Kleine-Levin syndrome presenting in later life

Kleine-Levin syndrome is more commonly known as recurrent primary hypersomnia. The patient can lapse into a deep sleep at any time without warning, sometimes lasting as long as 16 hours. It is often associated with compulsive overeating and hypersexuality—this is not a passing desire for a quick nap, but is excessive daytime sleepiness, which is a much more significant problem. On awakening the person appears listless, speaks gibberish, and does not remember anything about events before falling asleep (short-term retrograde amnesia). We discuss the presentation, course of illness, pathophysiology, laboratory investigations, diagnosis, possible treatments, and the importance of early recognition of this disorder.

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This disorder was first described by Kleine in 1925 and elaborated on by Levin in 1936: it was named as Kleine-Levin syndrome by Crichtley and Hoffman in 1942. The description was improved by Critchley in 1962 and, in 1990, Schmidt established the diagnostic criteria.[1,2]

Definition and description

Hypersomnia refers to a set of related disorders that involve excessive daytime sleepiness. There are two main categories of hypersomnia: primary hypersomnia (idiopathic hypersomnia) and recurrent hypersomnia (recurrent primary hypersomnia; figure). Both are characterised by the same signs and symptoms and differ only in the frequency and regularity with which the symptoms occur.

Primary hypersomnia is characterised by excessive daytime sleepiness over a long period. The symptoms are present all, or nearly all, of the time. Recurring hypersomnia involves periods of excessive daytime sleepiness that can last from 1 to many days, and recur over the course of a year or more. Thus, the main difference between this and primary hypersomnia is that people experiencing recurring hypersomnia will have prolonged periods in which they do not exhibit any signs of hypersomnia, whereas those with primary hypersomnia are affected nearly all of the time. One of the best documented forms of recurrent hypersomnia is Kleine-Levin syndrome, although other forms exist (box 1).[4]

Patients are classified as having primary or secondary Kleine-Levin syndrome depending

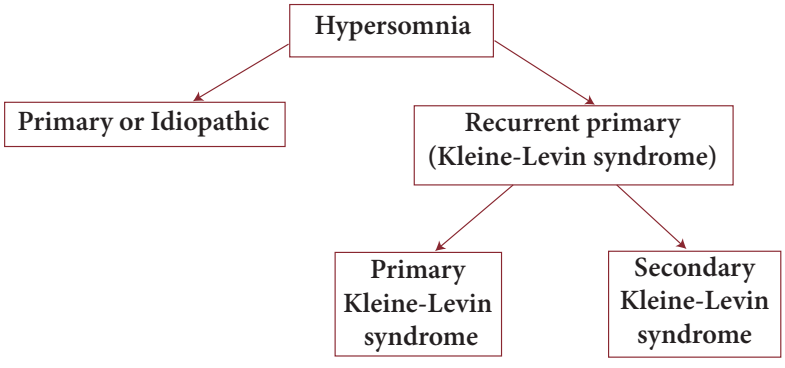

Figure: Classification of hypersomnia

on the absence or presence of neurological symptoms prior to the onset of the disorder.[5] In both types, the cardinal signs and symptoms have been described with similar terms and frequency. However, in secondary Kleine-Levin syndrome, the neurological symptoms persist between episodes of hypersomnia, the cardinal symptoms occur significantly later in life, and individual episodes last longer and occur about three times more frequently, meaning that patients with secondary Kleine-Levin syndrome are more incapacitated.

Prevalence and incidence

Kleine-Levin syndrome should be considered in elderly patients, who present with episodes of undue somnolence. The prevalence of primary hypersomnia in the general population is not known, but excessive daytime sleepiness without a definite cause may be found in 0·5–5% of the population.

Primary hypersomnia is diagnosed in 5–10% of all patients referred to the sleep laboratory for evaluation of excessive daytime sleepiness. The ratio of the rate of idiopathic hypersomnia to narcolepsy is reported as 28·7:76·9%[4]

Although no population-based studies reporting on the prevalence of Kleine-Levin syndrome are available, it is generally considered as an exceptionally rare disease with a possible predisposition in Jewish people.[5] Mostly men (around 68% of patients) are affected and the syndrome may last up to 8 years.[5] The episodes recur every 3–4 months and may last for up to 10 days, but can last longer in women.[1] Kleine-Levin and the disease process may continue for years, with spontaneous resolution

Box 1: Case report—Kleine-Levin syndrome in a 79-year-old female

Our patient was referred to our multidisciplinary assessment unit by her general practitioner for evaluation of excessive daytime sleepiness of 4-months' duration. During these hypersomnic episodes, if her family tried to keep her awake, she became more irritable, mildly aggressive, responded verbally with few coherent words, and displayed impulsive behaviour. She was also doubly incontinent during sleep, and hence was at risk of pressure sores, infections, dehydration, and malnutrition. But during her short waking periods, she was usually quiet, seemed to have complete lack of energy, and was apathetic.

She had extensive craving and food-seeking behaviour after finishing her usual meals. She experienced hallucinations (third-person commentary and second-person commands) and had an abnormally disinhibited sexual behaviour (walking naked in public, masturbation, and inappropriate ideas about medical staff). She was also confused—even her family and friends looked strange or unusual to her. She was careless about personal hygiene and avoided bathing, changing her clothes, combing her hair, and putting on make-up. Relevant past medical history was a cerebrovascular accident 2 years earlier from which she had recovered completely. She had no history of falls or head inury, no similar illnesses were seen in her family, and she did not use alcohol or illicit drugs. She was on medications for secondary prevention of stroke but could not adhere to the regimen due to the nature of her current illness.

The symptoms we observed as typical of Kleine-Levin syndrome were hypersomnia, hyperphagia, and an abnormally uninhibited sexual drive. We also noted behavioural disturbances and neuropsychological alterations including psychotic symptoms. Her Stanford Sleepiness score[3] was always greater than 6 at 9 am and 9 pm. Her laboratory tests including full blood count, serum calcium, magnesium, phosphorus, fasting morning glucose, thyroid function test, and urinalysis were normal, as was her chest X-ray. CT scan of the brain revealed an old infarct in the right middle cerebral artery territory and small vessel deep white matter ischaemia. EEG showed no epileptiform abnormalities or changes suggestive of prion disease, but did show some non-specific changes consistent with cerebrovascular accident. All these investigations excluded any underlying neurological and pulmonary disorders known to cause excessive sleepiness. The onset of illness, clinical features, and neuropsychological evaluation were consistent with a diagnosis of Kleine-Levin syndrome.

Modafinil was chosen as first agent for control of her hypersomnic symptoms.Within 2 weeks of starting the medication she brightened up, and her sleepiness decreased; she was more awake, and started participating in her surroundings. She seems to have responded well to modanafil and long-term use of this drug was planned. Her behavioural and sexual symptoms responded well to a tailored nursing plan. She was discharged home with a package of care and regular follow-up.

Signed consent was obtained for publication of this case report.

during adult life. It is a unique disease which may be more severe in females and secondary cases.[5] It is more common during adolescence[6] with a median age of onset of 15 years, and is rare in people older than 30 years. (range 4–82 years; 81% during the second decade).[5,6] Very few case reports describe this syndrome in elderly people—possibly because of under-recognition or underdiagnosis and possibly because it masquerades as part of ageing or dementia.

Symptoms

From a clinical point of view, the cardinal and constant symptom is hypersomnia. Psychiatric symptoms often co-exist. The other symptoms in order of frequency are:[5,6] cognitive changes, specifically a feeling of derealisation (96%); eating disturbances, megaphagia (80%); thymic disorders, depressed mood (48%); abnormal sexual behaviour, hypersexuality (43%); and compulsions (29%).

Pathophysiology

The Kleine-Levin syndrome is generally considered to be a benign functional disorder of hypothalamic structures (the symptoms occur when hypothalamus malfunctions, affecting body functions such as sleeping, eating, and body temperature).

Many causes have been suggested, although a definite trigger has not yet been identified. A genetic basis for idiopathic hypersomnia has been proposed, but the mode of inheritance has not been determined although some more frequent HLA genotypes suggest a possible autoimmune mediation of the disease[7,8]

Possible precipitating factors[5,6] include multiple cerebrovascular ischemia,[9] infections (38·2%), head trauma (9%), or alcohol consumption (5·4%). Some other contributory factors are brain tumours (especially hypothalamic and third ventricle tumours), inflammatory lesions in brain (especially in the thalamus, diencephalon, and midbrain), excessive workload, febrile illness, and respiratory infections.

Box 2: Treatments for Kleine-Levin syndrome

Stimulant drugs (eg, methylphenidate, modafinil, pemoline-piracetam-meclofenoxate, D-amphetamine, ephedrine, meta-amphetamine, amphetamine)

Antiepileptic drugs (eg, valproic acid, carbamazepine, amobarbital, phenobarbital, phenytoin)

Antidepressants (eg, imipramine, monoamine oxidase inhibitors, moclobemide, clomipramine, amineptine, fluoxetine, fluvoxamine, sertraline, methylsergide, trazodone)

Antipsychotic drugs (eg, haloperidol, chlorpromazine, levomepromazine, trifluoperazine, thioridazine, clozapine, risperidone)

Acyclovir

Lithium

Diagnosis

The diagnosis of Kleine-Levin syndrome is essentially clinical and the clinical examination is non-specific and non-contributory most of the time.

Critchley in 1962 and Schmidt in 1990 established the following diagnostic criteria:[2]

1. predominance in adolescent males;
2. onset in adolescence;
3. periodic hypersomnia;
4. hyper-, mega-, or polyphagia,
5. associated behavioural and psychological changes;
6. benign clinical course with spontaneous disappearance of

	Modafinil	Amphetamines
Duration of action	Long	Short
Specificity of action	High	Low
Dependency	Low risk	Moderate risk
Withdrawal symptoms	Absent	Common
Tolerance	Unknown	Seen in 30% of narcoleptic patients
Side-effects	Few and mild	Multiple, often serious
Contraindications	Few	Multiple
Drug interactions	Rare	Occasional
Effects of overdose	Insomnia	May be fatal

Table: Comparison of amphetamines and modafinil

clinical symptoms;
7. lack of other neurological or psychiatric disease.

The International Classification of Sleep Disorders in 1990 modified the diagnostic criteria to:[2]

1. recurring episodes of undue sleepiness lasting some days;
2. hyperphagia (not obligatory);
3. abnormal behaviour (not obligatory).

The diagnosis of primary hypersomnia is made after exclusion of neurological, pulmonary, and psychiatric disorders known to cause excessive sleepiness.[6] Therefore, if an underlying cause is suggested, appropriate consultations with a neurologist, chest physician, or psychiatrist should be obtained.

Differential diagnosis[6]

- Depression, particularly atypical depression and seasonal affective disorder
- Bipolar affective disorder
- Hypoactive delirium
- Narcolepsy
- Hypersomnia secondary to general medical conditions: ie, chronic fatigue syndrome or hypothyroidism
- Kluver-Bucy syndrome
- Upper-airway resistance syndrome
- Sleep apnoea
- Circadian rhythm sleep disorders
- Post-traumatic hypersomnia

Investigations

Baseline tests

Kleine-Levin syndrome and periodic hypersomnia are often misdiagnosed initially because there is no objective test for these conditions.[10] Diagnosis is basically clinical, but full blood count, screening biochemistry tests, and thyroid-stimulating hormone tests should be done to exclude common disorders that present with complaints of excessive tiredness and sleepiness.[6]

Specialised tests

Additional tests are mainly electroencephalogram for eliminating epilepsy, brain imaging for focal brain lesions such as neoplasm, and analyisis of cerebrospinal fluid (CSF) for meningitis or encephalitis.[5] Electroencephalogram may show an outburst of theta activity if performed during hypersomnia.[6]

Polysomnography of 24 or 48 hours during a hypersomnic episode will give diagnostic information such as fragmented and unstable sleep, reduction in stages 3 and 4 of non-random eye movement (REM) sleep, reduction in REM sleep latency, and frequent awakenings from sleep stage 2.[11]

Multiple sleep latency testing is done to evaluate the presence of pathological sleepiness. Individuals are studied during five daytime naps taken 2 hours apart. Findings during episodes of hypersomnia include short sleep latencies and the presence of REM sleep in one or more naps.[11,12] Information about sleep characteristics and long-term follow-up of patients with Kleine-Levin syndrome is scant.[12]

CT and MRI of the brain is essential to exclude structural brain lesions. Single photo emission tomography shows hypoperfusion in left hypothalamus, bilateral thalami, basal ganglia, bilateral medial and dorsolateral frontal regions, and left temporal lobe during the symptomatic period.[1,13,14]

CSF white-cell counts and protein levels were normal ruling out infectious meningitis. Immunoelectrophoresis of CSF can exclude the possibility of frequent oligoclonal secretion of antibodies as observed in multiple sclerosis.

Treatment

There is no definite treatment for this condition although several strategies have been tried including stimulants, neuroleptics, and antidepressants but because of the rarity of the disorder no long-term follow-up therapies have been described. A wide range of medications have been tried and reported to provide some benefit for patients with Kleine-Levin syndrome (box 2).[2]

The only medications that have brought partial and often intermittent relief are the stimulant drugs. Somnolence is decreased with stimulants (mainly amphetamines), the drug dose is titrated so that the patient stays alert during the day, but adverse effects should be avoided. The most effective drug for wakefulness is modafinil (table). This agent is chemically unrelated to the amphetamines and is licensed for treatment of excessive daytime sleepiness due to chronic pathological conditions. Its peak blood level is reached within 2 or 3 hours and its half life is 10–15 hours. It is metabolised in the liver and the initial dose of 100–200 mg daily often needs to be increased to 400 mg daily, and occasionally beyond this. Around two-thirds of the daily dose should be given on waking and one-third in the middle of the day.

Modafinil increases the activity of the histaminergic neurons in the tuberomammillary nucleus,[3] which promote wakefulness, and inhibits the ventrolateral

preoptic nucleus. Its main side-effects are headaches, nausea, and dry mouth but it is usually well tolerated. Mental hyperactivity, anxiety and nervousness occur with high doses. Tolerance has not been documented and it has little potential for dependency. It can be used in combination with amphetamines and related drugs, if necessary.

Because of similarities between Kleine-Levin syndrome and certain mood disorders, lithium and carbamazepine may be prescribed. Lithium rather than carbamazepine or any other antiepileptic has a higher success rate for stopping relapse.[5,15] In secondary Kleine-Levin syndrome, patients were older and had more frequent and longer episodes, but they had clinical symptoms and treatment responses similar to those of primary cases.[5] Behavioural approaches and sleep hygiene techniques are recommended, although they have little overall positive impact on this disease.

Course of illness

Kleine-Levin syndrome is an incurable neurological disorder and its greatest challenge is not knowing when a sleep episode can strike. The syndrome may cause patients to fall behind in family commitments and social lives as they struggle to stay awake, and friends and family hope for a miracle cure. In young patients this ailment can be present for long periods of time without symptoms; however, these can reappear at any time without warning. Between episodes, patients have normal physical and behavioural health.

The disorder can last through a decade or more and undoubtedly people suffering from it live in constant fear of the symptoms recurring. On the one hand, the periods of hypersomnia occur for days to weeks at a time but recur several times a year. On the other hand, in elderly patients the presentation is often subacute and the illness can last for life while deteriorating gradually over time.

Patient's education

While treating patients with primary hypersomnia, the patient's close family should be involved in education and decision-making. Since these disorders may lead to marriage breakdown, extensive counselling for the patient's partner, educating them about the symptomatology and treatment options, must be part of a comprehensive management plan.

Patients with primary hypersomnia often need significant support because they are at risk of being misunderstood as being incompetent or lazy. Therefore, education of relatives, friends, and colleagues helps the patient to function much better with this incurable disease.

Conclusion

Considering the diagnosis of Kleine-Levin syndrome is important in elderly patients who present with recurrent episodes of somnolence, increased appetite, and abnormal neuropsychiatric behaviour. Unlike classic (primary) Kleine-Levin syndrome, which is less severe and self-limiting, in elderly people (secondary Kleine-Levin syndrome), it is often more severe, incessant, and leads to loss of functional abilities and independency.[5] Although sleep hygiene may be of some help, drug therapy may need to be added for treatment.

We have no conflict of interest.

Key points

- Kleine-Levin syndrome is a rare, under-recognised or underdiagnosed condition, which probably masquerades as part of ageing or dementia
- In elderly patients it is a rare sequelae of cerebrovascular disease
- It has significant impact on patients' social, personal, and family lives, which necessitates the involvement of the patient's close family in the overall education and decision-making process
- It is generally considered to be a benign functional disorder of hypothalamic structures in young patients
- It should be considered in all elderly patients who present with episodes of undue somnolence
- The most characteristic symptoms are periodic hypersomnia, excessive eating, hypersexuality, irritability, and apathy
- Diagnosis of primary hypersomnia is made after excluding neurological, pulmonary, and psychiatric disorders known to cause excessive sleepiness
- There is no definite treatment for this condition though modafinil[16] may be administered to treat sleepiness

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