Dysgeusia in a Patient with Guillain-Barré Syndrome Associated with Acute Hepatitis E: A Case Report and Literature Review

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Abstract

Guillain-Barré syndrome (GBS) is usually triggered by viral or bacterial infection. In addition, it was recently reported that infection with hepatitis E virus (HEV) also causes GBS. A 49-year-old man presented with acute-onset paralysis in all extremities and dysgeusia during an episode of acute hepatitis. Serological tests showed the presence of anti-HEV IgM antibodies and HEV-RNA in the serum. As an electrophysiological examination showed acute demyelinating polyradiculoneuropathy, the patient was diagnosed as HEV-associated GBS. Following the initiation of treatment with intravenous immunoglobulin, his paralysis and dysgeusia rapidly improved. This case suggests that HEV-associated GBS may rarely be complicated by dysgeusia.

Key words: Guillain-Barré syndrome, hepatitis E, IVIg, muscle weakness, dysgeusia

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Introduction

Guillain-Barré syndrome (GBS) is an acute polyradiculoneuropathy that is divided into five major subtypes: acute inflammatory demyelination polyneuropathy (AIDP); two axonal subtypes, namely acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN); acute sensory neuropathy; and acute pan-dysautonomia (1). In more than two-thirds of cases, infection precedes the onset of GBS by one to three weeks (1). Infections with Campylobacter jejuni, Mycoplasma pneumoniae, Cytomegalovirus and Epstein-Barr virus are each associated with GBS. In addition, it has been reported that hepatitis viruses, including hepatitis A, B and C, are possibly associated with the development of GBS (2-4). Furthermore, recent reports have suggested that hepatitis E virus (HEV) infection is linked to GBS onset (5-17). We herein report the case of a patient with HEV-associated GBS who presented with limb weakness, numbness and dysgeusia.

Case Report

A 49-year-old non-immunocompromised man developed low back pain, abdominal discomfort and general fatigue one week after having eaten undercooked pork. Two weeks later, he developed numbness of the bilateral upper and lower extremities followed by rapidly progressive leg weakness and difficulty walking in addition to a loss of taste sensation. He was admitted to a local hospital, where blood tests revealed liver dysfunction, as evidenced by elevated levels of total bilirubin (T-bil) (0.9 mg/dL; normal, <0.9 mg/dL), aspartate aminotransferase (AST) (275 U/L; normal, 13-33 U/L), alanine transaminase (ALT) (1,246 U/L; normal, 13-33 U/L), alanine transaminase (ALT) (1,246 U/L; normal, 13-33 U/L), alkaline phosphatase (ALP) (472 U/L; normal, 115-359 U/L) and gamma-glutamyl transpeptidase (γ-GTP) (744 U/L; normal, 10-47 U/L). Because the muscle weakness and numbness were rapidly progressive, he was transferred to our hospital.

The patient had not travelled outside Japan and had no history of hepatotoxic or neurotoxic drug use. On admission,
his blood pressure was 115/72 mmHg, his heart rate was 74 bpm with a regular rhythm, his body temperature was 36.6 °C and the general examination findings were unremarkable. A neurological examination revealed a normal mental function. He reported dysgeusia of sweet, salty, sour, bitter and umami tastes. Motor weakness was present in the upper and lower extremities with distal predominance, although no facial palsy was noted. Sensory testing showed hypoesthesia with a glove-and-stocking type distribution. The deep tendon reflexes were absent in all limbs, and the patient exhibited no urinary retention or bowel dysfunction. His medical history included hypertension and hyperlipidemia treated by a general physician.

Blood tests performed on admission to our hospital showed a T-bil level of 1.2 mg/dL (normal, 0.3-1.2 mg/dL), AST level of 98 U/L (normal, 13-33 U/L), ALT level of 571 U/L (normal, 6-30 U/L), ALP level of 386 U/L (normal, 115-359 U/L) and γ-GT level of 594 U/L (normal, 10-47 U/L). The levels of vitamin B1, vitamin B12 and folic acid were within the normal ranges, while the serum zinc level was slightly elevated at 115 μg/dL (normal, 65-110 μg/dL). Lumbar puncture was performed on the fourth day after the onset of neurological symptoms, which showed the following findings in the cerebrospinal fluid: 7 cells/μL (95% lymphocytes, 3% neutrophils and 2% monocytes), a glucose level of 98 mg/dL and a protein level of 102 mg/dL (normal, 15-45 mg/dL). A serological study showed positivity for IgA, IgM and IgG antibodies to HEV. Furthermore, HEV RNA was detected in a serum sample on polymerase chain reaction on the day of admission. The HEV genotype was HEV genotype 3 (HEV3). Hepatitis B surface antigens and hepatitis B and C antibodies were negative. The results of serological examinations for the following pathogens were also negative: human immunodeficiency virus, varicella-zoster virus, Cytomegalovirus, Campylobacter spp. and Epstein-Barr virus.

Nerve conduction studies revealed prolongation of the distal motor latency in the median and peroneal nerves (Table 1). Temporal dispersion was observed in the peroneal nerve. The F-wave latency was prolonged in the median nerve, while F-waves were absent in both the ulnar and peroneal nerves. No sensory nerve action potentials were evoked in the median nerve. These findings were consistent with a diagnosis of AIDP (18). Notably, tests for all serum antiganglioside antibodies, measured at Kinki University, were negative (GM1, GM2, GD1a, GD1b, GQ1b, GT1a and GT1b).

The patient was diagnosed with acute HEV-associated GBS, and intravenous immunoglobulin (IVIg) treatment (0.4 g/kg per day) was administered for five days. His muscle weakness immediately improved, and he continued to recover until he was able to walk without assistance after two weeks. His muscle strength fully recovered after two months, and his taste impairment improved after one month. Three months after the administration of IVIg treatment, blood testing revealed normal serum levels of AST and ALT. A serological study showed that the IgA and IgM antibodies to HEV had become negative, while only IgG antibodies to HEV remained positive. Furthermore, HEV RNA was negative, suggesting a full recovery from the acute phase of hepatitis E.

### Discussion

HEV was first identified as a leading cause of acute fulminant hepatitis in tropical and subtropical countries in the 1980’s (18, 19). HEV genomes can be divided into four major genotypes. HEV1 and HEV2 are restricted to humans and transmitted mostly via contaminated water in developing countries (19, 20). HEV3 and HEV4, which infect both humans and other mammalian species (deer, pigs, boars, cows, horses and others), are responsible for sporadic cases of autochthonous HEV infection in both developing and developed countries (19, 20). In a recent report from France and the UK, seven of 126 patients with acute HEV infection developed neurological complications (9). Moreover, a recent study in the Netherlands demonstrated that 5% of patients with GBS also have acute HEV infection (17). HEV infection may also be associated with neurological complications, such as inflammatory polyradiculopathy, GBS, bilateral brachial neuritis, encephalitis, transverse myelitis, myopathy and myositis (9, 19-21). According to previous reports and the current case, HEV3 is of the most common HEV genotype causing GBS (9, 13, 14). Geurtsvankessel et al. (16) recently investigated 100 patients with GBS in Bangladesh and detected HEV1 in one patient. This result suggests that

<table>
<thead>
<tr>
<th>Table 1. Nerve Conduction Studies.</th>
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<tbody>
<tr>
<td><strong>MCV</strong> (m/s)</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>R. Median</td>
</tr>
<tr>
<td>R. Ulnar</td>
</tr>
<tr>
<td>R. Tibial</td>
</tr>
<tr>
<td>R. Peroneal</td>
</tr>
<tr>
<td>R. Sural</td>
</tr>
</tbody>
</table>

MCV: motor nerve conduction velocity, CMAP: compound muscle action potential, DML: distal motor latency, SCV: sensory nerve conduction velocity, SNAP: sensory nerve action potential, dist/prox: stimulation at the wrist or ankle, prox: stimulation below elbow or knee, n.e: not evoked, *conduction block, **temporal dispersion
neurological complications are not induced only by HEV3 infection. Further studies are therefore needed to identify which HEV genotypes tend to cause neurological complications.

We searched the English-language scientific literature for patients who developed GBS during acute HEV infection in order to clarify the clinical characteristics of GBS associated with HEV infection and found 12 non-immunocompromised patients with HEV-associated GBS among 11 reports (Table 2) (5-15). Based on this search, the clinical characteristics of HEV-associated GBS are as follows. First, most patients are middle-aged men; 10 of 13 patients with HEV-associated GBS in our search were male. Additionally, the age of onset varies from 27 to 66 years. These data are almost identical to those of a large cohort study of HEV-associated GBS in the Netherlands (17). Second, GBS symptoms usually appear within two to three weeks after the onset of hepatitis symptoms, such as jaundice, nausea and vomiting. Third, the severity of the illness varies; in our literature search, some patients only showed mild to moderate muscle weakness (7, 11, 12), while others became bedridden within a few days (5, 6, 9, 13) and three patients required mechanical ventilation within approximately one week due to respiratory failure (8, 14, 15). Fourth, most neurophysiological findings observed in previously described patients with HEV-associated GBS indicated AIDP (Table 2). In one large study, one patient had AMSAN and one patient had AMAN, whereas half of the patients with HEV-associated GBS exhibited AIDP (17). These reports suggest that the major subtype of HEV-associated GBS is AIDP. Finally, IVIg treatment or plasmapheresis may be effective for achieving an earlier recovery from HEV-associated GBS in some patients, including the present case (6-15). In contrast, some patients recovered spontaneously without IVIg treatment (5, 9). Almost all patients in previous reports recovered fully; however, several months to a year may be required to achieve a full recovery from limb weakness in some patients (7, 9, 13-15). In one large cohort study, the disability scores in nine of 10 patients with HEV-associated GBS improved after six months (17), suggesting that the prognosis of HEV-associated GBS may be good.

The most distinctive clinical feature in our patient was dysgeusia. There are two possible reasons for the development of dysgeusia in this case: acute hepatitis and GBS. In the acute phase of hepatitis, the rate of excretion of zinc into the urine increases, resulting in a decreased serum zinc concentration (22); the development of dysgeusia in patients with acute hepatitis may be associated with the serum zinc concentration. In the present case, the serum zinc concentration was not decreased in the acute phase of the patient’s hepatitis. Moreover, the onset of dysgeusia and muscle weakness was simultaneous and the dysgeusia showed a good response to IVIg therapy. Therefore, we consider that the dysgeusia was associated with the GBS. Dysgeusia is a rare symptom, even in patients with GBS. Odaka et al. (23) reported that only five of 457 patients with GBS developed

### Table 2. GBS Associated with Acute Hepatitis E.

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Country</th>
<th>Anti-glycoprotein antibodies</th>
<th>HEV IgM/IgG</th>
<th>HEV genotype</th>
<th>Duration of GBS onset from hepatitis</th>
<th>Nerve conduction studies</th>
<th>Symptoms</th>
<th>Treatment</th>
<th>Prognosis</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>M</td>
<td>IN</td>
<td>+/-NA</td>
<td>NA</td>
<td>9 days</td>
<td>AIDP</td>
<td>Mo/Se</td>
<td>None</td>
<td>Full recovery</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>F</td>
<td>IN</td>
<td>+/-NA</td>
<td>NA</td>
<td>7 days</td>
<td>AIDP</td>
<td>Mo/CP</td>
<td>PF</td>
<td>Full recovery</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>M</td>
<td>BE</td>
<td>+/-NA</td>
<td>NA</td>
<td>2-3 days</td>
<td>AIDP</td>
<td>Mo/CP</td>
<td>IVIg</td>
<td>Almost full recovery</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>M</td>
<td>IE</td>
<td>+/-NA</td>
<td>NA</td>
<td>14 days</td>
<td>AIDP</td>
<td>Mo/Se/CP</td>
<td>IVIg</td>
<td>Full recovery</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td>M</td>
<td>UK</td>
<td>+/-NA</td>
<td>3e</td>
<td>14 days</td>
<td>Equivocal</td>
<td>Mo/Se</td>
<td>None</td>
<td>Full recovery</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>M</td>
<td>FR</td>
<td>+/-NA</td>
<td>3f</td>
<td>7 days</td>
<td>NA</td>
<td>Mo</td>
<td>IVIg</td>
<td>Partial recovery</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>51</td>
<td>F</td>
<td>BE</td>
<td>+/-NA</td>
<td>RNA (+)</td>
<td>NA</td>
<td>Polineuropathy</td>
<td>Mo/CP</td>
<td>IVIg</td>
<td>Recovery</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>F</td>
<td>HK</td>
<td>+/-NA</td>
<td>NA</td>
<td>4 days</td>
<td>AIDP</td>
<td>Mo/Se/CP</td>
<td>PF</td>
<td>Full recovery</td>
<td>11</td>
</tr>
<tr>
<td>9</td>
<td>27</td>
<td>M</td>
<td>IN</td>
<td>+/-NA</td>
<td>NA</td>
<td>40 days</td>
<td>AIDP</td>
<td>Mo/Fa</td>
<td>IVIg</td>
<td>Recovery</td>
<td>12</td>
</tr>
<tr>
<td>10</td>
<td>60</td>
<td>M</td>
<td>DE</td>
<td>+/-NA</td>
<td>3c</td>
<td>7 days</td>
<td>AIDP</td>
<td>Mo/Se</td>
<td>IVIg</td>
<td>Almost full recovery</td>
<td>13</td>
</tr>
<tr>
<td>11</td>
<td>50s</td>
<td>M</td>
<td>PL</td>
<td>+/-NA</td>
<td>3a</td>
<td>17 days</td>
<td>AIDP</td>
<td>Mo/Se</td>
<td>IVIg</td>
<td>Partial recovery</td>
<td>14</td>
</tr>
<tr>
<td>12</td>
<td>64</td>
<td>M</td>
<td>CN</td>
<td>+/-NA</td>
<td>NA</td>
<td>12 days</td>
<td>NA</td>
<td>Mo/Se</td>
<td>IVIg</td>
<td>Full recovery</td>
<td>15</td>
</tr>
<tr>
<td>13</td>
<td>49</td>
<td>M</td>
<td>JP</td>
<td>+/-NA</td>
<td>3</td>
<td>10 days</td>
<td>AIDP</td>
<td>Mo/Se/CP</td>
<td>IVIg</td>
<td>Full recovery</td>
<td>Our case</td>
</tr>
</tbody>
</table>

altered taste sensation during the course of illness. Taste impairment can result from damage at any location along the neural gustatory pathway from the taste buds via the peripheral nerves to the central pathways of taste sensation, including the brainstem, thalamus and cerebral cortex. In patients with GBS, taste impairment usually coexists with facial palsy or sensory disturbances. Our patient had no apparent signs of facial palsy, suggesting that facial nerve damage may not contribute directly to the presence of taste impairment. The nerve damage observed in our patient may have been restricted to the chorda tympani nerve, a branch of the facial nerve containing taste sensory fibers. Interestingly, we identified a report of a patient with GBS associated with taste impairment without other cranial nerve signs, similar to our case. Although GBS usually involves demyelination of large fibers in general, it has been reported that small fibers in cranial nerves may also be affected. Both the patient’s taste impairment and motor paresis rapidly resolved with IVIg treatment in this case, supporting the speculation that demyelination of the chorda tympani nerve contributed to his taste impairment. To the best of our knowledge, this is the first report of dysgeusia taste impairment caused by GBS associated with acute HEV infection.

In conclusion, we herein reported the first patient with GBS associated with acute HEV infection in Japan. Physicians should carefully investigate the occurrence of taste impairment in patients with GBS.

Author’s disclosure of potential Conflicts of Interest (COI).

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