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Case Reports

Treatment of Kleine-Levin Syndrome with Acetazolamide

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ABSTRACT

Kleine-Levin syndrome (KLS) is a rare and disabling disorder characterized by recurrent episodes of hypersomnia as well as cognitive and behavioral abnormalities. Sadly, the treatment options are very limited and often ineffective. To our knowledge, there have been no reports in the literature for the use of acetazolamide as a treatment for this disorder. We report the case of a 26-year-old female patient with KLS in whom acetazolamide was used to treat recurrent hypersomnia and cognitive abnormalities. The patient had a dramatic improvement on acetazolamide in both the frequency and severity of her symptoms. The symptoms recurred when acetazolamide was stopped on two occasions and improved with resumption of the drug, leading us to conclude that its therapeutic effect was significant.

Citation

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Kleine-Levin syndrome (KLS) is a rare and disabling disorder characterized by recurrent episodes of hypersomnia as well as cognitive and behavioral abnormalities for which treatment options are limited.[1,2,3] Our case describes a remarkable improvement in the symptoms of KLS in response to acetazolamide.

REPORT OF CASE

Our patient was a 26-year-old female with an unremarkable medical history until the age of 17 years when she started to experience recurrent episodes of severe sleepiness, fatigue and confusion. During these episodes the patient was arousable but unable to maintain concentration or recall recent events, and when awake, was noted to be irritable and depressed. She also complained of mild generalized weakness. She denied hyperphagia or hypersexuality during or after the events. Her symptoms improved somewhat with sleep. The episodes progressed in frequency and intensity from every 2-4 weeks to every other week, lasting from 5 to 8 days. The patient would sleep between 14 and 22 h daily. Episodes would end spontaneously, with the patient describing partial amnesia for the events. Between events, the patient was able to function normally, without excessive daytime sleepiness. She was seen by a neurologist who observed no focal findings and ordered a 24-h EEG (between events) which was read as normal. Additionally, the patient had a 2-week continuous video EEG study performed before and during an episode showing mild background slowing only during the episode. She had normal MRI and CT of the brain, muscle biopsy, and EMG results. The patient had cerebrospinal fluid analysis done during an episode which was found to be normal (white count, protein, glucose).

The neurologist made a diagnosis of either complicated migraines or complex partial seizures and prescribed multiple migraine and anti-epileptic medications (topiramate, verapamil, rizatriptan, gabapentin, levetiracetam, and zonisamide) with no improvement in her symptoms. She was then prescribed stimulants to use during events (amphetamines, modafinil, and amantadine), which were ineffective. Given the episodic nature of her symptoms, the possibility of a channelopathy was considered (a disturbance in Ca, Na, Cl, or K channels in the central nervous system). The patient was prescribed acetazolamide,

1 g daily, and improved dramatically within one month of starting the drug. There was a reduction in the frequency of her events from every other week to, at times, once every few months; in addition, the duration of her symptoms shortened to 2-5 days and their intensity diminished. The patient was subsequently seen at a university sleep disorders center where she was diagnosed with KLS. After taking acetazolamide for 3 years, the patient discontinued the drug to see if her events would worsen. Within 3 months she reverted to her baseline symptoms with compromise of her function. She restarted acetazolamide and returned to her previous state of improvement within one month. Two years later, acetazolamide was again discontinued because of renal stones, with recurrence of symptoms after one week. The symptoms lasted up to 7 days, and would occur every other week. The patient then presented to our sleep disorders center where polysomnography and a multiple sleep latency testing (MSLT) were performed between events. Polysomnography was negative for sleep apnea, with normal appearing sleep architecture. Her MSLT demonstrated a mean sleep latency of 12.4 min with no REM onsets during 4 nap opportunities. At this time, the patient remains off acetazolamide, but is experiencing spontaneous amelioration of her symptoms over time, which is often seen in patients with KLS.[3]

DISCUSSION

Our patient has KLS with prominent features of recurrent hypersomnia with mood and behavioral disturbances. Although the patient met the ICD-9 criteria for KLS, her recurrent hypersomnia was certainly more frequent at onset than most reported cases of KLS.[4] The patient's clinical diagnosis was delayed for several years because of the rarity of the disorder and its being a diagnosis of exclusion. The amelioration of her symptoms over time even without using any medications is consistent with other reported cases.

To our knowledge, there has never been a clear linkage of KLS to any specific channel defect, despite our patient's very impressive response to a medication that is often used to treat channelopathies. The clinical manifestations of known channelopathies are extremely variable but often occur episodically.[5] Some known channelopathies such as L-type calcium ion channels have been linked to significant mood disorders, where there is also a clear change in mental state.[6]

There are rare forms of channelopathies (such as childhood absence epilepsy) in which most patients eventually outgrow their seizures, which is consistent with the disease course of KLS. Given our patient's impressive response to a medication that is used to treat channelopathies, future investigation into a possible channel defect among KLS patients may be warranted.[5] Sadly, the mechanism by which acetazolamide treats channelopathies is poorly understood.

In closing, we acknowledge that while acetazolamide provided our patient with a marked benefit, acetazolamide does predispose to renal stones. For physicians who may consider trying this medication, close observation for the development of renal stones and electrolyte abnormalities is strongly recommended.

DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

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