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ORIGINAL ARTICLE

SARS-CoV-2-associated Guillain–Barré syndrome in four patients: what do we know about pathophysiology?

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Abstract

Background A growing number of Guillain–Barré syndrome (GBS) and Miller Fisher Syndrome (MFS) cases following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are reported. Nevertheless, this association is still debated, and pathophysiology remains unclear.

Methods Between April and December 2020, in three hospitals located in Brussels, Belgium, we examined four patients with GBS following SARS-CoV-2 infection.

Results Neurological onset occurred 3 weeks after SARS-CoV-2 symptoms in all patients. Three patients presented with acute inflammatory demyelinating polyneuropathy (AIDP) and had negative anti-ganglioside testing: two suffered from a severe SARS-CoV-2 infection and had good clinical outcome after intravenous immunoglobulin (IVIG) treatment; one with mild SARS-CoV-2 infection had spontaneously favorable evolution without treatment. The fourth patient had critical SARS-CoV-2 infection and presented acute motor and sensory axonal neuropathy (AMSAN) with clinical features highly suggestive of brainstem involvement, as well as positive anti-ganglioside antibodies (anti-GD1b IgG) and had partial improvement after IVIG.

Conclusions We report four cases of SARS-CoV-2-associated GBS. The interval of 3 weeks between SARS-CoV-2 symptoms and neurological onset, the clinical improvement after IVIG administration, and the presence of positive anti-ganglioside antibodies in one patient further support the hypothesis of an immune-mediated post-infectious process. Systematic extensive antibody testing might help for a better understanding of physiopathology.

Keywords Guillain–Barré syndrome · SARS-CoV-2 · Case series · Anti-gangliosides · Anti-GD1b · Pathophysiology

Introduction

Since the beginning of the COVID-19 outbreak, there has been a growing number of reports of Guillain–Barré syndrome (GBS) and Miller Fisher Syndrome (MFS) following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, suggesting a post-infectious immune-mediated process [1]. However, the association between SARS-CoV-2 and GBS is still debated since a recent epidemiological study found no association between both entities [2]. In addition, pathophysiology remains unclear as there is no clear evidence of structural homology between SARS-CoV-2 and nerve compounds to support a molecular mimicry mechanism. Moreover, anti-ganglioside antibodies, which play a central role in pathogenesis—at least in the axonal forms—of GBS, have only been reported in a few cases [3]. Although there is no direct homology between

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SARS-CoV-2 structure proteins and any axonal or myelin surface proteins, it has been suggested that SARS-CoV-2 binds to respiratory tract gangliosides through its spike protein. Cross-reactivity between epitopes on SARS-CoV-2 spike-bound gangliosides and surface peripheral nerve glycolipids is currently considered as a pathophysiological hypothesis [4].

Methods

Between April and December 2020, four patients with a diagnosis of GBS according to the Brighton criteria, occurring after SARS-CoV-2 infection, were examined at Cliniques universitaires Saint-Luc, Universitair Ziekenhuis Brussel and Cliniques de l'Europe—Saint-Michel, three hospitals located in Brussels, Belgium. A positive diagnosis of COVID-19 infection was established by SARS-CoV-2 PCR assay of nasopharyngeal swab. Anti-ganglioside antibodies were tested by enzyme-linked immunosorbent assay (ELISA) for IgG and IgM antibodies against single gangliosides GM1, GM2, GM3, GM4, GD1a, GD1b, GD2, GD3, GT1a, GT1b, GQ1b and anti-sulfatides. Clinical and ancillary test descriptions were retrieved by the authors, who examined the patients. Consent was obtained from each patient for publication.

Results

Clinical characteristics and laboratory findings of the four patients with SARS-CoV-2-associated GBS are detailed in Table 1. The electrodiagnosis (EDX) findings are detailed in the Supplementary Appendix (S1-S4).

All patients presented with sensorimotor symptoms and tendon areflexia about 3 weeks (20–24 days) after documented COVID-19 infection. SARS-CoV-2 infection was associated with a severe pulmonary disease in three of them. No other GBS triggering event was identified in all patients. CSF examinations revealed albuminocytologic dissociation in two patients (case1 and case2) and an increased albumin quotient in one (case4). Positive serum anti-GD1b antibodies were found in one patient (case4). The latter was the only patient showing brainstem involvement, with EDX (S4) compatible with an acute motor and sensory axonal neuropathy (AMSAN), and only partial clinical improvement after IVIG administration (2 g/kg for 5 days). This case was previously reported [5] but EDX was not available at that time. In the three other cases, the EDX (S1-S3) was consistent with acute inflammatory demyelinating polyneuropathy (AIDP) and no serum anti-ganglioside antibodies were detected. Two of the other patients (case1 and case2) presented severe SARS-CoV-2 infection and had good clinical outcome after IVIG treatment (2 g/kg for 5 days). The third other patient (case3) had mild SARS-CoV-2 infection and had spontaneously favorable evolution without treatment.

Discussion

We describe four cases of SARS-CoV-2-associated GBS, adding evidence to the probable association between these two entities. The lag time between COVID-19 infection and the neurological onset, the response to IVIG, and particularly the presence of anti-ganglioside antibodies in one patient are highly suggestive of a post-infectious immune-mediated mechanism.

Our patient with positive anti-ganglioside antibodies (anti-GD1b IgG) was the only one with brainstem involvement, suggestive of GBS/Bickerstaff brainstem encephalitis (BBE) overlap, and with electrophysiological features suggestive of AMSAN, a previously reported association [6]. The three other patients presented with AIDP and had negative anti-ganglioside screening. While our patient presented myoclonus limited to the palatal region, myoclonus has already been described in BBE [7]. Anti-GD1b have been described in the clinical spectrum of GBS—classically in acute sensory ataxic neuropathy (ASAN), but also in AMSAN—, MFS and BBE, and are associated with more severe disease and slower recovery [5, 8, 9]. Although, the 7-week delay of EDX raises the question of a probable critical illness polyneuropathy component—which is difficult to distinguish from an AMSAN—, the other features and the response to IVIG are in favor of a post-infectious immune-mediated process.

According to a recent review of the literature, anti-ganglioside antibodies in COVID-19-associated GBS were positive in only 5/36 patients (14%) [3]. Four new anti-ganglioside positive cases, including one of our patients, were identified reviewing the literature for this paper and are summarized in Table 2. In COVID-19 patients, anti-ganglioside antibodies were found not only in patients with GBS but also in patients with variable neurological presentations (cranial neuropathy with meningo-polyradiculitis, choreic movements, myelitis) [5, 8–10] which casts doubt on whether these are truly pathogenic in all cases. Interestingly, anti-ganglioside antibodies have been described in other neurological diseases besides the GBS/MFS/BBE spectrum, even though their clinical significance remains unsure [11]. On the other hand, the role of anti-ganglioside antibodies in the genesis of axonal subtypes of GBS after Campylobacter jejuni infection is well established, and associated with severe disability [12].

Prevalence of anti-ganglioside antibodies in GBS was, respectively, 31.7% and 50% in two large cohorts of, respectively, 306 and 119 patients [13, 14]. The current low rate of positive anti-ganglioside antibodies in

Table 1 Clinical characteristics and laboratory findings of four patients with SARS-CoV-2-associated Guillain–Barré syndrome

	Case 1	Case 2	Case 3	Case 4
Age, gender, origin	80, male, North African	57, female, Central African	22, Female, North African	62, Male, Caucasian
Comorbidities	Hypertension, polyneuropathy	None	None	Obesity, hypertension, smoker, throat cancer
Symptoms of COVID-19	Fever, cough, dyspnea, hyposmia, pulmonary embolism (severe disease)	Fever, headache, and myalgia, pulmonary embolism (severe disease)	Myalgia, asthenia, headache and anosmia (mild disease)	Fever, cough, and dyspnea with ARDS (critical disease)
SARS-CoV-2 PCR of *nasopharyngeal swabs*	Positive	Positive	Positive	Positive
Time to neurological symptoms onset (days)	24	21	20	21 (unclear because of prolonged sedation)
Neurological signs and symptoms	Tetraparesis (MRC 4/5 in the muscles of lower limbs and proximal upper limbs) Hyperesthesia and allodynia of lower limbs and of both hands, sensory ataxia of the four limbs Diffuse areflexia Peripheral facial palsy	Lower back pain Paraparesis (MRC 3/5 in lower limbs) Sciatalgia, aroparesthesia, decreased light touch and proprioception in the feet and fingertips Areflexia in lower limbs, hyporeflexia in upper limbs	Gait difficulties, distal weakness for dorsiflexion and toe extension (MRC 4/5) Paresthesia, decreased light touch and proprioception in the feet Areflexia in lower limbs	Flaccid tetraplegia Diffuse areflexia Altered consciousness Bilateral ophthalmoplegia, palatal myoclonus
EMG-NCS	(7 days after neurological onset) AIDP	(5 days after neurological onset) AIDP	(4 weeks days after neurological onset) AIDP	(7 weeks after admission) AMSAN
CSF findings	(8 days after neurological onset) Albuminocytologic dissociation (protein levels 0.89 g/L) Mirrored pattern oligoclonal bands	(5 days after neurological onset) Albuminocytologic dissociation (protein levels 1.11 g/L) Mirrored pattern oligoclonal bands	(7 weeks after neurological onset) Normal (protein levels 0.22 g/L) Mirrored pattern oligoclonal bands	(25 days after admission) Elevated albumin quotient (CSF/serum albumin 7.4) (protein levels 0.32 g/L) Mirrored pattern oligoclonal bands RT-PCR SARS-CoV-2 negative
Level of Brighton criteria	1	1	2	2
SARS-CoV-2 serologies	Not performed	IgG 69.5 UA/mL	IgG 38.8 UA/mL	IgG 56.5 UA/mL
Other infectious serologies	Not performed	HIV, syphilis, HCV, HBV, CMV, EBV, M. pneumoniae negative*	HIV, syphilis, CMV, EBV, M. pneumoniae negative*	HIV, syphilis, HCV, HBV, HSV, CMV, EBV, M. pneumoniae negative*
Anti-ganglioside antibodies	Negative	Negative	Negative	Anti-GD1b IgG (1:100)
MR imaging	Normal spine MRI	Not performed	Normal spine MRI	Normal cerebral MRI
Treatment (interval between neurological onset)	IVIG (8-day interval)	IVIG (5-day interval)	No treatment	IVIG (17-day interval after sedation withdrawal)
Outcome at 6 weeks	Full recovery to baseline *GBS disability score 0/6*	Able to walk without assistance *GBS disability score 2/6*	Decreased reflexes and light paresthesia *GBS disability score 1/6*	Partial improvement: proximal MRC 2/5; distal MRC 4/5 *GBS disability score 4/6*

**Campylobacter jejuni, HEV and Haemophilus influenzae* were not systematically tested. Nevertheless, there was no suggestive clinical context

Table 2 Anti-ganglioside antibodies in SARS-CoV-2-associated neurological syndromes

Authors	Neurological syndromes	Anti-ganglioside antibodies (titer)
Gutierrez [9]	MFS	GD1b (NA)
Lantos [10]	MFS	Asialo GM1 ("equivocal range")
Gigli [18]	GBS (AIDP)	GD1a (NA)
Chan [19]	GBS (EDX deferred)	GM2 (NA)
Dufour [3]	GBS (EDX deferred)	Asialo GM1 (1:76), GM1 (1:58), GD1A (1:76), GD1b (1:60), GQ1b (1:56)
Tatu [20]	GBS (AIDP)	GM1 (NA), GM2 (NA)
Masuccio [8]	GBS (AMAN) and myelitis	GD1b (NA)
Kopscik [21]	MFS	GQ1b (1:100)
Civardi [22]	GBS (AIDP)	GM1 (1:70), GD1a (1:72), GD1b (1:64)
Guilmot [5]	GBS (AMSAN) with brainstem involvement	GD1b (> 1:100)
Guilmot [5]	Cranial neuropathy with meningo-polyradiculitis	GD1b (> 1:100)
Guilmot [5]	Choreic movements	GD1b (> 1:100)

SARS-CoV-2-associated GBS could be underestimated due to lack of testing, or due to the fact that a majority of reported SARS-CoV-2-associated GBS are of the AIDP variant (48/62 [77.4%];40/75 [75%]) [1, 15], which is known to be less frequently associated with serum anti-ganglioside antibodies than the axonal forms [12, 13, 15–17]. Another explanation might be the presence of antibodies against untested gangliosides, ganglioside complexes or other more atypical antigens. Anti-ganglioside complex antibodies are difficult to detect and are not tested in routine clinical practice but can be useful in patient with negative antibodies against single gangliosides [18]. It may be hypothesized that the SARS-CoV-2 spike-bearing gangliosides could form a complexed neoantigen recognized by unidentified specific anti-complex antibodies. On the other hand, antibodies less typically associated with GBS could also have a pathophysiological role. Positive anti-CASPR2 antibodies have been reported in rare cases of GBS [9], and one patient suffering from an encephalitis following SARS-CoV-2 infection had positive anti-CASPR2 antibodies [5]. Currently, anti-CASPR2 antibodies are not routinely screened in GBS patients and might thus be underreported.

Finally, other mechanisms such as the 'cytokine storm' could hypothetically be involved in the pathogenesis of SARS-CoV-2-associated GBS, especially in the acute onset within days after onset of viral infection, since many of the released cytokines have been implicated in the pathogenesis of 'classical' GBS [19].

Conclusion

We report four cases of SARS-CoV-2-associated GBS. The interval of 3 weeks between SARS-CoV-2 symptoms and neurological onset, the favorable response to IVIG, and the positive anti-ganglioside in one patient further support the hypothesis of an immune-mediated post-infectious process. Further autoantibody testing (including anti-ganglioside, anti-neuronal antibodies like anti-CASPR2, or anti-complex antibodies) in SARS-CoV-2 patients exhibiting neurological symptoms could allow a better understanding of these probable immune-mediated post-infectious processes.

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Data availability MG had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All the procedures were performed in accordance with the institutional ethics committee and the Declaration of Helsinki.

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