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Kleine-levin syndrome (kls)-a review

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Abstract

Kleine-Levin Syndrome is a rare sleep disease characterized by relapsing episodes of hypersomnia interconnected with behavioral and cognitive disorders along with hyperphagia and hypersexuality. This disease occurs more often in young male adolescents. The diagnosis was clinical, primarily based on the nosologic distinction of non-identical forms of recurrent hypersomnia. The brief duration of KLS varies from 7 days to 2 months and the people affected are completely asymptomatic between episodes but during episodes, electroencephalography shows diffuse or local slow activity. Investigations for KLS comprise of medical history, magnetic resonance imaging, polysomnography, 24- hours time profile of growth hormone, melatonin, TSH, and cortisol. The Pathophysiology of this sleeping beauty syndrome is based on Neuropathological examinations, cerebrospinal fluid hypocretin-1 monitoring, clinical patterns, and neuroimaging. Imaging of brain function reveals the hypoactivity in thalamic and hypothalamic regions and imaging along with the cognitive capacity evaluation gives insights into neurobiological mechanisms of KLS. No effective treatment, as well as indefinite pathology, has been identified even though the illness is having clearly defined clinical features but some medications like stimulants and mood stabilizers can be beneficial in the treatment of severe cases.

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Introduction

Kleine-Levin syndrome (KLS) is an infrequent or rare disorder which is characterized by recurrent experiences of hypersomnia usually accompanied by cognitive and like stimulants are relatively effective on sleepiness but not very effective for cognitive and behavioral abnormalities. For preventing recurrent symptoms behavioral disturbances like megaphagia and hypersexuality. Initially it affects male adolescents [1]. The individuals develop nearly identical symptoms one after another within the span of 5 months. Compatible hypothalamic abnormalities are absent in KLS. The Structural brain imaging, evaluation of CSF and serological inflammatory markers are normal. The EEG recording slows down during the episodes without epileptic activity, diffuse brain hyperperfusion mostly concentrated on frontotemporal and thalamic regions. Almost many of the cases were misdiagnosed [2]. Drugs Lithium is very effective [3]. Several biological markers include the collection of serum and DNA from subjects to detect abnormalities in serum leptin, C-reactive

protein levels, high resolution human leukocyte antigen (HLA) DRB1 & DQB1 type [4]. In 1862, the first case of KLS was reported by Brierre de boismont and was first described by Kleine 1925 & Levin 1929. Multiple KLS cases were reported in 1962 with unknown etiology. Psychiatrists observed that Kleine-Levin syndrome is recurrent due to endogenous depression and gets subset by mood stabilizing drugs [5]. About 60% among 10-20 years of age people are and 20% among 20-30 years age group people are affected by KLS. Several case reports showed the triggering factors like coexisting infections, head trauma, alcoholism, genetic diseases, thalamic ischemic stroke and auto immune encephalitis. The precipitating factors are unspecified fever, flu like fever have 43% chances to get KLS and Respiratory tract infection people have 25%, tonsillitis, cough, sore throat have 12%, alcohol, marijuana consumption people have 4%, head trauma have 2.5%, sleep deprivation, stress, mental effort have 3%, menses or lactation have 3.6% and general anesthesia administered patients have 3.6% of chances to get affected with KLS [6]. The primary KLS neurological symptoms observed are hypersomnia (100%) is observed at least 12-24 years. Sudden waking, tired feeling and rapid eye movement sleep were reported during day time. Cognitive disturbances (96%) like confusion, loss of concentration, memory defects and abnormal speech were reported. Derealization (24%), hallucination (16%), paranoid delusion (14%), eating behavior disorder (80%), mood disturbances (48%), hypersexuality (43%), compulsive behavior (29%) like singing, writing on walls, crying, switching the lights on & off were experienced by patients and irritability (92%) were reported. The secondary symptoms observed are megaphagia, cognitive impairment and impaired verbal abilities and the neuro psychiatric symptoms reported are Whipple's disease, Malaria and California encephalitis [7].

Table 1: Neuropathological findings of Kleine–Levin syndrome (KLS) [8]

	Primary KLS		**Secondary KLS**	
Typical symptoms	Hypersomnia, megaphagia, Sexual inhibition	Hypersomnia, megaphagia, masturbation, Several attacks	Hypersomnia, megaphagia, Aggressive, 4 attacks	Hypersomnia, megaphagia, Agitation, 2 attacks
Atypical symptoms	Late onset, attacks lasts 3 months	Autonomic dysfunction, muscle weakness	Late onset, Uterine carcinoma	Upward-gaze palsy, mild ptosis
Cause Of death	Aspiration pneumonia (due to megaphagia)	Cardiopulmonary arrest	Cancer complications	Pulmonary embolism
Lesions corte	Normal	Normal	Perivascular temporal infiltrate	Normal
Amygdala	Normal	Normal	Perivascular infiltrate	Normal
Thalamus	Microglial proliferation	Normal	Normal	Infiltrates
Hypothalamu	Very mild Proliferation	Normal	Perivascular infiltrate	Infiltrate In The Hypothalamus
Brainstem	Normal	Mildly depigmented substantia nigra	-	Microglial nodule

Polysomnography and Neuroendocrinological assays

These are performed during the asymptomatic (ASMP) and symptomatic (SMP) 24 hours period to determine the clinical features of the patient with KLS. Patients experience prolonged periods of apparent sleep but are capable of attending bodily needs spontaneously. International classification of Sleep disorders (ICSD-2) PSG examination 4-channel EEG (Electroencephalogram), 2 channel EOG (Electrooculogram), Mandibular muscle criteria should be followed to diagnose recurrent hypersomnia. The sleep attack should last for 2 days to 4 weeks and at least 1 attack should occur yearly and the patient should experience normal wakefulness level along with one of the finding like hyperphagia, hypersexuality, irritability, aggression, disorientation, confusion and hallucination should be present [9]. In electromyography, electrocardiography, oral and nasal airflow, thoracic & abdominal respiratory movements and percutaneous O2 saturation were measured. The

abnormal behavior, aggression and confusion symptoms were experienced in the period of sleep attack in male patients. It was found that the total sleep time and the percentage of stage-2 were higher, the latency of REM is shorter, and the REM percentage and stage-3 percentage were lower in the symptomatic period compared to asymptomatic period [10].

Reduced Hypothalamic Dopaminergic Tone

During the symptomatic, sleep data revealed poor nocturnal efficiency, increased sleep fragmentation and reduced stages 3, 4 and rapid eye movement and no sleep onset REM episodes were observed. In asymptomatic the sleep staging was found to be normal. The blood samples were assayed for thyroid stimulating hormone (TSH), cortisol (CORT), prolactin (PRL), and growth hormone (GH). During symptomatic and asymptomatic 24 hours mean and mean sleep period time values were compared. In SMP the mean 24 hour level and mean sleep period time of TSH, PRL was increased and GH, CORT was decreased. Due to presence of hormone changes in symptomatic condition the hypothesis support the reduced hypothalamic dopaminergic tone in patients with Kleine-Levin syndrome [11].

In KLS, hypothalamus is the major area of brain dysfunction because it plays key role in the sexual behavior control of sleep, alertness and sleep. In thalamus as well as hypothalamus pathologic abnormalities were reported. Limbic pathological changes showed most widely to paraneoplastic encephalitis. The circumstantial evidence supports that idiopathic cases have more hypothalamic dysfunction [12].

Table 2: KLS nature and frequency of symptoms [3]

<table>
<tr><td>Hypersomnia 100%
Sleep drunkenness 83%
Post episode transient insomnia 72%
Intense dreaming 59%
Hypnagogic hallucinations 42%
Sleep paralysis 14%</td><td>Meningeal and autonomic symptoms 89%
Fever 68%
Photophobia 59%
Headache 48%
Sweating 46%
Hot flashes 24% & Nausea 18%</td></tr>
<tr><td>Eating behavior disorders 95%
Hyperphagia 66%
Increased food intake 56%
Automatic eating 37%
Decreased appetite 34%
Eat whatever is presented 31%
Increased drinking 16%</td><td>Altered perception 100%
Dreamy state 81%
Erroneous perception 72%
Derealization 63%
Mind-body disconnect 52%
Altered taste 50% & Altered smell 35%
Blurred vision 23%</td></tr>
<tr><td>Sexual drive 59%
Disinhibition, hypersexuality 53%
Increased masturbation 29%
Unwanted sexual advances 17%
Decreased sexuality 6%</td><td>Psychological change 87%
Irritability 65% & Frustration 55%
Depressed mood 53% & Anxiety 45%
Agitation 47% & Less polite 47%
Compulsions 36% & Delusions 35%
Hallucinations 27%</td></tr>
<tr><td colspan="2">Cognitive impairment 100%
Impaired speech 94%
Impaired concentration 91%
Incomplete recollection of episode 87%
Temporal disorientation 87%
Impaired reading 75%
Unable to perform two tasks simultaneously 67%
Unable to make a decision 66%
Impairment of memory 66%
Eye–hand coordination impairment 66%
Apathy 54%</td></tr>
</table>

Electrophysiological changes

A variety of electrophysiological changes were reported like rapid eye movement sleep in short diurnal electroencephalogram during attacks, but not in the asymptomatic intervals. The features of EEG vary a bit little attention for the people with KLS. Presence or absence of hyperphagia, hypersexuality, truculence and withdrawal behavior, monosyllabic answers or refusals were monitored. According to recommendations of Rechstaffen and Kales the nocturnal records were made and scored. During diurnal wakefulness and sleep with 8 or 16 channel electroencephalographs utilizing the international 10-20 system of electrode replacement, bipolar and referential montages were recorded in EEG's. Assesment of the waking parieto occipital rhythm and EEG activity slower than average frequency of rhythm were observed. In sound proofed laboratory all night sleep polygraphic records were taken in bed by patient. The first over night recording showed the patient was restless and awaked several times throughout the night. During second session the patient slept much more soundly. The recorded tracking revealed increased wakefulness and stage-1 sleep and decreased stage-3, 4 and REM sleep during a clinical attack [13].

Memory function assessment with neuro imaging of thalamus

The key features of KLS that persist between sleep episodes are working memory dysfunction and thalamic hyper activation. The relation between the individual working memory capacity and measures of thalamus activation during a functional magnetic resonance imaging working memory task was investigated. In KLS the thalamic hyper activation results in neural inefficiency and increases the activity higher in patients who perform worst on working memory task. Similarly if the hyper activation results in compensatory mechanism, higher thalamic activity is observed in high performing KLS patients than low performing KLS patients. The brain imaging results revealed that the KLS patients had reduced activation in the medial frontal and anterior cingulated cortices and larger activation clusters in the left dorsolateral prefrontal cortex and left inferior frontal cortex when compared to healthy individuals. Patients with higher cognitive capacity have lower levels of brain activation, this referred to as neural efficiency. KLS patients with high working memory capacity had comparable high thalamic activation. The abnormal function of the thalamus is the source of neuropathology of KLS [14].

CSF Hypocretin-1 levels in KLS

In KLS, the primary reason for the hypersomnia is due to the hypocretin system malfunction. It is characterized by megaphagia and recurrent hypersomnia episodes. To measure hypocretin levels in patients with KLS, the CSF is collected by lumbar puncture. The low levels of hypocretin indicate the KLS. During symptomatic condition the decreased levels of hypocretin-1 levels are observed whereas normal levels in asymptomatic condition. CSF hypocretin-1 resembles with HLADQB1*0602 allel may trigger the KLS. The behavioral changes and wakefulness are associated with affected patients [15]. The higher cognitive function spares the context of extreme lethargy and persistency is nearly unique in KLS. In patients with chronic sleep deprivation the symptoms like sleepiness, irritability and dysphoria are similar. Sleep deprivation greater than 72 hours produces increased hunger, irritability, mild autonomic changes and subtle hallucinations along with the increased sleepiness. First Critchley and Hoffman suggested an inflammatory or infectious etiology of KLS for upto 50% cases by frequent mild viral illness. Several reports showed KLS occurring months after viral encephalitis but do not resemble the illness. Salter and white described KLS after clinically and serologically detected Epstein-Barr and Varicella zoster infections isolated from CSF. Viral infections may be a non specific stress capable of triggering an attack [16].

Only lithium (but not Carbamazepine or other antiepileptic) had a higher reported response rate (41%) for preventing reoccurrence when compared to other drugs. Antidepressant therapies were ineffective. Additional therapeutic trials using other medications, such as immunosuppressive or novel antiviral agents, with double-blind blind placebo-controlled multicentre design were warranted [7]. The use of Amantadine, dopamine reuptake inhibitor stimulants and Anti viral drugs shows significant effect initially later on the continuous usage leads to the reduced effectiveness. Sometimes the condition might improve by using the Modafinil, methylphenidate, and amphetamine. Occasional preventive effects can be obtained by using valproate and lithium [17]. Commonly patients with KLS are misdiagnosed with a psychiatric entity and sometimes may be hospitalized, considering the negative consequences by exacerbating the cognitive

symptoms in novel environments. In some conditions occasional trails of valproate and amantadine may be proposed. Some studies suggest that the KLS involves strong Genetic predisposition [18].

Table 3: Effects of Treatments in Kleine–Levin Syndrome [7]

Treatment	No Change or Worse	Partial Benefit	Important Benefit
Stimulants			
Modafinil	79%	21%	0%
Methylphenidate	89%	11%	12%
Amantadine	58%	29%	0%
Amphetamine	87%	13%	0%
Bupropion	50%	50%	0%
Anti-depressants			
Sertraline	100%	0%	0%
Fluoxetine	81%	19%	0%
Others	87%	13%	0%
Melatonin	87%	13%	0%
Phototherapy	94%	6%	0%
Neuroleptics			
Risperidone	63%	37%	0%
Others	100%	0%	0%
Antiepileptics			
Carbamazepine	91%	95	0%
Valproate	75%	19%	6%
Benzodiazepines	96%	4%	0%
Lithium	77%	17%	7%
Others			
Immunoglobulin's	66%	33%	0%
Acyclovir	100%	0%	0%
Corticosteroids	100%	0%	0%
Nonmedical therapies			
Vitamin supplements	100%	0%	0%
Phototherapy	83%	17%	0%

Conclusion

For more than a century Kleine Levin syndrome is an intriguing as well as severe homogenous disease with intricate clinical features. It is caused by environmental factors depending on a vulnerable genetic background and due to the rarity it is difficult to identify the underlying biological cause of the disease. It is a unique disease that more often affects the male adolescents. During symptomatic period several changes occurs in sleep over the time with clear impairment of slow wave sleep. The functional neuroimaging of the thalamus along with the assessment of working memory function provide to guide appropriate diagnosis of KLS. Till now there is no effective treatment for KLS during interepisodic periods. Lithium had been reported to be effective but the long-term usage may leads to other complications and stimulants like Modafinil is used in some conditions but not effective than lithium.

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