

Possible association between Guillain-Barré syndrome and SARS-CoV-2 infection in children: A case report and literature review

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Abstract. Neurological manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been reported in adults and in children, varying from mild to more debilitating symptoms, including fatigue, headache and dizziness. A series of studies have revealed a possible association between Guillain-Barré syndrome (GBS), the most common cause of acute flaccid paralysis at all ages, and SARS-CoV-2 infection. Case reports of novel coronavirus disease 2019 (COVID-19)-associated GBS mainly include adult patients, while only a few pediatric cases have been reported. The present study describes a case of GBS in an Italian 9-year-old girl with previous SARS-CoV-2 infection as a possible trigger, and also conducts a literature review on pediatric COVID-19-associated GBS cases.

Introduction

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide since December 2019; overall, >280 million cases have been reported globally and the number of deaths exceeds 5 million (1).

Neurological manifestations of SARS-CoV-2 infection are common, varying from mild cases (including dysgeusia,

anorexia, olfactory dysfunction and nausea) to more debilitating symptoms, including fatigue, headache and dizziness. Severe diseases such as encephalitis and meningitis have also been reported as complications of novel coronavirus disease 2019 (COVID-19) (1). A series of studies (2-7) have also shown a possible association between Guillain-Barré syndrome (GBS), the most common cause of acute flaccid paralysis in all ages (8), and SARS-CoV-2 infection.

The incidence of GBS increases with age, peaking at 70-80 years old (4-5 cases/100,000 individuals). By contrast, it is a rare pathology at pediatric age, with an incidence of 0.62 cases/100,000 children aged 0-9 years, and 0.75/100,000 children aged 10-19 (9). GBS is usually triggered by common infections such as minor respiratory illnesses, gastrointestinal illnesses and immunizations. The pathogenesis of SARS-CoV-2-associated GBS remains under debate; several reports suggested a para-infectious etiology, while others suggest a classical immune-mediated post-infectious mechanism.

GBS may present in a number of clinical variants, ranging from the acute demyelinating inflammatory polyneuropathy (AIDP) to the acute motor axonal neuropathy (AMAN). Both are characterised by rapidly-progressing, ascending symmetrical weakness, with attenuation or loss of muscle proprioceptive reflexes.

Campylobacter plays a significant role among the infectious triggers, in particular for Miller Fisher Syndrome (MFS), the localized form of GBS characterized by ophthalmoplegia, ataxia, and areflexia. In the differential diagnosis of GBS, Borrelia, Citomegalovirus infection and rare cases of paraneoplastic isolated myelopathy must be excluded (10).

Among pediatric patients, 75% can no longer walk unaided in the acute phase, 30% are tetraparetic, 35-50% show cranial nerve involvement, and 15-20% have respiratory failure and/or autonomic dysfunction (9). Localised forms of GBS such as MFS and Chronic inflammatory demyelinating polyneuropathy (CIDP) are extremely rare in childhood (11).

Case reports of COVID-19-associated GBS mainly include adult patients, while only a few pediatric cases have been reported (12-25).

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Abbreviations: AIDP, acute inflammatory demyelinating polyradiculoneuropathy; AMAN, acute motor axonal neuropathy; COVID-19, novel coronavirus disease 2019; CSF, cerebrospinal fluid; GBS, Guillain-Barré syndrome; IVIG, intravenous immunoglobulin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; NCS, nerve conduction study; MRI, magnetic resonance imaging

Key words: coronavirus disease 2019, Guillain-Barré syndrome, intravenous immunoglobulin, children

Here we describe the case of a GBS in an Italian 9-year-old girl with previous SARS-CoV-2 infection as a possible trigger and we conduct a literature review on pediatric COVID-19-associated GBS cases.

Materials and methods

Infectious and immunological research kits. We used the following kits for the infectious and immunological tests carried out in our patient: PCR analysis on cerebrospinal fluid (CSF): BioFire® FilmArray® meningitis/encephalitis (ME) panel (BioFire Diagnostics, LLC); CMV PCR search on CSF: CMV ELITE MGB® Kit(ELITE InGenius® ELITechGroup); Campylobacter search on stools: culture on Biomerieux plates and identification with VITEK MS Maldi-Toff Biomerieux; Autoantibodies search on CSF: GanglioCombi™ ELISA (Buhlmann Laboratories AG); Paraneoplastic antibodies search on CSF: EUROLINE paraneoplastic neurological syndromes 12 Ag (IgG) (EUROIMMUN Medizinische Labordiagnostika AG); Viral serologies (SARS-CoV-2, CMV and EBV) on plasma: LIAISON SARS-CoV-2 S1/S2 IgG; CMV IgG and IgM; EBV IgG and IgM; DiaSorin

Magnetic resonance imaging (MRI) parameters. Philips Ingenia 1,5T; Spin-echo, Turbo Spin-Echo, Inversion Recovery, Gradient Echo, Echo Planar with T1, T2, DP weighted sequences, pre and post-contrast.

Literature review criteria. We systematically reviewed literature available on PubMed until November 2021 in order to find all pediatric cases of GBS associated with SARS-CoV-2 infection (3-17 years) reported as case report, meta-analysis, randomized controlled trial, review and systematic review. We only considered papers written in English.

The PubMed search string was: ('Coronavirus' OR 'Coronavirus disease' OR 'novel coronavirus' OR 'Severe acute respiratory syndrome coronavirus 2' OR 'COVID-19' OR 'nCoV 2019' OR 'SARS-CoV-2') AND ('Guillain-Barré syndrome' OR 'GBS' OR 'Miller Fisher syndrome' OR 'MFS' OR 'Miller Fisher-GBS overlap syndrome' OR 'MFS-GBS overlap syndrome' OR 'acute inflammatory demyelinating polyneuropathy' OR 'AIDP' OR 'acute motor axonal neuropathy' OR 'AMAN' OR 'acute motor sensory axonal neuropathy' OR 'AMSAN') AND ['Child'(Mesh) OR pediatric* OR children].

Reference lists of all articles were manually searched for cross-references and additional cases were identified from the references of the case reports.

We reviewed 41 articles, 14 of which were included. We have included only articles that reported original case reports involving pediatric subjects with a form of GBS associated with SARS-CoV-2 infection.

We excluded articles that repeated cases already included in our reviewed, those involving subjects aged >18, infections other than SARS-CoV-2, those written before 2020 and those not in English.

We obtained the full text of each case we included. Each article was selected and analysed for inclusion by two authors in parallel.

For each case, the following data were extracted by the two authors: Publication data: title and authors of the article, name

Table I. Cerebrospinal fluid analysis.

Parameter	Value
Chemical-physical analysis	
Appearance	Clear
Pressure	Normal
Glucose	52 mg/dl (S-glucose 92 mg/dl)
Total proteins	1.884 g/l (S-total proteins, 7.4 g/dl; S-albumine, 4.7 g/dl)
White blood cell	2/mm ³
Isoelectric focusing	Negative for intrathecal oligoclonal immunoglobulin G synthesis
Viral and microbial PCR searches	
Film array	
Escherichia coli K1	Negative
Haemophilus influenzae	Negative
Listeria monocytogenes	Negative
Neisseria meningitidis	Negative
Streptococcus agalactiae	Negative
Streptococcus pneumoniae	Negative
CMV	Negative
Human Herpesvirus 6	Negative
Human Parechovirus	Negative
Varicella zoster virus	Negative
Enterovirus	Negative
Herpes simplex virus 1	Negative
Herpes simplex virus 2	Negative
Cryptococcus neoformans/gattii	Negative
Single PCR	
CMV	Negative
SARS-CoV-2	Negative

CMV, cytomegalovirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

and year of the journal; patient information: age, gender, underlying clinical condition, medical history and SARS-CoV-2 exposure, signs and symptoms of GBS; and diagnostic tests for SARS-CoV-2 infection and for GBS, treatment type and duration, outcome.

Case description. At the end of June 2021, a 9-year-old girl presented to the pediatric emergency department of the Chivasso Civic Hospital for progressive weakness and gait instability over the last month. She claimed no infectious or febrile episodes in the last months, no COVID-19-contacts. Her family history was negative for autoimmune or neurological disease.

General examination showed good general condition, T 36.5°C, bilateral inferior limb weakness with gait instability, altered sensitivity and complete absence of the patellar

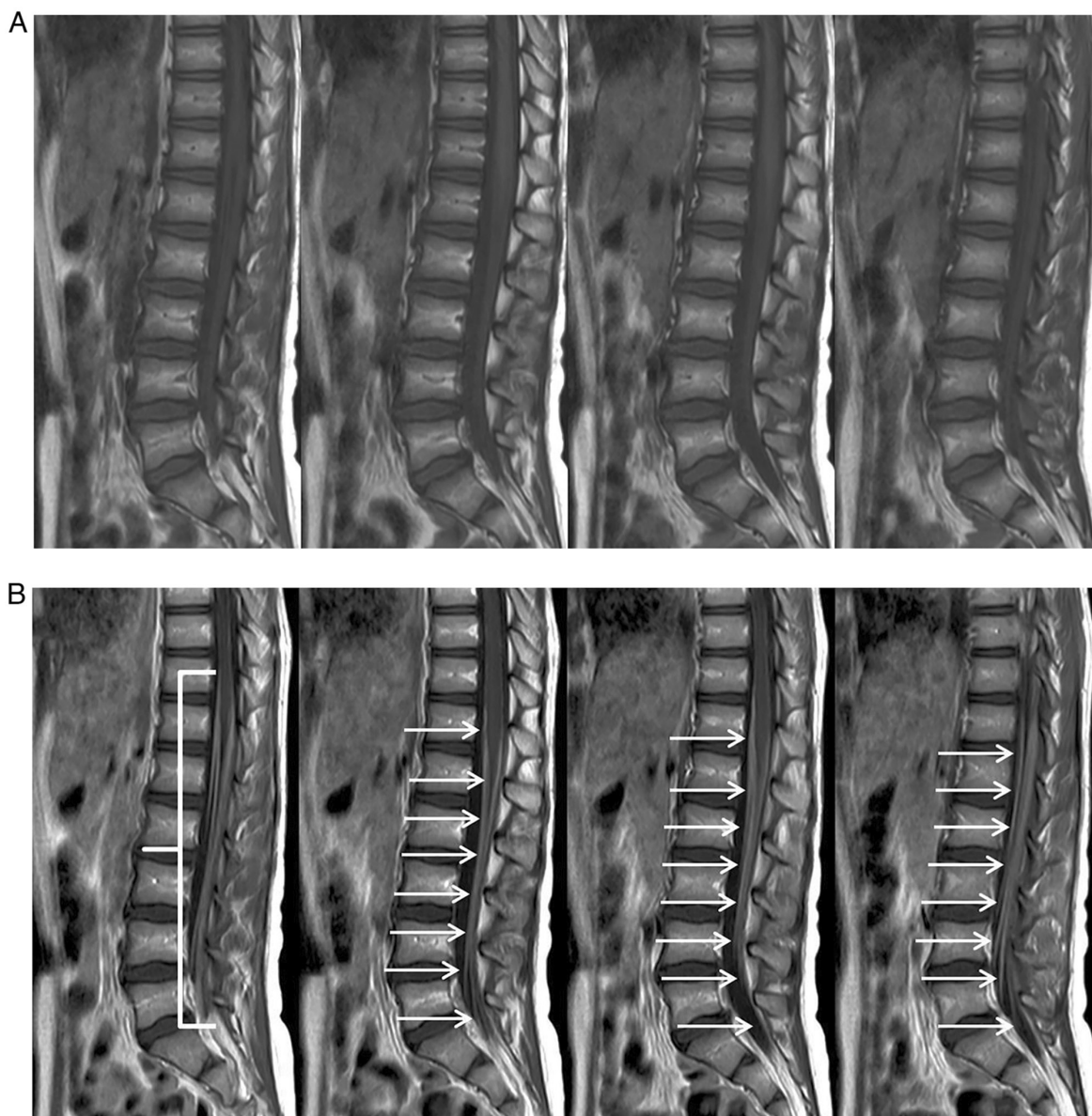


Figure 1. Sagittal T1w turbo spin echo (A) pre- and (B) post-contrast magnetic resonance imaging. The marked contrast enhancement of cauda equina roots, suggestive of Guillain-Barré syndrome, is indicated by the arrows in (B).

reflexes. Cranial nerves examination was normal, and she showed no difficulties in breathing and swallowing.

Lumbar puncture showed increased protein level with normal cell count (CSF appearance: clear; pressure: normal, glucose: 52 mg/dl; proteins 1.884 g/l, WBC: 2/mm³). CSF isoelectric focusing was negative for intrathecal oligoclonal immunoglobulin G synthesis (Table I).

Cranial and spinal MRI (Philips Ingenia 1.5T; Spin-echo, Turbo Spin-Echo, Inversion Recovery, Gradient Echo, Echo Planar with T1, T2, DP weighted sequences, pre and post-contrast) showed marked enhancement of cauda equina roots after contrast injection, both in the sagittal (Fig. 1) and axial (Fig. 2) views, according to the clinical hypothesis of Guillain-Barré polyradiculoneuropathy.

Nerve conduction study (NCS) pattern was consistent with acute inflammatory demyelinating polyradiculoneuropathy of moderate/marked degree in the lower limbs and of a more modest degree in the upper limbs.

A panel for CSF paraneoplastic and autoimmune antibodies was negative, in particular we excluded the presence of IgG anti-GM1 and anti-GQ1b antibodies, respectively frequently described in AMAN and MFS.

Molecular rhino-pharyngeal swab for SARS-CoV-2 was negative. Extensive virological and microbiological PCR searches on CSF, including SARS-CoV-2, and *Campylobacter* search on stools were negative. Epstein Barr Virus, Cytomegalovirus and *Borrelia* serology were negative, while COVID-19 serology was positive (45.2 AU/ml, nv<12.0) (Table II). We did not perform specific test for Influenza virus for the absence of suggestive symptoms (no fever, headache, dizziness, malaise, rhinitis nor cough) and epidemiological data to support this suspect (<https://www.epicentro.iss.it/influenza/flunews>).

The girl was initially treated with two courses of intravenous immunoglobulins (IVIg, 2 g/kg per time, repeated after 7 days) with mild improvement of the clinical picture. She was discharged after 15 days of hospitalization.

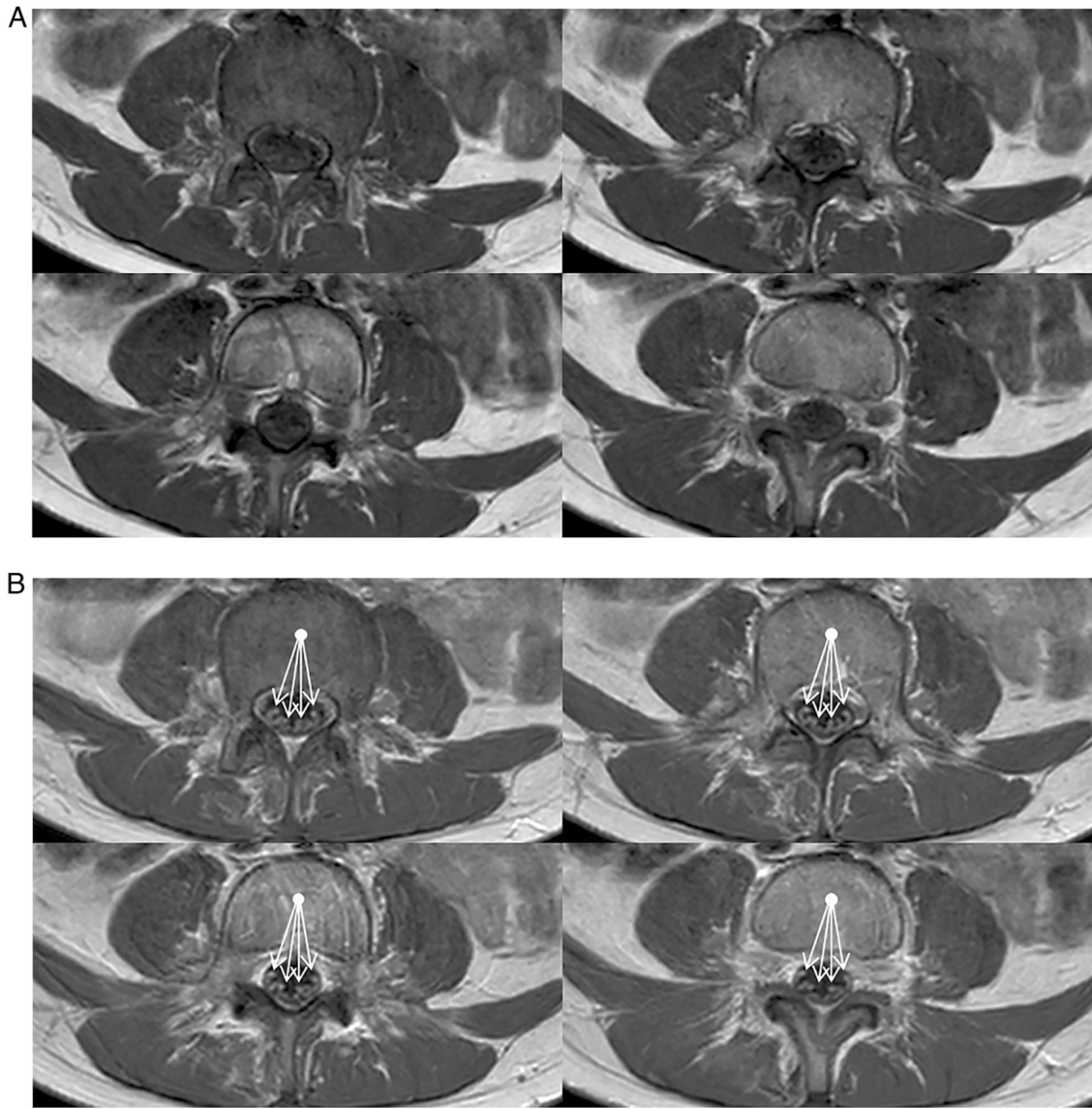


Figure 2. Axial T1w turbo spin echo (A) pre- and (B) post-contrast magnetic resonance imaging showing marked contrast enhancement of cauda equina roots, suggestive of Guillain-Barré syndrome, is indicated by the arrows in (B).

Two months later, shortly after summer holidays, she experienced a mild recrudescence of gait instability and ataxia with NCS worsening, and a third course of IVIG was administered.

The girl is now on strict neurological follow up and undergoes regular physiotherapy. She underwent the last neuropsychiatric evaluation in February 2022. Motor and sensory deficits (hypotonia and hyporeflexia) persisted mainly in the lower limbs, despite the slight improvement. There was no evidence of deficits in the cranial nerves. Given the slow clinical improvement, an additional course of IV immunoglobulin will be given over the next few weeks.

Discussion

Clinical description of the 19 pediatric cases is detailed in Table III. Our case is reported as the 20th.

The GBS reported cases (12-25) come from Africa (Morocco, Tanzania), Asia (Saudi Arabia, India, Iran), South

America (Brasil), North America (USA). The case we describe is the first from Europe.

Past history showed a recent (1 week to 1 month before the onset of neurological symptoms) infection suggestive for COVID-19, or a proven exposure to SARS-CoV-2, in 16/20 children. 17 children were tested for SARS-CoV-2 (antigenic or molecular swab) on admission, 9/17 were positive. Serology for SARS-CoV-2 was performed in 14/20 children, resulting positive in all cases. CSF PCR for SARS-CoV-2 was performed only in 4 cases, resulting positive in one child.

In our case, we found no history of respiratory or intestinal symptoms in the previous months. Other two children out of the reported cases were completely asymptomatic for COVID-19, had a negative SARS-CoV-2 swab on admission but were proven to have met the virus by serology (at that time, no vaccine against COVID-19 had been approved for pediatric age).

This finding is in line with COVID-19 presentation at pediatric age, often with an asymptomatic course (4).

Table II. CSF and serum autoantibodies screening and serologies for infectious diseases.

Parameter	Value
CSF paraneoplastic auto-antibodies	
Ab anti-YO	Negative
Ab anti-Hu	Negative
Ab anti-GAD65	Negative
Ab anti-CV2	Negative
Ab anti-Ri	Negative
Ab anti-MA2	Negative
Ab anti-recoverin	Negative
Ab anti-anfifisin	Negative
Ab anti-Tr	Negative
Ab anti-Sox1	Negative
Ab anti-Zic4	Negative
Ab anti-titin	Negative
Serum auto-antibodies	
s-Ab anti-GD1a ganglioside (IgG and IgM)	Negative
s-Ab anti-GD1b ganglioside (IgG and IgM)	Negative
s-Ab anti-GQ1b ganglioside (IgG and IgM)	Negative
s-Ab anti-GM1 ganglioside (IgG and IgM)	Negative
s-Ab anti-GM2 ganglioside (IgG and IgM)	Negative
s-Ab anti-MAG IgG	Negative
Serologies for infectious diseases	
s-anti-SARS-CoV2	
Sample 1	Positive
Sample 2	Positive
Hepatitis B Virus	Negative
Hepatitis C Virus	Negative
Human Immunodeficiency Viruses	Negative
Borrelia	Negative
Epstein Barr Virus	Negative
Cytomegalovirus	Negative

Ab, autoantibody; GAD, glutamic acid decarboxylase antibodies; MAG, myelin-associated glycoprotein; s-, serum.

Our patient did not receive recent vaccinations; she showed negativity of the common infectious researches on CSF and serum. In particular, Epstein Barr Virus, Cytomegalovirus and Borrelia serology were negative, as well as *Campylobacter* search on stools.

We did not perform specific test for Influenza virus, because the girl had no suggestive symptoms (no fever, headache, dizziness, malaise, rhinitis nor cough) in the previous months. Moreover, during winter 2020-2021, virtually no cases of Influenza were reported in our region, perhaps thanks to the prevention measures taken during the COVID pandemic (<https://www.epicentro.iss.it/influenza/flunews>).

In our girl, the only positive infective result was the presence of SARS-CoV-2 antibodies in serum.

At the time of her hospital admission, in Italy, 400,000-700,000 total children aged 0-12 years have experienced COVID-19 since the beginning of the current

pandemic, and no COVID-19 vaccine had been licensed for pediatric age. The positivity of our patient's SARS-CoV-2 serology test in such epidemiological frame prompts us to consider an asymptomatic COVID-19 infection as a possible trigger of GBS.

Regarding the diagnostic challenge, GBS remains a clinical diagnosis that can be sustained by laboratory and instrumental tests.

CSF analysis was reported in 14/20 children of the reported series, showing the classical pattern of albumin-cytologic dissociation in 13/14. CSF was normal in one case.

In our case, the CSF examination showed the typical increase of total proteins without cellular reaction. We excluded, by the GanglioCombi™ ELISA kit, the presence of anti-ganglioside antibodies, frequently described in AMAN (IgG anti-GM1 antibodies) and MFS (anti-GQ1b antibodies) (26). The panel for CSF paraneoplastic syndromes (EUROLINE paraneoplastic neurological syndromes 12 Ag) was negative too.

Central nervous system MRI was reported in 10/20 children, with different results: abnormal enhancement of the cauda equina nerve roots was the most common finding (6/10), 2/10 were negative, one case was compatible with acute disseminated encephalomyelitis (ADEM), one case with posterior reversible encephalopathy syndrome (PRES) and one with longitudinally extensive transverse myelitis associated.

Spinal MRI of our girl showed marked enhancement of cauda equina roots (Figs. 1 and 2).

NCS was performed in 17/20 children, showing alterations consistent with demyelinating polyneuropathy in all cases. In 6 of these children, the NCS pattern was compatible with the acute motor axonal form of GBS (AMAN). One case presented the rare Miller Fisher variant of GBS. In our case, NCS pattern was consistent with AIDP.

From 2020, several reports (2-6) have described the possible causal association between SARS-CoV-2 infection and GBS. A recent systematic review has reported 99 cases of GBS with confirmed COVID-19 infection, with an average age of 56.07 years (7).

A study in Northern Italy has suggested an increased incidence of GBS during the pandemic period (from 0.077/100,000/month to 0.202/100,000/month) (27). In contrast, other studies have reported a reduction in GBS incidence during the pandemic period, probably due to the influence of lockdown measures on conventional GBS-inducing pathogens (28).

A clear relationship between specific autoantibodies and the occurrence of GBS in patients with SARS-CoV-2 infection, such as that observed in GBS associated with *Campylobacter jejuni*, has not yet been shown (28).

The common absence of SARS-CoV-2 in cerebrospinal fluid reinforces the hypothesis of a post-infectious immune-mediated mechanism, rather than a para-infectious etiology (3). However, in one of the cases reviewed here, SARS-CoV-2 PCR was positive on CSF, indicating a possible direct action of the virus in the SNC system.

GBS associated with SARS-CoV-2 infections have shown a distribution of clinical variants and electrophysiological subtypes resembling those of classic GBS, with a higher prevalence of the classic sensorimotor form and the acute

Table III. Patient information, SARS-CoV-2 exposure, signs and symptoms of GBS, diagnostic tests for SARS-CoV-2 infection and for GBS, treatment type and duration, clinical outcome of 21 paediatric patients with GBS-associated with SARS-CoV-2 infection.

Author and Country	Case	Sex	Age years	Medical history	Past SARS-CoV-2 symptoms	Presenting symptoms and neurological onset	Sars-coV2 airways test/ serology/ PCR analysis on CSF	CSF analysis	MRI	Nerve conduction study	Specific therapy for GBS	Outcome	Final diagnosis (Refs.)
Manji HK, Tanzania	1	M	12	PH	Low grade fever and cough a week earlier	- 5 days of lower back pain, followed by acute progressive symmetric ascending quadriparesis with bilateral facial paresis Progression to altered level of consciousness (GCS 6/15), oxygen saturation of 88% - Decreased strength and muscle tone: MRC score: LE 1/5, UE 2/5 - Deep tendon reflexes absent in all four limbs	Positive/ NR/NR	NR	NR	NR	400 mg/kg of IVIG for 5 days	- PICU admission and mechanical ventilation - Neurological improvement after IVIG - Death from respiratory conditions	GBS with acute respiratory distress in a child with COVID-19 infection (12)
Curtis M, USA	1	M	8	PH	None	7 days of lower back pain, followed by bilateral lower extremity weakness, progression to paralysis and dyspnea (oxygen saturation of 88%) - Upper extremity weakness - Possible left sixth nerve palsy - Muscle strength: MRC score: UE 3/5, LE 2/5 - Deep tendon reflexes absent in all four limbs and abnormal proprioception of the distal LE	Positive/ positive/ negative	Albumino-cytological dissociation	Abnormal enhancement of the posterior nerve roots from the T11 level through the cauda equina	Consistent with AIDP	2 g/kg of IVIG over 48 h	- PICU admission, 5 days of mechanical ventilation - Improvement after IVIG - After 6 weeks, regained bilateral dorsiflexion and plantarflexion, the ability to sit independently, and was working on ambulating	GBS, AIDP form, in a child with COVID-19 infection (13)

Table III. Continued.

Author and Country	Case	Sex	Age years	Medical history	Past SARS-CoV-2 symptoms	Presenting symptoms and neurological onset	Sars-coV2 airways test/ serology/ PCR analysis on CSF	CSF analysis	MRI	Nerve conduction study	Specific therapy for GBS	Outcome	Final diagnosis (Refs.)
Khalifa M, Saudi Arabia	1	M	11	PH	Low grade fever 20 days earlier and persistent mild dry cough	- Acute onset of unsteady gait, followed by inability to walk - Symmetrical weakness of LE, MRC score 3/5, hypotonia No involvement of the UE - Lost ankle and knee reflexes - Impaired proprioception of both feet up to the mid-legs	Positive/ NR/NR	Albumino-cytological dissociation	Abnormal enhancement of the cauda equina nerve roots	Consistent with AIDP	1 g/kg/day of IVIG for 2 days	Gradual improvement of lower limb power, balanced gait, decreased numbness and normal proprioception after 14 days of admission	GBS, AIDP form, in a child with COVID-19 infection (14)
Mehra B, India	1	F	13	PH	Fever one month earlier	High-grade fever, cough, vomits, progressive body rash, evolution to shock: diagnosis of MIS-C - After 7 days: no motor response to painful stimuli, no spontaneous eye-opening, quadriparetic with facial weakness, poor diaphragm excursion, seizure: diagnosis of ADEM, and GBS	Negative/ positive/NR	Not performed	Consistent with ADEM	Consistent with AIDP	1 g/kg IVIG repeated after 7 days + 5 cycles of plasmapheresis 7 days + 5 cycles of plasmapheresis after 6 weeks of hospitalization	- PICU admission and 2 weeks of ventilation - Complete neurological recovery and discharged home after 6 weeks	MIS-C complicated with ADEM and GBS, AIDP form, in post Covid-19 infection (15)
Khera D, India	1	F	11	PH	History of fever without any other viral prodrome	- Acute onset of severe flaccid paralysis with respiratory failure on day 3, bowel and bladder incontinence - Hypotonia in all four limbs, bilateral MRC score: UE 4/5, LE 0/5 - No bowel and bladder sensation	Negative/ positive/NR	Albumino-cytological dissociation	Acute lesion in brain along with cauda equina nerve roots enhancement, consistent with GBS + LETM	AMAN	IVIG (dosage not available) + 5 cycles of plasmapheresis	- PICU admission and mechanical ventilation - After 6 weeks she walks independently with good bowel and bladder control and no neurological deficit	LETM and GBS, AMAN form, in post Covid-19 infection (16)

Table III. Continued.

Author and Country	Case	Sex	Age years	Medical history	Past SARS-CoV-2 symptoms	Presenting symptoms and neurological onset	Sars-coV2 airways test/ serology/ PCR analysis on CSF	CSF analysis	MRI	Nerve conduction study	Specific therapy for GBS	Outcome	Final diagnosis (Refs.)
El mezzoui S, Morocco	1	F	3	PH	Mild respiratory symptoms 2 weeks earlier	- Reflexes absent in ankle, knee and other superficial reflexes - Progressive symmetric and ascending quadriparesis - MRC score: UE4/5, LE 2/5 - Deep tendon reflexes absents - Decrease in sensitivity, swallowing inability	NR/positive/ NR	Albumino-cytological dissociation	Negative	NR	0.5 g/kg/day IVIG for 5 days	Clinical improvement, discharged after one month	GBS in post Covid-19 infection (17)
Araújo NM, Brasil	1	F	17	PH	Fever, abdominal pain, nausea and severe diarrhea 8 days earlier	- 2 days of severe low back followed by symmetrical flaccid tetraparesis, worse in the LE - Mild distal hypoparesis in the LE - Areflexia of patellar and Achilles tendons and hyporeflexia in the UE	Positive/ NR/Positive	Albumino-cytological dissociation	Abnormal enhancement of cervical and cauda equina nerve roots	Consistent with AIDP	2 g/kg IVIG	Clinical improvement	SARS-CoV-2 detection in cerebrospinal fluid in a child with GBS, AIDP form (18)
Das KY, India	1	M	7	PH	None	8 days of bilateral, symmetrical LE weakness and paresthesia - Areflexia, poor gag reflex, low respiratory rate requiring mechanical ventilation	Negative/ positive/NR	Albumino-cytological dissociation	NR	Suggestive of the inexcitable variant of GBS (AMAN)	IVIG, doses not reported	- PICU admission, mechanical ventilation - Extubated after 3 days - Clinical improvement	GBS (inexcitable variant, AMAN) in post Covid-19 infection (19)
Frank CHM, Brazil	1	M	15	PH	Frontal headaches, fever and sweating	Emetic episodes, weakness and pain in the LE, progression to the UE	Positive/ positive/ negative	Negative	Negative	Compatible with the AMAN variant of	400 mg/kg/day of IVIG for 5 days	- Clinical improvement, persistent weakness in the	GBS, AMAN form, in a child with COVID-19 (20)

Table III. Continued.

Author and Country	Case	Sex	Age years	Medical history	Past SARS-CoV-2 symptoms	Presenting symptoms and neurological onset	Sars-coV2 airways test/ serology/ PCR analysis on CSF	CSF analysis	MRI	Nerve conduction study	Specific therapy for GBS	Outcome	Final diagnosis (Refs.)
Paybast S, Iran	1	F	14	PH	Upper respiratory tract infection 3 weeks earlier	<ul style="list-style-type: none"> - Progressive symmetrical limb weakness (MRC score: UE 3/5, LE 2/5) - Absent deep tendon reflexes 	Positive/NR/ NR	Albumino-cytological dissociation	NR	Not performed	20 g/die IVIG for 5 days	- Complete recovery of the symptoms except for generalized hyporeflexia and decreased light touch sensation in distal limbs	Familial occurrence of Guillain-Barré syndrome in a child with COVID-19 infection (21)
Al Haboob AA, Saudi Arabia	1	M	11	PH	3 weeks of vomiting, abdominal pain, mild diarrhea and mild headache	<ul style="list-style-type: none"> - Lethargic, tachypnic, fatigued, drowsy, no fever, bilateral sixth nerve palsy and double vision on his lateral gaze; Miller-fisher variant of GBS 	Positive/NR/ NR	Albumino-cytological dissociation	Consistent with PRES	Abnormal	0.4 g/kg/day IVIG for 5 days	PICU admission and intubation. Discharged to go home with normal level of consciousness, cranial nerve palsy, normal muscle tone, grade 4 motor power, normal gag and cough reflexes	GBS, Miller Fischer variant, with PRES in association with COVID-19 infection (22)

Table III. Continued.

Author and Country	Case	Sex	Age years	Medical history	Past SARS-CoV-2 symptoms	Presenting symptoms and neurological onset	Sars-cov2 airways test/serology/PCR analysis on CSF	CSF analysis	MRI	Nerve conduction study	Specific therapy for GBS	Outcome	Final diagnosis (Refs.)
Akçay N, Turkey	1	M	6	PH	2 days of fever	- Symmetric ascending paralysis progressed over a 4 day course - Bilateral LE and UE flaccid weakness of I/5 with absent deep tendon reflexes - Severe respiratory muscle weakness requiring invasive mechanical ventilation	Positive/ NR/NR	Albumino-cytological dissociation	Contrast enhancement of cauda equina and nerve roots	Suggestive of AMAN	10 cycles of plasma-pheresis, followed by methyl-prednisolone (30 mg/kg/day for 5 days) and IVIG (2 g/kg/day, repeated after 14 days)	- PICU admission and intubation - On Day 60, discharged from the hospital with weakness (MRC score 2/5) in UE and LE - Discharged with home ventilation - His reflexes remained absent.	Axonal GBS (AMAN form) associated with SARS-CoV-2 infection (23)
LaRovere KL, USA	1	NR	6-12	PH	Within 1 month following SARS-CoV-2 exposure	- Classic neurological signs and symptoms of GBS	Negative/ Positive/ NR	NR	NR	Classic electro-physiologic features of GBS, AIDP form; one with AMAN form	NR	New deficits, required outpatient physical therapy	Guillain-Barré syndrome, 3 AIDP and 1 AMAN form (24)
	2	NR	6-12	PH			Positive/ Positive/ NR	NR	NR		NR	New deficits, required outpatient physical therapy.	
	3	NR	13-17	PH			Negative/ Positive/ NR	NR	NR		NR	New deficits, required outpatient physical therapy	
	4	NR	13-17	Underlying neurological disorder			Positive/ Positive/ NR	NR	NR		NR	Discharged home	
Sánchez-Morales AE, Mexico	1	M	9	GBS at age of 6	NR	- Pain in LE, ascendant weakness, hypotonia, diminished tendon reflexes	Negative/ positive/ NR	Albumino-cytological dissociation	NR	AIDP	NR	The patients recovered the ability to walk and run independently	Recurrent case of GBS, AIDP form, probable relationship with SARS-Cov2 (25)

Table III. Continued.

Author and Country	Case	Sex	Age years	Medical history	Past SARS-CoV-2 symptoms	Presenting symptoms and neurological onset	Sars-cov2 airways test/ serology/ PCR analysis on CSF	CSF analysis	MRI	Nerve conduction study	Specific therapy for GBS	Outcome	Final diagnosis (Refs.)
	2	M	14		Fever, rhinorrhea	- Paresthesia in feet, ascendant weakness, hypotonia, diminished tendon reflexes in LE	NR/ positive/ NR	Albumino-cytological dissociation	NR	AIDP	NR	The patients recovered the ability to walk and run independently	GBS, AIDP form, possible relationship with SARS-Cov2
	3	F	12	GBS 4 months earlier	NR	- Dysphonia, hypotonia, ascendant weakness, diminished tendon reflexes in UE, absent in LE	NR/ positive/ NR	Albumino-cytological dissociation	NR	AIDP	NR	The patients recovered the ability to walk and run independently	Recurrent case of GBS, AIDP form, possible relationship with SARS-Cov2
Mussinatto I, Italy	1	F	9		None	- 3 weeks of progressive ascending weakness with gait instability - Deep tendon reflexes absent in LE	Negative/ Positive/ Negative	Albumino-cytological dissociation	Abnormal enhancement of the cauda equina nerve roots	Consistent with AIDP	1 g/kg IVIG over 24 h, repeated after 7 days and after 2 months	Clinical improvement	GBS, AIDP, in post Covid-19 infection

NR, not reported; UE, upper extremities; LE, lower extremities; AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; PRES, posterior reversible encephalopathy syndrome; PH, previously healthy; LETM, longitudinally extensive transverse myelitis; GBS, Guillain-Barré syndrome; IVIG, intravenous immunoglobulin; PRES, posterior reversible encephalopathy syndrome; ADEM, acute disseminated encephalomyelitis; ADEM, acute disseminated encephalomyelitis; MRI, magnetic resonance imaging; GCS, Glasgow Coma Scale; MIS-C, multisystem inflammatory syndrome in children; MRC, Medical Research Council muscle strength grading; CSF, cerebrospinal fluid.

inflammatory demyelinating polyneuropathy, although rare variants such as Miller Fisher syndrome have also been reported (4).

Progressive symmetrical muscle weakness starting from lower limbs and marked reduction of deep tendon reflexes remain the hallmark of this syndrome, as reported in the totality of cases. In 3 cases, lower back pain preceded the onset of muscle weakness by a few days.

Altered sensitivity was expressly reported in 9/20 cases, described as altered proprioception, decreased perception of light touch, position, and vibration, paresthesia or bowel and bladder dysfunction.

A more severe course requiring mechanical ventilation was reported in 7 children. Involvement of the cranial nerves was described in 4 cases, all of which required mechanical ventilation.

The therapy of GBS is focused on supportive treatment. Treatment with IVIG is recommended in children and adolescents with severe GBS (9) and should preferably begin as soon as possible after diagnosis, within 4 weeks of the onset of symptoms, since early treatment positively affects prognosis (29).

Among the 19 pediatric cases described in Table III, the therapeutic management required pediatric intensive care unit admission for 7 children in the first phase of the disease.

All cases in which treatment was detailed (13/20) were treated with IVIG with different schedules (mainly 400 mg/kg for 5 days or 1 g/kg for 2 days). Three children required some sessions of plasma-exchange therapy.

The overall long-term prognosis for children with GBS is more favorable than that in adults, whereby the majority of children largely regain motor function. The AMAN variant has a more acute and severe course than AIDP, with a higher rate of ventilated patients and delayed recovery. Nonetheless, it has been repeatedly shown that the long-term prognosis for both variants is equally favorable in children (9). The SARS-CoV-2 associated form had a good prognosis in more than 70% of patients, especially after treatment with intravenous immunoglobulins (4): 19/20 children of the reported series were dismissed from the hospital with varying degrees of motor improvement. One child died from respiratory complications. In one case, a familial recurrence of GBS (father of the young girl) was reported.

In conclusion, the SARS-CoV-2 infection is proving capable of extremely varied clinical pictures at pediatric age, especially concerning neurological complications. Interestingly, a substantial similarity has been observed in clinical and laboratory presentation of COVID-19-associated GBS compared to the clinical pictures described before the characterization of this novel virus.

In the absence of universally accepted diagnostic criteria, the cases we reviewed and the one described above were attributed to COVID-19 because of the finding of a positive swab test on admission or a positive serology and the exclusion of other possible diagnoses, such as infections, autoimmune diseases (in particular with the exclusion of anti-ganglioside antibodies, frequently described in AMAN and MFS) and malignancies (paraneoplastic syndromes).

We suggest our findings need further research for confirmation, and the clinical suspicion of a possible association with SARS-CoV-2 infection must remain high to allow a greater

understanding of the disease, its prevention and therapy at pediatric age.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors substantially contributed to the present work, both in the clinical setting and in the elaboration of the present article. MI, MB, EG and FT were involved in the diagnosis of the patient through the acquisition, analysis and interpretation of data. IM, CB, MMC, AC, MI, MB and FT were involved in diagnosis and clinical management of the patient. IM and CB acquired, analyzed and interpreted the literature data. IM, CB and FST wrote and edited the manuscript. FT supervised the study. FT and IM confirm the authenticity of all data. All authors have read and approved the final manuscript, and agree to be accountable for all aspects of the work.

Ethics approval and consent to participate

The publication of the case report has been approved by the local ethics committee AOU San Luigi Gonzaga AA SS LL TO3-TO4-TO5 (approval no. 722; 17/01/2022).

Patient consent for publication

Written informed consent to publication has been obtained from the parents on behalf of the patient.

Competing interests

The authors declare that they have no competing interests.

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