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Acute neurological symptoms in multisystem inflammatory syndrome in children: A case series

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ABSTRACT

Introduction: Severe acute respiratory syndrome coronavirus-2 infection mostly involves pediatrics lesser than adults; however, the multisystem inflammatory syndrome in children is shown to be the following condition in children infected with SARS-CoV-2, even asymptomatic ones. To date, there is few evidence of the association of multisystem inflammatory syndrome in children with acute neurological symptoms.

Case presentations: This case series was recorded demographic, clinical, laboratory, radiographic and EEG data of patients with the multisystem inflammatory syndrome in children who diagnosed simultaneously with acute neurological symptoms. Children with the multisystem inflammatory syndrome in children and evidence of central nervous system involvements participated in the study. Data are reported as median (interquartile ranges) for quantitative data without normal distributions. The present study was conducted at the children's referral hospital of Isfahan province, Iran between March 1, 2020, and December 28, 2021. Simultaneous diagnosis of multisystem inflammatory syndrome in children and acute neurological symptoms was made in 12 children. The median age of patients was 4.5 years (10–144 months). The most common symptoms were seizures (58%). Cerebrospinal fluid analysis showed that only one patient had pleocytosis. In addition, one patient had a low glucose level. Finally, 11 patients were discharged in good condition and one patient died after full recovery from acute neurological symptoms due to her underlying disease.

Conclusion: According to our series and other studies, children with MIS-C may present signs and symptoms of acute neurological symptoms. Although its pathophysiology is unclear, studies showed that immunomodulatory agents, i.e., intravenous immunoglobulins and corticosteroids, provide a relatively good prognosis.

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged first in Wuhan, Hubei Province, China, in December 2019 and has spread worldwide, making it a global health concern [1]. SARS-CoV-2 also is responsible for a rare complication entitled

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Table 1
Clinical and laboratory findings of each patient.

ID	Gender	Age	Presenting symptoms	Days before admission	Past medical history	Neurological sign	Organ involvements	Cells blood count	
								White blood (cells per $mm^{3)}$	absolute lymphocyte count (cells per mm3)
1	M	16 years	Altered consciousness, fever, skin rash	1	CD, CND	seizure	Skin, CNS	5400	1458
2	F	11 years	Altered consciousness, skin rash, fever	3		seizure	Skin, CNS	11,300	1130
3	M	1 years	Altered consciousness, fever, skin rash	1		seizure	Skin, CNS, Gastrointestinal	4500	1687
4	F	3 years	Altered consciousness, fever	0		seizure	CNS, Gastrointestinal	18,000	1980
5	F	6 months	Altered consciousness, fever	0	Cobalamin deficiency	None	CNS, Gastrointestinal, Respiratory	5400	4482
6	F	4 years	Altered consciousness, fever	1	CND	seizure	CNS, Gastrointestinal	9200	1223
7	F	10 years	Altered consciousness, fever	2	CND	None	CNS, Gastrointestinal	9000	1350
8	M	15 years	Altered consciousness, fever	3		None	CNS, Gastrointestinal, Respiratory	6500	1196
9	M	13 years	Altered consciousness, fever	5		None	CNS, Respiratory	10,600	996
10	F	1 month	Altered consciousness, fever, skin rash	1		seizure	Skin, CNS	7600	4674
11	M	5 years	Altered consciousness, fever	2	Malignancy	seizure	CNS, Gastrointestinal	700	[a]
12	F	9 months	Altered consciousness, skin rash, fever	2		7th nerve palsy	Skin, CNS	12,100	3267
Median (Q_1, Q_3)	M:F (5:7)	4.5 years (10 months, 12.5 years)		1.5 (1, 2.5)				7050 (4725, 10,250)	1458 (1196, 3267)

Gender (F: Female, M: male), Past medical history (CD: cardiac disease, CND: Chronic neurological disease, IUGR: Intrauterine growth retardation), CNS: Central Nervous System, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, Nl: Normal.
[a] Since the WBC count was below 1000 per mm^3, the patient had lymphopenia.

"Multisystem inflammatory syndrome" [2]. Multisystem inflammatory syndrome can affect children [3] or adults [4]. Multisystem inflammatory syndrome in children (MIS-C) can present severe clinical manifestations. Various neurological involvements, such as Guillain-Barre syndrome, transverse myelitis, reversible cerebral vasoconstriction syndrome and acute encephalitis, are reported in patients with COVID-19 or MIS-C [5–7].

This study aimed to describe acute neurological symptoms associated with MIS-C in Isfahan pediatric hospitals.

2. Case presentation

Between March 1, 2020, to December 28, 2021, 12 children were diagnosed simultaneously with acute neurological symptoms and MIS-C in two hospitals affiliated with the Isfahan University of Medical Sciences, which were referral hospitals for children with COVID-19 in Isfahan province.

Diagnosis of MIS-C is made according to WHO criteria and American College of Rheumatology recommendations as listed below [8, 9], in addition to the prior detection of SARS-CoV-2 by nasopharyngeal RT-PCR test (PT.COVID.100, PISHTAZ TEB, 2020).

1. Fever (more than 24 hours or documented ≥38 Celsius)
2. Laboratory evidence of inflammation, such as reduced lymphocytes and albumin or elevated neutrophil count, CRP, ESR, ferritin and LDH
3. Illness requiring hospitalization
4. Multi-system (≥2) organ involvement, i.e., cardiac, renal, respiratory, gastrointestinal, circulation, skin and nervous systems.
5. No alternative diagnosis is susceptible

Acute encephalitis diagnosis fulfilled the major criterion and at least three minor criteria. Altered consciousness or behavioral changes for more than 24 hours with no alternative cause identified is the major criterion. Minor criteria included fever, seizure, focal neurologic findings, abnormal CNS imaging, abnormal EEG, and abnormal CSF analysis [10]. Acute neurological symptoms are defined as the presence of seizures, muscle weakness, altered consciousness, or paralysis when the criteria for acute encephalitis are

Cells blood count		ESR (mm/hr)	CRP (mg/L)	Ferritin (ng/mm^3)	LDH (U/L)	CSF analysis				Electroencephalogram	Brain imaging	
Hemoglobin (gr/dL)	Platelets ($\times 10^3$ per mm^3)					WBC (per mm^3)	Glucose (mg/dL)	LDH (U/L)	Protein (U/L)		CT scan	MRI
14.4	207	5	30	443	501	1	58	12	25	Epilepticus wave	Nl	Nl
11.3	99	83	18	310	524	3	53	20	30	Slow wave	Nl	Cortical
12	123	4	56	768	560	0	46	0	28	Not performed	Nl	Not performed
8.9	287	6	68	156	475	5	69	108	18	Not performed	Nl	Not performed
10.8	214	2	4	1650	698	0	40	25	7	Normal	Nl	Cortical
12	259	33	35	400	562	0	51	24	91	Normal	Nl	Not performed
12.2	247	31	8	390	427	11	40	19	10	Slow wave	Nl	Cortical
11	119	50	37	469	619	5	45	30	28	Not performed	Nl	Not performed
13.7	219	3	5	280	560	4	77	25	35	Not performed	Nl	Not performed
10	187	5	4	465	832	2	10	39	73	Not performed	Nl	Not performed
12.4	21	6	23	1650	1488	2	25	35	32	Epilepticus wave	Nl	Cortical
9.5	224	18	15	36	435	4	35	25	38	Not performed	Nl	Not performed
11.65 (10.2, 12.35)	210 (120, 241.25)	6 (4.25, 32.5)	20.5 (5.75, 36.5)	421.5 (287.5, 693.25)	560 (481.5, 678.25)	2.5 (0.25, 4.75)	29 (19.75, 37.25)	25 (19.25, 33.75)	45.5 (36.25, 56.75)			

not met.

The median age of patients was 4.5 years (10–144 months), while three patients were one-year-old or younger. Five patients were 10-year-old or older. Underlying diseases included chronic neurological disorders (3 patients, 25%), cardiac disease (1 patient, 8.33%) and malignancy (1 patient, 8.33%). Immunodeficiency was not observed in any patient. Chronic neurological diseases included neurodegenerative disease and seizure disorder. The most common symptoms were seizure (7 patients, 58%) and diarrhea (6 patients, 50%). Other symptoms included rash (5 patients, 42%), headache (5 patients, 42%) and abdominal pain (3 patients, 25%). One patient had 7th cranial nerve palsy. In physical examinations, tachypnea (4 patients, 33%), cyanosis (2 patients, 17%) and respiratory distress (2 patients, 17%) were the three most common findings.

At admission time, two patients (16.7%) had lymphopenia. Two patients (17%) were admitted with anemia. Also, thrombocytopenia was detected in two patients (17%). Five patients had abnormally high ESR. The C-reactive protein of 10 patients (83.3%) was greater than 5 mg/l. All patients had high lactate dehydrogenase levels. Eleven had elevated ferritin levels (>140 ng/ml for children 6 months to 15 years). Elevated liver enzyme levels were found in one patient; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 519 U/l and 411 U/l, respectively. INR abnormality was detected in two patients (17%). Also, partial thromboplastin time (PTT) was 120 seconds in the first two days after admission in one patient. The clinical, laboratory and imaging findings and electroencephalogram of each patient are shown in Table 1. The MRI study of five patients showed that two patients with neurolgic sign (NS) had cortical hyperintensity, while the MRI study of one patient with NS was normal. Besides, MRI studies of two patients without NS reported cortical hyperintensity. Fig. 1 shows MRI study of Case No. 2, demonstrating bilateral hyperintensity in both mesial temporal lobes, both insular cortices, both frontal lobes, and both mamillary bodies.

Among patients for whom electroencephalography was performed, two patients had slow waves, the other two had epileptic waves, and two patients had normal EEG. Among 8 patients with NS, three cases had abnormal EEG, two cases with the epileptic wave and one with a slow wave. However, one of these eight patients had normal EEG and electroencephalography was not performed for the rest. All EEGs were recorded between day 5 to day 8 of the acute neurological symptoms course.

CSF analysis showed that only one patient had an abnormally high white blood cell count, 11 cells/ml. In addition, one patient had a low glucose level, 10 mg/dl. CSF protein was higher than 40 mg/dl in two patients, 91 and 73 mg/dl. The culture growth of CSF samples was negative. IgM and IgG related to SARS-CoV-2 and PCR of SARS-CoV-2 particles were negative in all CSF samples. However, the blood culture of one patient was positive for gram-positive cocci and staphylococcus epidermidis. The rest of the blood cultures were negative.

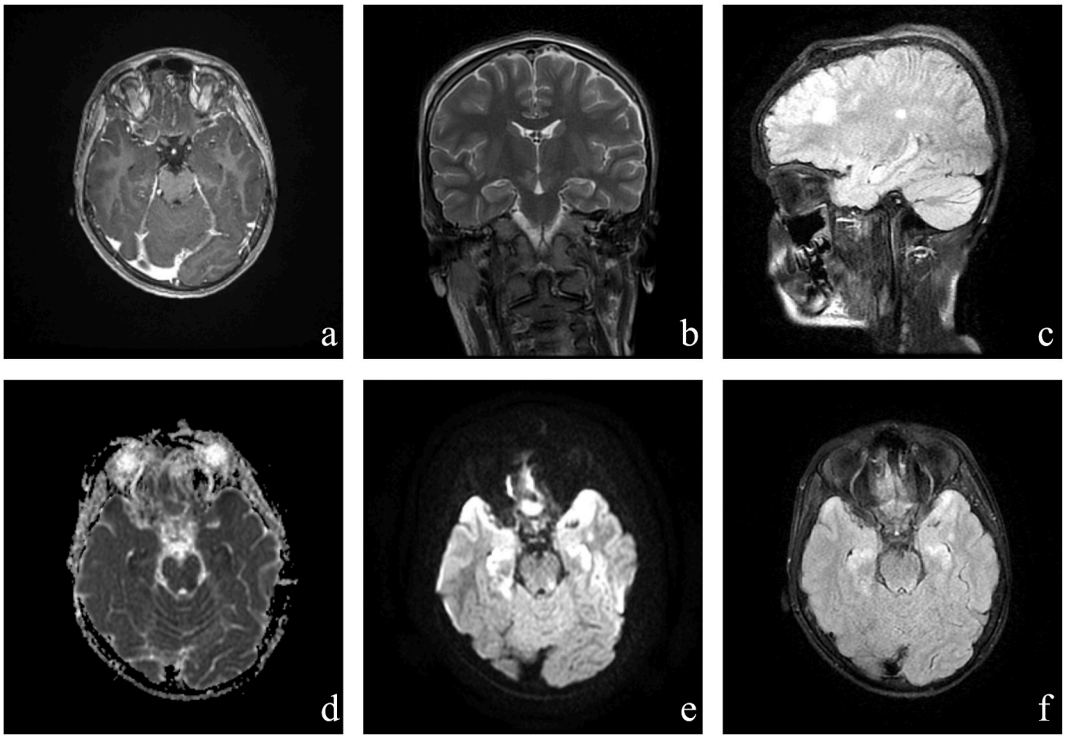

Fig. 1. Axial T1-weighted with intravenous contrast (a), coronal T2-weighted (b), sagittal FLAIR (c), axial ADC (d), axial FLAIR (e), and axial DWI (f) of MRI study of case No. 2, demonstrating bilateral hyperintensity in both mesial temporal lobes, both insular cortices, both frontal lobes, and both mamillary bodies.

Standard treatment, based on the Iranian treatment protocol for children with MIS-C [3], was performed for all patients (Table 2). Two patients were admitted to ICU during hospitalization. Complications such as myocarditis and vegetation-like lesions in the endocardium occurred during hospitalization in one patient. Finally, 11 patients were discharged in good condition. Ten patients of them in four-week follow-ups showed no complaints. One patient suffered from short-term memory loss. Relapses of MIS-C occurred in two patients because of rapid tapering of corticosteroids at 2 weeks instead of the standard protocol at 4–6 weeks. Unfortunately, one patient who suffered from cobalamin deficiency died after full recovery from acute neurological symptoms and the reason for death was irreversible shock due to cobalamin deficiency. Each patient outcome is shown in Table 2.

3. Discussion

Based on observations, the central nervous system involvement is a non-rare associating condition with MIS-C. Acute neurological symptoms are life-threatening conditions mentioned in studies [11–13]. However, the epidemiology, pathophysiology and prognosis of acute neurological symptoms in children with MIS-C are not clear yet.

The clinical presentation of 8 patients in our series included neurological signs [8], i.e., seizure and 7th nerve palsy, although two of them had previously had seizure disorder. Symptoms resolved after 7–10 days of hospitalization in most cases. However, case#7 developed short-term memory loss in the 4-week follow-up visit. Case#5 was admitted to ED in shock and because of an underlying disease, cobalamin deficiency, the shock progressed irreversibly, and she died, unfortunately. In the case series of seven patients with acute neurological symptoms in MIS-C by Olivotto et al. [12], four patients developed severe NS and all cases recovered in 10 days. Our findings are similar to their study in this regard.

CSF analysis of cases was almost insignificant; however, case#7 had pleocytosis in CSF analysis, which has been reported previously in patients with COVID-19 [14]. Notably, lumbar puncture of cases was performed within 24 hours of admission, which may not be enough time for white blood cells to migrate to the CSF.

Also, PCR of SARS-CoV-2 particles, IgM and IgG antibodies of SARS-CoV-2 were negative in CSF of all cases. Negative serology of CSF diminished the role of humoral immunity since it was suggested that immune-mediated pathophysiological mechanisms triggered by previous SARS-CoV-2 infection play an important role in the pathophysiology of acute neurological symptoms in MIS-C [12] and COVID-19 [15,16]. On the other hand, apart from immune response, a study stated that neural edema is a cause of CNS signs and symptoms in patients with COVID-19 [17]. Nevertheless, the brain imaging of our patients was contrary to this theory. However, further studies on inflammatory markers and cytokines of CSF should be performed to enlighten this aspect of acute neurological symptoms.

Table 2
Type of treatment and outcome of each patient.

ID	Antibiotic Therapy	IVIg[a]	Pulse corticosteroid therapy[b]	Remdesivir[c]	Acyclovir[d]	ICU caring	Hospitalization length (days)	outcomes	
								At discharge	4-week follow-up
1	×		×			×	14	Full recovery	Good shape
2	×						15	Full recovery	Good shape
3	×	×					14	Full recovery	Good shape
4	×						21	Full recovery	Good shape
5	×	×	×	×		×	20	Death	–
6	×	×	×		×		16	Full recovery	Good shape
7	×		×				20	Full recovery	Short-term memory loss
8	×	×	×	×			14	Full recovery	Good shape
9	×						15	Full recovery	Good shape
10	×	×					10	Full recovery	Good shape
11	×		×	×			14	Full recovery	Pulmonary Embolism[e]
12	×	×	×				13	Full recovery	Good shape

IVIg: Intravenous immunoglobulin.
[a] 2 gr/kg intravenous immunoglobulin (IVIg) for two consecutive days.
[b] 20–30 mg/kg/day methylprednisolone for three consecutive days.
[c] 5 mg/kg once (max 200 mg), followed by 2.5 mg/kg (max 100 mg) every 24 hours for ten consecutive days.
[d] 20 mg/kg per dose orally 4 times daily (80 mg/kg/day) for five consecutive days.
[e] After 20 days, he developed a pulmonary embolism, which presents with sudden respiratory distress and was diagnosed with CT pulmonary angiography.

Our findings of MRI studies are contrary to Olivotto's study; their study revealed no MRI findings. Also, it differs from previous studies on MRI findings of encephalopathy in MIS-C [18] or any neurological problems in the COVID-19 [14]. Our study reported abnormal waves in the EEG of 4 patients. EEG abnormalities are also seen in Olivotto's study, which documented a correlation between the extent and during of EEG abnormality and the severity of NS.

We had some limitations. First, this study was conducted retrospectively; thus, investigations of patients were not similar and depended on the guidelines of their time. However, neurologic evaluation, including neurological examination, CSF analysis and brain CT scan, was performed for all patients in the same way. Second, Since MIS-C is a clinical diagnosis and diagnostic test is lacking, it is not possible to distinguish between acute neurological symptoms as part of MIS-C and as a coincidence.

Since MIS-C and its association, such as acute neurological symptoms, are newly known, further studies on larger samples are required to clarify many aspects of them. Long-term follow-up should also be done to reveal sequels and their incidence.

4. Conclusion

According to our series and other studies, children with MIS-C may present signs and symptoms of acute neurological symptoms. Although its pathophysiology is unclear, studies showed that immunomodulatory agents, i.e., IVIg and corticosteroids, provide a relatively good prognosis.

Ethical statements

The present study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. This study was approved by the ethics committee of Isfahan University of Medical Sciences with the ethical code number: IR.MUI.MED.REC.1399.024.

Patients' privacy was protected by assigning an identification code (ID) to each patient without recording the name and file number. Written informed consent was obtained from patients for the publication of all images, clinical data and other data included in the manuscript, after explaining the study to them.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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