

## CASE REPORT

# Kleine–Levin syndrome with comorbid iron deficiency anemia

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## Abstract

Kleine–Levin syndrome (KLS) is a rare chronic sleep disorder of unknown etiopathology, which typically occurs in adolescent males. Although the severity of symptoms and disease course varies between the KLS patients, it usually resolves spontaneously, but sometime comorbid conditions may worsen the symptoms. Herein, we report a case of KLS who presented with severe episodic hypersomnia. During episodes, the patient used to sleep as long as 20 h in a day, affecting his daily living activities. All the relevant investigations including electroencephalography, magnetic resonance imaging of brain and cerebrospinal fluid analysis were normal except for severe iron deficiency anemia (IDA). In our patient, the severity of symptoms worsened due to coexistent IDA. The treatment of IDA along with modafinil decreased the severity of symptoms and shortened the hospital stay during episodes. This might be the first case report of KLS with comorbid IDA.

## INTRODUCTION

Kleine–Levin syndrome (KLS) is an uncommon chronic sleep disorder, primarily occurring in adolescent males [1]. It is characterized by episodic hypersomnia and other variable features like hyperphagia, mood changes or hypersexuality. Individual episode usually last for weeks with symptom-free interval of several months [2]. Since KLS is a rare disease, its diagnosis should be made after ruling out other causes like sleep deprivation, sleep apnea, psychiatric disorders, narcolepsy, sedative medications, hypothyroidism, brain tumor, nonconvulsive status epilepticus, encephalitis and Klüver–Bucy syndrome. Iron deficiency anemia (IDA) by itself can cause symptoms of excessive tiredness and hypersomnia. Here we discuss a case of KLS, whose symptoms worsened due to coexisting IDA and improved on treatment.

## CASE PRESENTATION

A 35-year-old male presented with an 8-year history of episodic hypersomnia, lasting for about 15–20 days. The episodes were abrupt in onset and occurred approximately once every 2–3 months. During the episodes, the patient would remain somnolent, inactive and sleep for an average period of about 20 h in a day. He had to be woken up forcefully by family members to perform daily living activities including eating and bathroom visits. He also gave history of increased sexual desire. In between the hypersomnic episodes, the patient remained asymptomatic. There was no history of seizure, altered sensorium, hyperphagia, aggressive or impulsive behavior and no such type of illness in family. The physical examination revealed generalized pallor. The rest of the neurological examination was unremarkable.

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Previous hospital records revealed diagnosis of KLS with microcytic-hypochromic iron deficiency anemia with hemoglobin level ranging from 6.8 to 8.5 mg/dl. He was on carbamazepine prophylaxis along with oral iron and folic acid supplementations. However, due to non-compliance of the treatment, patient used to have repeated episodes and hospitalizations.

Six-month back patient was hospitalized with similar complaints. His hemogram revealed severe microcytic-hypochromic anemia (hemoglobin; 6.3 mg/dl), without any evidence of hemolysis or hemoglobinopathies. Osmotic fragility testing was negative. The mean corpuscular hemoglobin concentration (MCHC) and mean corpuscular volume (MCV) were 18 g/dl (32–36 g/dl) and 65 fl (83–97 fl), respectively. The serum iron was 32 µg/dl (60–170 µg/dl), ferritin 6 ng/ml (12–300 ng/ml) and total iron binding capacity (TIBC) 360 µg/dl (240–450 µg/dl). Bone marrow aspiration cytology showed evidence of microcytic-hypochromic anemia without stainable iron in tissue. Stool examination was negative for occult blood, ova and cyst. Serum biochemistry including thyroid function tests and serum vitamin B12 levels were normal. Abdominal ultrasonography, upper and lower gastrointestinal endoscopy were normal. Electroencephalography and gadolinium-enhanced magnetic resonance imaging (MRI) of brain were normal (Fig. 1a and b). Epworth sleepiness scale (ESS) score during hypersomnic episode and asymptomatic period were 20 and 6 (out of possible 24 points), respectively. The polysomnography (PSG) study was done after blood transfusion near the end of episode. The recordings included electrocardiogram, pneumogram, nasal and buccal thermistors, submental and tibialis anterior surface electromyography, electrooculography, electroencephalography (EEG) and transcutaneous pulse oximeter finger probe for oxygen saturation. The PSG study during asymptomatic period was normal. Overnight PSG recordings during hypersomnic episode showed sleep onset latency and mean sleep latency of multiple sleep latency testing (MSLT) were 9.5 and 8 min, respectively, with normal sleep architecture without evidence of breathing or heart rate dysfunction, narcolepsy, obstructive sleep apnea or periodic limb movements. During sleep, the technician faced difficulty to wake up the patient because of severe drive to sleep.

The acute episode was managed with modafinil (100 mg twice a day) along with three-units of blood transfusion. He

was discharged on carbamazepine (300 mg twice a day) and nutritional supplements including iron. At 6-month follow-up, his hemoglobin was 11.7 mg/dl and he did not have further episodes of hypersomnia.

## DISCUSSION

KLS is a rare sleep disorder, which predominantly occurs in adolescent male patients. It is characterized by episodic hypersomnia, hyperphagia, mood disorders and hypersexuality [1, 2]. Our patient had severe degree of somnolence during episode, which was evident on ESS score of 20 during episode [3]. The other symptoms like hyperphagia, hypersexuality, apathy, hallucinations, delusions, mood disorders (anxiety, depression) are variable and not necessarily present in all the patients [4]. KLS patients usually sleep for 15 to 20 h in a day during episodes. Multiple triggers of KLS have been suggested including infections, dehydration, cold, alcohol, sleep deprivation, mental or physical stress and trauma. Though, etiopathology is still unknown, various pathophysiologic hypotheses have been proposed including the role of hypocretin [5], diencephalic-hypothalamic dysfunction [6], central serotonin and dopamine abnormalities [7]. The young onset, recurrent symptoms, frequent infectious trigger factors (70%) and increased frequency of the human leukocyte antigen (HLA) DQB1\*0201 allele, suggest an autoimmune etiology for KLS [8].

The diagnosis of KLS is clinical; however, other causes of hypersomnia should be ruled out with appropriate laboratory investigations including hemogram, biochemistry, thyroid function tests, EEG, MRI brain, PSG and CSF analysis. The close differential diagnosis in our patient is bipolar depression, structural brain lesion (frontal-lobe syndromes), metabolic encephalopathy, nonconvulsive status epilepticus, and Klüver–Bucy syndrome. The PSG study is helpful in the diagnosis of KLS, which is normal during asymptomatic period. During the episode of hypersomnia, sleep onset latency, mean sleep latency of MSLT and REM latency are of shorter duration [9].

Iron-deficiency anemia (IDA) is common in developing countries like India. It may be due to inadequate dietary iron intake, increase requirement like pregnancy, impaired intestinal iron absorption, blood loss from intestine, uterus and urinary tract. One of the common causes of IDA in India is parasitic infestations (roundworms and hookworms). The clinical features of IDA are pallor of skin and mucous membranes, anxiety, irritability and lightheadedness. Like KLS, fatigability, hypersomnia, depression and poor appetite are also common features of IDA.

Although the clinical history and physical examination can identify the condition and etiology, iron deficiency anemia is primarily a laboratory diagnosis. Our patient had chronic iron deficiency anemia, which was evident on hospital records of multiple admissions. The patient was evaluated for anemia, including complete blood counts, reticulocyte, peripheral blood smear, osmotic fragility, serum iron study, hemoglobin studies, bone marrow aspiration for histopathology and iron staining. He was also investigated for blood loss from gastrointestinal system including stool examination for occult blood, upper and lower gastrointestinal endoscopy, which did not reveal any source of blood loss. Stool examination for ova and cyst was negative. During workup patient did not show any evidence of chronic infection, illness or parasitic infestations. The cause of anemia could not be ascertained in our patient, it may be related to abnormal eating pattern during episodes.

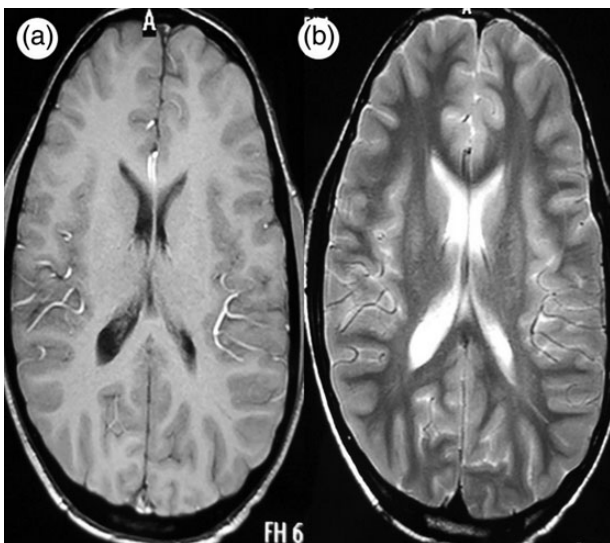


Figure 1: Magnetic resonance imaging of brain showing normal study (a and b).

KLS has major impact on patient's social, professional and personal lives. Although the severity of symptoms and disease course varies between the KLS patients, it usually resolves spontaneously, but sometime coexistent conditions can worsen the symptoms. In our patient, the severity of symptoms (hypersomnia, fatigability, depression and poor appetite) worsened due to comorbid IDA. Blood transfusions decreased the severity of these symptoms and shortened the duration of hospital stay when compared with previous hospital records.

KLS patients usually do not require hospitalization, but sometime other associated conditions like severe anemia as in our patient require hospital admission. Definite treatment for KLS has not been established. A randomized, placebo-controlled trial (Cochrane review) found no benefit of pharmacological treatments for KLS [10]. Several studies have been reported to support that mood stabilizer Lithium decreases the length and severity of symptoms and delays the time between episodes [11]. Though antiepileptic drugs like carbamazepine and valproic acid are less effective than lithium, they are preferred due to less side effects [12]. Central nervous system stimulant drugs such as modafinil, amphetamines and methylphenidate help in wakefulness and alleviating the hypersomnia during episodes but do not have disease stabilization effect [13]. The nutritional support during episode and treatment of comorbid condition like IDA is also an important part of management in such patients. On 6-month follow-up, our patient had no symptoms of KLS (hypersomnolence, hypersexuality, fatigability, apathy, mood disorders) and hemoglobin was near normal. During that period, the frequency and severity of these symptoms were decreased that might be due to better control of comorbid condition.

To conclude, KLS may be associated with comorbid condition like IDA, which causes worsening of symptoms and prolongation of hospital stay. Therefore, all the clinicians must be aware of proper evaluation and management of anemia in such patients to prevent comorbidity. This might be the first case report of KLS with comorbid IDA where the KLS symptoms improved when the anemia was improved.

## CONFLICT OF INTEREST STATEMENT

None declared.

## REFERENCES

1. Arnulf I, Zeitzer J, File J, Farber N, Mignot E. Kleine–Levin syndrome: a systematic review of 186 cases in the literature. *Brain* 2005;128:2763–2776.
2. Arnulf I, Rico TJ, Mignot E. Diagnosis, disease course, and management of patients with Kleine–Levin syndrome. *Lancet Neurol* 2012;11:918–928.
3. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* 1991;14:540–545.
4. Mukaddes NM, Alyanak B, Kora ME, Polvan O. The psychiatric symptomatology in Kleine–Levin syndrome. *Child Psychiatry Hum Dev* 1999;29:253–258.
5. Dauvilliers Y, Baumann CR, Carlander B, Bischof M, Blatter T, Lecendreux M, et al. CSF hypocretin-1 levels in narcolepsy, Kleine–Levin syndrome, and other hypersomnias and neurological conditions. *J Neurol Neurosurg Psychiatry* 2003;74:1667–1673.
6. Hong SB, Joo EY, Tae WS, Lee J, Han SJ, Lee HW. Episodic diencephalic hypoperfusion in Kleine–Levin syndrome. *Sleep* 2006;29:1091–1093.
7. Chesson A, Levine S, Kong LS, Lee S. Neuroendocrine evaluation in Kleine–Levin syndrome: evidence of reduced dopaminergic tone during periods of hypersomnolence. *Sleep* 1991;14:226–232.
8. Dauvilliers Y, Mayer G, Lecendreux M, Neidhart E, Peraita-Adrados R, Sonka K, et al. Kleine–Levin syndrome: an autoimmune hypothesis based on clinical and genetic analyses. *Neurology* 2002;59:1739–1745.
9. Gadoth N, Kesler A, Vainstein G, Peled R, Lavie P. Clinical and polysomnographic characteristics of 34 patients with Kleine–Levin syndrome. *J Sleep Res* 2001;10:337–341.
10. Oliveira MM, Conti C, Saconato H, Fernandes do Prado G. Pharmacological treatment for Kleine–Levin Syndrome. *Cochrane Database Syst Rev* 2009;2:CD006685.
11. Poppe M, Friebe D, Reuner U, Todt H, Koch R, Heubner G. The Kleine–Levin syndrome—effects of treatment with lithium. *Neuropediatrics* 2003;34:113–119.
12. Mukaddes NM, Kora ME, Bilge S. Carbamazepine for Kleine–Levin syndrome. *J Am Acad Child Adolesc Psychiatry* 1999;38:791–792.
13. Aggarwal A, Garg A, Jiloha R. Kleine–Levin syndrome and response to modafinil in a young woman. *J Neuropsychiatry Clin Neurosci* 2011;23:E33–E34.