

KLEINE-LEVIN SYNDROME

CLINICAL COURSE, POLYSOMNOGRAPHY AND MULTIPLE SLEEP LATENCY TEST

Case Report

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ABSTRACT - A case of Kleine-Levin syndrome, with chronic severe periodic hypersomnia is described in a 17-year-old female. The first episode started when she was 15 years old. The episodes were characterized by periodic hypersomnia accompanied by hyperphagia, lasting 5 days, and repeating at 28 to 60 day intervals. The severity of hypersomnia prevented her from attending school activities. Outside the hypersomnia periods, she was asymptomatic. EEG, brain computerized tomography and brain nuclear magnetic resonance were normal; all-night polysomnography, Multiple Sleep Latency Test (MSLT) and Epworth Sleepiness Scale (ESS) were within normal limits. During the period of hypersomnolence, polysomnography showed short sleep latency and short REM latency. MSLT mean sleep latency was 1.8 min; and REM period was present in one subtest; the ESS was markedly elevated.

KEY WORDS: Kleine-Levin syndrome, recurrent hypersomnia, sleep disorder, sleep, adolescent, polysomnography, Epworth Sleepiness Scale.

Síndrome de Kleine-Levin: aspectos clínicos, polissonografia e teste das latências múltiplas do sono. Relato de caso.

RESUMO - Relata-se o caso de paciente com síndrome de Kleine-Levin, de 17 anos de idade, sexo feminino, com períodos de hipersônia recorrente, severa e crônica. O início do quadro foi aos 15 anos de idade. Os períodos de hipersônia acompanhavam-se de hiperfagia, duravam cerca de 5 dias e repetiam-se a intervalos de 28 a 60 dias. A severidade da hipersônia impedia a participação em atividades escolares. Entre os períodos de hipersônia, a paciente encontrava-se assintomática, EEG, tomografia computadorizada cerebral, ressonância nuclear magnética cerebral, polissonografia, Teste das Latências Múltiplas do Sono (TLMS) e Escala de Sonolência Epworth (ESE), foram normais. Durante período com hipersônia, a polissonografia evidenciou latência do sono e latência REM reduzidas. TLMS teve latência do sono, em média, de 1,8 min; presença de um período REM em no segundo subteste; o índice da ESE foi acentuadamente elevado.

PALAVRAS-CHAVE: síndrome de Kleine-Levin, hipersônia recorrente, distúrbio do sono, sono, adolescente, polissonografia, escala Epworth de sonolência.

Kleine-Levin syndrome (KLS) is characterized by recurrent hypersomnia, usually starting in the second decade of life, and is associated with hyperphagia¹⁻⁴. This report describes an adolescent female with severe and chronic KLS, focusing on clinical aspects, polysomnography, Multiple Sleep Latency Test (MSLT)⁵ and the Epworth Sleepiness Scale (ESS)^{6,7}.

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CASE REPORT

CJ, a 17-year-old black female was referred to the sleep disorders center, presenting periodic hypersomnia for almost two years (Fig 1). The patient and her father recalled that the first episode occurred accompanied by an acute febrile short-term mild upper airway infection. The hypersomnia periods lasted around 5 days and repeated at 28 to 60 day intervals. The hypersomnia episodes had a relatively abrupt onset in the course of one day; they also ended abruptly in the same one day pattern. These episodes were unrelated to menstrual cycles.

During the episodes of hypersomnia, the patient slept for more than 18 hours per day, waking only to eat and void. She did not wake up for regular meals. However, she would wake up suddenly eating voraciously, binge eating, with rapid consumption of large amounts of food, specially sweets, chocolate and hamburgers. At these times, she might rapidly eat three large sandwiches at once. After eating, she avoided talking and went back to bed, sleeping promptly.

When food was not present in her room, she displayed craving and food-seeking behavior. During the hypersomnia period, if the family tried to keep her awake, she might respond verbally, with few coherent words, irritability, mild aggressive and impulsive behavior. During the short wake periods, she was usually quiet and apathic. She reported to feel confused and that even her family and friends looked strange or unusual. She was careless about personal hygiene, and avoided bathing, changing her clothes and combing her hair. Urinary incontinence did not occur. There was no inappropriate sexual behavior. She did not use alcohol or illicit drugs. The hypersomnia period was severe enough to prevent her from regular school attendance and to study at home. During the last year, she was absent about 5 days per month.

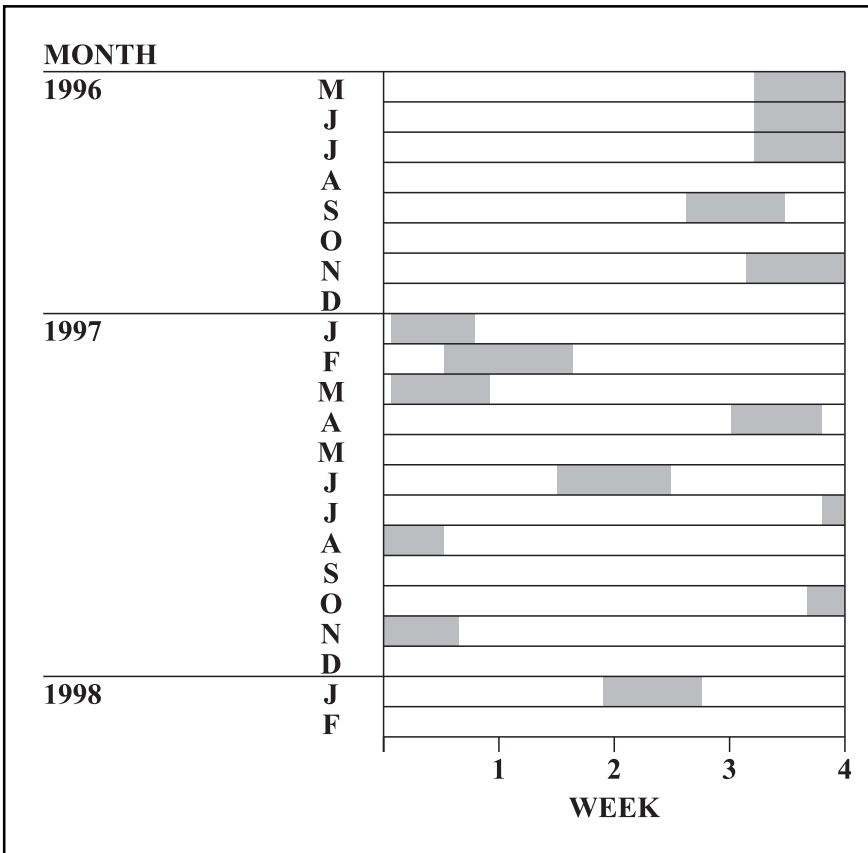


Fig 1. Recurrent episodes of hypersomnia in the Kleine-Levin syndrome 22 months time course.

Table 1. All-night polysomnographic data obtained during baseline non-excessive daytime somnolence period (NDS) and during a period with excessive daytime somnolence (DS).

	DS	NDS
Total time in bed (min)	491	507
Total sleep time (min)	484	494
Sleep efficiency (%)	98.5	97.4
Sleep latency (min)	3	6
REM latency (min)	71	104
Stage 1 (%)	1.0	3.8
Stage 2 (%)	56.1	48.5
Stage 3 (%)	1.8	2.0
Stage 4 (%)	17.1	23.6
Stage REM (%)	23.7	21.8

ratory tests were normal, including blood count and urinalysis; serum calcium, magnesium, and phosphorus, fasting morning glucose, T3, T4, TSH were normal. Abdominal and specifically pelvic ultrasound examinations were normal. During the asymptomatic period, EEG, CT brain scan (CT) and brain nuclear magnetic resonance (NMR) were normal.

All-night polysomnography recordings were performed in periods with and without hypersomnolence, using standard criteria⁸ and the data obtained are shown in Table 1. An adaptation night was performed previously to each monitoring night. The recordings included EEG, electrooculogram, submental and anterior tibialis electromyogram, nasal and buccal thermistors, pneumogram, electrocardiogram and transcutaneous oximetry (O₂sat) with standard finger probe. The monitorings did not demonstrate any breathing or heart rate abnormalities - including any snoring - or periodic movements of sleep (nocturnal myoclonus). Short REM latency was the main finding in the hypersomnia period. Short sleep latency was also present (cut-off > 5 min) to a less degree. Other differences were slight in comparison with the baseline non-hypersomnia period.

Using standard criteria⁹, the MSLT, was obtained twice. During the basal, non-hypersomnia period, she slept in 3 out of the 5 subtests; mean sleep latency was 17.6 min; with no REM sleep detected. During a hypersomnolent episode, she slept in all the 5 subtests; MSLT mean sleep latency was 1.8 min; REM period was detected in the second of the five subtests only; in the latter subtest, REM latency was 4 min. It is essential to point out that it was impossible for the staff to maintain the patient awake between the subtests, due to her severe drive to sleep.

The ESS^{6,7} was applied three times. During the basal, non-hypersomnia period ESS was obtained twice, over a month's interval, and in both the score was 9. During the hypersomnolent episode, the score was 24.

The Hamilton Rating Scale for Depression (HAM-D) was obtained three times. During the basal, non-hypersomnia period the HAM-D was applied twice, over a month's interval, and the scores were 6 and 3. During the hypersomnolent episode, the score was 8.

Regarding previous treatment, she had tried valproic acid 500 mg p.d., for two days but discontinued its use because of side effects (vomiting and somnolence). She had also taken amitriptyline 25 mg p.d. for three months without improvement. Over the last two weeks, after polysomnography and MSLT evaluations, she was started on carbamazepine CR 200 mg p.d.; and long term use was planned.

DISCUSSION

KLS is a chronic disorder with typical onset during adolescence¹⁰⁻¹³. It is more prevalent in males; however, in a large series of 162 cases, 21% were females¹⁴⁻¹⁶, as in case presently reported.

Outside the hypersomnia periods she was asymptomatic. She had proper sleeping habits, going to bed at 10 PM, and waking up at 6 AM in order to attend school in the morning. She performed adequately in school, as well as in after school activities including gymnastic classes, swimming and foreign language. She was slim and expressed her concern about putting on weight, although she has never been overweight, nor showed any voracious eating in the non-hypersomnia periods. In fact, in almost two years, she had lost one kilogram since the onset of the disease. She tightly used to control her own sweets and sandwiches consumption. She presented inhibition of her sexuality.

Past medical history was uneventful. There was no other similar case in her family, nor consanguinity. She was the second daughter of four children; she had three brothers. The parents had been divorced for ten years and the children were living with their father. Physical and neurological examinations were normal; body weight, 58 kg; height 170 cm. During the hypersomnia episodes, she could be easily aroused, and then, neurological examination was normal. Labo-

Billiard¹⁶, evaluating 162 KLS patients, observed that in 39% of the cases, the onset occurs with an influenza-like illness with upper airway infection. Smolik and Roth¹⁸, mention that the first hypersomnia episode was described associated with an acute mild febrile affection, including tonsillitis, in 5 out of 11 cases (45.4%). The case here reported had a mild acute febrile upper airway infection accompanying only the first hypersomnolence episode.

The attacks of hypersomnolence usually occur and end suddenly, lasting from several days to several weeks^{17,18}. Intervals between attacks can last for several weeks to months, and sometimes even years.

Megaphagia, or binge eating, with rapid consumption of large amounts of food, is the second characteristic of this syndrome, and present in 81.8% of the KLS patients¹⁸. However, it may not be present in every hypersomnolence episode¹⁵. The remarkable preference for sweets and chocolate clearly observed in our case has also been consistently described by others¹⁵.

Despite the fact that hypersexuality was reported in the early KLS cases, larger series recently published did not note this so frequently. Billiard¹⁵ noticed hypersexuality in 1/3 of the male patients and reported that it was less common in females. Smolik and Roth¹⁸ have found it in 3 out of 11 patients (27.2%). The present case did not exhibit any sexual drive dysfunction.

Between the hypersomnolence episodes, behavior and sleep are within normal limits in typical KLS cases, as it was in this case. On the other hand, the recurrent episodes of hypersomnia and hyperphagia can be incapacitating, with frequent absence from school or work^{10,12,15}. Smolik and Roth¹⁸ noticed impairment in the private life of 81% of their patients. Total or partial retirement or limited work activities was present in 54.5% of their cases¹⁸.

The diagnosis of KLS is basically clinical. CT and NMR are usually normal, and are applied in order to rule out other organic hypersomnias^{14,15}. In the presently described case they were also normal.

Reports of all-night polysomnography, during the episodes of hypersomnia are scarce. Increase in sleep efficiency; short REM sleep latency, and reduced stages 3 and 4 have been described^{14,15,17}. In the presently reported case, the main finding was short REM latency. The sleep latency was mildly reduced. Other differences were modest in comparison with the baseline non-hypersomnia period.

MSLT findings during the episodes of hypersomnia were described⁵, i.e., short sleep latencies and the presence of REM sleep in one or more naps. This pattern was present in this case. Furthermore, we would like to emphasize in the present case that the drive to sleep in the intervals between MLST subtests prevented the staff from keeping her awake, despite all efforts. Her drive to sleep was certainly more intense than we usually see in the MSLT performed with more common disorders, like narcolepsy or obstructive sleep apnea syndrome.

The ESS score difference described in our case is relevant, supporting the remarkable somnolence. It has been previously shown that ESS scores are strikingly stable over time for normal populations, differing by no more than one unit in more than 9 out of 10 normal individuals^{6,7}.

HAM-D scores were 6, and 3, in baseline conditions, and 8 during the hypersomnia episode. Cut-off values may be considered as 0-7 absence of depression; 8-15 mild depression; 16 or more major depression. However, one must also consider that HAM-D includes items for physical symptoms and that accounted for the higher index during the period of hypersomnia and megaphagia.

The typical presentation of this case with recurrent hypersomnia accompanied by hyperphagia starting in the second decade of life leaves little room for other diagnoses, also characterized by periodic hypersomnia. Menstrual-associated hypersomnia¹ may be ruled out due to the lack of time relation to those cycles. It is also clearly distinguishable from the periodic hypersomnia observed in

congenital ectodermal disorders and multiple exostosis¹⁹ because of the absence of these adjuvant signs. The diagnosis of recurrent monosymptomatic hypersomnia^{17,20} is also excluded due to the presence of hyperphagia, which distinguishes the former from KLS.

The KLS etiology is largely unknown, and has been interpreted as a manifestation of diencephalic, possibly hypothalamic, dysfunction^{15,18,21,22}. As a rare disease, systematic treatment trials are still lacking. Therefore, therapy is mainly symptomatic, including stimulants such as amphetamines, methylphenidate or pemoline. Preventive treatment includes lithium carbonate, tricyclic antidepressants, moclobemide, carbamazepine, and valproic acid. These drugs have been reported as useful in a small number of patients^{18,23-29}. The case here described is presently starting on carbamazepine, and its long term use has been considered.

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