

Case Report

Refractory Kleine-Levin Syndrome at Age 3 Years: Response to Lithium Therapy

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Abstract

Kleine-Levin syndrome (KLS) is a rare disease characterized by recurrent episodes of hypersomnia, compulsive hyperphagia and behavioral disorders. KLS affect predominantly male adolescents. We report an unusual presentation of KLS at an early age refractory to a variety of therapeutics and finally controlled with lithium.

INTRODUCTION

Kleine-Levin syndrome (KLS) is a disorder characterized by sudden onset episodes of hypersomnia accompanied by altered behavior, hyperphagia and hypersexuality; this neuropsychiatric disease affects mostly teenagers and young adults [1]. The episodes can last several weeks, and alternate with long periods of normal sleep and behavior [2]. They tend to be less common with age and tend to disappear after the third decade of life [1]. Until now the causes of this condition persists unknown. [1]

A study where functional magnetic resonance imaging (fMRI) was performed identified hyperactivation of the thalamus as a potential biomarker that could be used as a diagnostic procedure [3]. SPECT findings show hypoperfusion in areas like the thalamus, caudate nucleus, and temporal or fronto-temporal regions [4,5].

The high frequency of an infectious disorder at disease onset suggests viral or post-infectious encephalitis with impact on the hypothalamus [6]. Treatment options include antidepressant therapies, amphetamine-stimulants, antiepileptic drugs and lithium [6]. This article reports a refractory case of KLS at an early age, with no response to several therapies until control with lithium.

CASE REPORT

A 3-year-old boy was brought to the emergency room with profound hypersomnia that lasted for 24 hours. He was born from a 40 years-old age mother, history of prematurity labor (32 weeks gestation). Immediately after birth he was admitted in the Neonatal Intensive Care Unit (NICU) for 8 days, to clinical observation and weight gain. After discharge he was followed in an outpatient clinic in a tertiary hospital and had a

normal neuropsychomotor development. No family history of neuropsychiatric illness or sleep disturbances. A year earlier, he was admitted to another hospital with a diagnosis of viral encephalitis. Parents did not have any information about treatment or investigation done at this time.

According to his mother, the present clinical condition started with irritability and asthenia, evolving to deep sleep in few minutes. A similar episode occurred eight months before, lasting 19 hours and, since then, episodes happened every 20 days, approximately, associated to infection or not, and with a progressive increase in duration (the last one lasted 5 days). The events starts with an elevation of the body temperature evolving to hypersomnia, and, when the patient wakes, he presents irritability, hyperphagia and insomnia for 48 hours approximately. Between the episodes there were no reports of mood or behavior alterations.

Physical examination demonstrated dehydration, distended bladder and hyperthermia (38.5°C axillary temperature). Neurological exam showed altered sensorium (3/15 Glasgow) and no focal signs. During his hospitalization, a complete investigation was performed, including toxicological screening, lumbar puncture, tests for inborn errors of metabolism and organics acidemias, and hormonal profile from the hypothalamus-pituitary axis, all with normal results.

Electroencephalogram (EEG) during sleep showed normal basal activity, no epileptic form discharge and normal sleep architecture. Brain MRI was within the normal range and the ictal cerebral scintigraphy showed bilaterally symmetric and homogeneous cortical perfusional distribution and a probable reduction of captation in thalamus. The patient was discharged with oxcarbazepin 40mg/kg/day.

Four months later he had a new crisis (lasting four days), when it was associated valproate 20mg/kg. Three weeks later a new recurrence, valproate and oxcarbazepin were suspended. A trial with methylphenidate was done, but the patient presented paradoxical reaction. Imipramine 25mg/day was initiated, and lasted for thirteen days until next hospitalization, when nortriptyline 12.5 mg/day was given. The patient persisted symptom free for a month and a half until a new relapse. Another EEG realized during a crisis, showed rare sleep elements, normal basal rhythm and no epileptic discharges.

Six days later, the patient woke up spontaneously, presenting irritability, hyperphagia and insomnia for 48 hours, being indicated the use of lithium at a dose of 300mg/day. Posteriorly, the patient had a new episode in face of acute otitis media and kept being asymptomatic later, with a proper development for his age until today. Nowadays, he uses lithium 300mg/day and nortriptyline 25mg/day.

DISCUSSION

The present case report shows an unusual age presentation and response to treatment of KLS. Considering the diagnostic criteria proposed by Critchley [7] and subsequently by the American Academy of Sleep Medicine [8,9], the exceptions, in our case, were the absence of inappropriate sexual behavior, which might be a symptom age-related.

The episodic hypersomnia (18±2 hours) is the clinical symptom with the highest diagnostic utility [6], which, in our patient, lasted 19 hours in the first episode, and ascending progressive feature, lasting 5 days in the last crisis.

The age of presentation of three years in our patient is different comparing to the available clinical data, where the average age of presentation was 16.9±8.5 years (81% of the cases began during the second decade of life) [6].

The etiology and the pathogenesis of Kleine-Levin's Syndrome (KLS) are still unknown. The most accepted theory associate the syndrome to hypothalamic alterations (for being physiological centers associated to sleep, hunger and sex) and to the pituitary gland (hypothalamus-pituitary axis) [10]. Other causes are the relation of the serotonergic and dopaminergic metabolism and frontal lobe, thalamus and basal ganglia alterations [8]. A relationship with problems at labor and delivery that might be associated with perinatal brain injury was previously explored [11].

Our case report reinforces that KLS's diagnosis is based on clinical findings, after ruled out organic or infectious disorders that could explain the symptoms and with a normal EEG, to exclude status epilepticus [12].

There is no consensus in the literature regarding the best treatment option perhaps because the self-limited feature of the disease and the lack of controlled studies with placebo [6]. Lithium is widely used as prophylaxis for relapse's prevention and is an option treatment in patients with behavioral changes [13,14].

Arnulf et al [6] reviewed 186 cases of KLS, where 29 patients were treated with lithium and 41% had successful results. Instead, another study [11] with 108 patients, obtained effective results in only 24%. Muratori et al [15] suggests that lithium therapy can be very important not only to stop attacks but also for reduction in the frequency of episodes. Efficacy of lithium in KLS raises the question of its relation with mood disorders [15], but larger samples of patients might be investigated in order to establish a relationship.

In conclusion, despite the origin of KLS, our case demonstrates an unusual age presentation and treatment response, since the patient did not have any behavioral or psychiatric disease.

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