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CASE REPORTS

A strange New Year's Eve: triggers in Kleine-Levin syndrome

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Kleine-Levin syndrome is a rare neurological disease of unknown cause beginning typically during adolescence, characterized by remittent-relapsing episodes of severe hypersomnia associated with cognitive and behavioral disturbances. Triggering factors at Kleine-Levin syndrome onset include infection, sleep deprivation, as well as alcohol, drug, and substance intake. A young woman had 6 episodes over 2 years, including hypersomnia, confusion, derealization, cognitive impairment, anxiety, feeling of being scrutinized, anorexia (and sweet craving once) but no hypersexuality. The first episode started after a party where she experienced a complete, 4-hour-long blackout despite moderate alcohol intake. The patient suspected having been poisoned. Twenty-five months after the party, when Kleine-Levin syndrome was eventually diagnosed, her long hair was analyzed and exogenous γ-hydroxybutyrate was found in the tips (corresponding to the party time). This case illustrates the interest of looking for γ-hydroxybutyrate in the hair when Kleine-Levin syndrome starts after a party.

Keywords: Kleine-Levin syndrome, hypersomnia, gamma-hydroxybutyrate (GHB), poisoning

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INTRODUCTION

Kleine-Levin syndrome (KLS) is a rare neurological disease of unknown cause predominantly affecting males and beginning during adolescence (3 cases per million). This syndrome is characterized by remittent-relapsing episodes lasting to several weeks, alternating with asymptomatic periods lasting weeks to months.[1] During episodes, patients experience major hypersomnia, cognitive slowness, mental confusion, derealization, and apathy. In addition, around half of the patients may present megaphagia, hypersexuality, and depressive mood, and less frequently, psychotic symptoms. The disorder usually disappears spontaneously after the age of 30 years. The diagnosis is based on this striking association of symptoms plus ruling out neurological (eg, encephalitis), psychiatric (eg, bipolar disorder), and sleep (eg, idiopathic hypersomnia) disorders. Morphological brain imaging is normal, but functional brain imaging (or sometimes electroencephalogram) mostly shows markers of hypoactivity in the associative cortical, prefrontal, and orbito-frontal areas.[2] Several triggering factors have been identified at KLS onset, including mostly infection, but also sleep deprivation, head trauma stress, and alcohol, drug, and substance intake. We report on a KLS case in which the patient suspected having been poisoned during a party.

REPORT OF CASE

A 21-year-old woman was referred to the sleep center in February 2020 for suspected KLS. During the past 2 years, she had 6 episodes of hypersomnia associated with confusion, apathy, derealization, and anorexia. Each episode lasted 8 days, separated by 3 weeks to 6 months of normal sleep and behavior.

She studied in a school of applied art in fashion design. She had no history of birth and developmental difficulties, had seasonal allergic rhinitis, and took an oral contraceptive pill. She was a nonsmoker, a nonregular alcohol drinker (restricted to parties, 3 times per month, and never until being drunk), and did not use any substance.

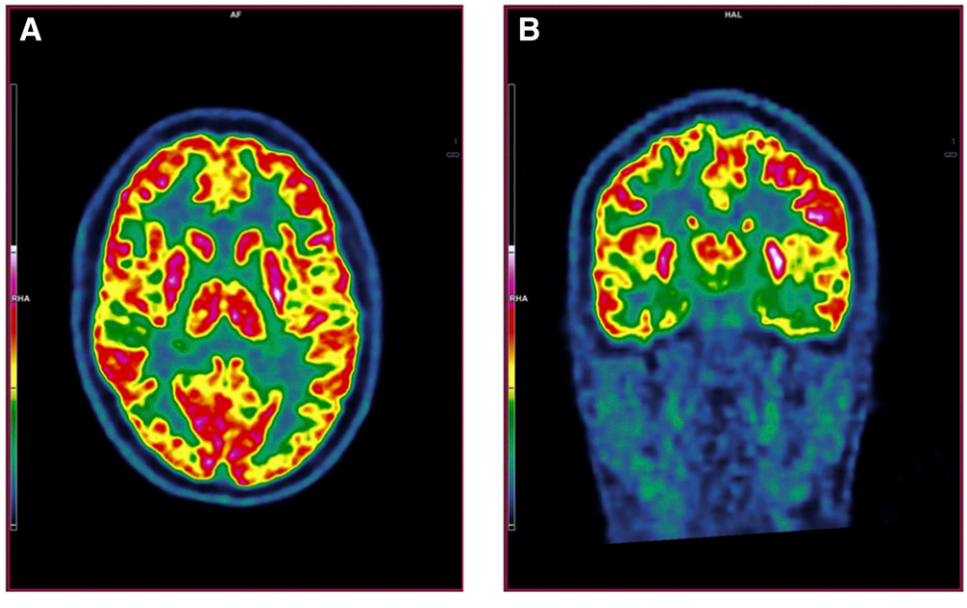
The first episode started on 1 January 2018 when she was 19 years old. The night before, she joined a New Year's Eve party at a friend's home. Before midnight, she drank 2 glasses of alcohol (a mixture of whisky and soda). At midnight, as she was chatting with a male stranger at the party, she suddenly felt weak and fell on the floor. From this time, she had a complete black out until 4:00 AM; when she regained her senses as she was sitting on a bench in the street with a female friend. They returned home. She fell asleep and woke up in the afternoon, feeling weird, and experiencing the first KLS symptoms. She felt exhausted for 8 days, repeatedly saying that she felt weird and slow, and slept a lot. She had to sew a velvet shirt for the design school but could not see the details of the fabric (everything was blurry) and the fabric thread (to cut it in the right direction), although this was her routine work. She could not feel the temperature of the shower or see the hair on the hairbrush, and could not recognize herself in the mirror (details like eyebrows were missing). She pinched and hit herself to observe a reaction, without feeling any pain. As she watched television, the death of a famous singer was announced. However, she thought that it was fake news, and that her brain had played tricks on her. She called her mother to check the reality of this news. Her mother confirmed

the news, but she still was not convinced and doubted its reality. She went out and took the subway but felt that her brain was gradually building the reality around her, as in a dream. On the eighth day of the episode, she suddenly became clearheaded in the afternoon (within 1 hour) and felt relieved. After this first episode, she presented 5 other similar episodes of KLS. The diagnosis of KLS was suspected by a local neurologist and psychiatrist (who found no psychiatric condition) after the fourth episode, and she was sent to our center.

At the reference center, the diagnosis of KLS was confirmed as she had experienced 6 discrete episodes with hypersomnia (usually 16 hours of sleep/day, with excessive dreaming, sleep-related hallucinations, and sleep paralysis), apathy, a striking derealization, cognitive impairment (spatial and temporal disorientation, partial amnesia of the episodes, mental slowness), eating disorder (one episode of sweet craving, the other episodes with anorexia), sweating, low blood pressure, anxiety, crying, feeling of being scrutinized when going out (but no formed hallucinations and delusions), and no abnormal sexual behavior, aggressiveness, or irritability. She was interviewed during an asymptomatic period and had no residual sleepiness and excellent cognitive performance on tests (executive function, attention, visual and verbal memory as well as instrumental function). The psychiatric interview did not identify any mood disorder or any psychosis. She had a mildly anxious personality. An electroencephalogram performed during an episode was normal, as was brain magnetic resonance imaging. On the 18-fluorodeoxyglucose positron emission tomography, there was a bilateral hypometabolism in the posterior associative temporo-occipital cortex (mild) and in the medial temporal cortex (moderate) during this asymptomatic period (**Figure 1**). As the 2 last episodes had milder symptoms than the previous ones and were better tolerated since there had been a diagnosis of an identified disorder, no preventive treatment (eg, lithium therapy) was suggested.

The triggers of the episodes were carefully reviewed with the patient in order to avoid them. Lack of sleep was the main triggering factor for each of the 6 episodes (New Year's Eve, birthday parties, usual parties). She had no history of infection prior to the episodes. Alcohol could be a trigger, but she noticed that higher intakes during parties, either before the KLS onset or during the last 2 years, had not triggered any episode. Because of the blackout experience, she was convinced that someone had poisoned her during the New Year's Eve party. One month after that date, she went to the police to file a lawsuit. The male stranger who was alone with her during the beginning of the blackout was interviewed by the police. In absence of any proof, the charge was dismissed. However, when she was referred to the expert center 25 months after 1 January 2018, her hair length was 27 cm. We assumed that hair growth was about 1 cm/month (0.7 to 1.4 cm/month) so that the hair area from 1 January 2018 would be 25 cm from the roots. After she gave her consent, we sampled 2 strands of hair and sent them to a laboratory specializing in forensic toxicology. In the first lock, the first 19 cm were dismissed, and the last 8 cm were cut into 4 segments, as they should include a period elapsing from November 2017 to June 2018. The dark blond hair without cosmetic treatment for 2 years was washed, ground, incubated at 37°C, and analyzed using liquid chromatography–high resolution mass spectrometry.[3] No amphetamine, cocaine, opiates, new psychoactive substances (cathinones, synthetic cannabinoids, or opiates), LSD (lysergic acid diethylamide), or psychoactive drugs were found.

Figure 1—Brain imaging.



Functional brain imaging (using 18-fluorodeoxyglucose positron emission tomography) during an asymptomatic period in the patient with KLS. **(A)** Axial slice showing mild bilateral hypometabolism in the posterior associative temporo-occipital cortex. **(B)** Frontal slice showing bilateral hippocampal hypometabolism. KLS = Kleine-Levin syndrome.

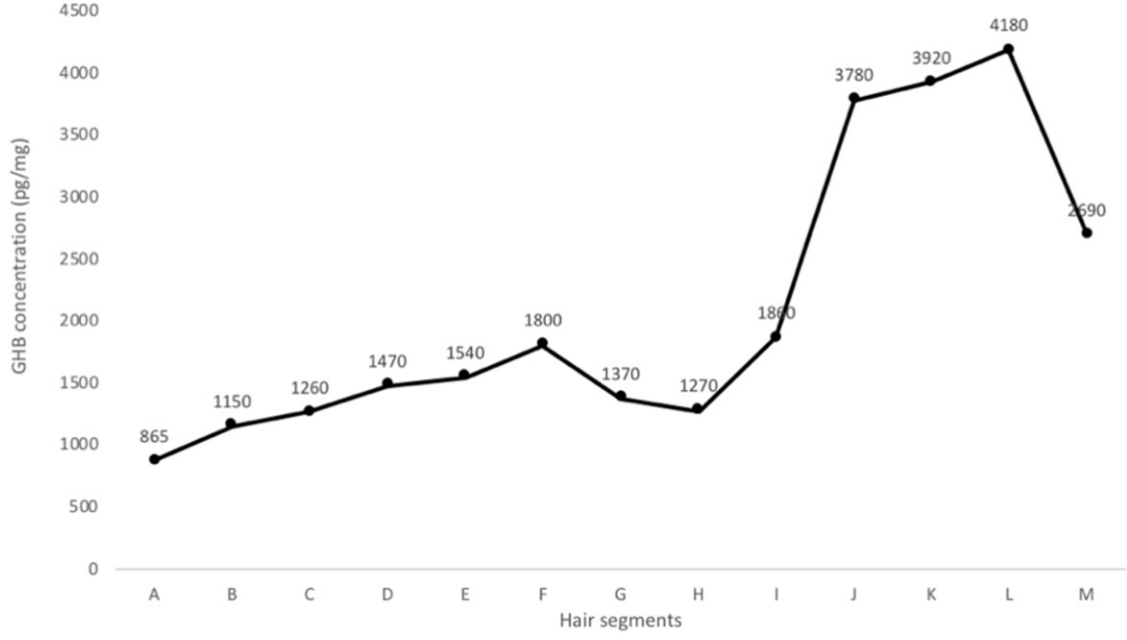
γ-Hydroxybutyrate (GHB) testing was carried out in the second strand using gas chromatography coupled to tandem mass spectrometry. After excluding the 20 first centimeters, the 12 last 0.5-cm-long hair segments (labeled "A: for the segment closer to the roots to "L" for the tips) and a last 1-cm-long segment (labeled "M") covering the period from November 2017 to May 2018 were analyzed. The putative intoxication on 1 January 2018 was predicted to be located in segment L. However, hair growth rate is variable (3 different phases exist for hair, including the anagen with growth and integration of molecules, and catagen and telogen without growth and integration) and there had been a long delay between intoxication and sampling (which could induce axial migration): consequently, it is usual to observe increases in some surrounding segments.[3] The hair contained GHB (**Figure 2**). GHB is an endogenous molecule derived from γ-aminobutyrate acid metabolism (a neurotransmitter), and hair from all individuals contains GHB at an endogenous concentration averaging 1000 pg/mg. Here, the concentration was higher in the segments from the tips, enclosing the segments corresponding to the New Year's Eve party. Indeed, the ratio between the higher exogenous concentration of the targeted segment (4180 pg/mg, segment L) and the median concentration of endogenous GHB in the 8 first segments (1340 pg/mg, segments A to H) was greater than 3, as proposed by different authors for confirmation of exogenous GHB intake.[4] The result was in favor of an exogenous GHB exposure at the period of New Year's Eve 2017–2018. The patient felt relieved after receiving this information. She gave her consent for her case to be published.

DISCUSSION

Kleine-Levin syndrome is a rare neuropsychiatric disorder of unknown cause and mechanism. However, several potential triggers have been identified before KLS onset, including infections (35–97%), sleep deprivation (2–45%), head trauma (2.4–9%), and intake of alcohol, drugs (including general anesthesia), or other substances.[1,4,5] Indeed, 4.2–23% of patients reported having consumed alcohol before the first KLS episode. The same causes can be found, although less frequently, before KLS remittent episodes. In addition to alcohol, cannabis smoking was identified before KLS onset in 1% (mixed with LSD and cocaine) to 6.5% of patients.[4,5] We have the experience of 1 patient with KLS with onset and later episodes triggered by cocaine intake. To the best of our knowledge, this is the first case in which GHB poisoning has been associated with KLS onset—here, in combination with a moderate alcohol intake and sleep deprivation.

Endogenous GHB is a metabolite of γ-aminobutyrate acid, a brain neurotransmitter stimulating γ-aminobutyrate acid–B and GHB receptor, mostly in the cortex and hippocampus.[6] Exogenous GHB rapidly crosses the blood–brain barrier and acts 10 to 20 minutes after oral intake, for a duration of 2–4 hours. At low doses, the drug has stimulatory effects and promotes

Figure 2—GHB concentrations in hair segments.



GHB concentration (*y* axis) according to function of the hair segment closer to the root (point A on the *x* axis) to tips (point M on *x* axis). New Year's Eve should correspond to several segments between I and M on the *x* axis. The single poisoning is observed in several segments. Indeed, after a single poisoning, a single segment is usually raised when the hair is removed 1 month after administration. When sampling hair 2 years later, even after a single poisoning, concentrations in some segments surrounding the date of poisoning are high due to the different phases of hair growth (anagen, catagen, and telogen). GHB = γ-hydroxybutyrate.

euphoria, disinhibition, enhanced vitality, amnesia, and has prosexual effects, for which the drug is used for illicit purposes (rape and theft).[7] Deep slow-wave sleep is induced at higher dosages, followed by coma and respiratory depression at very high dosages. The effects of GHB and alcohol are synergistic. Exogenous GHB was an anesthetic drug in the 1960s (GammaOH) and is currently approved for treating narcolepsy (sodium oxybate or Xyrem [Jazz Pharma Ltd, Philadelphia, PA]) and alcohol withdrawal (Alcover [Intsel Chimos Ltd, Saint-Cloud, France]). Sodium oxybate has even been beneficial during late insomnia/hypersomnia episodes in a single case of KLS,[8] although one should be cautious in interpreting drug benefit in single cases, as KLS improves spontaneously. When ingested (in a translucid liquid, white powder form, or in its precursor γ-butyrolactone form), GHB is rapidly eliminated from plasma with a half-life of 30–50 minutes and becomes undetectable after 10 hours in urine samples. However, it is stored in the hair, which allows detection several months after ingestion. Hair analysis is therefore the preferred method after sexual abuse with suspected poisoning.[9]

How could GHB possibly have triggered KLS here? The cause of KLS is unknown, but several reports point toward an inflammatory or autoimmune encephalitis, mostly affecting the associative posterior cortex, the hypothalamus, and the orbitofrontal cortex.[2] Some KLS triggers, including infection, alcohol intake, and head trauma, share the property of crossing the blood–brain barrier, possibly favoring the passage of a toxic and/or an (auto)-antibody from the plasma to the brain.[5] However, GHB does not alter the blood–brain barrier.[10] GHB intake is associated with increased activity in the mesolimbic system, the bilateral anterior cingulate cortex, and right anterior insula, which correlates with increased sexual arousal and prohedonic effects.[7] In patients with KLS, the anterior cingulate cortex is hypoperfused during asymptomatic periods, compared with controls, but the insula is unaffected.[2] One may note that some effects (including amnesia, cognitive impairment, disinhibition, euphoria, increased sex and food drive followed by sleepiness and sleep) after GHB intake resemble some symptoms observed during KLS episodes, to the point that our patient here thought that the symptoms of the first episodes, which lasted 1 week, were still in relation with her suspected GHB poisoning. However, the comparison stops here, because KLS symptoms also include apathy and derealization, and because GHB effects do not last more than 4 hours.

This case illustrates the utility of an in-depth examination of KLS triggers. In case of KLS having started after a party, it could be interesting to also look for GHB in patients' hair.

ABBREVIATIONS

GHB, γ-hydroxybutyrate
KLS, Kleine-Levin syndrome

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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. Work for this study was performed at Sorbonne University, Paris, France. The authors report no conflicts of interest.