Review Article

KLEINE LEVIN SYNDROME – AN OVERALL LITERATURE REVIEW WITH CASE STUDIES

ABSTRACT

The rare condition known as Kleine-Levin syndrome (KLS) primarily affects teenagers. Extreme somnolence is interspersed with behavioral signs, psychomental abnormalities, and megaphagia. The etiopathogenesis of this disease is unknown, although its prevalence worldwide varies between 1 and 5 cases per million people, with a predisposition for males, primarily during puberty. Relapsing-remitting periods of severe hypersomnia, cognitive impairment, apathy, derealization, and behavioral and mental health issues are the hallmarks of Kleine-Levin syndrome. It affects boys more often than it does females. The misdiagnosis and treatment of KLS as another sleep problem, neurological illness, or mental issue often understates its incidence. Males are more likely than females to have KLS, and it is more frequent during puberty than at later ages. The diagnosis of KLS is difficult since there are presently no clear imaging testing results or established biomarkers. Even though KLS is difficult, some people recover completely; however, there may be long-term psychological and cognitive repercussions. This page discusses the disorder's symptoms, risk factors, complications, diagnosis, course of treatment, and a few case stories.

Keywords: kleine-levin syndrome (KLS), somnolence, megaphagia, psychoment, hypersomnia, polysomnographic (PSG).

INTRODUCTION

A rare condition known as Kleine-Levin syndrome (KLS) is characterized by recurrent periods of hypersomnia, as well as varying degrees of compulsive eating, hypersexuality, and behavioral or cognitive abnormalities[1]. Adolescent males are the primary victims of the condition. Even though there isn't any population-based research on the prevalence of Kleine-Levin syndrome (KLS), the condition is usually regarded as extremely uncommon.

After being initially identified by Kleine in 1925 and further developed by Levin in 1936, the disease was renamed Kleine-Levin syndrome in 1942 by Critchley and Hoffman. The symptoms of hypersomnia and hyperphagia, which lasted for days to weeks at a time and recurred every few months, were described in their seminal paper, "The Syndrome of Periodic Somnolence and Morbid Hunger," by two males in their 20s. The symptoms of one of those individuals appeared six months after receiving a vaccine. In the other case, there was no trigger. The hypothalamus and frontal lobes may be affected by a mild form of encephalitis, according to the authors' hypothesis[2]. The international classification of sleep disorders (ICSD) defined kleine-levin syndrome in 1990. When the international classification of sleep disorders (ICSD) – revision 2 (ICSD-2) was released in 2005, it underwent revisions to become its current form[3].

SYNONYMS

- Sleeping beauty syndrome
- Familial hibernation syndrome
- Kleine-levin hibernation syndrome
- Periodic somnolence and morbid hunger

HISTORIOGRAPHY

An early account of the disease may have come from a report in 1815 about a young man who had a fever, increased appetite, and protracted slumber. Brierre de Boismont reported a case with the same symptoms in 1862[4]. A detailed description of five individuals exhibiting persistent tiredness was provided in 1925 by Frankfurt-based neurologist Willi Kleine. Details of a comparable case by psychiatrist Max Levin, who is based in New York, were released four years after this report. Levin provided details of five other occurrences in 1935, one of which Kleine had mentioned. Levin observed that, in addition to their chronic fatigue, some patients also showed signs of excessive appetite. In a 1962 publication, Macdonald Critchley—who had written on the illness for the first time in 1942—described 11 cases he had looked at and evaluated 15 other examples that had been published. He noted that agitation and depersonalization frequently happened when patients were conscious in the paper, which featured cases he had evaluated in the Royal Navy during World War II. Four characteristics he identified as common to the disorder—hypersexuality, spontaneous resolution, adolescent onset, and obsessive eating—he dubbed it Kleine-Levin syndrome. He thought the illness primarily afflicted men, but later research revealed some cases were female. Numerous psychoanalytic and psychodynamic theories were put out to explain the illness in the 1970s. Nine of the Hawaiian-Caucasian family's members were discovered to have the illness in 1980. Schmidt developed the diagnostic standards for Kleine-Levin syndrome (KLS) in 1990, and the International Classification of Sleep Disorders improved upon them[7]. Kleine-Levin syndrome (KLS) is categorized as a type of sleep disorder, more precisely as recurrent hypersomnia. Prior to 2005, it was believed that hyperphagia and hypersexuality would always occur. The rules next year amended that, pointing out that they didn't always happen.

EPIDEMIOLOGY

An estimated 1–4 occurrences of Kleine-Levin syndrome (KLS) occur for every million individuals, making it a rare disorder[9]. With between 70 and 90 percent of patients being men, men are disproportionately more likely than women to be impacted. The illness primarily affects youth, despite reports of cases with adult onset[10]. There are reports of Kleine-Levin syndrome (KLS) patients from a variety of racial and geographic backgrounds; however, Ashkenazi Jews are disproportionately affected by the illness.11 Among 108 Kleine-Levin syndrome (KLS) patients in a case series, Arnulf et al. found that 15% had developmental deficits and 25% experienced delivery problems (e.g., protracted labor, hypoxia, premature or delayed birth). Nonetheless, just 8% of parents of Kleine-Levin syndrome (KLS) patients and 7% of controls experienced delivery issues[12]. Additionally, KLS patients were more likely to have specific or probable genetic abnormalities, such as autism, polycystic kidney disease, von Willebrand syndrome, mental retardation coupled with a family history of optic atrophy and ataxia, or Klinefelter's syndrome and delayed development with no established cause compared to controls[13].

AETIOLOGY

There is no known cause of Kleine-Levin syndrome. According to certain research, the hypothalamus—the area of the brain responsible for controlling sleep—may be harmed by disease or trauma. The majority of Kleine-Levin syndrome

(KLS) cases follow an infection or a flu-like illness[14]. According to research, KLS may trigger an autoimmune reaction in which healthy tissue is mistaken for an invasive organism by the body, leading to symptoms. Additional studies indicate that KLS might be inherited and linked to mutations in the LMOD3 and TRANK1 genes.

CONTRIBUTING ELEMENTS

The initial Kleine-Levin syndrome (KLS) episode peaked in December (14.8%) and happened most frequently in the autumn (31.1%) or winter (31.1%). Ninety-nine percent of patients could recall an incident that was closely related to the onset; the most common events were infections (72%), lack of sleep (22%), unusual levels of stress (20%), vigorous activity (19%), head trauma (9%), and consumption of marijuana (6%).

CLINICAL MANIFESTATIONS

Neurological symptoms

- **Hypersomnia**

One of the primary clinical symptoms of Kleine-Levin syndrome (KLS), hypersomnia, was evident in every instance and is required for diagnosis. The duration of sleep during episodes, when recorded, varied between 12 and 24 hours per day (mean: 18.62 hours, median: 18 hours). Prodromic symptoms were extreme fatigue that came on suddenly, such as "reluctant to get up in the morning" or "feeling drawn towards bed"[15].

- **Cognitive disorders**

The majority of patients experienced cognitive problems, including memory problems, disorientation, focus, and attention issues. When questioned during episodes, these were obvious (weird question responses, for example), or they were mentioned in later interviews as recollections of past incidents. Academic decline and minor, persistent memory impairment in between episodes have been documented in a few cases. 16, 17. The frequency of temporal disorientation was double that of spatial confusion. Perceptions were always altered, affecting all senses and causing sensations of unreality and dreaminess[18,19].

- **Food behavior issues**

During episodes, eating behaviors changed for 75% of the patients. The majority tended to eat more frequently (megaphagia), preferring sweets, and made unusual meal selections. Patients had a tendency to consume every food item that was offered. A 7–30 lb (3.2–13.6 kg) weight gain was associated with increased food intake, which varied from a slight rise to "three times his usual diet" or "6–8 meals a day"[20]. There was also occasionally an increase in the consumption of juice and water, but this was never seen on its own. A small percentage of patients experienced food aversion or reduced eating during one or more episodes, yet overindulged in food during other episodes. Megaphagia and food cravings were the most important factors[21].

Neuropsychiatric symptoms

- **Hypersexuality as well as additional compulsive habits**

During episodes, over half of the patients exhibited symptoms associated with hypersexuality; men experienced these symptoms much more frequently than women. These included exposing oneself, fondling genitalia, filthy language, increasing or overt masturbating, and making unwelcome sexual advances to men. Attacks on female nurses, female guests, patients' sisters, daughters, or other female relatives, as well as three instances involving another man, were examples of inappropriate sexual advances. Throughout the episodes, there were also other compulsions that included body rocking,

chewing lips, inappropriate and obsessive singing, obsessive writing on walls and wallpaper removal, and the want to start a fire[22,23].

Psychiatric symptoms

- **Mood problems and hypersensitivity**

During episodes, half of the patients experienced depression, especially the women. Two patients made an attempt at suicide, and 15% of the patients reported having suicidal thoughts. The melancholy mood usually subsided at the conclusion of each episode, though it occasionally lingered longer. A few instances were noted to experience a brief period of hypomania following a Kleine-Levin syndrome (KLS) episode. Nearly every sufferer exhibited irritability, particularly when it came to forbidden activities like eating, sleeping, or having sex[24,25].

- **Hallucinations, delusions, and derealization**

According to the majority of patients, the most distinct symptom of the condition is a sense of unreality—that is, an impression that things are incorrect, distorted, or unreal, much like in a dream—or of disjointed thinking during episodes. Feeling "strange," "detached," or "different" were qualitative descriptions of altered perception[26]. Depersonalization, agony, and "a persistent sense of unreality and disconnection" from the surroundings were experienced along with the perception of distant voices and far-off objects. Other sensations included "a nightmarish sense of the surroundings," "an unpleasant perception, bizarre and wrong," and "the feeling of being almost in a dream"[27].

RISK FACTORS

Numerous Kleine-Levin Syndrome (KLS)-related incidents have been reported. Among them are [28]:

- a feverish cold or flu-like illness
- Head injuries
- Lack of sleep
- High levels of stress Physical effort
- Travel-related Vaccinations
- Use of alcohol with marijuana

COMPLICATIONS

1. Disturbance of daily life: relationship troubles, issues at work or at school.
2. Psychological effects: Because the disorder is unexpected and disrupts regular routines, people with KLS may feel depressed, anxious, frustrated, and alone. Therapy and psychological assistance may be necessary to address these psychological impacts, which might worsen during episodes.
3. Cognitive difficulties: Memory problems, confusion, and disorientation are examples of cognitive impairments.
4. Adverse drug reactions: Stimulant drugs are frequently used in Kleine-Levin syndrome (KLS) treatment to assist control excessive sleepiness. Increased blood pressure, an accelerated heartbeat, and sleeplessness are possible adverse effects of these drugs.

DIAGNOSIS

Guidelines for diagnosing Kleine-Levin syndrome (ICSD-3)

1. The patient has at least two bouts of extreme tiredness and duration of sleep that occur frequently and last anywhere from two days to five weeks each.
2. Episodes typically recur at least once every eighteen months and more frequently than once a year.
3. Between episodes, the patient's behavior, mood, and level of alertness are all within normal limits.
4. During episodes, at least one of the following must be displayed by the patient:

- Deficit in cognition
- Modified awareness
- Anorexia or hyperphagia as an eating disorder
- Uninhibited conduct (like hypersexuality)

5. There are no more plausible explanations for hypersomnolence and associated symptoms than another sleep problem, a different medical, neurological, or psychiatric condition (particularly bipolar disorder), or other drug or pharmaceutical use[29].

Examinations

Every instance of primary KLS had an unremarkable clinical evaluation. Specifically, it was noteworthy that there were no neurological symptoms suggestive of meningitis or a localized lesion. The primary goals of the medical testing performed on Kleine-Levin syndrome (KLS) patients were to rule out epilepsy (electroencephalogram), meningitis or encephalitis (cerebrospinal fluid analysis), and focal brain lesions (brain imaging) as potential causes.

Tests on hormones

Pituitary hormone alterations were infrequently observed in Kleine-Levin syndrome (KLS) patients. The major purpose of the thyroid, pituitary, adrenal, and blood sugar profiles was to rule out any endocrinological causes of the recurrent hypersomnia.

Interpretation of cerebrospinal fluid

In cases where recurrent hypersomnia may have been caused by an infectious etiology, a cerebrospinal fluid (CSF) investigation is performed. A few examples involved cerebrospinal fluid examinations (CSF) with differing outcomes in terms of looking for biological alterations in the cerebrospinal fluid (CSF) and determining the underlying cause of KLS. Five KLS patients had levels of hypocretin-1, a hypothalamic peptide that has been demonstrated to be lacking in narcolepsy, within normal ranges; however, two patients saw a modest reduction during an episode. One patient had elevated levels of serotonin and a serotonin metabolite.

Brain imaging and electroencephalograms

While the electroencephalogram (EEG) abnormalities in three-fourths of the patients are nonspecific and not definitive, they do allow us to narrow down the likelihood of epilepsy. While clinical symptoms persisted, polysomnographic (PSG) investigations of 17 individuals in the early stages of the disease (before the completion of the initial half of the symptomatic phase) consistently showed a significant decrease in slow-wave sleep (SWS). During the second half, slow-wave sleep (SWS) gradually returned to normal. The first and second halves of the episodes differed significantly in terms of slow-wave sleep (SWS) and REM sleep. REM sleep dropped in the second half of the episode, but it stayed normal in the first. Though most studies describe a generic diffuse slowdown of the background EEG movement, such as a slowing of the alpha frequency range towards 7–8 Hz, in 70% of the patients, this slowing was noted. Bilateral temporal or temporofrontal areas were the primary locations of less often occurring low-frequency, high-amplitude waves (delta or theta), either alone or in sequence. The omnipresent lack of epileptic activity was an astounding observation. Slightly less common but thought to have little clinical importance were sharp waves, self-limited photoparoxysmal response, and single spike discharges[31]. In every instance, magnetic resonance imaging and brain-computed tomography results were normal. A small number of individuals between the ages of 13 and 27 underwent functional imaging using single photoemission tomography, which revealed reduced blood flow in some and normal blood flow in others. The basal ganglia, in addition to the temporal or temporofrontal regions of one or both sides, saw a decline. Single photon emission computed tomography (SPECT) was used in one case report to assess hypoperfusion during the symptomatic period. The results

showed significant hypoperfusion in the basal ganglia, bilateral medial, bilateral thalami, along with dorsolateral frontal regions, the left temporal lobe, and the left hypothalamus[32].

Polysomnography, or sleep study

Generally speaking, patients with Kleine-Levin syndrome (KLS) should not undergo polysomnography (PSG); also, there is a dearth of information regarding polysomnographic (PSG) in Kleine-Levin syndrome (KLS) patients due to the rarity of illness, low patient adherence, and lack of follow-up. The sleep pattern was largely unremarkable, despite the fact that studies that used polysomnographic (PSG) throughout episodes reported varying findings. Polysomnographic (PSG) data may be impacted by the duration of the sleep study's observation period, the timing of the hypersomnia episode, and the course of the illness. Most people sleep for nine to twelve hours longer each night. Later sleep studies conducted during the duration of the illness revealed that patients would have periods of 3 to 9 hours per day in which they would withdraw, close their eyes, and have an awake electroencephalogram (EEG) pattern[33]. In one research study, polysomnographic (PSG) measures of sleep during a hypersomnia episode showed a little decrease in slow-wave sleep during the first half of the KLS episode and a minor decrease in REM sleep during the second half of the session. Due to the limited number of reports of comprehensive polysomnographic (PSG) investigations carried out between and during the hypersomnia episodes of KLS, the prevalence of different dyssomnias throughout sleep, such as sleep-disordered respiration, is not extensively established. Nevertheless, case studies of KLS patients with sleep-disordered breathing are few. Numerous abnormal sleep breathing patterns, including periodic respiration and hypopneic periods connected to transient arousals, have been seen in KLS patients. Extensive sleep studies focusing on breathing sequences during hypersomnia episodes are required to investigate whether breathing difficulties during sleep represent another clinical feature of Kleine-Levin syndrome (KLS)[34].

Multiple sleep latency test (MSLT)

This is a daylight test designed to find out how easily you nod off in quiet environments. It displays the quality of your daytime sleep. Prior to the multiple sleep latency test (MSLT), your physician could request that you undergo a drug test. Numerous medications may have an impact on the sleep study's findings. The drug screen will assist the physician in understanding the true findings of the multiple sleep latency test (MSLT) regarding your sleep issue. A maintenance of wakefulness test is another option for you. This assesses your capacity to remain awake in quiet environments**.**

Autopsy

In the literature, there aren't many autopsy reports[35]. Two patients' hypothalamus and two patients' thalamus both showed signs of inflammatory infiltrates[36]. In a single patient, the substantia nigra showed only modest hypopigmentation[37].

TREATMENT

Nonpharmacological therapy

- Keeping up a basic hygiene regimen
- Permit the patient to take a nap in a secure and comfortable setting at home while being watched after.

- Establish a cozy and secure sleeping space for the patient.
- Keep an eye out for psychological, behavioral, and cognitive abnormalities in patients, particularly signs of anxiety or sadness.
- Prevent triggers in between episodes by adhering to regular sleep and waking patterns, abstaining from alcohol, and avoiding sick people.

Pharmacological therapy

Many drugs have been tested, such as steroids, amantadine, clarithromycin, stimulants, antidepressants, antipsychotics, and antiepileptics. Although some progress has been made, the disorder is so uncommon that, over time, participant follow-up is difficult[38].

Using stimulants early during the symptoms may be helpful for treating them. Various reports have suggested that modafinil (Teva Pharmaceutical Industries Ltd., Fraser, PA, USA) can reduce symptoms[39]. Notably, stimulants do not lower the rate of recurrence, even though they can shorten the length of the symptomatic period. Furthermore, some cases of paradoxical agitation brought on by stimulants have been reported[40]. Taking medication near the conclusion of an episode, when individuals are less lethargic and more readily agitated, increases the likelihood that this may happen. For extended episodes of psychosis, antipsychotics like risperidone have been employed. Anxiety disorders can be treated with benzodiazepines. When administered on the first day of symptoms, amantadine was found to have a preventative effect, halting episodes in 42% of patients.

- **Stimulants:** During episodes, doctors may give stimulant drugs such as methylphenidate or modafinil to help increase wakefulness and decrease daytime sleepiness.
- **Lithium:** In certain situations, it has been suggested that lithium carbonate may help lessen the number and severity of KLS episodes. It's believed to control sleep cycles and mood stability.
- **Sodium oxybate, or gamma-hydroxybutyrate,** is another name for it. It is occasionally used to treat KLS symptoms and enhance the quality of sleep, especially when there are concomitant sleep disorders like insomnia.
- **Antidepressants:** For the treatment of depression or mood disorders that accompany KLS episodes, antidepressant medications such as tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs) may be suggested.
- **Antipsychotics:** Atypical antipsychotic drugs, such as quetiapine or olanzapine, are occasionally recommended to treat behavioral symptoms that arise during KLS episodes, such as agitation or illusions.
- **Melatonin:** Although the effectiveness of melatonin supplements in Kleine-Levin syndrome (KLS) is particularly unknown, they may be used to control sleep-wake cycles and enhance sleep quality.
- **Behavioral therapies:** CBT, or cognitive-behavioral therapy, is one type of behavioral therapy that may help people manage their symptoms and deal with the difficulties of having Kleine-Levin syndrome (KLS).

LIFESTYLE MODIFICATIONS

Although having Kleine-Levin syndrome is difficult, it is controllable with the correct techniques. Here's how you can deal with it in your daily life:

- **Recognizing Kleine-Levin Syndrome (KLS):** Recognizing Kleine-Levin Syndrome (KLS) is the first step towards living a life that is manageable. Understanding this neuropsychiatric disorder, recognizing its signs, and appreciating its effects are crucial. In addition to giving, you a foundation for explaining your circumstances to others, this knowledge can help you deal with the events that eventually occur.
- **Establishing a secure atmosphere:** It's critical to make sure that the surroundings are secure and comfortable because KLS episodes can induce people to sleep for prolonged periods of time. Make sure the person is able to rest without interruption and remove any potential threats.
- **Changing your lifestyle:** acquire the ability to adjust to KLS patterns. To keep track of episodes and search for any trends or possible triggers, keep a symptom journal. You can use this to organise and get ready for episodes.
- **Sustaining an invigorating lifestyle:** good sleep hygiene, frequent exercise, and a balanced diet all support overall health and wellness, which could decrease the severity of KLS episodes.
- **Looking for assistance:** never be afraid to ask for help. Making connections with people who are aware of the difficulties associated with living with KLS can be a wonderful way to find solace and useful guidance.
- **Maintaining open communication:** Tell your employer or your school about your illness in order for them to make the appropriate arrangements[41].

Table -1 Case studies on kleine-levin syndrome (KLS)

Case no.	Age	Gender	Signs and symptoms	Duration of episodes	Frequency of episodes	Triggers	Treatment	Outcomes	Ref.
Case 1	33 yrs	Female	Over the previous two years, there have been repeated episodes of extreme drowsiness, hyperphagia, and cognitive impairment.	7-10 days	3 or 4 episodes throughout the previous two years	Stress	Lithium and modafinil	The patient reacted favourably to lithium therapy and has not experienced any symptoms since.	Dayal P et al.[42]
Case 2	16 yrs	Male	Hypersexuality, hyperorality, and recurring hypersomnia	12 days	1 - 2 episodes / year	Not reported	300 mg of lithium carbonate twice a day	Within a week of beginning lithium carbonate medication, the symptoms disappeared.	Das S et al.[43]

Case 3	20 yrs	Male	Excessive sleep and overeating	5 - 30 days	1 - 2 episodes / year	Sars-cov-2 infection	Modafinil (300mg) and lithium (200mg)	The patient had no symptoms following the treatment.	Marčić M et al.[44]
Case 4	13 yrs	Male	Hypersomnolence, hyperphagia, disinhibition from sexual inhibition and hypersexualit, disorientation to agitated mood, and amnesia are among the behavioural abnormalities that may be present.	2 - 4 weeks	3 episodes / year	Brain impairments.	450 mg of lithium carbonate every day	The patient was normalized	Malhotra S et al.[45]
Case 5	23 yrs	Male	Excessive sleep, overindulgence in food, hypersexuality, agitation, and memory loss.	2 - 3 weeks	Reemission happened on its own.	Stress	Lithium and modafinil	The patient returned to normal.	Llorente SS et al.[46]
Case 6	21 yrs	Male	Persistent headaches and drowsiness, visual hallucinations, mental health issues, inability to focus when reading, a number of behavioural abnormalities were observed,	2 – 10 days	3 – 4 episodes / year	Not reported	Lithium and modafinil	The patient was normalized	Assi B et al.[47]

			including thoughts related to sex, hypersexuality with an increase in libido, and bulimia.						
Case 7	26 yrs	Female	Periods of extreme weariness, disorientation, and sleepiness that occur frequently.	5 – 8 days	Two to four weeks, or every other week.	Not reported	1 g of acetazol-amide each day	Improved significantly in just one month after taking the medication.	Kapson B et al.[48]
Case 8	44 yrs	Female	Excessive drowsiness linked to sporadic "sleep attacks"	2 – 3 days	Once or twice a month.	Not reported	Gabapentin and modafinil	The patient was normalized	Edaki O et al.[49]

CONCLUSION

The unusual self-limited condition known as Kleine-Levin syndrome often affects male adolescents and is typified by behavioral and mental abnormalities, increased hunger, and episodic hypersomnia. Before and after the assaults, people are normal. Compared to girls, boys are more commonly impacted. Moreover, there are no treatments that are consistently successful. However, the prognosis is generally considered optimistic, since most patients experience episodes that gradually get milder and less frequent until completely disappearing.

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