COVID-19-associated Severe Multisystem Inflammatory Syndrome in Children with Encephalopathy and Neuropathy in an Adolescent Girl with the Successful Outcome: An Unusual Presentation

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Abstract
Multisystem inflammatory syndrome in children (MIS-C) associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been reported from many countries where coronavirus disease 2019 (COVID-19) pandemic has peaked and/or fading. Though mild neurological symptoms as a part of this spectrum have been frequently reported in children, there are only anecdotal reports of severe neurological manifestations in MIS-C. We present here a yet not previously reported instance of dual neurological insult (involving both central and peripheral nervous systems) in an adolescent girl with severe MIS-C.

Introduction
Multisystem inflammatory syndrome in children (MIS-C) associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been reported from many countries where coronavirus disease 2019 (COVID-19) pandemic has peaked and/or fading. Though mild neurological symptoms as a part of this spectrum have been frequently reported in children, there are only anecdotal reports of severe neurological manifestations in MIS-C. We present here a yet not previously reported instance of dual neurological insult (involving both central and peripheral nervous systems) in an adolescent girl with severe MIS-C.

Case Description
A 13-year-old girl was admitted to a basic healthcare facility with a history of high-grade fever, throat pain, and cough for 2 days. She was initially managed as pharyngotonsillitis but referred to our center after 3 days, because of persistent fever, vomits, loose stools, progressive body rash, and breathing difficulty. There was a history of contact with a COVID-19 case in the family around 1 month ago. She also had fever around the same time, but no tests were performed and she had recovered completely within 3–4 days.

On examination, she had features of cold shock, respiratory distress, SpO2 of 84% on room air, and blood pressure of 66/34 mm Hg. She weighed 63 kg (obesity grade II), had generalized erythoderma without any eruptions. Her respiratory examination revealed decreased air entry with bronchial breath sounds in bilateral infrascapular regions. She was awake and following commands but was irritable and intermittently very much agitated.

Her initial investigations (Table 1) revealed extremely high inflammatory markers, deranged renal and liver function tests, and evidence of myocardial injury. RT-PCR for SARS-CoV-2 was negative. All cultures (blood, urine, tracheal secretions) were negative for pathogenic organisms. She had non-oliguric renal failure which was managed conservatively. Because of clinical spectrum consistent with MIS-C, she was started on methylprednisolone (2 mg/kg/day) along with intravenous immunoglobulin (IV-IgG, 100 g over 24 hours), within 24 hours of admission. COVID-19 IgG antibody by chemiluminescence immunoassay was positive left ventricular dysfunction. She was resuscitated and managed in pediatric intensive care unit (PICU) with inotropes, invasive ventilatory support, broad-spectrum antibiotics, and supportive care.

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Severe MIS-C with Encephalopathy and Neuropathy in an Adolescent Girl

(46.20 AU/mL), confirming the diagnosis of MIS-C. Within 48 hours of initiating therapy, significant clinical improvement was evident in hemodynamics, fever, rash, inflammatory markers, and organ dysfunction parameters (Table 1). By day 6, her ventilatory parameters improved and she was weaned off the ventilator and the inotropes were stopped. She had good spontaneous respiratory efforts, normal pupillary reaction but still no motor response to painful stimuli and no spontaneous eye-opening. On day 7, she developed repeated generalized convulsions which were controlled with intravenous lorazepam and levetiracetam. Contrast-enhanced MRI brain (Fig. 1) revealed extensive lesions with altered T2 and FLAIR signals at gray and white matter junction of both cerebral hemispheres with mild associated enhancement, diffuse cortical swelling with diffusion restriction, consistent with acute disseminated encephalomyelitis (ADEM). She was put on midazolam infusion along with the institution of pulse methylprednisolone (MPS) therapy. Lumbar puncture was deferred because of an unstable condition. Parents shifted her to another tertiary care hospital where MPS pulse therapy was continued for a total of 3 doses and IV-Ig (40 g) was given to complete a total of 2 g/kg of initial body weight. C-reactive protein (CRP) decreased to 16 mg/L, but ferritin was still high at 2,731 ng/mL. Because of no clinical improvement, five cycles of plasmapheresis were done. She showed gradual improvement in sensorium over the next 7 days. However, she remained quadriparetic with facial weakness, with poor diaphragm excursion evident on bedside ultrasound. Nerve conduction study (NCS) showed normal sensory nerve conduction but evidence of distal, symmetrical, large fiber motor axonal polyneuropathy involving upper and lower limbs along with phrenic nerve and facial nerve involvement, suggestive of Guillain–Barré syndrome (GBS). She had to be tracheostomized and ventilated for about 2 more weeks. She improved gradually with rehabilitation and achieved unassisted spontaneous respiration with complete neurological recovery and was discharged home after 6 weeks of hospitalization.

**DISCUSSION**

In recent months, coincident with the global spread of SARS-CoV-2, an increasing incidence of an unusual severe inflammatory illness in children, with features overlapping with Kawasaki syndrome and toxic shock syndrome is being reported.1 Temporal association and clustering of cases from countries where a pandemic has peaked or fading indicates a possible causal relationship with the SARS-CoV-2 virus.1,3,4 Majority of such cases are negative for SARS-CoV-2 RT-PCR but positive for COVID-19 IgG antibody.3,4

SARS-CoV-2 and related coronaviruses have not been shown to demonstrate primary neurotropism. Severe neurological manifestations are well reported in adults,5,6 but there is a paucity of data from the pediatric age group. They could be considered secondary to immune-mediated causative mechanisms or cerebrovascular disease or hypoxia-mediated insult.7 In their

| Table 1: Blood investigations (pre- and post- immunomodulatory therapy) |

|                | Day 1     | Day 6     | Day 1     | Day 6     |
|----------------|-----------|-----------|-----------|-----------|
| Hemoglobin (g/dL) | 8.1       | 9.4       | 298       | 139       |
| Total leukocyte count (×10⁹ cells/L) | 12.5      | 13.6      | >5,000    | 8         |
| Platelet (×10⁹ cells/L) | 140       | 323       | 4,238     | 2,048     |
| S. urea (mg/dL) | 111       | 140       | 3,222     | 1,039     |
| S. creatinine (mg/dL) | 3.82      | 1.08      | 195       | 194       |
| SGOT (IU/L) | 77        | 63        | 350       | –         |
| SGPT (IU/L) | 53        | 42        | 1,01      | –         |
| Total bilirubin (mg/dL) | 3.7       | –         | 35,000    | –         |
| Direct bilirubin (mg/dL) | 2.36      | –         | 448       | –         |
| S. albumin (g/dL) | 2.2       | 1.9       | –         | –         |

Figs 1A to C: T2/FLAIR axial MRI images demonstrating hyperintense signal at grey-white matter junction of bilateral cerebral hemispheres...
cohort of 186 children of MIS-C from the United States, Feldstein et al. reported that the majority of suspected MIS-C cases had gastrointestinal and cardiac symptoms at presentation while only 21% had associated neurological symptoms (headache, altered mental status, and confusion).3 Similarly, from the UK cohort, Abdel-Mannan et al. reported four children with severe MIS-C having encephalopathy with myopathic changes. Neuroimaging revealed lesions in the splenium of the corpus callosum in all patients and T2-hyperintense lesions with restricted diffusion in three children.4 In our case, the initial presentation was like that of a typical MIS-C with multisystem dysfunction, without any evidence of significant neurological involvement barring agitation. The central nervous system (CNS) symptoms worsened despite apparently improving renal, cardiac, and liver functions and a significant fall in inflammatory markers. The location of lesions on MRI, sparse contrast enhancement, a severe clinical course with an antecedent viral infection, and good recovery are all consistent with the diagnosis of an acute CNS demyelinating event. The findings of axonal polyneuropathy can be seen in both GBS and critical illness-related neuropathy. However, the absence of sensory nerve abnormalities, bifacial, and phrenic nerve involvement favors the diagnosis of GBS. We herein report the first 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 pediatrics but have been reported with cytokine storm associated multiorgan failure or hemophagocytic lymphohistiocytosis.8,9 Our case had cytokine storm-related multiorgan failure, triggered by antecedent COVID-19 infection, who recovered by a timely institution of intensive care measures along with the use of steroids, IV-Ig, and plasmapheresis. 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.

**Conclusion**
Multisystem inflammatory syndrome in children associated with antecedent SARS-CoV-2 virus can present with serious neurological manifestations in children, affecting 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, in children presenting with unexplained multisystem involvement. 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.

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**Highlights**
Severe neurological manifestations of COVID-19, such as, encephalopathy, inflammatory CNS syndromes, cerebrovascular disease, and GBS, have been well reported in adults, but there is a paucity of data from the pediatric age group. Moreover, the combination of both CNS and peripheral nervous system symptom profiles are extremely rare in pediatrics. We herein report the first case of ADEM along with symmetrical axonal motor polyneuropathy as a spectrum of MIS-C illness in an adolescent.