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Clinical Reasoning: A 14-year-boy with spells of somnolence and cognitive changes

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SECTION 1

A 14-year-old boy presented for admission after repeated episodes of lethargy and cognitive changes. He had a history of childhood absence epilepsy that had resolved with antiepileptics discontinued 1 year prior to presentation.

Two months prior to admission, the patient had a febrile illness with headache and diarrhea that lasted a few days. It was attributed to a nonspecific viral infection, and he recovered quickly. Over the ensuing days, however, he developed increasing sleepiness, cognitive slowing with difficulty concentrating, and an ill-defined abnormal perception. He stated feeling that "things were not right, it is as if I am not here." His parents reported changes in appetite that included hypophagia alternating with hyperphagia, as well as repeated purposeless behaviors such as tapping his fingers and verbal perseveration. His speech was described as "baby talk," as if he had regressed. This progressed to hypersomnolence, sleeping more than 15 hours/day.

Questions for consideration:

1. What is your differential diagnosis for this presentation?
2. What tests would you order to evaluate this condition?

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SECTION 2

Given the history of a febrile illness shortly prior to symptom onset, a postinfectious etiology was strongly considered. Alternative potential diagnoses included infectious encephalitis, recurrent seizures, structural lesions in the arousal system involving the diencephalon or the brainstem reticular activating system, or toxic ingestion.

He was taken to a local hospital and a lumbar puncture (LP) showed 0 leukocytes, glucose 61 mg/dL, and protein 22 mg/dL. He received acyclovir until his herpes simplex virus (HSV) PCR came back negative, and his mental status improved over the course of a few days. About a week later, symptoms recurred and he was brought to another hospital. A repeat LP was noninflammatory. MRI/magnetic resonance angiography of the brain was performed and showed an incidental left frontal developmental venous anomaly but was otherwise negative. Prolonged EEG monitoring was normal. Urine and serum toxicology panels were negative. Cultures and viral studies were sent and negative. His mentation once again gradually improved and he was discharged.

Additional bloodwork included serologies for rapid plasma reagin, HSV, mycoplasma, parvovirus, influenza, and Epstein-Barr virus. These were negative. Both cytomegalovirus and Coxsackie titers were elevated, and he received a course of ganciclovir with little improvement in his mental status. His thyroid function tests, B_{12}, and folate were normal. In consideration of Hashimoto encephalitis, anti-TPO antibody titer was sent and was negative. A vasculitis panel including antinuclear antibodies, antineutrophil cytoplasmic antibodies, von Willebrand factor antigen, SSA, and SSB was negative. To rule out postinfectious or autoimmune conditions, he had a paraneoplastic panel sent including autoantibodies for NMDA, voltage-gated potassium channel, anti-Ma, anti-Ta, and anti-Hu. These were also normal.

The patient went on to have a relapsing-remitting course, with episodes lasting 10–14 days during which he would sleep for 14–18 hours per day and have cognitive slowing with perseverative behavior and changes in appetite. Episodes would recur every 2–3 weeks and on his fourth relapse he was admitted to our institution.

Question for consideration:

1. Where do these symptoms localize?

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SECTION 3

Upon further questioning, the parents said that during episodes he was disinhibited, masturbating in public and occasionally not putting his clothes on. During hospitalization, it was also noted that he had wide swings of heart rate with intermittent bradycardia. The combination of sleep changes, hypersexual behavior, autonomic dysfunction, and mild confusion with perceptual changes localizes to diencephalic structures, specifically the hypothalamus, as well as cortical associative areas. A prolonged EEG was performed and showed intermittent delta slowing (figure).

Question for consideration:

1. What disorder would you consider?

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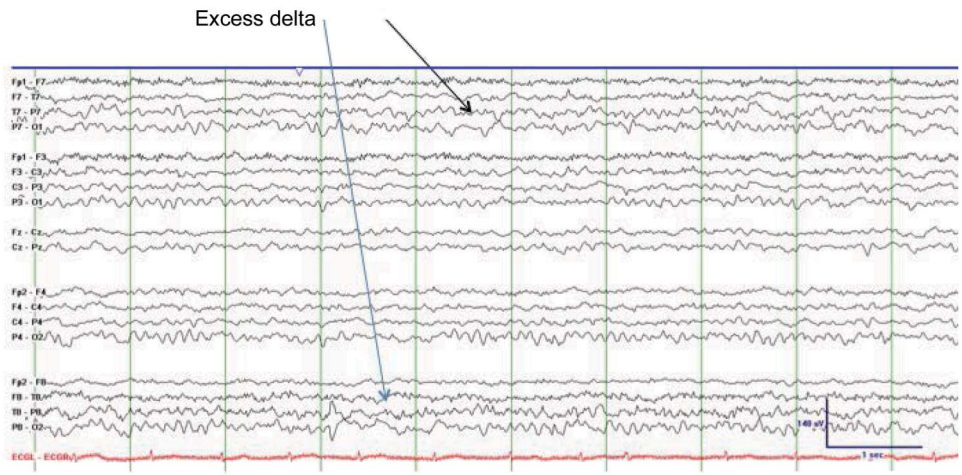
Figure EEG



Excessive intermittent generalized delta slowing seen in the background.

SECTION 4

The possibility of a primary sleep disorder with recurrent hypersomnia such as Kleine-Levin syndrome (KLS) was strongly considered. Repeat infectious and paraneoplastic workup was done and was negative. The differential diagnosis of recurrent hypersomnia also includes structural lesions, as can be seen with brain tumors, traumatic brain injury, or stroke, all ruled out by previous studies. Given his sex, the possibility of menstrual-related hypersomnia was excluded. Additional psychiatric considerations include somatic symptom disorder, seasonal affective disorder, and bipolar disease. Psychiatry followed him throughout hospitalization. Although there is no single test to rule out any of these disorders, extensive family and patient interviewing suggested these conditions to be less likely. Reinforcing this interpretation were his cycling aspect, the lack of clear stressors, and other clinically relevant symptoms that compound diagnostic criteria in these conditions.

Recurrent hypersomnia with cognitive abnormalities, including mild confusion and hypersexuality, is suggestive of KLS. His perceptual changes, expressed by a sensation that "things did not feel or look right, as if I was not there," are signs of derealization. This has been suggested as a very specific symptom of this condition.[1–3]

The EEG results are also compatible, as it has been estimated to be abnormally slow in up to 70% of patients during events. We believe that the fluctuations with swings of bradycardia represented dysautonomias previously described in KLS. Bloodwork was sent for human leukocyte antigen typing and he came back positive for DQB1*0201. Although not specific, this has been previously seen in association with KLS.[2,4–7]

The patient was started on modafinil and had a striking response. On the first day of medication, he started to have limited conversations with staff. On the second day, he was able to get out of bed and normalized his sleep/wake routine, although he still expressed a sense of derealization. He was discharged on valproic acid intended to prevent future episodes. However, he went on to have 3 more relapses over the course of 4 months and was switched to lithium.

Initially presumed to be a hypothalamic derangement, KLS is a disorder that exists in the borderland between neurology and psychiatry. Typically with onset in adolescence in 80% of cases, frequently in boys, it is usually preceded by a triggering event, such as a mild upper airway infection or fever (in 72%–96% of cases), alcohol intake (alone or combined with sleep deprivation), or head trauma.[1–3,7]

The diagnostic criteria have been published in the *International Classification of Sleep Disorders–II* and can be seen in the table.[8]

Usually episodes last from a few days to several weeks and end suddenly. Although hypersomnolence, hyperphagia, and hypersexuality have been previously considered mandatory diagnostic criteria, the more recent diagnostic framework reflects the fact that most patients do not have all symptoms but rather some combination. During episodes, the full triad is estimated to occur in fewer than 45% of cases. This underscores the shift in diagnosis to the presence of hypersomnia with at least one of confusion, apathy, or derealization.[1–3]

The pathophysiology has been elusive, with studies suggesting a localized encephalopathy but with multifocal involvement. Metabolic activity evaluated by SPECT is decreased in cortical (frontal lobe and internal temporal lobe) and deeper structures (especially thalamic and hypothalamic); the latter have also been found to be hypoactive with fluorodeoxyglucose PET studies.[2,9]

There are no randomized placebo-controlled trials on treatment for KLS. A systematic review suggests that based on case reports, stimulant drugs may improve sleepiness (but not other symptoms) and lithium significantly reduces duration of episodes and decreases relapses, with anticonvulsants having less robust data as preventive medications.[10]

Although uncommon, KLS can have significant morbidity and should be recognized within the framework of core symptoms including hypersomnia, slowed cognition, apathy, and derealization. This case exemplifies the difficulties in the diagnosis and management of a syndrome that went underrecognized until appropriate treatment was instituted. Neurologists in training should be mindful of conditions, such as KLS, with core symptoms that could be dismissed as mental illness if clinicians are not careful. Careful history taking, attention to perception changes (derealization), and subtle findings on EEG (slowing) coupled with recurring hypersomnia should suggest consideration of this diagnosis.

Table Diagnosis of Kleine-Levin syndrome[2,8]

Recurrent hypersomnia (recurrent episodes of sleepiness lasting from 2 days to 4 weeks; episodes recur at least once per year; alertness, cognitive function, and behavior are normal between episodes; the hypersomnia is not better explained by another sleep, neurologic, or mental disorder or substance abuse); and at least one of the following:
Cognitive abnormalities (e.g., derealization, confusion, hallucinations)
Abnormal behavior (e.g., irritability, aggression, uncharacteristic behavior)
Hyperphagia
Hypersexuality

AUTHOR CONTRIBUTIONS

Claudio M. de Gusmao: conception, preparation, and drafting of original manuscript. Kiran P. Maski: analysis and review of case discussion, suggestions to differential diagnosis and conclusion. David K. Urion: revision and editing of final text. All authors were directly involved in the care of the patient reported in this article.

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