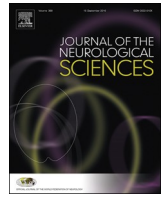




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Clinical short communication

COVID-19-related and not related Guillain-Barré syndromes share the same management pitfalls during lock down: The experience of Liguria region in Italy

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ABSTRACT

Recently, during the pandemic infection of the novel SARS-CoV-2, some cases of Guillain-Barré Syndrome (GBS) have been reported.

The aim of this work is to report the natural history of patients with GBS, both COVID and not-COVID related, hospitalized in Liguria region, during lock down period, in order to assess clinical features of both groups and possible managements pitfalls due to pandemic emergency.

Fifteen GBS patients were admitted to the Hospitals of Liguria, from February 15th to May 3rd 2020, six with SARS-CoV-2 infection and nine without infection.

In COVID-19 related GBS five patients presented with classical GBS and one with variant. Two patients presented neurologic symptoms during or shortly after the viral syndrome, suggesting the pattern of a para-infectious profile. Multi-organ involvement, delay in the diagnosis, incomplete work up and start of therapy, were registered in 50% of cases with a GBS-Disability scale ≥ 4 at follow-up evaluation.

In not-COVID-19 related GBS, main problem was diagnostic delay. In three patients the first neurological observation took place after a mean of 33,6 days. Moreover, five patients went to emergency room after an average of 30 days since the onset of neurological symptoms because of fear of contagion.

In conclusion, not only SARS-CoV-2 infection can cause GBS, but it can also, due to effects of pandemic on the health organization, affect the outcome of patients with not COVID-19 related GBS.

1. Introduction

Guillain-Barré Syndrome (GBS) is an immune-mediate inflammatory polyradiculoneuropathy characterized by acute ascending symmetrical weakness and hypo or areflexia that reaches maximum severity within 4 weeks [1]. In particular, 80% of patients reaches the

nadir of disease within 2 weeks and 97% within 4 weeks after the onset of neurological signs [2].

Cases of GBS have been described in relation to coronavirus (COV) family infections as severe acute respiratory syndrome (SARS) COV [3] and Middle East respiratory syndrome (MERS) COV [4]. Recently, during the pandemic infection of the novel SARS-COV-2, some cases of

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Table 1
Demographic, clinical and laboratory features of GBS COVID-19 related.

Patients (sex, age)	Antecedent event	Time between infectious event and GBS onset (days)	Protein (g/l) on CSF	COVID-19 on CSF	GBS type	MRC score (T0-T1)	GBS-DS (T0-T1)	FU (days)
1 (m,65)	Pneumonia	NC	NP	NP	Classical GBS (AIDP)	28–40	4–4	15
2 (m,73)	Pneumonia	0	0.6	ND	Classical GBS (EDX study NP)	30–5	5–6	30
3 (m,55)	Pneumonia	20	0.3	ND	MFS-GBS overlap	60–60	1–0	20
4 (f,46)	Diarrhea	3	1	ND	Classical GBS (EDX study NP)	48–54	4–3	28
5 (m,60)	Pneumonia	20	0.2	ND	Classical GBS (AMSAN)	33–58	5–3	45
6 (f,63)	Pneumonia	15	0.9	NP	Classical GBS (AMSAN)	56–31	3–4	20

LEGEND: GBS, Guillain Barré syndrome; COVID-19 Coronavirus disease 19; NC: not calculable; CSF: cerebrospinal fluid; NP: not performed; ND: not detectable, EDX: electrodiagnostic studies, AIDP: acute inflammatory demyelinating polyradiculoneuropathy; MFS: Miller Fisher Syndrome; AMSAN: acute motor-sensory axonal neuropathy; MRC; Medical Research Council; GBS-DS: GBS disability score; FU: follow up.

immune-mediated neuropathies have been detected [5–8,17]. Some authors described the rapid onset of neurological symptoms without an asymptomatic period after SARS-COV-2 infection suggesting a para-infectious disease profile as already reported in GBS related to ZIKA virus (ZIKV) infection [9].

The SARS-COV-2 pandemic focused all clinical and organizational attention on coronavirus disease 2019 (COVID-19), causing several patients with not-COVID diseases to avoid Hospitals' care, for fear of infection. Therefore, many not-COVID pathologies have been overlooked or the diagnosis and treatment have been delayed [24].

The aim of this work is to report the natural history of patients with GBS, both COVID-related and not-COVID related, hospitalized in Liguria region from February 15th to May 3rd 2020, in order to assess clinical and electrophysiological features of both groups, focusing in particular on the diagnostic process, the carried out treatment and the outcome, in the pandemic period.

2. Materials and methods

Analysis was carried out on patients who fulfilled the diagnostic criteria for GBS [10] admitted to 6 Hospitals that cover the whole Liguria Region, in the nord-west of Italy, from February 15th 2020 to May 3rd 2020. This period was selected based on the first case of COVID-19 recorded in this region, on February 11th in the city of Alassio, and the end of the “lock down” period, established for the containment of infection. The patients have been divided into two groups, respectively: GBS with or without COVID-19 infection.

Demographic and clinical history informations (age, sex, residence, date of disease onset, type of antecedent events) were collected for each patient.

The following clinical features were recorded: muscle strength, sensory disturbances, reflexes, pain, autonomic dysfunction, cranial nerves impairment and need for mechanical ventilation.

Regarding classical GBS, to properly distinguish the acute inflammatory demyelinating polyradiculoneuropathy (AIDP) from the acute motor and motor-sensory axonal neuropathy (AMAN-AMSAN), the Hadden criteria were applied [11] on the second electrodiagnostic (EDX) study [12] when available. The Waverley's classification was used for the GBS variants [13].

Degree of disability was assessed by means of the GBS disability score (GBS-DS) [14] and muscle strength was measured by Medical Research Council (MRC) sum score [15] on 12 muscles at the first neurological examination (T0) and at follow-up (FU) (T1).

Laboratory tests included: cerebrospinal fluid (CSF) analysis, anti-ganglioside antibodies dosage by enzyme-linked immunosorbent assay (Bühlmann ELISA) and with confirmation by Immunoblot (ALIFAX), oro/nasopharyngeal swab and CSF testing for SARS-COV-2. CSF

analysis and anti-ganglioside antibodies dosages were all centralized and carried out in the laboratory which participates in the external quality check of the Italian Neuroimmunology Association [16].

Treatment of GBS, namely plasma-exchange (PEX) or intravenous immunoglobulin (IVIG), was registered together with time of treatment from symptoms onset.

For both groups of patients, we recorded the following possible managements limitations due to pandemic emergency: diagnostic and therapeutic delay, difficulties to perform all the necessary diagnostic instrumental and/or laboratory tests, restrictions on therapeutic choices.

Finally, we retrospectively searched how many GBS were hospitalized in the 6 hospitals during the same period in 2019.

3. Results

We included fifteen GBS patients admitted to Neurology department or to Intensive Care Unit (ICU) of the hospitals of Liguria, from February 15th to May 3rd 2020: six of them presented SARS-COV-2 infection, nine not-COVID related GBS. In 2019 13 GBS patients were hospitalized in the same 6 hospitals during the same period.

3.1. COVID-19 related GBS

Demographic, clinical and laboratory features of the six COVID-19 related GBS are summarized in Table 1.

We included six COVID-19 related GBS cases (4 men), aged 46–73 years (mean age 60.34 years). All of them had a positive oro/nasopharyngeal swab for SARS-COV-2.

A previous infectious disease was reported in all patients (pneumonia in five cases and diarrhea in one case) and occurred about 15 days before the onset of neurological features in three patients, 3 days before in one patient, while for the other two patients we could not assess the timing of disease. In particular, in one case the patient came to Emergency Room (ER), without fever or respiratory symptoms, complaining four limbs' paresthesias; yet later on chest X-ray and computed tomography (CT) showed signs of interstitial disease; in another case, the presence of a neurological involvement was detected at the time of extubation in ICU and the onset remained unknown.

CSF data were available in 5/6 patients: 3/5 had albumino-cytological dissociation, four patients tested for CSF SARS-COV-2 detection resulted negative. Anti-gangliosides antibodies were undetectable in all of them.

We classified 5/6 patients as classical GBS (one AIDP, 2 AMSAN, in two cases EDX study wasn't performed) and 1/6 patient as variant: Miller Fisher Syndrome (MFS)-GBS overlap. The clinical and EDX features of one AMSAN and the MFS are reported in detail [17]. Dysphagia

Table 2
Demographic, clinical and laboratory features of GBS not COVID-19 related.

Patients (sex, age)	Antecedent event	Time between GBS onset and neurological evaluation (days)	protein (g/l) on CSF	GBS type	MRC score (T0-T1)	GBS-DS (T0-T1)	FU (days)
1 (m,38)	None	30	1.3	MFS	60–60	3–3	15
2 (m,51)	CMV related pneumonia and sepsis	20	1	AMAN	32–42	4–4	15
3 (f,51)	None	10	1.6	AIDP	40–48	4–2	45
4 (m,88)	Diarrhea	30	0.9	AMAN	12–24	4–4	21
5 (f,72)	Pneumonia	30	NP	AIDP	48–58	3–2	20
6 (m,50)	Flu syndrome	5	1.42	bilateral facial nerve palsies with paraesthesia	60–60	1–1	30
7 (f,81)	None	21	0.6	Bickerstaff encephalitis	48–48	4–4	< 5 days
8 (m,53)	Flu syndrome	50	1	AIDP	46–46	3–3	< 5 days
9 (m, 82)	Flu syndrome	60	0.3	AIDP	36–36	3–3	< 5 days

LEGEND: GBS, Guillain Barré syndrome; COVID-19 Coronavirus disease 19; CSF: cerebrospinal fluid; NP: not performed; MFS: Miller Fisher Syndrome; AIDP: acute inflammatory demyelinating polyradiculoneuropathy; MFS: Miller Fisher Syndrome; AMAN: acute motor axonal neuropathy; MRC: Medical Research Council; GBS-DS: GBS disability score; FU: follow up.

and dysphonia were present in three patients. All GBS patients with pneumonia developed respiratory failure and three patients needed mechanical ventilation.

Two patients developed autonomic dysfunction: arterial pressure instability and paralytic ileus in one AMSAN patient and bradycardia in one AIDP patient.

All the patients were treated with IVIG. MRC score and GBS-DS, calculated after an average of 26.34 days of FU after the end of therapy, are described in Table 1.

The diagnostic and therapeutic limitations included: in patients 2,4 EDX study was not performed due to the extreme circumstances in Hospital; in patient 1 lumbar puncture (LP) wasn't made for anticoagulant therapy; in patient 2 there was a diagnostic and therapeutic delay of 13 days due to the main interest on respiratory features and a late request for neurological evaluation.

3.2. COVID-19 not related GBS

Demographic, clinical and laboratory features of not-COVID-19 related GBS are summarized in Table 2.

We evaluated nine not COVID-19 related GBS cases (6 men), aged 38–88 years (mean age of 62.89 years). CSF data were available in 7/9 patients and showed albumino-cytological dissociation in all cases. In the seven samples available, anti-gangliosides antibodies were not detected.

We classified 6/9 patients as classical GBS (4 AIDP, 2 AMAN) and 3/9 as variants (one MFS, one bilateral facial nerve palsies with paraesthesia and one Bickerstaff encephalitis).

All the patients arrived at the first neurological observation in a probable phase of disease stabilization, none of them worsened during the FU (Table 2). No case of respiratory failure was present. Two patients developed isolated urinary retention as autonomic dysfunction. All the patients were treated with IVIG.

Diagnostic and therapeutic limitations related to the health emergency period consisted mainly in the late presentation in ER, due to fear of SARS-COV-2 contagion (patient 1,3,4,5,8) and to delay in requesting neurological evaluation in already hospitalized patients (2,7,9). Time between GBS onset and first neurological evaluation is specified in Table 2. The diagnostic delay led to therapeutic delay. In patient 5 LP and antigangliosides antibodies dosage, weren't performed due to the extreme circumstances in Hospital.

4. Discussion

In this paper we evaluated clinical features and outcomes of GBS diagnosed in a northwest region of Italy, that was severely involved by the COVID-19 pandemic. During the pandemic period, through

February and April 2020, we observed six GBS in patients infected by COVID-19 and nine GBS in patients that were COVID-19 negative, but where the clinical course was deeply influenced by the general health strategy, that during this period was deeply oriented to face the epidemic outbreak.

From an epidemiological point of view, there were no substantial changes of the number of GBS hospitalized in the same period a year earlier.

In the first group we had five classic GBS based on clinical features (among which one AIDP and two AMSAN) as already described in literature [6,7] while one patient could be classified as a case of MFS-GBS overlap [17], similar to two cases previously reported [5].

Recently, Toscano et al. reported that, 4 weeks after treatment, only one patient was able to walk independently, while two patients remained in the ICU, receiving mechanical ventilation, and two patients were undergoing physical therapy because of flaccid paraplegia and had minimal upper-limb movements [6].

Similarly we described a GBS-DS ≥ 4 at FU evaluation, in 50% of our cases. In particular, one patient died, and two other patients were still in ICU with quadriplegia and need mechanical ventilation. The short FU (one month) is certainly a limit of the paper but it is in line with what has been described so far [6].

We know that respiratory failure is generally related to a worse outcome in GBS [16,19], but in these cases it is not possible to determine the effect of reduced vital capacity due to neuromuscular failure in patient with severe pneumonia. It is thus possible that the association of the two components on respiratory failure contributed to the severity of outcome.

The patients with the best outcome included the MFS-GBS overlap patient, the AMSAN patients and the only one patient with diarrhea. The positive outcome of the MFS patient is supported by previous data that reported a generally good prognosis in MFS patients [18]. Moreover, in similar cases of COVID-19 related MFS a favorable outcome was reported [5]. The patient with diarrhea had a good outcome, despite usually patients with GBS preceded by diarrhea (frequently associated with *Campylobacter jejuni* infection), have poor outcome owing to axonal degeneration [18].

Looking at time of onset, two of our patients presented neurological symptoms during or shortly after the viral syndrome. This association might suggest the pattern of a para-infectious profile instead of the classic post-infectious one, similar to what may happen in ZIKV infection [5,6,8,9,20].

The pathogenesis of GBS in a SARS-COV-2 infection may therefore include direct viral neuropathogenic effects or immune mechanisms. In literature none of the COVID-19 related GBS presented SARS-COV-2 in the CSF [5,6]; similarly, the negativity of the search of virus RNA in our two patients confirms that virus seems not to be directly pathogenic.

On the other hand, anti-gangliosides antibodies were not detected in all our tested patients, as in previous report [6], in contrast with the hypothesis of a typical immune-mediated reaction.

Alternative hypotheses are that virus itself activated immune molecular mimicry against nervous system antigens before clinical symptoms of viral infection are manifested, or that virus produces immune dysregulation through a mechanism not related to molecular mimicry but to an aberrant immune response to SARS-COV-2. Patients with COVID-19 may show increased levels of plasma pro-inflammatory cytokines that could be involved in the damage induced by virus [21].

This report does not raise any new issues to COVID-related GBS, but reinforces the concept of para-infectious profile instead of the classic post-infectious one and brings up issues related to care of patients during the pandemic.

Management difficulties in patients with COVID-19 related GBS concerned mainly the possibility to carry out the necessary diagnostic tests. Although we know that clinical features are the main criteria in GBS diagnosis [10], both CSF analysis and EDX study are important diagnostic supports.

Fifty percent of our COVID-19 related GBS patients have not all diagnostic tests performed; in one patient LP was not made due to anticoagulation for pulmonary embolism treatment, in the other two cases, the EDX study were not carried out due to the extreme circumstances in the Hospitals at the peak of this pandemic [5]. Despite the fact that some patients have been studied incompletely, the differential diagnosis with critical illness polyneuropathy wasn't considered for several reasons: a previous infectious disease was reported in all patients; patient 1 presented demyelinating features in the EDX study; the two patients (2,4) without EDX study had increased protein on CSF; patient 3 had cranial nerves dysfunction and about the two patients classified as AMSAN (5,6) one had increased protein on CSF and the sensory-motor axonal damage was spread homogeneously to the 4 limbs in both patients while in critical illness disease it is length dependent, more severe to lower limbs and with greater motor involvement [22].

In one case we had a diagnostic and therapeutic delay of 13 days from neurological onset, due to the presence of main respiratory features.

The second group of patients includes nine not-COVID-19 related GBS. We focused on management pitfalls.

In one patient LP and anti-ganglioside antibodies could not be performed and one subject got SARS-COV-2 infection during hospitalization.

The main problem was diagnostic delay. In three out of nine patients, already hospitalized for other reasons, the first neurological observation was achieved after a mean of 33,6 days. Moreover, five patients went to ER after an average of 30 days since the onset of neurological symptoms because of fear of contagion.

Diagnostic delay involves therapeutic delay, which may affect final outcome.

In four of the nine patients GBS-DS was stable after an average of 20 days from IVIG ending. In three patients with a GBS-DS ≥ 3 , FU was too short to evaluate outcome (< 5 days), however their current neurological features can likely be considered as an outcome, since early IG treatment is recommended within 15 days of the onset of symptoms [23].

As the COVID-19 pandemic focuses medical attention on treating acute patients and protecting others from infection, radical transformation of the health care system was realized, carrying the risk of reducing quality of care for other diseases. This has been already observed in patients with heart diseases or cancer [24], and our case series is in line with this.

Therapeutic choices have been affected by pandemic, too. Some authors reported a patient with a cranial polyneuritis discharged home

and treated symptomatically with acetaminophen and telemedicine monitoring due to a complete Hospital saturation with COVID-19 patients [5].

All our patients were treated with IVIG rather than PEX. The same therapeutic choice in the two groups depends on different reasons: in COVID-19 related GBS main reason was to avoid an invasive procedure in infected patients, in the others probably to reduce the numbers of possible contacts both for patient and healthcare workers. In current literature only one patient performed PEX [6].

Although IVIG and PEX carry the same efficacy in GBS, PEX can be considered the gold standard for GBS, due to its speed of action [25].

Due to the fact that the follow-up is too short, we cannot compare the outcome of the two groups of patients but we can certainly state that they shared the same management pitfalls.

In conclusion, not only SARS-COV-2 infection can cause GBS, but it can also indirectly, due to effects of pandemic on the health organization, affect the outcome of patients with not-COVID-19 related GBS. Scientific societies and public health organizers should focus and cooperate on this important topic, for further planning of health system network, in view of this not yet resolved pandemic, or other possible future pandemic emergencies.

Declaration of Competing Interest

The authors report no conflict of interest.

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