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Guillain-Barré Syndrome after Novel Coronavirus Disease 2019

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□ **Abstract—Background: Novel coronavirus disease 2019 (COVID-19) has affected more than 89 million people worldwide. As the pandemic rages on, more complications of the disease are being recognized, including stroke, cardiovascular disease, thromboembolic events, encephalopathy, seizures, and more. Peripheral nervous system involvement, particularly Guillain-Barré syndrome (GBS), is of special interest, given the increasing reports of cases related to COVID-19. Because of the potentially delayed onset of symptoms of polyradiculoneuropathy and weakness after the traditional COVID-19 symptoms, it is vitally important for emergency physicians to be vigilant and to consider GBS as part of their differential diagnosis. GBS usually occurs after an infectious insult, and a variety of culprit pathogens have been identified in the literature. Case Report: We describe the case of a 35-year-old man who developed GBS after being diagnosed with COVID-19 infection. The patient displayed classic symptoms of neuropathy, areflexia, and lower extremity weakness. Cerebrospinal fluid evaluation demonstrated albuminocytologic dissociation seen in GBS, although anti-ganglioside autoantibodies were negative. These antibodies are often negative and do not exclude the diagnosis. The patient responded clinically to intravenous immunoglobulin therapy and was discharged home. Why Should an Emergency Physician Be Aware of This?: This case report contributes further evidence that COVID-19 joins other organisms as causes of GBS. Emergency physicians are the first point of contact for many patients. Increased awareness of this complication of COVID-19 will lead to higher detection. Prompt recognition could lead to speedier and more complete neurologic recovery of affected patients.**

□ **Keywords—Guillain-Barre syndrome; COVID-19; anti-ganglioside autoantibodies; SARS-CoV; SARS-CoV-2**

Introduction

In December 2019, the coronavirus disease 2019 (COVID-19) pandemic originated in Wuhan, China. The cause of this pandemic, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an illness with respiratory and systemic implications that commonly manifest as shortness of breath, fever, cough, diarrhea, and headache (1). Since the emergence of SARS-CoV-2, there have been several reports linking the disease to neurologic complications (2).

Guillain-Barré syndrome (GBS) is an autoimmune polyradiculoneuropathy that results in progressive symmetric muscle weakness accompanied by depressed or absent deep tendon reflexes. It can also manifest with cranioneuropathy and dysautonomia. The degree to which these signs are present is variable. It is thought that immune response to prior viral infection results in the formation of antibodies that cross-react with the axons of peripheral nerves, demyelination, or both. Most common infections associated with GBS include *Campylobacter*

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jejuni, cytomegalovirus, Epstein-Barr virus, Zika virus, and human immunodeficiency virus (HIV) (1,3,4).

Patients usually present within 1 week to 10 days after onset of viral infection, although an onset up to 24 days post viral infection has been reported. Symptoms vary from mild weakness in the lower extremities to complete paralysis of respiratory, bulbar, and facial muscles. Disease usually progresses for a period of about 2 weeks (5). Recognition of the disease process early on is crucial in initiating care and preventing long-term sequelae. The weakness usually starts in the lower extremities, but it begins in the arms or facial muscles in about 10% of patients. Severe respiratory muscle weakness necessitating ventilatory support develops in 10–30% (6).

We describe a case of 35-year-old man who developed GBS approximately 2 weeks after being diagnosed with COVID-19. Although the role of anti-ganglioside autoantibodies has been examined previously, it is unclear what percentage of patients with GBS after COVID-19 have serologic evidence of anti-ganglioside autoantibodies and what role these might play, if any, in the diagnosis of GBS in such patients.

Case Report

A 35-year-old Indian man with history of COVID-19 diagnosis 16 days prior to the visit presented to the emergency department with a chief symptom of weakness. The patient reported resolution of fever and cough 6 days prior to his hospital visit, but reported generalized fatigue and progressive weakness in the lower extremities during the period of 7 days. He also reported decreased grip strength that made tasks such as operating his phone more difficult. Intermittent tremors in arms and legs were likewise endorsed. He denied any fever, rash, nausea, vomiting, or diarrhea.

On initial neurologic examination, the patient was noted to have intact cranial nerves. The examination was significant for decreased grip strength in the hands, such that fine motor activities, such as holding a pencil or operating his cellular phone, were difficult. He was also noted to have bilateral upper extremity coarse resting tremor. Overall motor examination revealed strength 4/5, and there was sensory deficit to light touch and pinprick in the lower extremities. This corresponded with areflexia in the left lower extremity compared with hyporeflexia in the right lower extremity. There were intermittent left thigh fasciculations. Reflexes in the upper extremities were preserved. Physical examination did not reveal any signs of respiratory distress or other cardiopulmonary or constitutional abnormalities.

Complete blood count revealed a white blood cell count of 7.2×10^3 cells/mL, hemoglobin of 14.6 g/dL, and a platelet count of 305×10^3 cells/mL. Serum potassium was measured at 4.1 mmol/L and the remainder of the electrolytes, renal, and hepatic function were unremarkable. A lumbar puncture was performed in the emergency department, which did reveal albuminocytologic dissociation with a cerebrospinal fluid (CSF) protein level of 64 mg/dL. There were no CSF polymorphonuclear cells and the CSF glucose level was 61 mg/dL. Culture of the CSF demonstrated no growth. Anti-ganglioside antibodies were likewise sent from the CSF, all of which were negative.

Additional serologic workup was instituted. A vitamin B12 level was low at 204 pg/mL and the patient was treated with parenteral vitamin B12. Thyroid-stimulating hormone, folate, and glycosylated hemoglobin levels were unremarkable. Inflammatory markers, such as D-dimer, C-reactive protein, erythrocyte sedimentation rate, and ferritin, were likewise unremarkable. Serum heavy metals, such as arsenic, lead, cadmium, and mercury, were present in trace amounts within normal limits. Serum HIV-1 and 2 by polymerase chain reaction was nonreactive and the patient's SARS-CoV-2 test was now negative. A full respiratory panel testing for several viral respiratory pathogens, including parainfluenza viruses 1, 2, 3, and 4 was done and all resulted negative. Serum protein electrophoresis revealed a normal electrophoresis pattern. Anti-nuclear antibody testing was positive for speckled pattern at 1:320 ratio.

During the patient's hospitalization, neuroimaging was conducted with gadolinium-enhanced brain and cervical spine magnetic resonance imaging. There was no acute pathology or abnormal enhancement of either the brain or the cervical spinal cord. An electromyelogram with nerve conduction velocities was sought as an outpatient, but the patient ultimately declined the test.

Patient monitoring included serial measurement of vital capacity and negative inspiratory force. By day 3 of the patient's hospitalization, there was a modest decrease in spirometry testing from an initial measurement of vital capacity of 2900 and negative inspiratory force –60 to vital capacity of 2200 and negative inspiratory force –35. Subsequently, however, the patient's spirometry measurements stabilized at this level until discharge and there was never any pulmonary decompensation during the hospital stay.

The patient was admitted to the inpatient neuroscience unit, where serial neurologic assessment was performed. The patient was immediately started on a course of intravenous immunoglobulin (IVIg) therapy. The initial dosing was 0.4 g/kg IVIg for a total of 5 days. After the second dose of IVIg, the patient noted improved dexterity of his hands and on the third day of admission, the patient was able to ambulate more than 200 feet, which he was not able to do on admission. By hospital day 5, the patient had continued motor improvement on examination; the only

adverse effect possibly related to therapy was headache. He was subsequently discharged in stable condition.

In outpatient follow-up, the patient did refuse electromyography/nerve conduction study testing, which unfortunately precluded more precise electrodiagnostic classification of his disease process, but he noted that he continued to have improved ability with ambulation and dexterity of his hands. On examination, he was noted to have improved sensory examination to all sensory modalities with gradual return of reflexes in the lower extremities. He did not participate in any physical or occupational therapy post-acute care hospitalization.

Discussion

GBS remains the most common worldwide cause of acute flaccid paralysis, with an incidence of 0.89–1.89 per 100,000 person-years; two-thirds of these cases were preceded by either viral upper respiratory symptoms or diarrheal illness (7). *C. jejuni* is the most common offending pathogen, although Epstein-Barr virus, Zika virus, and cytomegalovirus have well-defined relationships with GBS as well. Classic diagnostic criteria include albuminocytologic dissociation and hyporeflexia or areflexia. However, these findings are present in only 50% of cases. Furthermore, 10% of patients have normal or brisk reflexes (7). To date, there is no reliable biologic markers that can be used to diagnose GBS (2).

Testing for anti-ganglioside autoantibodies has been advocated as part of the diagnostic workup for patients with questionable diagnosis or for variants of the disease (8). In one study, all patients with clinical diagnosis of GBS had negative anti-ganglioside autoantibodies (9). A study of Zika virus patients with GBS found positive serum anti-ganglioside autoantibodies. However, the cohort of Zika patients without GBS also tested positive for autoantibodies. Nonetheless, those patients who went on to develop GBS had markedly higher anti-ganglioside autoantibody activity (4). It is not clear whether there is any role for such testing to assist in the diagnosis of COVID-related GBS. In the case of the patient described in this report, anti-ganglioside autoantibodies were negative.

Much like previous outbreaks of coronaviruses, such as Middle East respiratory-related coronavirus and SARS-CoV, SARS-CoV-2 has been associated with the development of GBS, with an onset ranging from 3 to 24 days after onset of symptoms. It is thought to be due to either neuroinvasion via angiotensin converting enzyme 2 (ACE2) receptor or an inflammatory mechanism that caused GBS in patients with COVID-19 (5).

SARS-CoV-2 has a spike protein surface unit with affinity to bind to ACE2, which has expression throughout the body, particularly within the lower respiratory tract and the ventrolateral medulla, likely explaining the high impact of viral disease on the respiratory and central nervous systems (10). One study found that approximately 8.9% of patients with COVID-19 developed symptoms consistent with peripheral nervous involvement. In contrast to patients with central nervous involvement, patients who exhibit peripheral neuropathy usually lack any laboratory abnormalities. This is consistent with the presentation of the patient described in our report, who did not have any lymphopenia, thrombocytopenia, azotemia, or elevated inflammatory markers (11).

In our patient, the symptom development, neurologic examination, and mild albuminocytologic dissociation support the diagnosis of GBS as a post-infectious process due to SARS-CoV-2. Although the patient had tested positive 16 days prior to hospitalization, repeat testing on hospitalization was negative. The diagnosis is further supported by lack of diarrheal illness, making *C. jejuni* a much less likely etiology. Our report is limited by lack of further characterization with electrodiagnostic study, but taking together all of the findings reported here, along with previously reported cases of SARS-CoV-2–related GBS, we contribute another case of this disease process to the literature. This solidifies the place of SARS-CoV-2 alongside other viral pathogens as causative clinical entities of GBS.

Why Should an Emergency Physician Be Aware of This?

Hypercoagulability due to COVID-19 can result in increased risk of ischemic stroke; deep venous thrombosis; pulmonary embolism; and other prothrombotic, cardiovascular, and cerebrovascular events. However, with such a frequent focus on the cerebrovascular implications in patients with COVID-19, clinicians should remain vigilant to other neurologic sequelae, such as GBS. This can prove to be especially important for emergency medicine clinicians, as the emergency department is frequently the patient's initial point of contact with health care providers. Many patients might present with subtle symptoms of GBS several days to weeks beyond their initial COVID-19 diagnosis. There might be patients with neuropathic symptoms who do not present with typical symptoms of COVID-19, and heightened vigilance can have important implications for early detection of GBS. This heightened awareness among emergency physicians can lead to better neurologic outcome and improved prognosis.

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