A Case of Kleine-Levin Syndrome: Diagnostic and Therapeutic Challenge

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Abstract- Kleine-Levin syndrome (KLS) is a rare sleep disorder mainly affecting teenage boys in which the main features are intermittent hypersomnolence, behavioral and cognitive disturbances, hyperphagia, and in some cases hyper sexuality. Etiology is unknown, and there is no specific clinical or imaging test for this syndrome even though the illness has well-defined clinical features. Also, there is no effective treatment for KLS. KLS is self-limited, so the prognosis for these patients is not so bad. This study presents our case report and comprehensive workout that led to diagnosis which is primarily clinical. Our patient is a 20-year-old man referred to our clinic because of sleeping problems. At the age of 14, he presented with complaints of the excessive duration of sleep, increased appetite, excessive daytime sleepiness, loss of interest in social activities during attendance of high school and hallucinations. The excessive diagnostic procedure does not find pathological. Kleine-Levin syndrome (KLS) is a rare sleep disorder of unknown etiology which diagnosis is clinical and diagnostic workup is mainly to exclude other similar conditions. There is no specific therapy, but the disease is self-limited and with good prognosis.

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Introduction

Kleine-Levin syndrome (KLS) is a rare disease characterized by recurrent episodes of hypersomnia and often accompanied by additional symptoms like megaphagia, hyper sexuality and cognitive disturbances (1). The exact prevalence of KLS is unknown, but it is considered a very rare disease, possibly affecting one in a million. The disease predominantly affects adolescent males, mostly between 10 and 20 years of age (2,3). Majority cases were reported in western countries, among one-sixth of patients were found in Israel, suggesting that Jewish heritage could provide a vulnerability for the disease. Men were more frequently affected than women, with a gender ratio of 2:1. In one study median age at disease, onset was 15 years (range, 4-80 years), with 81% of the cases beginning during the second decade. Most cases are sporadic, but in few families, KLS have been reported in more than one sibling (4). Etiology is unknown. An underlying hypothalamic pathology is suggested by the critical role of this structure in regulating sleep, appetite, and sexual behaviors; however, no consistent hypothalamic abnormalities have been identified (5). In few cases, abnormalities in serotonin and dopamine metabolism have been reported, suggesting a neurotransmitter imbalance in the serotonergic or dopaminergic pathway (6). Viral and autoimmune causative factors have been suggested, on the basis of the frequent report of flu-like symptoms at onset, and the most frequent precipitating factor (70%). The first episode of KLS occurred most often in the cold season of the year, in autumn (31.1%) or winter (31.1%), peaking in December (14.8%), but no specific virus can be detached to KLS (7). The eventual, spontaneous disappearance of the syndrome is as mysterious as the mechanisms determining its periodicity.

Diagnostic criteria for Kleine-Levin syndrome were defined in 1990. Year by the International Classification of Sleep Disorders (8). KLS was defined as a syndrome composed of recurring episodes of undue sleepiness lasting some days, which may or may not be associated with hyperphagia and abnormal behavior (ICSD 1990). The KLS has been classified into primary and secondary depending on identifiable underlying organic causes for recurrent hypersomnia and other behavioral symptoms.

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Diagnosis of KLS is very difficult since there are no symptoms that allow for a positive diagnosis (9). KLS is instead a diagnosis of exclusion, where a doctor must first eliminate a long list of other conditions that could mimic the symptoms. The diagnosis is entirely clinical. According to the ICSD, it belongs to the category of recurrent hypersomnia, defined as episodes of excessive sleepiness lasting more than 2 days and less than 4 weeks, intermixed with long intervals of normal alertness lasting usually months to years, recurring at least every year, and not better explained by a sleep disorder; a neurologic disorder (e.g., idiopathic recurrent stupor, epilepsy); a mental disorder (e.g., bipolar disorder, psychiatric hypersomnia, depression); or the use of drugs (e.g., benzodiazepines, alcohol). The essential clinical criterion of KLS is recurrent episodes of hypersomnia. Moreover, patients have to experience at least one of these symptoms only during the episodes: (1) cognitive or mood disturbances (confusion, irritability, mutism, aggressiveness, derealization, hallucinations, and delusion), which is almost always present; (2) megaphagia with compulsive eating; (3) hyper sexuality with inappropriate or odd behavior; and (4) abnormal behavior such as irritability, aggression, and odd behavior. KLS usually run a benign course with complete recovery without any long-term consequence. Diagnosis of KLS is difficult due to lack of specific diagnostic marker and hence made by excluding other causes of excessive daytime sleepiness. The diagnostic challenges posed due to nonspecific symptoms of KLS and are highlighted in the following case. There is no definitive treatment for Kleine-Levin syndrome during the episode as well as interepisodic period. Cochrane review published in 2009. Year found no randomized, placebo-controlled trials of pharmacological treatments for Kleine-Levin syndrome. Various medications have been used during an episode in many case reports and found to be no consistent benefits from any one of the drugs. Various stimulants, including methylphenidate, modafinil, pemoline-piracetam-meclofenoxate, D-amphetamine, ephedrine, methamphetamine, etc. can be used to treat sleepiness, but unfortunately, do not improve sluggish cognition or other elements of the altered mental state. However, with amphetamine response rate found to be 71% compared to rest of stimulants.

Case Report

A 20-year-old man referred to our clinic because of sleeping problems. He had normal developmental milestones. His attention, activity and interpersonal interaction were normal both at school and in daily life. His academic grades consistently ranked first in his class. At the age of 14, he presented with complaints of the excessive duration of sleep, increased appetite, excessive daytime sleepiness, loss of interest in social activities during attendance of high school.

Before attending high school, he used to follow a regular sleep schedule, with bedtime at 11 pm and the total amount of sleep of 8 hours. He did not have any issue with sleep onset and used to sleep alone in his bed. According to his parents, he used to sleep in the supine position and did not show any sign of sleep-related breathing disorder. His mother used to wake him up at 7 am, and he usually left the bed within 10 minutes, feeling fresh. He was excellent student with many rewards in mathematics and chemistry school competitions. He had many friends and out school activities.

Seven months after shifting to high school, his father received complaints from the school regarding the deterioration in studies and sleeping in the class. His teachers had also noticed that he lost interest in sports activities. During the next six months, his parents noticed a gross change in his appetite with an increase in frequency and amount of food. His parents also noticed an increase in the time spent in sleep. For the next one year, he started feeling sleepy before 9 pm, and in some days, he sleeps more than 26 hours in the continuum. After waking up, he took nearly an hour to become active. In addition, he started taking 3-4 hour nap after lunch each day. Any force to avoid nap resulted in irritability. He lost interest in sports activities since then.

There was no history to suggest childhood depression, frequent rhinitis, tonsillitis, attention deficit hyperactivity disorder, restless leg syndrome or cataplexy. He had two episodes of visual hallucinations of his friends that last for few hours. There was no sleep paralysis or any other parasomnias. There was no evidence of any neurological disorder, epilepsy, head trauma or substance abuse. His birth history and developmental history were not contributory. His cousin from mother's family was diagnosed with Klein Levine syndrome by the age of 15.

His craniofacial examination was remarkable. Epworth Sleepiness Scale score was 24. His weight was 75 kg, and height was 178 cm, leading to body mass index (BMI) of 23.7. Mental status examination showed normal psychomotor activity. Neurological status was remarkable.

The blood and cerebrospinal fluid tests did not show an abnormality that could explain the hypersomnolence and behavior disturbance. Magnetic resonance imaging

(MRI) brain was noncontributory (Figure 1 and Figure 2). EEG shows α rhythm with normal reaction on eye opening and no pathological phenomena. IQ assessment was also ordered, and it was excellent. DAT scan of the brain shows perfectly normal (Figure 3) Lumbar puncture was noncontributory. Polysomnography followed by multiple sleep latency test (MSLT) was ordered and shows no abnormality.

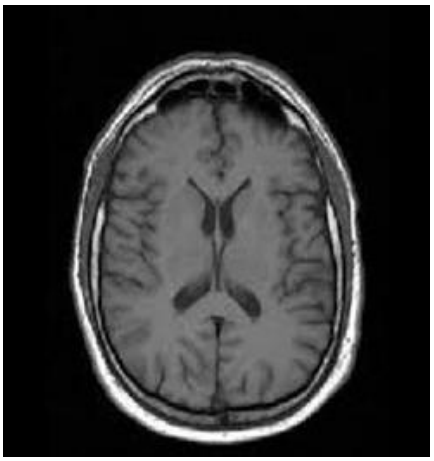

Figure 1. MRI, T1, transversal

We give him for therapy modafinil for 6 months in total dosage of 200 mg once a day. After 6 months therapy his total amount of sleep decreased to 12 hours per day, his eating habits were unchanged, and he has no hallucination experience no more.

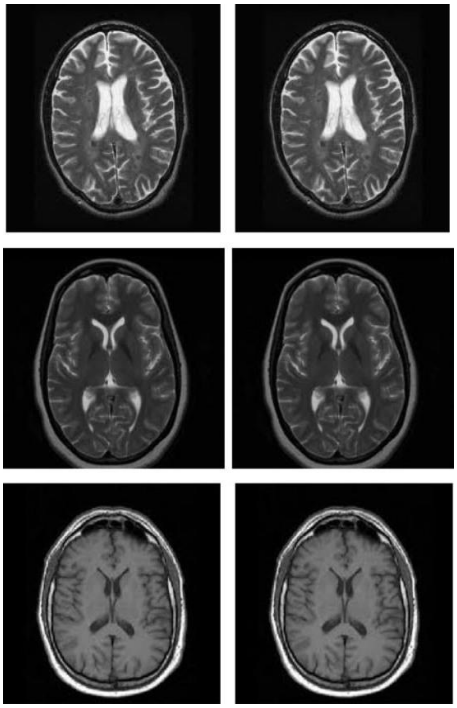

Figure 2. MRI, T2, transversal

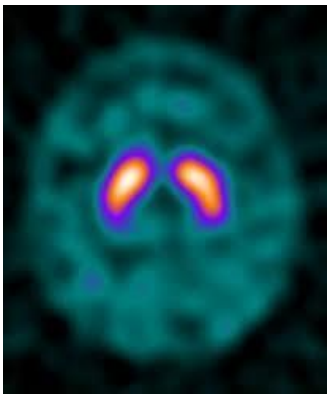

Figure 3. DAT scan

Discussion

KLS is an intriguing, severe, homogenous disease, known for more than a century, with defined clinical features, but no clear cause, no proposed diagnostic algorithms, and no definitive treatment. Studies on KLS were done exclusively with case reports or case series. There is limited systemic study on comparing well-defined KLS with the control group in terms of phenomenology, biological cause, and lists of investigations to identify disease and its management. KLS is commonly seen in adolescent boys and may present with prominent psychiatric features that may delay the diagnosis until a clear hypersomnia pattern is established. Periodic hypersomnia with an increase in total sleep time is an essential feature in the diagnosis of KLS. This was seen in the present case also. KLS may be precipitated after flu-like illness, overseas journey, anxiety, alcohol consumption or sleep deprivation, but not in our case. However, most cases, like our case, are idiopathic. Other illnesses that can be precipitated by stress (e.g. depressive disorder) were ruled out on the basis of history and mental status examination. Cognitive dysfunction is also common in KLS and in our case it was in the form of hallucination in two times. Sexual disinhibition is also seen in KLS cases; however, we could not find any evidence for the same in our case. Recent methods of radiological investigation, such as MRI and DAT SCAN were no contributory in our case. In some case reports SPECT indicate brain dysfunction in cortical and subcortical (and especially thalamus and hypothalamus) areas and DAT SCAN can be helpful in identifying dopamine metabolism dysfunction. Due to the rarity of disorder, it is difficult to identify the underlying biological cause. In future, we need further research on genetic etiology and management of this disorder and more randomized clinical trials on phenomenology, biological cause, and diagnostic

procedures to identify the disease, specific biomarkers, and management.

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