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CASE REPORT

Post SARS-CoV-2 Guillain-Barré syndrome in a child: case report and review of the literature

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Abstract
Guillain-Barré syndrome has been defined as a post-infectious immune-mediated polyneuropathy. COVID-19 usually presents with respiratory symptoms but can less commonly present with extra-respiratory manifestations such as neurological symptoms. Few cases were published in the literature regarding post-COVID-19 infection Guillain-Barré in the pediatric age group. In this paper, we present a 13-year-old male with possible Guillain-Barré syndrome occurring 2 weeks after a presumed COVID-19 infection. We conducted a systematic review and searched for published pediatric cases until March 2022. We included 35 patients in 25 publications.

Keywords Guillain-Barré syndrome · COVID-19 · Children · SARS-CoV-2 · Neurological manifestations

Introduction

Coronavirus disease (COVID-19) is caused by the novel coronavirus strain severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Studies showed that children have a lower incidence rate and milder symptoms when compared to adults [1]. Children typically present with fever, cough, pharyngitis, and rhinorrhea [2]. Immunocompromised children present with severe disease [3]. COVID-19 can less commonly present with extra-respiratory manifestations. Multiple studies have linked COVID-19 in adults and children with multiple central and peripheral neurological manifestations; however, children might be more susceptible to post-COVID-19 neurological injury due to their developing nervous system with differential expression of cell receptor targets over time [4]. Furthermore, a recent entity was recognized in late April 2020, called multisystem inflammatory syndrome in children (MIS-C) [5]. MIS-C is a post-infectious syndrome or inflammatory reaction following asymptomatic or mildly symptomatic COVID-19 related to SARS-CoV-2 infection in children and adolescents [6]. Both COVID-19 infection and MIS-C can give rise to neurological manifestations. In both scenarios, they present as central involvement such as encephalopathy, ischemic and hemorrhagic stroke, seizure, and meningoencephalitis or peripheral involvement such as cranial nerve impairment, myopathic involvement, or Guillain-Barré syndrome [7, 8]. Few studies reported an association between COVID-19 and Guillain-Barré syndrome (GBS) in children (Table 1) [8–28]. We present the first Jordanian case report of a 13-year-old male with possible GBS occurring 2 weeks after presumed COVID-19 infection.

Case presentation

A previously healthy 13-year-old male had a history of fever, cough, and runny nose with a history of concurrent direct contact with COVID-19-positive family members who live in the same household and did not quarantine. There was no diarrhea nor preceding history of vaccination. A nasopharyngeal SARS-CoV-2 PCR test yielded a negative result. Two weeks later, he presented with history of pain in thighs and back followed by progressive ascending weakness and unsteady gait. He visited the emergency room but was reassured that his complaint is related to his grief after the death of his grandfather from COVID-19. One month later, he presented to our child neurology clinic due to the persistence of weakness manifested

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Table 1 Summary of clinical findings, investigations, diagnosis, treatment, and outcomes in reported cases of post-COVID-19 Guillain-Barré syndrome in children

	Case report/series	Gender	Age of onset	Time elapsed from the onset of COVID-19 symptoms to GBS clinical manifestations (weeks)	Presentation	Serology test of COVID-19	PCR	GBS variant	Treatment	Outcome
Guillain-Barré syndrome										
1	Our patient	M	13	2	Ascending weakness Progressive weakness	+	-	AIDP with secondary axonal loss	Steroids and 2 doses IVIG	Improving
2	Akçay et al. [9]	M	6	1	Ascending progressive weakness	NM	+	AMAN	Plasmapheresis, steroids, 2 doses IVIG	Improving
3	Araújo et al. [10]	F	17	1	Ascending progressive weakness	NM	+	AIDP	IVIG	Recovered
4	Blanco et al. [11]	F	6	1	Ascending progressive weakness	NM	+	AIDP	IVIG	Recovered
5	Curtis et al. [12]	M	8	NM	Ascending progressive weakness	+	+	AIDP	IVIG	Recovered
6	Das KY et al. [13]	M	7	NM	Ascending progressive weakness	+	-	Unexcitable variant	IVIG	Improving
7	Declusin et al. [14]	F	2	6	Left facial droop and abnormal gait	NM	+	AIDP with secondary axonal loss	Steroids, IVIG	Recovered
8	El Mezzeoui et al. [15]	F	3	2	Ascending progressive weakness	+	NM	NM	IVIG	Improving
9	Frank et al. [16]	M	15	2	Ascending progressive weakness	+	+	AMAN	Steroids and IVIG	Improving
10	Goel et al. [17]	M	3	2	Ascending progressive weakness	NM	+	NM	IVIG	Recovered
		M	3	NM	Inability to walk	+	NM	NM	2 doses IVIG	Improving
11	Kanou et al. [18]	F	9	Asymptomatic	Unbalanced gait, back pain, and lower limb weakness	NM	+	NM	Conservative gabapentin	Improving
12	Khalifa et al. [19]	M	11	3	Inability to walk with parasthesia	NM	+	AIDP	IVIG	Improving
13	Krishnakumar et al. [20]	M	Adolescent	2	Ascending progressive weakness	+	-	AMAN	NM	NM
14	LaRovere et al. [8]	M	School-aged	NM	NM	NM	NM	NM	NM	NM
		M	School-aged	NM	NM	NM	NM	NM	NM	NM
		M	Adolescent	NM	NM	NM	NM	NM	NM	NM
		M	Adolescent	NM	NM	NM	NM	NM	NM	NM
15	Manji et al. [21]	M	12	1	Ascending progressive weakness	NM	+	NM	IVIG	Died
16	Meshref et al. [22]	F	18	NM	Ascending progressive weakness	NM	+	AMAM	IVIG	Recovered
17	Mozhdehipanah et al. [23]	F	14	NM	Ascending progressive weakness	NM	+	ND	IVIG	Improving
18	Ray et al. [24]	M	NM	NM	NM	NM	NM	NM	NM	NM
		M	NM	NM	NM	NM	NM	NM	NM	NM
		F	NM	NM	NM	NM	NM	NM	NM	NM
		F	NM	NM	NM	NM	NM	NM	NM	NM
		F	NM	NM	NM	NM	NM	NM	NM	NM
19	Sánchez-Morales et al. [25]	M	9	NM	Ascending progressive weakness	+	-	AIDP	NM	Recovered
		M	14	NM	Ascending progressive weakness	+	ND	AIDP	NM	Recovered
		F	12	NM	Ascending progressive weakness	+	ND	AIDP	NM	Recovered
20	Sandoval et al. [26]	M	8	4	Ascending Progressive weakness, Ophthalmoparesis, facial diparesis	+	-	AMAN with multiple cranial nerve involvement	IVIG	Improving
21	Rafiei Tabatabaei et al. [27]	M	11	NM	Ascending progressive weakness	+	+	AMAN	IVIG	Recovered

Table 1 (continued)

	Case report/series	Gender	Age of onset	Time elapsed from the onset of COVID-19 symptoms to GBS clinical manifestations (weeks)	Presentation	Serology test of COVID-19	PCR	GBS variant	Treatment	Outcome
22	Terencio et al. [28]	F	16	NM	Ascending progressive weakness	NM	+	AIDP	IVIG	Improving
Miller Fisher syndrome										
23	Al Haboob et al. [29]	M	11	3	Diplopia, ataxic gait	NM	+	MFS with PRES	IVIG	Improving
24	Aljomah et al. [30]	M	9	1	Dysarthria and gait instability	NM	+	MFS	IVIG	Improving
25	Castro et al. [31]	F	11	2	Parasthesia, progressive muscle weakness, and dysphagia	NM	+	MFS	IVIG and steroids Carbamezapine	Improving
26	Raghunathan et al. [32]	M	7	2	Diplopia, nasal twang, drooling and unsteady gait	+	-	MFS	IVIG and plasmapheresis	Recovered

References are presented in alphabetic order

GBS Guillain-Barré syndrome, *ND* not done, *NL* normal, *NM* not mentioned, *IVIG* intravenous immunoglobulins, *AIDP* acute inflammatory demyelinating polyradiculoneuropathy, *AMAN* acute motor axonal neuropathy, *MFS* Miller Fisher Syndrome, *PRES* posterior reversible encephalopathy syndrome

by the inability to walk without support. Physical examination revealed stable vital signs and a normal general exam. His neurological examination revealed normal cranial nerves, normal tone in the upper limbs, and decreased tone in the lower limbs. Power was decreased in both upper and lower limbs but more marked distally. Power of the upper limbs proximally was 5/5, distally was 4/5. Power of the lower limbs proximally was 4/5, distally feet plantar flexion 4/5, and dorsiflexion 3/5. Deep tendon reflexes were absent in the upper and lower limbs. His gait was unsteady, and he was unable to walk without assistance. The sensation was intact.

Based on the history and examination, suspicion of a diagnosis of Guillain-Barré was raised.

The following investigations were done for him: complete blood count, C-reactive protein, and CK were normal. Serology test of SARS-CoV-2 showed positive IgG antibodies. The nerve conduction study showed demyelinating polyneuropathy with secondary axonal loss involving the upper and lower limbs. Cerebrospinal fluid (CSF) analysis revealed the following: cells: nil, protein 92, glucose 71. CSF SARS-CoV-2 RNA and oligoclonal bands in addition to serum antiganglioside antibody and anti Gq1b antibody were not tested. Antibodies for other viruses (adenovirus, EBV, CMV, influenza virus) and bacteria (*Campylobacter jejuni*, *Mycoplasma pneumoniae*) were not tested due to late diagnosis. Screening for autoimmune diseases was not done because the history, physical examination, and family history were not suggestive. In addition, neuroimaging including brain and spine MRI with contrast were normal, which could be attributable to delay of neuroimaging from the onset of symptoms and/or the use of steroids few days prior to neuroimaging. Based on the aforementioned clinical picture and investigations, we diagnosed the patient to have Guillain-Barré syndrome. We treated him with IVIG (dose 2 g/kg over 5 days) and methylprednisolone succinate (dose 1 g/day for 5 days), followed by oral prednisolone which was tapered over 1 month. Although corticosteroids are not indicated in GBS, however, we decided to give him both IVIG and methylprednisolone due to delayed diagnosis in addition to lack of guideline on how to treat patients with post-COVID-19 GBS and paucity of data in the literature. The patient's power improved; however, a second dose of IVIG was given 1 month later because of incomplete recovery and persistence of unsteady gait. Follow-up 1 month later revealed normalization of power and gait with absent deep tendon reflexes.

Discussion

We presented a 13-year-old child who developed Guillain-Barré syndrome 2 weeks after COVID-19 infection. The clinical picture and diagnostic workup along with the presence of IgG to SARS-CoV-2 supported the diagnosis of missed post-COVID-19 GBS. We carried out a literature

review and searched for published cases until March 2022. We used the keywords "COVID-19" or "SARS-CoV 2" together with "Guillain Barre Syndrome" or "GBS" or "Miller Fisher syndrome" or "Bickerstaff Encephalitis" and "Pediatrics" or "Children". We included 35 patients in 25 publications. Their findings are summarized in Table 1 [8–32] and Table 2. Studies included 35 children in total, of which 22 were males and 13 were females. Ages varied between 2 and 18 years. The most common presentation was ascending progressive weakness. The clinical picture of COVID-19-associated GBS in children seems to resemble that of classic GBS [33]. The time elapsed from the onset of COVID-19 symptoms to the clinical GBS manifestations varied between 1 and 6 weeks. Of the 35 patients, the nasopharyngeal SARS-CoV-2 PCR test was performed in 22 patients; 17 patients yielded positive results. In contrast, similar to our patient, 5 patients yielded negative results. This can be attributed to the false-negative potential associated with the nasopharyngeal SARS-CoV-2 PCR test [34]. A serology test of SARS-CoV-2 was done for 12 patients, and all had positive serology. Our patient was diagnosed with acute inflammatory demyelinating polyradiculoneuropathy (AIDP) variant; likewise 9 patients had the same diagnosis. On the other hand, 6 patients were diagnosed with acute motor axonal neuropathy (AMAN), 3 patients with Miller Fisher syndrome (MFS), 1 with MFS with posterior reversible encephalopathy syndrome (PRES), 1 had unexcitable variant, and none had Bickerstaff encephalitis. Nerve conduction study was not done in 1 patient.

In congruence with our patient, the diagnosis was missed in 2 children. The first case was a 15-year-old male, who presented initially to the medical care with history of headache and fever followed by limb weakness but was not diagnosed until 2 weeks later [16]. The second case was a 2-year-old female, who presented initially to the medical care with left facial droop and abnormal gait but was diagnosed 3 weeks later with GBS [14]. Treatment was mentioned for 22 patients, 19 patients received 1 dose of IVIG, 2 patients received 2 doses of IVIG, 4 patients received steroids followed by IVIG, and 2 underwent plasma exchange. In all the reported pediatric cases of Guillain-Barré syndrome following COVID-19 infection, prognosis was good, as most showed complete recovery or significant improvement. Two treatment modalities have been proved to be equally effective for the treatment of GBS, either IVIG or plasma exchange with around 80% of patients being able to walk without assistance in 6 months [33].

Coronavirus is a family of enveloped positive-stranded RNA viruses [35]. WHO's provisional case definition for the association of SARS-CoV-2 with neurological disease is probable when the onset of symptoms is within 6 weeks of suspected acute infection, RNA detected in any sample or antibody evidence of infection, and absence of other probable etiology on evaluation [36]. Studies of possible SARS-CoV-2 entry points showed that upon infection the virus attaches to the olfactory epithelium via the ACE-2 receptor; once the virus establishes entry inside the cell, it replicates [37]. Neurological manifestations of COVID-19 occur due to the presence of ACE-2 receptors in the nervous system and skeletal system. Hematogenous spread, disruption of the blood–brain barrier (BBB), and direct transmission through cranial nerves are all possible entry points to the central nervous system [37]. There are multiple possible means by which COVID-19 affects the nervous system: first, a secondary effect is associated with the vascular and prothrombotic effect of the viral infection on the CNS or PNS vasculature; second, the direct neurotropic or neuro-invasive effect of SARS-CoV-2; third, a secondary effect of the systemic inflammatory responses triggered by the viral infection; lastly, an immune-mediated parainfectious or post-infectious autoimmune effect in response to the viral infection (e.g., GBS) [37, 38].

The US Vaccine Adverse Event Reporting System (VAERS) in adults estimated a crude reporting rate of 1 case of GBS per

Table 2 Summary of the 35 patients with GBS that were reported in the literature

Category		Number of cases
Total number of patients		35
Gender	Males	22
	Females	13
Presentation	Progressive weakness	19
	Not mentioned	9
	Other	7
Nasopharyngeal SARS-CoV-2 PCR test	Positive	17
	Negative	5
	Not mentioned/not done	13
Serology test of SARS-CoV-2	Positive	12
	Negative	0
	Not done	23
GBS variant	AMAN	6
	AIDP	9
	MFS	3
	MFS with PRES	1
	Inexcitable	1
	Not mentioned/NCS not done	15
Treatment	IVIG one dose	19
	IVIG two doses	2
	Steroids	4
	Underwent plasma exchange	2
	Not mentioned	13

GBS Guillain-Barré syndrome, *PCR* polymerase chain reaction, *IVIG* intravenous immunoglobulins, *AIDP* acute inflammatory demyelinating polyradiculoneuropathy, *AMAN* acute motor axonal neuropathy, *MFS* Miller Fisher syndrome, *PRES* posterior reversible encephalopathy syndrome, *NCS* nerve conduction study

100,000 doses administered [39]. However, apart from two pediatric case reports [40, 41], the exact incidence of post-COVID-19 vaccine in the pediatric age group has not been studied. The first case is a 14-year-old child who developed GBS within 1 month of the administration of the second dose of the Pfizer-BioNTech COVID-19 vaccine [40]. The second case is a 16-year-old female who developed GBS 2 days following the Pfizer-BioNTech COVID-19 s dose vaccine [41].

Conclusion

Our case emphasizes the importance of having high index of suspicion of COVID-19-associated Guillain-Barré syndrome even in cases with negative PCR. Prompt treatment is associated with good outcome. Based on our literature review, it seems that post-COVID-19 GBS and the classical GBS are similar in clinical presentation and outcome.

Author contribution Mira Al Jaberi contributed to acquisition, analysis, and interpretation of data; drafted the manuscript; gave final approval; and accountable for all aspects of the work. Raghad Shihadat contributed to acquisition, analysis, and interpretation of data; drafted the manuscript; gave final approval; and accountable for all aspects of the work. Amira Masri substantially contributed to conception and design; contributed to acquisition, analysis, and interpretation of data; critical review of the manuscript; gave final approval; and accountable for all aspects of the work.

Declarations

Conflict of interest No funding was received for conducting this study. All authors declare no conflict of interest.

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