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*Neurology®* Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.

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SECTION 1

On March 2020, a 49-year-old white Caucasian man was admitted in our emergency department due to a one-week history of fever (39-40 °C) and cough. His past medical history included arterial hypertension and a testicular seminoma in 2011 treated with surgery and platinum-based chemotherapy. Laboratory tests revealed increased C-reactive protein, mild lymphopenia and thrombocytopenia. Chest CT showed multifocal ground-glass opacities and nasopharyngeal swab was positive for severe acute respiratory coronavirus 2 (SARS-COV-2), leading to a diagnosis of Coronavirus Disease 2019 (Covid-19). The patient was hospitalized and treatment with hydroxychloroquine, lopinavir/ritonavir and ceftriaxone was started.

Four days later, his respiratory function rapidly worsened, requiring transfer to intensive care unit (ICU) and mechanical ventilation (MV). Despite early clinical stabilization, attempts of
weaning from ventilator failed due to persistence of respiratory failure. During ICU stay, anesthesiologists reported unusual symptoms, such as gastroparesis, alternating episodes of tachy-/bradyarrhythmia, and frequent hypertensive crises. Twenty-three days after ICU admission, respiratory function improved. Upon reversal of sedation, the patient was profoundly asthenic and since a generalized flaccid weakness was noted, he was transferred to our neurology department.

On neurological examination he was alert and oriented and showed dysphonia, dysphagia, left VII and right XII cranial nerve palsy, weakness of the neck flexors and proximal and distal muscles of the upper limbs in a symmetrical distribution (Medical Research Council scale or MRC 3/5), with diffuse hypotonia and muscle hypotrophy. Strength in the lower limbs was normal except for a mild weakness (4/5) of the extensor hallucis longus bilaterally. There was diffuse hyporeflexia in the four limbs. Decreased vibratory sensation in the ankles was detected. Gait and coordination were normal. Persistent sinus tachycardia was noted.

1. What is the differential diagnosis for patient’s neurological symptoms and signs?
2. May this clinical picture be a COVID-19-related neurological manifestation?
3. Which investigations would be appropriate for diagnostic workup?

SECTION 2

In the ICU setting neurological complications are common and include encephalopathy, seizures, stroke and neuromuscular disorders. In our patient, the acute/subacute onset of symmetric weakness in the upper limbs with flaccid tone, reduced tendon reflexes, and respiratory insufficiency should raise the suspicion of a neuromuscular disorder, such as myopathy, myasthenia gravis, critical illness polyneuropathy and myopathy (CIP/CIM), or Guillain-Barré Syndrome (GBS) and its variants. An underlying disorder of the central nervous system (CNS), such as stroke, neuroinflammatory diseases, CNS infection, paraneoplastic syndrome or a spine lesion, is less likely but it should also be taken in account.
Since December 2019, SARS-COV-2 infection has rapidly spread from China to a pandemic level causing a great healthcare concern worldwide. Its associated disease, COVID-19, mostly affects the respiratory system, ranging from mild flu-like symptoms to severe pneumonia. There is an overgrowing evidence of neurological manifestations in COVID-19, including febrile seizures, headache, dizziness, myalgia, encephalopathy/encephalitis, stroke, and acute peripheral nerve diseases. To date, a few cases of GBS in COVID-19 patients have been reported, with either a demyelinating or an axonal pattern. A potential unmasking of a myasthenic syndrome during the course of the infection should also be considered.

Institution of a proper diagnostic workup is essential and includes neurophysiologic studies, cerebrospinal fluid (CSF) analysis, anti-ganglioside and anti-acetylcholine receptor (AChR) antibodies testing, and imaging of brain and spinal cord and plexuses. A total body CT scan may be performed in case of a suspected paraneoplastic etiology.

CSF test showed normal glucose levels (62 mg/dL; normal 60-80 mg/dL), mild hyperproteinorrachia (48 mg/dL; normal 15-45 mg/dL), no cells. CSF viral PCR for herpes viruses as well as SARS-CoV-2 resulted negative. Cytology was negative for malignancies. Neurophysiologic studies (Table 1) showed reduced distal compound muscle action potential amplitudes in the peroneal nerve bilaterally, with normal conduction velocities and motor distal latencies. Motor and sensory parameters of the median, ulnar, tibial and sural nerves were normal, as well as F waves of the tibial and ulnar nerves. Repetitive nerve stimulation at right ulnar and accessory nerve was negative. Needle electromyography showed fibrillation potentials and positive sharp waves together with a reduced recruitment pattern in the deltoid, trapezium, biceps brachii, triceps brachii, and first interosseous muscles bilaterally.

Anti-ganglioside (IgG anti-GM1, GM2, GD1a, GD1b, GT1a, GT1b, GQ1b) and AChR antibodies were not detected. Autoimmune serological screening was negative, as well as repeated dosages of creatine kinase. Contrast-enhanced MRI of brain, cervical spine and brachial plexus was
negative. A total body CT scan excluded the presence of an oncologic disease. A follow-up electrophysiological study was performed 14 days later, overlapping with the previous one.

1. Considering the results of the instrumental and laboratory tests, how would you refine your differential diagnosis?

SECTION 3

The following differential diagnoses were considered:

1) Guillain-Barré Syndrome (GBS): is an acute inflammatory polyneuropathy characterized by acute/subacute motor weakness, hypo-/areflexia and mild to moderate sensory impairment. Cranial nerve and autonomic involvement may be present in a subset of cases. Antecedent infections may be potential triggers, preceding neurological symptoms by 2-3 weeks.

2) Critical illness polyneuropathy and myopathy (CIP/CIM): is the most frequent neuromuscular disorder occurring in ICU, detected in up to half of critically ill patients. It usually presents as a distal axonal sensory-motor polyneuropathy affecting limbs and respiratory muscles, and it is usually suspected upon failure of weaning the patient from ventilator when other causes have been excluded.

In our patient, the presence of a cranial nerve palsy, the distribution of weakness in the neck flexor muscles and in the upper limbs with a sparing of the lower limbs, and the presence of autonomic symptoms (gastroparesis, alternating episodes of tachy-/bradyarrhythmia, and frequent hypertensive crises) suggest a GBS diagnosis rather than a CIP/CIM. The Brighton Collaboration level 1 criteria were met. In CIP/CIM, cranial nerves and autonomic system are typically not involved while sensory impairment is very frequent; moreover, prognosis is often poor, requiring post-discharge rehabilitation for several months in order to improve functional independence.

Considering that the clinical picture and the neurophysiological exam were supportive for a diagnosis of an acute motor axonal neuropathy (AMAN), the patient was diagnosed with
Pharyngeal-Cervical-Brachial (PCB) variant of GBS. A Miller Fisher syndrome was excluded due to the absence of ophthalmplegia, ataxia and anti-GQ1b antibodies.

1. Which is the mainstay treatment and disease course in GBS?

**SECTION 4**

Rapid institution of high-dose intravenous immunoglobulins (IVIg) is warranted to halt GBS progression and favor clinical outcome. Nonetheless, the disease follows a monophasic course and spontaneous recovery in the absence of treatment may be observed.

In our case, during the first days of admission in our department (after 40 days from fever onset) the patient showed a spontaneous improvement of the clinical picture, thus treatment with intravenous immunoglobulin was not performed. In the following 15 days, the patient showed an improvement of dysphagia and weakness of the upper limbs, and at discharge (at day 56 after admission) only a mild weakness of the deltoid bilaterally and left biceps was evident.

**DISCUSSION**

At the moment of writing this paper, about 20 cases of GBS associated with COVID-19 infection have been reported encompassing several of its clinical variants, such as acute inflammatory demyelinating polyneuropathy (AIDP), acute motor/motor-sensory axonal neuropathy (AMAN/AMSAN), Miller Fisher syndrome, polynnuritis cranialis, and facial diplegia. Almost 50% of these cases required MV and 10% of them died, suggesting that GBS associated with COVID-19 is more severe than GBS related to other etiologies, although excellent recovery after therapy is reported. It is possible that the neuromuscular dysventilation caused by GBS adds to the COVID-19-related respiratory dysfunction, resulting in a more severe clinical presentation. The clinical course in our patient is similar to what described in previous cases, requiring ICU admission and MV, but after the acute phase he showed a good spontaneous improvement. Since patient was not
treated with any immunotherapy, we had the opportunity to observe the natural evolution of the
disease, confirming the possibility of a good prognosis despite a poor clinical condition of the acute
phase.

Here we report the first case of Pharyngeal-Cervical-Brachial (PCB) variant of GBS
associated with SARS-CoV-2 infection. PCB is considered a rare regional axonal variant of GBS
(about 3% of GBS cases\textsuperscript{10}). Clinical features include oropharyngeal, neck and arm weakness
associated with arm areflexia\textsuperscript{10}. Lower limb weakness may also be present in variable degrees,
although should never be more prominent than weakness in the other districts. Reflexes in the lower
limbs are typically preserved in PCB, but in our patient the hyporeflexia and mild vibration deficits
may be explained by considering the platinum-based chemotherapy performed in the past years.
Autonomic dysfunction in PCB may occur in up to 20% of cases. Differential diagnoses include
Miller Fisher syndrome, myasthenia gravis, botulism, diphtheria and brainstem stroke. Anti GT1a
IgG antibodies are a specific serological marker for PCB, being positive in about 50% of patients.
CSF albumin-cytological dissociation can be present in about 40-50% of patients. An antecedent
upper respiratory tract infection rather than diarrhea is usually reported\textsuperscript{10}.

As to the pathogenic relation with COVID-19 infection, we think that the possible
mechanism could be an aberrant immune response rather than a direct viral injury, considering the
time interval between the onset of the antecedent illness and the onset of the neurological symptoms
(10-15 days), the lack of cells in the CSF, and the negativity of the PCR for SARS-Cov-2 in the
CSF.

In conclusion, our case adds to the evidence that rare neurological manifestations are
possible during COVID-19 infection. GBS associated with COVID-19 infection seems more severe
than that related to other etiologies and our case expand the clinical spectrum of this specific
putative condition. More data are needed to confirm the pathogenic link between COVID-19 and
GBS, to explain the occurrence of relatively higher percentages of axonal forms and to clarify the
exact prognosis of these cases.
## Appendix. Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giuseppe Liberatore, MD</td>
<td>IRCCS Humanitas Clinical and Research Hospital, Rozzano (MI), Italy</td>
<td>Design and conceptualized study; major role in acquisition of data; analyzed the data; drafted the manuscript for intellectual content</td>
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<td>Major role in the acquisition of data; revised the manuscript for intellectual content</td>
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<td>Design and conceptualized study; analyzed the data; revised the manuscript for intellectual content</td>
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References


Table 1: Results of motor nerve conduction study.

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<tr>
<th>Motor Nerves</th>
<th>Onset Latency (ms)</th>
<th>Amplitude (mV)</th>
<th>Duration (mV*ms)</th>
<th>MCV (m/s)</th>
<th>F-wave (ms)</th>
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Neurology published online September 11, 2020
DOI 10.1212/WNL.0000000000010817

This information is current as of September 11, 2020