

Research Article

Neurological effects of COVID-19 in pediatric patients with the multisystem inflammatory syndrome in children (MIS-C).

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Abstract

Background: In December 2019, people residing in the Chinese region of Wuhan were reported to have developed a severe form of pneumonia brought on by a novel coronavirus that is now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since then, cases of the ensuing clinical syndrome, known as COVID-19, have been documented from every nation in the world. The authors of this article outline the present state of information regarding COVID-19 in children's neurologic sequelae. **Objective:** To assess the neurological impact in pediatric patients with COVID-19-associated Multisystem Inflammatory Syndrome in Children (MIS-C). **Methods:** Patients who were admitted to Minia University Hospital's Pediatric Intensive Care Unit (PICU) isolation unit between December 2020 and July 2022 were included in this cross-sectional study. We investigated at a total of 368 patients, of which 62 had PCR results that were positive for covid. **Results:** Convulsions was demonstrated among the patients by 20 (31.7%), p-value<0.0001. followed by DCL was 18 (28.2%) p-value<0.0001. Headache was also demonstrated among the patients also by 18 (28.2%) p-value<0.0001. Weakness was also demonstrated among the patients 18 (28.3%) p-value<0.0001. While, drowsiness among patients was (9 (14.52%), p-value<0.0001. Hypertonia, hyperreflexia, hypotonia, hyporeflexia, 4 (3.5%) and 2 (1.7%) respectively. The majority of the patients had abnormal ground glass opacities on their chest scans (CO-RADS III). The number of patients who had neurological manifestations show significantly increased mortality. **Conclusion:** pediatric patients with SARS-CoV-2 infection may have life-threatening neurological disorders, even if only neurologic symptoms are present, pediatric patients with neurologic presentations should be tested for SARS-CoV-2 due to its prevalence in children. In addition, many of these patients arrived at the hospital unaware of COVID-19 exposure and positivity, so testing is necessary to prevent infection.

Keywords: COVID-19, multisystem inflammatory syndrome in children (MIS-C), pediatrics, neurological symptoms, SARS-CoV-2

Introduction

Worldwide morbidity and mortality have increased since December 2019 as a result of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, which is the virus that causes coronavirus disease 2019 (Covid-19).¹ The National Health Service of the United Kingdom issued a warning to physicians on April 25, 2020, on a recently identified syndrome in children that causes severe multisystem inflammation and has

clinical signs like Kawasaki disease and toxic shock syndrome.² As more cases spread around the world, the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) designated the illness as multisystem inflammatory syndrome in children (MIS-C).³⁻⁵ The spread of SARS-CoV-2 coincided with the appearance of MIS-C. This hyperinflammatory condition revealed involvement of the cardiovascular, hematologic, pulmonary, gastrointestinal, and

mucocutaneous systems. In at least four biomarkers that indicate inflammation, the majority of patients (92%) reported increases.^{6,7}

It is possible for the SARS-CoV-2 virus to reach the brain via a hematogenous pathway and cross the blood-brain barrier, according to the evidence that is currently available. Additionally, it might traverse the cribriform plate via the olfactory system and enter trans-neuronally. The endothelial cells of the cerebral vasculature have angiotensin-converting enzyme 2 receptors, which serve as ports of entrance for the virus.⁸ In the absence of respiratory symptoms, children with MIS-C manifested with novel neurological symptoms involving both the central and peripheral nerve systems as well as splenic abnormalities on imaging. Encephalopathy, headaches, brainstem and cerebellar indications, muscle weakness, and slowed reflexes were among the symptoms.⁹

Patients and methods

In this cross-sectional study, patients who were admitted to Minia University Hospital's Pediatric Intensive Care Unit (PICU) isolation unit between December 2020 and July 2022 were included. The aim of this study was to evaluate the neurological manifestations in pediatric patients with MIS-C associated to COVID-19. In the study we observed a total of 368 patients from them we studied included 60 patients with MIS-C who had laboratory confirmed SARS-CoV-2 infection (positive SARS-CoV-2 RT-PCR) according to CDC case definition for MIS-C associated to COVID-19.³

inclusion criteria: Both male and female pediatric patients (under the age of 18), a severe illness requiring hospitalization, body temperature greater than 38.0°C or a report of a subjective fever lasting at least 24 hours, and laboratory proof of organ involvement and inflammation (i.e., involving at least two systems).

Ethical considerations:

The study protocol and all procedures were approved by the ethical committee of the Minia College of medicine. Before include the patient's family in the study, a signed consent was obtained from them. With the family members, the procedures, objectives, potential advantages, and risks were all reviewed.

data collection

All patients underwent the following:

1. Meticulous history taking including: Name, sex, age, residence, history of medical problems, history of chronic diseases, family history of recent COVID-19 infection.
- 2- presenting complain: Fever, respiratory, cardiovascular, neurologic, gastrointestinal tract (GIT), hematologic, renal and dermatologic.
2. Thorough clinical examination to all children including:
 - a) General examination.
 - b) A physical and local examination.
 - c) neurological evaluation: Convulsions, a lowered conscious level (DCL), weakness, drowsiness, irritability, hypertonia, hyperreflexia, ataxia, nystagmus, hallucinations, and lethargy were identified.
3. Lab tests, such as complete blood counts (CBC), prothrombin concentrations (PC), C-reactive protein (CRP), markers of coagulopathy (D-dimer), serum ferritin, liver function tests (Albumin), lactate dehydro-genase (LDH), troponin, creatine phosphor-kinase (CPK), and erythrocyte sedimentation rates (ESR).
4. Radiological evaluation such as abdominal ultrasound, echocardiography, brain and chest MRI, and chest CT.
5. Hospital stay and result (whether the patient survived or not) were also evaluated.

Statistical Analysis:

Data entry and all statistical analyses were performed using Statistical Package for Social Science (SPSS) version 21 (IBM Corp. 2011) under windows 7 operating system. For quantitative data, results are shown as means SD, while for qualitative data, they are presented as No. (%). Analyses were done for quantitative variables using one-way ANOVA test for comparison between the studied patients and post Hoc Tukey's correction between studied patients. The nonparametric quantitative variables analyzed by the same tests after logarithmic transformation. Chi square test, however, was employed to compare qualitative data between studied patients. P-values were considered significant if they were less than 0.05 and highly significant if they were less than 0.01. If the P-value was larger than or equal to 0.05, it was considered to be non-significant.

Results

Regarding the demographic and baseline data among the studied patients, the results revealed that the Mean $\pm$ SD age was 0.8 ± 0.3 , and the age range was 0.4-7.0 years. With regard to sex, males 43 (70.0%) were more demonstrated in the studied patients than female patients 19 (30.0%). However, this difference was non-significant. (Table 1).

Regarding symptoms 60 (96.77%) of patients had fever while 2(3.23%) show no fever at presentation with significant difference with p-value< 0.0001. The majority of the patients showed respiratory symptoms, 57 (93.3%). The cardiovascular symptoms were significantly highly demonstrated among the majority of the patients 43 (70.0%) with p-value< 0.0001, neurologic symptoms were demonstrated among the patients by 29 (46.77%). Gastrointestinal symptoms were demonstrated by 19 (30.0%) with significant difference p-value< 0.0001. Hematologic symptoms also were significantly highly demonstrated among the patients 48 (78.3%), p-value<0.0001. On the other hand, only a small number of the patients 3 (4.84%) and 2 (3.23%), showed renal and dermatologic symptoms respectively (Table 2).

Concerning neurological manifestations among the studied patients. Convulsions was demonstrated among the patients by 20 (31.7%), p-value<0.0001. followed by DCL was 18 (28.2%) p-value<0.0001. Headache was also more demonstrated among the patients also by 18 (28.2%) p-value<0.0001. Weakness was also demonstrated among the patients by 18

(28.3%) p-value<0.0001. While, drowsiness among patients was 9 (14.52%), p-value<0.0001. Hypertonia, hyperreflexia, hypotonia, hyporeflexia, 4 (3.5%) and 2 (1.7%) respectively (Table 3). The radiological data showed significant difference in the studied patients regarding the percentage of the normal and abnormal signs of Chest CT, Brain CT, and Brain MRI. The abnormal signs of Chest CT and Brain CT were more demonstrated in the studied patients, the percentage of the abnormal signs of Chest CT were 56(93.3%), the abnormal signs of Brain CT were 12 (20.0%), the abnormal signs of Brain MRI were 1(1.7%). (Table 4). Regarding Chest CT, the results revealed that the majority of patients in the studied patients showed abnormal Chest CT findings in the form of ground glass opacities (CO-RADS III) 45(73.3%) followed by (CO-RADS IV) 12(18.3%) then (CO-RADS V). CO-RADS IV 1(1.7%). However, these results were non-significant (Table 5). Brain CT results revealed that normal Brain CT was more demonstrated among patients 48(80%) Cerebral edema was demonstrated among patients by 12 (18.3%). Intracerebral hemorrhage was more demonstrated among patients by 2 (1.7%). Cerebral venous sinus thrombosis as well as cerebral infarction were not seen (Table 6). The duration of the hospital stay was (Mean $\pm$ SD is 7.8 ± 2.1 with a range of 6-11 days). With regard to the outcomes, the percentage of non-survived patients among the patients was 14 (22.58%) (Table 7). Concerning the outcomes of patients with neurological manifestations, the percentage of non-survived patients was (12(42.86%) (Table 8)

Table (1): demographic and baseline data of the studied patients:

Variable		Patients with MIS-C PCR +ve (n=62)		P. value (Sig.)
Age (year)	Mean ± SD	0.8 ± 0.3		0.08*
	Range	0.4-7.0		
Sex	Male	43 (70.0%)		0.52*
	Female	19 (30.0%)		
Weight (kg)	Mean ± SD	9.4 ± 2.9		
	Range	5-15		
Residence	Urban	33 (53.3%)		0.80*
	Rural	29 (46.7%)		

ANOVA and Chi-square tests were used to compare among studied patients.

*: Not significant.

Table (2): Comparison among the studied patients regarding symptoms:

Variable			
		Patients with MIS-C PCR +ve (n=62)	P. value (Sig.)
Fever	No	2(3.23)	P < 0.0001***
	Yes	60 (96.77%)	
Respiratory symptoms	No	5 (6.7%)	<0.0001***
	Yes	57 (93.3%)	
Cardiovascular symptoms	No	19 (30.0%)	<0.0001***
	Yes	43 (70.0%)	
Neurologic symptoms	No	33 (53.22%)	0.4744*
	Yes	29 (46.77%)	
Gastrointestinal symptoms	No	43 (70.0%)	<0.0001***
	Yes	19 (30.0%)	
Hematologic symptoms	No	14 (21.7%)	< 0.0001***
	Yes	48 (78.3%)	
Renal symptoms	No	59 (95.16%)	< 0.0001***
	Yes	3 (4.84%)	
Dermatologic symptoms	No	58 (93.55%)	< 0.0001***
	Yes	2 (3.23%)	

Chi-square test was used to compare among studied patients

*: Not significant.

**: Significant (p < 0.05)

***: Highly significant (p < 0.01)

Table (3): Comparison among the studied patients regarding neurological manifestations.

Variable			
		Patients with MIS-C PCR +ve (n=62)	P. value (Sig.)
Convulsions	- ve	42 (68.3%)	<< 0.0001***
	+ ve	20 (31.7%)	
DCL	- ve	44 (71.7%)	< 0.0001***
	+ ve	18 (28.2%)	
Headache	- ve	44 (71.8%)	< 0.0001***
	+ ve	18 (28.3%)	
Weakness	- ve	46 (74.19%)	< 0.00018***
	+ ve	16 (25.8%)	
Drowsiness	- ve	53 (85.48%)	<0.0001***
	+ ve	9 (14.52%)	
Irritability	- ve	60 (98.2%)	<0.0001***
	+ ve	2 (1.8%)	
Hypertonia, hyperreflexia	- ve	57 (96.5%)	<0.0001***
	+ ve	4 (3.5%)	
Hypotonia, hyporeflexia	- ve	60 (98.3%)	<0.0001***
	+ ve	2 (1.7%)	
Ataxia	- ve	60 (96.78%)	<0.0001***
	+ ve	2(3.23)	
Nystagmus	- ve	61 (98.39%)	<0.0001***
	+ ve	1(1.61)	
Hallucinations	- ve	60 (96.78%)	<0.0001***
	+ ve	2(3.23%)	
Lethargy	- ve	62 (96.78%)	<0.0001***
	+ ve	2(3.23%)	

Chi-square test was used to compare among studied patients.

*: Not significant, **: Significant (p<0.05), ***: Highly significant (p<0.01), DCL: Decreased conscious level

Table (4): Comparison among the studied patients regarding radiological data.

Variable			
		Patients with MIS-C PCR +ve (n=62)	P. value (Sig.)
Chest CT	Normal	4(6.7%)	<0.0001***
	Abnormal	56(93.3%)	
Brain CT	Normal	48 (80.0%)	<0.0001***
	Abnormal	12 (20.0%)	
Brain MRI	Normal	59(98.3%)	<0.0001***
	Abnormal	1(1.7%)	
Echo	Normal	52(86.7%)	0.002***
	Abnormal	8(13.3%)	
Abdominal Ultrasound	Normal	56(93.3%)	0.03***
	Abnormal	4(6.7%)	

Chi-square test was used to compare among studied patients.

*: Not significant.

**: Significant (p<0.05)

***: Highly significant (p<0.01)

Table 5: Comparison among the studied patients regarding Chest CT.

Chest CT		
	Patients with MIS-C PCR +ve (n=62)	P. value (Sig.)
Normal	4(6.7%)	0.27*
(CO-RADS III)	45(73.3%)	
(CO-RADS IV)	12(18.3%)	
(CO-RADS V)	1(1.7%)	

Chi-square test was used to compare among studied patients

*: Not significant.

CO-RADS: The COVID-19 Reporting and Data System.

Table 6: Comparison among the studied patients regarding brain CT.

Brain CT		
	Patients with MIS-C PCR +ve (n=62)	P. value (Sig.)
Normal	48 (80%)	0.88*
cerebral edema	12 (18.3%)	
intracerebral hemorrhage	2 (1.7%)	
cerebral venous sinus thrombosis	0 (0%)	
cerebral infarction	0 (0%)	

Chi-square test was used to compare among patients.

*: Not significant.

Table (7): Comparison among the studied patients regarding hospital stay and outcomes.

Variable			
		Patients with MIS-C PCR +ve (n=62)	P. value (Sig.)
Hospital stay (days)	Mean $\pm$ SD	7.8 $\pm$ 2.1	
	Range	6-11	
Outcome	Survived	48 (77.42%)	< 0.0001***
	Not-survived	14 (22.58%)	

ANOVA and Chi-square tests were used to compare among studied patients.

*: Not significant.

**: Significant (p<0.05)

***: Highly significant (p<0.01)

Table 8: Outcomes of patients with neurological manifestations.

Variable			
		Patients with MIS-C PCR +ve (n=62)	P. value (Sig.)
Outcomes	Survival	16 (57.14%)	0.2896*
	Non survival	(12 (42.86%))	

Chi-square test was used to compare among studied patients.

*: Not significant.

Discussion

In children with COVID-19, MIS-C is a disease that causes inflammation in a number of organ systems, including the heart, lungs, brain, kidneys, gastrointestinal tract, skin, and eyes¹⁰. Most of the patients with MIS-C in the research were younger than 5 years old, which is in line with Gupta Dch¹¹ observation that nearly 60% of children presenting with MIS-C were. In all studied patients, there were more male patients (43, 70.0%) than female patients (19, 30.0%). These results corroborated those of LaRovere et al.,¹² Additionally, a disproportionately high proportion of mortalities and critical cases have included men.¹³

Only 62 (27.17%) of the 368 MIS-C patients who were observed over the study period (in the current study) had positive COVID-19 RT-PCR results. These findings corroborated Chen¹⁴ claim that 46% of MIS-C patients had COVID-19 RT-PCR results that were positive. According to this data, even when MIS-C

occurred, the majority of the patients may not have an active COVID-19 infection. A large majority of MIS-C patients are PCR-negative but positive serologically for SARS-CoV-2 antibodies and/or have a history of mild COVID-19 infection or exposure several weeks prior to presentation, despite the fact that only about a third of patients with MIS-C are positive for SARS-CoV-2 by PCR. Given the chronology, it is likely that MIS-C is an immunological, autoimmune, or post-infectious condition.¹⁵ Contrary to research that showed COVID-19 in adults only causes moderate respiratory sickness in children, and the majority of cases are asymptomatic^{16,17}, in the current study, 60 (96.77%) of the patients had fever at the time of presentation, compared to 2 (3.23%), who did not, a significant difference with a p-value of 0.0001. 57 patients (93.3%) of the patients had respiratory symptoms. Neurologic symptoms were evident in 29 patients (46.77%), while 43 patients (70.0%) of the patients had cardiovascular

symptoms, which were much more prevalent. 19 patients (30.0%) reported having gastrointestinal manifestations with a significant difference p-value of 0.0001. The 48 patients (78.3%) showed a significant increase in hematologic symptoms, with a p-value of 0.0001. However, just a few of the patients—3 (4.84%) and 2(3.23%), respectively—exhibited dermatologic and renal symptoms. Our findings corroborated the findings of other studies that indicated individuals with MIS-C may experience respiratory symptoms, gastrointestinal problems, neurocognitive symptoms, sore throats, and myalgias. Patients with moderate symptoms at first may quickly escalate to severe sickness with multi-organ dysfunction since ¹⁸⁻²⁰ MIS-C is often a progressive illness.

Haemodynamic instability, tachycardia, left ventricular failure, and respiratory distress are examples of critical symptoms that may occur either on their own or as a result of cardiac dysfunction. ²¹ According to Duarte-Neto et al.,²² COVID-19 virus commonly infects the respiratory tract in MIS-C patients. The abdominal pain associated with MIS-C can be so severe that it has occasionally been misdiagnosed as appendicitis. ^{23,24} Regarding the neurological symptoms in the present study, Twenty (31.7%) of the patients showed evidence of convulsions, with a p-value of 0.0001. DCL came in second with 18 (28.2%), p-value 0.0001. Additionally, 18 (28.2%) individuals showed a greater occurrence of headaches, with a p-value of 0.0001. Weakness was also demonstrated among the patients 18 (28.3%) p-value<0.0001. While, drowsiness among patients was (9(14.52%), p-value<0.0001. 4(3.5%) cases of hypertonia, hyperreflexia, hypotonia, and hyporeflexia, and 2 (1.7%) cases, respectively. According to these findings, numerous studies have found that children with MIS-C exhibit neurological symptoms surprisingly frequently. ^{12,14,25} According to the results of this study, patients with neurological manifestations have had worse outcomes than those without neurological manifestations. The duration of the hospital stay was (Mean $\pm$ SD is 7.8 ± 2.1 with a range of 6-11 days). With regard to the outcomes, the percentage of non-survived patients among the patients was 14 (22.58%). Concerning the outcomes of patients with neurological manifestations, the percentage of non-survived patients was (12 (42.86%).

Conclusion

pediatric patients with SARS-CoV-2 infections may have life-threatening neurological disorders, even if only neurologic symptoms are present, pediatric patients with neurologic presentations should be tested for SARS-CoV-2 due to its prevalence in children. In addition, many of these patients arrived at the hospital unaware of COVID-19 exposure and positivity, so testing is necessary to prevent infection. The neurological manifestations in COVID-19 pediatric patients with MIS-C could include convulsions, DCL, headache, and weakness.

Declarations:

- **Ethics approval:** This study was approved by the ethical committee, faculty of medicine, all methods were performed in accordance with the relevant guidelines and regulations by including a statement.
- **Consent to participate:** A written consent was obtained from each parent to agree to participate in the study. Protect the participant's anonymity and confidentiality. Avoiding using deceptive practices. Giving participants the right to withdraw from our research. Consent for publication was taken.
- **Consent for publication:** Not applicable
- **Availability of data and materials:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
- **Competing interests:** We declared no conflict of interest concerning the study
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