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Original Article

Neurological manifestations in patients with multisystem inflammatory syndrome in children (MIS-C) in the post-COVID-19 era

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Abstract

Background Multisystem inflammatory syndrome in children (MIS-C) is an emerging condition associated with the COVID-19 pandemic. It occurs in approximately 2-8% cases of COVID-19, sometimes leading to shock, multiorgan failure, and the need for intensive care. Neurological manifestations are uncommon and sometimes overlap with previous comorbidities.

Objective To explore the neurological manifestations in critically ill children with MIS-C.

Methods This cross-sectional study included children aged <18 years, diagnosed with MIS-C according to *World Health Organization* (WHO) criteria and admitted to the pediatric intensive care unit (PICU) at a tertiary hospital in Bali, Indonesia. Retrospective data were extracted from electronic medical records covering January 2022 to December 2023. Demographic characteristics, clinical manifestations, treatments, and outcomes were collected and analyzed using *SPSS*. Patient were grouped based on the presence or absence of neurological symptoms for comparison.

Results There were 47 children diagnosed with MIS-C; 78.7% of them were critically ill and treated in our intensive care unit. Thirty-seven subjects were included in the study. The most common symptom was fever (83.8%). Neurological manifestations were found in 12 children (32.4%), most commonly decreased consciousness (58.3%), followed by seizures (25.0%), hemiparesis (8.3%), and behavioral changes (8.3%). When comparing subjects with vs. without neurological symptoms, those with neurological manifestations had higher proportions of invasive mechanical ventilation (58.3% vs. 36.0%, respectively), combined use of intravenous immunoglobulin and methylprednisolone (83.3% *vs.* 64.0%, respectively), and mortality (58.3% *vs.* 28.0%, respectively).

Conclusion Neurological manifestations, particularly decreased consciousness, were common in critically ill MIS-C patients. These patients exhibited higher rates of invasive ventilation and mortality, emphasizing the need for early recognition and targeted management. **[Paediatr Indones. 2025;65:239-44; DOI: https://doi.org/10.14238/pi65.3.2025.239-44].**

Keywords: *children; critical illness; neurological manifestation; MIS-C*

Since the onset of the COVID-19 pandemic, the incidence of the infection among children and adolescents has remained relatively low. Data from various regions, including Asia, Europe, and North America, indicate that children represent between 2.1% and 7.8% of all confirmed COVID-19 cases. Typically, children experience less severe symptoms and generally have more favorable outcomes compared to adults. Despite the generally milder nature of the disease in this age group, a minority of children still require hospitalization and intensive care.[1]

In some instances, children and adolescents who contract COVID-19 develop a condition known as multisystem inflammation, which emerges after the initial infection rather than during the acute phase. This post-COVID-19 inflammatory condition shares similarities to toxic shock syndrome, but occurs without any microbial infection. This condition, termed the multisystem inflammatory syndrome in children (MIS-C), can lead to severe complications, including shock and failure of multiple organs, often requiring intensive medical care.[2]

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The World Health Organization (WHO) defines MIS-C in individuals aged 0-19 years as having a fever persisting for over three days, confirmed previous COVID-19 infection, and elevated inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or procalcitonin. Additionally, there must be no microbial cause of inflammation, and at least two of the following symptoms must be present: rash or bilateral non-purulent conjunctivitis, signs of mucocutaneous inflammation (affecting the mouth, hands, or feet), low blood pressure or shock, myocardial dysfunction, pericarditis, valvulitis, coronary abnormalities (identified via echocardiography or elevated troponin/NT-proBNP), evidence of coagulopathy (assessed by prothrombin time, partial thromboplastin time, or elevated D-dimer levels), and/or acute gastrointestinal issues like diarrhea, vomiting, or abdominal pain.[3]

Children diagnosed with MIS-C often need intensive treatment in the pediatric intensive care unit (PICU). Some of these children require respiratory support; research indicates that MIS-C patients have a higher propensity for requiring invasive respiratory support compared to COVID-19 patients without MIS-C. Moreover, many MIS-C patients suffer from potentially fatal shock caused by widespread inflammation in multiple organ systems.[4,5]

Various risk factors play a role in the emergence of MIS-C in children who contract COVID-19, such as age, viral load, and preexisting health conditions. These factors can impact the intensity of the inflammatory response. In COVID-19 cases, severity of illness by age forms a U-shaped curve, with infants under one year experiencing higher severity levels. Furthermore, children with comorbidities such as congenital or acquired cardiovascular disease, chronic respiratory conditions such as asthma and bronchiectasis, hepatic or renal dysfunction, genetic disorders, inherited metabolic disorders, and preexisting neurological impairments exhibit an elevated risk of developing MIS-C.[6,7]

Numerous studies suggest that, beyond age, viral load, and comorbidities, racial factors also pose particular risks for MIS-C, especially among African and Latin American children.[8,9] Despite COVID-19's profound impact in Indonesia and its widespread prevalence among children, detailed data on MIS-C remains scarce. This gap in comprehensive information about the characteristics of children with MIS-C has driven the need for this study. Consequently, we seek to investigate the neurological manifestations in critically ill children suffering from MIS-C.

Methods

This research employed a cross-sectional design, utilizing secondary data sourced from the electronic medical records of pediatric MIS-C patients in the PICU of Ngoerah Hospital in Bali, Indonesia from January 2022 to December 2023. This study was approved by the Research Ethics Committee of the Faculty of Medicine, Udayana University/Ngoerah Hospital.

The aim of this study was to investigate the neurological manifestations observed in severely ill children diagnosed with MIS-C. Subjects were children under 18 years who met the WHO criteria for MIS-C and were admitted to the PICU. Children with pre-existing chronic conditions, such as congenital heart disease (CHD), malignancies, and chronic obstructive pulmonary disease (COPD), were excluded from the study. Subjects were included using a consecutive sampling method.

Data analysis was performed using *SPSS (IBM,* Armonk, New York). Prior to analysis, data normality was assessed using the Kolmogorov-Smirnov test, with a P value >0.05 indicating normal distribution. Categorical variables were summarized as frequency distributions and percentages, while numerical data following a normal distribution were presented as mean and standard deviation. Comparisons between categorical variables were conducted using the Chi-square test or Fisher's exact test, depending on the expected cell counts. A P value <0.05 was considered statistically significant.

Results

Among the 47 children diagnosed with MIS-C, 37 (78.7%) required critical care treatment in the PICU. **Table 1** illustrates the clinical characteristics of the subjects. There was a slight predominance of children under five years old (19/37) and males (19/37). Most children (24/37) had normal nutritional status. The

most prevalent symptoms was fever (31/37), while neurological symptoms were observed in 12/37. Most of the children either did not need ventilatory support (17/37) or required mechanical ventilation (16/37). The majority of patients (26/37) were treated with both intravenous immunoglobulin (IVIG) and glucocorticoids. Of the 37 children, 23 were survived. The average hospital stay for patients was 16 (SD 13) days.

Of the 12 children who had neurological manifestations, seven showed decreased consciousness, three had seizures, and one each experienced hemiparesis and behavioral disorders, respectively. Six children had comorbidities, including sepsis, septic shock, acute respiratory distress syndrome (ARDS), rapidly progressive glomerulonephritis (RPGN), failure-stage acute kidney injury (AKI), hypertensive crisis, pulmonary edema, community acquired pneumonia (CAP), acute liver failure, acute hepatitis, and metabolic encephalopathy.

Of the total sample, 12 subjects exhibited neurological manifestations, while 25 subjects had none. As shown in **Table 2**, children with neurological manifestations, compared to those without, had a higher rate of invasive mechanical ventilation (7/12 *vs.* 9/25), administration of both IVIG and methylprednisolone (10/12 *vs.* 16/25), and mortality (7/12 *vs.* 7/25). However, these differences did not reach statistical significance.

Table 1. Clinical characteristics of all MIS-C patients in the PICU

Characteristics	N=37
Age, n	
<5 years	19
5-10 years	4
>10 years	14
Gender, n	
Female	18
Male	19
Nutritional status, n	
Severely wasted	2
Wasted	8
Normal	24
Overweight	3
Clinical manifestation(s), n	
Fever	31
Dyspnea	15
GI tract symptoms	18
Neurological symptoms	12
Mucosal involvement	10
Need for ventilation, n	
None	17
Non-invasive ventilation	4
Mechanical ventilation	16
Treatment, n	
Supportive care only	3
Glucocorticoids only	8
IVIG and glucocorticoids	26
Outcomes, n	
Died	14
Survived	23
Mean length of stay (SD), days	16 (13)

Table 2. Treatment and outcomes of subjects with and without neurological manifestations

Characteristics	Neurological manifestations		P value
	Yes (n=12)	No (n=25)	
Need for ventilation, n			0.438[a]
None	4	13	
Non-invasive ventilation	1	3	
Mechanical ventilation	7	9	
Treatment, n			0.355[a]
Supportive care only	0	3	
Glucocorticoids only	2	6	
IVIG and glucocorticoids	10	16	
Outcome, n			0.146[b]
Died	7	7	
Survived	5	18	

[a]Chi-square test; [b]Fisher's exact test

Discussion

Our cross-sectional study focused on the neurological symptoms observed in 47 children diagnosed with MIS-C in the hospital. We found that 37 (78.7%) of these critically ill children required PICU treatment and were consequently included in the study. Clinically, MIS-C manifests with dysfunction in various organ systems, including the gastrointestinal (GI), cardiovascular, neurological, and respiratory systems, as well as mucocutaneous symptoms such as conjunctivitis, edema of the extremities, and rash. Treatment often involves organ support therapies such as inotropic or vasoactive medications, and, in some cases, mechanical ventilation.[10]

A slight majority of our subjects were under 5-year-old (19/37) and male (19/37). A study conducted in the United Kingdom reported a median age of 3.4 years among MIS-C patients, with 70% being under the age of 5. Susceptibility arises from the ongoing development of both the innate and adaptive immune systems, heightening the risk of infection from various pathogens such as bacteria, viruses, fungi, and parasites.[11,12] A previous study reported that 60.0% of their subjects were male.[13] Males generally constitute the majority of children diagnosed with COVID-19, especially during the initial phase linked to MIS-C. However, a study reported that gender did not notably impact PICU admission or the severity of illness necessitating PICU care.[14] Studies indicate that overweight or obese children tend to exhibit higher MIS-C severity scores (MSS). This association has been attributed to factors such as increased inflammatory cell presence, elevated levels of proinflammatory cytokines, and enhanced expression of receptors that bind to the SARS-CoV-2 virus.[15-17] In our study, 24 of 37 subjects had normal nutritional status, aligning with the findings of a study which reported that more than half of the individuals diagnosed with MIS-C had a healthy body weight.[18]

In our hospital, the clinical presentation of patients with MIS-C mirrored common observations. Most patients exhibited fever (31/37), followed by gastrointestinal symptoms (18/37), respiratory distress (15/37), neurological symptoms (12/37), and mucocutaneous involvement (10/37). Numerous studies conducted in Europe and the United States have documented a rise in sporadic cases of MIS-C among children and adolescents.[6,7] This syndrome shares similarities with Kawasaki disease and toxic shock syndrome.[13,19] We noted that half of the subjects did not require ventilatory support. After receiving fluid therapy, patients were subsequently often prescribed immunomodulatory medications, typically considered as the primary therapeutic intervention.[20] According to multiple studies, nearly all patients commonly receive IVIG.[1,2,4] More than half of our patients were treated with glucocorticoids, consistent with findings from several other studies.[4,8,13] In our study, 26/37 of patients were treated with a combination of IVIG and glucocorticoids.

Twenty-three of the 37 children requiring PICU admission did not survive. The mean length of hospital stay in our study was 16 days. In previous reports, the neurological symptoms associated with MIS-C have included headache, fatigue, cognitive decline, and irritability. Severe complications, such as encephalopathy, seizures, coma, stroke, meningoencephalitis, and meningitis have less frequently been observed.[21] In our study, 12 children exhibited neurological symptoms, of whom seven experienced decreased consciousness, three had seizures, one had hemiparesis, and one showed behavioral changes. According to a previouscohort study, only 22.0% of hospitalized children with SARS-CoV-2 infection (data not segregated by acute SARS-CoV-2 or MIS-C specifically) displayed neurological symptoms. Among these, fatigue or weakness was the most prevalent, followed by altered consciousness or confusion, and then headache.[22,23] A recent meta-analysis examining neurological symptoms in children with SARS-CoV-2 infection reported fatigue or myalgia as the most frequent symptom, affecting 14.0% of cases. Acute encephalopathy was observed in 13.0% of instances. Headaches occurred less commonly, impacting 4% of cases, while seizures affected 3%.[9]

Up to half of children admitted with neurological conditions had pre-existing comorbidities. Invasive mechanical ventilation was provided in 7/12 of those with neurological symptoms. Consistent with findings from studies conducted in India, 37 subjects (78.7%) of our MIS-C patients required intensive care, with 20/37 necessitating ventilatory assistance, of whom 16 required mechanical ventilation. Similarly, a previous study reported that children with MIS-C frequently

presented with severe illness, often necessitating intensive care management, including advanced interventions such as intubation or mechanical ventilation.[24]

Presently, there are no standardized treatment guidelines for MIS-C linked to COVID-19. Nevertheless, the primary goals of treatment are to reduce inflammation, support organ function, and prevent the worsening of long-term complications. In this study, a substantial majority (10/12) of patients with neurological symptoms were treated with both IVIG and methylprednisolone. All identified cases of MIS-C treated with IVIG and/or methylprednisolone recovered fully without any permanent neurological sequelae. In a cohort study on MIS-C, four children with Kawasaki-like illness were treated using IVIG and steroids, all showing positive responses to the treatment. Steroid therapy was administered to 80.0% of MIS-C-afflicted children, with prognosis varying based on the severity of their initial diagnosis.[22]

Our study revealed that children presenting neurological symptoms had a higher mortality rate than those without (7/12 *vs.* 7/25) . Similarly, a previous study reported that patients with severe neurological manifestations during hospitalization had a significantly higher mortality rate than those without such manifestations. The occurrence of neurological manifestations was associated with a higher likelihood of mortality or moderate disability upon discharge among the surviving patients.[23]

The retrospective nature of our study was a constraint. At present, there is insufficient data to determine if this condition will lead to different long-term outcomes compared to similar diseases. To define transient and permanent neurological complications, prognostic factors, and both acute and chronic adverse effects of MIS-C, multicenter long-term follow-up studies are necessary.

In conclusion, neurological manifestations, particularly decreased consciousness, were common among our critically ill MIS-C patients. These patients had higher rates of invasive ventilation and mortality, highlighting the importance of early diagnosis and appropriate management. Given the potential overlap of neurological symptoms with comorbidities, a thorough clinical assessment remains crucial for timely intervention, especially in patients without a prior history of neurological conditions.

Conflict of interest

None declared.

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