Familial Kleine-Levin Syndrome

Two Siblings With Unusually Long Hypersomnic Spells

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Kleine-Levin syndrome is a rare, sporadic disorder, with discrete spells of hypersomnia occurring during adolescence, variously accompanied by megaphagia, behavioral changes, psychosis, and mild autonomic symptoms. Familial cases have not previously been reported. We describe 2 siblings who shared uncharacteristically prolonged episodes of hypersomnia, and the HLA-DR2 haplotype. In one patient, levels of cerebrospinal fluid orexin (hypocretin) during an attack were normal. The presence of an increased sleep drive, despite the occurrence of large amounts of ostensibly restorative sleep, suggests the possible existence of a disorder of sleep satiety.


Kleine-Levin syndrome (KLS) is a rare but striking idiopathic form of episodic hypersomnia described first by Kleine and then Levin in the 1920s and named by Critchley and Hoffman.1 It most often begins in adolescence with a relapsing course that extends across 5 to 10 years before the symptoms abate. The cardinal clinical features are recurring spells of hypersomnia, accompanied by altered behavior and megaphagia (compulsive eating). Hypersexuality, behavioral disinhibition, delusions, mild autonomic alterations (facial flushing, bradycardia), hallucinations, and poor recollection of the spells have all been described, but are not consistent findings. In most cases, patients are otherwise healthy and do not display psychopathology. The duration of recorded spells has typically been between 7 and 30 days.2 The occurrence of KLS is sporadic, and familial cases have not been reported. We encountered 2 siblings with the syndrome who had the unusual feature of very protracted but otherwise typical spells.

REPORT OF CASES

CASE 1

A 15-year-old boy developed flulike symptoms without fever. For 9 days, he remained in bed, slept excessively, and when awake, he frequently requested unusual (for him) salty foods, which he ate mechanically, finishing whatever amount he was given. When awake, he had no interest in social interactions and was irritable when disturbed. His behavior returned to normal abruptly after a lumbar puncture. During the following 10 months, he had 8 similar episodes of hypersomnia lasting between 7 and 12 days. The eating abnormalities became less prominent with subsequent spells. Throughout the following 5 years, he continued to have spells intermittently, with lessening frequency but of longer duration (as long as 81 days). In 5 years, the patient had 16 spells (Figure, A). Often, attacks were immediately preceded by stress or slight alcohol consumption. Toward the end of some of the episodes, the patient displayed repetitive, compulsive activity (eg, pacing, card playing, repeatedly touching objects in his room).

While affected, the patient was observed to be in a light sleep for much of the day, frequently shifting positions and remaining easily arousable. He spent the entire day and night in bed and was irritable when disturbed, becoming agitated if made physically uncomfortable. When confronted, he gave brief answers and repeatedly asked to be left alone, or would groan or mumble before turning away and pulling a blanket over his head. He behaved as though casually awakened when in the middle of deep sleep. He would

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spontaneously arise from bed to void, defecate, or occasionally to obtain food, but he did not attend to personal hygiene unless forced to do so. When eating, he focused his attention exclusively and intensely on the food. At the time, he denied paranoid ideation or delusions; was fully oriented; and performed normally on attention, memory, language, and calculation tests, but was abrupt and irascible and needed constant prodding to cooperate. The patient had no perseveration or difficulty performing the Luria hand sequence. Testing of cranial nerves, strength, sensation, reflexes, and coordination had normal results during episodes. Between spells, he was animated and articulate, with normal social behavior, functioning at a high level in college, and maintaining normal peer relationships.

On later reflection, he described feeling constantly tired, “drugged,” “isolated,” and removed from the environment during the spells. All sensations and perceptions felt vaguely unpleasant, bizarre, and “wrong,” with a nightmarish sense to the surroundings. He interpreted his behavior as a deliberate withdrawal to minimize stimulation. His emotional state while affected was generally negative, with feelings of depression, confusion, and fear. As the spells resolved, he had a clear sense of “lifting,” with increased energy, but initially, poor attention and concentration. He explained the performance of the aforementioned repetitive compulsive activities as a way to expend nervous energy. Between episodes, he generally felt well, although he was concerned about relapses and preferred not to dwell on his illness.

**CASE 2**

The sister of the patient in case 1 began having hypersonsomnolent spells at age 13 years, with the first preceded by a brief “flulike” illness. During episodes, she spent as many as 20 hours per day in bed sleeping or physically inactive. When awake, she was irritable and withdrawn. Her behavior and personal account of her mental state during the spells were essentially identical to her brother’s. They had not discussed their experiences extensively. Initially, her symptoms occurred serially for 7 to 10 days, with intervals of 4 to 8 weeks between spells. Two years into her illness, she had a spell of 62 days’ duration. The frequency subsequently decreased, but the duration of episodes increased to 72 days. In 5 years, she had 18 spells (Figure, B).

She described the spells as “a persistent sense of unreality and disconnection” from her environment, as though she were “underwater.” Everything was “unpleasant because things that are normal don’t seem normal.” When affected, she found multiple simultaneous stimuli “overwhelming” and felt paranoid at times. She was generally dysphoric during the spells, with a sense of “desperation and depression” above and beyond a normal response to feeling unwell. Between spells, she had no psychiatric disorder and maintained normal social and intellectual function, performing well in college.

During and between attacks, both patients’ cranial magnetic resonance imaging scans, Epstein-Barr virus titer, sedimentation rate, endocrinologic evaluation, and electroencephalogram readings were normal, and in the brother (case 1), lumbar puncture, single-photon emission computed tomography scan, and cerebrospinal fluid hypocretin levels during an attack were normal. Both patients shared the HLA-DR2, DQ1, and DR5 haplotypes. Treatments with numerous medications, including lithium, sertraline, methylphenidate, modafinil, clonazepam, flumazenil, and risperidone were ineffective in either preventing or reducing the duration of spells in either patient.

These cases of KLS are exceptional because of their occurrence in siblings. The age of onset, symptoms, and clinical course in both patients were otherwise typical, but the prolonged later episodes were noteworthy. In both patients, spells were 7 to 10 days in duration early in the illness, but subsequent spells lasted as long as 81 days, making them some of the longest spells reported. Megaphagia was not a prominent feature, though both patients displayed some element of compulsive eating early in the course of their illnesses. Their cognitive, affective, and behavioral symptoms were indistinguishable from those of Critchley’s patients and other reported idiopathic cases of KLS.²

It is of interest that our patients developed virtually identical symptoms in early adolescence, and within...
5 months of one another. A nondescript flulike illness preceded the onset of symptoms, but the 5-month separation between each patient’s first hypersomnic attack makes an infectious pathogenesis doubtful. Neither patient had a psychotic or affective disorder, but the close temporal proximity of the onset of their illnesses and similar clinical features raised the question of an imitative psychiatric cause. However, both were well-adjusted and accomplished students, as determined by ours and others’ extensive interviews. Additionally, there was no family history of psychiatric illness and no response to treatment with any antidepressant, psychotropic, or mood stabilizing agents. The prolonged spells in our patients could be distinguished from catatonia by the preserved responsiveness, restlessness, absence of preceding depression, and failure to improve with benzodiazepines.

The hypothalamus is the putative area of dysfunction in KLS because of its prominent role in the control of sleeping, alertness, eating, and sexual behavior. Pathologic abnormalities in the thalamus and hypothalamus have been reported in 3 symptomatic cases. However, those patients all had unusual clinical features that suggested they were not comparable to typical idiopathic cases. One of the most widely cited cases that showed limbic pathological features was more than likely of paraneoplastic encephalitis. Nonetheless, circumstantial evidence supports the notion that idiopathic cases have hypothalamic dysfunction.

The sparing of higher cognitive functions in the context of persistent and extreme lethargy (stupor without confusion) is virtually unique in KLS. The sleepiness, irritability, and dysorphic symptoms are similar to those encountered in patients with chronic sleep deprivation. Experimental sleep deprivation in excess of 72 hours produces increased hunger, irritability, mild autonomic changes, and subtle hallucinations, along with a markedly increased need for sleep. Multiple sleep latency tests and electroencephalogram studies during KLS episodes show both a marked increase in daytime sleepiness and an increase in amounts of moderately fragmented but otherwise normal sleep, including slow-wave sleep. In KLS, there seems to be no corresponding reduction in sleep drive, despite large amounts of sleep that should be restorative, suggesting that normally, there is a brain function that provides satiety for sleep. A disorder of sleep satiety can be conceptualized as the proximate cause for increased sleep in KLS. A similar mechanism could possibly explain the hyperphagic component of the disorder as well.

The linkage of narcolepsy with HLA-DR2 and DQ1b antigens, and the discovery of the gene for orexin in dogs has led to speculation of a similar genetic basis for KLS. Our patients shared the HLA-DR2 and DQ1 antigens. Other patients with KLS who had these antigens have not been reported. Thus far, only a small number of patients have been genetically analyzed, but 4 reported patients with KLS had the HLA-DR1 haplotype. There is rarely, if ever, an identified family history of KLS, and so far, it does not seem to be a heritable disorder with distinct genetic markers. The role of hypocretin in KLS is unknown, but a connection is suggested by the recent findings of decreased spinal fluid levels in 11 narcoleptic patients, and in one patient with a hypothalamic tumor and hypersomnolence.

Critchley and Hoffman first suggested an infectious or inflammatory etiology for KLS—a notion that has been perpetuated by frequent reports of a mild viral illness preceding the first attack in up to 50% of cases. There are several reports of KLS occurring months after viral encephalitis, but in these cases, subsequent attacks did not resemble the original encephalitic illness, and a specific pathogen was not identified. Salter and White described a patient with KLS after clinically and serologically detected Epstein-Barr and varicella-zoster infections, but neither virus was isolated from the cerebrospinal fluid. Despite the putative association of KLS with viral infections, there is little evidence to support a direct connection. Cerebrospinal fluid pleocytosis does not occur during typical attacks. Kleine-Levin syndrome spells have also been precipitated by lack of sleep, trauma, alcohol use, and emotional stress, suggesting that viral infection may be a nonspecific stress capable of triggering an attack. It is also possible that the initial KLS attack is mistaken for a flulike illness, leading to spuriously increased reports of preceding infections. The association with particular HLA haplotypes in our cases suggests that there may potentially be a heritable cause, or perhaps a shared proclivity to a unique infection.

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