Introduction

Febrile seizures (FSs) are convulsions that occur in young children, typically between the ages of 6 months and 5 years, and are associated with fever without evidence of central nervous system (CNS) infection. They are the most common type of seizures in childhood, affecting approximately 2% to 5% of children worldwide [1]. FS is more common among boys than girls, and its prevalence varies among ethnic groups [2,3]. These seizures usually happen within 24 to 48 hours of the onset of fever and are more frequent in children with a family history of FS than in those without such a history.

The pathogenesis of FS is multifactorial and heterogeneous. Studies investigating a link between systemic or local inflammation and the CNS, as well as those examining the mechanisms leading to increased CNS excitability during fever, have yielded inconsis-

Comparison of Clinical Characteristics in Patients with Febrile Seizures Based on Prior COVID-19 Infection

Su-Jeong You, MD

Department of Pediatrics, Inje University Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea

Purpose: Febrile seizures (FSs) are neurological events associated with fever, typically occurring in children between 6 months and 5 years of age in the absence of central nervous system infection. Growing evidence suggests that coronavirus disease 2019 (COVID-19) can cause immune system dysregulation. This study compared the clinical characteristics of patients with FS based on whether they had experienced prior COVID-19 infection.

Methods: A retrospective analysis was conducted of the medical records of 114 patients with FS who visited Inje University Sanggye Paik Hospital between January 2019 and December 2022.

Results: The study cohort included 70 (61.4%) boys and 44 (38.6%) girls, with a mean age of 22.99 ± 11.68 months at seizure onset. Among the 114 patients with FS, 19 had a history of COVID-19, while 95 did not. These groups differed significantly in the interval between the onset of fever and seizure. Specifically, when using a 12-hour threshold for analysis, a significantly greater proportion of patients with a history of COVID-19 exhibited intervals exceeding 12 hours compared to those without such a history. No significant differences were noted regarding sex, age, seizure frequency, personal history of FS, or family history of FS or epilepsy between the groups.

Conclusion: Pediatric patients with FS and prior COVID-19 infection exhibited longer intervals between the onset of fever and seizure compared to those without previous COVID-19 infection. This finding suggests that COVID-19 may influence the mechanisms underlying FS. To better understand this relationship, long-term follow-up studies with larger cohorts are warranted.

Keywords: Coronavirus; Seizures; Fever
tent and inconclusive results. However, the age group most often affected by FS coincides with a period of rapid CNS development. In this vulnerable, immature CNS, heightened neuronal excitability can lead to seizures. Moreover, cytokines produced and released during the acute inflammatory responses associated with fever may contribute to neuronal hyperexcitability [4]. Inflammatory responses outside the CNS can increase cytokine levels within the CNS through the neuroimmune network. Once released, these cytokines can trigger neuronal hyperexcitability in the CNS (illustrating the role of cytokines in the brain parenchyma), potentially leading to the onset of FS [4,5].

Like other coronaviruses, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is recognized as neurotropic. Both neurons and glial cells express angiotensin-converting enzyme 2, which serves as the host receptor for SARS-CoV-2 [6,7]. As a result, direct invasion of the CNS by SARS-CoV-2 can lead to neurological symptoms [8]. Furthermore, indirect CNS damage caused by inflammatory responses following infection—similar to those observed with other respiratory viruses—can also result in neurological manifestations, including FS [7].

SARS-CoV-2 infection can lead to complex and varied immune alterations across different hosts and throughout the course of the disease. Initially, the subtle immune dysregulation observed in coronavirus disease 2019 (COVID-19) was largely attributed to changes in innate cytokines. However, a more intricate pattern of both innate and adaptive immune changes has been revealed, marked by concurrent hyperinflammatory and immunosuppressive responses in effector cells [8]. Recent studies have also indicated that COVID-19 infection in children can be associated with FS, with 0.5% to 2.7% of included pediatric COVID-19 cases being diagnosed with FS and approximately 9% requiring critical care services [9,10].

Growing evidence indicates that COVID-19 may cause dysregulation of the immune system. Consequently, this study sought to determine whether the clinical characteristics of pediatric patients with FS who have experienced prior COVID-19 infection differ from those of patients with no history of the virus.

2. Study design and population
A retrospective analysis was conducted of the medical records of pediatric patients with FS who visited the emergency department of Inje University Sanggye Paik Hospital in Seoul, South Korea, between January 1, 2019, and December 31, 2022.

The eligibility criteria were as follows: participants had no personal history of afebrile or neonatal seizures, no evidence of intracranial infections or head trauma, and no pre-existing neurological disorders or conditions predisposing them to an increased risk of seizures. None of the children were on chronic antiseizure treatment, including intermittent diazepam prophylaxis. Patients with electrolyte imbalances, hypoglycemia, or neurological problems were excluded from the study. Additionally, none of the patients who presented at the hospital with seizures and fever had an intracranial infection.

3. Data collection
The following clinical and demographic data were collected from patients’ medical records, typically completed by pediatric residents or pediatric neurologists: age, sex, date and time of fever onset, seizure onset, history of COVID-19, other medical conditions, family history of febrile or any convulsive disorder, fever etiology, and seizure characteristics, including number, duration, and type. The types of seizures were primarily reported by parents and caregivers; however, these reports were not considered due to the uncertainty of their accounts.

4. Statistical analysis
Continuous variables, such as age, are presented as mean±standard deviation and were compared using t-tests. Categorical variables, such as sex and the interval between the onset of fever and the onset of FS, were compared using the chi-square or Fisher exact test, as appropriate. All statistical analyses were performed using SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). A P value of less than 0.05 was considered to indicate statistical significance.

Results
Medical records of 70 boys (61.4%) and 44 girls (38.6%) with FS were retrospectively examined (Table 1). The mean age at the onset of seizures was 22.99±11.68 months (range, 7 to 90; median, 20). Prior to the FS diagnosis, all patients exhibited normal psychomotor development. Of the patients, four experienced focal seizures, while the rest had generalized seizures. Only one patient experienced a seizure lasting longer than 30 minutes. Nineteen patients (16.7%) were diagnosed with complex FS. The mean time from the onset of fever to the onset of seizure was 13.04±15.11
hours (range, 0 to 72 hours; median, 8). Twenty-eight patients (24.6%) had experienced previous FS episodes, and a family history of FS was noted in 26 patients (19.3%).

Of the 114 total patients with FS, 19 had a history of COVID-19, while the remaining 95 patients did not. A significant difference was observed in the interval between the onset of fever and seizure between the groups with and without previous COVID-19 infection (23.50±21.71 hours vs. 11.05±12.72 hours, respectively; t-test, P<0.05) (Table 2). Furthermore, the analysis was based on a 12-hour threshold, a significantly higher proportion of cases with intervals exceeding 12 hours was found in the group with prior COVID-19 infection compared to the group without such a history (Fisher exact test, P<0.05) (Table 2). However, no significant difference was detected between the two groups when the intervals were examined on a 24-hour basis (chi-square test, P>0.05). No significant differences were observed between the groups regarding sex, age, seizure frequency, history of FS, or family history of FS or epilepsy (Table 2).

### Discussion

In this study, the medical records of 114 pediatric patients with FS were analyzed, comparing the clinical characteristics of those with and without a history of COVID-19. Previous research has primarily concentrated on FS occurring concurrently with COVID-19. In contrast, the present study distinguished between groups based on prior COVID-19 infection. A significant difference was found between these groups in the time from the onset of fever to seizure. Moreover, when the data were categorized based on a 12-hour threshold, the group with prior COVID-19 infection exhibited a significantly greater proportion of cases with intervals exceeding 12 hours compared to those with no COVID-19 history.

FS typically occurs within the first day of fever onset [11,12]. Seizures that arise 3 or more days after the onset of fever warrant further investigation. In this study, all patients with prior COVID-19 infection were clinically diagnosed with FS, despite the extended period between the onset of fever and the seizure event. Notably, the sample size of this group was limited. A comparative study that analyzed FS based on the presence or absence of concurrent COVID-19 infection found no significant difference in the time from fever onset to seizure [13]. This finding suggests that the inflammatory storm in the early stages of COVID-19 may not immediately alter the interval between fever and seizure onset. Instead, it may gradually affect the neuroimmune network, potentially leading to longer intervals between these two events. Further research is necessary to thoroughly investigate the temporal changes in the interval between fever and seizure onset following COVID-19 infection.

FS, which results from sensitivities to fever in the developing brain, generally has benign outcomes and exhibits a significant genetic predisposition. Some patients with FS may experience recurrence and potentially face an increased risk of developing epilepsy. Children with simple FS are at a slightly higher risk of subsequent epilepsy (approximately 1%) compared to the general population, which has an incidence of about 0.5% [14]. The risk of future epilepsy in children with complex FS is estimated to be between 4% and 6%, depending on the number of complex features present.

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**Table 1.** Clinical characteristics of pediatric patients with febrile seizures (n=114)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mo)</td>
<td>22.99±11.68 (7–90)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male:female 70 (61.4):44 (38.6)</td>
</tr>
<tr>
<td>Complex febrile seizure</td>
<td>19 (16.7)</td>
</tr>
<tr>
<td>History of COVID-19</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>19 (16.7)</td>
</tr>
<tr>
<td>Negative</td>
<td>95 (83.3)</td>
</tr>
<tr>
<td>Previous febrile seizures</td>
<td>28 (24.6)</td>
</tr>
<tr>
<td>Family history of febrile seizures</td>
<td>26 (19.3)</td>
</tr>
<tr>
<td>Family history of epilepsy</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are presented as mean±standard deviation (range) or number (%). COVID-19, coronavirus disease 2019.

**Table 2.** Comparison of characteristics of pediatric patients with febrile seizures based on COVID-19 history

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients without previous COVID-19 infection (n=95)</th>
<th>Patients with previous COVID-19 infection (n=19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male:female 55:40</td>
<td>15:4</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Age (mo)</td>
<td>22.34±11.62:26.26±11.69</td>
<td>11.05±12.72:23.50±21.71</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Interval between fever onset and seizure (hr)</td>
<td>≤12:59≤12:36</td>
<td>6≤12&lt;24:14&gt;24</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Seizure type</td>
<td>Present:8 Absent:11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure duration (min)</td>
<td>&gt;15:1&lt;15:0</td>
<td></td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Values are presented as number or mean±standard deviation. COVID-19, coronavirus disease 2019.
Other risk factors for epilepsy include a fever duration of less than 1 hour before the seizure, onset of FS before the age of 1 or after 3 years, an underlying neurodevelopmental abnormality, a positive family history of epilepsy, and epileptiform discharges observed on electroencephalography [16-18].

The exact pathogenesis of FS is not well understood, but predisposing factors such as genetic susceptibility, infection or immune-mediated factors, and the development of a cytokine storm have been proposed [19]. A family history of FS is the most influential risk factor, with an increased number of affected relatives correlating with a higher risk [20]. Cytokines are mediators of the host response to infection and are responsible for inducing fever, leukocytosis, and the synthesis of acute-phase proteins [21]. Recent observations have revealed abnormalities in cytokine and immune cell expression in patients with seizures and in animal seizure models. Numerous studies have indicated that the immune system regulates the production and release of cytokines, which can exacerbate brain damage by acting as mediators of seizures [22]. Cytokines have the capacity to produce both pro- and anti-inflammatory effects [19]. Pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α, are responsible for inducing fever during infection. The threshold temperature at which fever leads to FS varies among individuals and is also influenced by age and maturation [23]. The frequency of potential future neurologic complications may depend on whether pro-inflammatory or anti-inflammatory reactions predominate during the interval between the onset of fever and seizure. However, it remains unclear whether a longer duration between fever and FS following prior COVID-19 infection increases the risk of developing epilepsy or other neurological diseases. Long-term follow-up studies are necessary to explore potential changes in FS that could lead to unprovoked seizures, epilepsy, or other neurological conditions.

In a previous study, 30% of children experienced recurrent FS during subsequent illnesses [24]. Risk factors for recurrence, as opposed to the risk of initial FS, include onset before 18 months of age, a relatively low temperature threshold (approximately 38°C), a short duration of fever (less than 1 hour) before the seizure, and a family history of FS [25,26].

Further evaluations are necessary to understand the impact of prolonged intervals between the onset of fever and seizure on the recurrence of FS in patients with a history of COVID-19.

Although this investigation revealed no significant difference in age between patients with and without prior COVID-19, a separate study reported that patients with FS and concurrent COVID-19 infection were on average older at the onset of FS than those without COVID-19 [13]. This suggests that the inflammatory response in the early stage of COVID-19 may have varying impacts on FS over time.

In conclusion, this study demonstrated that pediatric patients with FS and prior COVID-19 infection experienced a longer duration between the onset of fever and seizure compared to those with no COVID-19 history. This finding suggests that the inflammatory storm triggered by COVID-19 may affect the time from fever to seizure onset by gradually altering the neuroimmune pathways involved in the development of FS. However, this was a retrospective study with a small patient cohort. Consequently, a prospective study with a larger sample size is required to fully comprehend how this interval evolves and its implications for long-term prognosis.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

ORCID

Su-Jeong You, https://orcid.org/0000-0001-5200-4773

Author contribution

Conceptualization: SJY. Data curation: SJY. Formal analysis: SJY. Methodology: SJY. Visualization: SJY. Writing - original draft: SJY. Writing - review & editing: SJY.

References