Late diagnosis of a rare urea cycle disorder mimicking Kleine-Levin syndrome

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Kleine-Levin syndrome (KLS) is a rare disorder characterized by recurrent episodic hypersomnia, cognitive changes, and neuropsychiatric symptoms between months of interictal normality (table). Triggers include infection, sleep deprivation, or alcohol intake, and diagnosis requires exclusion of other medical etiologies.¹ Urea cycle disorders are most commonly diagnosed via newborn screening or during workup of early, life-threatening hyperammonemia. We describe a young man with a late-onset urea cycle disorder who initially presented with phenomenology akin to KLS.

PRACTICAL IMPLICATIONS

Consider extended metabolic workup for patients with suspected Kleine-Levin syndrome and for patients with suspected urea cycle disorders and normal ammonia levels.

Case report

A 24-year-old man presented with his second discrete episode of hypersomnolence, executive dysfunction, and irritability. Both episodes, separated by one year, occurred while visiting family for holiday break and was preceded by increased protein and alcohol consumption.

After drinking 5–6 beers, the patient awoke in the middle of the night with vomiting. This resolved, but the next day his family noticed slumped posture and slowed speech. He began sleeping 12–16 hours per day, becoming agitated when awoken. The family noted that when awake, he was talking about the opposite sex. He required assistance with walking and dressing. Four days after symptom onset, he presented to our emergency department for evaluation.

On examination, the patient was disoriented and had impairments in short-term memory, language comprehension, and visual-spatial tasks. He also exhibited mild ideomotor apraxia, psychomotor retardation, and *la belle indifférence*. Cranial nerve examination revealed sharp optic discs, miosis, saccadic pursuits, hypometric saccades, gaze-evoked nystagmus, and mildly dysarthric speech. Reflexes were brisk. Cerebellar findings included square wave jerks with central gaze, overshoot on finger chase, terminal dysmetria, dysdiadochokinesia, and a wide-based, ataxic gait with decreased arm swing.

MRI brain demonstrated small subcortical white matter lesions, frontal more than parietal, and decreased blood flow on arterial spin labeling sequence in the posterior brain and cerebellum. Continuous EEG was negative for seizure and demonstrated a well-defined posterior rhythm in the awake state with nonspecific slowing. SPECT revealed delayed perfusion in bilateral thalami and right occipital temporal regions (figure).

CSF showed elevated citrulline (557 nmol/mL; ref 0–2 nmol/mL) and glutamine (1,203 nmol/mL; ref 376–652 nmol/mL), with low ornithine (0 nmol/mL). Serum studies showed high serum methionine (57 nmol/mL) and α -Aminobutyric acid (45 nmol/mL). Otherwise, CSF was negative/normal for profile, flow cytometry, oligoclonal bands, paraneoplastic antibodies, viral panel, and A β /tau ratio. Serum studies were negative/normal for HIV, rapid

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Table International Classification of Sleep Disorders–3 diagnostic criteria for Kleine-Levin syndrome

A. The patient experiences at least 2 recurrent episodes of excessive sleepiness and sleep duration, each persisting for 2 days to 5 weeks.
B. Episodes recur usually more than once a year and at least once every 18 months.
C. The patient has normal alertness, cognitive function, behavior, and mood between episodes.
D. The patient must demonstrate at least one of the following during episodes:
1. Cognitive dysfunction
2. Altered perception
3. Eating disorder (anorexia or hyperphagia)
4. Disinhibited behavior (such as hypersexuality)
E. The hypersomnolence and related symptoms are not better explained by another sleep disorder, other medical, neurologic, or psychiatric disorder (especially bipolar disorder), or use of drugs or medications.

Adapted with permission from American Academy of Sleep Medicine.⁷

plasma reagin, NMDA antibody, antinuclear antibodies, C-reactive protein, erythrocyte sedimentation rate, prolactin, ceruloplasmin, anti-TPO, anti-thyroglobulin, thyroid-stimulating hormone, thiamine, vitamin B12, methylmalonic acid, and acylcarnitine profile.

The patient improved over 4 days of hospitalization without intervention. At discharge, his only deficits were subtle cerebellar symptoms. He was advised to avoid alcohol, take daily arginine, and limit protein intake. Outpatient genetic testing demonstrated a p.Arg272His mutation in the arginine succinate synthetase 1 gene (*ASS1*), consistent with type 1 citrullinemia (CT1).² He has returned to complete his graduate studies. His sister was referred for genetic counseling.

Discussion

We describe a patient presenting with symptoms of KLS that, based on preliminary workup, did not have an apparent medical etiology. However, the patient’s early episode of vomiting with preceding dietary changes and subtle movement deficits on examination triggered an extended metabolic workup that revealed elevated citrulline and glutamine, for which genetic testing later confirmed CT1.

CT1 is typically screened for at birth and presents in the neonatal period with profound lethargy, hyperammonemia, and cerebral edema.³ Late-onset and asymptomatic forms have been described but are rare.² Our case represents a milder, late-onset form that presents with cerebellar features and lacks the classic hyperammonemia. It is also the first to describe bilateral thalamic and occipital cortex hypometabolism (a finding associated with KLS) in a patient with CT1.⁴ In addition, while prior CT1 studies describe MRI findings of atrophy in the basal ganglia, thalami, and cortex, the white matter hyperintensities seen in our patient have not been reported.⁵ As such, our case expands upon current understanding of genotype–phenotype correlations in CT1 with an example of an individual with a specific *ASS1* mutation and late-onset CT1.

Distinguishing KLS from urea cycle disorders is important as the two differ in both natural history and treatment. While the former tends towards a benign course, the latter involves recurrent metabolic crises that require dietary modifications and regular surveillance to prevent complications.⁶ In our case, without extensive metabolic investigation, the patient would have been misdiagnosed with KLS. This case also highlights the utility of considering an extended metabolic workup, beyond ammonia screening, for patients with similar presentations.

Figure Magnetic resonance spectroscopy with moderately delayed perfusion in the bilateral thalami and right occipital temporal region

Author contributions

N. Bozinov: acquisition of data and conceptualization. M. Han: drafting and revision of manuscript. W. Lau: acquisition of data and conceptualization. V. Santini: interpretation of data and supervision.

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