

Between Neurology and Psychiatry, a Difficult Preliminary Diagnosis of Kleine-levin Syndrome: Case-report of a Young Girl

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Introduction

Kleine-Levin syndrome is a rare neurological condition with both somatic and psychiatric symptoms. In 1990, Kleine-Levin syndrome was classified in the International Classification of Sleep Disorders (ICSD) and was revised to its current state in 2005 (Table 1) [1].

Kleine-Levin syndrome appears suddenly, sometimes without a triggering factor or sometimes being precipitated by an infection (38.2%), head trauma (9%) or acute consumption of alcohol (5.4%) [2-5]. The etiology remains unclear, but there may be a genetic predisposition (haplotype HLA-DR1), associated with environmental factors [6,7]. The syndrome is characterized by hypersomnia (up to 20 hours a day), cognitive symptoms (mainly derealisation, but also confusion, delusions, and/or hallucinations, memory impairments), behavioral symptoms (sexual disinhibition, irritability/aggression, compulsive eating), and mental symptoms such as depression and anxiety [4,8-13]. There are also physical signs such as autonomic dysfunction, weight gain; and at the end of the episodes, amnesia, elation, and depression. It is important to underline that these symptoms and signs are generally not combined in a single patient. The average length of an episode is 8 to 10 days, and episodes lasting several months are relatively exceptional. They usually recover after a period of about 8 years.

Recurrent hypersomnia
Recurrent episodes of excessive daytime sleepiness lasting 2 days to 4 weeks
Episodes recur at least once per year
Alertness, cognitive functions and behavior are normal between episodes
Hypersomnia is not explained by another sleep, medical, neurological, or psychiatric disorder, medication use, or substance abuse
Kleine-Levin syndrome
In addition to the recurrent hypersomnia criteria, the patient should also have at least one of the following
Cognitive abnormalities – ex : confusion, derealization, hallucinations
Abnormal behavior – irritability, aggression
Hyperphagia
Hypersexuality
Abbreviation: ICSD-2, International Classification of Sleep Disorders – second edition

Table 1: Diagnostic criteria for recurrent hypersomnia and Kleine-Levin syndrome (ICSD-2) [2].

The diagnosis is based on clinical findings, but some analysis, electroencephalogram, and brain imaging must be carried out to rule out infectious or neurological diseases [11].

Bipolar disorder is a chronic disease which can be diagnosed during childhood; two-thirds of all adult bipolar illness had it onset in childhood and adolescence [14,15]. There is often genetic vulnerability, as family history of bipolar disorder, anxiety or depression disorder and/or psychosocial vulnerability as physical/sexual abuse and a lack of social support [15]. It is very important to identify bipolar disorder and to propose a special care as early as possible for a better outcome in adulthood [15,16].

Patients recover naturally and medication is limited. There is no therapeutic trial of pharmacological symptomatic treatment [17]: antipsychotics, anti-epileptic drugs and anti-depressants are not very effective. Lithium (41% efficacy for an episode) and psycho-stimulants (40% effective for somnolence) give the best results [18-21]. Furthermore, lithium can be used long-term as prophylaxis [22]. Moreover, Clarithromycin has shown a short-term beneficial effect, which implies a role of GABAA receptors in Kleine-Levin syndrome pathophysiology [23].

The Kleine-Levin syndrome affects mainly males (68%) and the first episode occurs on average at the age of 15. A literature review performed in 2005 [24] found 186 cases worldwide between 1962 and 2004, with 34 cases in North America and 75 in Europe.

We received into our unit a young girl in whom we diagnosed Kleine-Levin syndrome after a complex diagnostic and therapeutic procedure.

Case Report

In early 2008, we met a girl aged 14, hospitalized in the general paediatric department for "asthenia and sudden-onset behaviour disorders". A neurological examination did not suggest a possible diagnosis.

The young girl had a neglected appearance: her hair was not done, her clothes were dirty... She stared fixedly, occasionally with great intensity, and alternated between apathy, panic attacks and euphoria. Within a few minutes she could pass from being almost completely mute to a relatively coherent dialogue. She suffered temporal and spatial disorientation at times and had memory impairment. She focused on her hands, always saying that she could "no longer see them". She was sometimes very aggressive with hospital staff, friends and family, but did not seem to remember this once the episode of aggression was over. The same was true of her seductive attitude, particularly towards women, which even included masturbation. It was difficult to wake her up in the morning and wasn't possible before 10

am. And then, she didn't manage to stay awake during more than 1 hour consecutively and often asked to return to bed or slept on a sofa. So, she was asleep up to 6 hours a day (i.e. from 10 am to 9 pm in her case) and often yawned during the interview. And during a 24-hour day, she slept about 18 hours. She also had eating disorders, constantly seeking food that she never ate and losing 3 kg in five days, and suffered from headaches and dizziness. She said that she did not know what she was doing in hospital and insisted on going home.

We then met her parents who were shocked by their daughter's symptoms. They reported no history of psychiatric or somatic disorders concerning their daughter or their family. However, the parents did report that in recent months, their daughter had been harassed at school and might have been forced to ingest a toxic substance the previous week.

Methods

This array of disorders, belonging to manic disease, with very atypical psychotic features and sudden onset derealisation, in an adolescent with no medical history, made us doubt the purely psychiatric origin of the disorder. In close co-operation with the paediatricians, we tried to rule out any toxic or organic origin for these symptoms: we had to ensure that our patient's disease was not caused by intoxication, encephalopathy, brain tumor, stroke, trauma, epilepsy, infection or hormonal imbalance, etc. Complementary examinations were then performed during several days.

Blood

Screening for toxins (medicinal products, narcotics), complete blood count, urea, creatinine, glycemia, sedimentation rate, C-reactive protein, serum ammonia, serum copper, folates, cobalamine, anti-nuclear antibodies, anti-smooth muscle antibodies, anti-mitochondrial antibodies, anti-native DNA antibodies, anti-myelin antibodies, anti-Hu antibodies, anti-Yo antibodies, anti-Ri antibodies, anti-thyroperoxidase antibodies, anti-thyreo-stimulating-hormone receptor antibodies, anti-thyroglobulin antibodies, serodiagnostic testing for Lyme's disease, syphilis, hepatitis A/B/C, HIV, CMV, and T3/T4/thyreo-stimulating-hormone.

Urine

Toxins (medicinal products and narcotics), cyto-bacteriological examination.

Cerebrospinal fluid

Cyto-bacterio-chemistry, virology, assay for lactate, chloride, pyruvate and glucose, protein electrophoresis, anti-Yo antibodies, anti-Hu antibodies and anti-Ri antibodies.

Computed tomography scan, magnetic resonance imaging, fundus oculi, electrocardiogram, thyroid ultrasound. Electroencephalograms (during wake and sleep) could not be performed under optimal conditions.

They all proved normal

At last, some hypersomnia syndromes were eliminated [25]. Idiopathic hypersomnia, restless leg syndrome and sleep apnea syndrome because of all associated symptoms with hypersomnia in this case Insufficient sleep syndrome because the girl had not been

chronically sleep-deprived before the episode. Given the possibility of a sexual aggression, we considered a gynecological consultation, but the patient would not agree to it.

A few days after our first meeting we had still not made a diagnosis, but, given the patient's increased anxiety, we started treatment with a first-generation antipsychotic (cyamemazine: 3×25 drops/day), soon combined with a second-generation antipsychotic (risperidone: 2 mg/day). Two weeks after admission, because of depressed disorder, we introduced an anti-depressant (Sertraline started at 25 mg then increased to 50 mg), which we were obliged to withdraw rapidly because of the secondary exacerbation of psychomotor agitation. We then started an anti-epileptic treatment to regulate mood (carbamazepine 2×200 SR/day), which reduced her hypersexuality.

After about a month, organic tests were completed but the patient's clinical condition had not changed, despite treatment; the patient was transferred to our unit full-time. The young girl stayed in bed for up to 15 hours a day, shouted when frustrated and was sometimes subject to severe anxiety. She presented bouts of motor agitation, endlessly repeating the same questions, asking to phone her parents and requesting food. She was still disorientated in time and could behave in a violent and insulting manner. She regularly slapped the care team and other patients, yet was uncritical of her actions.

We gradually increased the doses of the medications, but after 1 month, given the lack of effect of these, we stopped all the therapeutics over a few days without noting any exacerbation of symptoms. Then, naturally, 3.5 months after the start of the episode, symptoms regressed and the young girl was able to return home. During outpatient consultations after discharge, we met quite a different young girl, just like the one her parents had described. At this point, we could finally reach the diagnosis of Kleine-Levin syndrome, but to be able to confirm it, a second episode was necessary. However, we informed the young girl, her parents and the medical team who may meet her later, about the disease and its evolution. We also addressed the family to the reference center for this orphan disease in Paris, for confirmation and new treatment guidelines.

The young girl suffered another episode 10 months later, which resolved after 2.5 months. The symptoms were less "noisy" so she was not hospitalized. She and her parents then accepted prophylactic lithium. This treatment has adverse effects and requires regular laboratory tests, but the only recurrence she has experienced was 2.5 years after the second, following vaccination, an episode which then lasted days and was treated at home.

She was treated for 3 years after the last crisis, according to the recommendations and she is now a young mother. Before the end of her treatment, her young brother developed symptoms evocating a Kleine-Levin syndrome when he was 15: we addressed him to the reference center and he has been treated with Lithium.

Discussion

Kleine-Levin syndrome is a rare disease that is difficult to diagnose, especially at the first episode. Two of them are necessary to make the diagnosis with certainty. In the case of this young girl, even when all the likely organic causes had been eliminated, we still hesitated between Kleine-Levin syndrome and a bipolar disorder (mixed episode).

Indeed, the suddenness of the symptoms and the age at which they appeared, a neglected appearance, cognitive disturbances such as

confusion and memory impairment, derealisation and delusion, mood disturbance, anxiety, aggressive behaviour, and hypersexuality are common to both diagnoses.

In favour of the Kleine-Levin syndrome, there was the cardinal manifestation of the disease, hypersomnia, and the lack of family history of psychiatric disorders. Besides, "psychiatric forms" of Kleine-Levin syndrome have already been reported in the past [4,8-13]. However, men tend to be more affected by Kleine-Levin syndrome (68%), the crisis usually lasts about 10 days only (yet young girls generally suffer longer crises and for certain patients, episodes lasting up to several months have been reported). Moreover, patients with Kleine-Levin syndrome normally gain weight and hypersexuality is reported more rarely in women. Several arguments that made us doubt [26].

The symptoms in favour of a mixed episode were hypersexuality and the response to treatments: SSRIs increased agitation and the hypersexuality decreased with carbamazepine, a treatment for mood regulation. However, although there was a small clinical improvement with carbamazepine associated with antipsychotic medications, the major symptoms still persisted.

In summary, even if they are not always very typical, psychiatric symptoms described in this case are included in Kleine Levin syndrome, a polysymptomatic disease. So, even if you can't diagnose Kleine Levin syndrome after the second episode, hypersomnia must be the symptom that guides your diagnostic approach, once all other organic causes are eliminated.

By the way, we couldn't be sure about the diagnosis in this case and our doubts made the situation especially uncomfortable for the parents because we could not assure them that their daughter would recover. Eventually, it is the natural evolution of the disease that gave us the final diagnosis.

Conclusion

A diagnosis of Kleine-Levin syndrome is difficult to make before the end of the crisis and before other diseases have been ruled out, but it should be considered in the case of an adolescent who suddenly develops psychiatric-like disorders associated with hypersomnia, as the young girl presented. It is necessary to address the young patient to the reference center of Kleine-Levin syndrome.

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