RESEARCH PAPER

Neurological Manifestations of COVID-19 Associated Multisystem Inflammatory Syndrome in Children (MIS-C) in Yogyakarta, Indonesia

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Objective: This observational cohort study aims to provide data on pediatric patients with neurological manifestations associated with multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease (COVID-19). **Methods:** Patients aged <18 with neurologic symptoms and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection from January, 2021 to January, 2022 at the Dr. Sardjito Hospital in Yogyakarta, Indonesia were evaluated. We used WHO diagnostic criteria to classify patients as MIS-C or non-MIS-C. Demographic information, symptoms, and outcomes were compared between MIS-C and non-MIS-C groups. **Results:** Between January, 2021 and January, 2022, 74 pediatric patients were considered eligible. More than half of the patients were female (54.1%), and 24.3% presented with MIS-C. Length of hospitalization was significantly longer in MIS-C individuals (*P*=0.006). The commonest neurological findings were involuntary movements (43.2%) and paresis (27%). The commonest neuroimaging findings were meningoencephalitis (18.9%) and hydrocephalus (22.9%). Among all the variety of neurologic manifestations in non-MIS-C and MIS-C patients, a statistically significant result was found for fever (71.4% vs 100%; *P*=0.015*)*, altered mental state (14.2% vs 50%, *P*=0.004*)*, and paresis (33.9% vs 5.5%, *P*=0.030*)*. **Conclusion:** MIS-C was found in 24% of our patients with acute neurologic symptoms, and most cases (51.8%) had positive SARS-CoV-2 antibody results.

Keywords: *Hydrocephalus, Neuroimaging, Outcome, Stroke*.

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Until January 10, 2022, there were more than 500,000 pediatric coronavirus disease 2019 (COVID-19) cases in Indonesia, leading to 5,000 deaths in children [1]. Approximately 22-47% of pediatric patients in the US experience neurological symptoms related to COVID-19, such as seizures, status epilepticus, difficulty walking, anosmia, ageusia, head-ache, altered mental status, and fatigue [2]. Whereas, about 5% experienced life-threatening neurologic manifes-tations related to multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C), including severe encephalopathy (white matter hyperintensities and splenial lesions), acute ischemic or hemorrhagic stroke, acute central nervous system infection/acute disseminated encephalo-myelitis (ADEM), acute fulminant cere-bral edema, aseptic meningitis, and Guillain-Barré syndrome (GBS) [2-4]. SARS-CoV-2 may cause neurological damage through two mechanisms: a direct viral infection of the central nervous system (CNS) through ACE2 receptors, and inflammatory injury mediated by cytokine release [5]. Only 20%-46% of patients have positive PCR results in MIS-C-associated neurologic cases, whereas 80-99% have positive serum anti-bodies. This evidence shows that when MIS-C occurs, most children are not experiencing acute COVID-19 infection [6].

Invited Commentary: Pages 347-49.

Patients who experience these severe neurological symptoms may develop residual neurologic symptoms that impact their quality of life [2]. This article aims to provide the data of patients who had neurological mani-festations of COVID-19-associated MIS-C.

METHODS

This observational cohort study was conducted on patients younger than 18 years with acute onset of

neurologic manifestations and SARS-CoV-2 infection based on clinical or laboratory evidence, from January, 2021 to January, 2022 at the Dr. Sardjito Public Hospital, a tertiary referral hospital for Yogyakarta and the southern part of Central Java provinces, Indonesia. SARS-CoV-2 infection was confirmed by reverse transcription-quantitative polymerase chain reaction (RT-qPCR) assay from nasopharyngeal swab or a positive serum IgG SARS-CoV-2 test or presumed (clinical diagnosis). Presumed acute SARS-CoV-2 infection was defined as a patient diagnosed clinically based on clinical suspicion and/or a close contact is positive for the virus; this situation occurred most frequently in the early stages of the pandemic when testing was limited due to a lack of testing facilities. Acute onset neurological manifestations looked for in this study were seizures, seizures with fever, focal/general neurological deficits, decreased consciousness, neuropsychiatric disorders, acute neuromuscular disorders, cerebrovascular accidents, movement disorders, and aphasia in children. The patients were also confirmed to have no other underlying neurological diagnosis. All patients were then classified into MIS-C and non-MIS-C groups based on the WHO diagnostic criteria [4].

All children were subjected to detailed clinical history, and completed physical and neurological examinations to find neurological deficit. Additional data as demographics, comorbidities, neurological symptoms, and supporting examinations (brain magnetic resonance imaging (MRI), head computed tomography (CT) scan, and cerebrospinal fluid analysis), therapy and outcome were taken from the medical record. Blood samples were taken for qualitative and quantitative SARS-CoV-2 serologic examinations, as well as a neutrophil-lymphocyte ratio (NLR), C- reactive protein (CRP), and coagulation profile such as prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen levels, and D-dimer.

Statistical analysis: Patients were grouped into non-MIS-C and MIS-C based on the WHO criteria of multisystem inflammatory disorder in children [4]. The normality of the data was verified using the Shapiro-Wilk test. Categorical data are presented in frequencies (percentages), normally distributed data are presented in mean (SD), and non-normally distributed data are presented in median (IQR). Independent *t*-test, Fisher exact test, and Kruskal-Wallis test were used to find the association between the non-MIS-C and MIS-C groups, with *P* value <0.05 considered statistically significant. Data entry and analysis were performed using SPSS v.25 (IBM Corp).

RESULTS

From January, 2021 until January, 2022, a total of 74 children presented acute onset of neurologic manifestations with clinical or laboratory evidence of SARS-CoV-2 infection. Most of the patients (28.3%) were aged 1-5 years, and 54.1% were female. Eighteen patients (24%) had MIS-C with a mean (SD) age 7.7 (6.2) years. The median (IQR) length of stay was 14 (1-81) days. There were significant differences in antibody serology test results ($P<0.001$) and hospital length of stay ($P=0.006$) between the non-MIS-C and MIS-C groups. The mortality was found to be higher in the MIS-C group compared to the non-MIS-C group (44.4% vs 33.9%; $P=0.06$) (**Table I**).

Table I Characteristics of Children With Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) Infection and Neurological Findings (N=74)

Characteristics	*Non MIS-C (n=56)*	*MIS-C (n=18)*
Age (y)[a]	6.4 (5.6)	7.7 (6.2)
Male gender	26 (35.1)	8 (10.8)
RT-qPCR positive	3 (4.1)	4 (5.4)
Antibody test positive	13 (17.6)	14 (18.9)
Hospital stay (d)[b,c]	12 (1-66)	26 (5-81)
Death	11	8

Values in no. (%), [a]mean (SD) or [b]median (IQR). MIS-C: multisystem inflammatory syndrome in children; RT-qPCR: reverse transcription-quantitative polymerase chain reaction. [c]P<0.01.

From a total of 18 patients who experienced MIS-C, all had a fever for more than three days, and had elevated markers of inflammation such as erythrocyte sedimen-tation rate (ESR), CRP, or procalcitonin, no other obvious microbial cause of inflammation and evidence of COVID-19 (RT-qPCR, antigen test or serology positive) (**Web Fig. 1**). The mean prothrombin time (PT) was 18.2 s, partial throm-boplastin time (PTT) was 36.1 s, and D-dimer was 2,291 mg/L. The mean (SD) value of inflammatory markers was 65.2 (65.5) mg/dL for CRP, and 13.25 (33.5) ng/mL for pro-calcitonin.

There were significant differences in neurological manifestations and radiographic findings between the non-MIS-C and MIS-C groups (**Table II**), especially for fever [OR (95% CI) 1.4 (1.2-1.7), $P = 0.015$], altered mental status [OR 6.0 (1.8-19.7), $P = 0.004$], and paresis [OR 0.1 (0.01-0.9), $P=0.030$]. Patients who survived had lesser need of inotropes (12.9% vs 36.8%; $P=0.035$), and lesser use of antiviral agents (3.7% vs 26.3%; $P=0.010$).

DISCUSSION

In our study, 18 children (16.2%) out of 74 children with acute neurologic symptoms were confirmed with MIS-C, which is similar to a study conducted in the US that found 12% of cases of neurologic symptoms were associated with MIS-C [7]. Our study population's mean age of MIS-C cases was similar to previous reports [7,8].

Table II Clinical and Radiologic Findings in Children With SARS-CoV-2 Infection in Yogyakarta, Indonesia

Findings	*Non MIS-C (N=56)*	*MIS-C (N=18)*	*OR (95% CI)*	*P value*
Fever	40 (71.4)	18 (100)	1.4 (1.2-1.7)	0.015
Seizure	32 (57.1)	11 (61.1)	1.2 (0.4-3.5)	0.767
Respiratory distress	7 (12.5)	4 (22.2)	2.0 (0.5-7.8)	0.445
Neurological findings				
Altered mental status	8 (14.3)	9 (50)	6.0 (1.8-19.7)	0.004
Paresis	19 (33.9)	1 (5.5)	0.1 (0.01-0.9)	0.030
Aphasia	2 (3.6)	0	-	0.416
Involuntary movement	23 (41.1)	9 (50)	1.4 (0.5-4.2)	0.506
Stroke/transient ischemic attack	6 (10.7)	3 (16.7)	1.7 (0.4-7.5)	0.679
Guillain-Barré syndrome	1 (1.8)	1 (5.5)	3.2 (0.2-54.5)	0.430
Neuroimaging				
Cerebral edema	10 (17.8)	6 (33.3)	2.0 (0.6-7.0)	0.325
Cerebral atrophy	7 (12.5)	1 (5.5)	0.4 (0.04-3.1)	0.669
Hydrocephalus	12 (21.4)	5 (27.8)	1.2 (0.3-4.2)	0.756
Meningoencephalitis	13 (23.2)	1 (5.5)	0.2 (0.02-1.3)	0.086
Microcalcification	9 (16.1)	2 (11.1)	0.6 (0.1-2.9)	0.710
Cerebral ischemia/hemorrhage	7 (12.5)	0	-	0.173

Values in no. (%). SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; MIS-C: multisystem inflammatory syndrome in children. Neuroimaging included either computed tomography scan or magnetic resonance imaging.

A total of 22.2% of our MIS-C patients had a positive RT-PCR test, 77.8% had a positive antibody test, and one of them had positive findings in both results. Studies in the US showed that 44% of MIS-C patients with neurologic manifestation had positive PCR results, 35% of patients had positive antibody test results, and 30% of patients had both positive results [2]. This may have been due to differing testing strategies and differing healthcare settings of the two studies.

The duration of hospitalization was for the MIS-C group longer compared to a previous systematic review [9]. In our study, hospital stays were longer because most patients were admitted to the hospital in critical condition. For the same reason, the mortality rate in our study was also higher than previous multinational data (1.7%) [9], and that from Latin America (0%) [10].

A study in Germany reported frequent neurologic symptoms associated with MIS-C were altered mental state (33.3%), new paresis (30%), impaired consciousness (23.3%), hypo/areflexia (30%), anosmia/hyposmia or ageusia/hypogeusia (20%, underreported in critical care patients) and seizures (16.7%) [11]. The range of neurologic symptoms associated with COVID-19 in children and adolescents is broad and varies by age, including seizures/ status epilepticus in younger patients and reports of anosmia and/or ageusia, headache, and fatigue/weakness in older patients. Approximately one in every four patients with neurologic involvement, regardless of age group, presented with altered awareness or confusion. The wide range of neurologic complications, including peripheral nerve disorders (GBS and variants), focal central nervous system (CNS) disease (ischemic stroke due to large vessel occlusion, cerebral venous sinus thrombosis, and focal cerebral arteriopathy), and diffuse CNS involvement (CNS infection, ADEM, severe ence-phalopathy with white matter and corpus callosum lesions, and acute fulminant cerebral edema), suggests that multiple mechanisms underpin this wide spectrum of disease [2].

In a study conducted in the United Kingdom, four out of 27 children exhibited corpus callosum splenium MRI or CT alterations. Reversible lesions of the corpus callosum have also been observed in Kawasaki disease [12]. Sixty of our 74 patients underwent neuroimaging, with 27 (45%) receiving a brain MRI and 33 (55%) a head CT scan. The previous study reported acute to subacute infarcts (24%) as the most common neuroimaging finding in patients with COVID-19, followed by cerebral microhemorrhages, acute spontaneous intracerebral hemorrhages, and encephalitis/ encephalopathy [13]. A previous study [14] also reported acute or subacute infarct and hemorrhage as the most common neuroimaging findings. Cerebral edema findings have been reported to be the result of intracranial hypertension associated with multisystem inflammation [15].

This research was conducted as a cross-sectional study with a small sample size from one tertiary referral hospital. Therefore, the results are not representative of

WHAT THIS STUDY ADDS?

- MIS-C was diagnosed in a quarter of patients with acute neurologic symptoms and history of SARS-CoV-2 infection, with the majority of cases being post-asymptomatic infection (positive antibody test).

the entire population. The non-availability of standard drugs and supporting investigation facilities in our country makes it difficult to describe the actual response to therapy.

MIS-C was found in 24% of our patients with neurologic symptoms related to COVID-19, and 77% had positive antibody results. A multicenter study, as well as long-term interdisciplinary follow up, are needed to be done in future research. This will give healthcare providers better understanding concerning the major neurological issues in pediatric patients with SARS-CoV-2, allowing them to make rapid decisions and initiate treatment to reduce morbidity and mortality.

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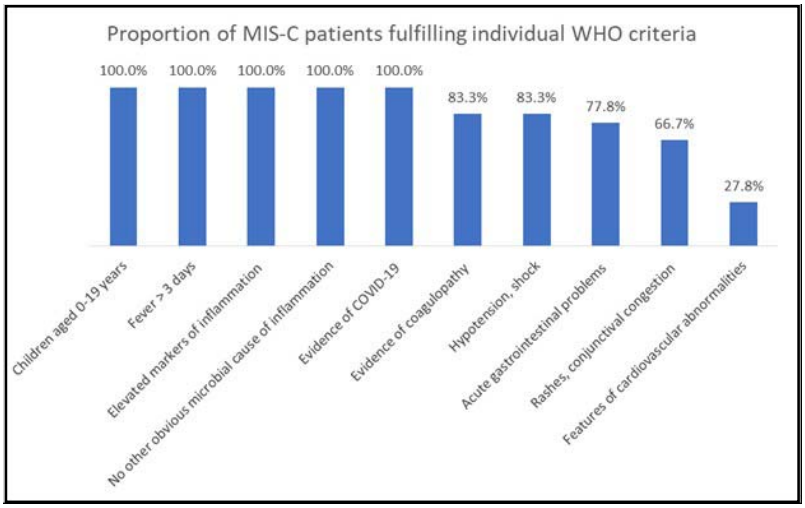

Web Fig. 1 Proportion of multisystem inflammatory syndrome in children (MIS-C) patients fulfilling individual WHO criteria.