REVIEW ARTICLE

Revisiting Kleine-Levin Syndrome – a case report and review

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Abstract

A 15 year-old girl who was previously well presented with severe recurrent episodic hypersomnia associated with abnormal behavior and hyperphagia after recovery from a mild upper respiratory tract infection (URTI). Physical examination was unremarkable with normal blood tests, brain imaging and electroencephalogram (EEG). A multiple sleep latency test (MSLT) during a typical episode showed moderate hypersomnolence in contrast to a normal MSLT performed an the interval between episodes. Clinical features were consistent with Kleine-Levin syndrome (KLS). She was started on carbamazepine treatment after failing a trial of methylphenidate and is currently being followed up for her symptoms.

Keywords: Hypersomnia, Episodic, Recurrent, Multiple sleep latency test, Polysomnogram, Carbamazepine, Hyperphagia, Kleine-Levin Syndrome.

Abbreviations: KLS: Kleine-Levin syndrome; **URTI:** Upper respiratory tract infection; **EEG:** Electroencephalogram; **REM:** Rapid eye movement; **MRI:** Magnetic resonance imaging; **MSLT:** Multiple sleep latency test; **PSG:** Sleep polysomnogram; **PANDAS:** Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections.

Key Messages

Kleine-Levin syndrome presents often as recurrent daytime hypersomnolence in concert with cognitive and behavioral disturbances. Although more commonly described in adolescent males it can occur in females. Exact pathophysiology is still unclear. Diagnosis is based on the criteria for KLS described in the International Classification of Sleep Disorders (ICSD-2). The role of drug treatment is limited and management is mainly supportive. Spontaneous resolution is frequent occurring in more than two-thirds of patients after 15 years.

Introduction

Kleine–Levin syndrome is a rare disease entity, first described eight decades ago, typified by relapsing-remitting episodes of hypersomnia associated with cognitive dysfunction and behavioral abnormalities, such as binge eating and hypersexuality.

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Case history

KM, a 15 year-old previously healthy girl, presented with 2 months history of severe recurrent episodic daytime hypersomnia associated with behavioral and appetite changes. The onset of these symptoms first occurred acutely and was well documented in a diary by her mother who was a registered nurse by profession. The girl's mother had noted

excessive sleepiness a week after apparently complete recovery from a typical run-of-the-mill bout of upper respiratory tract infection. She had had 3 episodes by the time she presented in the clinic. During a typical bout, she would sleep for 16 to 22 hours in a row and wake up still feeling unrefreshed. Her mother would notice she appeared disoriented about the location of the bathroom and confused about the identity of her parents and sister. She would develop an unusually voracious appetite consuming twice her usual serving portions and snacking frequently in between meals with an insatiable appetite. As a result, her weight had increased by 10 pounds over 2 months. She did not have symptoms of cataplexy, hypnagogic hallucinations or sleep paralysis and there were no delusional thoughts or psychosis. This constellation of symptoms recurred periodically, each attack lasting from 7 to 10 days separated by 2-3 weeks of normal sleep, behavior and eating patterns similar to her pre-illness state. These episodes did not coincide with her menstrual period. When she returned to her baseline normal self, she would have only a foggy recollection of her preceding unusual behavior. She began to be schooled at home as she was unable to participate in regular classes.

KM was born with normal weight after an uneventful pregnancy at 41.5 weeks gestation via Caesarian section due to cephalo-pelvic disproportion. Newborn course and early developmental milestones were normal except for some speech delay at pre-school age for which she received speech therapy. She scored 77 on her latest intelligence quotient (IQ) testing a year prior to her presentation. There had not been any history of febrile convulsions, significant head injury, loss of consciousness, meningitis or encephalitis, major illnesses, hospitalizations or operations. Family history was significant for early onset hearing impairment. Her father had hearing impairment starting in his teens. Her 16 year-old sister, who had both hearing and visual impairment, was born with a solitary kidney, single ovary and was reported to have skeletal anomalies comprising short digits, kyphosis and lordosis. A previous full endocrine and genetic evaluation of her sister did not yield any chromosomal abnormality or malformation syndrome. There was no family history of epilepsy or psychiatric disorders.

Except for mild kyphosis, the physical examination was essentially unremarkable including a full neurological, skeletal, vision and hearing surveillance. Blood testing for complete blood count, renal function, electrolytes, liver function, thyroid screen, ammonia and lactate levels, acylcarnitine profile and mononucleosis antibody were normal. Urine toxicology screen was negative for common substances of abuse. A magnetic resonance imaging (MRI) of her brain was negative for space-occupying lesion or structural abnormality and the electro-encephalogram did not show any seizure activity. An overnight sleep polysomnogram (PSG) and multiple sleep latency test (MSLT) performed at another facility during a "normal" period following her 2nd episode were normal with normal sleep times and no evidence of sleep apnea or periodic limb movement disorder. The mean sleep latency was17 minutes with no sleep-onset REM periods (SOREMPs) on the MSLT.

Repeat sleep studies at our facility during her 4th symptom recurrence showed 2 events of what appeared to be confusional arousal occurring during slow wave sleep during the overnight polysomnogram. An MSLT done the next day was associated with one SOREMP during the first nap trial.and a mean sleep latency of 8 minutes despite 10 hours of sleep recorded the previous night.

A diagnosis of Kleine-Levin syndrome was made based on clinical features and patient was prescribed methylphenidate 20mg tablet once, and subsequently twice, daily for her daytime hypersomnolence. Due to lack of response, she was switched to extended-release carbamazepine at 200mg bid which was titrated up to 400mg bid over 2 weeks. This resulted in KM "skipping" the next 2 "expected" episodes and improvement in her daytime functioning with improved participation in her home school program. Unfortunately, the sleepiness returned 2 months later. The medication was further increased by another 200mg 1 month following a 5th attack.

Discussion

Kleine–Levin syndrome (KLS) is a rare disorder first described by Kleine more than 8 decades ago and further expanded by Levin 10 years later [1]. It is characterized by a triad of recurrent episodic hypersomnia associated with cognitive dysfunction and behavioral changes such as compulsive eating and hypersexuality. The diagnosis is usually established clinically and diagnostic criteria are described in the latest revision International Classification of Sleep Disorders [2]: Episodes of excessive sleepiness occur usually lasting more than 2 days and less than 4 weeks and recur at least once a year. The patient exhibits normal sleep and behavior patterns during the intervening periods which may range from weeks to months. This is a diagnosis of exclusion and requires that somnolence be unexplained by another sleep disorder, a neurological disease (e.g., idiopathic recurrent stupor, epilepsy) or a psychiatric condition (e.g., bipolar disorder, seasonal affective disorder, depression), or

substance abuse (e.g., benzodiazepines, alcohol). In addition to hypersomnia, KLS patients should experience at least one of these symptoms: hyperphagia, hypersexuality, cognitive or perceptual disturbances (e.g., confusion, feeling of derealization, or hallucinations).

Although onset is primarily in adolescence with male predominance, adult disease and female involvement is not uncommon. The median duration of each episode is around 10 days and interval between episodes about 4 months although the interval periods to the next recurrence tend to be shorter in those with childhood onset form [2-3].

The disease course follows a relapsing and remitting pattern and generally disappears spontaneously after reported median duration between 4 to14 years with longer period in males and adult-onset disease [2-3]. In a small case series of 34 patients with KLS, three-quarter experienced complete spontaneous recovery [4].

The underlying pathogenesis of Kleine-Levin syndrome remains unknown although several hypotheses exist. Brain hypoperfusion involving thalamus and frontotemporal regions and especially the hypothalamus which is known to regulate sleep, appetite and sexual function has been postulated to be one of the mechanisms although no consistent structural abnormalities had been detected on neuroimaging [5].

The increased prevalence found in patients with history of obstetric complications is supportive of perinatal brain injury as a vulnerability factor for subsequent symptom development similar to neuropsychiatric conditions such as autism, epilepsy and schizophrenia [6-8]. In one study involving questionnaires, 25% of patients reported birth difficulties as compared to 7.4% in the control group. Delayed motor or language developmental issues were 6.5 times more common in patients with KLS than in healthy individuals [2]. Genetic predisposition may also explain the familial clustering and increased incidence in the Jewish population [2]. Viral and autoimmune causative agents had been suggested in view of frequent reports of infections and flu-like symptoms preceding disease onset as well as association with DQB1*27, DQB1*0201 and HLA-DQ2 allelic variants [9-10]. This autoimmune response is hypothesized to be driven by "molecular mimicry," whereby reactive lymphocytes and antibodies produced in response to an infection enter the blood–brain barrier and cross-react with neural cells to produce dysfunction or inflammation in the central nervous system. Group-A beta-hemolytic streptococcus is one infective agent which had aroused much academic interest in recent years [11]. Kirvan et al. were the first to provide the first possible model of a direct pathogenic mechanism exerted by antineuronal antibodies in post-streptococcal neuropsychiatric disorders [12]. It remains speculatory that KLS may well be a Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) variant. Imbalances in neurotransmitters such as serotonin and dopamine had also been implicated [13-14]. It could also be possible that KLS is another subset of the metabolic syndrome as it had been found that BMI was increased in KLS patients without hyperphagia, in remission and less time spent in bed suggesting a core derangement in the metabolism however in the absence of stronger evidence, this could only be speculative [2]. Triggers which had been loosely linked to KLS have also included cold or flu-like syndrome, physical exertion, head injury, marijuana use, traveling, intense stress, ethanol binge and sleep deprivation with infections being the most commonly cited association [2, 15]

Due to the rare occurrence of the disease, randomized controlled studies on prophylactic and therapeutic drug treatments as well as data on long-term treatment efficacy are lacking. The current available evidence stems from anecdotal case reports and shows some of the treatments to be at best minimally or partially effective. In the largest cross-sectional survey of patients with KLS, the vast majority did not perceive significant benefits from most pharmacological or non-medical treatment in comparison to a watchful waiting approach at home until the episodes resolved [2]. Several pharmacological therapies have been tried for KLS including stimulants (methylphenidate, modafinil, amphetamines), anticonvulsants (carba-mazepine, valproic acid, barbiturates, phenytoin), antidepressants (monoamine oxidase inhibitors, tricyclics, serotonin reuptake inhibitors), antipsychotics (haloperidol, chlorpromazine, trifluoperazine, thio-ridazine, clozapine, risperidone), anti-virals (acyclovir), lithium, steroids, melatonin, hypno-sedatives (benzodiazepines) and dopamine agonist (leveodopa-benserazide) [16].

Thus far, amantadine and anticonvulsants e.g. lithium, valproic acid and carbamazepine are the only drugs to demonstrate marginal clinical benefits.

Amantadine which is both an antiviral and a dopamine reuptake inhibitor appears to resolve most symptoms in half of patients at least for the first episode[2]. However it seems to be significantly less effective for subsequent recurrences. Lithium and valproic acid had been reported to improve disruptive behavior, help with the recovery of symptoms by

reducing the duration of episodes and prevent and delay relapses in some of the patients [17-20]. Carbamazepine has also been shown to improve abnormal behavior [21]. However, a recent article described a more promising preventive role of carbamazepine in inducing remission for 2 years in a 27 year old male KLS patient at a daily dose of 600mg with the disease recurring after patient ceased treatment. It was shown again to be effective in preventing further episodes when patient restarted his medication [22]. Moclobemide, a monoamine oxidase inhibitor, had also been reported to be effective in preventing a recurrence [23]. A recent case report from Japan was the first to record the use of 'gabapentin' in successfully preventing subsequent attacks in a 17 year old girl with KLS and speculated that one of the pathophysiological mechanisms could be related to thalamic seizure-like neuronal activity secondary to GABA-nergic receptors dysfunction [24]. Although stimulants particularly amphetamines may significantly improve hypersomnia, they do not help with the cognitive or behavioral changes [25]. The neuroleptic 'risperidone', has shown partial efficacy in reducing delusions and psychotic symptoms in KLS [26].

Frequent recurrences can be physically and socially disabling to a KLS patient due to severe daytime hypersomnia and destructive behavioral issues. There is no robust pharmacological treatment to-date. Management is still primarily supportive and educational. This includes close supervision by the care-giver, avoidance of driving and active surveillance for depression. A majority of patients do eventually follow a self-limited course with spontaneous resolution, over a period of a decade.

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