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Sleeping Beauty Syndrome

Alexis Shusterove
Boise State University

Aubrie Tubach
Boise State University

Adriana Rodriguez
Boise State University

Julia Oxford
Boise State University

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Abstract

Kleine Levin Syndrome (KLS), also known as Sleeping Beauty Syndrome, is characterized by progressive drowsiness and sleep for most days and nights. It is a rare neurological disorder with a prevalence of one to five cases per million. Those with KLS have recurring periods of excessive sleep, altered behavior, and a reduced understanding of the world. KLS primarily occurs in adolescents, boys more frequently than girls with a higher prevalence in Ashkenazi Jews. The exact cause of KLS is unknown but damage or malfunction of the hypothalamus may be involved. Although there is no definitive treatment for KLS, pharmaceuticals such as stimulants have been used to combat the sleepiness. However, these can cause irritability and mood swings, so alternatives to pharmaceuticals are also considered. Recent research suggests that a mutation in the gene LMOD3 may be the cause of KLS. LMOD proteins are structural proteins and appear to be developmentally regulated. In this poster, we will present the molecular mechanism for the disease and potential therapeutic targets for treatment on this disease.

Kleine-Levin syndrome (KLS)

Lexi Shusterove, Aubrie Tubach, Adriana Rodriguez, & Julia Oxford

Developmental Biology, Department of Biological Sciences, Boise State University

DISEASE NAME/SYNONYMS

- Kleine-Levin Syndrome
- Kleine-Levin hibernation syndrome
- Familial Kleine-Levin syndrome
- Familial hibernation syndrome
- Sporadic Kleine-Levin Syndrome

DEFINITION

- KLS is a rare disorder characterized by the need for excessive amounts of sleep, excessive food intake, and behavioral changes.
- The exact cause is unknown, but researchers believe that there may be some hereditary factors at play and that the symptoms that manifest may involve the hypothalamus portion of the brain that helps regulate sleep, appetite, and body temperature.

EPIDEMIOLOGY

- KLS is a rare disease that is estimated to affect one in a million.
- From 1962 and 2004 there were only 186 cases reported worldwide. Since then, the estimated number of individuals with KLS is around 500.
- Most of the reported cases were in Western countries, with one-sixth of the patients found in Israel.
  - -This data suggests that those with Jewish heritage may have a pre-existing genetic disposition for KLS.
- Men were more frequently affected than women with the onset of symptoms occurring in the teenage years and after puberty.
- Most of the cases are sporadic but there have been a few KLS families that have been reported, suggesting that genetics may play a role in developing the disorder.

CLINICAL DESCRIPTION

- Hypersomnia, is a major clinical symptom and mandatory diagnosis.
- Sleep duration ranges from 12 to 24 hours a day.
- The Majority of patients also have cognitive disturbances like confusion, trouble concentrating, trouble paying attention, and memory defects.
- Abnormal speech has been reported in about two-thirds of cases.

DIFFERENTIAL DIAGNOSIS

- There are various diseases and syndromes that have similar symptoms and are ruled out to get a diagnosis.
  - -Metabolic problems with KLS are similar to those caused by diabetes, metabolic encephalopathies, and hypothyroidism.
  - -Cognitive symptoms with KLS could be caused by a lesion, tumor or inflammation.
  - -Multiple sclerosis and bipolar disorder can also mimic some of the symptoms of KLS.

ABSTRACT:

Kleine Levin Syndrome (KLS), also known as Sleeping Beauty Syndrome, is characterized by progressive drowsiness and sleep for most days and nights. It is a rare neurological disorder with a prevalence of one to five cases per million. Those with KLS have recurring periods of excessive sleep, altered behavior, and a reduced understanding of the world. KLS primarily occurs in adolescents, boys more frequently than girls with a higher prevalence in Ashkenazi Jews. The exact cause of KLS is unknown but damage or malfunction of the hypothalamus may be involved. Although there is no definitive treatment for KLS, pharmaceuticals such as stimulants have been used to combat the sleepiness. However, these can cause irritability and mood swings, so alternatives to pharmaceuticals are also considered. Recent research suggests that a mutation in the gene LMOD3 may be the cause of KLS. LMOD proteins are structural proteins and appear to be developmentally regulated. In this poster, we will present the molecular mechanism for the disease and potential therapeutic targets for treatment on this disease.

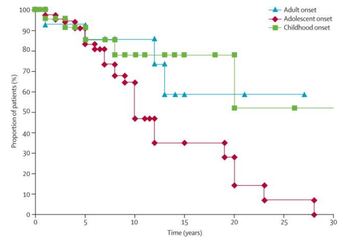
ETIOLOGY:

The exact cause of KLS is unknown. It is speculated that the symptoms may develop due to malfunction or damage to the hypothalamus which is the portion of the brain that regulates sleep, appetite, and body temperature. There have been no consistent hypothalamic abnormalities identified as of yet. Structural brain images and cerebrospinal fluid have been evaluated were not helpful in identifying the causation of KLS. Viral and autoimmune causative factors have also been suggested by researchers as well. In some cases, KLS development followed a flu-like illness indicating an infection leading to the speculation that an underlying autoimmune process may play a role in the development of the disorder. In extremely rare cases, more than one family member has been affected by KLS (familial KLS) which could be an indication that genetic factors may cause some individuals to have a predisposition to developing the disorder.

In a paper titled, *" Kleine-Levin syndrome is associated with LMOD3 variants."* the researcher performed whole-genome single nucleotide polymorphism genotyping and exome sequencing in a large family with seven affected individuals. The identified gene with a mutation was resequenced in 38 sporadic KLS patients and the expression of the gene product was mapped in the mouse brain. The analysis identified a heterozygous missense variant in LMOD3 in the linkage interval. LMOD3 is expressed in the brain and colocalized with major structures involved in the regulation of vigilance states. LMOD proteins are structural proteins and seem to be developmentally regulated. Their findings suggest that KLS might be a structural/neurodevelopmental brain disease due to a mutation of the LMOD3 gene.

DIAGNOSIS/DIAGNOSTIC METHODS

- It can be difficult to diagnose due to the primary symptom, hypersomnia is common with a number of different disorders.
- The process of diagnosing involves excluding other possible disorders through tests involving various specialties.
- There is not just one test or way to diagnose, just a process of excluding all other possible causes of symptoms.



MANAGEMENT/TREATMENT

- KLS does not have a specific, definitive treatment used to cure or control it.
- Pharmaceuticals such as stimulants have been used to combat hypersomnia but can cause irritability and mood swings. Lithium and carbamazepine, normally used to treat bipolar disorder, have been used by doctors in some cases to prevent or shorten episodes.
- Many researchers feel it may be more beneficial to wait out episodes, instead of or using pharmaceuticals and thus preventing the negative effects of pharmaceuticals.
- An understanding of KLS can help with management such as knowing effects and recognizing an episode and having the support of friends and family.

PROGNOSIS

- KLS, is a rare neurological disorder with no known cure that is believed to alter the part of one's brain that helps regulate sleep, appetite, and body temperature causing them to need excessive amounts of sleep, excessive food intake, and experience behavioral changes.
- However, episodes eventually decrease in frequency and intensity over the course of eight to twelve years.

UNRESOLVED QUESTIONS

- The cure?/is there a cure?
- Will it ever go away?
- What exactly does KLS affect inside the body?
- What causes/why does an episode come and go without any warning? (very unpredictable)
- Find easier ways to test/diagnose it

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