Guillain-Barré syndrome and COVID-19: an observational multicentre study from two Italian hotspot regions

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ABSTRACT

Objective Single cases and small series of Guillain-Barré syndrome (GBS) have been reported during the SARS-CoV-2 outbreak worldwide. We evaluated incidence and clinical features of GBS in a cohort of patients from two regions of northern Italy with the highest number of patients with COVID-19.

Methods GBS cases diagnosed in 12 referral hospitals from Lombardy and Veneto in March and April 2020 were retrospectively collected. As a control population, GBS diagnosed in March and April 2019 in the same hospitals were considered.

Results Incidence of GBS in March and April 2020 was 0.2/100 000/month (estimated rate 2.43/100 000/year) vs 0.077/100 000/month (estimated rate 2.43/100 000/year) vs 0.202/100 000/month (estimated rate 2.43/100 000/year) in the same months of 2019 with a 2.6-fold increase. Estimated incidence of GBS in COVID-19-positive patients was 47.9/100 000 and in the COVID-19-positive hospitalised patients was 236/100 000. COVID-19-positive patients with GBS, when compared with COVID-19-negative subjects, showed lower MRC sum score (26.3±18.3 vs 41.4±14.8, p=0.006), higher frequency of demyelinating subtype (76.6% vs 35.3%, p=0.011), more frequent low blood pressure (50% vs 11.8%, p=0.017) and higher rate of admission to intensive care unit (66.6% vs 17.6%, p=0.002).

Conclusions This study shows an increased incidence of GBS during the COVID-19 outbreak in northern Italy, supporting a pathogenic link. COVID-19-associated GBS is predominantly demyelinating and seems to be more severe than non-COVID-19 GBS, although it is likely that in some patients the systemic impairment due to COVID-19 might have contributed to the severity of the whole clinical picture.

INTRODUCTION

In December 2019, Wuhan in China became the centre of an outbreak of pneumonia caused by a novel coronavirus named SARS-CoV-2.1 COVID-19 rapidly spread all over the world, acquiring the characteristics of a pandemic, and since February 2020, it has been spreading in Italy, particularly in the Lombardy and Veneto regions.2 With the increasing understanding of the disease, many non-pulmonary symptoms were recognised, including neurological complications such as acute cerebrovascular diseases, seizures, meningitis, encephalitis and skeletal muscle involvement.3–5 From 1 April to 30 June 2020, 42 patients with SARS-CoV-2 infection and Guillain-Barré syndrome (GBS) have been reported mostly from Europe, and the number of cases is increasing weekly, suggesting a possible association.6

Nowadays, GBS is considered a diagnostic umbrella including a number of related autoimmune polyneuropathies classified in variants and subtypes.7 8 On the basis of electrophysiological and pathological characteristics, GBS has been classified into acute inflammatory demyelinating polyradiculoneuopathy (AIDP), acute motor axonal neuropathy (AMAN) and acute motor sensory axonal neuropathy (AMSAN).9–13 Several infecting agents, including Campylobacter jejuni, influenza virus, Epstein-Barr virus, Cytomegalovirus and, more recently, Zika virus have been shown to precede GBS.9–14

This retrospective multicentre study aimed at evaluating the incidence and clinical characteristics of GBS during the COVID-19 pandemic in the two regions mostly affected by COVID-19 in northern Italy.
Neuromuscular

PATIENTS AND METHODS

Patients

Patients with GBS diagnosed during the outbreak of SARS-CoV-2 infection in 12 referral hospitals of seven cities (Bergamo, Brescia, Cremona, Milano, Padova, Pavia and Verona) from northern Italy between March and April 2020 were collected. They were divided into COVID-19-positive and COVID-19-negative patients. As a control group, patients with GBS diagnosed in the same hospitals and in the same months of 2019 were also considered due to the small sample size of 2020 COVID-19-negative patients with GBS. Inclusion criteria were age >18 years and GBS diagnosed according to clinical findings and the Brighton Collaboration GBS Working Group criteria. Level 1 of Brighton criteria indicates the highest degree of diagnostic certainty supported by nerve conduction studies and the presence of albumin–cytological dissociation in cerebrospinal fluid (CSF). A level 2 diagnosis is supported by either a CSF white-cell count of less than 50 cells/μL (with or without an elevated protein level) or nerve conduction studies consistent with the polyradiculoneuropathy patterns described for GBS (if the CSF is unavailable). A level 3 diagnosis is based on clinical features without nerve conduction or CSF study support. Exclusion criterion was a diagnosis of GBS-mimicking conditions, including critical illness myopathy and/or neuropathy and other nerve and/or muscle acute diseases which can be misdiagnosed as GBS.

Clinical scales

The Medical Research Council (MRC) sum score was used to evaluate muscle strength in 12 muscle groups (range from 0 to 60, with the higher scores indicating the more preserved strength). For the patients who were unresponsive or delirious, we reported the last assessment before the deterioration of consciousness.

Disability was measured at or in proximity of GBS nadir by the Hughes scale according to the following scores: 0, healthy state; 1, minor symptoms and capable of running; 2, able to walk 10 m or more without assistance but unable to run; 3, able to walk 10 m across an open space with help; 4, bedridden or chair bound; 5, requiring assisted ventilation for at least part of the day; and 6, dead. For COVID-19-positive patients, we employed the sequential organ failure assessment (SOFA) score that tracks a subject status determining the extent of organ function and rate of failure. The score consists of six different subscores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems (0–24).

Response to treatment was globally assessed on the clinical basis by expert neurologists at discharge.

Electrophysiological studies and electrodiagnostic criteria

Nerve conduction studies were performed according to standardised techniques. Distal motor latency, amplitude and duration of negative peak of compound muscle action potential (CMAP), motor conduction velocity and minimal F-wave latency were measured from different stimulation sites (median, ulnar, peroneal and tibial nerves). The cut-off values for the distal CMAP duration were determined according to normal values for the low-frequency filter used +2 SD. Proximal/distal (p/d) CMAP amplitude and duration ratios were also assessed. Sensory studies were performed antidromically in median, ulnar and sural nerves and amplitude of sensory nerve action potential was measured baseline to negative peak. Electrophysiological findings were normalised as percentages of upper and lower limits of normal according to reference values of each centre. For the electrodiagnosis of GBS subtypes, we used a recently proposed criteria set (online supplemental table 1).

Statistical analysis

The analysis was performed using V24.0 of the IBM SPSS software.

Continuous variables were expressed as mean±SD and median value and IQR when appropriate. Categorical variables were shown as frequencies and percentages. The value of variables was approximated to the first decimal number when appropriate.

Considering the unknown frequency of the association between COVID-19 and GBS, it was not possible to perform an a priori estimation of the sample size required. Statistical analyses were performed with non-parametrical tests (Mann-Whitney U test, χ² test or Fisher’s exact test) due to the small sample size. The statistical threshold was set at 0.05.

The incident risk was calculated by putting in the numerator the number of GBS cases recorded during the observation period and in the denominator the number of people at risk of getting sick, taking into account the number of the general population of the seven cities (8 400 107 inhabitants) according to the 2019 Italian National Institute of Statistics official data. The incidence rate in COVID-19 was calculated by placing COVID-19-positive individuals who developed GBS in the numerator and in the denominator the total COVID-19-positive people of the seven cities involved in the study (62 679 inhabitants) derived from Lombardy and Veneto official data on 30 April 2020.

The incidence of cases per month was calculated, and the incidence of cases per year was then estimated. Relative incidence was derived from comparing 2019 and 2020 GBS populations.

The number of total COVID-19-positive patients admitted to the participating hospitals was also obtained.

RESULTS

A total of 34 patients with GBS with symptom onset between 1 March and 30 April 2020 were collected. Thirty (88.2%) patients were diagnosed with confirmed SARS-CoV-2 by nasopharyngeal swab infection and/or serum-specific SARS-CoV-2 antibodies and labelled as COVID-19-positive GBS. The remaining four patients were negative for SARS-CoV-2 infection.

Thirteen patients were diagnosed with GBS in the same hospitals in March and April 2019. These patients were pooled, for clinical comparisons, with the four 2020 patients negative for SARS-CoV-2 infection and labelled as COVID-19-negative GBS.

Incidence of GBS

The incidence of GBS in March and April 2020 in the seven cities of Lombardy and Veneto considering all 34 cases was 0.202/100 000/month (estimated rate 2.14/100 000/year), while COVID-19-positive patients admitted to hospitals was 0.178/100 000/month (estimated rate 0.29/100 000/year). The 30 COVID-19-positive patients with GBS (88%) represented 0.178/100 000/month (estimated rate 2.14/100 000/year), while COVID-19-negative patients with GBS (four cases) were 0.024/100 000/month (estimated rate 0.29/100 000/year).

In the total COVID-19-positive population, the estimated incidence of GBS was 47.9/100 000 cases. When considering only the COVID-19-positive cases hospitalised in March and April 2020, the incidence of GBS was 23.0/100 000 cases.
Features of COVID-19-negative patients with GBS

The detailed clinical and laboratory findings of the 17 COVID-19-negative patients are reported in table 2.

All the patients presented with a classical GBS form. Seven (41.1%) fulfilled the Brighton level 1 and 10 (58.9%) the Brighton level 2. Six (35.3%) patients were classified as AIDP; six (35.3%) as AMAN, one (5.9%) as AMSAN, 3 (17.6%) as equivocal and one (5.9%) had no abnormalities at neurophysiological study (table 1).

Comparison between COVID-19-positive and COVID-19-negative patients with GBS

Results are detailed in table 2. Compared with COVID-19-negative patients with GBS, COVID-19-positive patients with GBS had lower MRC sum score (26.3±18.3 vs 41.4±14.8; p=0.006—median 23, IQR 10–39 vs 46, IQR 31–53) and more frequent involvement of four limbs (83.3% vs 47%, p=0.018), which were more frequently admitted to the intensive care unit (ICU) (50% vs 17.6%, p=0.03) and more frequently showed arterial hypertension (50% vs 11.8%, p=0.023).

The frequency of AIDP was significantly higher in COVID-19-positive than in COVID-19-negative patients with GBS (76.6% vs 35.3%, p=0.011), whereas AMAN was more frequent in the COVID-19-negative subjects (6.7% vs 35.3%, p=0.019).

Both COVID-19-positive and COVID-19-negative patients with GBS received similar treatment (intravenous immunoglobulin or plasma exchange), and no significant difference in the response was observed. No deaths were recorded in both groups.

DISCUSSION

The overall incidence of GBS is 1.1–1.8/100 000/year and increases up to 3.3/100 000/year in the population over the age of 50 years.24 In northern Italy, the incidence of GBS is 0.75–1.09/100 000/year in Lombardy and 1.04–1.51/100 000/year in Piedmont and Valle d’Aosta.22 23 To date, the incidence of GBS in the ‘COVID-19 era’ has been analysed only in a small cohort from Friuli-Venezia Giulia, Italy, where an unusual cluster occurred in the months of March and April 2020.24 Monthly incidence during the pandemic was 0.65 cases/100 000 vs 0.12 cases/100 000 in the March–April period of previous years with a 5.4-fold increase of GBS cases in 2020.24 However, only one patient, who was twice negative at swab test, had positive serology and chest CT scan in this study.24

Our study, carried out in two Italian regions with the highest number of COVID-19-positive patients, showed a considerably higher GBS incidence in March and April 2020 than in the same months of 2019 with a 2.6-fold increase. The majority of GBS cases (88%) were COVID-19 positive with an estimated incidence of 4.86/100 000 COVID-19-positive cases and of 236/100 000 in the hospitalised COVID-19-positive population.

These findings support a pathogenic link between the COVID-19 pandemic and GBS. The virus may induce nerve damage both directly and/or by dysregulation of the immune response through a cytokine storm.25 26 As SARS-CoV-2 spike protein interacts with the N-acetylgalactosamine residue of GM1 for anchoring to the cell surface, an immune cross-reaction between epitopes within the spike-bearing gangliosides and sugar residues of surface peripheral nerve glycolipids is also possible.27 28

GBS is considered the prototype of postinfectious neuropathy usually developing 2–4 weeks after an acute infection.29 Differently, parainfectious neuropathies develop during or within a few days after the infection and are due to the direct effect of the
### Table 2  Demographic, clinical features and laboratory findings of 2020 COVID-19-positive patients with GBS and 2019–2020 COVID-19-negative patients with GBS

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<td>73.3 (22)</td>
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<td>Female</td>
<td>26.7 (8)</td>
<td>47.1 (8)</td>
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<td><strong>Age</strong></td>
<td>59.2±12.1 years (median 59, IQR 51.5–61.3)</td>
<td>57.2±17.9 years (median 57, IQR 43.5–73.5)</td>
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<td>Unresponsive/delirium</td>
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<td>Tetraparesis 47.1 (8)</td>
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<td>Predominant paraparesis 3.3 (1)</td>
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<td>Predominant upper limb paresis 10 (3)</td>
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<td>Any limb paresis 3.3 (1)</td>
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<td><strong>MRC sum score</strong></td>
<td>26.3±18.3 (median 23, IQR 10–39)</td>
<td>41.4±14.8 (Median 46, IQR 31–53)</td>
<td>0.006*</td>
<td>4.6 to 25.6</td>
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<td>Lower limb hypoesthesia 61.9 (13)</td>
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<td>Upper limb paraesthesia 42.9 (9)</td>
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<td>Lower limb paraesthesia 47.6 (10)</td>
<td>Lower limb paraesthesia 47.1 (8)</td>
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<td><strong>Cranial neuropathies</strong></td>
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<tr>
<td>Olfactory</td>
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<td>0 (0)</td>
<td>0.08</td>
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<td>Oculomotor nerves</td>
<td>10.0 (3)</td>
<td>5.9 (1)</td>
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<td>Bilateral 20 (6)</td>
<td>Bilateral 0 (0)</td>
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<td>Normal 76.4 (13)</td>
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<td>Classical GBS 100 (17)</td>
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<td>Pure sensory form 3.3 (1)</td>
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<td>Pharyngeal–cervical–brachial 3.3 (1)</td>
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<td><strong>Electrodiagnosis</strong></td>
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<td>AIDP 35.3 (6)</td>
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<td>AMAN 6.7 (2)</td>
<td>AMAN 35.3 (6)</td>
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<td>Equivocal 16.7 (5)</td>
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<td><strong>CSF findings</strong></td>
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<td>Normal 66.7 (14)</td>
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<td><strong>Brighton criteria</strong></td>
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<td>Level 1 41.1 (7)</td>
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<td>Level 2 70 (21)</td>
<td>Level 2 58.9 (10)</td>
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<td>Not classifiable 3.3 (1)</td>
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<td>Hughes disability score at nadir of GBS</td>
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<td>3.44±1</td>
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<td><strong>ICU admission</strong></td>
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<td>17.6 (3)</td>
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<td>Hypertension 50 (15)</td>
<td>Hypertension 35.3 (6)</td>
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<td><strong>IVIG</strong></td>
<td>83.3 (25)</td>
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<td>No treatment</td>
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<td><strong>Response to treatment</strong></td>
<td>Yes 85.2 (23)</td>
<td>Yes 93.8 (15)</td>
<td>0.12</td>
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</table>

*Statistical significance, p<0.05.
AIDP, acute inflammatory demyelinating polyradiculoneuropathy; AMAN, acute motor axonal neuropathy; AMSAN, acute motor and sensory axonal neuropathy; CSF, cerebrospinal fluid; GBS, Guillain-Barré syndrome; ICU, intensive care unit; IVIG, intravenous immunoglobulin; MRC, Medical Research Council.
agent or to a hyperimmune response. Infectious agents thought to cause parainfectious neuropathies include Borrelia burgdorferi, Brucella, Clostridium botulinum and West Nile virus. More recently, infection with the flavivirus Zika has been associated with the development of both postinfectious and parainfectious GBS. On the basis of the interval between the onset of COVID-19 and of GBS symptoms, both parainfectious and postinfectious GBS cases have been reported.

In our series, only five patients presented with a course clearly indicating a postinfectious disease. In the remaining patients, GBS started while COVID-19 symptoms were still ongoing. Whether the latter cases should be considered as parainfectious remains undefined as the course of COVID-19 is very complex. The incubation period of SARS-CoV-2 infection is up to 14 days, making difficult the calculation of the time interval between infection and development of GBS. SARS-CoV-2 infection, in the most severe form, includes three stages: early infection, pneumonia and hyperinflammatory response. The active viremia occurs in the first two stages, while the immunological and inflammatory complications are observed in the hyperinflammatory phase. In clinical practice, especially for ICU patients, it is difficult to establish which stage GBS symptoms occurred since COVID-19 may evolve seamlessly through the different stages, and respiratory symptoms as well as chest CT scan abnormalities may persist beyond the acute infection phase. Moreover, since the virus has not been demonstrated in CSF and pathological evidence of peripheral nerve invasion is currently unavailable, a direct role of SARS-CoV-2 in nerve damage remains uncertain.

Regarding the clinical features, although the classical GBS is the predominant form in the cohort of GBS COVID-19-positive patients, cases of facial diplegia, pure sensory form and pharyngeal–cervical–brachial weakness also occurred. Although not present in our series, cases of COVID-19-related Miller-Fisher syndrome and sensory axonic neuropathy have been also reported, thus demonstrating that COVID-19 may be associated with virtually all the clinical variants and subtypes of GBS.

A great majority of previously reported patients with GBS and SARS-CoV-2 infection received an electrodagnosis of AIDP, although the employed criteria sets were often not reported.

Since the electrodagnosis of GBS subtypes is greatly dependent on the applied criteria set and the number of electrophysiological studies performed in the patient, in our study, we used in both COVID-19-positive and COVID-19-negative patients the same electrodagnostic set characterised by quite stringent criteria for demyelination. This set showed the highest diagnostic accuracy at first study in a cohort with a balanced number of AIDP and patients with axonal GBS and was also employed in the electrodagnosis of GBS associated with Zika virus infection. We confirmed that most COVID-19-positive patients were classified as AIDP, thus supporting the association between SARS-CoV-2 infection and demyelinating nerve damage. The significant difference in AIDP frequency between COVID-19-positive and COVID-19-negative patients in our sample could be due to the small sample size.

COVID-19-positive patients with GBS had worse MRC sum score and more frequent arterial hypotension and ICU admission, thus resulting in clinically more severe cases than COVID-19-negative cases. However, at least for the patients in whom GBS occurred during COVID-19 symptoms and for those hospitalised in the ICU, it is likely that COVID-19-related respiratory and systemic impairment have contributed to the severity of the whole clinical picture. Anyway, the mean Hughes score at the nadir of GBS was not significantly different in the two groups, maybe due to the small sample size and the inherent characteristics of the Hughes scale.

Interestingly, the response to therapy was not different in COVID-19-positive and COVID-19-negative patients, thus confirming that the usual GBS treatment should also be used for GBS cases related to COVID-19.

The current study has some limitations. First, it is a retrospective study and some findings such as antiganglioside antibody titres and spinal MRI were available only in few patients and therefore were insufficient for an adequate analysis. However, it should be considered that these patients were studied in a pandemic context and under the pressure of an unprecedented and exceptional health emergency in the hospitals of northern Italy. Second, clinical observation and incidence calculation are limited to 2 months, even though this period represented the pandemic peak. Third, although our study includes the main reference centres for acute neurological patients in seven cities of Lombardy and Veneto, it is likely that additional patients with GBS may have been admitted to other hospitals. Therefore, the incidence of GBS in the general population may be underestimated. However, the incidence of GBS calculated in 2019 on the basis of the cases diagnosed in the same hospitals is comparable to what is known from the literature, thus supporting the fact that the sample is representative. On the other hand, it is likely that the real number of COVID-19-positive patients is higher than that in the official data, and this could cause an overestimation of the GBS incidence in the COVID-19-positive population.

Despite these limitations, our results represent the first snapshot of the relationship between COVID-19 and GBS in a large cohort of patients.

In conclusion, our study showed a significantly higher than expected number of GBS cases during the COVID-19 outbreak in northern Italy and a high frequency of GBS in patients with COVID-19, thus supporting a role of SARS-CoV-2 in triggering GBS. COVID-19-associated GBS is predominantly demyelinating and seems more severe than non-COVID-19 GBS, although in some patients the relative role of COVID-19 and GBS in determining the whole clinical picture is difficult to dissect.

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