33]. At first sight, the complications of IH appear similar to those of narcolepsy, including poor performance at school or at work, sleeping during recreational activities, and car or machine accidents. However, in the case of patients complaining of long sleep time and difficulty on awakening, complications have some peculiarities such as arriving late at work, lengthy time in bed hardly tolerated by family members, and not benefiting from night sleep or from naps.

Several non-mutually exclusive hypotheses have been proposed to explain the pathophysiology of IH, but the outcome is still limited. Reduced cerebrospinal fluid (CSF) histamine levels have been observed in hypocretin-deficient narcolepsy with cataplexy, in hypocretin non-deficient narcolepsy and in IH patients but not in OSAS patients [34]. This finding has led to the suggestion that CSF histamine is a biomarker reflecting the degree of hypersomnia of central origin. However, using a new validated method of CSF histamine and tele-methylhistamine (t-MHA) measurement [35], Dauvilliers et al. did not find any CSF histamine and t-MHA level differences between the various etiologies of central hypersomnia (narcolepsy with and without cataplexy, idiopathic hypersomnia, unspecified EDS. and neurological controls) [36].

Another perspective comes from a recent experiment showing that CSF from hypersomnolent subjects (excluding known causes of excessive sleepiness) contains a small (500–3000 daltons) not yet identified trypsin-sensitive substance that stimulates the in vitro function of selected γ-aminobutyric acid receptors, only in the presence of GABA, relative to the stimulation obtained with CSF from control subjects [37]. Furthermore, flumazenil, a drug that is generally believed to antagonize the sedative-hypnotic action of benzodiazepines, improved psychomotor vigilance and subjective alertness in seven hypersomnolent patients [37].

Before the eventual identification of IH in 1976, a series of 23 probands with hypersomnia with data from 190 families was published by Czech authors [27]. Nine of these probands (39.1 %), of whom seven had hypersomnia of the sleep drunkenness type, had a positive family history of the disease, and an autosomal dominant mode of inheritance was suggested. In 2001, in a series of 35 IH patients, 25 with the polysymptomatic form and 10 with the monosymptomatic form, a familial history was found in 10 patients with the polysymptomatic form (40 %), including three with several relatives, and in three subjects with the monosymptomatic form (30 %), including one with several relatives [25]. Recently a report of three adolescent-onset cases of IH, assessed clinically and by use of ad libitum PSG, was published, arguing for a genetic origin in this family [38]. The pedigree was compatible with an autosomal dominant inheritance. By analogy with narcolepsy, there has been an early interest

in potential HLA markers in IH, but no consistent findings have emerged so far.

Another pathophysiological hypothesis lies in an alteration of the homeostatic or circadian regulation. In a study comparing the level of slow-wave activity (SWA) in the first two NREM–REM sleep cycles, this level was significantly lower in IH patients than in controls [39]. Thus, patients with IH may need a prolonged sleep time due to lower intensity of NREM sleep. Two other studies compared the sleep spindle index in idiopathic hypersomnia and controls [40] and in IH and narcolepsy [41]. They documented an increased spindle index predominating by the end of night sleep in IH, which may explain the symptoms of difficulty waking up and "sleep drunkenness." In addition, a disturbed circadian rhythm has been hypothesized on the basis of a phase delay in the rhythm of melatonin and cortisol secretion in 15 patients with IH with long sleep time [42]. In a more recent study, Horne and Östberg scores were lower in IH patients than in controls, consistent with a delayed sleep phase in IH [31]. Moreover, investigation into the diurnal dynamics of circadian clock gene expression in dermal fibroblasts of IH patients in comparison with those of healthy controls has shown that the amplitude of the rhythmically expressed BMAL1, PER1, and PER2 was significantly dampened in dermal fibroblasts of IH patients compared with healthy controls, suggesting an aberrant dynamics in the circadian clock of IH patients [43].

Given its phenotypic variety, IH is certainly a heterogeneous condition. Based primarily on clinical symptoms, different divisions of the condition have been proposed: polysymptomatic and monosymptomatic [21], classic, narcolepsy-like and mixed [32], complete and incomplete [44], and with and without long sleep time [24]. However, several studies published after the introduction of the ICSD-2 have suggested that a division of IH based on clinical symptoms lacks validity and that future separation of the disorder into distinct conditions must await progress in understanding the underlying biology [30, 31].

Another issue is the relationship between narcolepsy type 2 and IH. The ICSD-3 clinical criteria, A and C in the case of narcolepsy type 2 and A and B in the case of IH, are similar [1]. As for MSLT criteria, mean sleep latency greater than or equal 8 min is the same in both conditions, and the distinction between two SOREMPs or more for narcolepsy type 2 and fewer than two SOREMPs or none for IH seems rather arbitrary, as the number of SOREMPs may vary from one MSLT to another in a same individual in narcolepsy without cataplexy and in IH [45]. Thus, distinction between the two conditions might be provisional, dependent upon further pathophysiological insights. A further difficulty remains in the recent description of narcolepsy with long sleep time, a condition combining features of both narcolepsy with cataplexy and IH with long sleep time [46]. Indeed narcolepsy with long sleep time resembles IH with long sleep time but manifests numerous REM sleep abnormalities, further complicating the spectrum of IH.

Kleine–Levin Syndrome

The name Kleine-Levin syndrome (KLS) was coined in 1942 [47]. However "a syndrome of periodic somnolence and morbid hunger" had been described as early as 1936 [48], and reports of patients with episodes of hypersomnia, gluttony, odd behaviors, and cognitive symptoms had been published in the 1920s [49–51]. In 1962, Critchley wrote a masterpiece article "Periodic hypersomnia and megaphagia in adolescent males" in which he collected 15 "genuine" instances from the literature and 11 cases of his own which he described in depth [52]. He gave the definition of "a syndrome composed of recurring episodes of undue sleepiness lasting some days associated with an inordinate intake of food, and often with abnormal behavior." In addition, he emphasized four hallmarks: (1) sex incidence whereby males are preponderantly if not wholly affected, (2) onset in adolescence, (3) spontaneous eventual disappearance of the syndrome, and (4) the possibility that the megaphagia is in the nature of compulsive eating rather than bulimia. From this time on, several reviews have been published with the emphasis put on clinical features. In 2005, the second edition of the ICSD published diagnostic criteria of recurring hypersomnia and gave a definition of KLS

modifying Levin's and Critchley's views that hyperphagia was no more necessary for the diagnosis but only one of the possible symptoms of the syndrome: "A diagnosis of KLS should be reserved for cases in which recurrent episodes of hypersomnia are clearly associated with behavioral abnormalities. These may include binge eating, hypersexuality, abnormal behavior such as irritability, aggression, odd behavior; and cognitive abnormalities such as feeling of unreality, confusion and hallucination [24]." Following this publication, several large reviews came out, allowing quantitative evaluations of predisposing factors, circumstances at onset, symptoms, physical signs, and comparisons of symptoms in men and women [53–55].

Finally, the third edition of the International Classification of Sleep Disorders recently came out and changed the name recurrent hypersomnia (including KLS and menstrual-related hypersomnia) to the name KLS [1].

KLS is a rare disorder. There is no prevalence study available. Today, over 400 cases have been published in the world literature. Age of onset is predominantly adolescence and young adulthood. Familial cases are not exceptional: 5 of 194 patients (4.8 %) in one series [53] and 9 of 297 patients (3 %) in a larger series [55]. Prevalence is high in Israel [56] and among American Jews [53] suggesting a founder effect in the Jewish population.

Factors precipitating the first episode are mentioned in all series, consisting most frequently of an upper airway infection or a flulike illness and less frequently of an emotional stress, an alcohol intake, a head trauma, an anesthesia, a vaccination, or an exhaustion.

The episodes begin within a few hours or gradually over a period of 1–3 days, with patients becoming extremely tired or complaining of headache. Hypersomnia is the major symptom present in each episode. Patients lie in bed, sometimes with restlessness and untidiness. Vivid dreams may occur. Usual sleep duration ranges from 12 to 18 h, especially during the first days. Patients wake up spontaneously to void and eat. They may be irritable or even aggressive when awakened or prevented from sleeping. Behavioral symptoms include compulsive eating, disinhibited sexuality, and odd behaviors. Patients do not necessarily look for food, but cannot refrain from eating food within reach, in a compulsive manner. A preference for sweets is common. Increased drinking is sometimes associated. In some cases or in some episodes, compulsive eating may be replaced by anorexia. Sexual disinhibition can take the form of overt masturbation, sexual advances, and shamelessly expressed sexual fantasy. It is apparently less frequent in females than in males. Odd behaviors, also designated as compulsive behaviors, are very special to KLS. They include stereotyped behaviors (repetitive and excessive), disinhibited social behavior, childish behavior, aggression, loss of decency, bizarre postures, or imaginative actions.

Cognitive symptoms may be severe such as altered perception (with people and objects appearing as distorted, distant, unreal), confusion, delusions, or hallucinations or less spectacular such as abnormal speech, impaired concentration, impaired memory, and apathy.

Mental symptoms include depression during the episodes, less frequently in men than in women. Anxiety is less frequent and equally reported by men and women.

KLS is remarkable for the absence of any neurological sign. On the other hand, dysautonomic symptoms such as profuse sweating; reddish, congestive, or puffy face; low or high blood pressure; bradycardia or tachycardia; and intense body odor or nauseating urines are found in about 20 % of men and women. In addition, weight gain of a few kilograms may be observed during the attack and is significantly more frequent in women than in men [55].

The episodes of hypersomnia may end abruptly or insidiously over a few days. In up to a third of cases, the episode is followed for 1 or 2 days by amnesia of the past events, elation with insomnia as if the subject was trying to catch up for lost time.

The diagnosis of KLS is purely clinical. Routine blood tests including blood count, plasma electrolytes, urea, creatinine, and hepatic function are normal. Static and dynamic function hormonal tests (growth hormone, prolactin,

thyroid-stimulating hormone, testosterone, and cortisol) are normal. Agents responsible for upper airway infection, flulike illness, or other infections are rarely identified. CSF, white blood cell count, and protein levels are normal in all patients, ruling out infectious meningitis. Immunoelectrophoresis is also normal. Electroencephalography is often remarkable for a general slowing of the background activity. Bursts of bisynchronous, generalized, moderate to high voltage, 5–7 Hz waves 0.5–2 s in duration, mainly in the bilateral temporal or temporofrontal areas, are frequent and often cause of misdiagnosis with epilepsy. PSG is not easy to organize within 24 or 48 h and difficult to interpret due to the frequent rapid evolution of sleep patterns throughout an attack. The duration of recorded sleep is often shorter or much shorter than the behavioral sleep as observed by parents or nurses. Sleep efficiency is poor, while SOREMPs are frequent. MSLT is of questionable interest in view of the frequent limited cooperation of patients. Structural brain imaging, computerized tomography or MRI, is normal in primary forms of KLS. Psychological interview and testing should be performed during and after the episode.

KLS is characterized by episodes lasting a median of 7–9 days (range: 1–180 days) and a cycle length (time elapsed from the onset of one episode to the onset of the next episode) of 60–100 days [55]. KLS vanishes spontaneously within months or years. However, the overall duration of the condition is variable and, in some patients, may exceptionally last up to 20–30 years. It is commonly assumed that the episodes of KLS decrease in frequency, severity, and duration with time before fading out. Yet, this was clearly evidenced in a limited number of cases only in one series [55].

Menstrual KLS is a very rare disease characterized by episodes of hypersomnia, plus or minus other symptoms and physical signs, which occur in association with the menstrual cycle and sometimes with puerperium [55]. The condition occurs for the first time within the first months after menarche or later. Episodes generally last about 1 week, with resolution at the time of menses.

Neuropathological examinations have been performed in three cases of typical KLS [57–59] and in one case of KLS secondary to a presumptive brain tumor [60]. They have shown various abnormalities in different locations of the brain, which however did not lead to consistent conclusions.

As indicated before, familial cases of KLS have been reported. In one series [55], nine cases were familial and three of these families had more than two affected relatives [61–63] in favor of an autosomal Mendelian inheritance. Moreover, two cases of monozygotic twins have been reported, suggesting a strongly genetic basis for the condition [64, 65].

Single-photon emission computed tomography (SPECT) performed during symptomatic periods and asymptomatic intervals has documented widespread decreased tracer perfusion during symptomatic periods. Of 30 KLS patients, 18 (66.7 %) showed unilateral hypoperfusion in the left thalamus, 3 (11.1 %) in the right thalamus, 3 (11.1 %) in the left basal ganglia, 6 (22.2 %) in the right basal ganglia, and 2 (7.4 %) in the right cerebellum, during the symptomatic periods [66]. In 41 KLS patients, persistent hypoperfusion was documented in the hypothalamus, the thalamus (mainly the right posterior part), the caudate nucleus, and cortical associative areas, e.g., the anterior cingulate, the orbitofrontal, and the right superior temporal cortices extending to the insula, also during the symptomatic periods [67]. It has been suggested that decreased thalamic activity may mediate increased sleep, decreased diencephalic/hypothalamic activity may mediate deregulated instinctual behaviors, and widespread and variable cortical changes may mediate abnormal perception and cognition.

Based on the generally young age at onset, the recurrence of symptoms, the frequent infectious trigger, and a significant increased frequency of the HLA-DQB1* allele in a multicenter group of 30 unrelated patients with KLS, an autoimmune origin had been suggested [68]. However, the increased frequency of the HLA-DQB1* allele was not supported by a later large American study [53].

Due to the role of hypocretin neuropeptides in both sleep–wake regulation and feeding,

hypocretins seem good candidates to be involved in KLS. Although it is generally considered that CSF concentrations of hypocretin-1 are most frequently in the normal range, a recent study, in a large population of 42 Chinese KLS patients, has shown that CSF hypocretin-1 levels were lower in KLS patients during episodes, as compared with controls, and in KLS patients during episodes as compared with KLS patients during remissions [69].

Hypersomnia Due to Medical Disorders

The direct cause of EDS is a coexisting medical disorder. In most cases, EDS only stands as an associated symptom, to the extent that it is often neglected in comparison with the main manifestations and signs of the medical disorder.

Neurologic Disorders

Brain Tumors

Clinically, EDS tends to be continuous, interspersed with brief arousals either spontaneous or provoked. EDS may occur in any intracranial hypertension syndrome or more rarely result from tumors of the diencephalon or peduncular region, with no associated intracranial hypertension. These tumors include glioma or hamartoma affecting the posterior hypothalamus, posterior and superior suprasellar craniopharyngioma compressing the floor of the third ventricle, and pinealoma or teratoma affecting the posterior part of the third ventricle. A number of cases of narcolepsy symptomatic of brain tumors affecting the hypothalamus or midbrain regions have been reported [70].

Stroke

EDS is often a transient state between confusion, agitation, or even coma marking the initial period of the stroke. Among the most frequent causes of sleepiness of vascular origin are paramedian uni or bithalamic infarcts characterized by vertical ocular paresis, "skew deviation," paresis of the third cranial pair, dysarthria and instability in walking; paramedian peduncle-thalamic infarcts characterized by altered ocular motility due to paresis of the third or of the sixth cranial pair; and tegmental infarcts affecting the pontine tegmentum and the reticular formation of this region [71].

Neurodegenerative Disorders

EDS affects 16–50 % of Parkinson's disease patients [72]. It may precede Parkinson's disease by several years and often worsens after the introduction of dopaminergic treatment. A degeneration of hypocretinergic neurons and monoaminergic neurons is most probably involved. Of concern, the occurrence of sudden irresistible sleep episodes is facilitated by the intake of dopaminergic agonists [73].

Multiple system atrophy gives rise to EDS in 25–30 % of patients [74]. However, the mechanism is not the same as in Parkinson's disease. It often depends on OSAS present in 15–37 % of patients [75].

EDS is common in Alzheimer-type dementia. This symptom may be the expression of three different conditions: a sundowning syndrome which affects a quarter of subjects with dementia, the intake of psychotropic medications, or the presence of OSAS [76].

Neuromuscular Diseases

Any neuromuscular disease, motoneurone disease, motor neuropathy, neuromuscular junction disorder, or muscular disease is likely to be accompanied by sleep-related breathing impairment resulting in EDS. A typical example is myotonic dystrophy characterized by weakness of limb, facial and respiratory muscles, myotonia, cardiomyopathy, endocrinopathy, frontal baldness, neuropsychological deficits, and cataract. Myotonic dystrophy type 1 (DM1), or Steinert's disease, is the most common adult-onset form of muscular dystrophy. It also constitutes the neuromuscular condition with the most significant sleep disorders including EDS, central and obstructive apneas, restless legs syndrome, and periodic leg movements. EDS is present in about 70–80 % of patients [77]. In a study comparing six patients with DM1 and 13 healthy controls, the mean sleep latency on the MSLT was abnormally short in all patients, and hypocretin-1 levels were significantly lower in patients versus controls ($p<0.001$) [78]. Thus a dysfunction of the hypothalamic

hypocretin system may mediate EDS. Sleep disturbances are not as well characterized in myotonic dystrophy type 2 (DM2). However, a recent survey performed in 30 patients and 43 controls showed EDS and fatigue independently associated with DM2 diagnosis [79].

Posttraumatic Sleepiness

In addition to residual symptoms such as focal neurological deficit, posttraumatic epilepsy, movement disorder, hormonal disturbance, cognitive deficit, and psychotic disorder, subjects with traumatic brain injury (TBI) may develop sleep–wake disturbances including posttraumatic sleepiness. Subjective posttraumatic sleepiness (as assessed by the ESS) was found in 28 % of 65 consecutive patients, 6 months after TBI and objective posttraumatic sleepiness (as assessed by the MSLT) in 25 % [80]. Another prospective study conducted in 87 subjects, at least 3 months after TBI, found posttraumatic sleepiness in 25 % of subjects [81]. The etiology of posttraumatic sleepiness has not yet been elucidated, and multiple factors, both physical and psychological, may be involved.

Epilepsy

Although epilepsy can be the cause of sleepiness, the association of epilepsy and sleepiness is not clear-cut. Some studies demonstrated EDS in 17–28 % of patients with epilepsy [82, 83], while others did not find a difference in ESS scores in patients with epilepsy and in controls [84, 85]. The location of the ictal focus likely influences the expression of sleepiness; patients with frontal lobe epilepsy have increased sleep fragmentation and EDS [86]. Moreover, many antiepileptic drugs are known to induce EDS.

Multiple Sclerosis

There is conflicting evidence regarding EDS in multiple sclerosis (MS), with one study reporting sleep disturbances and EDS in MS patients compared to non-MS groups [87] and others revealing ESS scores at the high end of normal [88, 89]. When present, sleepiness in MS is likely due to hypothalamic lesions and low CSF hypocretin levels [90]. Cases of narcolepsy with EDS and several SOREMPs, with or without cataplexy, secondary to bilateral hypothalamic lesions and hypocretin levels <40 pg/ml have been reported [91].

Infectious and Parasitic Diseases

Infectious Mononucleosis

In the aftermath of infectious mononucleosis, the subject may feel intense asthenia and lengthening of his total sleep time, difficulty awakening, and EDS evoking idiopathic hypersomnia [92]. This type of hypersomnia also develops following viral pneumopathy, hepatitis B viral infection, and the Guillain–Barré syndrome, probably through the same mechanism.

Viral Encephalitides

Disorders of wakefulness and/or consciousness are found in virtually all patients affected by viral encephalitis. However, in the absence of PSG studies, it is very difficult to define the border between wakefulness disorders and disorders affecting consciousness. Two nosological entities are worthy of mention: arbovirus diseases and epidemic encephalitis. The arboviruses represent a heterogeneous group of viruses whose common characteristic is that they are transmitted by arthropod vectors. The various arbovirus diseases share the same first symptoms evoking a fairly severe state of flu with high fever, headache, and myalgias. Encephalitic signs then develop, which vary according to the agent responsible. Sleepiness is a fairly characteristic feature of the European tick-borne encephalitis [93].

First appearing in Europe in 1917, epidemic encephalitis affected tens of thousands of subjects in the 10 years which followed. Its cause has never been fully identified, even if the pathological lesions and inflammatory sites located mainly in the gray matter of the diencephalon and basal ganglia strongly suggest a viral infection. The most common form, referred to as the lethargic form, consisted of a febrile flulike condition, rapidly complicated by sleepiness culminating in a permanent state of sleep, stupor, and coma, associated with frequent oculogyric crises with nystagmus. This clinical picture corresponded to lesions in the posterior hypothalamus and midbrain tegmentum [94]. Sporadic cases are still exceptionally reported.

Acquired Immunodeficiency Syndrome (AIDS)
Subjects infected by HIV sometimes complain of EDS. HIV-infected patients are significantly more likely to sleep more, nap more, and have diminished midmorning alertness in comparison with nonaffected subjects [95]. More recently, poor nighttime sleep was significantly correlated with fatigue intensity ($p<0.05$) and EDS ($p<0.05$) in a sample of 128 individuals on a longitudinal study [96].

African Trypanosomiasis (Sleeping Sickness)
African trypanosomiasis is a subacute or chronic parasitic disease caused by the inoculation of a protozoon, *Trypanosoma brucei*, transmitted by the tsetse fly. It is endemic to certain regions of tropical Africa. The form found in West and Central Africa is due to *Trypanosoma gambiense*. It causes over 98 % of reported cases. The form found in East Africa is caused by *Trypanosoma rhodesiense*. The first form is divided in three successive stages. Several hours after the sting, a hot, edematous, and erythematous tender nodule, referred to as the chancre, appears around the inoculation point. After a phase of inoculation varying from several days to several months, the invasion of the blood and lymphatic organs by multiple trypanosomiasis constitutes the hemolymphatic stage 1. This stage lasts until the appearance of the parasite in the CSF, referred to as meningoencephalitic stage 2. It is characterized by exacerbated headache and fatigue, mental disturbances, and a wealth of neurological signs including disorders of tone and mobility. Sleep and wake alterations consist of sleep episodes randomly spread over 24 h, causing a loss of circadian alternation of sleep and wakefulness and the occurrence of SOREMPs in several sleep episodes [97]. Demyelinating encephalitis ends the time course of the disease along with apathy, dementia, epileptic seizures, incontinence, and death in a state of cachexia.

Multisystem Diseases

Sarcoidosis, a chronic, multisystem disease, most frequently affects the lung. However, CNS involvement is thought to occur in about 10 % of cases. Neurosarcoidosis can affect any part of the CNS, specially the hypothalamus and pituitary gland and in that case includes symptoms of EDS, hyperphagia, polydipsia, and variations in body temperature.

Systemic lupus erythematosus is also a chronic, multisystem disorder which may be associated with EDS.

Endocrine Disorders

EDS has been associated with several endocrine disorders, in part due to the co-occurrence of OSAS.

Several studies have demonstrated that OSA is more prevalent among patients with hypothyroidism than among control subjects [98]. However, a primary effect of hypothyroidism on sleep is also possible [99].

Sleep-disordered breathing is common in acromegaly in relation with the insidious onset of facial features, bony proliferation, and soft tissue swelling. In a study involving 17 patients (11 women and 6 men) diagnosed with acromegaly, 10 patients (58.8 %) had an apnea/hypopnea index greater than 10, 9 had OSAS, and one had central sleep apneas [100]. Seven patients, 5 with an AHI >10 and 2 with an AHI <10, reported EDS with an ESS score greater than 10.

Diabetes and OSAS share a high prevalence in industrial nations. The presence of OSAS seems to promote the development of diabetes mellitus and vice versa. There are limited data regarding EDS in type 2 diabetes patients. In one study involving 614 type 2 diabetes patients, EDS, as measured by the ESS, occurred in 8.5 % of the patients [101]. However, apneas were assessed by the Sleep Disorders Questionnaires using sleep apnea subscales only, and the relationship between apneas and EDS was not specifically assessed. In another study involving 110 patients with type 2 diabetes, EDS was found in 55.5 % of patients, in association with depressive symptoms in 44.5 % of them [102].

Genetic Disorders

EDS is highly prevalent in patients suffering from various genetic syndromes. It is often the consequence of nocturnal breathing disorder, most often OSAS, but it may also be due to a primary wakefulness dysfunction. An excellent review of these syndromes was recently pub-

lished [103], and the present subchapter will only review the most common genetic disorders accompanied by EDS.

Chromosomal Abnormalities

Three chromosomal abnormalities, trisomy 21, translocation of the long arm of an extra chromosome 21 to chromosome 14 or 22, and mosaicism of trisomy 21, may be involved in Down syndrome. EDS is frequent, in relation with OSAS, the prevalence of which is higher than 50 %, or in relation with sleep fragmentation, independent of respiratory events and periodic limb movements.

Prader–Willi syndrome (PWS) is due to a lack of expression of the paternally active genes in the q 11–13 region of chromosome 15. EDS is a common symptom in PWS. Camfferman et al. identified 13 studies that have undertaken MST [104]. Eighty-nine patients underwent MSLT. Thirty-seven (41.6 %) showed a mean sleep latency of less than 5 min, and 27 (32.7 %) showed at least one SOREM. Given the risk factors for OSA, obesity, narrowing of the upper airway, facial dysmorphism, scoliosis, and hypotonia, one of the proposed causes of EDS in PWS is a combination of obesity and OSA. However, no convincing correlation has been established between OSA severity and EDS intensity. Therefore, additional mechanisms of EDS including hypothalamic dysfunction supported by decreased CSF hypocretin-1 level may be involved [105].

Smith–Magenis syndrome is associated with a deletion of 17p 11.2. Most patients exhibit sleep attacks occurring at the end of the day, suggesting an advanced sleep phase syndrome.

Norrie disease is a rare genetic form of blindness and variable mental retardation due to a Xp11.3–p11.4 microdeletion. Features of narcolepsy including irresistible episodes of sleep and attacks resembling cataplexy have been described in three related boys in North America [106].

Inherited Metabolic and Neurodegenerative Diseases of the Nervous System

These diseases result from a single mutant gene coding for an enzymatic protein mostly involved in the catabolic pathways. Most striking sleep disorders are found in lysosomal storage disorders including glycogenoses, mucopolysaccharidoses, and sphingolipidoses. Pompe's disease results from an acid α-glucosidase deficiency. Diaphragm weakness responsible for respiratory insufficiency or sleep apnea may appear at any stage of the disease and be associated with EDS.

Mucopolysaccharidoses are heterogeneous syndromes consisting of mental and physical retardation. OSAS associated with EDS is almost systematic. Niemann–Pick disease type C (NPC) is a lysosomal storage sphingolipidosis with four main forms: early infantile, late infantile, juvenile, and adult. Five patients with juvenile NPC have been reported [107]. Cataplexy was present in one patient. Nocturnal PSG revealed shortened mean sleep latencies on the MSLT in three patients and SOREMPs in the case with cataplexy. CSF hypocretin-1 levels were reduced in two patients (one with cataplexy), while in the two other patients, the levels were at the lower range of the normal values.

Hypersomnia Due to a Medication or Substance

Patients with this type of disorder have excessive nocturnal sleep, daytime sleepiness, or excessive napping attributable, either to sedating medications or to alcohol, to drugs of abuse, or to withdrawal from amphetamine and other drugs. The sleep disorder has become a public health concern, due to the consequences of somnolence, not only on driving but also on occupational activities and thus on productivity.

Sedating medications lead to "a state of calm or reduced nervous activity" (Collins's dictionary) which may eventually result into EDS. They cause sedation via effects on the neural systems involved in the sleep–wake regulation, primarily by increasing GABA or inhibiting histamine, norepinephrine, or serotonin. Important factors affecting the degree of sedation include receptor binding profile, dose, half-life, and time of administration as well as age and association with multiple medication ingestion. These medications include benzodiazepine and nonbenzodiazepine hypnotics, antianxiety drugs, some antidepressants, first-generation antihistamines, antipsychotic drugs, antiepileptic drugs, opiates,

anticholinergic drugs, and skeletal muscle relaxants. A frequent source of excessive somnolence is also the use of some dopamine agonists such as pramipexole and ropinirole. Excessive somnolence may less frequently be caused by various medications including antihypertensive drugs, mostly α2 agonists (e.g., clonidine and methyldopa) and less frequently nonselective beta-antagonists (e.g., propranolol) and α1 antagonists (e.g., prazosin), nonsteroidal anti-inflammatory drugs, and antispasmodic drugs. Of note, EDS occurs only in a fraction of patients using these drugs, and its severity can vary considerably rending the diagnosis uneasy. In some cases, failure to provide treatment by the incriminated drug may be more disruptive than EDS.

Alcohol intoxication causes sedation for 3–4 h and then insomnia, whereas intake of caffeine or cocaine causes insomnia and their withdrawal sedation. Sedation is a common adverse effect of opioid medications. The degree of sedation may depend on the specific drug, dosage and duration of use, as well as on the severity of the underlying disease. Cannabis use may be associated with EDS, sluggishness, giddiness, and inability to concentrate. In chronically heavy amphetamine users, EDS peaks during the first week of withdrawal and can persist for up to several weeks. In people consuming caffeine daily, discontinuation can produce EDS and fatigue for several days.

Hypersomnia Associated with a Psychiatric Disorder

Significant evidence links EDS to depression. In a study conducted with a large-scale American population sample of 16.583 men and women, 8.7 % had EDS, which was strikingly associated with depressive symptoms [108].

EDS can be a symptom of various psychiatric disorders involving depression (Table 10.2).

However, EDS is not systematically present in these disorders. First, the accompanying sleep symptom is either insomnia or EDS; second, the sleep symptom is only part of a list of symptoms, a certain number of which have to be present during the same 2-week period and represent a change from previous functioning; third, subjective sleepiness, as assessed by the ESS or other subjective tests, has been evidenced in most of these psychiatric disorders, but rarely objective sleepiness as measured by MSLT, actigraphy, or continuous PSG [109].

Table 10.2 Psychiatric disorders potentially associated with hypersomnolence (DSM-5)

Psychiatric disorders	Subtypes	Specifiers
Bipolar and related disorder	Bipolar I disorder	With atypical features
	Bipolar II disorder	With seasonal patterns
Depressive disorders	Major depressive disorder	With atypical features
	Persistent depressive disorder	With seasonal patterns
	Premenstrual dysphoric disorder	
	Other specified depression disorder	
Schizophrenia spectrum and other psychiatric disorder)	Schizoaffective disorder	

Despite the significant evidence linking EDS to depression, the pathophysiological mechanisms underlying this relationship remain uncertain. Among the current hypotheses are a cholinergic–aminergic imbalance [110] and disturbances in the circadian system [111].

Insufficient Sleep Syndrome

"Insufficient sleep syndrome occurs when an individual persistently fails to obtain the amount of sleep required to maintain normal levels of alertness and wakefulness" [1]. As a consequence, the subject is abnormally sleepy with daily periods of irrepressible need to sleep or daytime lapses into sleep. The patient's sleep time, established by personal or collateral history, sleep diary, or actigraphy, is usually shorter than expected for age. Sleep time is markedly extended on weekend nights or during holidays compared to weekday nights. Depending upon extent of sleep loss, individuals are at risk for a range of neurobehavioral deficits,

including lapses of attention, slowed working memory, reduced cognitive function, depressed mood, and fatigue.

This syndrome has been systematically investigated for the first time in 1983, in a population of 59 adults, 37 men and 22 women, mean age 40.8 ± 12.2 [112]. Since then, studies have been mainly carried out in adolescents [113, 114], except for a Japanese study based on the interview of 1243 patients referred to a sleep disorder outpatient clinic for complaint of EDS: the combination of insufficient sleep and EDS was about 7.1 % of the sample [115]. However, no differential diagnosis was applied.

Positive diagnosis is primarily based on interview and actigraphy associated with sleep log for a minimum of 1 week. PSG and MSLT are not required to establish a diagnosis of insufficient sleep syndrome. Rather, sleep time is extended first, and the patient is clinically reevaluated; if the symptoms disappear, insufficient sleep syndrome is confirmed. If unchecked, insufficient sleep syndrome may predispose to depression and other psychological difficulties as well as poor work performances or traffic accidents.

Conclusion

In addition to OSAS and narcolepsy, etiologies of EDS are numerous. Some of them idiopathic hypersomnia, KLS, and insufficient sleep syndrome are well known to sleep physicians, while others, mainly symptomatic causes, are familiar to some of them only. It is of utmost importance that sleep physicians are aware of the possibility of EDS in a large variety of somatic and psychiatric conditions and that specialists, neurologists, psychiatrists, cardiologists, chest physicians, endocrinologists, and specialists of infectious diseases and internal medicine learn to recognize EDS as an important symptom, both in terms of diagnosis and treatment.

Financial Disclosure Dr. Billiard reports no conflict of interest.

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