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LETTER TO THE EDITORS

# Guillain-Barré syndrome in the COVID-19 era: just an occasional cluster?

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Dear Sirs,

In terms of epidemiology, Guillain-Barré syndrome (GBS) accounts for 1–2 new cases/100.000 inhabitants per year [1, 2]. During the last two weeks, in coincidence with the descending slope of the pandemic peak in our region (Friuli Venezia-Giulia, Italy), we noted an unusual cluster of patients affected by GBS. The Neurology of the Udine University Hospital is the only Neurology Unit for the entire territory of the province, making unlikely the possibility of missing new cases, since this is the only facility for neurophysiological investigation and cerebrospinal fluid (CSF) examination in an area of 4,969.3 $km^2$. Solicited by this observation and by a recent paper reporting the association of GBS with COVID-19 infection [3], we decided to re-examine the frequency of GBS cases during the March–April months of the last three years and to compare it with the admissions for GBS during the same months of the current year (up to April 16th).

After having the possibility to perform a quick test (Cellex™ q rapid test [4]) for the presence of IgM and IgG against SARS-CoV-2 nucleocapsid protein (N-protein), we tested the four patients still present in our ward and two more patients already discharged who accepted to come back to the hospital. Furthermore, we briefly described clinical, laboratory and neuro-physiological data of patients admitted this year in Table 1. Data dealing with COVID-19 are reported in Table 2.

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The total number of GBS in the March–April interval of the previous three years is four. In 2020, from March 1st to April 15th, we observed instead seven new cases diagnosed as GBS, in addition to a relapse in one more patient. This means 0.67 cases/month of observation (four cases in six months) in the previous three years, compared to 3.5 cases/month (seven cases in two months) during the current year, which increases to 4 cases/month (eight cases in two months), if we consider also the patient with relapse. Considering a population of 535,516 inhabitants in the province of Udine (2017 census), the monthly incidence in March–April period of previous years was 0.12 new cases/100.000 inhabitants per month (in line with the epidemiological literature [1, 2]) versus 0.65 cases/100.000 inhabitants per month during the ongoing pandemic. Accordingly, compared to years 2017–2019, the increase of GBS cases in 2020 is 5.41-fold.

The suspicion that this striking difference could be due to the pandemic curve in our region is, therefore, legitimate. In fact, it is well known that GBS and related syndromes are often post-infectious (as for the influenza epidemics and more recently for Zika virus [5]), with an usual latency of 10–14 days after infection [2]. However, in our series, only one patient (twice negative at swab test) had positive serology and thorax CT scan. Despite the serologic and swab negativity of the others, we think that the association with the descending slope of SARS-CoV-2 infection should still be evaluated, since the specificity and sensitivity of these tests are not yet completely assessed and the exact slope of the humoral immune response curve to this new virus is still unknown. It could also be possible that asymptomatic or paucisymptomatic infections may not develop an antibody response sufficient enough to be detected, especially considering that the available test is only qualitative.

We wonder if similar clusters have been observed elsewhere.

**Table 1** Demographic, clinical, CSF and neurophysiological findings in the observed population with GBS

| ID | Age, Sex | Previous infection symptoms | GBS symptoms | Symptoms onset | CSF proteins (*r*: 150–450 mg/L) | CSF leucocytes (*r*: 0–3/μL) | Neurophysiological studies |
|---|---|---|---|---|---|---|---|
| 1 | 76, M | No | Tetraparesis<br>Dysarthria<br>Dysautonomia | 27/02/2020 | 228 mg/L | 0.6/μL | AMSAN |
| 2 | 70, M | Diarrhea | Paraparesis<br>Paraesthesia<br>Ataxia | 07/02/2020 | 216 mg/L | 0.6/μL | AIDP |
| 3 | 80, M | No | Arthromyalgia<br>Low back pain<br>Paraesthesia<br>Paraparesis | 20/03/2020 | 933 mg/L | 0/μL | AIDP |
| 4 | 59, M | No | Emifacial paresthesia<br>Facial weakness (VII c.n.)<br>Dysarthria (XII c.n.) | 24/03/2020 | 701 mg/L | 2.8/μL | Altered blink reflex, demyelinating damage (MFS) |
| 5 | 59, F | Fever<br>Cough<br>Common cold | Low back pain<br>Paraesthesia<br>Tetraparesis | 01/03/2020 | 1124 mg/L | 0.4/μL | AIDP |
| 6 | 82, M | Fever | Asymmetric paraparesis | 28/03/2020 | 827 mg/L | 0.8/μL | AIDP |
| 7 | 53, M | Fever<br>Diarrhea | Paraesthesia<br>Ataxia | 01/04/2020 | 1928 mg/L | 2.6/μL | AIDP |
| 8 | 59, F | No | Tetraparesis<br>Paraesthesia | 11/02/2020 (relapse) | NA[a] (relapse) | NA (relapse) | AIDP relapse |

*ID* patient identification number, *GBS* Guillain-Barré syndrome, *CSF* cerebrospinal fluid, *M* male, *F* female, *AMSAN* acute motor-sensory axonal neuropathy, *AIDP* acute inflammatory demyelinating polyneuropathy, *MFS* Miller-Fisher syndrome, *c.n.* cranial nerve, *r* normal range for laboratory, *NA* not available

[a]During patient's first episode of AIDP, with onset on December 2019, CSF examination showed a protein content of 930 mg/L, with 0.8/μL cells. On the occasion of the clinical relapse, lumbar puncture was not performed

**Table 2** Data dealing with COVID-19 in the population with GBS

| ID | COVID-19 common symptoms[a] | Swab test | Thorax imaging suggestive for COVID-19 (Rx or thorax CT scan) | SARS-CoV-2 serology | PCR for SARS-CoV-2 on CSF | Serology or PCR for other infections | Serum anti-gangliosides antibodies |
|---|---|---|---|---|---|---|---|
| 1 | No | 24/03/2020 negative | Interstitial pneumonia | NA | NA | Negative Multiplex PCR[b] (CSF)<br>Negative serology for Borrelia[c] and TBE (CSF), WNV (serum) | Negative |
| 2 | Yes | 24/03/2020 negative | No | Negative (blood) | NA | Negative serology for Borrelia and TBE (serum) | Negative |
| 3 | No | 15/04/2020 negative | No | Negative (blood) | Negative | Negative Multiplex PCR (CSF)<br>Negative serology for Borrelia and TBE (CSF) | NA |
| 4 | No | 27/03/2020 negative | No | Negative (blood) | Negative | Negative Multiplex PCR (CSF)<br>Negative serology for Borrelia and TBE (serum and CSF) | Negative |

**Table 2** Continued

| ID | COVID-19 common symptoms[a] | Swab test | Thorax imaging suggestive for COVID-19 (Rx or thorax CT scan) | SARS-CoV-2 serology | PCR for SARS-CoV-2 on CSF | Serology or PCR for other infections | Serum anti-ganglioside antibodies |
|---|---|---|---|---|---|---|---|
| 5 | Yes | 20/03/2020 negative | No | Negative (blood) | NA | Negative Multiplex PCR (CSF) | Negative |
| 6 | Yes | 07/04/2020 negative | No | Negative (blood) | Negative | NA | NA |
| 7 | Yes | 06/04/2020 negative<br>14/04/2020 negative | Bilateral ground-glass opacities | Positive IgM and IgG (blood and CSF) | Negative | Negative PCR for influenza A and B viruses (nasal swab)<br>Negative serology for Borrelia and TBE (CSF) | Negative |
| 8 | No | 30/03/2020 negative<br>06/04/2020 negative<br>15/04/2020 negative | Ground-glass opacities<br>Peri-bronchovascular thickenings | NA | NA | NA | GD1a + GT1b, anti-sulfatide low titer + |

*ID* patient identification number, *CT* computed tomography, *PCR* polymerase chain reaction, *CSF* cerebrospinal fluid, *NA* not available, *CMV* Cytomegalovirus, *EBV* Epstein-Barr virus, *HSV-1* Herpes simplex virus 1, *HSV-2* Herpes simplex virus 2, *HHV-6* Human herpes virus 6, *HPeV* Human parechovirus, *VZV* Varicella-zoster virus, *TBE* Tick-borne encephalitis, *WNV* West-Nile virus

[a]We intend symptoms such as fever, cough, cold and diarrhea

[b]Mutliplex PCR: EBV, CMV, Enterovirus, HSV-1, HSV-2, HHV-6, HPeV, VZV

[c]Borrelia burgdorferi

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## Compliance with ethical standards

**Conflicts of interest** On behalf of all authors, the corresponding author states that there is no conflict of interest.

**Ethical standard statement** This study followed the tenets of the Declaration of Helsinki and was performed according to the guidelines of the Institutional Review Board of University of Udine Medical School.

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