INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its associated coronavirus disease 2019 (COVID-19) were first reported in December 2019 in Wuhan, China, and rapidly spread around the world. Based on data from Johns Hopkins University, as of June 21, 2021, around 178 million cases have been detected, and more than 3.8 million patients have died of COVID-19 globally. In Japan, around 786,000 cases have been detected, and 9662 patients have died of COVID-19 as of June 21, 2021. COVID-19 is a systemic disorder presenting typically with a fever and respiratory symptoms, but neurological manifestations, such as acute cerebrovascular diseases, seizures, ageusia, anosmia meningitis, and encephalitis, have also been reported.

Guillain-Barré syndrome (GBS) is relatively rare, but potentially fatal, immune-mediated disease of the peripheral nerves and nerve roots that is usually triggered by infections. The incidence of GBS can therefore increase during outbreaks of infectious diseases, as was seen during the Zika virus epidemics. Previous reports have shown that several viral (cytomegalovirus, Epstein-Barr virus, hepatitis E virus, and Zika virus) and bacterial (Campylobacter jejuni and Mycoplasma pneumoniae) infections can trigger an aberrant immune response attacking the peripheral nerves, thus leading to GBS.

Because of the ongoing outbreak of SARS-CoV-2 since December 2019, cases of GBS associated with SARS-CoV-2 have been reported in European countries as well as in the United States. However, such cases are still rare in Asia and Japan, and the geographical and/or racial differences are not fully understood.

We herein report a Japanese woman who developed GBS after SARS-CoV-2 infection and discuss similar previous reports.

CASE PRESENTATION

A 50-year-old woman was referred to our hospital because of numbness of the arms and legs, difficulty walking, and dyspnea. She has...
no remarkable history of complications or medications. Because one of her family was COVID-19 patient, she was considered a close contact without infectious symptoms. Her nasopharyngeal polymerase chain reaction (PCR) of SARS-CoV-2 was positive. Dysgeusia and olfactory abnormality appeared at day 6 but disappeared by day 9. Around day 10, cough and sputum were noted. Although the cough was improved by medication, numbness of the legs appeared at day 15, followed by numbness of the arms, difficulty walking, and dyspnea. She was referred to our hospital at day 24 after testing positive for infection.

Her consciousness was clear, and no objective abnormalities were observed in the chest or abdomen at admission. Although ataxia was not observed, she could not stand or walk. Mild dysphagia and bilateral peripheral facial palsy were observed. Eye movement was normal. A neurological examination revealed intact cranial nerves and decreased muscle strength with a manual muscle test (MMT) scale of 3/3 (R/L) in her lower extremities and 4/4 (R/L) in the upper extremities. Areflexia was observed in the Achilles tendon, patella, biceps, and brachioradialis. Sensational disturbance with a glove and sock pattern was observed.

A nasopharyngeal swab at the current admission was negative for SARS-CoV-2 PCR. The patient’s laboratory data were as follows: total protein, 8.0 g/dl; albumin, 4.3 g/dl; aspartate aminotransferase, 42 IU/L; alanine aminotransferase, 58 IU/L; lactate dehydrogenase, 237 IU/L; creatine kinase 106 IU/L; and C-reactive protein, 0.06 mg/dl. The blood cell count, creatinine, sodium, potassium, thyroid-stimulating hormone, thyroid hormone levels, hemoglobin A1c values, and urine test findings were within normal ranges. Antinuclear antibody, proteinase 3-antineutrophil cytoplasmic antibody (PR3-ANCA), myeloperoxidase (MPO)-ANCA, serum vitamin B12 levels, and serum protein electrophoresis values were also within the normal ranges. Anti-cytomegalovirus and anti-Epstein-Barr virus antibodies showed previous infection patterns. Stool culture for C. jejuni was negative. Oligoclonal bands were absent in the protein electrophoresis. Serum anti-GM1 ganglioside and anti-GQ1b ganglioside antibodies were negative.

Magnetic resonance imaging of the brain did not show findings of encephalitis or demyelinating diseases. Chest computed tomography showed a reticular shadow in the bilateral lower lobes of the lung, which was suspected of indicating changes after inflammation.

A cerebrospinal fluid (CSF) analysis showed a CSF protein of 207.8 mg/dl, white blood cell count of 6/mm³, and glucose level of 60 mg/dl. Myelin basic protein was negative, and SARS-CoV-2 PCR in the CSF was not performed. Albuminocytologic dissociation in CSF and the neurological examination findings suggested acute inflammatory polyneuropathy. Nerve conduction studies (Tables 1 and 2) showed an absent sensory response of the left median and ulnar nerve. The bilateral sural sensory response was spared. The abnormal bilateral median, tibial, and left ulnar motor response with prolonged distal motor latency indicated demyelinating polyneuropathy. Given the albuminocytologic dissociation in CSF, neurological examinations, and nerve conduction study findings, we finally diagnosed the patient with GBS. The time between the COVID-19 symptoms development and GBS onset was nine days.

Because of the risk of dyspnea progressing to respiratory muscle paralysis, she was treated with intravenous immunoglobulin (IVIG) therapy for 5 days at a dose of 400 mg/kg/day from days 26 to 30. IVIG was effective, and her symptoms improved. She received physical rehabilitation and was discharged after a hospital stay of 21 days.

3 | DISCUSSION

Guillain-Barré syndrome is an immune-mediated polyneuropathy. Molecular mimicry exists between nerve and microbial antigens, leading to the development of GBS. Previously discovered coronavirus types, including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), have been reported to be associated with GBS.

Uncini et al. systematically reviewed 42 cases. The median time between the COVID-19 and GBS onset was 11.5 (IQR: 7.7–16) days. The most common clinical features were limb weakness,

| Nerve/sites | Latency (ms) | Amplitude (mV) | Distance (mm) | Velocity (m/s) | Normal range (m/s) |
|-------------|--------------|----------------|---------------|----------------|-------------------|
| Right median nerve | | | | | |
| Wrist | 6.44 | 4.73 | 80 | | |
| Elbow | 10.58 | 4.37 | 180 | 43.5 | (54.3–63.9) |
| Left median nerve | | | | | |
| Wrist | 6.48 | 10.7 | 100 | | |
| Elbow | 10.06 | 11.3 | 150 | 41.9 | (54.3–63.9) |
| Right tibial nerve | | | | | |
| Ankle | 8.92 | 8.36 | 100 | | |
| Knee | 14.24 | 6.77 | 270 | 50.8 | (43.9–54.2) |
| Left tibial nerve | | | | | |
| Ankle | 9.6 | 5.69 | 100 | | |
| Knee | 14.98 | 3.79 | 240 | 44.6 | (43.9–54.2) |

TABLE 1 Motor nerve conduction study findings of the median and tibial nerve
hyporeflexia, sensory disturbances, and facial palsy. The most frequent phenotype was the classical sensorimotor demyelinating GBS. Albuminocytologic dissociation of CSF was found in 77.8% of patients, and SARS-CoV-2 PCR was negative in all tested patients. Most patients (95.5%) were negative for anti-ganglioside antibodies. In the present case, numbness of the legs appeared nine days after the initial symptoms of COVID-19. Limb weakness, hyporeflexia, sensory disturbances, and facial palsy were observed. Anti-ganglioside antibodies were also negative in our case. Although she fortunately recovered without mechanical ventilation, her respiratory state was worsened before IVIG treatment.

Because the number of COVID-19 patients in European countries is larger than those in other areas, it is little wonder that GBS patients associated with SARS-CoV-2 have mainly been reported from European countries. Whether or not racial differences are involved with the prevalence of GBS associated with SARS-CoV-2 is unclear. Reports of GBS associated with SARS-CoV-2 are mainly case reports or case series, and the systematic reviews published thus far are also meta-analyses of data from case reports. Hasan et al. discussed in their meta-analysis that reports from other geographical regions, especially South Asia, are required to confirm the presentation and outcome of SARS-CoV-2-associated GBS. The accumulation and analysis of cases from Asia are needed.

**CONFLICT OF INTEREST**

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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