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Frequency of Febrile Seizures in COVID-19 Children in Akbar Children's Hospital

Javad Akhondian [1], Elahe Derakhshan-Nezhad [2], Matin Dowlat Abadi [2], Sahel Yazdanpanahi[2], Niloofar Nikpour [2], * Zahra Chaichy [3]

[1] Department of Pediatrics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

[2] Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

[3] Department of Pediatric Diseases, Mashhad University of Medical Sciences, Mashhad, Iran.

Abstract

Background: Considering the increased incidence of Febrile Seizures (FS) after omicron emergence, this study aimed to evaluate the frequency of FS in COVID-19 children, under 14 years of age, in Akbar Children's Hospital in Mashhad, Iran. This study also compared the characteristics of FS children with and without COVID-19.

Methods: All patients under 14 years of age, who were hospitalized and diagnosed with COVID-19 in Akbar hospital, from March 2020 to 2022, were included in this study. The incidence of FS was determined in this group. Also, all patients who were diagnosed with FS, tested negative for COVID-19, and had no underlying diseases were included in the control group. Hospital Information System (HIS) was used to extract the desired information.

Result: Out of 220 COVID-19 children studied, eight (3.60%) had febrile seizures, of whom 50% were male, and 50% were female, and their average age was 13.9±6.96 months. Also, 62.5% had simple FS, and 37.5% had complex FS. Among them, 12.5% had leukopenia, 12.5% had lymphopenia, 62.5% had pneumonia symptoms, 50% had fever, 37.5% had tachycardia, and 25% had tachycardia symptoms. The average age of COVID-19 patients with FS was significantly lower than that of the patients with either COVID-19 or FS (p=0.01). Complex FS was significantly more prevalent in patients with COVID-19 than in patients without COVID-19 (p=0.01).

Conclusion: The frequency of COVID-19-associated FS increased during the omicron period. There are several potential mechanisms through which febrile seizures could occur. Considering that there are still many unknowns in this field, it is necessary to conduct more studies.

Key Words: Children, COVID-19, Febrile seizu.

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Corresponding Author:

Zahra Chaichy. Department of Pediatric Diseases, Mashhad University of Medical Sciences, Mashhad, Iran. Email: Zarichaichy@gmail.com

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1- INTRODUCTION

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China in December 2019 caused a massive wave of concern and soon became a global health problem, which was then confirmed as a pandemic in March 2020 (1-3). Its predominant manifestations were confined to the respiratory system like dry cough and dyspnea but over time, many reports from all over the world suggested that it could also bring about multisystem involvement, including cardiovascular, renal, gastrointestinal, and neurological complications (3-6).

The previous coronaviruses, SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) and MERS-CoV (Middle East Respiratory Syndrome Coronavirus), were associated with neurotropism, and the olfactory dysfunction in SARS-CoV-2 infection may also reflect neuroinvasion (6-8). This virus enters host cells via the angiotensin-converting enzyme 2 (ACE-2) receptor which could be found on glial cells. Some studies have shown that SARS-CoV-2 has a higher affinity to neurons compared to other viruses (9). It could directly invade the CNS (Central Nervous System) or target PNS (Peripheral Nervous System) and then be transmitted to the CNS by retrograde transfer (4). COVID-19 (Coronavirus Disease 2019) could present with central nervous system complications, such as headache, encephalitis, encephalopathy, strokes, and seizures, as well as peripheral nervous system complications, such as anosmia, ageusia, and Guillain-Barre syndrome (10). In a systematic review and meta-analysis conducted by Misra et al. (2021), up to one-third of patients with COVID-19 experienced at least one neurological manifestation (11). In another systematic review and meta-analysis conducted by Mahdizade Ari (2022), the pooled prevalence of neurological manifestations and mortality rate of COVID-19 patients with neurological features were estimated to be 23.0% (95% CI: 17.8–29.2) and 29.1% (95% CI: 20.3–39.8), respectively (12). In another study by Vohora et al. (2020), among the most severe neurological complications, seizures were reported to be the most common complication and thus a source of concern (5). Antoon et al. (2022) reported that hospitalized COVID-19 children with neurological complications had a worse prognosis, including a more severe course of the disease, more ICU (Intensive Care Unit) admissions, longer ICU stays, more hospital costs, and more deaths compared to those without neurological symptoms (13).

SARS-CoV-2 has undergone many mutations, resulting in the emergence of different variants. The most mutated variant, omicron, has been shown to be much more contagious but with milder symptoms (14). The incidence of Febrile Seizures (FS) has been reported to increase significantly with the emergence of omicron (15). Febrile seizures are the most common neurological emergency in children, which are described as seizures in the presence of fever and the absence of CNS infection, severe metabolic disorders, and a history of seizure without fever or convulsions. Febrile seizures usually affect children aged 6 to 60 months (16-18), although children above this age range could also experience FS (19). In western countries, the incidence of FS is 2-5% of the population, while this value could increase to 14% in some Asian countries (18, 20). Although fever itself lowers the seizure threshold, the exact mechanism of febrile seizures in SARS-CoV-2 infected patients is still unclear, but a number of theories have been proposed (21). One idea is that by disrupting the blood-brain barrier and via angiotensin receptor 2, the virus could invade the CNS directly or target PNS and then be transmitted to the

CNS by retrograde transfer (22). Another mechanism could be through inflammation. After entering the body, the virus could cause an inflammatory storm so that some mediators Like Interleukin IB (IL-IB), IL-6, and Tumor Necrosis Factor (TNF) could act as pro-stimulators and pro-convulsants and affect the excitability of neurons (21). Additionally, cytokine storms could lead to an indiscriminate influx of calcium into neurons through NMDA and AMPA receptors in the hippocampus. This could simultaneously cause severe seizures, excessive excitability, and brain cell death (23).

Febrile seizures may be simple or complex. Simple febrile seizures are mainly generalized tonic-clonic seizures that last up to 15 minutes and do not recur in a 24-hour period. Complex febrile seizures are focal and longer, last more than 15 minutes, and recur within 24 hours.

One third of children who have simple febrile seizures will have a second attack in the future, and half of them will experience a third attack as well (24).

Considering the increased incidence of febrile seizures after omicron emergence, this study aimed to evaluate the frequency of febrile seizures in COVID-19 children under 14 years of age in Akbar Children's Hospital in Mashhad, Iran. This study also compared the characteristics of febrile seizure in children with and without COVID-19.

2- MATERIALS AND METHODS

2-1. Design and participants

This cross-sectional study was conducted in Akbar research, educational, and therapeutic hospital in Mashhad during 2020-2022 using census method.

All patients under 14 years of age, who were hospitalized and diagnosed with COVID-19 (based on positive PCR, pulmonary involvement in favor of COVID-19, and positive COVID-19 serology) in Akbar hospital, during the study period, were included in this study. The incidence of febrile seizures was determined in this group.

Also, all patients who were diagnosed with febrile seizures, tested negative for COVID-19, and had no underlying diseases were included in the control group.

In this study, the exclusion criteria included patients who had an underlying disease or a history of epilepsy, patients who refused admission and treatment, and patients who lacked information in the HIS system.

2-2. Data collection

After removing the patients with incomplete data, the desired information was collected in a pre-prepared checklist by the project executive intern. The hospital information system (HIS) of Akbar hospital was used to extract the desired information.

The information of the participants was kept confidential, and none of their personal information, including their names and surnames, was entered into the software. All patients were assigned a specific project code, and analysis was done based on them.

2-3. Data analysis

First, the normal distribution of the data was measured using Kolmogorov-Smirnov test and histogram analysis. Then descriptive statistics including central and dispersion indices were calculated. Appropriate statistical indices such as mean and standard deviation were used to describe the data.

Considering the non-normal distribution of quantitative variables, Mann-Whitney test and t-test were used to compare these variables between groups. Chi-square or Fisher's exact test was used to analyze

nominal scale data. The software used in this research was SPSS (Ver. 23). The significance level of the tests was considered to be less than 0.05.

3- RESULTS

In this study, 220 children with COVID-19 were identified, of whom 121 (55.7%) were male. The average age of these children was 46.9±7.1 months. According to the information recorded in the patients' files, 45 (20.5%) patients had upper respiratory symptoms, 124 (56.3%) patients had clinical symptoms of pneumonia, and 98 (56.4%) patients had fever. Also, tachycardia and tachypnea were observed in 87 (39.5%) and 64 (29%) patients, respectively (Fig. 1). Also, white blood cells in 157 (71.4%) patients were within the normal range, while 21 (9.5%) patients had leukocytosis, 35 (15.9%) had leukopenia, and 29 (13.2%) had lymphopenia (Fig. 2).

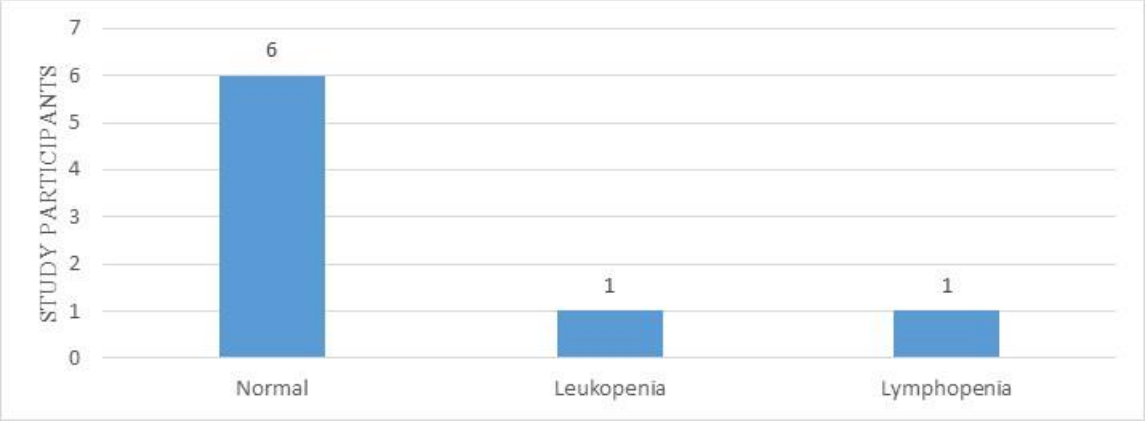

Fig. 1: Frequency of signs and symptoms in COVID-19 children admitted to Akbar hospital from 2020 to 2022

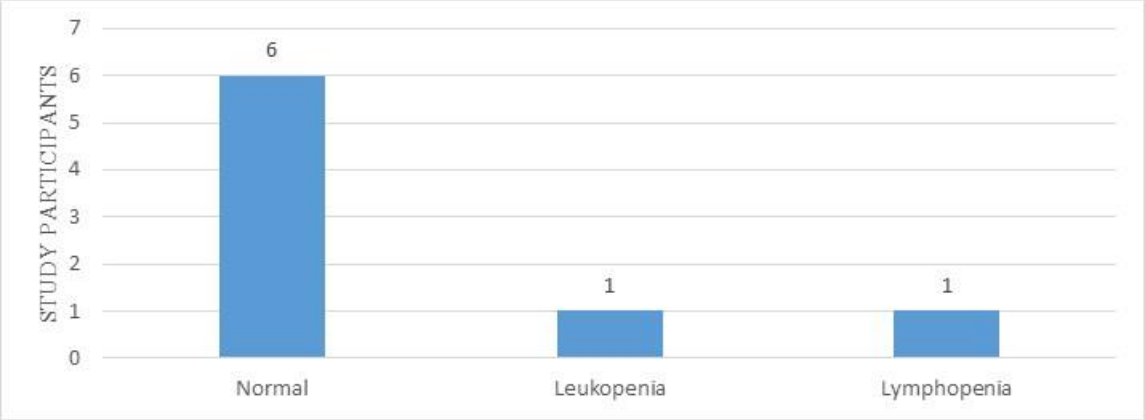

Fig. 2: Frequency of laboratory findings in COVID-19 children admitted to Akbar hospital during 2020-2022

Out of the 220 COVID-19 children studied, nine patients had febrile seizures, one case was removed from the study due to confirmation of glioblastoma tumor; finally, eight (3.60%) patients who had febrile seizures were examined. Of whom, four (50%) were males, and four (50%) were females, and the average age of them

was (13.9±6.9) months. Also, five (62.5%) children had simple febrile seizures, and three (37.5%) children had complex febrile seizures. In the recorded laboratory tests, one (12.5%) patient had leukopenia, and one (12.5%) patient had lymphopenia. Among the patients, five (62.5%) had pneumonia symptoms, four (50%) had fever, three (37.5%) had tachycardia, and two (25%) had tachypnea symptoms (Table 1).

Table-1: Demographic and clinical characteristics of COVID-19 children with febrile seizures

Age	Average (13.9±6.9)	N (%)
Gender	Male	4 (50)
	Female	4 (50)
Seizure type	Simple	5 (62.5)
	Complex	3 (37.5)
Laboratory findings	Leukopenia	1 (12.5)
	Lymphopenia	1 (12.5)
Clinical symptoms	Pneumonia	5 (62.5)
	Fever	4 (50)
	Tachycardia	3 (37.5)
	Tachypnea	2 (25)

In this study, 190 patients with febrile seizures and without COVID-19 signs and symptoms were admitted to Akbar hospital from 2020-2022. The average age of these patients was 19.1±3.9 months, of whom 116 (61%) were males, and 74 (39%) were females. Also, 163 (85.8%) children had simple febrile seizures, and 27 (14.2%) children had complex febrile seizures (Table 2).

Table-2: Demographic and clinical characteristics of children with febrile seizures

Age	Average (19.1±3.9)	N (%)
Gender	Male	116 (61)
	Female	74 (39)
Seizure type	Simple	163 (85.8)
	Complex	27 (14.2)

According to the results, no significant gender difference was found between the two groups of COVID-19 patients with and without febrile seizures (p=0.71). Also, there was no significant difference in the frequency of clinical symptoms between COVID-19 patients with and without febrile seizures (p=0.77). There was also no significant difference between COVID-19 patients with and without febrile seizures in the incidence of leukopenia and lymphopenia (p=0.68 and 0.49, respectively). The average age of patients with COVID-19 and febrile seizures was significantly lower than that of patients with either COVID-19 or febrile seizures (p=0.03 and 0.01, respectively). Complex febrile seizures were significantly more prevalent in patients with COVID-19 than in patients with febrile seizures without COVID-19 (p=0.01). Also, two cases (one girl and one

boy) under one year old were positive for MISC (Multisystem Inflammatory Syndrome in Children) and COVID-19, had febrile seizures, and had negative Cerebrospinal Fluid (CSF) PCR (Polymerase Chain Reaction).

4- DISCUSSION

In this single-center cross-sectional study, the frequency of febrile seizures was evaluated in COVID-19 children under 14 years of age in Akbar Children's Hospital in Mashhad, Iran. This study also compared the characteristics of febrile seizure children with and without COVID-19.

In this study, out of the 220 COVID-19 patients, eight (3.60%) cases had febrile seizures, among them male and female patients equally experienced febrile seizures, each accounting for 50% of all febrile seizure cases. Also, 62.5% had simple FS, while 37.5% endured complex FS. Complex febrile seizures were significantly more prevalent in patients with COVID-19 than in patients with febrile seizures without COVID-19. Also, the average age of patients with COVID-19 and FS was significantly lower than that of those with either COVID-19 or FS.

In a systematic review and meta-analysis conducted by Misra et al. (2021) on patients under 18 years of age, 4% of COVID-19-positive patients had febrile seizures (11). In another study by Cadet et al. (2022), it was shown that 7% of patients with COVID-19 presented with febrile seizures (25). In a recent study by Han et al. (2023), 44 out of 381 COVID-19-positive patients had febrile seizures, indicating a frequency of 11.5%, which is more than the results of other studies. This finding could be due to the increased frequency of febrile seizures with the emergence of new variants of SARS-CoV-2 (26).

The frequency of febrile seizures in COVID-19 children in this study was lower than those reported in similar studies (3.60%). Part of the difference in the results of the previous studies could be due to the difference in the study populations; for example, the severity of the COVID-19 disease could affect the frequency of febrile seizures in the study population, which should be evaluated in future studies.

In the studies conducted by Cadet et al. (2022) and Han et al. (2023), 68.2 and 60.9% of COVID-19 patients had simple febrile seizures, respectively, consistent with the present study findings (62.5%) (25, 26).

In a study by Joung et al. (2023), the frequency of complex FS cases during the omicron pandemic was 36.1% of all FS cases, which was significantly increased compared to the period before the omicron pandemic (28%) (17). This finding is consistent with the present study findings. In their study, the average age of the patients with both COVID-19 and febrile seizures was 33 months, which was significantly higher than that of the patients with only febrile seizures (23 months) (17).

This finding is inconsistent with that of the present study. Considering that the cause of increase in the average age of patients with both COVID-19 and febrile seizures has not been investigated in the studies mentioned above, it seems that conducting more studies in the field of neuropathological aspects of COVID-19 could help clarify the cause of these findings.

In the current research, no significant difference was found between COVID-19 patients with and without febrile seizures in the frequency of lymphocytes and leukocytes, while in a study by Seo et al. (2023), patients with COVID-19 showed a higher ratio of neutrophils and a lower ratio of lymphocytes compared to those without COVID-19 (27).

4-1. Limitations of the study

A limitation of this study was the fact that we did not have access to all information about all variables for each patient. Also, the number of patients surveyed was limited. The strength of the study was that it was the first study investigating febrile seizures in COVID-19 patients in Iran, which could provide valuable insights for epidemiologists. The findings could be complemented and strengthened by future studies with larger sample sizes. Besides, investigating other mechanisms involved in febrile seizure induction by COVID-19 might be beneficial.

5- CONCLUSION

Overall, the frequency of COVID-19 associated febrile seizures increased in the omicron period. There are several potential mechanisms through which febrile seizures could occur, which need to be explored in future studies. Considering that there are still many unknowns in this field, it is necessary to conduct more studies.

6- ETHICAL CONSIDERATIONS

This research was approved by the Organizational Ethics Committee of the Faculty of Medicine of Mashhad University of Medical Sciences under number 970478 and code IR.MUMS. MEDICAL.REC.1397.700. Informed consent was not applicable.

7- AUTHORS' CONTRIBUTIONS

Study concept and design: Z.CH, data collection: M.D, data analysis and interpretation: J.A and S.Y, drafting of the manuscript: E.D, S.Y, and N.N, critical revision of the manuscript for important intellectual content: Z.CH, J.A, and E.D, statistical analysis: J.A and N.N, administrative, technical, and material support: E.D and M.D, study supervision: Z.CH.

8- CONSENT FOR PUBLICATION

Not applicable.

9- COMPETING INTERESTS

The authors declare no competing interest.

10- AVAILABILITY OF DATA AND MATERIALS

Study data are available upon reasonable request from the corresponding author.

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