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Case Series

Neurological manifestations of multisystem inflammatory syndrome in children associated with COVID-19 in a tertiary care centre

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ABSTRACT

Multisystem inflammatory syndrome in children (MIS-C) and adolescents temporally related to COVID-19" is a new entity characterized by fever, multisystem organ involvement, laboratory evidence of inflammation, and laboratory or epidemiological evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, in individuals aged 0–19 years with no alternative diagnosis. Neurological manifestations are not part of the diagnostic criteria of MISC and hence remain poorly described. So, we wanted to note down the neurological involvement in multisystem inflammatory syndrome in children (MIS-C) related to severe acute respiratory syndrome with coronavirus infection. Here we describe 6 cases of COVID MISC who presented as acute febrile illness with drowsiness, irritability, convulsions and serious ones with encephalopathy. Focal neurological signs, abnormal brain magnetic resonance imaging (MRI) was present in four patients. MRI brain was normal in 2 cases CSF study was normal in all cases. These patients received intravenous methylprednisolone at 30 mg/kg/day for 3 days. Cases 3 to 6 were given intravenous immunoglobulin (IVIG), the clinical picture rapidly improved in the first three days, and all neurological symptoms disappeared within 10 and 30 days with some sequel in cases 4 to 6. In conclusion we describe clinical and laboratory parameters in these patients with neurological manifestations and we documented an increase in pro inflammatory markers correlating with severity of neurological presentation in children with MISC. High index of suspicion is needed to diagnose neurological manifestations of MISC following COVID-19 pandemic. Neurological spectrum can be broad range of manifestations though outcome was favorable with early treatment.

Keywords: COVID-19, SARS-CoV-2, Multisystem inflammatory syndrome in children, Encephalitis, Neurological symptoms

INTRODUCTION

Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19" is a new entity characterized by fever, multisystem organ involvement, laboratory evidence of inflammation, and laboratory or epidemiological evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, in individuals aged 0–19 years with no alternative diagnosis.[1] Although children are largely spared the severe acute effects of SARS-CoV-2 infection, multisystem inflammatory syndrome associated with COVID-19 MIS-C, albeit rare, is a severe disease that affects multiple organs including the central nervous system (CNS). Its pathophysiological mechanism is still unclear, but it is thought to be a highly complex postinfectious phenomenon resulting in hyperinflammation.[2] Acute SARS-CoV-2 infection triggers a proinflammatory reaction and, in a genetically susceptible child, a delayed hyperinflammatory reaction

consisting of vasculitis with augmented levels of lymphocyte T-helper 17 and T-helper 1 mediators, and a cytokine storm, including massive release of inflammatory mediators and exaggerated activation of the immune system leading to blood brain barrier (BBB) damage.[3] MIS-C was first described in April 2020 in Europe, but it is now reported and documented worldwide.[4] To date, the largest published study dealing with neurological involvement in children with SARS-CoV-2 infection is a retrospective study of a population of 1,695 patients; Of these patients, 365 (22%) developed neurological complications due to acute COVID-19 or MIS-C.[5] Neurological manifestations are not part of the diagnostic criteria and hence remain poorly described. Here we describe series of cases with MIS-C with predominant neurological presentations.

CASE SERIES

This retrospective analysis was carried out in pediatric department of MGM Hospital, Aurangabad, for the study period of January 2021 to December 2021. Children with a diagnosis of MISC and neurological manifestations meeting the relevant diagnostic criteria laid by World Health Organization (WHO), were included.[1]

Out of the 10 patients presented with neurological presentations in MISC, 6 patients underwent complete neurological examination, investigations and management. The data of those 6 patients is included in the study.

For all the patients, general demographic and clinical data, clinical presentations including the duration of fever, presence of organ and system involvement (neurological, cardiological, abdominal, respiratory, renal, mucocutaneous), shock, duration of hospitalization were noted.

All the children underwent investigations like complete blood count, C-reactive protein, ferritin, D-dimer, N-terminal proB-type natriuretic peptide (NTproBNP), CSF study and MRI brain). All the cases were treated with intravenous methylprednisolone (IVMP), 30 mg/kg/day, and /or with intravenous immunoglobulins (IVIg), 2 g/kg. This report describes the neurological and investigational characteristics of these 6 patients. Fever was considered the onset symptom, and the first day with fever was taken as day 1. Four of the 6 children, presenting focal neurological signs, also underwent CSF (including SARS-CoV-2 PCR and neurotropic viral PCR) and brain MRI evaluation (T1-and T2-weighted, FLAIR and diffusion sequences). The clinical features and investigations of these children are presented in Table 1.

There were 4 males and 2 females with age range of 2 years to 10 years (mean-4.7 years). All the patients presented with fever of 1-2 days with altered sensorium and convulsions. Patients 1 and 2 had milder presentation with irritability and headache whereas patients 3 to 6 had severe presentations including prolonged encephalopathy with neurological squeal. Patient 3 presented with stroke like features with right sided weakness. Amongst the lab parameters, patient 1 and 2, COVID antibodies were negative but their mothers had serious COVID-19 infection within 1 month of their presentation. Case no. 3 to 6 has strongly positive antibody test. Cases 1 and 2 had less deranged inflammatory markers as compared to cases 3 to 6. Their values correlated with severity of the clinical manifestations. Cases 1 and 2 recovered within 10 days of illness whereas cases 3 to 6 required more than 15 days for recovery with neurological sequel. CSF study was normal in all the children. EEG and MRI brain were normal in patient 1 and 2 and abnormal in patients 3 to 6.

All cases presented with acute encephalopathy with drowsiness, irritability, convulsions. Focal neurological signs, abnormal brain MRI were present in four patients. MRI brain was normal in cases 1 and 2 and CSF study was normal in all cases. These patients received intravenous methylprednisolone at 30 mg/kg/ day for 3 days. Cases 3 to 6 were given intravenous immunoglobulin (IVIG), the clinical picture rapidly improved in the first three days, and all neurological symptoms disappeared within 10 and 30 days with some sequel in cases 4 to 6.

Table 1: Demographic data and clinical features of the patients.

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	3 years	4 years	2 years	3 years 6 months	10 years	5 years
Sex	Female	Male	Male	Female	Male	Male
Chief complaints	Fever and convulsi-ons	Fever and convulsi-ons	Fever and convulsions, right sided weakness	Fever and convulsions and altered sensorium	Fever and convulsions and altered sensorium	Fever and convulsions and altered sensorium
Complete blood count Hb (gm)/ leucocyte (cmm)/platelet count (cmm)	10/29210/293000	9.4/4920/212000	11.3/22500/75000	11.3/15000/193400	12/9020/145000	13/14200/212000
CRP units/dl	11	8	18.7	1	5.7	28

Continued.

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
SARS COV-2 antibody	Mother COVID +	Mother COVID+	79	64	270	66
D dimer (ng/ml)	0.93	1.3	7.8	3	9.2	5.8
Ferritin (microgm/l)	35.9	10.8	448	392	884	776
PT/INR	1.8	1.9	1.7	1.9	2.1	1.5
LDH (U/l)	561	349	389	408	525	448
NT ProBNP (picogm/ml)	Normal	Normal	Normal	Normal	Normal	Normal
CSF routine	Normal culture-sterile	Normal culture-sterile	Normal culture-sterile	Normal culture-sterile	Normal culture-sterile	Normal culture-sterile
EEG	Normal	Normal	Abnormal	Abnormal	Abnormal	Abnormal
MRI brain	Normal	Normal	Hyperintensit-ies on left Fronto-parietal region	Hyperintensities in frontal parietal white matter patchy signal abnormality	Rt temporal hyperintensit-ies and multifocal central edema	Hyper intensities in bilateral cerebellar white matter, pons, anterior surface of medulla, mid brain
Treatment	Methyl prednisol-one	Methyl prednisol -one	Methyl prednisolone and IVIG	Methyl prednisolone and IVIG	Methyl prednisolone and IVIG	Methyl prednisolone and IVIG

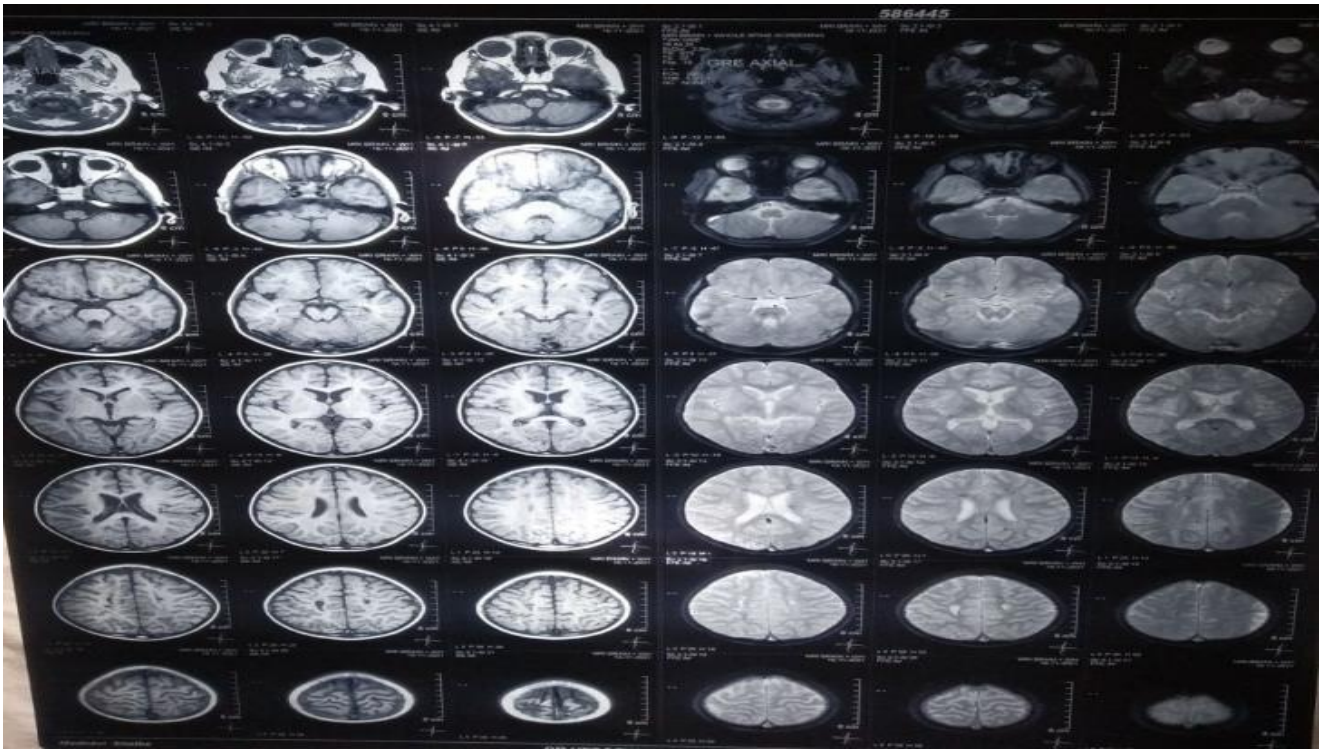

Figure 1: MRI brain of patient 6 - hyper intensities in bilateral cerebellar white matter, pons, anterior surface of medulla, mid brain.

DISCUSSION

Recent data from the literature suggest that neurological involvement may be frequent in MIS-C patients, noted to be 34% in a study.[6]

Between 1 and 5 days from the onset of fever, all the patients in our series developed encephalopathy characterized by the simultaneous presence of convulsions and irritability. In case 3 focal neurological sign like right sided were also present. Other 3 patients had

encephalopathy with coma. Only methyl prednisolone was given for first two cases and additional IVIG was given in remaining 4 cases. We documented a correlation between the severity of neurological involvement to the increase in inflammatory markers. The study by Olivotto et al documented a correlation between the severity of neurological involvement and the extent and duration of the EEG abnormalities.[7] However we had EEG documented only once. MRI brain showed many changes in patients 3 to 6 with stormy course whereas it was normal in first 2 cases. MRI is normal in most MIS-C cases, even though bilateral thalamic lesions and signal changes in the splenium of the corpus callosum and centrum semiovale have been reported.[5, 8]

CSF study was normal in all children in our study. CSF has previously been studied in a small number of patients and almost always found to be normal, although cases of pleocytosis have been described.[5,8]

All our cases recovered and were treated, in accordance with the guidelines on MIS-C, with IVIG and IVMP.

In conclusion in our experience, early milder presentation had complete recovery but those with severe presentation had some neurological sequel. The spectrum and frequency of the neurological involvement may be broader, and signs of it may be missed in many cases unless it is highly suspected.

As MIS-C is still a very new medical condition, long-term clinical and instrumental follow up is mandatory to understand its impact on neurodevelopment in affected children.

This study was conducted in a limited sample, and not all the children with neurological signs underwent full neurological evaluation.

CONCLUSION

Increase in pro inflammatory markers correlated with severity of neurological presentation in children with MISC. High index of suspicion is needed to diagnose neurological manifestations of MISC following COVID 19 pandemic. Neurological spectrum can be broad range of manifestations though outcome was favorable with early treatment.

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REFERENCES

1. WHO – World Health Organization Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. Available at: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. Accessed on 12 December 2022.
2. Chen MR, Kuo HC, Lee YJ, Chi H, Li SC, Lee HC, et al. Phenotype, susceptibility, autoimmunity, and immunotherapy between Kawasaki disease and coronavirus disease-19 associated multisystem inflammatory syndrome in children. Front Immunol. 2021;12:632890.
3. Wan D, Du T, Hong W, Chen L, Que H, Lu S, et al. Neurological complications and infection mechanism of SARS-COV-2. Signal Transduct Target Ther. 2021;6:406.
4. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. 2020;383:334-46.
5. Abel D, Shen MY, Abid Z, Hennigan C, Boneparth A, Miller EH, et al. Encephalopathy and bilateral thalamic lesions in a child with MIS-C associated with COVID-19. Neurology. 2020;95:745-8.
6. Chen TH. Neurological involvement associated with COVID-19 infection in children. J Neurol. Sci. 2020;418:1-3.
7. Olivotto S, Basso E, Lavatelli R, Previtali R, Parenti L, Fiori L, Dilillo D, Zuccotti GV, Veggiotti P, Bova SM. Acute encephalitis in pediatric multisystem inflammatory syndrome associated with COVID-19. Eur J Paediatr Neurol. 2021;34:84-90.
8. Abdel-Mannan O, Eyre M, Löbel U, Bamford A, Eltze C, Hameed B, Hemingway C, Hacohen Y. Neurologic and Radiographic Findings Associated With COVID-19 Infection in Children. JAMA Neurol. 2020;77(11):1440-5.

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