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HYPERSOMNIA DISORDERS (D PLANTE, SECTION EDITOR)

An Update on Kleine–Levin Syndrome

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Abstract

Purpose of Review Kleine–Levin syndrome (KLS) is a rare relapsing–remitting sleep disorder distinguished by recurrent periods of severe hypersomnia accompanied by cognitive, mood, and behavioral changes. This review focuses mainly on the most recent developments and articles concerning this illness in the preceding five years while attempting to provide a basic overview of KLS.

Recent Findings Genetic links were reported in some patients with KLS, like variation in TRANK1 in a worldwide case–control genome-wide association in patients with KLS, in addition to several uncommon variations in the LMOD3 gene, some of which are likely to be pathogenic, discovered by linkage analysis and exome sequencing in a sizable Saudi Arabian family with KLS and a European cohort of KLS patients. Additionally, recent data indicate that the amplitude of the circadian active/rest cycles significantly decreased during hypersomnia attacks, but during asymptomatic periods, it did not differ significantly from the controls. Moreover, patients with KLS are at a higher risk of developing emerging psychiatric disorders during follow-up. Recent data also points to possible discoveries of diagnostic-potential dysregulated proteomic patterns in KLS. Finally, new data suggest that functional imaging studies are often abnormal in KLS both during and between episodes.

Summary KLS is an uncommon, severe, and uniform illness. When it comes to the diagnosis and treatment of KLS, these characteristics offer both opportunities and challenges. Over the past five years, some promising work has appeared in genetics, functional imaging, and biomarker identification; nevertheless, these areas still need more focus to advance the detection and treatment of patients suffering from KLS.

Keywords Hypersomnia · Hyperphagia · Hypersexuality · Sleepiness · HLA-type · Hypersomnolence

Introduction

Kleine–Levin syndrome (KLS) is a rare relapsing–remitting sleep disorder characterized by recurrent episodes of severe hypersomnia accompanied by cognitive, mood, and behavioral alterations, such as hyperphagia, hypersexuality, confusion, derealization, and apathy [1, 2•]. Patients usually experience recurrent attacks, which typically last a few days to several weeks. Episodes are typically separated by weeks or months of normal sleep and behavior [3]. Patients vary in how severe their symptoms are and how the syndrome progresses [1].

This review is not intended to comprehensively appraise the literature on all aspects of KLS. It rather aims to provide a general overview of KLS while concentrating primarily on the most recent updates and publications related to this condition in the previous five years.

Search Methods

KLS was searched for in all articles published in the PubMed and Google Scholars databases. In the PubMed database, articles were searched for up to September 2022 using the following search terms: "Kleine-Levin

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syndrome"[MeSH Terms] OR ("kleine-levin"[All Fields] AND "syndrome"[All Fields]) OR "kleine-levin syndrome"[All Fields] OR ("Kleine"[All Fields] AND "Levin"[All Fields]. Overall, we found 430 articles, of which 337 were in English. These papers were reviewed for their applicability to the fields of KLS genetics, functional imaging, and biochemistry (cerebrospinal fluid (CSF) and serum); we mainly focused on new data over the last five years, which constituted 40 papers. We included all age groups and excluded papers written in languages other than English.

Although we targeted papers published after 2018, important studies published before 2018 were also included. Moreover, relevant publications were traced by looking through the references of recovered articles (backward search) and for more recent papers that cited the retrieved paper (ahead search). To determine eligibility and extract study data, the two writers independently reviewed each of the retrieved papers. Discussion and agreement between the two authors were used to settle any disagreements.

Diagnosis of Kleine–Levin Syndrome

In the latest International Classification of Sleep Disorders (Third Edition; ICSD-3) [3], KLS was considered a subgroup of central disorders of hypersomnolence. The eponymous term "Kleine-Levin syndrome" was preferred over "recurrent hypersomnia." Menstrual-related hypersomnia is now considered a subtype of KLS [1, 3].

KLS is a clinical diagnosis based on the clinical features of episodic hypersomnia with characteristic cognitive and behavioral changes after excluding alternative sleep, psychiatric, neurologic, and toxic or metabolic etiologies. Table 1 presents the diagnostic criteria for KLS as per the ICSD-3 [3].

Epidemiology

KLS is an uncommon condition, with an estimated prevalence of 1–5 cases per million people [4–8]. Males are significantly more likely to be affected than females; about 70–90% of patients are males [8]. Although cases with adult onset have been reported, the disease mainly affects teenagers [8]. Patients with KLS have been reported in different races and geographical locations; however, there is an over-representation of the disease among Ashkenazi Jews [9, 10•].

In a case series of 108 patients with KLS, Arnulf et al. discovered that 25% had birth complications (such as prolonged labor, hypoxia, or premature or delayed birth), and 15% had developmental delays [9]. However, only 7% of controls and 8% of parents of patients with KLS had birth problems. Patients with KLS were also more likely to have specific or likely genetic disorders, such as Klinefelter's syndrome, von Willebrand syndrome, polycystic kidney disease, mental retardation combined with a family history of optic atrophy and ataxia, or autism and developmental delay without a known cause than controls [9, 11••].

Etiology: Proposed Mechanisms

The etiology of KLS remains unknown but is likely to involve many factors and mechanisms [1, 2•]. Below, we discuss the proposed mechanisms and the latest updates.

Genetic Factors

Even though no specific genes have been definitely ascertained, the relatively significant number of cases among the Ashkenazi Jews, in addition to several reports of familial cases, including monozygotic twins, raises the likelihood

Table 1 Diagnostic criteria for Kleine–Levin syndrome (ICSD-3)

Criteria A to 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 five weeks
B. Episodes usually recur more than once a year and at least once every 18 months
C. The patient has normal alertness, cognitive function, behavior, and mood between episodes
D. The patient must demonstrate at least one of the following during episodes:
- Cognitive dysfunction
- Altered perception
- Eating disorder (anorexia or hyperphagia)
- Disinhibited behavior (such as hypersexuality)
E. Hypersomnolence and related symptoms are not better explained by another sleep disorder, other medical, neurologic, or psychiatric disorder (especially bipolar disorder), other use of drugs or medications

of some genetic involvement [1, 2•, 9, 12–14]. Furthermore, there is evidence that KLS has a hereditary component since first-degree relatives have an 800–4000-fold higher chance of developing the condition [12].

However, the majority of reported KLS cases are still sporadic, with familial cases accounting only for approximately 8% of patients with KLS [5, 9, 15].

Many papers have described the presence of HLA locus polymorphisms in KLS [1, 2•, 16]. Polymorphisms in tryptophan hydroxylase and catechol-O-methyltransferase have also been investigated, in view of the proposition that KLS could rise from abnormalities in central serotonin and dopamine metabolism, but this link could not be proved [1, 2•, 17].

A relationship with a genetic variation in TRANK1 was identified by a worldwide case–control genome-wide association (GWAS) study in 673 patients with KLS [11••]. The TRANK1 gene locus was formerly linked to bipolar disorder and schizophrenia and has been linked to circadian regulation as well [18]. The KLS-GWAS study also revealed that variants in the TRANK1 gene region might also predispose to KLS if patients have had a difficult birth, implying that the TRANK1 gene region affects newborns' response to brain injury, which can lead to mental and neurological health consequences in adulthood [11••]. In addition, several uncommon variations in the LMOD3 gene, some of which are likely to be pathogenic, were discovered by linkage analysis and exome sequencing in a sizable Saudi Arabian family with KLS and a European cohort of KLS patients [19••, 20]. However, the above GWAS study revealed no correlation between LMOD3 polymorphisms and KLS [11••]; nevertheless, LMOD3 variants were not thoroughly investigated in the whole study sample. Additionally, replication was done by imputation rather than by evaluating genuine polymorphisms.

Infectious and Immune-Mediated Theories

An infectious or immune-mediated cause has been proposed following recurrent reports of infectious-like symptoms preceding the onset of the illness, as several lesions have been found in autopsies [2•, 17]. Most cases of KLS indicate a possible trigger before the onset of symptoms, which is infectious in origin in more than two-thirds of the cases; manifestations suggestive of infection like flu, fever, colds, or gastroenteritis have been reported as a recognizable trigger just before the first episode [12, 21, 22].

Older reports suggested the presence of inflammatory infiltrates in certain brain regions, such as the thalamus [23], the diencephalon, and the midbrain [24], and a tiny locus ceruleus with diminished substantia nigra pigmentation [25].

A close connection between the immune system and sleep-regulating mechanisms has been suggested, such as the link between narcolepsy and particular human leukocyte antigen (HLA) antigens [26]. Therefore, a similar association between KLS and HLA has been proposed. The subtype DQB1*02 has been reported to be associated with KLS [5, 16]; however, this has not been replicated in larger reports [2•, 9, 22, 27].

Neuropathological Causes

Some patients with diencephalic-hypothalamic malfunction caused by tumors were noted to have symptoms similar to patients with KLS; this raised the possibility of hypothalamic involvement in the development of the disease [2•, 17]. The temporal and frontal lobes also seem to play a role, possibly through cognitive and behavioral changes that are observed in some patients suggesting that the condition might have frontal lobe involvement as well [28]. This connection between the thalamus, hypothalamus, temporal lobe, and frontal lobe of the brain suggests that there could be multifocal encephalopathy [12]; however, this possible association needs more studies to confirm it.

In summary, although genetics, inflammatory, and autoimmune origins have been hypothesized, the KLS mechanisms remain unknown.

Precipitating Factors

A few possible factors have been thought to precipitate hypersomnia episodes. Seasonal variation has been observed, with the first episodes usually happening in autumn or winter [2•, 9]. Few reports identified mild infection, alcohol ingestion, head trauma, physical exertion, stress, and sleep deprivation as possible predisposing factors [2•, 6, 9, 22, 29–31]. Vaccination, including typhoid, tuberculosis, human papillomavirus, H1N1 influenza, and tetanus, has also been reported to precede KLS onset [9, 32, 33]. Recently, the SARS-CoV2 vaccine has been reported to be associated with KLS relapse in some patients [21, 34].

Clinical Features

KLS is mainly characterized by the intermittent and periodic nature of its symptoms (see Table 2). During episodes, symptoms evolve quickly and would usually peak within 24 h. The episodes typically last between 1 and 3 weeks [2•, 7], and the time from the onset of one episode to the other is 60 to 100 days [29]. Patients could complain of insomnia near the end of an episode, and when the symptoms resolve, some patients could experience a state of relief and even euphoria [8].

Episodic hypersomnia is the major feature of KLS. Cognitive impairment, derealization, and severe apathy are

Table 2 Common symptoms in patients with Kleine–Levin syndrome

– Hypersomnia
– Cognitive impairment
– Derealization
– Apathy
– Hyperphagia
– Disinhibition and hypersexuality
– Mood disturbances

commonly present during episodes. However, it is important to note that the classic triad of hypersomnia, hyperphagia, and hypersexuality is not always present [9].

Recently, Lin et al. [35••] intended to evaluate the circadian rhythm and monitor the movements of patients with KLS using actigraphy. The study showed no significant difference in circadian rhythm between KLS patients in the asymptomatic period and healthy controls [35••]. Although there were significant differences in the day-to-night activity rhythm assessed by parametric and nonparametric analysis during hypersomnia attacks, the "amplitude" of this difference dropped considerably [35••]. Twenty-four hours of day–night motor activity cycle was weakened during hypersomnia attacks, and although day–night active/rest motor activity cycle was still observed, there was a disruption in the fractal regulations of active–rest rhythm especially for the short-term fractal control (< 4 h) [35••]. Moreover, the daytime and night time activities were diminished the most at the beginning of the hypersomnia attack, whereas a significant rise in daytime activity and the most active continuous 10 h were observed during the end of the attack [35••]. Overall, the study showed that the amplitude of the circadian active/rest cycles significantly decreased during hypersomnia attacks, but during asymptomatic periods, it did not differ significantly from the controls.

These results need to be confirmed by additional research using a larger patient group in conjunction with gene analysis and monitoring of circadian rhythm markers, such as melatonin.

Cognitive impairment is the second most encountered symptom after hypersomnia. A recent systematic review studied cognitive dysfunction in central disorders of hypersomnolence, including KLS [36••]. The review revealed that patients with KLS have reduced memory capacity (digit and listening span) and reduced declarative memory; on the other hand, visuospatial memory, procedural memory, and verbal learning were not affected [36••]. Working memory also appeared compromised in KLS patients who made more errors, recalled fewer words, and showed slower reaction times [36••]. KLS patients' executive functions and higher-order cognition were comparable to controls in tasks measuring inhibition, shifting, flexibility, and verbal fluency, but patients with KLS were noted to have lower non-verbal IQ scores than controls [36••].

Many patients describe a feeling of derealization during episodes, with a dream-like feeling. Derealization is common and could be the most specific symptom of the syndrome [2•, 9, 10•]. Patients also describe altered perceptions of sight, sound, smell, taste, temperature, and pain [12].

Apathy is another prominent and prevalent symptom during KLS attacks, which has been reported by more than 90% of patients [10•, 33]. There is usually a lack of motivation for nearly all activities, such as engagement in any social activities, reading, and using mobiles. The majority of patients will neglect their hygiene during episodes [2•, 33].

The majority of patients also tend to eat compulsively and in large amounts. This disinhibited behavior is usually directed to a specific type of food (e.g., sweet). Some patients would eat any food they see [2•].

However, nearly one-third of patients report losing their appetite and could eat less during some episodes. Those patients tend to experience more severe hypersomnia than those with hyperphagia [8].

Hypersexuality is a known symptom of KLS that is observed more in boys than in girls. Although hypersexuality is frequently highlighted as a critical symptom of KLS, it is likely to be another feature of disinhibition that is typical of KLS episodes [2•, 10•, 22]. Symptoms include increased sexual drive, sexual comments, inappropriate sexual behaviors, and frequent masturbation [8].

Contrary to the supposedly benign nature of KLS and the assumed normality between episodes, recent data suggest an increased risk of mood disorders in patients with KLS [11••, 37••]. In order to diagnose past and present concomitant psychiatric problems, patients with primary KLS ($n = 115$) received psychiatric interviews at diagnosis and yearly for 1–10 years [37••]. The study demonstrated that one KLS patient in five developed emerging psychiatric disorders [37••]. Developing these disorders is affected by personal susceptibility and is most likely related to psychiatric symptoms during episodes [37••].

Menstrual Recurrent Hypersomnia

Menstrual recurrent hypersomnia (MRH) is a very rare type of recurrent hypersomnia [3, 29]. However, the ICSD-3 considers MRH a variant of KLS [3], because both seem to be related to menstruation, making it challenging to differentiate between typical KLS and MRH. Compared to typical KLS, episodes of MRH tend to be shorter, less likely to affect cognitive function, and could occasionally show a response to estrogen-containing contraceptives [29].

Evaluation and Investigations

Because the syndrome is rare and its symptoms are nonspecific, patients who are suspected of having KLS should be investigated for other possible causes. Evaluating patients with KLS should include obtaining a detailed medical history from patients and family members. In addition, special attention should be paid to fluctuations in patient's cognitive abilities and behaviors. The physical examination is typically unremarkable in patients with KLS with no specific neurologic or psychiatric findings [6]. The presence of any abnormalities should raise the possibility of an alternative diagnosis [6].

In the next section, we will review areas in the investigation where new data is available.

Cerebrospinal Fluid and Biochemistry

Laboratory investigations should be done according to patients' symptoms and possible differential diagnoses. No distinctive cerebrospinal fluid (CSF), blood, or urine abnormalities exist in patients with KLS. Despite the possible autoimmune etiology, the serum and the CSF inflammatory markers do not show signs of inflammation [1, 2•, 38].

A recent study identified proteomic KLS biomarkers with possible diagnostic potentials by investigating the proteomic architecture of CSF and serum proteins in patients with KLS and controls [39••]. In univariate analyses, 28 and 141 proteins were differentially expressed in the CSF and serum, respectively. Upregulated CSF proteins included IL-34, IL-27, TGF-b, IGF-1, and osteonectin, while DKK4 and vWF were downregulated. Pathway analyses showed microglial changes and disruption in blood–brain barrier permeability. Serum profiles showed upregulation of Src-family kinases (SFKs), proteins implicated in cellular growth, motility, and activation [39••]. Tissue enrichment analysis of up- and downregulated proteins revealed changes in brain proteins, particularly from the pons, medulla, and midbrain[39••]. Moreover, differences in proteomic makeup in both CSF and serum were observed between in-episode and during-episode samples [39••].

Polysomnography

In general, polysomnography (PSG) is not indicated in patients with KLS; moreover, data related to PSG in patients with KLS are limited because of the disease's rarity, poor patient compliance, and loss of follow-up [40•]. However, studies that performed PSG during episodes reported variable findings; yet, the sleep structure was mostly unremarkable [40•].

PSG findings are possibly affected by the time of the sleep study in relation to the hypersomnia episode, the disease course, and the period of observation during the sleep study. Total sleep time is mostly increased (9 to 12 h) [40•]. Sleep studies performed later in the course of the disease showed that patients would spend 3 to 9 h per day in a withdrawal state with eyes being closed and an awake EEG pattern [41].

A study that assessed sleep via PSG during the course of a hypersomnia episode demonstrated a slight decrease in slow-wave sleep during the first half of the KLS episode, and a reduction in REM sleep during the second half of the episode [42]. To better link functional changes across the course of a hypersomnia attack, the sleep phenotype, and disease dynamics, a longitudinal PSG time course study may be combined with functional imaging tests like functional magnetic resonance imaging (MRI) [40•]. Between hypersomnia attacks, PSG in patients with KLS is generally normal [40•].

Due to the limited reports of complete PSG performed during and between hypersomnia episodes of KLS, there is scarce data on the prevalence of different dyssomnias during sleep, such as sleep-disordered breathing. Nevertheless, there are few case reports about the presence of sleep-disordered breathing in patients with KLS [43, 44]. Various forms of abnormal breathing patterns during sleep have been reported in patients with KLS, including periodic breathing and hypopneic episodes associated with brief arousals [44]. To explore if breathing problems while sleeping constitute an additional clinical hallmark of KLS, thorough sleep studies with a focus on breathing patterns during episodes of hypersomnia are needed.

Neuroimaging

Brain structural imaging using MRI and computed tomography (CT) are typically normal in patients with KLS [1, 2•, 6, 45], although some minor abnormalities have been described (e.g., frontal cysts, cortical, and cerebellar atrophy), those abnormalities are believed to be incidental findings [1, 2•, 8, 46]. However, more recent data suggest that functional imaging studies are frequently abnormal in patients with KLS both during and between episodes. A recent systematic review looked into the neuroimaging characteristics of patients with KLS and their clinical correlates and included ten studies [47••]. It showed that in individuals with KLS, functional MRI (fMRI) investigations vary both during symptomatic and asymptomatic times and in the intervals between episodes. The hypothalamus and thalamic regions were the most affected and displayed hypoperfusion and hyperperfusion in a few rare cases. Changes in cerebral perfusion were also documented in the frontal,

parietal, occipital, and prefrontal cortex [47••]. In addition, the changes in cerebral blood flow varied depending on the imaging method used (SPECT (single-photon emission computerized tomography), PET SCAN (positron emission tomography), or fMRI) [47••].

Reduced thalamic activity was linked to hypersomnia during the symptomatic phases. Moreover, functional imaging alterations were also associated with other KLS symptoms, such as apathy, hypersexuality, and depersonalization [47••]. Additionally, there were results connected to the deficiencies in working memory observed at this point during the asymptomatic intervals. The major characteristics observed during the asymptomatic period were hyperactivity of the thalamus and hypothalamus [47••]. Functional imaging also appears to improve as the disease progresses, showing that patients with KLS outgrow the condition [47••]. The authors concluded that these findings should warn doctors who analyze and correlate neuroimaging results with the disease [47••].

In a recent study among 138 untreated patients with KLS examined during asymptomatic periods, Dudoignon et al., in a cross-sectional study, assessed the frequency, localization, and clinical determinants of hypo- and hypermetabolism using 18F-fluorodeoxyglucose PET/CT [48•]. Up to 70% of patients showed hypometabolism, primarily impacting the hippocampus and posterior associative cortex. Younger age, a recent disease course (less than three years), and more episodes in the year prior were all related to hypometabolism [48•]. At the onset of the condition, there was more hypometabolism (from the left temporooccipital junction to the whole homolateral and eventually the bilateral posterior associative cortex). On the contrary, hypermetabolism was documented in the prefrontal and dorsolateral cortex in half of the patients (nearly all of whom also had concurrent hypometabolism in the posterior regions) [48•]. A shorter disease course and younger age were also related to this hypermetabolism. Interestingly, patients with and without hippocampal hypometabolism showed similar cognitive abilities, including episodic memory [48•]. The authors suggested that hypometabolism in the early years of KLS may serve as a characteristic marker that may aid practitioners in diagnosing KLS [48•].

Based on the above, hypothalamic hypoperfusion could support the hypothesis that KLS embodies a disorder of diencephalic or hypothalamic function [2•]. Hypoperfusion and metabolic deficiency in the other areas do not only explain hypersomnia; they could also explain behavioral changes, including apathy, disinhibition, and inappropriate sexual behavior, and cognitive impairment [1, 2•]. Cognitive dysfunction in patients with KLS, including impairment in language, executive, and salience networks, as well as deficiencies in verbal and working memory, speech, and reading impairments, could be related to functional abnormalities in frontotemporal, and occasionally in parietal regions, which are observed in symptomatic periods and may persist in asymptomatic periods in KLS patients [49, 50]. In addition, frontotemporal dysfunction may also contribute to behavioral changes in KLS patients; another important finding is the presence of hypoperfusion in the temporoparietal junction during symptomatic episodes associated with depersonalization and derealization [51].

Treatment

There is no definitive treatment for KLS as the etiology of the disease is still unknown (see Table 3). Medications, like stimulants, have been used to address some features of the disease, such as excessive daytime sleepiness; other drugs, like lithium, have been reported to reduce the episodes' length severity and to increase the interval between episodes [17, 52••]. However, the efficacy of these drugs is questionable.

A Cochrane Review in 2016 concluded that no evidence indicates that pharmacological treatment for KLS is effective and safe [17]. Therefore, treatment is mainly supportive

Table 3 Treatment of Kleine–Levin syndrome

A. Nonpharmacologic management
1. Maintaining a simple hygiene routine Allow the patient to rest at home under supervision in a safe and comfortable environment
2. Provide a safe and comfortable environment for the patient to rest
3. Monitor patients for behavioral, cognitive, and mood disturbances, including symptoms of depression or anxiety
4. Avoid precipitating factors between episodes, including maintaining consistent sleep–wake schedules, and avoiding alcohol and contact with sick people
B. Symptom-based pharmacotherapy
1. The task force commissioned by the AASM suggests that clinicians may give lithium (vs. no treatment) for the treatment of KLS in adults (CONDITIONAL)
2. Due to lack of good evidence, using drugs for KLS patients should be individualized, considering patients' symptoms, drug side effects, pratitioner's experience, and preferences

and involves increasing awareness and understanding of the disorder.

Nonpharmacologic Management

Providing education and support is essential in the management of patients with KLS. In addition, reassurance and maintaining a simple hygiene routine with home management are usually very helpful for most patients with KLS [12].

It is imperative to provide patients with a safe and familiar environment for sleep, avoid driving, and to monitor patients for any medical or psychiatric issues. Unfortunately, there is no evidence that other therapeutic modalities, like light therapy, melatonin, and vitamin supplements, are successful [6, 9].

Symptom-based Pharmacotherapy

Numerous medications have been tried, including stimulants, amantadine, antiepileptics, antidepressants, antipsychotic medications, steroids, and clarithromycin. Some success has been recorded, but long-term participant follow-up is challenging due to the rarity of the condition [17].

The Cochrane epilepsy group attempted to systematically review randomized control trials (RTCs) to decide if pharmacological treatment for KLS was effective and safe. Unfortunately, the investigators reported that no RCTs could be located [17]. The necessity for treatment trials using a double-blind, placebo-controlled design arises from the absence of high-quality evidence; due to the rarity of the illness, a multicenter design must be utilized.

The task force commissioned by the American Academy of Sleep (AASM) suggests that clinicians may give lithium (vs. no treatment) for the treatment of KLS in adults (CONDITIONAL recommendation) [52••]. This recommendation was very low based on the critical outcome reported in one prospective, open-label, single-center study [53] that demonstrated a clinically significant improvement in the severity of the disease measured by the reduction of the total number of episodes, frequency of episodes, and their duration, as well as improvement in the quality of life, and work/school performance/attendance. Although lithium has a narrow therapeutic range and major toxicity, there were no serious adverse events reported in this study. The most common adverse effects reported were tremors, polyuria-polydipsia, diarrhea, and subclinical hypothyroidism [53]. Nevertheless, the AASM stressed that the clinical state of patients and the lithium serum levels must be monitored regularly [52••].

Therefore, as the disease course is unpredictable, studies investigating the effect of pharmacologic therapy do not show consistently positive results, and the fact that at present, no data support the efficacy and safety of any pharmaceutical treatment for KLS, using drugs for KLS patients should be individualized, considering patients' symptoms, drug side effects, practitioner's experience, and preferences.

Natural History

Most patients present in the second decade of life, with 16 years old being the mean age of onset [9]. In diseases with late onset (age of > 35 years), the patients usually have classic symptoms, but episodes tend to be longer [23, 32]; patients with earlier onset presenting < 12 years tend to have more frequent episodes [6, 9, 54–56].

Symptoms during episodes evolve quickly within hours to days, with a median duration of 10 days [6, 9]. Episode duration ranges from a few days to weeks or even months. The frequency of episodes varies from one to three short episodes per year in milder cases to monthly episodes in moderate cases [6]. Severe cases could have longer episodes with higher frequency [33]. Nevertheless, over time, the frequency and intensity of KLS episodes tend to decrease particularly toward the end of the disease [47••].

It has been found that one KLS patient in five is at increased risk of developing psychiatric disorders, mainly mood disorders, bipolar disorder, and anxiety [37••]. TRANK1 gene and its vicinity have been weakly linked to bipolar disorder and schizophrenia, with a 10% greater risk, and KLS, with an increased risk of 50% [11••]. It has been proposed that possible KLS and bipolar disease might share a pathophysiological mechanism, which may explain the reported response to lithium therapy in some patients with KLS [11••]. Moreover, female sex, longer disease course, and patients with recurrent psychiatric symptoms during episodes are at the highest risk of developing psychiatric disorders [37••].

KLS patients typically return to their normal baseline between episodes and at the end of the disease course. However, an increasing proportion of patients' experience modest, persistent memory, and attention problems [6, 46, 57, 58].

Conclusion

KLS is an uncommon, severe, disabling, but uniform sleep disorder of an unknown origin. When it comes to diagnosing and treating KLS, the disease's unique characteristics offer both opportunities and challenges. Most of the available literature consists of case reports and brief clinical series; unfortunately, no clinical trials have been performed. However, over the past five years, some promising work has

appeared in genetics, functional imaging, and biomarker identification. Nevertheless, our report highlights critical information gaps in KLS immunopathogenesis, next-generation genomics, multimodal functional imaging, and clinical treatment trials. These areas still need more focus to advance the detection and treatment of patients suffering from KLS. An international biorepository must be developed with a centralized global database of affected patients to enable good clinical research.

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Declarations

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