CASE REPORT

First Attack of Kleine-Levin Syndrome Triggered by Influenza B Mimicking Influenza-associated Encephalopathy

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Abstract

Six days after the onset of influenza B symptoms, a 14-year-old Japanese boy presented with encephalopathy-like symptoms, somnolence, irritability, and childishness, which we first considered was an atypical type of influenza-associated encephalopathy because the infection symptoms disappeared by day 4. His encephalopathy-like symptoms gradually improved, although he had repetitive hypersomnia attacks. Owing to the patient’s clinical presentation and normal interleukin-6 levels in the cerebrospinal fluid during the first period of hypersomnia, we diagnosed him with Kleine-Levin syndrome (KLS) triggered by influenza B. The preceding influenza infection was not only a diagnostic clue of KLS but also a diagnostic confounding factor.

Key words: Kleine-Levin syndrome, recurrent hypersomnia, preceding infection, influenza, influenza-associated encephalopathy


Introduction

Recurrent hypersomnia, which is a rare disorder that causes recurring periodic episodes of hypersomnia, has a male predominance with a typical age of onset in the teen-age years (1). Kleine-Levin syndrome (KLS) is a disorder that is classified as a subtype of recurrent hypersomnia and that presents with recurrent hypersomnia plus binge eating, hypersexuality, cognitive disturbances, and/or odd behavior (1, 2). Various infections often precede the onset and recurrence of KLS (2, 3), although the infectious agents have rarely been identified (4-8). Patients with KLS often present with cognitive disturbances, mood disorders, and irritability (1, 2), and, thus, they are sometimes misdiagnosed as psychiatric disorders or encephalopathy (9). In this paper, we report on a 14-year-old Japanese boy who presented with normal interleukin-6 (IL-6) levels and slightly decreased levels of hypocretin in the cerebrospinal fluid (CSF) during the first attack of KLS, which occurred just after an influenza B infection, and, thus, his disorder was confused with influenza-associated encephalopathy.

Case Report

A previously healthy 14-year-old Japanese boy who had no family history of hypersomnia presented with high-grade fever, cough, and general fatigue in March 2011. He was diagnosed with influenza B by a rapid antigen test that was performed the following day, and he was treated with zanamivir inhalation (10 mg, twice daily). His symptoms disappeared on day 4, but he was somnolent all day after day 6. He exhibited disturbed concentration, cried, and on day 7, said, “I cannot concentrate on studying.” Brain computed tomography (CT) and magnetic resonance imaging (MRI) scans that were performed at another hospital detected no abnormal findings on day 8. Influenza-associated encephalopathy was suspected, and he was transferred to our hospital for intensive care on day 9.

Upon admission, findings from a physical examination showed a temperature of 36.0°C, a pulse of 70 beats/min, and a blood pressure of 116/66 mmHg. No abnormal find-
An electroencephalogram (EEG) showed a slightly diffuse slowing of basic activity without epileptic abnormalities.

Findings from laboratory examinations, including blood counts, electrolytes, and liver and kidney function tests, were all within normal limits. The levels of C-reactive protein were 0.02 mg/dL, blood sugar, 98 mg/dL, and ammonia, 22 μg/dL. Thyroid function, antithyroid antibodies, antinuclear antibody, anti-DNA antibody, and complement activity were negative and normal. An analysis of the CSF demonstrated white blood cell counts of 2 cells/mm³; blood sugar, 98 mg/dL; and ammonia, and the EEG again showed a slightly diffuse slowing of basic activity. Encephalopathy of unknown origin was suspected, but his somnolence, irritability, and childishness gradually decreased, and he was alert on day 51 without any therapy. However, a third somnolent attack occurred 1 month later. We diagnosed him with KLS due to his clinical presentation, recurrent hypersomnia, cognitive disturbances, irritability, and childish behavior according to the diagnostic criteria of the International Classification of Sleep Disorders II (ICSD-2) for recurrent hypersomnia, and his disorder was believed to be triggered by influenza B (1). In the analysis of the CSF that was performed during the first attack of KLS (day 9), IL-6 levels were not elevated (0.7 pg/mL), and tests for the oligoclonal band and anti-influenza B antibody were negative. Hypocretin levels in the CSF during the first attack of KLS were 189 pg/mL (normal, 200 pg/mL or more; intermediate, 110-200 pg/mL; low/undetectable, 110 pg/mL or less). We could not reexamine the CSF hypocretin levels during the other symptomatic and asymptomatic periods because of his and his family’s refusal. The symptoms of KLS disappeared about 1 week later, and the EEG findings were normal during the asymptomatic period. He had the fourth attack of KLS on day 98, and he was treated with methylphenidate (18 mg once daily). Methylphenidate slightly decreased the degree of sleepiness, but he had had repetitive hypersomnia attacks monthly for 6 months.

Discussion

KLS is a rare disorder that consists of recurring periodic hypersomnia episodes that last more than 2 days and less than 4 weeks, binge eating, hypersexuality, cognitive disturbances, and/or odd behavior (1). Theoretically, it is possible to diagnose recurrently hypersomnic patients with KLS from the second hypersomnia attack onward, although they are sometimes misdiagnosed as psychiatric disorders or encephalopathy due to the rarity of KLS and the psychiatric and encephalopathy-like symptoms (9). About one-quarter of patients with KLS experience a precipitating flu-like fever before the onset and reoccurrence of the hypersomnia attack (2). A strong relationship between an upper respiratory infection and the first attack of KLS has recently been reported (3), although identification of the infectious agents has been very rare (4-8). The clinical profiles of 5 patients who were reported to have KLS that was triggered by identified infectious agents are summarized in Table 1. All of them were male and teenagers, which was consistent with typical KLS patients. Infections of streptococci and various viruses preceded the onset and recurrence of KLS. Except for 1 patient of the 5, infection preceded the first attack of KLS. The symptoms of KLS occurred between 3 and 7 days after the onset of infection symptoms. Patients presented with various cognitive and psychiatric symptoms in addition to hypersomnia. Therefore, 1 patient was misdiagnosed with viral meningitis at first (7), and 2 patients were diagnosed...
with KLS after 5 and about 40 attacks of KLS (4, 6). The current patient presented with typical KLS symptoms 6 days after the onset of infection symptoms, as did other patients with KLS that were triggered by identified infectious agents, although we could not discriminate the first attack of KLS that were triggered by identified infectious agents, after the onset of infection symptoms, as did other patients. The current patient presented with typical KLS symptoms 6 days after 5 and about 40 attacks of KLS (4, 6). The CSF were negative at the onset of KLS in the present patient. Steroid pulse therapy was given during the first attack of KLS, but we could not determine the effects of the steroid therapy.

Dysfunction of the hypothalamus has also been suggested as one of the sites of pathophysiology in KLS (6). Hypocretin, which is a neuropeptide that is generated by hypothalamic neurons, regulates sleep-wake rhythms and feeding (14). A marked decrease of CSF hypocretin levels is the hallmark of narcolepsy (15). The measurement of CSF hypocretin levels in other types of hypersomnia has been attempted, but studies of patients with KLS are limited, especially during the symptomatic period. Hypocretin levels were normal during asymptomatic intervals in patients with KLS (16) and during symptomatic periods in some patients (17). However, hypocretin levels during symptomatic periods in 2 patients with KLS were relatively low compared to the levels during the asymptomatic period, which were within normal or intermediate levels (18, 19). We measured hypocretin levels during the first attack of KLS, which occurred just after the influenza B infection, and the levels were intermediate. Although the meaning of the slightly decreased levels of hypocretin during the first attack of KLS was limited because we could not reexamine the hypocretin levels during subsequent symptomatic and asymptomatic periods, the slightly decreased hypocretin levels may contribute to the onset of KLS. Further investigation is needed to elucidate the pathophysiology of KLS.

In this paper, we report a 14-year-old Japanese boy who was affected by KLS just after an influenza B infection. At the third hypersomnia attack, KLS was suspected for the first time. The preceding influenza infection was not only a diagnostic clue of KLS, but also one of the diagnostic confounding factors. A first attack of KLS that is triggered by influenza should be considered in patients presenting with atypical features of influenza-associated encephalopathy, such as delayed onset and no findings of inflammation. Slightly decreased levels of hypocretin may play a part in the onset of KLS, and, thus, the measurement of the levels

Table 1. Clinical Profiles of the Patients with Kleine-Levin Syndrome Triggered by Identified Infectious Agents

<table>
<thead>
<tr>
<th>Author</th>
<th>Onset age/ Sex</th>
<th>Triggered attack of KLS</th>
<th>Agents/Method to identify agents</th>
<th>Duration from onset of infection to onset of KLS</th>
<th>KLS symptoms</th>
<th>CSF hypocretin concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garland et al.</td>
<td>15/M First attack</td>
<td>Asian influenza virus/ NA</td>
<td>NA</td>
<td>NE</td>
<td>hyponormia, hypersexuality, binge eating, odd behavior</td>
<td></td>
</tr>
<tr>
<td>Gallinek (1967)</td>
<td>18/M First attack</td>
<td>Streptococci septicemia/ NA</td>
<td>NA</td>
<td>NE</td>
<td>hypersomnia, depression, irritability</td>
<td></td>
</tr>
<tr>
<td>Smolik and Roth (1988)</td>
<td>14/M First attack</td>
<td>Scarlet fever/ NA</td>
<td>NA</td>
<td>NE</td>
<td>hyponormia, hypersexuality, aggression, binge eating</td>
<td></td>
</tr>
<tr>
<td>Fernandez et al. (1990)</td>
<td>17/M First attack</td>
<td>Enterovirus/ serum antibody test</td>
<td>3 days</td>
<td>NE</td>
<td>hyponormia, hypersexuality, irritability, delusion, incoherent speech</td>
<td></td>
</tr>
<tr>
<td>Salter and White (1993)</td>
<td>12/M Second attack</td>
<td>Epstein-Barr virus/ serum antibody test</td>
<td>7 days</td>
<td>NE</td>
<td>hyponormia, hypersexuality, irritability, incoherent speech, mood alternation</td>
<td></td>
</tr>
<tr>
<td>Fourth attack</td>
<td></td>
<td>Varicella-Zoster virus/ serum antibody test</td>
<td>NA</td>
<td>NE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Our patient</td>
<td>14/M First attack</td>
<td>Influenza B virus/ rapid antigen test</td>
<td>6 days</td>
<td>NE</td>
<td>hyponormia, irritability, cognitive disturbance, childish behavior</td>
<td>slightly decreased</td>
</tr>
</tbody>
</table>

CSF: cerebrospinal fluid, KLS: Kleine-Levin syndrome, NA: not apparent, NE: not examined
of IL-6 and hypocretin in the CSF may help in the early differential diagnosis of KLS from influenza-associated encephalopathy.

The authors state that they have no Conflict of Interest (COI).

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References