ABSTRACT

Idiopathic hypersomnia (IH) and Kleine-Levin syndrome (KLS) are rare disorders of central hypersomnolence of unknow cause, affecting young people. However, increased sleep time and excessive daytime sleepiness (EDS) occur daily for years in IH, whereas they occur as relapsing/remitting episodes associated with cognitive and behavioural disturbances in KLS. Idiopathic hypersomnia is characterized by EDS, prolonged, unrefreshing sleep at night and during naps, and frequent morning sleep inertia, but rare sleep attacks, no cataplexy and sleep onset in REM periods as in narcolepsy. The diagnosis requires: i) ruling out common causes of hypersomnolence, including mostly sleep apnea, insufficient sleep syndrome, psychiatric hypersomnia and narcolepsy; and ii) obtaining objective EDS measures (mean latency at the multiple sleep latency test ≤8 min) or increased sleep time (sleep time >11h during a 18-24h bed rest). Treatment is similar to narcolepsy (except for preventive naps), including adapted work schedules, and off-label use (after agreement from reference/competence centres) of modafinil, sodium oxybate, pitolisant, methylphenidate and solriamfetol. The diagnosis of KLS requires: i) a reliable history of distinct episodes of one to several weeks; ii) episodes contain severe hypersomnia (sleep>15h/d) associated with cognitive impairment (mental confusion and slowness, amnesia), derealisation, major apathy or or disinhibited behaviour (hypersexuality, megaphagia, rudeness); and iii) return to baseline sleep, cognition, behaviour and mood after episodes. EEG may contain slow rhythms during episodes, and rules out epilepsy. Functional brain imaging indicates hypoactivity of posterior associative cortex and hippocampus during symptomatic and asymptomatic periods. KLS attenuates with time when starting during teenage, including less frequent and less severe episodes. Adequate sleep habits, avoidance of alcohol and infections, as well as lithium and sometimes valproate (off label, after agreement from reference centres) help reducing the frequency and severity of episodes, and IV methylprednisolone helps reducing long (>30 d) episode duration.

KEYWORDS

Hypersomnia, Kleine-Levin syndrome, derealisation, sleep drunkenness, excessive daytime sleepiness

ABREVIATIONS

EDS: excessive daytime sleepiness

ICSD: International Classification of Sleep Disorders

IH: idiopathic hypersomnia

KLS: Kleine-Levin Syndrome

MSLT: Multiple sleep latency test

1. INTRODUCTION

Chronic excessive daytime sleepiness (EDS) is reported by 10% of the population. Beyond common causes (including mostly chronic sleep deprivation, use of sedative drugs and substances, obstructive sleep apnea-hypopnea syndrome and depression), central disorders of hypersomnolence include narcolepsy, idiopathic hypersomnia (IH), Kleine-Levin syndrome (KLS) and hypersomnia associated with medical and neurological disorders. Compared with narcolepsy, for which major progress has been made in recent decades thanks to animal models and understanding of pathophysiology, IH and KLS have been somehow neglected. EDS and prolonged sleep times are dramatically marked in IH and KLS, in contrast to other causes of sleepiness. IH is rarer than narcolepsy, and KLS is exceptional. Because of rarity, diagnosis is often delayed by several years and best met in Reference/Competence centres for narcolepsies and rare hypersomnia, where neurologists and psychiatrists follow large cohorts and are experienced in treatment options. In both disorders, the onset is at a young age (adolescent for KLS and young adult for IH), the cause is unknown (including the affected arousal system), and treatments are used off-label, mainly based on the consensus IH diagnosis and treatment recommendations of the French national reference centres and on the National Program of Diagnosis and Care for KLS [1, 2]. IH affects women more often than men, whereas KLS affects boys more often than girls. IH is a daily and chronic disorder that rarely (10-20%) tends to disappear over time, whereas KLS is intermittent (like multiple sclerosis) and often tends to disappear after the age of 30. In both cases, future research is focused on understanding the cause and pathophysiology of symptoms, which should lead to personalized treatments.

2. IDIOPATHIC HYPERSOMNIA

2.1. Introduction

Idiopathic hypersomnia is a chronic neurological sleep disorder where individuals experience EDS that is not explained by any other sleep, medical, neurological or mental disorder. Despite sufficient sleep at night (and often long sleep times), those affected find it challenging to maintain alertness and struggle to perform daily activities. The IH classification has evolved over the years, as defining clinical phenotypic clusters is challenging, but recent clustering studies confirm the clinical impression that IH with long sleep time is different from IH without long sleep time, the latter resembling narcolepsy type 2 [3, 4]. Unlike narcolepsy type 1, which has a pathognomonic symptom (cataplexy), neurophysiological markers (short MSLT latency, sleep onset in REM periods) and a specific biological marker (CSF hypocretin-1 deficiency), IH has no pathognomonic symptom (major sleep inertia is rarely observed in other disorders), no specific neurophysiological markers (short MSLT latency and prolonged sleep time occur in other disorders) and no known biological marker. In addition, prolonged sleep time is objectively measured during 24 h bed rest procedures in many centres in France, but not in other countries, which may lead to different IH types being diagnosed worldwide. Consequently, although most experts agree on the existence of a "classic" form of IH with long sleep time associated with EDS, major difficulties waking from sleep and prolonged sleep times, they do not always measure sleep times over 24 h and rely on MSLT latency, which can be abnormally short in many other conditions and can change over time. This attitude has led to the diagnosis of IH often being regarded as dubious, which has failed to support quality research and convince companies to test drugs in IH for decades. Beyond these debates between hyper-specialists, IH is not so rare (at least slightly rarer than narcolepsy) and extremely disabling. It affects younger women more frequently than men. The diagnostic criteria have been slightly modified in the new International Classification of Sleep Disorders (ICSD)-3 revised in 2023 (Table 1), but the distinction between forms of IH with and without long sleep times proposed in ICSD-2 has not been reinstated [5].

2.2. Symptoms

2.2.1. Excessive daytime sleepiness

Idiopathic hypersomnia is characterized by EDS despite normal or prolonged night-time sleep. While all IH patients experience EDS, its quality varies among individuals [6]. Sleepiness can range from frequent, brief, and restorative naps (mostly observed in the IH form without long sleep time, which resembles narcolepsy) to continuous drowsiness with rare, prolonged (e.g., 1 -3 h long), and non-restorative naps, to the point that many patients avoid napping to prevent severe post-napping inertia. They often describe a continuous non-imperative sleepiness, feeling "foggy," or "sub-awake" and lacking adequate alertness [7-9]. Patients may resort to motor hyperactivity and logorrhoea to resist drowsiness and can exhibit cognitive fatigability. In patients with severe morning sleep inertia, the drowsiness is maximal upon awakening and may transiently fade in the evening [7]. Hallucinations and sleep paralysis are reported by 11% of patients [10]. Other symptoms of EDS include automatic behaviours, when patients display out of topic sentences or continue automatically a task without shifting. Complaints of poor memory and reduced attention are frequent. However, IH patients are often organized, making "to do lists" and reacting rapidly and precisely to requests, in sharp contrast with the frequent procrastination and disorganization observed in patients with narcolepsy or attention deficit hyperactivity disorder [11].

2.2.2. Difficulties waking up

Sleep drunkenness, characterized by major sleep inertia and difficulties waking up, is a significant complaint among IH patients, mostly those with long sleep time [9]. It is conceptualized as a state intermediate to sleep and wake, and an exacerbation of the normal sleep inertia observed in the normal population, especially during post-deprivation sleep rebound, and in delayed sleep phase syndrome. The symptom is independent from sleep time and the presence of N3 sleep at the end

of the night [12]. Patients with unipolar depression also report difficulty waking up, but unlike IH, it is associated with morning anhedonia and decreased motivation that fades later. Sleep drunkenness is extremely severe in IH, as patients may not hear the alarm clock, or may hear it but immediately go back to sleep, despite the alarms ringing incessantly and increasingly loudly. Sleep drunkenness leads to confusion, slowness, incoordination, and aggressiveness. Some patients have organized their lives to minimize the time they spend after waking up in the morning, by showering in the evening, preparing their clothes the night before and living close to their work place. The main problems associated with sleep drunkenness is the risk of being late for work (and getting fired) or school, and the frequent need of another person to wake up.

2.2.3. Excessive sleep time

The major sleep episode in IH varies from normal sleep duration with frequent awakenings (a feature also observed in narcolepsy, and more characteristic of IH without long sleep time) to prolonged sleep duration with high sleep efficiency, particularly specific to IH with long sleep time. The term "long sleep time" in IH refers to the main sleep period exceeding 10 hours per night or to the total sleep time over 24h exceeding 11h. This figure is however observed only during unrestricted schedules including weekend or vacation, as patients must wake up with an alarm clock during working days [7]. Sleep mentation varies from a complete blackout in more than half of IH patients, to being exhausted of "dreaming too much" (a symptom called "epic dreaming") in 20% of them [13].

2.2.4. Other symptoms and signs

Autonomic and physical symptoms including orthostatic hypotension, headache [14], and Raynaud phenomenon are reported by half of IH patients [15]. More IH patients than healthy controls have an evening chronotype [12]. Patients with IH are on average thinner than controls and narcolepsy patients [8]. The prevalence of inflammatory disorders (9%) and allergies (14%) is

(unlike comorbid autoimmune disorder) higher in IH patients than in controls, suggesting that inflammation may play a role in some IH cases [16].

2.3. Epidemiology

The exact prevalence of IH is unknown, but it is estimated to be slightly lower than narcolepsy in reference centres, which should be around 1 to 2 affected individuals per 10,000 inhabitants. The disorder usually begins during adolescence and early adulthood, with a higher prevalence (60-75%) of women and Caucasian individuals. IH may show some familial aggregation, and in this case is often present since childhood. Notably, while child narcolepsy is well identified, IH in children is exceptional.

2.4. Course of the disorder

The mean age of IH onset is 16.6–21.2 years. Once established, the disorder is generally stable in severity and long lasting, although spontaneous remission rate of 14% to 32% has been observed [17, 18]. Complications are mostly social and professional, and include poor work or school performance, reduced earnings, and loss of employment [19].

2.5. Diagnosis procedure

The procedure for diagnosing IH is long, as it involves first a thorough evaluation of sleep patterns, medical history, and exclusion of other potential causes of EDS (including medical, neurological, mental and sleep disorders associated with EDS, because they are more frequent) and then to prove that objective EDS or increased total sleep time are present.

2.5.1. Scales and specific measures

Although many patients with IH do not recognize their symptoms among the items of the Epworth sleepiness scale (as they may not formally fall asleep,) they usually have high scores on

this scale, which decrease using stimulants [20]. A specific scale has been developed for IH in France by the Montpellier group [21, 22], which has the advantage of quantifying subjectively EDS, prolonged sleep time, sleep drunkenness and IH impact on daily functioning (Table 2). Some methods have been developed to capture sleep drunkenness, including psychomotor vigilance task and forced awakening potentials, but they are used for research purposes and not in routine practice.

2.5.2. Differentiating idiopathic hypersomnia from other disorders

Almost all sleep disorders can be associated with EDS or morning sleep inertia. Sleep-disordered breathing, defined by an apnoea-hypopnoea index greater than 15, is observed in 23% (women) and 50% (men) of the general adult population [23]. Patients with sleep-disordered breathing are more frequently middle-aged obese males, a profile somehow opposite to the HI profile. Some overlap however exists, so that a cardiorespiratory polygraphy or a polysomnography should first rules out sleep-disordered breathing and treat it before considering that it is (or not) causing EDS. Insufficient sleep syndrome should be ruled out by using two-weeks long sleep logs or actigraphy and evaluating the benefit on EDS of increasing sleep time, for example during vacation [5]. EDS can be associated with numerous chronic neurological disorders (including multiple sclerosis, Parkinson's disease, and any tumour in the hypothalamic area,…, see the corresponding chapter), use of sedative drugs or substances, medical disorders (e.g., cancer, chronic pain, severe hypothyroïditis, psychotropic virus including Epstein Barr virus, and long COVID-19) and mood disorders The most puzzling of these differential diagnoses is probably depression, which is associated with insomnia in 2/3 of patients and hypersomnia in 1/3 of them [24]. Concurrent anhedonia, sadness, and lack of projection helps meeting the diagnosis. Low mood is concomitant with morning sleep inertia in depression, whereas patients with IH have normal mood in the morning. Plus, in some undiagnosed bipolar disorders, sleep time can fluctuate, including periods of several days with long (e.g., 14h) and short (e.g. 4h) sleep duration.

A frank benefit of antidepressants on EDS helps confirming the suspected diagnosis of depression.

2.5.3. Measuring EDS

Multiple sleep latency test (MSLT), performed after a normal night-time polysomnography as recommended, is mandatory when IH is suspected. In one third of IH cases, the mean sleep latency is ≤8 min (and there is 0 or 1 sleep onset in REM period across the 5 tests), supporting objective sleepiness and ruling out narcolepsy. However, MSLT has a poor specificity and sensitivity in IH [25]. Short latencies on MLST are poorly reproducible over time. In addition, around 2/3 of patients with IH have normal results on MSLT [12], requiring in this case other tests (mostly measures of sleep time over 24-36h) to support the IH diagnosis.

2.5.4. Measuring long sleep time

The measure of total sleep time during a 24h day is commonly used in expert centers in France for decades [12, 26] and recently developed in Japan, where illustrative cases experiencing increased sleep times contrasting with normal or subnormal MLST latencies have been found too [27]. Two current protocols are valid (detailed procedure are published and measures vs. controls have been tested) and recommended by the consensus of national centres for rare hypersomnia [6]. One procedure ("Paris procedure") consists in a 48h recording in hospital, starting with a polysomnography during Night #1 (ended at 6:30 am), followed by 5 MSLT tests on Day #2, and then by ad libitum bed rest sleep during Night#2 and Day #3 from 9 pm to 3 pm (a sleep opportunity of 18 h), including an unlimited night followed by morning and afternoon unlimited naps [12]. Daylight and notion of time are allowed. An example of how IH patients sleep, compared to normal subjects is shown in **Figure 1.** During this procedure, the first 24h resemble a week day and the second 24h resemble a weekend day, allowing to capture markers of EDS and excessive need for sleep in a single procedure. The total sleep duration during 18h bed rest is

frankly abnormal when greater than 11h (**Figure 2**), which is observed in 2/3 of IH patients [12]. Some patients may combine short MSLT latency and long sleep during bedrest. An alternative procedure ("Montpellier procedure") consists in starting by a classical polysomnography followed by MSLT. If MSLT are between 8 and 10 min, or if longer but the clinician strongly suspects IH, patients are scheduled for a second, longer procedure which starts with polysomnography (Night#1)and MSLT (Day#2) interrupted after 1 min of sleep (to maintain sleep pressure) and then 36h of bedrest (Night#2, Day #3 and Night #4) with no daylight and clocks (to avoid circadian zeitgebers). A total sleep time longer than 18h during 36h or longer than 12h during the first bed rest 24h is abnormal and indicative of IH [26].

2.6. Potential causes and mechanisms

2.6.1. Triggers

Increased sleep time associated with EDS has been reported in post-traumatic hypersomnia [28], post viral hypersomnia and in various hypersomnia associated with neurological disorders (including tumors of the diencephalon, Prader-Willi syndrome [29] and inflammatory disorders [30]), making it important to rule out these causes (e.g., to perform brain MRI, identify head trauma within the last year before hypersomnia onset, and assess for recent viral conversion) before reaching the diagnosis of IH. The IH onset is usually progressive, making it difficult to identify a trigger. Severe subjective hypersomnia can suddenly occur after a viral infection (e.g., Epstein-Barr virus, cytomegalovirus, and long COVID) but the symptoms usually improve after six months. However, some patients remain sleepy for years. Similarly, some patients have hypersomnia for decades, but seek for medical advice when their life factors change (e.g., raising young children, changing of job schedule), and jeopardize the previous adjustment to what was not considered yet as a disorder.

2.6.2. Potential mechanisms of IH

The exact cause of IH is unknown. Several research groups tried to determine whether patients had evidences of deficient brain arousal systems (as in narcolepsy), excessive secretion of pro-sleep factors, or a longer biological night. Animal models, which have been pivotal in narcolepsy research, are lacking in IH, if one excludes the severely increased sleep (and REM sleep) time found when manipulating the midbrain periaqueductal gray matter in cat models [31].

Histamine and hypocretin-1 (which are the main arousals systems) as well as melanin-concentrating hormone (which promotes REM sleep) levels are normal in the CSF of IH patients [32]. Studies from the Atlanta group indirectly suggested that an endogenous hypnotic neurotransmitter in IH patients stimulates GABA-A receptors [33, 34] (as if patients with IH could be under the influence of a hypnotic), a finding not reproduced in another study [35]. Lipocalin-type prostaglandin D, a sleep-inducing factor, is moderately increased in the CSF of patients with IH, but also of patients with narcolepsy type 1 and type 2 compare to controls, suggesting a non-specific contribution to EDS [36].

Several evidences point towards a longer biological night in IH, including a prolonged night-time and morning secretion of melatonin [37], a more frequent evening chronotype [12], a 1-h longer circadian period length in peripheral skin fibroblasts [38], a mildly reduced melanopsin-mediated pupil response [39] and a smaller relative post-illumination pupil response [40]. However, bright light illumination in the morning and melatonin intake in the evening, which should reduce the duration of the biological night, yield only a mild benefit in IH, suggesting that a longer biological night is only part of the IH mechanisms.

Genetic factors may also play a role, as instances of familial clustering of the disorder have been reported, but no susceptibility loci associated with IH have been clearly identified. A rare genetic variant in the cleavage site of pre-pro-orexin (leading to decreased orexin signalling) has been found in 1.32% of patients with IH [41].

New insights into the pathophysiology of IH have come from functional brain imaging. In awake participants with IH vs. controls, the medial prefrontal cortex appears "asleep" (hypoperfused) during wakefulness, in proportion to subjective and objective EDS measures [42]. This result raises the tantalizing hypothesis that low alertness without true sleep episodes in IH results from local sleep. Indeed, local slow wave in frontal or posterior cortical area are observed in normal people with wide open eyes making mistakes on a cognitive test, whether when they are sleep deprived volunteers or fatigued by a prolonged performance task [43]. This should however now be demonstrated. The default mode network was also studied by functional imaging [44]. The functional connectivity at rest was lower within the anterior default mode network (medial prefrontal cortex) in IH, and correlated with self-reported daytime sleepiness, suggesting that a disruption of the default mode network contributes to the clinical features of IH.

2.7. Treatment and management

2.7.1. **Non-pharmacological treatment**

General approaches like maintaining a regular sleep schedule, engaging in regular exercise, having an interesting job, and implementing good sleep hygiene practices can be beneficial. Napping can benefit to the rare patients finding this condition refreshing, otherwise most patients avoid it. The ability to drive should be regularly assessed by interview (as patients with IH and reduced MSLT latencies have a higher risk of crashes than controls [45]) and, if needed, maintenance of wakefulness tests although the result of the latter may not predict the real on-the-road driving performances [46].

The confinement associated with the COVID-19 epidemic was a full-scale experiment, allowing to test the effect of working at home, more at one's own pace, in people with HI. Working from home was associated with an average one-hour increase in sleep time (including

working days), a delayed shift in bedtime and wake-up times, and a reduced EDS (often associated with a reduction in stimulant dose) [47, 48]. This benefit was mostly linked to reducing commuting time by 70 min. The benefit of teleworking in IH was confirmed in a further work [49]. These results support the recommendation of providing people with HI with several days' teleworking a week, whenever possible, and favouring a work place close to home. Allowing patients to come later at work, if possible, can reduce the problems associated with sleep drunkenness. Some patients need a work physically active to maintain alertness. On the other hand, the socio-educational level of people with IH is often higher than in people with narcolepsy (possibly because the disorder starts later in life) and allows many patients to have high levels jobs. They have however difficulties to adapt to change in sleep schedules (e.g., attending a wedding party may be compensated only after a full week of sleep). The risk for them is to alternate between work and sleep, leaving little room to family and social life. All in all, the risk of depression induced by IH fatigue is important, and should be regularly evaluated by the physician in charge.

2.7.2. **Pharmacological treatment**

Currently, there is no cure for idiopathic hypersomnia, but several treatment options alleviate symptoms and improve quality of life [50]. All drugs used in narcolepsy have been suggested in IH. Stimulants and wake promoting medications, such as modafinil [20], methylphenidate, amphetamine [17, 51], pitolisant [52] and solriamfetol, are commonly prescribed to reduce EDS. Sodium oxybate reduces sleep time, sleep drunkenness and EDS. They have shown good benefit and safety in open, long term series. Modafinil has been tested vs. placebo, mostly in IH without long sleep time, and has both improved the score at the Epworth sleepiness scale [53] and the latency at the maintenance of wakefulness test [54]. Low sodium oxybate has been given once or twice per night at various dosages vs. placebo in a prospective double blind placebo controlled withdrawal study [55], and has shown a clear benefit (-6 points) on the score at the Epworth

sleepiness scale and on the IH severity scale (including benefits on sleep drunkenness and prolonged sleep time). Results were maintained over long term use [56]. Low sodium oxybate is labelled for IH in USA but not in France, where sodium oxybate can be a good proxy [57]. One may however keep in mind that all these drugs are indicated for narcolepsy but not for IH in France, hence they should in theory be prescribed off label and not reimbursed. However, they are often expensive (except for methylphenidate), should be initially prescribed and annually continued by a physician from a neurological or sleep hospital unit, may be subject to misuse (e.g., enhancing alertness and cognition in people without medical disorder) and have cardiovascular and psychiatric side effects. Consequently, the French consensus highlighted their benefit, conditions of use and limits in practical sleep medicine, and recommended that patients with IH requiring a pharmacological treatment should be addressed to a reference centre or their files should be discussed during tele-expertise or concertation meetings organised by reference centres [2]. This procedure is aimed at avoiding misdiagnosis of IH and misuse of these potent drugs.

Following the concept that some patients with IH may have an endogenous secretion of a sleep inducing peptide, the Atlanta group tried to block GABA-A receptors using anexate and clarithromycine. Open series and a single double blind trial of anexate in a small, miscellaneous group have yielded some evidence of benefit [58]. Anexate cannot be prescribed orally, but clarithromycine can. Therefore, it is easy to test this drug during 2 weeks in a patient, and stop if no benefit is found. In our experience, very few patients benefit from clarithromycine.

More interesting, orexin-A (hypocretin-1) agonists have been recently tested in narcolepsy with success, and their use has been extended in IH (although orexin is not deficient in IH), in a single IV infusion, leading to a complete absence of sleep bouts during prolonged maintenance of wakefulness tests [59]. If this success is transferred to the future oral orexin-A (hypocretin-1) agonists and maintain over time, patients with IH would benefit from a new, potent treatment of

their EDS [50, 60]. Orexin is the conductor of all arousal systems, hence the stimulation of orexin receptors may compensate deficits in several different arousal systems.

3. Kleine-Levin syndrome

3.1. Definition

Kleine-Levin syndrome (KLS) is a rare relapsing/remitting neuropsychiatric disorder of the young. The recurrent episodes associate a characteristic clinical tetrad, including hypersomnia, confusion, apathy and derealization [5] (Table 2). The episodes last from two days to several weeks, and are interspersed with several symptom-free weeks or months (named asymptomatic periods). It is a clinical diagnosis based mainly on questioning and description of episodes by relatives. In case of doubt, it is useful to see patients during episodes, and refer them to an expert center. The neurological examination is normal during asymptomatic periods. There are no biological or radiological markers for a definitive diagnosis, but some tests indirectly support the diagnosis and rule out differential diagnoses.

3.2. Symptoms

3.2.1. Hypersomnia

Hypersomnia is characterized by its prolonged duration. For several days, the adolescents sleep more than 18 hours out of 24 [61]. It is possible to wake them up, but with difficulty. Sleep duration progressively reduces over the course of the episode, and in two-thirds of patients ends with a brief 24-hour insomnia [61-63].

3.2.2. Derealization

The perception of the environment is almost constantly altered [62, 64]. This is the most specific symptom, and should be systematically asked about when questioning patients. The derealisation is described as being "in a dream, unreal, disconnected from body and mind". Visual (blurred

vision), auditory, tactile, gustatory, temperature and pain perceptions may be felt as "wrong". Derealization is unpleasant, to the point that some children ask their parents: "Am I dead or alive?" The derealization score correlates with hypometabolism of the parieto-temporal junction, an area that integrates sensory-motor, auditory and visual information [65].

3.2.3. Cognitive impairment

Patients are slowed down, do not initiate conversation, answer in monosyllables or mumbles, with slowness or childlike language. Basic cognitive functions (arithmetic, reading, speech) are preserved, but slowed down. Temporal disorientation, more rarely spatial, and partial or total amnesia are common.

3.2.4. Apathy

The patients generally stay in their room, lying down, without going out, using their smartphone, seeing friends or going on social networks. Some parents have to push their teenagers into the bathroom and sometimes wash them like children. Taking the initiative, making a decision or carrying out two tasks simultaneously is difficult for two-thirds of patients. Apathetic patients tend to eat less, in order to go rapidly back in their room.

3.2.5. Behavioral disinhibition

Although rarer than apathy, behavioral disorders are often present, including mostly rudeness and irritability, but also megaphagia or sexual disinhibition in half of patients (mostly boys). Megaphagia is an increased food intake (gaining an average of 5 kg per episode), food preferences (mostly towards sweet or salted foods) or frontal-syndrome-like eating behavior, with patients taking all available food, without stopping, and sometimes in a rude manner [66]. Contrary to bulimia, there is no vomiting or restrictive behavior. Changes in sexual behavior are among the most publicly embarrassing symptoms, and can lead to medicolegal problems. It involves mental,

behavioral and physical disinhibition, leading to hypersexuality. Curious compulsions such as watching the same films over and over again, tapping on a piano or wall or playing with their fingers are sometimes observed.

3.2.6. Psychological symptoms

They can cause misdiagnosis in the early stages of the disease. In half of patients (more often in girls), mood is blunted or totally collapsed, suddenly and transiently. At the same time, there are bouts of anxiety. The patient is afraid of being alone, of being abandoned, and has a desire for isolation. Psychotic symptoms, including hallucinations and sometimes delusions (resembling a brief psychotic or manic episode) or strong aggression are observed in one third of patients. Some patients have mild ideas of reference, including the impression that their disorder is visible, and that strangers look at them strangely or unkindly.

3.2.7. Physical symptoms

Photophobia and painful hyperacusis are common, headaches and nausea rarer, orthostatic hypotension fairly frequent [67].

3.2.8. Clinical forms

There are mild or benign KLS forms (e.g., two to three episodes per year, each lasting one week), but also "malignant" forms including monthly episodes, or long-lasting episodes (3-6 months). Rare patients may have 40-80 episodes without recovery in adulthood. Menstrual-related hypersomnia is a form of KLS [68]. There are rare cases associated with comorbidity, mostly a severe neurological disease (Prader-Willi, Asperger or Robert syndromes, mental retardation, ...). [56]. The disease is usually not life-threatening, but drowsiness and cognitive impairment prohibit driving during episodes. Agitation, aggressiveness and psychotic disorders may endanger the

patients or those close to them. Rare suicide attempts and one death by suicide have been reported.

3.2.9. Disease course

The syndrome is characterized by frequent episodes at the onset of the disease, which then become less frequent over the years and often heal spontaneously. It is usually a disease with a good prognosis. The duration of episodes varies from 2 to 270 days (extreme cases), with a median of around 10 days [62, 64, 66]. Asymptomatic periods average 3.5 to 4 months, but are variable within the same individual. Episodes gradually change, with less hypersomnia and less marked symptoms. KLS duration is variable and unpredictable for any given subject. In a prospective cohort, the median duration was 13.6 years [62]. The disease lasted longer in men, in people with hypersexuality, and in those who had started the disease after the age of 20 [69]. Patients with a high number of attacks in the first year recover more quickly than others [66]. Symptoms become chronic but less intense in a small number of patients.

Several points are important to check every year during asymptomatic periods, including residual cognition, mental health, daytime sleepiness and motivation. Indeed, mild cognitive impairment may persist during asymptomatic periods, affecting logical reasoning, information processing, attention and verbal episodic memory retrieval strategies [70]. In terms of mental health, 21% of patients develop psychiatric comorbidities (mainly anxiety and mood disorders), after KLS onset. Vulnerable factors include female gender, long KLS duration, long (> 1 month) episode duration, and psychiatric symptoms during episodes [71]. Therefore, we recommend that patients are evaluated by a psychiatrist every year. Residual apathy, EDS or excessive need for sleep may appear in a minority of patients after several years of KLS.

3.3. Triggering factors

Almost all patients recall a triggering event prior to the first episode, including mostly an infection, and more rarely alcohol intake, sleep deprivation, head trauma or unusual stress. The infectious agents involved are varied (mostly seasonal flu, more rarely Epstein-Barr virus, varicella-zoster virus, enterovirus, Covid-19 virus, streptococcus), which makes it impossible to single out any one in particular [66]. These same events can precede some relapses, as can vacations or change in waking time [72].

3.4. Epidemiology

In France, the national reference center registry estimates the prevalence of KLS at 4 cases per million inhabitants (just over 280 cases followed in the Paris center), and its incidence at 0.3 new cases per million per year [64]. The disease begins in 85% of cases in adolescence, with a median age of 15, and in a few cases before puberty or in adulthood (rarely before age 12 or after age 20 [62]. Males are twice as often affected as females. Around 1/3 of patients have had a developmental problem or difficult birth (more than controls) [62, 64]. Worldwide, patients have been described on every continent[66]. Most cases are sporadic, but there are around 5% of multiplex families (two affected individuals in the family, including several pairs of twins) [73].

3.5. Pathophysiology

The cause of KLS is unknown. The clinical picture is that of a recurrent encephalopathy. Functional imaging and EEG help localize the affected brain area, but not its cause. No specific virus, neuronal antibody or HLA genotype has yet been identified, and the epileptic hypothesis has been ruled out. The benefits of lithium (which has anti-inflammatory properties) and corticosteroid infusions support at least an inflammatory hypothesis [74].

In addition to young age and male sex, vulnerability factors for KLS include difficult birth/development and familial cases. One third of KLS patients had problems at birth (prematurity, long labor, hypoxia) or during development (language delay, attention deficit

disorders), a figure much higher than that of controls or parents [62, 64]. This suggests that minimal brain damage is a vulnerability factor rather than a cause, as in epilepsy or autism.

As 5 % of cases have an affected family member, there is an increased KLS risk in first-degree relatives [62]. To date, 19 multiplex families with 2 to 6 affected members, including 4 pairs of monozygotic twins have been described [73]. Familial cases are more frequent in the same generation and are clinically similar but less severe than sporadic cases [73]. The karyotype of 112 patients in France is normal in all except one with sporadic KLS boy [73]. A genome-wide association analysis in 673 patients indicates that TRANK 1 gene polymorphisms in chromosome 3 are more frequent (relative risk: 1.5) in KLS patients than in controls, but only in those who had a difficult birth and who were born before 1990 [75].

3.6. Tests

3.6.1. EEG

The EEG is abnormal in 70% of patients during episodes, including a slowing of the alpha rhythm, or slow delta or theta waves, isolated or in burst, generally in the temporal or temporofrontal areas. [69]. Rare cases of sharp waves or spikes without epileptic characteristics have been observed. EEG also helps to exclude the differential diagnosis of epilepsy.

3.6.2. Polysomnography

Although hypersomnia is a cardinal symptom in KLS, its objectivation by sleep studies is difficult, whether or not combined with MSLT, depending on the duration of the recording (one night or 24 hours), and on the time of recording during the episode (beginning or end of the episode) and during the course of the disease (first or later episodes). Frank sleep excess between 14 and 22 h of sleep per day have been occasionally reported [61, 76, 77]. Mean nocturnal sleep time is prolonged during attacks (568 min versus 384 min during an asymptomatic period). Sleep architecture may be altered, with reduced sleep efficiency, frequent awakenings, increased N1 and

N2 stages, and decreased N3 and REM sleep stages [63] [69]. Aspects of "subwakefulness" including N1 stage alternating with wakefulness have also been described. As the disease progresses, patients sleep less but remain in bed with their eyes closed. The results of MSLT depend on patient compliance, as many sleep between tests. They may be normal or abnormal, with short latencies or even REM sleep onset. This test is not discriminatory [78].

3.6.3. Brain imaging

Morphological brain MRI is normal. Functional imaging by brain scintigraphy or fluorodeoxyglucose position emission tomography on the other hand, are more demonstrative, showing hypoactivity in the thalamus region [79] and, to a lesser degree, the hypothalamus, frontal and medial temporal regions and the right or left temporo-parietal junction [65]. These abnormalities are present both during symptomatic and asymptomatic periods. The fluorodeoxyglucose position emission tomography is easy to perform and helpful during asymptomatic periods. It documents a mild hypometabolism in the hippocampus and posterior cortical associative regions in 70% of patients [80] (**Figure 3**). Because such areas are not affected in patients with bipolarity or other sleep disorders, the test can help to rule out difficult differential diagnoses.

3.6.4. Cerebrospinal fluid

Standard CSF analysis is normal. Hypocretin levels are normal or decreased (but not absent, as in narcolepsy type 1) during episodes, and normalize after the episodes [67]. However, it hardly explain the severity of hypersomnia.

3.7. Differential diagnoses

During the first episode, patients are usually brought to the emergency unit, and undergo a standard workup for acute confusion and behavioral disorders (often including EEG, brain imaging, a tox screen, alcohol levels and ammoniemia). A lumbar puncture is usually performed to check for meningitis (such as herpetic meningoencephalitis), particularly in the presence of fever, or autoimmune encephalitis. All these tests are normal in KLS. Continuous symptoms rule out the diagnosis, at least in the early stages of the disease. Remittent disorders with neuropsychiatric expression include mood disorders (including short-cycle bipolarity), autoimmune encephalopathies and metabolic disorders. The most common disorders that we have observed when a suspected KLS case was referred to our center are indicated in **Figure 4.**

3.8. Treatment

3.8.1. General

As a rare disease with no formal, labelled management, we recommend that all patients with suspected KLS should be referred at least once to one of the French reference centers (**Table 4**). The multidisciplinary team in the center confirms the KLS diagnosis, evaluates residual cognitive, sleep and psychological symptoms, answers many questions that patients and parents may have about the disease (including triggers, genetic risk, academic adjustment, driving ability, patient association, plan if going abroad...), and enables them to discuss the management of future episodes and the need for further treatment, depending on the impact on daily life. It is important not to underestimate the impact of these attacks on the daily life of teenagers at a pivotal moment in their life, and the upheaval they can cause in a family. Simple recommendations on lifestyle and home layout can help patients and their families feel more reassured.

3.8.2. Episode management

During episodes, patients should be left quiet in their room, often in the dark, under the family supervision, to limit the behavioral troubles. Driving is not allowed. Minimal hygiene, food and drinking should be provided. Hospitalization is needed in case of suicidal ideas, major aggression or severe psychotic/manic-like symptoms, after a psychiatric evaluation. Symptomatic treatment includes anxiolytic if anxious, paracetamol or acetazolamide in case of headaches, and risperidone in case of delusional ideas. Amantadine or prednisone can be tried to limit episode duration at least once, although benefit is variable. One third of patients has long (> 1 month) episodes. In this case only, intravenous prednisolone (1 g for 3 days) yields a 40-60% benefit in reducing the duration of episodes without any major adverse effects [81].

3.8.3. Long term prevention

Avoiding alcohol intake and infection (including via regular seasonal flu vaccination) and keeping regular sleep schedule and sufficient sleep time help reducing the relapses. During asymptomatic periods, adaptation of school, academic or professional goals may be needed, as well as cognitive remediation and psychological support.

When episodes are frequent, incapacitating or prolonged, preventive treatment may be proposed, notably with lithium therapy, as 30% of patients become episode-free, and over 50% have less frequent and shorter-lasting episodes [74]. Lithium can be discontinued after a several episodes-free years and after the age of 30. Valproate, carbamazepine and lamotrigine appear less effective than lithium in our experience. In the case of menstruation-associated KLS, estrogen-progestogens blocking the hypothalamic axis can be tried [68]. Because these drugs are all off labelled, the advice of a reference center is strongly recommended.

3.9. Conclusion

KLS is a neuropsychiatric entity whose main symptoms (hypersomnia, derealization, apathy, confusion) appear abruptly in young subjects, last a few days to a few weeks, then fade, before

returning a few months later, for 4 to 14 years. New contributing factors (perinatal problems, TRANK 1 gene mutation, frequency of family cases) have been identified, which should help, along with patient cohorts, to determine the cause and treatment. In the meantime, treatment consists essentially of meeting and explaining the diagnosis, monitoring the patient during episodes, limiting the recurrence of seizures with lithium and their long duration with corticosteroid boluses, and supporting families.

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Legend of the figures

Figure 1. Hypnograms during 18-hr sleep monitoring for a healthy control (A) and a patient with idiopathic hypersomnia (B) illustrating sleep excess. The x-axis represents the time from 10 PM to 5 PM the next day, and the y-axis represents the sleep stages (A: awake; R: REM sleep; 1: stage N1, 2: stage N2, 3 and 4: stage N3. Note 6 sleep cycles in the normal subject and 8 cycles n the IH patient.

Figure 2. Normal values of total sleep time during 18h of unlimited sleep monitoring in 70 patients with idiopathic hypersomnia (IH, red circles) and 30 healthy controls (blue triangles). The dotted green line corresponds to 662 min, the limit with the best accuracy to distinguish IH patients from healthy controls. Detailed measures in [12].

Figure 3. Functional imaging in Kleine-Levin syndrome (KLS) in three patients. In fluorodeoxyglucose positron emission tomography during asymptomatic periods, 30% of patients with KLS have a normal imaging (A), but 70% have mild (B) to marked (C) hypometabolisms in the hippocampus (B: left side, slice # 22; C: left and right sides, slice #23) and associative temporo-parieto-occipital cortex (B: left side, slices#26-27; C: left and right sides, slices #25-26). Colour code: red (normal); yellow (mild/moderate hypometabolism); yellow/green severe hypometabolism. Hypometabolism is associated with younger age, recent (<3 y) disease course, and a higher number of episodes during the preceding year. Hypometabolisms affect 86% patients during an episode.

Figure 4. Differential diagnoses of Kleine-Levin syndrome, depending on main symptoms.

Table 1 - Diagnostic criteria of idiopathic hypersomnia and notes (International Classification of Sleep Disorder-3 R, 2023)

Criteria A-F must be met:

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.[1]

B. Cataplexy is absent.

C. Polysomnography and multiple sleep latency test (MSLT) findings are not consistent with a diagnosis of narcolepsy type 1 or 2.[2]

D. The presence of at least one of the following:

1. The MSLT shows a mean sleep latency of ≤ 8 minutes.
2. Total 24-hour sleep time is ≥ 660 minutes (typically 12–14 hours)[3] on 24-hour polysomnographic monitoring (performed after correction of chronic sleep deprivation), or by wrist actigraphy in association with a sleep log (averaged over at least seven days with unrestricted sleep).[4]

E. Insufficient sleep syndrome is ruled out (if deemed necessary, by lack of improvement of sleepiness after an adequate trial of increased nocturnal time in bed, preferably confirmed by at least a week of wrist actigraphy).

F. The hypersomnolence and/or MSLT findings are not better explained by another sleep disorder, other medical or psychiatric disorder, or use of drugs or medications.

Notes

[1]Severe and prolonged sleep inertia, known as sleep drunkenness (defined as prolonged difficulty waking up with repeated returns to sleep, irritability, automatic behaviour, and confusion) and/or long (> 1 hour), unrefreshing naps are additional supportive clinical features.

[2]A high sleep efficiency (≥ 90%) on the preceding polysomnogram is a potentially supportive finding (as long as sleep insufficiency is ruled out).

[3]The total 24-hour sleep time required for diagnosis may need to be adapted to account for normal changes in sleep time associated with stages of development in children and adolescents as well as for variability across cultures in all age groups.

[4]Occasionally, patients fulfilling other criteria may have an MSLT mean sleep latency longer than 8 minutes and total 24-hour sleep time shorter than 660 minutes. Clinical judgment should be used in deciding if these patients should be considered to have IH. Great caution should be exercised to exclude other conditions that might mimic the disorder. A repeat MSLT at a later date is advisable if the clinical suspicion for IH remains high.

[5]

Table 2- Idiopathic hypersomnia severity scale

On the basis of your symptoms during the past month:

1. What for you is the ideal duration of night-time sleep *(at the weekend or on holiday, for example)?*
   - 3 □ 11 hours or more
   - 2 □ more than 9 hours and less than 11 hours
   - 1 □ between 7 hours and 9 hours
   - 0 □ less than 7 hours

2. When circumstances require that you get up at a particular time in the morning *(for example for work or studies, or to take the children to school during the week),* do you feel that you have not had enough sleep*?*

   3 □ always 2 □ often 1 □ sometimes 0 □ never

3. Is it extremely difficult for you, or even impossible, to wake in the morning without several alarm calls or the help of someone close?

   3 □ always 2 □ often 1 □ sometimes 0 □ never

4. After a night's sleep, how long does it take you to feel you are functioning properly after you get up *(in other words fully functional, both physically and intellectually)*?
   - 4 □ 2 hours or more
   - 3 □ more than 1 hour but less than 2 hours
   - 2 □ between 30 minutes and 1 hour
   - 1 □ less than 30 minutes
   - 0 □ I feel I am functioning properly as soon as I wake up

5. In the minutes after waking up, do you ever do irrational things and/or say irrational things, and/or are you very clumsy *(for example, tripping up, breaking things or dropping things)*?

   3 □ always 2 □ often 1 □ sometimes 0 □ never

6. During the day, when circumstances allow, do you ever take a nap?
   - 4 □ very often (6-7 times a week)
   - 3 □ often (4-5 times a week)
   - 2 □ sometimes (2-3 times a week)
   - 1 □ rarely (once a week)
   - 0 □ never

7. What for you is the ideal length of your naps *(at the weekend or on holiday, for example)?*
Note: If you take several naps, add them all together
   - 3 □ 2 hours or more
   - 2 □ more than 1 hour and less than 2 hours
   - 1 □ less than 1 hour
   - 0 □ no naps

8. In general, how do you feel after a nap?

   3 □ very sleepy 2 □ sleepy 1 □ awake 0 □ wide awake

9. During the day, while carrying out activities that are not very stimulating, do you ever struggle to stay awake?
   - 4 □ very often (at least twice a day)
   - 3 □ often (4-7 times a week)
   - 2 □ sometimes (2-3 times a week)

1 □ rarely (once a week or less)
0 □ never

10. Do you consider that your hypersomnolence has an impact on your general health (*i.e. lack of energy, no motivation to do things, physical fatigue on exertion, decrease in physical fitness)*?
4 □ very significant 3 □ significant 2 □ moderate 1 □ minor 0 □ no impact

11. Do you consider that your hypersomnolence is a problem in terms of your proper intellectual functioning *(i.e. problems with concentration, memory problems, decrease in your intellectual performance)*?
4 □ very significant 3 □ significant 2 □ moderate 1 □ minor 0 □ no problem

12. Do you consider that your hypersomnolence affects your mood *(for example sadness, anxiety, hypersensitivity, irritability)*?
4 □ very severely 3 □ severely 2 □ moderately 1 □ slightly 0 □ not at all

13. Do you consider that your hypersomnolence prevents you from carrying out daily tasks properly *(family-related or household tasks, school, leisure or job-related tasks)*?
4 □ very significantly 3 □ significantly 2 □ moderately 1 □ slightly 0 □ not at all

14. Do you consider that your hypersomnolence is a problem in terms of your driving a car?
4 □ very significant 3 □ significant 2 □ moderate 1 □ minor 0 □ no problem
□ I do not drive

Total score: 0-50. The scale has 3 dimensions including long sleep time/sleep inertia (items#1, 2, 3, 4 and 8), napping (Items #6,7), and daytime functioning (Items #5, #9-14). A score >22/50 discriminates IH from healthy controls [21, 22]

Table 3 - Diagnostic criteria of Kleine-Levin syndrome

International Classification of Sleep Disorder-3 R, 2023

Criteria A-E must be met

A. The patient experiences at least two recurrent episodes of excessive sleepiness and sleep duration, each persisting for two days to several weeks.

B. Episodes recur usually more than once a year and at least once every 18 months.

C. The patient has normal alertness, cognitive function, behaviour, and mood between episodes, at least during the first years of the syndrome.

D. The patient must demonstrate at least one of the following during episodes:

1. Cognitive dysfunction.
2. Derealization.
3. Major apathy (i.e., severely reduced motivated behaviour).
4. Disinhibited behaviour (such as hypersexuality or hyperphagia).

E. The hypersomnolence and related symptoms are not better explained by another sleep disorder, other medical, neurologic, or psychiatric disorder (especially bipolar disorder), or use of drugs or medications.[5]

Table 4: Reference centres for Kleine-Levin syndrome in France

Adults and teenagers aged 15 and more :

Pitié-Salpêtrière Hospital (Pr Arnulf), Paris.

Gui de Chauliac Hospital (Pr Dauvilliers), Montpellier

Children

Robert Debré Hospital (Dr Lecendreux), Paris.

Woman, mother and child hospital (Pr Franco), Lyon.