IVIG TREATMENT FOR REPEATED HYPOTHERMIC ATTACKS ASSOCIATED WITH LGI1 ANTIBODY ENCEPHALITIS

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Hypothermia, defined as a core body temperature of \(<35.0°C (\langle95.0°F)\), is a life-threatening and emergency situation. Various conditions and diseases can cause hypothermia, including environmental exposure, drug intoxication, CNS diseases, and metabolic abnormalities, such as hypopituitarism, hypoadrenalism, hypothyroidism, and hypoglycemia.

Leucine-rich glioma-inactivated 1 (LGI1) antibody–associated encephalitis is an autoimmune-mediated encephalitis in which autoantibodies are directed against a voltage-gated potassium channel (VGKC) complex protein named LGI1.\(^1\) The LGI1 protein is widely expressed in the neurons of the CNS and also in the hypothalamus.\(^2\) Central hypothermia associated with autoimmune-mediated encephalitis is rare; however, it is a potentially life-threatening symptom of encephalitis. Here, we describe a patient who experienced repeated hypothermic attacks associated with anti–LGI1 encephalitis.

Case report. A 56-year-old Japanese man was admitted to our hospital with hypothermia and consciousness disturbance. He had been diagnosed with VGKC antibody encephalitis 1 year earlier based on the detection of VGKC-complex antibodies and neurologic symptoms. He was initially admitted to our hospital because of seizures and acute consciousness disturbances accompanied with a 6-month history of psychiatric symptoms, such as violent behavior toward his family, and audiovisual hallucinations since the summer of 2007. Brain MRI revealed a slightly hyperintense area in the right medial temporal region at the initial admission to our hospital. The findings of whole-body CT and routine CSF analysis were normal. Corticosteroid treatment enhanced his psychiatric symptoms. He was transferred to a psychiatric hospital because of the continuing psychiatric symptoms which were mainly suppressed with antipsychotic drugs. Thereafter, he had stayed in the psychiatric hospital in an air-conditioned room, and the temperature of which was maintained above 20°C. In February 2009, he experienced consciousness disturbance after breakfast. His axillary body temperature could not be obtained, and he was transferred to our hospital. The staff at the psychiatric hospital denied that he was exposed to a cold environment or overdosage of drugs before or after the hypothermic attack.

After arriving at our hospital, his core body temperature was 33.3°C without piloerection or shivering. His blood pressure was 99/54 mm Hg, and heart rate was 55 beats per minute. Neurologic examination revealed mild disturbance of consciousness. Results of routine laboratory tests were normal, except for mild hyponatremia (serum sodium of 133 mEq/L). Endocrine tests showed a free T4 level of 0.97 ng/dL, thyroid-stimulating hormone level of 0.42 μIU/mL, and adrenocorticotropic hormone level of 10.3 pg/mL. Brain MRI and whole-body CT were unremarkable. Therefore, sepsis, endocrine disease, and exposure to cold environment were excluded. He was diagnosed with moderate hypothermia associated with anti–LGI1 encephalitis based on the detection of LGI1 antibodies in his serum and CSF, and active rewarming was performed until his body temperature returned to normal. His body temperature recovered within 24 hours after hospitalization, and his level of consciousness ameliorated with the increase of body temperature. Hypothermic attacks with mild disturbance of consciousness occurred repeatedly 7 times, and he recovered by rewarming in each occasion; however, rewarming was not effective for preventing recurrences.

We administered methylprednisolone pulse therapy which showed no effects. The mean recurrence interval of hypothermic attacks was 15.8 (5–37) days. After administration of the first course of IV immunoglobulin (IVIG), the recurrence interval increased to 79 days; and no hypothermic attacks occurred for 5 years after the second course of IVIG treatment.

Discussion. The center of thermoregulation is in the hypothalamus. The effector mechanisms for cold defense include cutaneous vasoconstriction, piloerection, and heat production by means of shivering. Therefore, the absence of piloerection and shivering during hypothermia in our case suggested a dysfunction of the hypothalamus thermoregulatory center.

To better understand this clinical problem, we reviewed the reports of 6 patients with VGKC-complex...
or LGI1 antibody–associated encephalitis who presented with central hypothermia during the disease course, including the current patient (table). Almost all cases, except for a patient with continued hypothermia, developed single or dual attacks. Three or more repeated hypothermic attacks had not been previously reported in patients with anti–LGI1 encephalitis. The patients reported by Jacob et al. likely had anti–LGI1 encephalitis; however, encephalitis associated with contactin-associated protein–like 2 (Caspr2) antibodies cannot be ruled out because this type of VGKC-complex antibody can also associate with limbic encephalitis.

To the best of our knowledge, some patients with anti–NMDAR encephalitis can also develop hypothermia. The mechanism of hypothermia in autoimmune-mediated encephalitis is not clear. The LGI1 protein is widely expressed in the neurons of the CNS and also in the hypothalamus. The hypothermic attacks repeatedly occurred before effective immunotherapy. Therefore, we speculated that the hypothermic attacks were related to anti–LGI1 encephalitis. Although repeated hypothermic attacks are rare, it is important that clinicians are aware of these attacks that can occur during the course of anti–LGI1 encephalitis, as these attacks can be fatal if undetected or overlooked.

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### Table 1

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Study</th>
<th>Age at hypothermia onset, y/sex</th>
<th>Underlying disease/tumor</th>
<th>Underlying drugs</th>
<th>Disease duration between initial symptoms of the underlying disease and hypothermia</th>
<th>Core body temperature at hypothermia identification, °C</th>
<th>Realization of hypothermia</th>
<th>Severity of hypothermia following AHA 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Jacob et al., 2008³</td>
<td>46/M</td>
<td>VGKC-related encephalitis/thymoma</td>
<td>NA</td>
<td>3–4 mo</td>
<td>33</td>
<td>Hospital</td>
<td>Moderate</td>
</tr>
<tr>
<td>2</td>
<td>Jacob et al., 2008³</td>
<td>72/M</td>
<td>VGKC-related encephalitis/none</td>
<td>NA</td>
<td>5 mo</td>
<td>34.5</td>
<td>NA</td>
<td>Mild</td>
</tr>
<tr>
<td>3</td>
<td>Jacob et al., 2008³</td>
<td>62/F</td>
<td>VGKC-related encephalitis/none</td>
<td>NA</td>
<td>9 y</td>
<td>34.8</td>
<td>NA</td>
<td>Mild</td>
</tr>
<tr>
<td>4</td>
<td>Jacob et al., 2008³</td>
<td>57/M</td>
<td>VGKC-related encephalitis/none</td>
<td>Phenobarbital, phenytoin</td>
<td>1 y</td>
<td>33.4</td>
<td>Hospital</td>
<td>Moderate</td>
</tr>
<tr>
<td>5</td>
<td>Montiel, et al., 2008⁴</td>
<td>65/F</td>
<td>VGKC-related encephalitis/none</td>
<td>NA</td>
<td>2.5 y</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>Present case</td>
<td>56/M</td>
<td>LGI1 antibody encephalitis/none</td>
<td>Phenytoin, clonazepam, haloperidol, quetiapine, brotizolam, and valsartan</td>
<td>1.5 y</td>
<td>33.3</td>
<td>Hospital</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

**Abbreviations:** AHA = American Heart Association; AZP = azathioprine; CS = corticosteroids; IVIG = IV immunoglobulin; LGI1 = leucine-rich glioma-inactivated 1; NA = not available or not described; PE = plasma exchange; VGKC = voltage-gated potassium channel; VT = ventricular tachycardia.

### Table 2

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Season</th>
<th>Disturbance of consciousness at admission</th>
<th>Cardiac abnormalities</th>
<th>Absence of pilomotor erection, and/or shivering</th>
<th>How many episodes of hypothermic attack</th>
<th>Abnormalities of the hypothalamus on MRI</th>
<th>Immunotherapy after rewarming</th>
<th>Long-term outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NA</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
<td>Twice</td>
<td>None</td>
<td>First episode: IVIG + AZP, second episode: IVIG + CS</td>
<td>Recovered</td>
</tr>
<tr>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Prolonged 6 mo</td>
<td>None</td>
<td>PE + IVIG</td>
<td>Recovered</td>
</tr>
<tr>
<td>3</td>
<td>NA</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
<td>Single</td>
<td>Bilateral hyperintensities</td>
<td>CS</td>
<td>Recovered</td>
</tr>
<tr>
<td>4</td>
<td>Autumn</td>
<td>None</td>
<td>Bradycardia</td>
<td>Absent pilomotor erection and shivering</td>
<td>Single</td>
<td>Bilateral hyperintensities</td>
<td>CS</td>
<td>Recovered</td>
</tr>
<tr>
<td>5</td>
<td>Winter</td>
<td>NA</td>
<td>NA</td>
<td>Single</td>
<td>None</td>
<td>None</td>
<td>IVIG + CS</td>
<td>Recovered</td>
</tr>
<tr>
<td>6</td>
<td>Winter</td>
<td>Mild</td>
<td>Absent pilomotor erection and shivering</td>
<td>7 times</td>
<td>None</td>
<td>CS was ineffective, IVIG was effective</td>
<td>Recovered</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** AHA = American Heart Association; AZP = azathioprine; CS = corticosteroids; IVIG = IV immunoglobulin; LGI1 = leucine-rich glioma-inactivated 1; NA = not available or not described; PE = plasma exchange; VGKC = voltage-gated potassium channel; VT = ventricular tachycardia.


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