Guillain-Barré syndrome after COVID-19 in Japan

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SUMMARY
We report the first case of Guillain-Barré syndrome (GBS) associated with SARS-CoV-2 infection in Japan. A 54-year-old woman developed neurological symptoms after SARS-CoV-2 infection. We tested for various antiganglioside antibodies, that had not been investigated in previous cases. The patient was diagnosed with GBS based on neurological and electrophysiological findings; no antiganglioside antibodies were detected. In previous reports, most patients with SARS-CoV-2-infection-related GBS had lower limb predominant symptoms, and antiganglioside antibody tests were negative. Our findings support the notion that non-immune abnormalities such as hyperinflammation following cytokine storms and microvascular disorders due to vascular endothelial damage may lead to neurological symptoms in patients with SARS-CoV-2 infection. Our case further highlights the need for careful diagnosis in suspected cases of GBS associated with SARS-CoV-2 infection.

BACKGROUND
Guillain-Barré syndrome (GBS) is an acute type of polyradiculoneuropathy, that occurs following immune events such as infection and vaccination. Approximately 40%–70% of GBS cases develop following infection, and autoantibodies against glycolipids (mainly ganglioside antibodies) are detected in over 50% of cases. The cause is generally accepted to be an abnormality in the immune process. Recently, several reports of GBS associated with SARS-CoV-2 infection have emerged. However, as far as we have investigated, there are still no reports in Japan. However, in a review of 37 cases of SARS-CoV-2-infection-related GBS, less than half of the studies investigated antiganglioside antibodies. Furthermore, few reports have provided detailed results related to the antiganglioside antibody investigated, and clear descriptions of the relevant tests are available only for anti-GM1, anti-GQ1b and anti-GD1b antibodies. Most reported cases (64.8%) of SARS-CoV-2-infection-associated GBS were of the acute inflammatory demyelinating polyneuropathy type. Acute motor and sensory axonal neuropathy and acute motor axonal neuropathy types were observed in 13.5% and 2.7% of cases. In the present report, we discuss a case of axonal-type GBS associated with SARS-CoV-2 infection, where the patient was tested for various antiganglioside antibodies. Furthermore, we review the cases of SARS-CoV-2-infection-related GBS reported to date, in order to provide insight into the clinical characteristics and pathological mechanisms underlying the disease. Our report also highlights the need for clinicians to remain cautious when attempting to diagnose SARS-CoV-2-infection-related GBS, and when using high-dose IV gamma globulin therapy in patients at risk of thrombosis.

CASE PRESENTATION
A 54-year-old woman with a history of asthma was admitted to our hospital in May 2020 with reports of numbness and weakness in her extremities. Twenty days prior to the onset of neurological symptoms, she developed cough and fever; oropharyngeal reverse transcriptase PCR test results were positive for SARS-CoV-2. Although she had pneumonia on CT of the chest, oxygen was not needed. Therefore, we did not administer additional treatment, and continued budesonide, formoterol fumarate hydrate and montelukast sodium, that were originally being used to treat asthma. In addition, we used betamethasone only for the first 2 days to avoid the risk of exacerbation of asthma. Following approximately 2 weeks of treatment, PCR results were negative. However, at that time, she began to experience numbness in the lower extremities, that gradually spread to the upper extremities. Within the next week, she began to develop weakness in the extremities. Neurological examination revealed no findings suggestive of abnormalities in the central nervous system. Tendon reflexes in the upper extremities were normal, although they were absent in the lower extremities. The Medical Research Council Scale grade for muscle strength was 4/4 for proximal and 5/5 for distal muscles of the lower extremities, and 4/4 for proximal and 4/4 for distal muscles of the upper extremities; she was able to walk. Her modified Erasmus GBS Outcome Score (mEGOS) was 3/9, while her Hughes’ functional grade was 2. Superficial sensation was mildly impaired in the distal extremities, deep sensation was normal and she had no ataxia.

INVESTIGATIONS
Blood tests revealed normal blood glucose levels and no findings suggestive of collagen disease, thyroid disease or vitamin abnormalities. Cerebrospinal fluid (CSF) assessment at admission at approximately 3 weeks after onset revealed normal protein levels and cell counts. All tests for antiganglioside antibodies were negative. The ganglioside antigens used in the ELISA were GM1, GM2, GD1a, GD1b, GD3, GalNAc-GD1a, GT1a, GT1b, GQ1b and GA1 (asialo-GM1). Ganglioside complexes containing two of the above 10 antigens were also used as described in a previous study. CSF was not tested for SARS-CoV-2 PCR. On admission, the patient’s first electrophysiological examination was normal. However, the second examination performed 1 week later revealed decreases in compound muscle action potential (CMAP) amplitudes in the...
median, radial and tibial nerves compared with those obtained in the first examination (table 1). Since the patient had a history of asthma, we did not perform lumbar MRI using a contrast agent.

### DIFFERENTIAL DIAGNOSIS

This case fulfilled two of the required features for the diagnosis of GBS based on the criteria described by Asbury and Cornblath. In addition, several other clinical features strongly supported the diagnosis.

She had no systemic symptoms, multiorgan involvement or elevation of serological markers (eg, elevated sedimentation rate or rheumatoid factor) suggestive of vasculitis. Furthermore, she had no malignancy or history of exposure to heavy metals and other toxins.

### TREATMENT

Although the patient was diagnosed with GBS, she was followed up without IV immunoglobulin therapy due to her mEGOS and functional grade.

### OUTCOME AND FOLLOW-UP

Approximately 2 weeks later, her symptoms had begun to improve, and she was discharged home on day 18; normalisation of the Achilles tendon reflex was also observed. An electromyographical examination performed 1 month later revealed improved CMAP amplitude in most nerves. Although her weakness had improved, she continued to experience numbness.

### DISCUSSION

Although the possibility of GBS associated with SARS-CoV-2 infection remains to be clarified, the number of GBS cases reported between March 2020 and April 2020 is greater than five times that reported in the last 3 years. Given that reports have begun to describe GBS and neurological complications following SARS-CoV-2 infection, the onset of GBS requires special attention.

Among the 37 patients described by Caress et al, 17 were tested for anti-ganglioside antibodies, 15 of whom were negative. In addition, two patients were positive for Miller-Fisher syndrome, and all were negative for GBS. However, specific description of types of the anti-ganglioside antibodies tested were not provided in many cases. Although some reports specifically described the types of anti-ganglioside antibodies tested, patients appear to have been tested only for anti-GM1, anti-GQ1b and anti-GD1b antibodies. Although we tested for various additional antiganglioside antibodies, all tests were negative in the present case as well. GBS was also reported in a case–control study of the 2016 Zika virus, where most patients were
negative for antiganglioside antibodies, suggesting the existence of unknown antibodies. There, therefore, it is important to test for as many kinds of antibodies as possible when suspecting GBS associated with SARS-CoV-2. However, some authors have reported nearly simultaneous development of neurological and respiratory symptoms in patients with COVID-19 and GBS. Thus, the cause of GBS may not be immune related in all cases. Previous research has suggested that SARS-CoV-2 damages the vascular endothelium. Therefore, axonopathy may have been caused by a microvascular disorder. In addition, McGonagle et al proposed that hyperinflammation following macrophage activation syndrome (ie, ‘cytokine storm’) may be a cause of GBS in patients with SARS-CoV-2 infection. Together, these findings suggest that, if neurological symptoms develop early following the appearance of respiratory symptoms in patients with COVID-19, both autoimmune and other factors should be considered in the diagnosis.

Whittaker et al noted that the GBS associated with SARS-CoV-2 infection manifests mainly as lower extremity weakness and paraesthesia. Similarly, neurological symptoms began in our patient’s lower limbs. Axonal disorders and lower extremity dominant symptoms may be similar in character to the length-dependent neuropathies observed in patients with microangiopathy. The present case satisfied the essential diagnostic criteria for GBS described by Ashby and Cornblath, and the patient’s clinical course supported the diagnosis of GBS. Nonetheless, the CSF test yielded atypical findings.

In conclusion, our report supports the notion that patients with GBS associated with SARS-CoV-2 infection tend to test negative for antiganglioside antibodies. In addition to careful diagnosis, further reports are required to elucidate the characteristics and the mechanisms underlying the onset of GBS due to SARS-CoV-2 infection.

**Patient’s perspective**

I was anxious when COVID-19 symptoms improved and neurological symptoms such as numbness and weakness developed. My symptoms gradually progressed and peaked in about 3–4 weeks. My doctor told me that I might have Guillain-Barré syndrome. I was told about gamma globulin treatment, but I declined that option due to the risk of side effects and the mild nature of my symptoms. After that, the symptoms gradually improved and the weakness disappeared, although the numbness remained. I was satisfied with the treatment protocol.

**Learning points**

- Patients with Guillain-Barré syndrome (GBS) associated with SARS-CoV-2 infection may test negative for many known antiganglioside antibodies.
- Careful diagnosis of GBS is required, because peripheral neuropathy in patients infected with SARS-CoV-2 may have causes other than autoimmune conditions.
- Further studies and case reports are required to facilitate discussion of the mechanisms underlying GBS associated with SARS-CoV-2 infection.

**Case report**

**Contributors** TH and OK performed and reviewed literature searches, interpreted and drafted the manuscript, and have both agreed to be personally accountable for the accuracy and integrity of the entire work. TH performed examination and provided clinical care to the patient. YH and KK analysed the antibody. All authors reviewed and revised the manuscript and approved the final manuscript.

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