Case Report

Management of Guillain-Barre Syndrome with SARS-CoV-2 Infection in Pediatrics: A Case Series

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ABSTRACT

Guillain-Barre Syndrome (GBS) is an immune-mediated response that causes muscle and limb weakness. Coronavirus 2019 (COVID-19) is an infectious disease caused by the attack of Severe Acute Respiratory Syndrome Coronavirus 2 viruses (SARS-CoV-2) in which patients show symptoms such as fever, cough, and headache. We had studied five different cases of pediatric patients who came across GBS secondary to COVID-19. The analyzed cases represent patients between 2-16 years old who were admitted with complaints of muscle weakness, back pain, difficulty walking, and ascending paralysis with clinical findings of SARS-CoV-2 infection. Each patient's diagnosis was confirmed by a number of factors like Cerebrospinal fluid (CSF) analysis, nerve study and Magnetic Resonance Imaging (MRI) scan, and Intravenous Immunoglobulin (IVIG) therapy was given to stop the disease progression. The analysis shows that it is very crucial to carry out tests for COVID-19 before confirmation of the diagnosis because there are high chances of GBS even in case of sub-clinical COVID-19.

Keywords: SARS-CoV-2, Guillain-Barre syndrome, IVIG.

INTRODUCTION

COVID-19 has now become a pandemic with more than 102 million cases all over the world with fever, cough, malaise, pneumonia and respiratory syndrome as its clinical presentation. With the emergence of COVID-19, it has been observed that impairment of the nervous system is also linked with SARS-CoV-2 infection and its neurological manifestations includes meningitis, encephalitis, acute necrotizing hemorrhagic encephalopathy, acute disseminated encephalomyelitis and Guillain–Barre Syndrome (GBS).[1] GBS is a paralytic neuropathy which is led by various infections or by excitation of the immune system. The incidence rate of GBS was estimated as 0.6 per 1,00,000 per year in children and 2.7 per 1,00,000 per year in elderly and it is mainly seen in males rather than females.[2] It is a rare condition that arises when an immune response is produced towards a particular kind of viruses like SARS, Middle East Respiratory Syndrome (MERS), Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), Human Immuno deficiency Virus (HIV) along with Zika and Influenza virus and bacteria like *Campylobacter jejuni*. The common variants of GBS involve Acute Motor Axonal Neuropathy (AMAN), Acute Motor and Sensory Axonal Neuropathy (AMSAN) and Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP), other than this the rare variants of GBS include Miller Fisher Syndrome (MFS), paraparetic GBS, pharyngeal-cervical-brachial weakness, Bilateral Facial palsy with Paresthesia (BFP).[3] The immune responses showed molecular mimicry between lipo-oligosaccharide components of *Campylobacter jejuni* and Monosialotetrahexosyl (GM1) and N-Acetylgalactosaminyl (GD1a) ganglioside.[4] The symptoms observed in patients with GBS are upper and lower limb weakness, paresthesia and facial diplegia.[5] There is no specific treatment for GBS but full recovery can be achieved through

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aggressive supportive care like IVIG, physiotherapy and by providing symptomatic treatment.[6] Standard dose of IVIG for GBS was calculated as 2g/kg body weight but if it is not sufficient for some patients repeated dose of IVIG can be given because some patients might deteriorate even after completing the course of IVIG on standard dosing, therefore in order to achieve stabilization additional dosing of IVIG can be administered.[9]

This article mainly focuses on GBS associated with SARS-CoV-2 infection in pediatrics and in this case series, we have analyzed five case reports of pediatric patients who were admitted with neurological symptoms associated with either history or presence of SARS-CoV-2 infection.

CASE DESCRIPTIONS

Case Report 1

Nihal Akcay *et al.,* conducted a study in which a 6-year-old male patient was admitted to the pediatric intensive care unit with complaints of symmetric ascending paralysis progressing over four days along with fever from the past two days. Analysis of history revealed that the patient was diagnosed with COVID-19 which was communicated by an already infected person. The patient was conscious and oriented and his cranial nerves were undamaged, the bulbar muscles were strong but there was flaccid weakness of the upper and lower limbs, equally in capacitating the distal and proximal muscles. Patient was COVID positive up to day 14 post admission, an delevation in level of protein was seen after CSF analysis. Spinal magnetic resonance imaging showed enhancement of nerve roots and caudaequina which were indicative of GBS and nerve conduction study was indicating AMAN.

As management for GBS four sessions of plasma exchange therapy with 5% albumin replacement was given for 10 consecutive days along with plasma therapy, and methyl prednisolone (dose-30mg/kg/day) was administered for five days due to severe motor weakness, IVIG therapy (dose - 2g/kg/day) was started and continued for 14 days. The patient was discharged on day 60 with neck flexor and extensor muscles weakness and abnormal reflexes. The patient had persistent weakness and had an aggressive course of physiotherapy. The bridge connecting SARS-CoV-2 to GBS may be an immune mediated response to the nervous system, which might be most likely triggered by SARS-CoV-2virus.[1]

Case Report 2

Hussein Karim Manji *et al.,* published a report of a 12-year-old boy who was presented to the emergency department with the complaints of acute progressive symmetric ascending quadriparesis and bilateral facial nerve palsy. He had complained of low-grade fever and dry cough a week previously, which was treated by symptomatic treatment like expectorant and antipyretics, he also complained of back pain leading to weakness of both lower limbs five days previously.

The condition worsened over the days and he lost function of both the upper and lower limbs, the patient was barely conscious, his vital signs were abnormal and the physical examination showed strength and muscle tone of the lower limb as compared to the upper limb. Due to history of mild fever and dry cough, the patient was suspected of having COVID-19, for which nasopharyngeal polymerase chain reaction samples were sent in for testing, which turned out to be positive, and before the patient was transferred to the pediatric intensive care unit, the child lost the pulse and cardiopulmonary resuscitation was initiated, which returned child's pulse shortly after one cycle,

The diagnosis of GBS along with COVID-19 was made and immediately after making the diagnosis, the patient was administered with IVIG (dose-400mg/kg) for a period of five days and after completing the course, the weakness of the upper limb was excluded, and the tone and strength of the lower limbs gradually improved, but accidentally child self-extubated at night and quickly decompensated, as a result, the child went into cardiac arrest and resuscitation also failed, resulting in the death of the child.

Although there is no direct evidence of a link between GBS and SARS-CoV-2 virus, various reports from around the world have suggested that the pandemic virus may be the possible trigger, and much research suggests that COVID-19 is linked to various neurological manifestations.[5]

Case Report 3

Charmy Parikh *et al.,* presented a case of a 2.5-year-old girl who was admitted with complaints of lower limb weakness with difficulty walking for the past two days. The disease worsened due to progressive lower limb weakness along with an inability to walk and sit. For further evaluation, the patient was admitted to the pediatric intensive care unit, which revealed bilateral lower and upper limbs muscle tone was decreased and tendon reflexes were absent in the bilateral lower limbs. GBS was diagnosed on the basis of clinical features and laboratory examination, but taking into account the risk of COVID-19, a random antigen test and a real time polymerase chain

reaction test were performed, which turned out to be negative but IgG antibodies to SARS-CoV-2 virus came positive, and investigation from family explained that there was no history of COVID infection or vaccination. Therefore, all things considered, the confirmed diagnosis was GBS as evident for sub-clinical COVID-19.

IVIG therapy (dose-0.4g/kg/day) was started on day one of hospital admission as a treatment for GBS and continued for five days but since there was no resolution of symptoms, the patient was transferred to the general pediatric ward and physiotherapy was given to prevent limb atrophy and regain lost muscle strength. The patient was discharged after one week from the day of her admission with the recommendation of regular physiotherapy and follow up. In this report, the GBS was confirmed by CSF analysis and nerve conduction studies. The therapy provided did not reduce the symptoms but stopped the progression of the disease.

This study concluded that all GBS cases should be analyzed after testing for the SARS-CoV-2 virus in order to improve the therapeutic outcome and rule out COVID-19 as the cause of this disease.[6]

Case Report 4

Samir Kanou *et al.,* reported a case of a 9-year-old boy who was admitted to the pediatric ward with complaints of unsteadiness and back pain that had worsened over the past three weeks. No other autonomic symptoms were observed except that the child had difficulty walking and dressing. There was only one history of low Vitamin-D treated with cholecalciferol. Upon further evaluation, all neurologic findings were normal except for the child's inability to walk or jump properly, and the nasopharyngeal swab for COVID-19 was positive with no observable symptoms. Since there were only complaints of back pain and difficulty walking and standing, all possible causes were investigated and based on albuminocytological dissociation CSF, areflexia in both lower extremities, MRI and asymptomatic COVID-19, everything pointed to GBS secondary to COVID-19. Since the patient's degree of disability was 2-3 and his condition did not worsen after admission, he was not given IVIG, but instead received analgesic therapy for pre-existing back pain along with an increasing dose of gabapentin (dose-10mg/kg once daily) for day one which was increased to (10mg/kg twice daily) on day two and then (10mg/kg thrice daily) on day three and then stopped. At the same time, physical therapy was also given to quickly restore strength in both limbs, and the patient was discharged to continue therapy at home.

The patient's condition gradually improved, he could walk independently and his reflexes were also normal, but he still had not returned to baseline because he get tired very quickly, which was followed up in the clinic for a speedy recovery.

There may be multiple reasons for muscle weakness, but since all reports other than COVID-19 were normal, GBS has been implicated as its manifestation and in most of the cases, immunoglobulin therapy was found to be the only therapy that halted the progression of the disease. Since this patient was the first case who presented with GBS associated with COVID-19 with limited disability and self-improvement in nature, IVIG therapy was not indicated in this case.[7]

Case Report 5

Carlos Henrique Michiles Frank *et al.,* presented a case of a 15-year-old boy who presented with complaints of headache and retro-orbital pain along with fever and profuse sweating. In the coming days he suffered from nausea, pain in the lower limbs, which spread towards the upper limbs. With all these ailments, the patient was admitted to the local children's hospital and on admission and a rapid COVID-19 test was performed which came positive, symptomatic treatment was given including methylprednisolone, azithromycin and albendazole. The patient was transferred to another hospital for further treatment, where neurological examination revealed progressive symmetrical limb weakness and absent deep tendon reflexes. The nose and throat swab test using the polymerase chain reaction was positive for the SARS-CoV-2 virus. All neurological findings were normal, but the electroneurography study revealed that there was a large reduction in the amplitude of the nerve junction-muscle action potential and the absence of F-wave in the examined nerves. These abnormalities pointed towards AMAN and based on the clinical findings a diagnosis of COVID-19 related to GBS was made. After confirmed diagnosis, the patient was administered IVIG (dose - 400mg/kg/day) for the interval of five days. Despite the successful therapy, weakness in the upper and lower extremities persisted which was treated by physiotherapy. Usually, the diagnosis of GBS depends on CSF findings, medical history, and electrophysiological studies that help differentiate between variants of GBS. There are many possible neurological symptoms associated with COVID-19, and recently many studies also came on the same conclusion indicating GBS as a manifestation of COVID-19 responsible for neuropathy in pediatrics.[8]

DISCUSSION

Despite being a rare but life threatening disease, GBS has been identified as one of the neurological manifestation of the SARS-CoV-2 virus in pediatrics, but the incidence of GBS has no direct relationship with the severity of SARS infection in children.[8] In this case series, we analyzed that all the patients were admitted with complaints of neurological symptoms like upper and lower limb weakness, bilateral facial nerve palsy, lost tendon reflexes, inability to walk and pain in limbs which was diagnosed as GBS through CSF analysis, nerve conduction study and spinal MRI. In one of the cases there was reduction in amplitude of nerve junction and muscle action potential, lack of F-wave endured through electroneurography. Along with this all the patients either had history or presence of SARS-CoV-2 virus which was confirmed by real time polymerase chain reaction and random antigen test.[1,5-8] The most common variant of GBS which was indicated after carrying out nerve conduction study was AMAN,[1,8] and the immune mediated response generated due to molecular mimicry between gangliosides and SARS-CoV-2infection which may have led to GBS was treated through IVIG that has been proven effective in most of the cases though in some cases, elevation in the levels of standard dose of IVIG is needed in order to attain recovery and prevent prognosis of disease.[9] But till date, there is no solid evidence which can link GBS with COVID-19, so post pandemic it is suggested to confirm the traces of SARS virus in patients presented with neurological symptoms of GBS inspire they are assymptomatic[6] and IVIG as its actual management. Therefore, further studies are needed to understand the pathogenesis of GBS secondary to COVID-19 and efficacy of IVIG therapy to shed light on the model of GBS as a result of SARS-CoV-2 virus.

CONCLUSION

By analyzing quoted case reports, we came to the conclusion that COVID-19 can be responsible for many future complications, including GBS. So, presence of SARS-CoV-2 needs to be confirmed by performing a real time polymerase chain reaction and random antigen test as soon as possible, since presence of SARS-CoV-2 can provoke nerve damage, regardless of symptoms. By analyzing various cases of GBS we learnt that immunoglobulin therapy is indicated only when patient's condition keeps deteorating over the days even after administration of the symptomatic treatment.

Therefore, an association between COVID-19 and GBS has been proposed by the authors of summarized case reports, but still further more case studies are required to bridge the gap between association of SARS-CoV-2 virus with various neurological manifestations.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

GBS: Guillain - Barre Syndrome; **CSF:** Cerebrospinal Fluid; **IVIG:** Intravenous Immunoglobulin; **AMAN:** Acute Motor Axonal Neuropathy; **AMSAN:** Acute Motor and Sensory Axonal Neuropathy; **AIDP:** Acute Inflammatory Demyelinating Polyradiculoneuropathy; **MFS:** Miller Fisher Syndrome; **BFP:** Bilateral Facial palsy with Paresthesia; **MRI:** Magnetic Resonance Imaging; **SARS-CoV-2:** Severe Acute Respiratory Syndrome Coronavirus 2; **COVID-19:** Coronavirus 2019; **MERS:** Middle East Respiratory Syndrome; **CMV:** Cytomegalovirus; **EBV:** Epstein-BarrVirus; **HIV:** Human Immuno deficiency Virus; **GM1:** Monosialotetrahexosyl; **GD1a:** N-Acetylgalactosaminyl.

SUMMARY

Admitted paediatric patients mentioned in the above case reports have shown close association between SARS-CoV-2 virus and GBS, IVIG being the only effective therapy to prevent further prognosis of the disease.

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