Neurological Disorders Identified during Treatment of a SARS-CoV-2 Infection

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Abstract:
A 69-year-old man was admitted to our hospital under diagnosis of pneumonia due to SARS-CoV-2 (Day 0). He underwent endotracheal intubation from Day 3. Although his respiratory condition improved and anesthetic drugs were discontinued, no cough reflex was observed despite intubation having been performed until Day 17. His tendon reflexes were also diminished. We suspected that he had developed Guillain-Barré syndrome (GBS), and administered intravenous immunoglobulin from Day 18. The absence of cough reflex improved and extubation was successfully performed on Day 23. Neurological disorders including GBS should be considered when intubated SARS-CoV-2 patients present with a loss of cough reflex during the treatment period.

Key words: Guillain-Barré syndrome, acute disseminated encephalomyelitis, SARS-CoV-2, glycolipid antibody, intravenous immunoglobulin

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Introduction
Severe acute respiratory syndrome-corona virus 2 (SARS-CoV-2) has reportedly been causing pneumonia since December 2019 (1). This atypical pneumonia is often severe and associated with a high mortality. The outcomes for patients who develop severe pneumonia and are admitted to the intensive care unit (ICU) have been reported to be unfavorable, with half dying within a week of ICU admission (2). Although therapeutic agents such as lopinavir, ritonavir, favipiravir and hydroxychloroquine have been administered for the treatment of SARS-CoV-2 infection, no optimal therapy has yet been established (3, 4).

As SARS-CoV-2 has been suggested to induce various neurological disorders such as meningitis and Guillain-Barre syndrome (GBS), the relationship between SARS-CoV-2 and these neurological disease remains unclear (5-7). We encountered a patient with severe pneumonia and SARS-CoV-2 infection who developed a loss of cough reflex during treatment.

Case Report

A 69-year-old man with diabetes mellitus presented to our hospital (Day 0) with a 7-day history of fever and fatigue. Throat swabs for influenza virus, respiratory syncytial virus, and adenovirus yielded negative results. Anti-Mycoplasma antibody (PA) was also negative from blood testing. Chest computed tomography (CT) showed ground-glass opacities...
in both lungs. Pneumonia due to SARS-CoV-2 infection was diagnosed after SARS-CoV-2 was detected by polymerase chain reaction (PCR) testing of a sputum sample. Although lopinavir and ritonavir were administered from Day 1, his respiratory condition gradually deteriorated. He developed acute respiratory distress syndrome (ARDS) and was placed on ventilatory support with intubation in the ICU from Day 3. Further, continuous hemodiafiltration (CHDF) was performed for acute kidney injury from Day 4. Fortunately, the pneumonia improved under combination therapy with hydroxychloroquine. To allow for extubation, all anesthetic drugs were discontinued by Day 13. (midazolam and rocuronium: by Day 7, propofol: by Day 10, fentanyl: by Day 13). However, no cough reflex was observed despite the state of intubation being maintained with spontaneous breathing. A neurological examination on Day 17 revealed a Glasgow Coma Scale of G4VTM6 and deep-tendon reflexes were diminished. Babinski reflexes had not evolved. The possibility of motor and sensory disorders could not be fully assessed because of the risk of infection and the state of intubation. Muscle weakness of the limbs was slightly observed. Autonomic symptoms, such as paralytic ileus, mydriasis, and anhidrosis were unremarkable. Although CHDF was continued, no abnormality in the liver function or body temperature affecting pharmacokinetics was observed. Cerebrospinal fluid (CSF) showed a normal cell count (1/μL) and elevated protein (202 mg/dL). A nerve conduction study could not be sufficiently carried out due to the edema and interference of the alternative current. Brain CT showed no abnormality suggesting ischemic stroke or acute disseminated encephalomyelitis (ADEM).

We suspected GBS and treated the patient with intravenous immunoglobulin (IV Ig) (0.5 g/kg) from Day 18. The cough reflex gradually improved and he was extubated on Day 23. CHDF was also discontinued on Day 30 due to an improvement of the renal function. He was discharged on Day 49 after confirming two negative results of SARS-CoV-2 from sputum samples. He was able to walk independently and speak normally at discharge. A blood examination at admission revealed positive antibodies to a mixture of galactocerebroside (Gal-C) and phospholipids.

**Discussion**

We suspected GBS based on diminished tendon reflexes, mild muscle weakness and an elevated protein level in CSF. We administered IV Ig therapy which proved to be effective for the treatment.

A loss of cough reflex is sometimes observed in patients with GBS due to demyelination (8). It may be also present in critical illness polyneuropathy, however, an elevated protein level in CSF is unusual (9). In addition, cough episodes may be induced by dysregulation of autonomic innervation and alteration of sensory function in the airway, considering that serum tests revealed positive results for antibodies to a mixture of Gal-C and phospholipids in our case (10). The mixture of Gal-C and phospholipids enhances antigen-antibody interactions compared to Gal-C alone (11, 12). By this feature, the measurement of antibodies may thus allow for a diagnosis of GBS with Gal-C positivity at an early stage. Gal-C antibody is reportedly positive in patients with not only GBS, but also acute autonomic and sensory neuropathy (AASN) and ADEM (11, 13). In our case, the diagnosis of AASN seemed inadequate since autonomic symptoms were lacking and brain CT showed no low-density area suggested ADEM. Although imaging by only CT was not enough to exclude the possibility of ADEM, it was possible that some demyelination disorders occurred including GBS (13, 14).

A small number of reports have suggested a relationship between SARS-CoV-2 and GBS (5, 15-17). Positivity for Gal-C antibody is often observed in patients with GBS after a mycoplasma pneumonia infection, since mycoplasma contains Gal-C and cross-reactivity between mycoplasma and peripheral nerves is triggered (18-20). On the other hand, the relationship between Gal-C-antibody and SARS-CoV-2 infection is still not fully known. Antiretroviral drugs may also have been associated with the onset of GBS in our patient (21). Further study is needed to clarify the mechanisms underlying GBS onset in SARS-CoV-2 patients.

We have described the case of a patient showing GBS during treatment for SARS-CoV-2 infection. Tracheostomy for patients with SARS-CoV-2 should be considered carefully due to the high transmissibility (22). Moreover, treatment for a loss of cough reflex is important since poor coughing strength is one of the risk factors in predicting extubation failure (23). Neurological disorders including GBS therefore need to be considered for intubated SARS-CoV-2 patients presenting with a loss of the cough reflex during the treatment period.

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

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**Disclosure of Statement**

All authors declare no disclosures.

**Author contributions**

Shinichi Wada, Yoji Nagasaki, Yoko Arimizu, Masatoshi Shimo, Yuta Matsukuma, Masaki Okamoto, and Shinichiro Yoshida treated the patient. Ikkei Ohashi and Go Hashimoto reviewed clinical data. Takahiro Kuwashiro, Masahiro Yasaka, and Shinichi Wada revised the manuscript.

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