Brief Report

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A case study of Kleine-Levin syndrome with decreased intracranial pressure in adolescent female

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Abstract

We found a rare case of Kleine-Levin syndrome in an adolescent female with decreased intracranial pressure. The patient developed symptoms of decreased appetite, depression and anhedonia. The clinical symptoms were similar to an affective disorder of depression attack since the patient had periodic symptoms of excessive sleep and gluttony, accompanied by an involuntary special "Crouching phenomenon" involving hip and knee flexion while holding her legs tightly and lying on her knees. She was not considered narcoleptic after polysomnography and multiple sleep latency tests. Finally, a lumbar puncture revealed low intracranial pressure (65mm H_2O). Hypothalamic orexin-A detected in the cerebrospinal fluid was at the lower normal limit. After symptomatic treatment involving fluid infusion and increasing intracranial perfusion pressure, the patient's periodic symptoms and social functioning improved with reduced instances of the special "Crouching phenomenon."

Keywords: Depressive episode, Narcolepsy, Kleine-Levin syndrome, Hypothalamus, Orexin A, Low intracranial pressure

Introduction

Kleine–Levin syndrome (KLS) is a rare sleep disorder characterized by intermittent hypersomnolence, behavioral and cognitive disturbances, hyperphagia, and in some cases, hypersexuality [1]. Each episode is of brief duration, varying from a week to 1 to 2 months, and affected people are asymptomatic between episodes. No definite cause has been identified, and no effective treatments are available even though the illness has well-defined clinical features. Although imaging studies indicate decreased activity in hypothalamic/thalamic areas during episodes, a growing body of literature supports the concept of KLS affecting multiple brain areas in both cortical and subcortical regions [2].

Multiple relapses occur every few weeks or months, and the condition may last for a decade or more before spontaneous resolution. The incidence of the disease biblioin adolescents is one in a million. About 70% of the patients are male. This case is female, which is rare in the clinic. Therefore, we call it the real "Sleeping Beauty syndrome". The patient has an involuntary special "Crouching phenomenon", bending her hips and knees, holding her legs tightly, and lying on her knees. This is rarely observed in KLS. Lumbar puncture indicates that the intracranial pressure is low, and the symptoms are relieved after improving the intracranial pressure, suggesting that the low intracranial pressure may play a role in its pathogenesis.

2. Case presentation

2.1 General information

A 19-year-old female patient was first admitted to the hospital mainly because of four years of paroxysmal sleep behavior abnormality, which was aggravated for three days. During this admission, she had been asleep for approximately 20 hours a day with instances of insomnia. When she awakened, she was in a trance, complaining that something had blurred her vision and felt that the outside world was not real. She asked and answered relevant questions and did not communicate with any family. There was no sleepwalking, falling, twitching, or urinary incontinence.

Her condition had severe impacts on her quality of daily activities and learning. After more than half a month, the symptoms improved. After waking up, she could live normally and go to school without special attention. After three years, she became sleepy again. The onset of the symptoms was similar to those before, and the conditions were completely relieved after more than ten days.

The symptoms recurred 6-7 times, every episode lasting 5-15 days. Her father stated that there would be an involuntary special "Crouching phenomenon" during the attack. She bent her hips and knees, hugged her legs, and fell on her knees. She had normal cognitive function during the intermittent period.

Because of sleep rhythm disorder and mood disorder in the early stage, the patient went to the mental health center and was easily diagnosed with a "depression attack". After the scale evaluation, the patient was treated with fluoxetine, a serotonin reuptake inhibitor. However, the patient's symptoms still had recurrent attacks each time they occurred after being stimulated by spirit. This emotional disorder is common in narcolepsy and KLS and is the main confounding factor.

Before attending our clinic, her sleep behavior was abnormal again due to life events, manifested by her slow response and reduced communication with family and friends. Family members complained of decreased language coherence, sometimes speaking out of focus, fabricating stories of events, and personality and behavior abnormalities such as not paying attention to personal hygiene, laziness, light sleep, early awakening, and decreased appetite. During the day, her activity decreased significantly. Since the onset of the disease, the patient has had poor spirit, appetite and sleep, with no obvious abnormality in sexual desire.

Physical examination: blood pressure: 105/65mmhg, short, thin, no abnormal changes in nervous system physical examination. Mental state examination: she was lethargic, and she had cognitive disturbances such as confusion, concentration, attention, and memory defects. She had abnormal speech, monosyllabic or short sentences with limited vocabulary, childish stereotypical language, and was slow to speak and comprehend. Temporal orientation and spatial orientation were abnormal. While she did not exhibit any hallucinations or delusions, her concentration was affected and appeared to be distraught. She has an involuntary special "*Crouching phenomenon*".

2.2 Auxiliary inspection

After admission, no obvious abnormality was found in biochemical indexes such as liver, renal function, and electrolytes. Mental state scale score: HAMA/HAMD 5/9 SAS/SDS 31/43, overall clinical impression: borderline personality and behavior abnormality. No obvious abnormal changes were found in cranial MRI, cardiac color Doppler ultrasound, EEG and other examinations. The improved polysomnography and multiple sleep latency tests showed that the sleep latency was >8 min, and no two or more times of sleep began with REM sleep.

The cerebrospinal fluid examination showed that the pressure was 65mm H_2O, routine: colorless and transparent, white blood cells $1x10^6$/L, red blood cells $0x10^6$/L. Biochemistry: sugar 4.31 mmol/l, protein 0.1300 g/l, chloride 127.10 mmol/l. The patient had acute paroxysmal cerebrospinal fluid hypothalamic orexin-A of 110.89 pg/ml. At the same time, the tests of sex hormone and adrenal hormone showed that estrogen, progesterone, glucocorticoid, mineralo-corticoid and androgen increased to varying degrees, melatonin levels decreased, and no obvious abnormal changes were found in the series of antibody tests for autoimmune encephalitis.

Further serum blood tests were investigated: serum thyrotropin 0.73 ulu/ml and serum follicle-stimulating hormone 3.08 mlu/ml, serum luteinizing hormone 0.502 mlu/ml, serum ACTH 44.6 pg/ml, cortisol 8:00 am 283 ng/ml, cortisol 16:00 pm 132 ng/ml, cortisol 00:00 am 88.5 ng/ml, no obvious abnormality was found. The hormone level in the patient was disorderly. Considering the abnormal function of the hypothalamus pituitary-gonadal axis, the determination of serum thyrotropin was further improved by 0.73 ulu/ml.

The determination of serum follicle-stimulating hormone was 3.08 mlu/ml, serum luteinizing hormone 0.502 mlu/ml, serum ACTH 44.6 pg/ml, cortisol 8:00 am 283 ng/ml, cortisol 16:00 pm 132 ng/ml, cortisol 00:00 am 88 5ng/ml, no obvious abnormality was found. No obvious abnormality was found in pituitary MRI plain and enhanced scan, double kidney + adrenal gland and gynecological ultrasound.

3. Diagnostics

The patient with periodic episodes of sleep disorders should be differentiated from narcolepsy. International classification of sleep disorders divides central sleep increase into narcolepsy type 1, narcolepsy type 2, idiopathic sleep increase, KLS, disease-related excessive sleepiness, excessive sleepiness caused by drug or substance abuse, a mental disorder related

excessive sleepiness and sleep deficiency syndrome. Narcolepsy is a common primary central sleep-increasing disease, with a prevalence rate of about 0.07% ~ 0.20% [3]. The core clinical symptoms are uncontrollable sleep with sudden onset during the day. It can be divided into narcolepsy Type 1 (cataplexy seizure) and narcolepsy Type 2 (non-cataplexy seizure) Of which type 1 account for 85% [4, 5]. Cataplexy seizure is the most characteristic manifestation of Type1 narcolepsy. A recent study [6] has found that the hypothalamic Secretan (Hcrt) decrease is the core pathological mechanism of Type1 narcolepsy. Basic studies suggest that the central cholinergic and noradrenergic systems, besides the orexin signaling pathway, are involved, follows:

(1) The patient has daytime sleepiness and sleep attacks that are difficult to control, with the symptoms lasting for at least three months.
(2) Meet one or two of the following conditions: (i) have a sudden onset after the standard multiple sleep latency test, the average sleep latency was ≤ 8min, and there were ≥ 2 sleep-onset rapid eye movement periods (soremps). (ii) The concentration of hcrt-1 in cerebrospinal fluid measured by immunoreactivity is ≤ 110 pg/ml or < 1/3 of the normal reference value. Our patient had no typical type 1 symptoms of narcolepsy, including sudden onset, sleep paralysis, sleep hallucinations, and the concentration of hypothalamic secretin was 110.89 pg/ml, which did not meet the diagnostic criteria of ≤ 110 pg/ml or < 1/3 of the normal reference value and the critical level, so the diagnosis of narcolepsy could not be established.

The diagnosis of KLS mainly depends on its typical clinical manifestations and seizure patterns. According to the diagnostic criteria in the international classification of sleep disorders: the patient has experienced at least two recurrent episodes of excessive sleepiness and remission, each lasting from two days to five weeks. Usually, this recurrent episode occurs more than once a year or at least once every 18 months. The patient's alertness, cognitive function, behavior, and mood in the interictal period are normal.

During the interictal period, the patient must have at least one of the following symptoms: cognitive dysfunction, sensory and perceptual changes, abnormal diet (anorexia or anorexia), incontinence, and excessive sleepiness caused by other diseases and drugs or device abuse. The patient met the above diagnostic criteria, so a diagnosis of KLS was decided.

4. Treatment

At present, there is no effective treatment for KLS. The treatment objectives are for symptomatic relief, with the goal of improving the patient's symptoms for return to society. The following is the protocol:

(1) The patient's lumbar puncture showed that the cerebrospinal fluid pressure was 65mm H_2O. The patient was given a fluid replacement and other measures to increase the intracranial pressure and was instructed to avoid severe postural changes.
(2) Reduce excessive daytime sleep and improve nighttime sleep through drugs. The patient was given zopiclone 3mg orally every night to improve sleep. At the same time, venlafaxine hydrochloride sustained-release tablets were given to minimize daytime sleepiness. Starting from 37.5mg, the dosage was gradually increased to 112.5mg. At the same time, it was suggested that she drink a small amount of coffee in the morning. After about two weeks of treatment, the patient's daytime sleepiness improved, activities and food intake increased, and her communication with family improved.

(3) Psychological behavior adjustment through medical intervention to help the patient recover daily life and social functions as much as possible; reduce and avoid adverse reactions caused by drug intervention.

(4) Behavioral psychotherapy: maintaining regular sleep-wake rhythm, avoiding sleep deprivation, avoiding inappropriate use of sedatives and other sleep hygiene behaviors can effectively alleviate daytime sleepiness, enhance the efficacy of drugs on daytime sleepiness and reduce accompanying diseases.

After giving symptomatic treatment for about two weeks, the special "Crouching phenomenon" was reduced. After six months of follow-up, the number of seizures reported by the patients' family members decreased significantly.

5. Discussion

KLS is characterized by narcolepsy with behavioral abnormalities such as cognitive impairment and hyperactivity. Studies [9-11] have found that the orexin A level in KLS patients is low during the attack period but normal during the asymptomatic period. It is considered that acute inflammatory substances are

released to the posterolateral hypothalamus to cause dysfunction, thus inhibiting orexin neuron activity. Further studies have shown that the perfusion of the left medial thalamus decreases during the attack period of KLS while glutamine metabolites increase [12].

The difficulty in diagnosing and treating this patient lies in the differentiation of her presentation from narcolepsy. Narcolepsy is characterized by uncontrollable narcolepsy, paroxysmal cataplexy, sleep paralysis, sleep hallucinations and nighttime sleep disorders. It is the second leading cause of daytime narcolepsy after sleep breathing disorders. Its basic characteristics are unpredictable and irresistible narcolepsy and the transition from waking to REM sleep, namely sudden REM (sorem).

Previous studies [12-14] have shown that the decrease of the orexin A level in narcolepsy leads to decreased binding with receptors, weakening the activity of REM sleep inhibition brain areas.

Then the activity of REM sleep activation brain areas is enhanced, resulting in increased REM sleep and the shortening of latency. In severe cases, sudden onset may occur: epidemiological investigation shows that up to 10% of patients with narcolepsy have normal orexin A levels, which may be due to the specific damage of orexin receptors and their downstream pathways. The binding with some orexin ligands is reduced. The patient was excluded from narcolepsy by polysomnography monitoring and multiple naps.

Wang et al. [14] found lower orexin A levels in the symptomatic phase than in remission and a fall and rise in blood pressure and heart rate, suggesting a role for orexin dysregulation in KLS pathophysiology. Orexin is a potential biomarker of KLS.

The patient had decreased intracranial pressure. The symptoms have been relieved after improving the intracranial pressure, suggesting that low intracranial pressure may play a role in the pathogenesis. Some previous studies [15-18] also suggest this phenomenon. Decreased intracranial pressure leads to hypothalamic hypoperfusion resulting in decreased secretion of hypocretin (orexin-1) due to inadequate blood flow, which has a certain relationship with the occurrence of the disease (see **Fig. 1**).

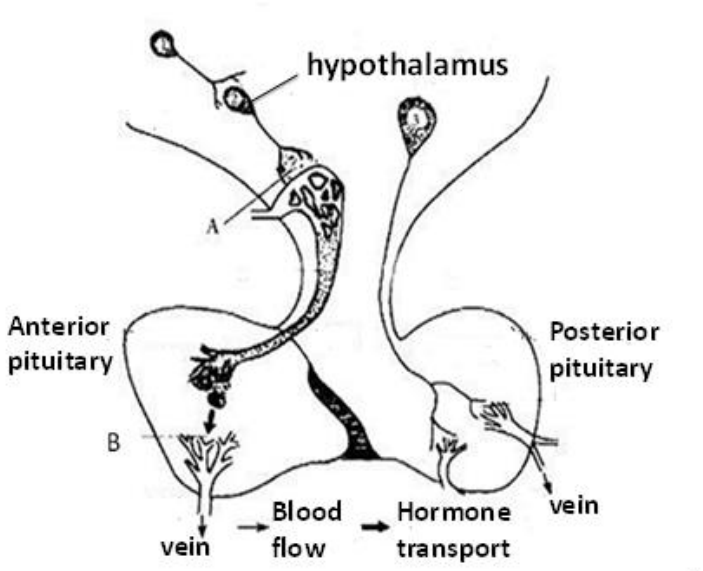

Fig. 1 *Schematic diagram of orexin secretion. A: orexin, B: anterior pituitary hormones (for example,* Luteinizing Hormone, Follicle Stimulating Hormone, Thyroid Stimulating Hormone, Adrenocorticotropic Hormone *etc.)*

When the patient was tested for hypothalamic orexin-A in cerebrospinal fluid, the levels of all hormones were higher than normal, so complete tests for adrenocorticotropic hormone, thyroid-stimulating hormone, and gonadotropin were carried out, but no obvious abnormality was found.

Orexin, also known as hypocretin, is a neuropeptide. It is a hormone mainly secreted by hypothalamic neurons, including orexin A and orexin B (hypocretin-1 and hypocretin-2). It can bind to two paired G protein receptors, OX1R and OX2R. The calcium regulatory signal system is activated through the coupling of G protein, leading to physiological and biochemical reactions. Orexin's function is not limited to increasing food intake but also plays an important regulatory role in physiological processes such as energy metabolism, endocrine, sleep-wake cycle, etc. [19].

The content of orexin is directly related to human hunger and sleep. When the content of orexin is low, people will feel drowsy and do not want to exercise. When the orexin content is high, the situation will be the opposite, and people will become awake and active. Some animal studies [20, 21] have found that when the blood glucose concentration is high, the secretion of orexin will be inhibited, the orexin content will decrease, and sleepiness will follow. If more protein is ingested, the amino acids obtained from this can stimulate orexin secretion and maintain the awake state. Eating is usually quiet, and food stimulation will make the parasympathetic nerve relatively excited. The excited parasympathetic nerve will enhance digestive function, promotes the absorption of nutrients and reduce blood pressure, heart rate, body temperature, and respiration rate, resulting in sleep.

Orexin receptor antagonists, which can competitively block the binding of orexin and orexin receptors, can be used to treat insomnia and sleep disorders. Suvoresen can block orexin A and orexin B receptors simultaneously. It can significantly improve sleep and sleep maintenance.

Finally, the mechanism of KLS is complex, possibly linked to genetic variants in the TRANK1 gene loci [22], and more studies are needed to explore its mechanism in the future.

Conflict of Interest

The authors declare no conflict of interest.

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