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Clinical and Biochemical Features of Kids with COVID-19 Febrile Seizures during the Omicron Wave

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Abstract

Objective Mild symptoms are the norm for children with coronavirus disease-2019 (COVID-19), but data on the Omicron form are few. One of the most frequent neurological symptoms of COVID-19 in children is febrile seizure (FS).

Methods Patients with FS who visited the pediatric fever clinic between December 6 and December 31, 2022, when the Omicron version of SARS-CoV-2 was the predominant strain, were included in this retrospective, single-center analysis.

Results Children who tested positive for COVID-19 had a 5.58% incidence of FSs. Compared to patients without COVID-19, a greater percentage of COVID-19 patients (29.5 vs. 7.5%, $p < 0.01$) experienced complex FSs. In the COVID-19-positive group, four cases were critically unwell and were admitted to the Intensive Care Unit (1.4 vs. 0%, $p < 0.01$), and the admission proportion was greater (18.9 vs. 1.9%, $p < 0.01$). The proportion of lactic acid and IL-6 increase was larger in the COVID-19-positive group (33.5 vs. 21.5%, 22.1 vs. 17.8%, $p = 0.022$, $p = 0.006$, respectively).

Conclusion Infections with COVID-19 in children have been linked to FSs in the Omicron era. To fully understand the neuropathogenesis of seizures in children with COVID-19, more research is required.

Keywords
- febrile seizures
- COVID-19
- Omicron
- pandemic
- convulsions

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Introduction

The virus with the highest prevalence during the ongoing coronavirus disease-2019 (COVID-19) pandemic has been severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Although respiratory symptoms were the most prevalent in children of pediatric age, many kids also display neurological problems.[2,3] Acute disseminated encephalomyelitis, meningitis, encephalitis, myelitis, Guillain–Barre syndrome, and other central and peripheral neurological injuries in adults and children have all been linked to COVID-19. These injuries range from moderate ones like headaches and anosmia to more severe ones like meningitis. However, headache, anosmia, and febrile seizures (FSs) are the three neurological symptoms most frequently affecting children.[4,5] One of the primary symptoms of acute COVID-19, particularly in children, is FS, which prompts them to seek the pediatric fever clinic.[6]

Convulsions that happen when children have a fever but no intracranial infection are referred to as FS, a frequent neurologic condition in infants aged 6 to 60 months. Between 2 and 5% of kids will have an FS.[7] Simple FS, complex FS (CFS), and febrile status epilepticus are the three additional classifications for FS. Simple FS are generalized seizures that occur once every 24 hours, during the same feverish episode, and with an attack time of less than 15 minutes. Seizures with a focal onset, lasting ($>$15 min), or recurring within 24 hours are considered CFS.[8,9] Although the cause of FSs is unknown, it is most likely complex. It may be brought on by factors such as the rate at which the body temperature rises, viral and bacterial infections, particular vaccines, and familial genetic abnormalities and dispositions. The main offenders are said to be adenoviruses, influenza, human herpesvirus-6, and rhinoviruses.[10,11] It has been proposed that respiratory viruses may generate cytokines that act on the central nervous system (CNS) and cause neuronal hyperexcitability, which results in FS.[12,13] According to an article written in 2022 and published in the United States, the frequency of FS was 0.5%.[14] Children may be more susceptible to nonlife-threatening neurologic episodes such as FSs due to the hyperinflammatory response brought on by SARS-CoV-2 and the increased neuronal excitability in a growing CNS. There were, however, few investigations that compared the clinical traits of FS in kids with and without COVID-19.

The objective of this study was to examine the clinical traits of children who visited the fever clinic during the pandemic dominated by the Omicron version of SAR-CoV-2 and those who did not.

Materials and Methods

During the period from December 6, 2022, to December 31, 2022, when the Omicron version of SARS-CoV-2 was the predominant strain, we collected information retrospectively from children under the age of 5 who had confirmed COVID-19 and came with convulsion and fever. The patient's throat swab was collected and detected by real-time fluorescent quantitative PCR method, and the virus dual target (open reading frame1-a/b, N) was detected. If the results of both targets were positive, the novel coronavirus nucleic acid was determined to be positive. According to the International League Against Epilepsy, FS refers to seizures that happen as a result of a high-grade fever (above 38 °C) without signs of an acute metabolic malfunction or infection of the CNS that could cause convulsions.[14,15] The convulsive patients who met the aforementioned criteria were eliminated from the FS group, as were those who had underlying epilepsy, no fever, or additional convulsive reasons, such as electrolyte imbalances and structural abnormalities on brain magnetic resonance imaging (MRI).

During the study period, data on the demographics, such as age, sex, previous medical and family history, length of time between the development of a fever and the onset of a seizure, time between the onset of a fever peak, convulsive time, and laboratory tests, were gathered.

The statistical analysis was carried out using the SPSS 26.0 program. The presentation of continuous variables is given as mean standard deviation. One-way analysis of variance was used to compare the differences between the groups, and a p-value of less than 0.05 was regarded as statistically significant.

Results

A total of 18,186 pediatric patients between the ages of 0 and 18 visited the fever clinic over the course of the study, of whom 4,682 tested positive for COVID-19 and 13,504 tested negative. The study comprised 388 patients who met the inclusion criteria, with the exception of 18 epileptic children. Of these, 281 tested positive for COVID-19, while 107 tested negative. Children who tested positive for COVID-19 had a 5.58% incidence of FSs, while those who tested negative had a 0.79% incidence (►**Fig. 1**).

►**Table 1** provides a summary of the clinical features of the FS children treated with or without COVID-19 during this time. Children in the COVID-19-positive group were generally the same age as those in the COVID-19-negative group (2.5 ± 1.3 vs. 2.6 ± 1.1, $p = 0.299$). In both groups, there were more boys than girls with FSs (185/96 vs. 65/42, $p = 0.349$). The COVID-19-positive group had a higher fever peak (39.4 ± 1.1 vs. 39.1 ± 0.7, $p = 0.004$). The time from the onset of the fever and the beginning of the seizure did not differ between the COVID-19-positive and negative groups (19.7 ± 13.9 vs. 20.6 ± 19.1, $p = 0.617$). The COVID-19-positive group had a shorter interval between fever peaks (3.6 ± 1.9 vs. 5.1 ± 1.5, $p < 0.01$).

Convulsions lasted longer and occurred more frequently in the COVID-19-positive group (3.8 ± 5.0 vs. 2.4 ± 2.8, $p = 0.005$; 1.4 ± 0.9 vs. 1.1 ± 0.2, $p < 0.01$). The percentage of patients who had previously experienced an FS was the same in both groups (38.1 vs. 39.3%, $p = 0.832$). Compared to patients without COVID-19, a greater percentage of COVID-19 patients (29.5 vs. 7.5%, $p < 0.01$) experienced CFSs. The percentage of follow-up visits to the neurology department was greater in the COVID-19-negative group (67.3 vs. 36.3%, $p < 0.01$), as were the percentages of head CT or MRI scans

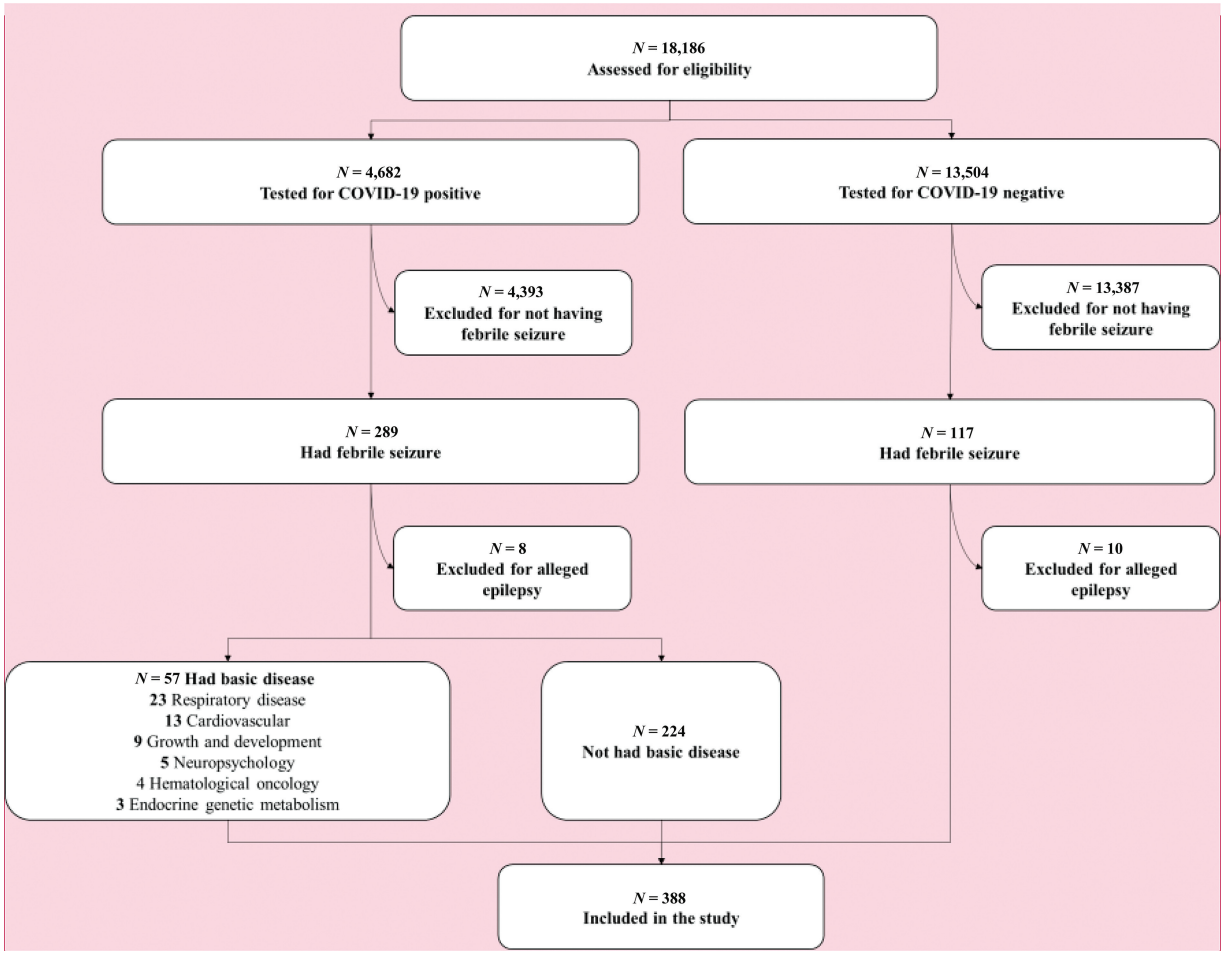

Fig. 1 Flow chart of the study children. COVID-19, coronavirus disease-2019.

Table 1 Comparison of children with febrile seizures who tested positive or negative for coronavirus disease-2019

Characteristics	COVID-19 positive ($n = 281$)	COVID-19 negative ($n = 107$)	*p*-Value
Age (mean ± SD; years)	2.5 ± 1.3	2.6 ± 1.1	0.299
Gender (male/female)	185/96	65/42	0.349
Fever peak (°C)	39.4 ± 1.1	39.1 ± 0.7	0.004
Time from the onset of the fever and the beginning of the seizure (h)	19.7 ± 13.6	20.6 ± 19.1	0.617
Interval between fever peaks (h)	3.6 ± 1.9	5.1 ± 1.5	<0.01
Lymphopenia	27(9.7%)	14 (13.1%)	0.32
Thrombocytopenia	1 (0.3%)	0	1
Anemia	1 (0.3%)	0	1
C-reactive protein elevation	41 (14.6%)	33 (30.8%)	<0.01
Increased lactic acid	94 (33.5%)	23 (21.5%)	0.022
Increased procalcitonin	77 (27.4%)	22 (20.6%)	0.167
Increased IL-6	89 (22.1%)	19 (17.8%)	0.006
Convulsive time (min)	3.8 ± 5.0	2.4 ± 2.8	0.005
Convulsive number	1.4 ± 0.9	1.0 ± 0.2	<0.01
Simple FS	198 (70.5%)	99 (92.5%)	<0.01

(*Continued*)

Table 1 (*Continued*)

Characteristics	COVID-19 positive ($n = 281$)	COVID-19 negative ($n = 107$)	*p*-Value
Complex FS	83 (29.5%)	8 (7.5%)	<0.01
History of febrile seizures	107 (38.1%)	42 (39.3%)	0.832
Visit neurology department	102 (36.3%)	72 (67.3%)	<0.01
Head CT or MRI	155 (55.2%)	74 (69.2%)	0.03
Electroencephalogram	99 (35.2%)	73 (68.2%)	<0.01
Accompanied with underlying diseases	57 (20.3%)	19 (17.8%)	0.575
Disposition			
Admission	53 (18.9%)	2 (1.9%)	<0.01
ICU admission	4 (1.4%)	0	<0.01
Discharge	228 (81.1%)	105 (98.1%)	<0.01

Abbreviations: COVID-19, coronavirus disease-2019; FS, febrile seizure; ICU, intensive care unit; MRI, magnetic resonance imaging; SD, standard deviation.

and EEGs (69.2 vs. 55.2%, 68.2 vs. 35.2%, $p = 0.03$ and $p < 0.01$, respectively). The percentage of underlying disorders did not differ between the two groups (20.3 vs. 17.8%, $p = 0.575$). In the COVID-19-positive group, four cases were critically unwell and were admitted to the intensive care unit (ICU; 1.4 vs. 0%, $p < 0.01$), and the admission proportion was greater (18.9 vs. 1.9%, $p < 0.01$).

The proportion of lactic acid and IL-6 increase was larger in the COVID-19-positive group (33.5 vs. 21.5%, 22.1 vs. 17.8%, $p = 0.022$, $p = 0.006$, respectively), but procalcitonin, lymphopenia, thrombocytopenia, and anemia were the same in both groups. When compared to the COVID-19-positive group, the proportions of elevated C-reactive protein were higher (30.8 vs. 14.6%, $p < 0.01$).

The most common diseases were respiratory and cardiovascular disease (36 instances), which included congenital heart problems and cardiomyopathy, and respiratory diseases (23 cases), which included asthma. There were four cases of renal disorders such as nephrotic syndrome and dialysis, nine cases of growth retardation, and five cases of leukemia, lymphoma, and other hematological oncology diseases. Three cases of endocrine diseases were also seen, including 5α reductase deficiency (►**Fig. 1**).

►**Table 2** provides a summary of the clinical features of the FSs in children with COVID-19. The average age of the group with basic disorders was higher (2.8 ± 1.2 vs. 2.4 ± 1.2, $p = 0.018$) than that of the group without basic diseases. Males made up the majority of the FS patients in both groups (148/76 vs. 27/20, $p = 0.869$).

There was no difference between the two groups in terms of fever peak, time between fever peak, convulsion time, or convulsive number. When compared to the basic disease group, the proportion of follow-up to the neurology department was greater (49.1 vs. 33.0%, $p = 0.024$), and as a result, the proportion of follow-up to the EEG was also higher (47.4 vs. 32.1%, $p = 0.032$). The admittance rates for the two categories were identical.

There were no differences in lymphopenia, thrombocytopenia, or anemia between the two groups, but the proportion of C-reactive protein and lactic acid increase in the group with basic illness was higher (26.3 vs. 11.6%, $p = 0.005$; 45.6 vs. 28.1%, $p = 0.011$). Procalcitonin and IL-6 levels were identical in the two groups.

Discussion

Since December 2022, when the Omicron variation was widely popular in China, we have seen a considerable rise in the number of patients with FS. This increase was not seen when the previous variant was widely popular. Fever, a dry cough, and exhaustion were the most prevalent symptoms of COVID-19 in children.[16,17] Multisystem inflammatory syndrome (MIS-C) may develop in more severe cases.[18–20] Numerous studies have documented an increase in the proportion of juvenile patients during the Omicron wave.[21] Other research discovered that 16.5% of hospitalized patients developed FS following the Omicron surge.[22] Children with COVID-19 had experienced seizures and convulsions, but these symptoms were uncommon in the first year of the pandemic[20] and were infrequently reported.[23] We discovered that during the Omicron wave, 5.58% of COVID-19 children were diagnosed with FSs, compared to 0.79% of COVID-19-negative children, and that 1.4% of these children needed critical care services.

We aimed to investigate the prevalence, clinical, and laboratory features of FSs linked to COVID-19 in the juvenile population. In this study, patients with COVID-19 tended to have a higher likelihood of CFSs among the patients with FS who visited the pediatric fever clinic. The duration between fever peaks was shorter and the fever peak was higher among COVID-19 patients. The admission percentage was higher for COVID-19 children because they had more convulsions and for longer periods. Published literature alludes to genetic predispositions for FS. In some studies, they observed a previous history of FS and a family history of FS in 20.0% and 11.1% of the cases and only 2.9%. Seizures may be a symptom of a condition affecting the CNS or they may be brought on by viral infections. The

Table 2 Comparison between basic and nonbasic diseases in febrile seizures children with coronavirus disease-2019

Characteristics	COVID-19 children with febrile seizures ($n = 224$)	COVID-19 children with febrile seizures and basic diseases ($n = 57$)	*p*-Value
Age (mean ± SD; years)	2.4 ± 1.2	2.8 ± 1.2	0.018
Gender (male/female)	148/76	37/20	0.869
Fever peak (°C)	39.4 ± 1.0	39.3 ± 1.5	0.519
Time from the onset of the fever and the beginning of the seizure (h)	19.5 ± 13.4	20.3 ± 14.4	0.711
Interval between fever peaks (h)	3.6 ± 1.9	3.6 ± 1.8	0.921
Lymphopenia	19 (8.5%)	8 (14.0%)	0.204
Thrombocytopenia	0	1 (1.8%)	1
Anemia	1(0.4%)	0	1
C-reactive protein elevation	26 (11.6%)	15 (26.3%)	0.005
Increased lactic acid	63 (28.1%)	26 (45.6%)	0.011
Increased procalcitonin	67 (29.9%)	16 (28.1%)	0.786
Increased IL-6	74 (33.0%)	15 (26.3%)	0.330
Convulsive time (min)	4.0 ± 5.4	3.4 ± 3.6	0.407
Convulsive number	1.4 ± 0.8	1.6 ± 1.4	0.086
Simple FS	65 (29.0%)	39 (68.4%)	<0.01
Complex FS	159 (71.0%)	18 (31.6%)	<0.01
History of febrile seizures	82 (36.1%)	27 (43.5%)	0.245
Visit neurology department	74 (33.0%)	28 (49.1%)	0.024
Head CT or MRI	119 (53.1%)	36 (63.2%)	0.174
Electroencephalogram	72 (32.1%)	27 (47.4%)	0.032
Disposition			
Admission	41 (18.3%)	12 (21.0%)	0.636
ICU admission	3 (1.3%)	1 (1.8%)	0.813
Discharge	183 (81.7%)	45 (78.9%)	0.636

Abbreviations: COVID-19, coronavirus disease-2019; FS, febrile seizure; ICU, intensive care unit; MRI, magnetic resonance imaging; SD, standard deviation.

neuropathogenesis of COVID-19 is still unknown, but some investigations have suggested that SARS-CoV-2 could enter the CNS through the olfactory mucosa, blood–brain barrier, and axonal transport.[24,25]

The fact that we tested for COVID-19 antigen and novel coronavirus nucleic acid in all of the patients at the fever clinic throughout this time period was a significant strength of our study. Children infected with the Omicron variant have significantly higher body temperatures than those infected with the Delta variant.[26] The higher peak body temperature caused by SARS-CoV-2 infection during the Omicron period may have contributed to increased FSs. The COVID-19-positive group in our study had a higher fever peak and a shorter interval between fever peaks. These findings are consistent with other studies.[27] FSs are generally defined as seizures occurring in children aged typically 6 months to 5 years, with a peak incidence between 12 and 18 months of age. Given that our study's basic disorder group had a higher average age, it is plausible that the basic disorder encouraged the occurrence of FSs.

Among the respiratory viruses, the coronavirus was most frequently linked to FS, followed by the influenza virus.[13] Although MIS-C in children and respiratory symptoms predominated in medical literature, there were various neurologic consequences of infection in the pediatric population.[4] Four kids who tested positive for COVID-19 were admitted to the ICU and were later diagnosed with acute necrotizing encephalopathy. Despite the fact that the pathophysiology was not fully known, it is believed to entail three major categories: direct viral harm to brain cells, vascular endothelial injury, and inflammatory and autoimmune injury.[28,29] In a separate analysis of COVID-19 children with fundamental disorders, we discovered that these conditions did not increase the likelihood of hospital admission or ICU admission, suggesting that they might not be risk factors for disease aggravation.

Higher levels of lactic acid and IL-6 are present in COVID-19-positive individuals. Numerous studies have discovered that, compared to children who do not experience FSs, patients with FSs exhibit considerably higher levels of IL-6

and lactic acid.[30] Because lymphopenia had already been widely described as a general hallmark of COVID-19,[31,32] data showing higher incidence of lymphopenia in FS patients with COVID-19 may be expected. According to a new study, more severe inflammation was linked to neurologic disorders such as severe encephalopathy, cerebral edema, stroke, and Guillain–Barre syndrome that were life-threatening and related to COVID-19.[4] The pathophysiology of FS involves immune mediators such as TNF-α, IL-1β, and IL-6.[5,33] The clinical features of FS in COVID-19 may be explained by SARS-CoV-2's direct CNS invasion and breakdown of the blood–brain barrier, as well as the significantly greater amount of cytokines seen compared to seasonal viruses: the unusual age of start and increased likelihood of multiple convulsive episodes.[7,20]

This study was the first study to examine the incidence of FSs in children infected with the SARS-CoV-2-Omicron variant in Shanghai, China. We examined detailed clinical presentations and risk factors associated with FSs in children infected with the SARS-CoV-2-Omicron variant. Nevertheless, the following are the limitations of our study: (1) The sample size was rather small and this could limit the study's power. (2) Because this study is retrospective, it has the inherent flaws of that type of research, including missing data and recollection bias. (3) This study only involved one facility; it is not possible to extrapolate the results to determine the incidence of FS among children nationally who have contracted COVID-19. (4) Since we did not get the children's family history, we were unable to investigate the connection between FSs and family history in children who tested positive for COVID-19.

Conclusion

In summary, a significant increase in FSs was observed in children with SARS-CoV-2-Omicron infection. Approximately 5.58% of participants with COVID-19 suffered from FSs. Compared to patients without COVID-19, a greater percentage of COVID-19 patients experienced CFSs. The proportion of lactic acid and IL-6 increase was larger in the COVID-19-positive group.

Author's Contributions

Y.S., S.M., and X.Z. designed the study, participated in its implementation, analyzed, and wrote the initial draft of the manuscript. G.S., J.F., X.G., and X.D. collected the data and carried out the initial analyses. G.H., X.Z., and S.Z. reviewed the study results. X.Z. and S.Z. conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript. All authors approved the final manuscript and agreed to be responsible for all aspects of the work.

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Conflict of Interest

Y.S. reports that financial support was provided by the Shanghai Hospital Association (202150028) and Shanghai Hospital Development Center (2022SKMR-17). The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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