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Case Report

MISC (Multisystem Inflammatory Syndrome in Children) Presenting as AIE (Auto Immune Encephalitis) among Indian Children: A Systematic Review of the Literature

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or corona virus disease 2019 is a currently ongoing global pandemic. SARS-CoV2 virus can affect both the central and peripheral nervous system, and SARS neurological manifestations have also been rarely reported in children. We here in report SARSCOV2 triggered MISC presenting as AIE in a 3-year-old boy who presented with fever, vomitings and altered sensorium with complete resolution of neurological symptoms in 48 hours post IVIG. We also present the data collected from systematic review of literature over the topic from Indian data. Further studies are required to investigate all the neurological complications of SARS-CoV-2 infection and their underlying pathogenic mechanism. Clinicians shouldn't miss the diagnosis of possibility of MISC in such unusual presentations.

Keywords: *Autoimmune Encephalitis (AIE); Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2); MISC (Multisystem Inflammatory Syndrome in Children)*

Introduction

Autoimmune encephalitis (AIE) is an important and treatable cause of acute encephalitis. Diagnosis of AIE [1] in a developing child is challenging because of overlap in clinical presentations with other infectious diseases and newer syndromes like SARSCOV2 triggered MISC.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or corona virus disease 2019 is a currently ongoing global pandemic. SARS-CoV2 virus can affect both the central and peripheral nervous system, and SARS neurological manifestations have also been rarely reported in children. In later April 2020, a novel syndrome in children and adolescents, termed multisystem inflammatory syndrome in children (MIS-C), related to SARS-CoV-2 infection was first described [2]. This condition, similar to Kawasaki disease and toxic shock syndrome, is characterized by persistent fever, a multisystem (≥ 2) organ involvement, elevation of inflammatory markers, link to SARS-CoV-2 (verified by polymerase chain reaction, serology or COVID-19 contact) and the exclusion of alternative diagnosis [3].

The Center for Disease Control and Prevention (CDC) [4] together with World Health Organization (WHO) [5] released a Health Advisory on severe complications of SARS-COV-2 Infection in children called as Multisystem Inflammatory Syndrome in Children (MIS-C).

We here in report SARSCOV2 triggered MISC presenting as AIE in a 3-year-old boy who presented with fever, vomitings and altered sensorium with complete resolution of neurological symptoms in 48 hours post IVIG.

Methodology

We performed a systematic review of the literature contextualizing our new case among all the cases retrieved in our search pertaining to Indian data. A computerized search was performed using PubMed, combining the terms (neurolog* OR CNS OR nervous OR encephal*) AND (COVID OR SARS-CoV-2 OR coronavirus) AND (baby OR child* OR pediatr*) AND (MISC) AND (INDIA) with English language filter, to identify studies on neurological manifestations in children with SARS-CoV-2 infection, published until March 31, 2022. The following data were evaluated for each case: age, sex, comorbidities, clinical features, radiological and other neurological investigations, laboratory test for confirmation of SARS-CoV-2 infection and MISC; The selected articles were reviewed by two independent authors and judged on their relevant contribution to the subject of the study. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [6] guidelines were followed.

Case Report

A 3 year old male child presented with history of fever, cold for 3 days followed by insidious onset of drowsiness and altered sensorium which worsened over next 12 hours. Child was screened for sepsis with CRP, ESR, Procalcitonin and Blood culture. CRP was 200 mg/l, PCT was 22 ng/ml, ESR was 180 mm/hr. Child had history of parent death due to SARSCOV2. As SARSCOV2 RNA PCR was negative for this child, MISC was suspected and was confirmed once we found his Serum SARSCOV2 IgG was 150 IU/ml. His IL-6 was 65 pg/ml.

CSF analysis was performed which showed only 3 cell count (100% lymphocyte), high protein (118 mg/dl) and normal glucose. MRI brain done was reported to be normal without any significant abnormalities. EEG showed encephalopathic slowing of wave pattern. Cardiac Echo showed dilated coronaries (LAD and RCA with Z scores > 3.0). Blood and CSF Cultures were negative for bacterial growth. Child was given IVIG 2 g/kg over 48 hours and pulse dose IV Methylprednisolone (30 mg/kg/dose) for 5 days. Child had dramatic response within 48 hours. GCS improved from 11 to 15. Child was discharged home on oral prednisolone and aspirin.

Systematic Review of Literature Results

There are very few such cases reported from India and worldwide. We could collect data relevant to our title, topic, study area from two publications and there is another single case report data which was unpublished but presented as a poster in a national conference. All of them are tabulated in table 1.

Sl.no	Study	Age	Sex	CNS	MISC	PCR	CSF	MRI
1	Natrajan S., *et al*.	13Y	F	Encephalopathy	No	Pos	High Cells	Normal
2	Raj sl., *et al*.	2Y	M	Seizures	Yes	Pos	Normal	Normal
3	Raj sl., *et al*.	15M	M	Seizures	Yes	Neg	Normal	Normal
4	Raj sl., *et al*.	8M	M	Seizures	No	Pos	Normal	Normal
5	Joel Wesley	5Y	M	Seizures, Encephalopathy	Yes	Neg	Normal	Normal
6	Our case	3Y	M	Encephalopathy	Yes	Neg	High Protein	Normal

Table 1: *Cases of neurological involvement in SARSCOV2 infection/MISC from India.*

There were total 6 children including our case, of which 5 are boys and 1 girl. Mean age was 4 years. All children have no comorbid illnesses. The most common CNS manifestation was seizure. 4 of them are MISC encephalitis and 2 of them are non MISC, SARSCOV2 infection encephalitis. Of the 4 MISC encephalitis 2 of them are RNA PCR positive and 2 of them only IgG. All of them have normal MRI appearance. CSF analysis was normal in 4 of them. One showed lymphocytic pleocytosis and our case showed high protein. Outcome was good in all of them.

Natarajan S., *et al*. [7] from Chennai, India reported a case of SARSCOV2 encephalitis but that was not MISC. Raj SL., *et al*. [8] from Chennai, India reports 2 cases of MISC presenting with encephalitis and seizures but of them 1 was positive for SARSCOV2 RNA PCR and another with contact history positive. They report another SARSCOV2 encephalitis which was not MISC.

Joel Wesley., *et al*. [9] from Bangalore, India report a similar case of 5 years old male child with MISC who presented as Autoimmune Encephalitis. This data was unpublished but was presented as poster in a national conference.

Discussion

In the course of MIS-C, neurological complications, such as ADEM, pseudotumor cerebri, cerebral edema, seizure, cerebral stroke and cytotoxic lesions of the corpus callosum have been described but none of them reported like AIE as mentioned by Siracusa., *et al*. [10] in their systematic review on worldwide literature over neurological complications of SARSCOV2. Very few studies are available on Auto immune encephalitis associated with SARSCOV2 but they deal with adults [11].

We report a case of MISC presenting as Autoimmune encephalitis. Our patient fulfilled the criteria for diagnosis of MISC [4] and AIE [1]. As recommended by guidelines [1,4] we treated with IVIG (2 g/kg over 48 hours) and IV Methylprednisolone (30 mg/kg/dose) for 5 days followed by oral Prednisolone (1 mg/kg/day). This condition of MISC triggered AIE could be explained by cytokine storm and high IL6.

Limitations

This systematic review has several limitations as we have included data from only India and these case series don't represent the full population and potential impact of publication bias.

Conclusion

Further studies are required to investigate all the neurological complications of SARS-CoV-2 infection and their underlying pathogenic mechanism. Clinicians shouldn't miss the diagnosis of possibility of MISC in such unusual presentations.

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Ethics Approval and Consent to Participate

Not applicable.

Parents Informed Consent

Taken in our case.

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