



Neurologic Manifestation in Children with Coronavirus Disease 2019 at Prof. Dr. I.G.N.G Ngoerah Tertiary Hospital

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Abstract

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AIM: The objective of the study is to describe neurologic manifestation in children with coronavirus disease-2019 (COVID-19) at Prof. Dr. I.G.N.G Ngoerah Hospital.

METHODS: This was a retrospective descriptive study using the medical record with a total sampling of children with confirmed COVID-19 that manifests neurologic symptoms. Exclusion criteria were pre-existing neurologic comorbidities and incomplete medical records.

RESULTS: From March 2020 to December 2021, from 308 children with confirmed cases of COVID-19, 106 had neurologic symptoms, 17 were excluded (16 pre-existing comorbidities, and 1 incomplete medical record), and total samples were 89 (28.8%) from inpatient and outpatient. Most children were male (57.3%) with a median age of 13 years. Most symptoms found were anosmia (73%), followed by a decrease in consciousness (19.1%) and seizure (10.1%). Children with anosmia median age were 14 years. There were 84 (94.3%) children with specific neurological symptoms (encephalopathy, seizures, and anosmia) and 5 (5.7%) with non-specific neurological symptoms (headache).

CONCLUSION: There were 28.8% confirmed cases of COVID-19 with a neurologic manifestation, and most symptoms found were anosmia (73%).

Introduction

The coronavirus disease-2019 (COVID-19) is an ongoing pandemic since the discovery of the first case in December 2019 in Wuhan, China. The transmission of COVID-19 is caused by severe acute respiratory syndrome-associated coronavirus 2 (SARS-CoV-2). The COVID-19 virus is a single-stranded RNA virus isolated from various types of animals that can originate from bats and then be transferred to a human. The first case in Indonesia was announced in March 2020 which was about 4 months after the first case in China was discovered [1].

Since 2019, this case is still ongoing and continues to develop many symptoms including neurological system. Later, the COVID-19 guidelines updated the clinical manifestation of suspected COVID-19 with a decrease of consciousness as one of the clinical manifestations [2]. Neurological manifestations that had been reported were acute encephalitis, seizures, and status epilepticus [3]. Previous studies had shown that the prevalence of neurologic manifestation in children with COVID-19 varies between 1.1% and 43%, which was wide in range [4], [5], [6].

The mechanism of the neurological events' occurrence is thought from a viral infection that attacks the central nervous system (CNS) or secondary due to hypoxia and cytokine involvement in COVID-19 patients [3]. The mechanism of COVID-19 virus entry into the CNS is due to the attachment of the virus to the olfactory epithelium through the angiotensin-converting enzyme-2 receptor. After entering the cell, the virus will replicate and induce an immune response that causes the release of cytokines, resulting in a maladaptive immune response. The virus particles reach the CNS retrogradely through cranial nerve pathways: Nerve V through the corneal epithelium or oropharyngeal cutaneous sensory receptors; nerve I through the crib form, infect the olfactory sensory neurons; nerve VII and IX through tongue chemoreceptors; and nerve X through pulmonary mechanoreceptors. After reaching the CNS nuclei, various neurological symptoms may appear. Until now, COVID-19 virus has not been found in the cerebrospinal fluid so it is still theoretical [4].

The condition of this pandemic still cannot be predicted when it will end. Neurological symptoms in an adult with COVID-19 have been extensively studied and often happen in adults with comorbidities. With the development of the COVID-19 virus, symptoms in

children are increasingly diverse and begin to show the emergence of neurological manifestations. In pediatric patients, COVID-19 symptoms are often asymptomatic and neurological symptoms have not been studied extensively.

Methods

This study is a retrospective descriptive study with total sampling using secondary data from the register and medical records. The study was done in Prof. Dr. I.G.N.G Ngoerah Hospital from March 2020 to December 2021. Inclusion criteria were inpatient and outpatient children aged 1 month to 18 years with confirmed cases of COVID-19 with neurologic symptoms (decrease of consciousness, seizure, headache, or anosmia). Exclusion criteria were pre-existing neurologic comorbidities and incomplete medical records. With the assumption of error alpha is 5%, the proportion from the category of interest 1.7% [7], and z_{α} 1.96, the minimum sample requirement is 26 patients.

Diagnosis of COVID-19 was established with positive polymerase chain reaction test for SARS-CoV-2 and then divided into asymptomatic if the patient had no sign and symptoms; mild symptoms if patients had a fever, fatigue, myalgia, cough, throat pain, coryza, or sneeze; moderate symptoms if the patient had a clinical sign of pneumonia (fever, cough, and tachypnea); severe symptoms if the patient had a clinical sign of severe pneumonia with nostril breath, cyanosis, subcostal retraction, desaturation (<95%) or present of seizure, a decrease of consciousness, profuse vomiting; critical sign if the patient had acute respiratory distress syndrome, respiratory failure, coagulopathy, and myocardium dysfunction. For the operational definitions of variable, age was defined as chronological age at the time patient enrolled in the hospital. Age was defined based on date, month, and year and expressed in years. Age was presented in numeric form. Sex was defined as phenotypic appearance, presented in categorical form as male and female. A decrease of consciousness is defined as an altered level of consciousness due to diffuse or global brain dysfunction, presented in categorical form as present or not present. A seizure is defined as sudden, uncontrolled movement due to uncontrolled electrical disturbance in the brain, presented in categorical form as present or not present. Headache is defined as a subjective feeling of pain in any region of the head, presented in categorical form as present or not present. Anosmia is defined as a subjective feeling of inability to smell.

Collected data were analyzed using the SPSS program for Mac OS version 26.0. Data analysis included descriptive analysis, and a categorical

variable was presented as an absolute value. The continuous variable will be tested for normality and was presented as mean or median and standard deviation with minimum and maximum limits.

Results

From March 2020 to December 2021, there were a total of 308 confirmed case patients. From 153 confirmed cases of COVID-19 inpatients, there were 41 (26.7%) confirmed cases of COVID-19 with neurologic manifestation. From the outpatient COVID-19 clinic, there were 155 confirmed patients. Of all confirmed case patients, there were 65 (49.6%) with neurologic manifestations. Of 106 children, 17 were excluded due to pre-existing neurologic comorbidities ($n = 16$) and incomplete medical records ($n = 1$). The total samples were 89 (28.8%) children, with an inpatient total of 24 children and an outpatient of 65 children (Figure 1).

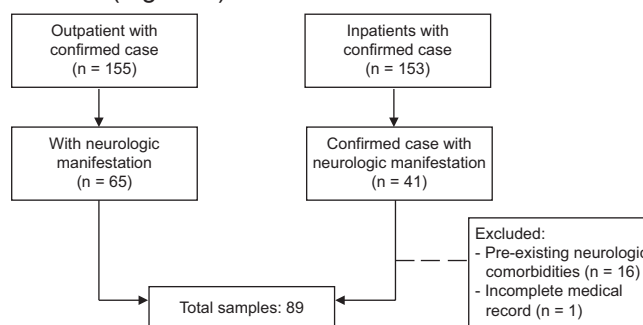


Figure 1: Samples gathering

Most patients were male (57.3%) with a median age of 13 years (range: 1 month–17 years). Most symptoms found were anosmia (73.0%), followed by a decrease in consciousness (19.1%), seizure (10.1%), and headache (5.6%). All children with anosmia were found as outpatients. Patients with anosmia median age were 14 years (range: 6–17 years). The median age for a decrease in consciousness, seizure, and the headache was 9 years (range: 3 months–17 years), 4 months (range: 4 months–17 years), and 10 years

Table 1: Characteristic of the children with the neurologic manifestation of coronavirus disease 2019

Variables	Total, n (%)
Age (year), median \pm SD	13 (0.1–17)
Sex	
Male	51 (57.3)
Female	38 (42.7)
Neurological manifestation	
Decrease of consciousness	17 (19.1)
Seizure	9 (10.1)
Headache	5 (5.6)
Anosmia	65 (73.0)
COVID-19 severity	
Asymptomatic	0
Mild symptoms	65 (73.0)
Moderate symptoms	2 (2.3)
Severe symptoms	14 (15.8)
Critical symptoms	8 (8.9)
Mortality	11 (12.3)

SD: Standard deviation, COVID-19: Coronavirus disease 2019.

(range: 8–17 years). The severity of COVID-19 mostly was mild symptoms (73.0%). The mortality in our research was 12.3%. The characteristic of the patients is shown in Table 1.

In our research, children with specific neurological symptoms are 84 (94.3%) and non-specific neurological symptoms are 5 (5.7%) (Table 2). Most of the neurological symptoms found were anosmia.

Table 2: Neurological manifestation categories

Neurological symptoms	n (%)
Specific (encephalopathy, seizures, anosmia)	84 (94.3)
Non-specific (headache, myalgia, fatigue)	5 (5.7)

Discussion

COVID-19 can lead to mild to serious manifestations in children with very varied symptoms from respiratory, gastrointestinal, cardiovascular, and neurological symptoms. Neurological symptoms that appear in patients with confirmed COVID-19 invasion are due to invasion of COVID-19 or due to sequelae due to secondary hypoxia, cytokine involvement, or another mechanism. Neurological symptoms are common manifestations in adults but are not well known in children and have been under-reported [8], [9]. The development of the COVID-19 virus that can manifest in the neurological system needs further study because there are potential neuroinvasive and neuropsychiatric effects. Mechanisms of infections to CNS are neuroinvasive, neurotrophic, neurovirulent, and neuroinflammatory (Table 3).

In this research, 28.8% of children with confirmed cases of COVID-19 had neurologic manifestations. It is lower than research in Columbia which found 43% of patients developed neurologic manifestations (headache 34%, fatigue 25%, altered mental status 23%, weakness 14%, and seizure 11%) [10]. In the USA, only 1.7% of children were reported to have neurologic symptoms [7]. In multicenter studies from the Global Consortium to Study Neurological Dysfunction in COVID-19 (GCS-neuro-COVID), the prevalence of neurologic manifestations in children was 40% [11]. This high difference might be due to symptoms that categorize as neurologic symptoms and under-reported symptoms in children. Children sometimes are unable to express symptoms.

From the characteristic in our study, the median age was 13 years (range: 1 month–17 years). In a study from a tertiary center in Turkey, the age range was 3 months to 17 years [6]. For the sex, our research found a higher prevalence in males (57.3%). The same finding was found in another study in which the prevalence of male children was higher (53% and 58.9%) [11], [12].

Table 3: Viral infections of the central and peripheral nervous system [4]

Characteristic	Mechanism
Neuroinvasive	The ability of the virus to enter the nervous system
Neurotrophic	The ability of the virus to infect the neuron cell in the nervous system
Neurovirulent	The ability of the virus to cause disease in the nervous system
Neuro-inflammatory	The ability of the virus to cause a secondary inflammatory response in the nervous system

The most common findings in our study were anosmia (73%), followed by a decrease in consciousness (19.1%) and seizure (10.1%). In a study in a tertiary center, they found that the most common symptom was a decrease in consciousness (50%), followed by seizures (40%) [6]. From a multicenter study by GCS-neuro COVID, the most common symptoms were headache (16%) and encephalopathy (15%) while seizure and anosmia were only 8% and 4%. Seizure or status epilepticus was more prevalent in children than in adults (8% vs. 1%) [11]. Other single-center studies in the United States also reported headache as the most common symptom (28%) and seizure as the least common symptom (11%). However, in this study, they did not assess anosmia in children [8].

Anosmia in our study had a high prevalence (73%), and it is predominantly reported in older children >10 years old. In another study, the prevalence of anosmia in adults was varied between 30% and 80% but in children often underdiagnosed or underreported due to children being unable to express symptoms. Research by Kumar *et al.* which specifically study about the loss of smell and taste made the inclusion criteria for children aged 10–19 years due to the difficulty to diagnose olfactory disorders in children [12]. Our research is by systematic review in 2020 which has a 62% prevalence of anosmia [9]. Anosmia occurs in at least 5%–20% of pediatric patients [13]. From a study by Kumar *et al.*, the prevalence of anosmia was 28.4% [12]. In a study by Panda *et al.*, the prevalence of anosmia was 62% which was consistent with our finding [9].

In our research, we divided neurological manifestation into two categories. The first categories are patient with specific neurological symptoms due to COVID-19 involving neurological systems directly such as encephalopathy, seizures, and anosmia. The second categories are patient with non-specific neurological symptoms such as headache, myalgia, and fatigue. We found that children with specific neurological symptoms were 84 (94.3%) and non-specific neurological symptoms (headache) were 5 (5.7%). Our findings were different from the systematic review in 2020 which had higher non-specific neurological symptoms (16.7%) and only 1% had specific neurological symptoms. The previous study found that children with pre-existing neurological conditions had 3.48 higher odds for neurological manifestation compared to children without pre-existing neurological conditions [11]. This difference may be due to the high prevalence of anosmia in our research; in the previous systematic review, there was not enough data

according to anosmia. Furthermore, encephalopathy can be confused between the direct neurotrophic effects of the virus or caused by hypoxia or septic shock.

In an adult patient, there is a 5% chance of patients at risk for developing stroke, but in children, it was less likely [9]. Stroke was reported as a less common manifestation (0.9%) [11]. In our findings, there was 1 patient that developed into stroke later after COVID.

In the adult population, neurologic manifestation was more likely in severe cases than in mild cases [6], [14]. In comparison to the adult population, most manifestations in children are limited to appearing in mild cases [12], [14], [15]. In our study, COVID-19 manifestations mostly were mild symptoms (73.0%). Of 73% of children with mild symptoms, most patients had only anosmia as the symptom. This might show that neurological manifestation could be an initial presentation of COVID-19 without evidence of respiratory symptoms. Severe cases were fewer found in our study, with a total of 24.7%.

This study has several limitations. First, due to retrospective methods, several symptoms (fatigue, myalgia) might be underdiagnosed. Second, the causal versus coincidental relationship of neurological manifestation in COVID-19 still needs further study. Long-term impact on neurodevelopment after COVID-19 needs further investigation.

Conclusion

There were 28.8% confirmed cases of COVID-19 with a neurologic manifestation; most symptoms found were anosmia (73%). The virulence and invasiveness of COVID-19 to the nervous system deserve attention due to the neurotropism of the virus.

Contributors

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted.

Ethical Approval

This study was approved by The Ethics Committee of the Medical Faculty of Medicine/I.G.N.G

Ngoerah General Hospital with ethical approval number 2895/UN14.2.2.VII.14/LT/2021.

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