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Case Report

Guillain-Barré syndrome in a child with COVID-19 associated multi-system inflammatory syndrome

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ABSTRACT

Multi-system inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 is a new entity affecting a small percentage of children during the COVID-19 pandemic. This usually presents with multi-organ dysfunction, predominantly affecting cardiovascular, muco-cutaneous, and gastrointestinal systems. Till now, neurological manifestations as a part of this spectrum, such as, encephalopathy, inflammatory CNS syndromes, cerebrovascular disease, and Guillain-Barré syndrome (GBS), have been well reported in adults, but there is a paucity of data from the paediatric age group. Here, we present a case of a 6-year-old girl who presented to us with progressive, bilaterally symmetrical ascending weakness of lower limbs followed by upper limbs along with drooling of saliva and dyspnea. Nerve conduction studies showed motor axonal neuropathy suggestive of GBS and child was treated accordingly with intravenous immunoglobulin. On 4th day of admission, the child developed high grade fever spikes, hypotension and diarrhoea. Hence, worked up for MIS-C which revealed elevated inflammatory markers with positive SARS-CoV-19 IgM, IgG antibodies. The diagnosis was hence revised to GBS with MIS-C, the child was then started on methylprednisolone following which the child showed both clinical and biochemical improvement and was then discharged. A high index of suspicion for the possibility of MIS-C should be kept in mind in the present pandemic times, as the immune-mediated damages in MIS-C are potentially treatable with a timely institution of intensive care measures along with the use of steroids, IV-Ig, and plasmapheresis.

Keywords: GBS, Intravenous immunoglobulin, MIS-C, Steroids, Plasmapheresis

INTRODUCTION

Guillain-Barre syndrome (GBS) is an autoimmune disorder where the immune system attacks the peripheral nerves through the mechanism of molecular mimicry. GBS is typically preceded by a viral or bacterial illness. The pathogenesis of GBS is believed to be through an antecedent infection that leads to an immune response that cross-reacts with peripheral nerves through a process called molecular mimicry.

Many viral illnesses have been hypothesised to be associated with the development of GBS, including the novel COVID-19. Since the identification of SARS-CoV-2 or COVID-19 in Wuhan, several case reports have proposed a possible association between GBS and COVID-19. MIS-C associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a new entity affecting a small percentage of children during the coronavirus disease 2019 (COVID-19) pandemic.

MIS-C is a hyper inflammatory syndrome usually presents with multi-organ dysfunction. The common systems that are predominantly affected are cardiovascular, muco-cutaneous, and gastrointestinal systems. However, severe neurological manifestations as

a part of this spectrum have hardly been reported till now in children.[1]

Neurological manifestations as a part of this spectrum include a wide range of manifestations such as, encephalopathy, inflammatory CNS syndromes, cerebrovascular disease, and GBS. There have been multiple well reported associations with SARS-CoV-2 in adults, but there is a paucity of data from the paediatric age group. The proportion of infections leading to neurological disease will probably remain small in children, but these patients might be left with severe neurological sequelae and hence it's very important for us to understand the etiopathogenesis, epidemiology, the clinical course of MIS-C and its temporal association with coronavirus disease 2019 (COVID-19), given the clinical and public health implications of this syndrome including the prevention of the various neurological sequelae of the disease.[2]

The prevalence and association of GBS following COVID-19 infection require further research to understand the short and long-term neurological effects of COVID-19, as well as the management of these various neurological manifestations.

CASE REPORT

Here, we present a case report of a six-year-old girl hailing from Siddalingapura village, Mysore district, Karnataka who was first born to a non-consanguineously married couple, who presented to us with progressive, bilaterally symmetrical ascending weakness of lower limbs.

Over the next two days, her lower limb weakness worsened and she also developed weakness of the upper limbs. Child also had dyspnea and drooling of saliva one day prior to admission.

Child did not have a history of urinary or faecal incontinence. The child also had a past history of low-grade fever three weeks ago and it apparently subsided in two days. There was no history of any recent febrile or respiratory illnesses in the family or any contact with a COVID case. Child was a developmentally normal child.

At presentation, child was irritable, anxious, but was oriented. Child was dyspneic, only able to speak 2-3 words at a time, had a single breath count of 5 at admission. Cranial nerves were intact except IX and X (gag reflex absent). Motor examination revealed hypotonia with decreased power (with 2/5 in upper limbs and 1/5 in lower limbs bilaterally) and absent deep tendon reflexes with bilaterally mute plantar reflex.

Child was initially taken to a private hospital, where child was provisionally diagnosed as a case of GBS and was started on intravenous immunoglobulin. Cerebrospinal fluid analysis done outside, which was normal (Table 1).

Table 1: CSF analysis.

CSF analysis	Results
Protein	51 mg/dl
Sugar	76 mg/dl
Cell count	Nil
Gram's stain	Negative
Z-n stain	Negative
CSF culture and sensitivity	No growth

At our hospital, Nerve conduction studies were done and revealed features of suggestive of severe motor axonal polyradiculoneuropathy-that is suggestive of GBS and was continued on intravenous immunoglobulin at 2 g/kg.

On 4th day of admission, the child developed high grade fever spikes, hypotension and diarrhoea. Hence worked up for MIS-C which revealed elevated inflammatory markers with leucocytosis (Table 2).

Table 2: Inflammatory markers.

Markers	Results
LDH	198 U/L
Serum ferritin	365 ng/ml
C-reactive protein	Positive
ESR	117 mm/HR

Child was also positive for SARS-CoV 19 IgM, IgG antibodies. Electrolytes, hepatic function were normal. Blood, urine, stool cultures were negative. 2D echo was done to rule out cardiac involvement, which revealed a normal study.

The child had met the Centre for Disease Control and Prevention criteria for MIS-C and hence the diagnosis was revised to GBS with MIS-C. The child was then started on methylprednisolone at 10 mg/kg for three days, following which the child showed both clinical and biochemical improvement and was then started on oral prednisolone. Child was slowly started on feeds and also started on physiotherapy.

Child improved clinically, with upper extremity strength of 3/5 and lower extremity of 2/5 at the time of discharge. Now, child continues to demonstrate slow improvement, is able to sit, and walks with 2-person assistance.

DISCUSSION

The organisms involved in the aetiology of axonal and demyelinating subtypes of GBS include *Campylobacter jejuni*, Cytomegalovirus, Epstein-Barr virus, influenza A virus, *Haemophilus influenzae*, and *Mycoplasma pneumoniae*. Predominantly, *Campylobacter jejuni* is the most common organism that causes GBS. Off late, several types of coronaviruses (SARS-CoV and MERS) and Zika virus have also been added to with wide list of organisms associated with GBS.

There are several proposed mechanisms on how corona viruses cause the wide spectrum of the neurological manifestations that have been reported. It all begins with coronavirus affecting the genetically predisposed individuals. Following which these genetically predisposed individuals acquire an infection with the above-mentioned organisms. The development of neurological symptoms take place in a time interval after a preceding infection, which is the classical phenotype of GBS. After the infection with COVID-19, the onset of the neurological symptoms related to GBS was found to be about 1 to 4 weeks.[4]

Coronaviruses are thought to cause GBS in certain genetically predisposed patients either directly through neuro-invasive mechanism/inflammatory mechanism. The neuro-invasive mechanism functions with the help of ACE2 receptors. These receptors are located in various regions of the body, like nasal and oral mucosa, neurons, glial cells, and blood vessels of central nervous system. The other mechanism is inflammatory mechanism that acts indirectly through the response of immune system.[3]

The main culprit in the pathogenesis of corona virus attacking the neurological system and hence causing GBS lies in the concept of "molecular mimicry". This occurs between the epitopes of SARS-CoV2 and the ganglioside antibodies that are eventually produced against the virus. This process acts through various T cell-B cell interactions. Due to similarity in the epitopes of SARS-Cov-2 and gangliosides antibodies formed, they may bind the gangliosides located on the peripheral neurons. This likeness has been termed "molecular mimicry". This molecular mimicry is defined as the theoretical possibility that sequence similarities between foreign and self-peptides lead to the cross-activation of auto-reactive B cell or T cell by pathogen-derived peptides.[4]

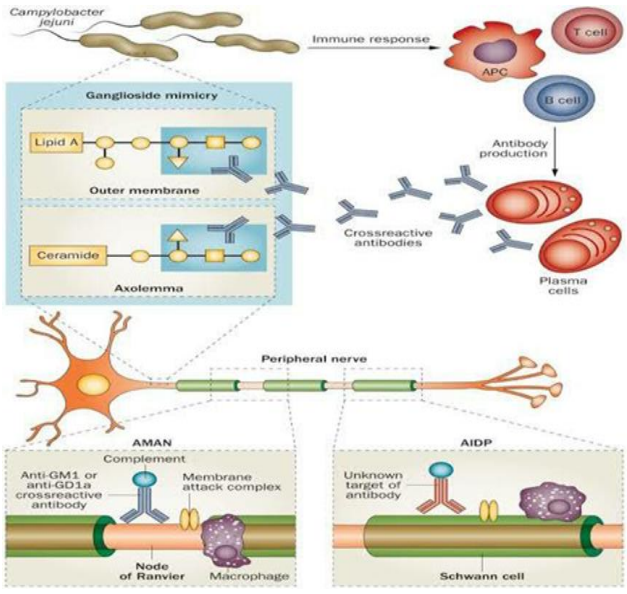

Figure 1: Immunopathogenesis of GBS: molecular mimicry and anti-ganglioside antibodies.[11]

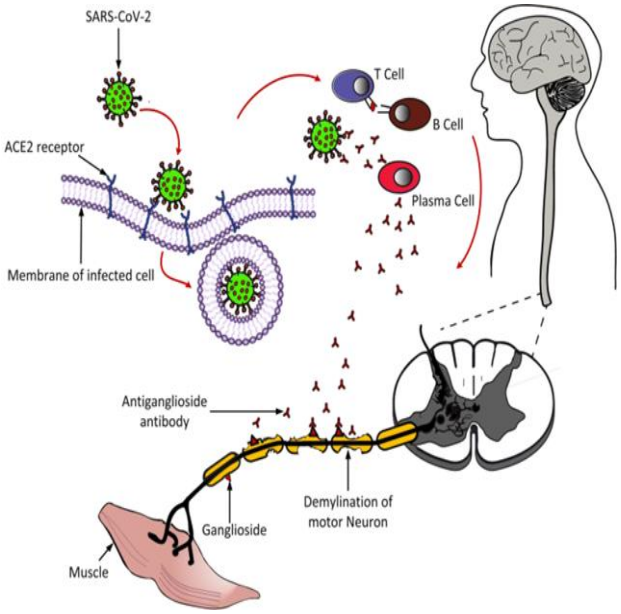

Figure 2: The likely pathophysiology of COVID-19-associated GBS. This picture depicts the SARS-COV-2 and its high affinity for the angiotensin-converting enzyme 2 (ACE2) receptor. Due to similarity in the epitopes of SARS-Cov-2 and gangliosides (molecular mimicry), the antibodies formed against the virus, may result in an autoimmune response that destroys the myelin and/or axons.[12]

This molecular mimicry eventually results in an autoimmune response that destroys the myelin and/or axons. Destruction of the myelin and/or axons thus damages the nervous system. This damage is responsible for the spectrum of GBS symptoms that we know such as muscle weakness, paralysis, coordination problems, breathing difficulties, and autonomic dysfunction. SARS-CoV-2 also causes an immune reaction via the inflammatory mechanism by producing increased levels of interleukin-6 (IL-6). The production of IL-6 is responsible for stimulating the inflammatory cascade that eventually damages nervous tissue.[2]

Evidence, in the form of animal models and clinic pathological evidence also support an autoimmune mechanism and potential molecular mimicry between antibodies against myelin and gangliosides in the nervous system. Out all the various agents that cause Guillain-Barré syndrome, SARS-CoV2 virus has now made it's entry into the list. These studies also suggest a potential role for anti-ganglioside antibodies in immuno-modulatory therapies that can help us in the management of the disease.[5]

Therefore, inflammatory factors may play an important role in the organ dysfunctions of patients with COVID-19 infection. These immunological processes are probably responsible for most of the neurological manifestations. Targeting these mediators will help us prevent the various

neurological sequelae that are a part of the spectrum of the disease.[6]

A study done by Curtis et al GBS in a child with COVID-19 infection had a similar case presentation of an 8-year-old boy who presented with progressive, ascending weakness with areflexia.[7] MRI of the spine of the child revealed an abnormal enhancement of posterior nerve roots. A lumbar puncture was done, that revealed albumin-cytologic dissociation. Electro diagnostic findings revealed sensorimotor demyelinating polyneuropathy. All these findings were consistent with GBS. Results of SARS-CoV-2 nucleic acid amplification and SARS-CoV-2 immunoglobulin G antibody tests were also positive. Hence, treatment was initiated with intravenous immunoglobulin-child received a total of 2 g/kg. His neurologic examination revealed improvement in the subsequent days and the child was discharged. This case reveals the wide scope of presentations of COVID-19 and post-infectious processes. Clinicians should constantly have a high level of suspicion for COVID-19.

Mehra et al COVID-19-associated severe MSI-C with encephalopathy and neuropathy in an adolescent girl with the successful outcome: An unusual presentation, their study discusses about a 13-year-old girl who presented with features of shock and respiratory distress.[1] Her initial investigations revealed extremely high inflammatory markers, deranged renal and liver function tests, and evidence of myocardial injury. RT-PCR for SARS-CoV-2 was negative. Because of clinical spectrum consistent with MIS-C, she was started on methylprednisolone (2 mg/kg/day) along with intravenous immunoglobulin (IV-Ig). COVID-19 IgG antibody by chemiluminescence immunoassay was positive, confirming the diagnosis of MIS-C. Within 48 hours of initiating therapy, significant clinical improvement was evident in hemodynamics.

On day 7 however, she developed repeated generalised convulsions, worked up with an MRI revealing acute disseminated encephalomyelitis (ADEM). She was then started on MPS pulse therapy, IV-Ig and five cycles of plasmapheresis were done. However, she remained quadriparetic with facial weakness, for which nerve conduction studies done, revealed large fibre motor axonal polyneuropathy involving upper and lower limbs along with phrenic nerve and facial nerve involvement, suggestive of GBS.[1]

So, in this case, the initial presentation was like that of a typical MIS-C with multi-system dysfunction, without any evidence of significant neurological involvement. The central nervous system (CNS) symptoms worsened and revealed a case of ADEM along with symmetrical axonal motor polyneuropathy as a spectrum of MIS-C illness in an adolescent. The combinations of both CNS and peripheral nervous system symptom profiles are rare in paediatrics but have been reported.

Both these cases give us an insight into the wide spectrum of the neurological manifestations associated with corona viruses. These cases recovered by a timely institution of appropriate multidisciplinary intensive care and immunomodulation, intravenous steroids, IV-Ig, and plasmapheresis.

CONCLUSION

MIS-C associated with antecedent SARS-CoV-2 virus can present with serious neurological manifestations in children. It can affect both the peripheral and/or central nervous systems. A high index of suspicion for the possibility of MIS-C should be kept in present pandemic times, especially in children presenting with unexplained multi-system involvement.

So, our case illustrates the case of a child with GBS in the setting of an acute SARS-CoV-2 infection to our knowledge and an ever-widening scope of presentations of COVID-19 and its associated complications. Clinicians are hence advised to constantly have a high level of suspicion for COVID-19 in all patients admitted to the hospital, especially in patients with unexplained symptoms and children who present with multi-system involvement.

Given the importance of COVID-19, further studies are needed to understand the effects of this infection on the nervous system and the various mechanisms by which the virus attacks the immune system. Future immunologic studies of cell-mediated and cytokine immune responses in young individuals may provide insight into the pathogenesis of neurologic disease in COVID-19 and MIS-C. Additional research is also needed to assess the association of neurological symptoms with immune-mediated changes among children with COVID-19.

The mechanism of molecular mimicry also suggests a potential role for anti-ganglioside antibodies in immuno-modulatory therapies, that need to be further explored so that it helps us in the management of the disease.

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