Guillain-Barré syndrome in a patient with antibodies against SARS-COV-2

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To the editor,

There are now several reports on neurologic features of SARS-CoV-2 infection [1,2].

In a recent study of 214 patients with COVID-19, 78 (36.4%) patients had neurological manifestations, including headache, dizziness, acute cerebrovascular diseases, and impaired consciousness [2]. Helms et al. report neurologic features in 84% (49/58) of patients with severe SARS-CoV-2 infection presenting with acute respiratory distress syndrome [1]. In this case series, neurological signs and symptoms included encephalopathy, prominent agitation and confusion, and corticospinal tract signs. Other reports suggest para- and post-infectious neurologic diseases associated with SARS-CoV-2 infection, including Guillain-Barré syndrome, Miller Fisher Syndrome and polyneuritis cranialis [3,4]. Here, we report a case of Guillain-Barré syndrome (GBS) with an onset 2 weeks after SARS-CoV-2 infection with highly elevated serum antibodies against SARS-CoV-2, which supports the association between SARS-CoV-2 disease and the GBS.

Case

On March 20th, a 68 years old man developed dry cough, headache, fatigue, myalgia and fever up to 39°C followed by anosmia and ageusia. He was tested for SARS-CoV-2 RNA 10 days after symptom onset, which revealed a negative result and was treated by the primary care physician at home. Premedical history was uneventful and the patient did not take regular medication. On April 1st, oral methylprednisolone 10 mg/day was started for suspected rheumatoid arthritis due to persistent pelvic girdle and muscle pain of the proximal lower extremities, a C-reactive protein of 8.5 mg/dl (normal: 0.0–0.5 mg/dl), and an elevated erythrocyte sedimentation rate (63 mm/1 h). On April 3rd (14 days after onset of pulmonary disease) the patient had recovered from respiratory symptoms, but still complained of severe fatigue and developed symmetric distal tingling in both feet followed by ascending dysesthesias up to the knees and proximal weakness. The next day he presented at the neurological emergency room with inability to walk. On examination, the patient was alert and fully oriented, afebrile with normal vital signs (oxygen saturation 98% on room air, blood pressure 143/90 mmHg, heat rate 85 bpm). Laboratory examination revealed slightly elevated C-reactive protein (2.3 mg/dl, normal: 0.0–0.5 mg/dl), fibrinogen level 650 mg/dl (normal: 210–400 mg/dl), white blood cell count 8.1 G/l (normal: 4.0–10.0 G/l), lactate dehydrogenase 276 U/L (normal: 100–250 U/l) and erythrocyte sedimentation rate 55 mm/1 h. Neurological examination showed decreased sensation to touch and pinprick in the lower extremities, absent ankle jerk, atactic stance and inability to walk without assistance. Additional truncal dysesthesia prompted spinal cord MRI with unremarkable findings. Lumbar CSF on day 2 after onset of neurological symptoms showed normal cell counts (2/mm [3]) and protein level (64 mg/dl) and a serum/CSF glucose ratio of 0.83. Due to the history of pulmonary symptoms a chest-computed tomography was performed and revealed residual ground-glass opacities in both lower lungs suggestive for coronavirus disease 2019 (COVID-19). Based on the neurological presentation GBS was diagnosed, the patient was admitted to the COVID-19 isolation ward and intravenous immunoglobulin therapy (IVIG, 30 g) was initiated. His respiratory condition worsened, and the patient required oxygen supplementation (3 l/min) followed by pressure support non-invasive ventilation after 36 h. Nerve conduction studies performed on the following day showed F-wave abnormalities in all nerves, delayed distal motor latency in one nerve, reduced distal amplitudes in two and a sural-sparing pattern supporting acute inflammatory demyelinating

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polyneuropathy subtype of the GBS (Table 1). Simultaneously, the neurologic presentation worsened with progressive weakness (Medical Research Council grading 1–5) in both arms (2/5) and hands (4/5) and both legs (2/5) and feet (4/5) and generalized areflexia. PCR for SARS-CoV-2 RNA was repeatedly negative in oropharyngeal swabs (three times) as well as in CSF and the patient was transferred to the neurological intensive care unit. At the same time, Anti-SARS-CoV-2- antibodies were highly positive in serum and CSF with an optical density (OD) ratio relative to the calibrator OD (normal < 0.8) of 9.6 in serum (diluted 1:100) and 9.1 in CSF (diluted 1:2) determined by commercially available CE-marked ELISA (Euroimmun, Lübeck, Germany; https://www.coronavirus-diagnostik.de) according to the manufacturer's instruction. Due to the non-linearity of the read-out the intrathecal fraction (i.e. antibody specific index) could not be quantified and it is not possible to differentiate intrathecal synthesis of antibodies or passive transfer across the blood-CSF barrier. As yet, we detected no false positives or negatives using this ELISA. Anti-ganglioside antibodies, PCR for *Cytomegalovirus*, *Epstein-Barr virus*, *Influenza virus A/B*, *Respiratory Syncytial Virus* and IgM antibodies for *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* were negative in this patient. Due to muscle weakness accompanied by respiratory failure the patient underwent elective intubation in a fully conscious state and the initial intravenous immunoglobulin therapy, which was initiated on April 6th (total dose 30 g) was switched to plasma exchange on April 7th, which was 3 days after symptom onset. In total four cycles of plasma exchange were performed. Again, SARS-CoV-2 on PCR assay from bronchoalveolar lavage (BAL) fluid was negative. The patient improved gradually and was transferred to a neuro-rehabilitation facility 4 weeks after symptom onset, where he regained mobility without significant help another 4 weeks later.

To the best of our knowledge, this is the first case of SARS-CoV-2 seropositivity associated with GBS. Given the patient's symptoms of infection, the origin from a highly endemic area of SARS-CoV-2 cases, ground-glass opacities on chest CT-scan on admission, repeatedly negative PCR- SARS-CoV-2 testing in oropharyngeal swabs, CSF and BAL fluid, and the highly positive SARS-CoV-2 antibody testing, we believe that the patient had recovered from COVID-19 with adequate immune response at the onset of GBS. Importantly, respiratory failure was triggered by progressive weakness of in- and expiratory muscles in our patient. Considering the temporal association, we speculate that GBS might have been triggered by humoral immune response against SARS-CoV2 in this patient. Our findings and recently published cases support the hypothesis that SARS-CoV-2 may trigger GBS as para-/ post-infectious disease as reported by Zika virus [5,6]. Underling mechanisms for this process may include immune molecular mimicry against nervous system antigens before clinical symptoms of COVID-19 are manifested (para-infectious), [3] or a postinfectious hyperacute immune response as suggested in our patient. Whether anti-SARS-CoV-2 antibodies cross-react with axonal or Schwann cell epitopes needs further evaluation.

The limitation of this case is the absence of a positive SARS-CoV-2-PCR before admission. Still, the preceding febrile illness and high antibody titer at the onset of neurological symptoms suggests a post-COVID-19 state with adequate immune response. It remains imminent to exclude common triggers for GBS as was performed in our patient. In summary, this case report only suggests a possible association between COVID-19 and GBS and needs more evidence from epidemiologic data supported by

Table 1 Motor and sensory nerve conduction studies; Amplitudes are in mV for motor and in in μV for sensory nerve conduction studies

Nerve	Distal latency (ms)	Amplitude (mv; μV)	Conduction velocity (m/s)	F-Latency (ms); Persistence
Median motor right				
Wrist-ABP	5.10 (≤4.2)	4.4 (≥ 5)		40.5 (≤30); 1/8
Elbow-wrist	9.96	3.7	51 ((≥ 49)	(≥2/8)
Ulnar motor right				
Wrist-ABP	2.94 (≤3.3)	6.1 (≥ 4)		30.7 (≤31); 6/8
Elbow-wrist	7.29	6.0	51 (≥ 50)	(≥3/8)
Peroneal motor right				
Ankle-EDB	6.72 (≤6.0)	3.7 (≥ 2)		Absent
Fibula head-ankle	13.51	3.1	43 (≥ 42)	Multiple A-Waves
Tibial motor right				
Anke-AHB	4.01 (≤6.5)	3.9 (≥ 5)		Absent
Popliteal fossa- ankle	13.34	2.7	41 (≥ 41)	Multiple A-Waves
Median sensory right				
Wrist-Digit 2		8.9 (≥ 10)	44.2 (≥ 45)	
Ulnar sensory right				
Wrist-Digit 5		23.0 (≥ 8)	48.0 (≥ 45)	
Sural right				
Calf-posterior ankle		16.4 (≥ 9)	44.6 (≥ 40)	

ADM, m. abductor digiti minimi; AHB, m. abductor halluces brevis; APB, m. abductor pollicis brevis; EDB, m. extensor digitorum brevis.

immunological studies. Clinicians should be vigilant for the occurrence of immune mediated neurological diseases during the COVID-19 pandemic in order to elude on a potential novel mechanism of coronavirus-triggered diseases.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Helms J, Kremer S, Merdji H, *et al*. Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med* 2020; **382:** 2268–2270
2. Mao L, Jin H, Wang M, *et al*. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurology* 2020; **77:** 683.
3. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barre syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol* 2020.**19**(5)**:**383–384.
4. Gutierrez-Ortiz C, Mendez A, Rodrigo-Rey S, *et al*. Miller Fisher Syndrome and polyneuritis cranialis in COVID-19. *Neurology* 2020. https://doi.org/10.1212/WNL.0000000000009619
5. Brasil P, Sequeira PC, Freitas AD, *et al*. Guillain-Barre syndrome associated with Zika virus infection. *Lancet* 2016; **387:** 1482.
6. Parra B, Lizarazo J, Jimenez-Arango JA, *et al*. Guillain-Barre Syndrome Associated with Zika Virus Infection in Colombia. *N Engl J Med* 2016; **375:** 1513–1523.