Guillain-Barre Syndrome Secondary to COVID-19 Infection: A Case Report

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Abstract

Guillain-Barre syndrome (GBS) is a rare autoimmune disease that often manifests as a post-viral complication. However, its association with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is unclear. We present a rare case of GBS secondary to COVID-19 infection complicated by rapidly progressive sensorimotor deterioration resistant to plasma exchange therapy.

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Abstract

Guillain-Barre syndrome (GBS) is a rare autoimmune disease that often manifests as a post-viral complication. However, its association with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is unclear. We present a rare case of GBS secondary to COVID-19 infection complicated by rapidly progressive sensorimotor deterioration resistant to plasma exchange therapy.

Introduction

Starting at the end of 2019 in Wuhan, China, the coronavirus disease 2019 (COVID-19) has been responsible for millions of infections worldwide. Patients commonly present with cough, myalgia, fatigue, and diarrhea [1]. In a retrospective observational case series of 214 cases of COVID-19 in Wuhan, China, 78 patients were found to have neurological manifestations [2]. Neurologic symptoms of COVID-19 ranged from impaired consciousness, dizziness, fever, headache, anosmia, and dysgeusia to acute large vessel cerebrovascular disease, acute disseminated encephalomyelitis, and Guillain Barre syndrome (GBS) [3]. GBS has been reported to have a higher incidence after various epidemics around the world. During the epidemics of the Middle East Respiratory syndrome and Zika Virus in the French Polynesia, the incidence of GBS increased [4,5].

GBS has multiple classifications of autoimmune polyradiculopathies ranging from a spectrum of disease. Complications vary from muscle weakness, sensory abnormalities, dysautonomia, and cranial neuropathies. Variants of GBS include: classical, Miller Fisher syndrome, pharyngeal-cervical-brachial, bifacial weakness with paresthesia of limbs, and paraparetic. The association between these neurologic symptoms in patients with recent COVID-19 is not completely understood. Several proposed mechanisms include multiorgan dysfunction, peripheral nerve damage secondary to a cytokine storm, molecular mimicry, and direct injury from the virus itself. Evidence behind the role of molecular mimicry is controversial. On one hand, there is no homology between any SARS-CoV-2 genetic or linear protein structure and human linear protein structures. On the other hand, there is the possibility of post-translational modification of viral proteins by their host cells leading to the formation of an immunogenic surface. This creates the necessary trigger for the immune system and thus the formation of antibodies against ganglioside components of the peripheral nerves [6]. More thorough research into the characterization of the molecular basis is needed to understand potential causal links. Here, we report a patient with a confirmed GBS diagnosis following a recent COVID-19 diagnosis.

Case Report

A previously healthy 60-year-old man with pectus excavatum was brought in by ambulance for a 2-day history of rapidly progressive bilateral ascending weakness, bilateral paresthesia of the hands and feet, difficulty standing, and low back pain. Three days prior to presentation, he tested positive for COVID-19 and reported myalgias, fever and nausea. He was unvaccinated against COVID-19. Neurologic examination revealed weakness in neck extension, neck flexion, and leg extension. Furthermore, areflexia and flaccid paralysis were noted in all four extremities. No bulbar or respiratory symptoms were noted. Patient denied sensation below the level of the neck. The following day, the patient's strength was 2/5 in the bilateral upper extremities, and 2/5 in the bilateral lower extremities. Additionally, there was mute plantar response bilaterally. He had length-dependent loss of temperature and pain in the bilateral lower extremities and hands. Absent proprioception at toes, ankles, and knees with sparing of the proximal interphalangeal joints was noted. Magnetic resonance imaging (MRI) of the spine with contrast was performed which revealed diffuse enhancement with thickening of the cauda equina nerve roots, mild enhancement of lower thoracic and few cervical nerve roots consistent with GBS. Lumbar puncture (LP) was significant for protein 295, white blood cell count 27, red blood cell count 1, and glucose 54 (Table 1).

Electromyography (EMG) performed several days later revealed severe axonal sensorimotor neuropathy. Differential diagnosis included GBS, myelitis, tick paralysis, toxin exposure, and arboviruses. Myelitis was ruled out based on the lack of motor and sensory symptoms localized to one or more contiguous spinal cord segments, as well as lack of MRI findings consistent with the diagnosis. Lyme disease was ruled out with negative Lyme serology and lack of recent travel to a tick infested territory or lack of rash or lesion. Toxin associated exposure was ruled out given no history of reported toxin exposure. Arbovirus exposure was ruled

out on the basis of this case occurring in the winter season.

Given the rapidly progressive bilateral ascending weakness; sensory loss greater in the lower extremities compared to upper extremities; severe low back pain; and EMG, LP, and MRI findings, a presumptive diagnosis of GBS was made. The patient was started on plasma exchange (PLEX) treatment and corticosteroids for GBS. Despite medical management, his clinical condition deteriorated during the hospital course with hypotension, bradycardia and respiratory distress which was presumed to be secondary to dysautonomia and neuromuscular weakness. The patient was intubated and managed in the intensive care unit (ICU), followed by the neurological critical care service. On hospital day 12, the patient began to desaturate to 86%, developed fever at 39.1 degrees Celsius. The hospital course was complicated by sepsis from aspiration pneumonia requiring vasopressin and phenylephrine and treated with piperacillin, tazobactam, and vancomycin, which was later escalated to linezolid.

The patient subsequently developed acute respiratory distress syndrome secondary to bacterial pneumonia. Bronchial culture grew methicillin resistant staphylococcus aureus (MRSA). Therapeutic bronchoscopy was performed for MRSA pneumonia with poor secretion clearance. Worsening hypoxia warranted BIPAP, and he developed acute kidney failure requiring continuous renal replacement therapy. Repeat neurologic examination on hospital day showed no improvement: patient remained areflexic, flaccid quadriplegic, and with absent cough/gag reflex. On hospital day 29, computerized tomography (CT) of the chest showed persistent consolidation with evidence of engulfed emphysema versus necrosis of the right upper lung. The patient developed persistent fevers, vasodepressor dependent hypotension and lymphocytosis and was started on empiric cefepime for suspected septic shock. Interventional pulmonology attempted to perform a bronchoscopic assisted percutaneous tracheostomy tube placement, however the procedure was aborted due to hypoxia in the setting of mucus plugging. Subsequently, the patient required a surgical tracheostomy, and the patient was discharged to a long-term acute care hospital for continued management and ventilator weaning.

Discussion

The incidence of GBS is between 1.1/100,000/year and 1.8/100,000/year with lower rates reported in children (<16 years) of around 0.6/100,000/year according to a systematic literature review conducted in 2009 [7]. More recently, a one-year observational multicenter study in Northern Italy found that the cumulative incidence of GBS increased by 59% in the period of March 2020 to March 2021, with COVID-19-positive GBS patients representing 50% of the total GBS cases [8]. To our knowledge, a strength of our study is that this is the first reported case of rapidly progressive neurologic deterioration resistant to PLEX therapy in a patient whose COVID symptoms started three days prior to manifestation of neurological symptoms.

In a recent systematic review of 79 COVID-19-associated GBS cases, clinicians used PLEX therapy in 10 cases, 4 of the 10 also received intravenous immunoglobulin (IVIG). Compared to our case of a time to onset of neurologic symptoms, there was three-day lag between the onset of COVID-19 symptoms and the onset of neurological symptoms, whereas the patients reported in this study had days ranging from 7 to 21 days [9]. Therefore, to our knowledge, this is the first reported case of PLEX therapy given to a patient with the shortest time to onset of GBS neurological symptoms. Interestingly, of all the patients in this review, there was one case of a patient with GBS who was asymptomatic for COVID-19, with the exception of a low-grade fever, who responded well to PLEX therapy [10].

In addition to this case, six other COVID-positive patients presented without COVID symptoms or within six days of neurologic manifestations. Altogether, this indicates a para-infectious process. On the other hand, the majority of patients developed GBS symptoms with a mean of 11±6.5 days, with a range of 3-28 days supporting the notion that GBS is a post-infectious process in COVID-19 patients [9]. Similar results were found in a review of 37 published cases of GBS associated with COVID-19, which reported the median time of onset of neurologic symptoms to be 12.2 days with a reported male to female ratio of 2.5:1 [11].

Considering the wide variability in time to onset of GBS symptoms in some COVID-19 patients, it may be theorized that a threshold of inflammation, rather than a cytokine storm, must be reached in combination with immune dysregulation to produce peripheral nervous injury albeit through direct cytokine-induced

macrophage activation or molecular mimicry, respectively [12,13]. Therefore, reaching this threshold is not associated with symptoms but rather may be a time-dependent process, which would explain the variability in onset of GBS symptoms. This is supported by the fact that even asymptomatic COVID-19 patients develop GBS neurologic symptoms indicating that perhaps their threshold level of inflammation is so low that they do not produce symptoms. However, even at this low threshold they still develop neurological features of GBS.

PLEX therapy is suggested as a viable treatment for COVID-19 induced cytokine storm given its direct removal of cytokines such as interleukins-3, 6, 8, 10, interferon-gamma, tumor necrosis factor-alpha, and various immunoglobulins of the IgG class. In theory the rationale for using PLEX is to promote an anti-inflammatory state that adequately suppresses thrombo-inflammation and therefore the ensuing microangiopathy [14]. Given that PLEX therapy's efficacy is in its ability to reduced cytokine-induced inflammation, the central question is to what degree we can attribute GBS symptoms in COVID patients to inflammatory damage alone versus genetic predisposition or molecular mimicry. Considering IVIG has been efficacious, perhaps the pathophysiology of neurological damage in the setting of COVID-19 is related to multiple different pathological processes. However, this theory has limitations. We cannot definitively rule out the possibility that in some cases of GBS developing before or concurrently with COVID-19 symptoms, the disease might have progressed sub-clinically in the early phase to manifest afterwards with its typical clinical picture [9]. Lastly, the possibility of a host immunogenic background adds an additional point of consideration. Considering HLA polymorphisms, this may explain the increased rates of COVID-19 related GBS in Italy, per a recent systematic review of 99 GBS with confirmed COVID-19 cases found one third of cases were Italian [11].

When treated with IVIG, or PLEX and steroid, a majority of patients show clinical improvement with partial or complete remission. Little improvement or poor outcomes is associated significantly associated with advanced age. Sex, electrophysiological subtypes, COVID pneumonia, and latency between COVID-19 and GBS were less associated with better outcomes [9]. However, up to 30% of patients with GBS progress to respiratory failure [15]. Patients treated with IVIG have a significantly lower probability and shorter overall duration of mechanical ventilation compared to those treated by PLEX [16].

Current literature is highly contentious as to the correlation between COVID-19 and GBS. However, in a large population-based study investigating the neurologic adverse events and SARS-CoV-2 infection, Patone et al found the highest risk of GBS in the one to 28-day period after a SARS-CoV-2-positive test, with the highest rate of hospital admission or death from acute CNS demyelinating events on the day of the positive SARS-CoV-2 test, which attributed all neurologic conditions to SARS-CoV-2 itself in either vaccine or viral entity [17]. The purpose of disseminating this case report is to propose a possible mechanism linking COVID-19 with the neurological symptoms of GBS, and to highlight the necessity of immediate treatment with PLEX or IVIG. Our case of a 60-year-old-male is consistent with current literature supporting the average mean age at onset of COVID-19 and GBS to be over 50 years of age [13].

Conclusion

Guillain-Barre Syndrome (GBS) is oftentimes a post-infectious immune-mediated radiculopathy that commonly results in neuromuscular respiratory failure. We present a rare case of GBS secondary to COVID-19 infection. Clinicians should consider COVID-19 as a viral infection that can trigger immune-mediated pathologies such as GBS. More investigation is warranted to further understand the pathophysiology relating GBS and COVID-19.

Consent

Written informed consent was obtained from the patient's next of kin to publish this report in accordance with the journal's patient consent policy.

Conflict of Interest Statement

The authors declare no competing interests.

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`GBS_Table1.docx` available at https://authorea.com/users/571893/articles/617037-guillain-barre-syndrome-secondary-to-covid-19-infection-a-case-report