COVID-19 polyradiculitis in 24 patients without SARS-CoV-2 in the cerebro-spinal fluid

To the Editor,

The current hostage of mankind, coronavirus disease-2019 (COVID-19), has not only strong political, socioeconomic, and cultural implications, but also stimulates science. Meanwhile it is common sense that the causative virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), not only affects the broncho-pulmonary system, but can be found in nearly all compartments of the body, including the central and peripheral nervous system (CNS, PNS). 1 One of the recently described manifestations in the PNS is Guillain-Barre syndrome (GBS). 2,3 GBS covers a group of autoimmune disorders that share a common presentation of acute/subacute, progressive poly-radiculo-neuropathy in common. 3 According to the underlying pathology, clinical presentation, and findings on nerve conduction studies (NCSs), several subtypes are delineated. These include acute, inflammatory, demyelinating poly-radiculo-neuropathy (AIDP) with primarily demyelinating features and a favorable prognosis, 3 acute, axonal, motor neuropathy (AMAN) with primary axonal injury, pure motor involvement, and a worse prognosis, 3 acute, motor, sensory, axonal neuropathy (AMSAN), which shares a similar pathogenesis as AMAN but with additional sensory involvement, Miller-Fisher syndrome (MFS), characterized by ophthalmoplegia, areflexia, and ataxia, Bickerstaff encephalitis presenting similarly to MFS but additionally with impaired consciousness due to brainstem involvement, the pharyngeal-cervico-brachial variant, associated with GQ1b and GD1a antibodies and pandysautonomia, associated with GT1a antibodies. 3 The incidence of GBS ranges between 1.1 and 2.7/100,000/year. 3 This mini-review aims at summarising and discussing recent advances concerning SARS-CoV-2-induced polyradiculitis.

A literature search using the search terms “SARS-CoV-2,” “COVID-19,” and “corona virus” together with “Guillain-Barre syndrome,” “GBS,” “AIDP,” “AMAN,” “AMSAN,” “MFS,” “Bickerstaff encephalitis,” “pandysautonomia,” and “polyradiculitis” was carried out. Articles describing in detail cases with SARS-CoV-2-associated GBS were included. Additionally, reference lists of articles dealing with neurological disease in COVID-19 infected patients were screened for references describing polyradiculitis. Only articles published since the outbreak of the pandemic were included. Excluded were review articles.

Altogether, 18 articles reporting 23 patients with SARS-CoV-2-associated GBS were included. 2,4-20 Additionally, a case of COVID-19-associated AMAN from India became obvious by personal communication. Thus, 24 patients were included in this review. In 19 patients age ranged from 20 to 76 years (Table 1). Sex was reported in 19 patients. Thirteen patients were male and 6 were female (Table 1). In 22 patients GBS began after onset of clinical manifestations of COVID-19. Latency between onset of COVID-19 and GBS respectively GBS and COVID-19 was reported in 24 cases and ranged from 3 to 23 days (mean: 9.6 days). Forteen patients were diagnosed with AIDP, four with AMAN, three with MFS, and two with AMSAN. In one patient the subtype was not specified (Table 1). SARS-CoV-2-related Bickerstaff encephalitis, the pharyngeal-cervico-brachial variant of GBS, or pandysautonomia were not reported in any of the included patients. Cerebro-spinal (CSF) was investigated for SARS-CoV-2 in 15 patients but was negative for the virus in all of them (Table 1). Twenty-one patients received intravenous immunoglobulins (IVIG), and one additionally plasmapheresis (Table 1). One of the Spanish patients received steroids (Table 1). Two patients with MFS remained without therapy and recovered spontaneously (Table 1). Seven patients required artificial ventilation (Table 1). In all patients requiring artificial ventilation respiratory insufficiency was attributed to the GBS and not to the COVID-19 infection. Thirteen patients recovered under this regimen. The outcome was poor in six patients and two died during hospitalization. The prevalence of SARS-CoV-2-associated GBS was 0.41 of 100,000 and thus lower than that of non-SARS-CoV-2-associated GBS.

This review shows that SARS-CoV-2 can manifest with polyradiculitis. As with non-SARS-CoV-2-associated GBS, there is a male preponderance. Elderly patients are more frequently affected than the younger generation. The most prevalent subtype of GBS is AIDP. In patients with SARS-CoV-2-associated GBS no virus is found in the CSF. In most cases the response to IVIG is favorable, and dependent on comorbidities. About one-third of the patients with SARS-CoV-2-associated GBS requires mechanical ventilation. In some cases the outcome is poor or even fatal.

The mechanism underlying the affection of the PNS in SARS-CoV-2-infected patients and the development of GBS is unknown. Since most patients with SARS-CoV-2-associated GBS developed GBS on the average 10 days after the first non-neurological symptoms of the viral infection, a causal relation is quite likely. In the two patients in whom GBS developed before non-neurological manifestations of the infection developed, 2,16 the infection most likely preceded the onset of GBS as well but may have remained subclinical or gone unrecognized. An argument against a causal relation, however, is that in none of the included patients SARS-CoV-2 was found in the CSF. Absence of the virus in the CSF suggests that GBS is not triggered by a direct viral attack against the nerve roots but rather by an immune-mediated mechanism, such as antibody precipitation on
myelin sheaths or axons. It is also conceivable that there is mimicry
between epitopes on the surface of the virus and on membranes of
motor or sensory neurons, why they are simultaneously attacked by
the immune response, a similar mechanism as in GBS due to C. jejuni.
Furthermore, there are indications that COVID-19 is associated with
a cytokine storm and a dysregulated immune response.

It is also conceivable that the virus directly invades motor and sensory neu-
rons since the virus has been found in neurons and endothelial cells
of the frontal lobe. There are speculations that the brain could be
even a reservoir for the virus in the absence of severe clinical man-
ifestations. Whether SARS-CoV-2-associated GBS is more pre-
valent in patients with than without pre-existing damage of
peripheral nerves remains speculative. Only one patient with dia-
betes was suspected to have had a premorbid neuropathy.

It is concluded that SARS-CoV-2 can cause GBS. The CSF is free
of virus-RNA in SARS-CoV-2-associated GBS. If SARS-CoV-2 is truly
the cause of GBS in all cases included in this review, remains spec-
ulative since a strong causative relation was not established in each
case. Clinical presentation, course, response to treatment, and out-
come are similar in SARS-CoV-2-associated GBS and GBS due to
other triggers but the prevalence of SARS-CoV-2-associated GBS is
lower than that of GBS due to other triggers.

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**TABLE 1** Patients with SARS-CoV-2 associated polyradiculitis so far reported

| Age, y | Sex | Onset | LOO, d | Subtype | CIC | CM | IVIG | AV | Recovery | Country | Reference |
|--------|-----|-------|--------|---------|-----|----|------|----|----------|---------|-----------|
| 61     | f   | B     | 9      | AIDP    | nr  | None | Yes   | No, yes | Yes       | China    | 2         |
| 65     | m   | 9     |       | AMSAN   | nd  | DM  | Yes   | No       | nr        | Iran      | 4         |
| 54     | m   | A     | 8      | AIDP    | nr  | None | Yes   | Yes      | Yes       | United States | 5         |
| 70     | f   | A     | 23     | AIDP    | nd  | None | Yes   | Yes, nr  | Italy     | 6         |
| 66     | f   | A     | 7      | AIDP    | No  | nr  | Yes   | Yes, Yes | Yes       | Italy     | 7         |
| 54     | f   | A     | 21     | AIDP    | nd  | None | Yes   | No       | Yes       | Germany   | 8         |
| 70     | f   | A     | 3      | AMSAN   | No  | RA  | Yes   | No, No   | No        | Marokko   | 9         |
| 20     | m   | A     | 5      | AMAN    | nd  | None | Yes   | No       | Yes       | India [pc] | 10        |
| 71     | m   | A     | 4      | AIDP    | No  | AHT, AAR, LC | Yes | Yes      | Death     | Italy     | 11        |
| 64     | m   | A     | 11     | AIDP    | nd  | None | Yes   | Yes, nr  | France    | 12        |
| nr     | nr  | A     | 7      | AIDP    | No  | nr  | Yes   | No       | No        | Italy   | 12        |
| nr     | nr  | A     | 10     | AIDP    | No  | nr  | Yes   | No       | Yes       | Italy    | 12        |
| nr     | nr  | A     | 10     | AMAN    | No  | nr  | Yes   | Yes      | No        | Italy    | 12        |
| nr     | nr  | A     | 5      | AMAN    | No  | nr  | Yes   | No       | No        | Italy    | 12        |
| nr     | nr  | A     | 7      | AMAN    | No  | nr  | Yes, PE | No       | No        | Italy    | 12        |
| 50     | m   | A     | 3      | MFS     | No  | None | Yes   | No       | Yes       | Spain    | 13        |
| 39     | m   | A     | 3      | MFS     | No  | None | No     | No       | Yes       | Spain    | 13        |
| 61     | m   | A     | 10     | MFS     | No  | None | S     | No       | Yes       | Spain    | 14        |
| 76     | f   | A     | 8      | GBS*    | nd  | None | No    | nr       | Death     | Spain    | 15        |
| ~75    | m   | B     | 10     | AIDP    | No  | None | Yes   | No       | Yes       | Switzerland | 16        |
| 43     | m   | A     | 10     | AIDP    | nr  | nr  | Yes   | No       | Yes       | Spain    | 17        |
| 64     | m   | A     | 23     | AIDP    | No  | nr  | Yes   | No       | Yes       | France   | 18        |
| 72     | m   | A     | 7      | AIDP    | No  | AHT, CHD, AL | Yes | Yes, partial | United States | 19        |
| ~65    | m   | A     | 17     | AIDP    | No  | None | Yes   | No       | Yes       | Italy    | 20        |

Abbreviations: A, onset of GBS after onset of non-neurological manifestations; AAR, aortic aneurysm repair; AHT, arterial hypertension; AL, alcoholism; AV, artificial ventilation; B, onset of GBS before onset of non-neurological manifestations; CHD, coronary heart disease; CIC, CoV-2 in CSF; CM, comorbidities; DM, diabetes; f, female; GBS*, no NCSs reported; LC, lung cancer; LOO, latency between onset of GBS and COVID-19 respectively vice versa; m, male; nd, not done; nr, not reported; pc, personal communication; PE, plasma exchange; RA, rheumatoid arthritis; S, steroids.
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