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Case Report

Kleine–Levin Syndrome: A case report ☆

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ABSTRACT

The Kleine–Levin Syndrome is a differential diagnosis for patients with diurnal excessive sleepiness and a suspicion of narcolepsy. It is characterized by paroxysmal attacks of diurnal excessive sleepiness, associated with one or more symptoms of hyperphagia, hypersexuality, coprolalia and copropraxia. During crisis intervals, there are no symptoms. This pathology predominantly manifests itself in teenagers, being more frequent among males. The course of this disease is unpredictable, with variable duration and frequency. The most accepted physiopathology is that of a hypothalamic dysfunction, although and recently, there has appeared a hypothesis of a post-infectious autoimmune disorder. These patients show an elevated body mass index, which can predispose to association with comorbidities such as the sleep obstructive apnea syndrome. Treatment involves medications with different effects, but there is no specific and effective therapy. Our article shows a classic case of Kleine–Levin Syndrome associated with sleep obstructive apnea syndrome, a rare association in the literature.

1. Introduction

The Kleine–Levin Syndrome (KLS) is a disease characterized by recurrent periods of hyper-sleepiness, with absence of urinary incontinence and the presence of verbal responses to intense stimuli. Hyperphagia, hypersexuality and behavioral or cognitive alterations (irritability, aggressiveness, mental confusion, and disorientation) are signs and symptoms found in isolation or in conjunction among these patients. A KLS patient might sleep for 18 hours a day and the crisis usually manifests at least once a year, ranging from 3 days to 3 weeks [1,2]. At crisis intervals, behavior, cognition and sleep are normal.

The disorder is more frequent among teenagers of the male gender [1–5] and has an unpredictable course with

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Table 1 – General characteristics.

	Basal	After 5 years
Age (years)	19	24
Height (m)	1.78	1.78
Weight (kg)	101.8	113.0
IMC (kg/m^2)	32.1	35.7
Cervical circumference (cm)	43	44
Abdominal circumference (cm)	100	110
Arterial blood pressure (mmHg)	130 × 80	140 × 80

Body mass index (BMI).

remissions and recurrences which can last for years. This disease can disappear as subtly as it appears (an average of 8–13 years duration) [2,5].

The first KLS episode is generally preceded by an event associated with the beginning of the symptoms, more commonly an infection, alcohol ingestion, sleep deprivation, stress, physical exhaustion, travels, brain trauma, surgeries with local or general anesthesia, lactation, menstruation and the use of drugs [2,3,5–7]. The precipitating factors are found more easily at the first episode of the disorder, being much less frequent in subsequent episodes [2,4].

Patients may also refer intense dreams, hallucinations, persecution nightmares and compulsions. They may also show difficulty of speech and reading, disorientation and perception alterations [2,5]. Sleep paralysis and cataplexy are not common. Patients during a crisis are able to wake up spontaneously to go to the bathroom and eat, but may become aggressive and irritated if awoken or impeded of sleeping [2]. Hypersexuality is more frequent among men and appears to be predictive of a more prolonged disease [2,4,5]. Dis-autonomic complaints may be identified in up to 25% of the patients (heavy sudoresis, blushing, congested or edematous face, hypotension, bradycardia and nausea) [4]. After the crisis, the patient might show insomnia, sometimes associated with euphoria and to partial amnesia with a duration of up to 24 h [2,4,5].

2. Clinical case

FSM, 19 years old, born in the state of São Paulo, began to show the symptoms in March, 2008, at 14 years of age, with "excessive sleepiness periods", referred by his parents.

The patient was born through a C section, normally and without any problems. The patient had normal neuropsychomotor development, vaccination according to the Brazilian schedule and without history of previous diseases. The patient's mother referred that the patient ate too much, although the food was not of a high nutritional content. His sleep pattern involved a 30 min nap after lunch, waking up well and sleepless. He usually went to bed between 22 and 23:00 h, taking about 30 min to sleep and waking up at 5:30 h in the morning. He slept about 6 h during the week and between 9 and 10 h on weekends. In addition, he showed eventual somniloquy and high and constant snoring, without episodes of observed apnea. There was no familiar history of excessive sleepiness. His parents demonstrated eventual snoring and the mother was hypertense and obese. The diurnal excessive sleepiness (DES) attacks began around 13 years of age and had a duration of 8–17 days and were only interrupted by familiar interference. The attacks were accompanied by a lethargic behavior with intense apathy as a triggering factor. Concomitantly, there was a decrease in verbal communication – "answered only when asked something" – demonstrating increased sudoresis as the crisis intensified.

At physical examination, the patient was of 1.78 m height, 101.8 kg weight, with cervical and abdominal circumference of 43 cm and 100 cm, respectively; regular 2-beat cardiac rhythm, heart rate of 80 bpm and arterial pressure of 130/80 mmHg. Table 1 shows the main characteristics of the patient. Oral examination demonstrated elongated uvula, web palate, tonsils occupying less than 50% of the oral-pharynx and a Mallampati index of grade II.

At first consultation, the patient was already being followed up by a psychiatrist and was taking venlafaxine 75 mg/day and oxycarbamezepine 300 mg/day. His performance at school had not been decreasing and his grades followed the pattern before the onset of the disease. The psychiatrist described that the teenager had shown persecutory delirium at the onset of the disorder and that the crisis were triggered by stress. There were no complaints of hallucinations or cataplexy. The patient referred "laziness", "sleepiness", and "slow thinking" at the beginning of the crisis, isolated himself during the crisis and only awoke to eat or go to the bathroom and stated that he did not have recollection of what was going on during the crisis. The family described hypersexuality during the crisis. The interval between crises was of 3 and 4 months' duration. The patient also referred that his anxiety triggered his crisis. When awake during the crisis, the patient stayed quiet, did not laugh or talk to the family, demonstrating sudoresis and normal thinking process.

The first polysonogram, in May 2009, demonstrated increase in the percentage of slow waves, without other alterations. The electroencephalogram demonstrated diffuse slowing waves during crisis. The diagnosis was that of Kleine–Levin Syndrome and we initiated a reduction of venlafaxine to 37.5 mg/day until posterior suspension. The dose for oxycarbamazepine was increased to 450 mg/twice daily.

His humor progressively improved along the days of treatment. He finished high school and is now working. However, since he has been taking oxycarbamazepine 600 mg/day, his family describes that his humor only improved ("he is less

irritated") and does not demonstrate effect upon his crisis. The young man retains his sleeping habits at periods between crises, referring heavy sleepiness during the week and naps during the afternoon, without sleepiness during weekends. He denies parasomnia, sleep paralysis, hallucinations and cataplexy.

After 5 years of the initial diagnosis, the patient referred snoring, agitated sleep and choking during the night, being directed to a new polysonogram. His weight was 113 kg, height was 1.78 m (IMC = 35.7), with abdominal circumference of 110 cm, cervical circumference of 44 cm and arterial blood pressure of 140/80 mmHg. He had an epworth sleepiness scale of 16 (of a total of 24). Biochemical evaluation showed normalcy. Brain nuclear magnetic resonance (MR) was normal (as tested on 09/04/2012). Test for the presence of HLA-DQB1*0602 resulted negative. The test for sleep multiple latencies during normal periods did not demonstrate DES (the patient did not sleep during any of the registries).

The last referred crises and their duration times were: 02/2012 (15 days); 04/2012 (8 days); and 21/06/2012 (the number of days were not reported); the last consultation was at 21/01/13 with one report of a crisis of 7 days' duration after 09/2012.

The polysonogram of 07/04/12 showed latencies for the beginning of sleep and normal REM sleep, good sleep efficiency and total sleep time of 442 min. Sleep stage N3, slightly increased (27.3%) and the REM sleep was normal (20.4%). An awakening index of 11.6/h was reported, along with the absence of repeated leg movements (RLMs) and the apnea and hypopnea index equal to 30.8/h, with basal saturation of 96.5% and minimum of 77%. The positive pressure titration (31/05/2012) indicated an ideal pressure for apnea and hypopnea control of 8 cmH_2O (Table 2). The patient initiated frequent use of the continuous pressure equipment (CPAP) in June 2012, being well adapted to the mask and with a total decrease of the sleepiness crisis frequency until today. Electrophysiological examinations were no longer conducted due to the good clinical evolution.

3. Discussion

The most studied physiopathology for KLS is that of a hypothalamic dysfunction, which would justify the alterations of the sleep regulatory system, sexual behavior and appetite. However, some published studies were not capable of identifying consistent abnormalities [1,5]. Actually, there is a new hypothesis of post-infectious autoimmune disorder, where a viral or any other etiological agent would trigger the development of this disease with association of histocompatibility complexes (HLA-DR and HLA-DQB1*0201) [4,6,8]. However, there is no definitive proof for it, since there are no studies that found that correlation [3,5]. Even though 98% of the cases are sporadic, there are also reports of familiar cases with multiple cases of KLS [2]. Homozygous twins do show the syndrome after a case of flu and HLA research found the presence of the alleles DQB1*0302/0601 and DRB1*0407/1502, strengthening the hypothesis of a immunologic etiology and genetically associated [8,9].

The presence of periodical respiration during the N1 and N2 phases and central apnea in patients with KLS has been described. However, they were not associated with CO_2 retention, suggesting a possible hypo-excitability of the respiratory center [10,11].

Patients with KLS used to demonstrate high level of body mass index (BMI) due to elevated blood levels of leptine [5]. Epidemiological studies have shown that weight and IMC are strong risk factors for Obstructive Sleep Apnea Syndrome (OSA), mainly in men. In theory, the progressive increase of IMC in these patients might lead to an increased prevalence of OSA.

The treatment of KLS involves several medications. However, there is no specific or effective therapy for the problem [3]. Among the stimulants, amantadine may possess significant effect upon the ending of a crisis at the beginning of the treatment, but it loses its efficacy with repeated use; modafinil, methylphenidate and amphetamine occasionally increase awareness, but do not improve the cognitive complaints [2,5]. Antidepressants such as bupropione and fluoxetine have limited effect upon cases with depressive behavior, but lack the prophylactic effect upon the disease [2,5]. Neuroleptics are not efficacious in treating the psychotic symptoms, de-realization and behavioral symptoms, although risperidone may act upon cases that are followed by delirium. Lithium and valproate might help to prevent the recurrence of this type of symptom [2,4,5]. Presently, the drug treatment does not help the patients with KLS. Very few improvements with this type of treatment have been reported [5].

Table 2 – Pre- and post-CPAP polysonogram parameters.

	Basal	After CPAP
Total sleep time (min)	442	422.5
Sleep efficiency (%)	91.8	94.9
Latency for beginning of sleep (min)	10.3	5.8
Latency for REM sleep (min)	94	103.5
N1 (%)	7.4	4.4
N2 (%)	45	34.4
N3 (%)	27.3	28.3
REM (%)	20.4	32.9
AHI (events/h)	30.8	0.9
Awakening index (events/h)	11.6	10.8
SaO_2 average (%)	96.5	97.1
SaO_2 minimum (%)	77	92

Oxygen arterial saturation (SaO_2); Apnea and Hypopnea Index (AHI).

Differential diagnoses like narcolepsy, no convulsive epileptic *status* [1,6], familiar hemiplegic migraine, hypothalamic tumors and psychiatric disorders must always be researched. In patients with KLS, OSA must always be included and treated for high prevalence in terms of weight gain in this population [6].

4. Conclusion

This article reports a very interesting case of KLS with clinical worsening after OSA association. It demonstrates that with OSA being diagnosed, this treatment is truly beneficial to patients with this comorbity.

REFERENCES

[1] American Academy of Sleep Medicine. In: Hauri P, editor. The international classification of sleep disorders—revised. Chicago; 2005. p. 43–6.
[2] Arnulf I, Zeitzer JM, File J, Farber N, Mignot E. Kleine–Levin syndrome: a systematic review of 186 cases in the literature. Brain 2005;128(12):2763–76.
[3] Huang Y, Lin Y, Guilleminault C. Polysomnography in Kleine–Levin syndrome. Neurology 2008;70:795–801.
[4] Billiard M, Jaussent I, Dauvilliers Y, Besset A. Recurrent hypersomnia: a review of 339 cases. Sleep Med 2011;15:247–57.
[5] Arnulf I, Lin L, Gadoth N, File J, Lecendreux M, Franco P, et al. Kleine–Levin syndrome: a systematic study in 108 patients. Ann Neurol 2008;63:482–92.
[6] Lisk R. Kleine–Levin syndrome. Pract Neurol 2009;9:42–5.
[7] Gadoth N, Kesler A, Vainstein G, Peled R, Lavie P. Clinical and polysomnographic characteristics of 34 patients with Kleine–Levin syndrome. J Sleep Res 2000;10:337–41.
[8] Bahammam AS, GadElRab MO, Owais SM, Alswat K, Hamam KD. Clinical characeristics and HLA typing of a family with Kleine–Levin syndrome. Sleep Med 2008;9:575–8.
[9] Ueno T, Fukuhara A, Ikegami A, Ohishi F, Kume K. Monozygotic twins concordant for Kleine–Levin syndrome. BMC Neurol 2012;12:31.
[10] Vardi J, Flechter S, Tupilsky M, Rabey JM, Carasso R, Streifler M. Kleine–Levin syndrome with periodic apnea during hypersomnic stages—E.E.G. study. J. Neural Transm 1978;43:121–32.
[11] Lavie P, Klein E, Gadoth N, Bental E, Zomer J, Bechar M, et al. Further observations on sleep abnormalities in Kleine–Levin syndrome: abnormal breathing pattern durind sleep. Electroencephalogr Clin Neurophysiol 1981;52:98–101.