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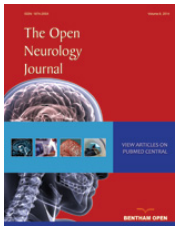

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CASE REPORT

Reworsening of Recurrent Guillain-Barré Syndrome Triggered by COVID-19 Infection

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Abstract:

Introduction:

Guillain-Barré Syndrome (GBS) is an acute, immune-mediated, generalized polyradiculoneuropathy often triggered by a bacterial or viral infection, vaccination, or surgery. During the SARS-CoV-2 pandemic, some patients were reported with GBS associated COVID-19 infection.

Case Presentation:

We report, herein, a patient who had a recurrent GBS after forty years. Intravenous immunoglobulins (IVIg) induced improvement, but her condition worsened suddenly after twenty days, coinciding with a COVID-19 infection. A second IVIg cycle was administered, and she improved again.

Conclusion:

The take-home message is that in the current pandemic, any re-worsening or lack of improvement after appropriate treatment of GBS or possibly other autoimmune neurological diseases must be checked to determine if it is related to COVID-19 infection.

Keywords: COVID-19, SARS-CoV-2, Guillain-Barré syndrome, Recurrence, Intravenous immunoglobulins, Pandemic.

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1. INTRODUCTION

Guillain-Barré Syndrome (GBS) is an acute, immune-mediated, generalized polyradiculoneuropathy triggered by a bacterial or viral infection, vaccination, or surgery in about two-thirds of cases. GBS has been associated with viral epidemics or pandemics, including H1N1, swine flu A/New Jersey influenza strain, West Nile virus, or Zika, and with coronaviruses including severe acute respiratory coronavirus (SARS-CoV) and recent SARS-CoV-2 causing coronavirus disease 2019 (COVID-19) infection [1].

Although GBS is a monophasic disease, it may recur in 2-6% of the patients. The reasons why some patients have a recurrence and whether there is a distinct group of subjects prone to recurrence are unknown. Recurrent patients are younger than non-recurrent subjects, and up to five episodes of recurrence have been reported [2]. So far, only one case of recurrent GBS (rGBS) triggered by COVID-19 infection has been published [3].

We report, herein, a patient who had an rGBS after forty years, in whom improvement induced by intravenous immunoglobulins (IVIg) suddenly stopped and the disease re-worsened, coinciding with a COVID-19 infection.

2. CASE REPORT

Forty years ago, a woman aged 39 years came to our hospital reporting a 4-day history of progressive weakness, affecting all four limbs and impairing mobility. She had experienced pharyngitis some days before. Neurological examination showed steppage gait, severe flaccid paresis of upper limbs, and moderate muscular weakness of the lower limbs. Tendon reflexes were absent. Cerebrospinal Fluid (CSF) analysis demonstrated 6 cell/µl and 42 mg/dl proteins. It was repeated 7 days later, and there were 2 cell/µl and 118 mg/dl proteins. GBS was diagnosed, and she was treated with IV betamethasone (the usual treatment in 1980). After seven days

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of further worsening, her muscle strength started to improve very slowly. Electrophysiological examination, performed thirty days after onset, revealed the presence of a severe axonal polyneuropathy. On needle Electromyography (EMG), there was evidence of denervation in all muscles of the upper and lower limbs studied. Motor unit action potentials (MUAPs) were large with decreased recruitment, especially in the abductor digiti minimi muscle. Motor conduction study showed the absence of the compound muscle action potential (cMAP) of the right ulnar nerve and a marked drop in amplitude of the peroneal nerve stimulated at the patient popliteal fossa bilaterally in the absence of F late response. The patient was discharged after seven months of neurorehabilitation.

The following forty years were characterized by the occurrence of bipolar disorder, stage 3 renal failure, post-traumatic seizures, hypertension, left breast cancer treated by surgery and hormonal chemotherapy, parkinsonian syndrome with restless legs syndrome, and a left femur fracture treated with intramedullary nailing. Neuromuscular conditions remained stable with a bilateral walking aid.

In August 2020, at age 79, the patient suffered from a worsening of muscular weakness, and in ten days, she lost the ability to stand and walk. She was presented at A&E in our hospital and, after a negative reverse transcription-polymerase chain reaction (RT-PCR) test for SARS-CoV-2 by rhinopharyngeal swab, was admitted to the Unit of Neurology. Routine blood and urine examinations were unremarkable except for a mild increase of creatine kinase level (325 U/L; n.v. < 200) and myoglobin level (101 ng/ml; n.v. < 51). Neurological examination showed severe flaccid quadriparesis (MRC scale: 1-2/5). Tendon reflexes were absent. EMG showed spontaneous activity with positive sharp waves and fibrillation potentials at distal muscles of upper and lower limbs. Long duration, high amplitude polyphasic MUAPs were seen with decreased recruitment in all muscles, especially in distal ones. Nerve conduction study revealed decreased cMAP in right ulnar and tibial nerves with slowed conduction velocities. F late responses were absent. Sural nerve study was normal. The patient underwent a lumbar puncture, which showed 1 cell/µl and 88 mg/dl proteins. She was diagnosed with recurrent GBS, and IVIg was administered at 0.4 g/kg for 5 days. After two days of treatment, she started to show a mild improvement of muscle strength proximally at upper limbs (2/5). After one day, blood sodium level decreased to 131 mmol/L (n.v. 134-145), and hypertonic saline was given for some days. On the last day of IVIg, a rhinopharyngeal molecular swab for SARS-CoV-2 was repeated, and the result was negative. The next day, on September 17th, she was discharged and admitted to the Neurorehabilitation (NR) clinic of the same hospital.

Once admitted to the NR clinic, the patient was bedridden and postural steps in bed, whether supine or sitting, were performed with much assistance. Standing and walking were impossible. Muscle strength testing by the MRC scale is reported in Table **1**. A chest x-ray showed bilateral basal consolidations. She started to perform active and passive muscular exercises three times a day for a total of 150 min. After two weeks, on October 2nd, she demonstrated further improvement of muscle strength (Table **1**). When positioned by a standing machine, she was able to maintain her position for 15 min.

Some days later, a patient of the NR clinic resulted positive at RT-PCR for SARS-CoV-2. Therefore, all patients and personnel of the NR clinic were tested, and our patient resulted negative. The following day, on October 8th, she had a sudden worsening of muscle weakness (Table **1**). A rhinopharyngeal swab was re-tested, and she resulted positive for SARS-CoV-2. She was, therefore, moved to the COVID ward. A chest x-ray showed a mild increase of previous bilateral basal consolidations and mild right perihilar consolidation. She had a fever, respiratory distress and desaturation, was treated with oxygen and steroids, and continued the use of heparin. A neurophysiological examination was not performed because of the high risk for intra-hospital virus dissemination. After 9 days in the COVID ward, pulmonary conditions improved and a second IVIg cycle was administered. During IVIg treatment, she became lethargic and confused. Hypernatremia (165 mmol/L; n.v. 134-145) was found and treated with half-normal saline. After the correction of serum sodium, consciousness improved, and physiotherapy was re-started. On November 9th, seventeen days after the second IVIg cycle, muscle power examination showed some improvements (Table **1**). A rhinopharyngeal swab was repeated every week and remained positive. On November 17th, she was moved to a COVID ward for asymptomatic patients at another hospital. After a negative rhinopharyngeal swab, she went back home on November 30th, where she is continuing neurorehabilitation.

3. DISCUSSION

GBS is one of the typical infection-triggered autoimmune neurological diseases, and GBS outbreaks have been associated with viral epidemics or pandemics [1, 2]. During the COVID-19 pandemic, a 2.6-fold increase of GBS incidence was reported in March and April 2020 in two Italian regions most stricken by COVID-19, compared to the same months of 2019 [4]. A recent review described 37 published cases with a certain diagnosis of COVID-19 associated with GBS. Most cases (91.9%) had COVID-19 symptoms 3-28 days before the onset of neurological symptoms. Two patients were presented with neurological symptoms. They had pulmonary ground-glass opacities on chest CT, indicating asymptomatic infection. CSF RT-PCR for SARS-CoV-2 was negative in all 18 patients tested [5]. Another systematic review reported 18 patients with an interval between the onset of symptoms of COVID-19 and the first symptoms of GBS ranging from 8 to 24 days. An overlap between symptoms of COVID-19 and symptoms of GBS was reported in five patients [6]. In one, a first rhinopharyngeal swab for SARS-CoV-2 performed after GBS onset, which was preceded 10 days earlier by mild fever and cough and spontaneous resolution of fever after a few days, was negative, but a second swab was positive [7]. Only in one case, SARS-CoV-2 antibodies were detected in the CSF, further strengthening the role of the virus as a trigger and the need to search for antibodies in serum and CSF [8].

Table 1. The course of MRC muscle testing in the patient.

Muscles	At admission to the NR Clinic (17th September)		After 2 Weeks (2nd October)		6 days Later (8th October)		17 days after 2nd IVIg Cycle (9th November)	
Neck flexors	2+		3		2+		3+	
Neck extensors	3		3		3		3	
Shoulder flexors	2-	2-	2	2	1	1	3-	3-
Shoulder extensors	2	2	2	2	1	1	3-	3-
Shoulder abductors	2-	2	2	2	1	1	2	2
Elbow flexors	3	3	3	3	2-	2-	3	3
Elbow extensors	3	3	3	3	1	1	3	3
Handgrip & Interossei	2-	2-	3	3	2-	2-	3	3
Hip flexors	2	2	2	2	1	1	2	2
Hip extensors	1	1	1	1	1	1	1	1
Hip abductors	3+	3	3+	3	2-	2-	3+	3+
Hip adductors	3	3	3	3	2-	2-	3+	3+
Knee flexors	3-	2	3-	3-	2-	2-	3-	3-
Knee extensors	3	2	3	3	2	2	3-	3-
Dorsiflexors	2+	1	2+	1	2+	1	2+	1
Plantar flexors	2	3	3	3	2	2	3	3

The patient here described had an rGBS after forty years and showed a clear IVIg-induced improvement, but COVID-19 infection acted as a trigger for very rapid deterioration. Her history is similar to that of the only patient so far reported with rGBS triggered by COVID-19 [3]. However, while the COVID-19 trigger in our case provoked a re-worsening of muscular weakness, the patient, fortunately, responded to a second IVIg cycle. A phenomenon called "treatment-related clinical fluctuations" is characterized by deterioration after initial stabilisation or improvement of GBS. It occurs in 5% of the patients who then usually improve after a second treatment with IVIg or plasma exchange [9]. In our patient, deterioration coincided with positive RT-PCR for SARS-CoV-2, despite a negative test two days previously, in a period of intense medical surveillance due to the finding of a positive patient in the same NR clinic. It clearly supports the supposition that the relapse was triggered by SARS-CoV-2 infection. The good response to the first IVIg cycle, lasting 27 days before the appearance of deterioration, which was concurrent with SARS-CoV-2 infection, runs against the hypothesis that the patient had a poor response to IVIg [9]. The take-home message from our case is that nowadays, with an ongoing pandemic able to trigger GBS or other autoimmune neurological diseases, any re-worsening or lack of improvement after appropriate treatment must be checked if it is related to COVID-19 infection. The present case is another piece of the puzzle in favour of a causal association and not a coincidence between GBS and COVID-19 [10].

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of the province of Messina, Italy (Report number E 44/12).

HUMAN AND ANIMAL RIGHTS

No animals/humans were used in this study.

CONSENT FOR PUBLICATION

The patient authorized the use of clinical data for descriptive scientific purposes.

AVAILABILITY OF DATA AND MATERIALS

All clinical data are reported in the Personal Medical Records which are confidential.

STANDARDS OF REPORTING

CARE guidelines and methodology have been followed.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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