Complex Febrile Seizures in Children with COVID-19 Infection

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Coronavirus disease 2019 (COVID-19), first reported in Wuhan, China in 2019, is an infectious disease caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The incidence rate is lower in children than in adults, but as the number of infected patients has increased recently, the number of pediatric patients has also increased [1,2]. The typical symptoms of COVID-19 include fever, cough, chills, aches, headaches, anorexia, and anosmia [1]. Neurological manifestations can also occur in patients with COVID-19. Several studies have reported neurological manifestations of COVID-19 in children [1-4]. Panda et al. [4] reviewed these manifestations and reported that 16% of all such patients showed non-specific neurological symptoms, such as headache, myalgia, and fatigue, whereas 1% of them showed specific neurological symptoms, such as seizures and encephalopathy. Another study reported that neurological manifestations, including febrile and non-febrile seizures, were observed in 3% of children with COVID-19 [1].

Febrile seizures are relatively common neurologic disorders, affecting 2% to 5% of children under the age of 5 years. There are two types of febrile seizures: simple and complex seizures. Simple febrile seizures refer to generalized seizures lasting less than 15 minutes. Complex febrile seizures are focal, last longer than 10 to 15 minutes, or occur several times within 24 hours [5]. Approximately 20% to 30% of all febrile seizures are complex [5,6]. Several cases of febrile seizures have been reported in patients with COVID-19, indicating that SARS-CoV-2 can cause febrile seizures [2,7-10].

We have recently observed an increase in complex febrile seizures among children with COVID-19. Thirteen pediatric COVID-19 patients who experienced febrile seizures visited Seoul National University Bundang Hospital from January 1 to June 30, 2022, during the pandemic period. Seven patients were diagnosed with simple febrile seizures, while the other six were diagnosed with complex febrile seizures. The rate of complex febrile seizures was higher than usual, as the previous literature suggests that the frequency of complex febrile seizures is generally around 20% to 30% [6]. Herein, we report six cases of COVID-19-associated complex febrile seizures. The Institutional Review Board of the Seoul National University Bundang Hospital approved the study protocol (No. B-2210-786-105), and the requirement for written informed consent was waived owing to the retrospective nature of our study.
**Patient 1:** A 37-month-old girl reported to the emergency room with prolonged febrile seizures but no significant medical history. She presented with a generalized tonic-clonic seizure that lasted 45 minutes and could be stopped with a bolus injection of intravenous lorazepam. Lumbar puncture revealed no abnormal findings, including COVID-19 polymerase chain reaction results of a cerebrospinal fluid specimen. Brain computed tomography (CT), brain magnetic resonance imaging (MRI), and sleep electroencephalography (EEG) were normal. She was stable during admission and discharged uneventfully.

**Patient 2:** A 23-month-old boy without a significant medical history was admitted for prolonged febrile seizure. The seizures were generalized tonic-clonic seizures that lasted for 40 minutes. His seizures persisted after a bolus injection of intravenous lorazepam and stopped after fosphenytoin administration. Brain MRI and sleep EEG results were normal. The patient had no further seizures and was discharged with an oral phenytoin prescription.

**Patient 3:** A 4-year-old girl who was previously healthy visited the emergency room because of a prolonged febrile seizure. She presented with a generalized tonic-clonic seizure that lasted for 50 minutes. The seizures persisted even after a bolus injection of intravenous lorazepam but ceased with a bolus injection of intravenous midazolam. Brain CT and sleep EEG did not reveal any abnormal findings. The patient had no further seizures and was discharged without complications.

**Patient 4:** A 14-month-old boy with a history of simple febrile seizures was admitted because of a complex febrile seizure. He had three episodes of generalized tonic-clonic seizures within 24 hours, which lasted less than 1 minute, followed by postictal sleep. No further seizures occurred after an injection of lorazepam, which was administered following the third seizure. The sleep EEG results were normal, and the patient was discharged without any complications.

**Patient 5:** A 20-month-old girl without a significant past medical history, including provoked or unprovoked seizures, was admitted with a complex febrile seizure. She had three hypomotor seizures within 24 hours that lasted approximately 15 to 30 seconds. Her sleep EEG results showed abnormal intermittent delta activity involving the posterior head region and focal interictal epileptiform discharges from both occipital areas. The patient had no further seizures during admission and was discharged without further complications.

**Patient 6:** A 43-month-old boy with a history of simple febrile seizures visited the emergency room with a complaint of febrile seizures. The seizure was a generalized tonic-clonic seizure associated with postictal confusion and lasted approximately 30 seconds. Within 6 hours of emergency room stay, the patient developed another episode of a generalized tonic-clonic seizure, following which he was admitted for observation and further evaluation of a complex febrile seizure. His sleep EEG was normal, and he had no further seizures. The patient’s neurologic condition was stable, and he was hence discharged on the 4th day of hospitalization.

Out of 13 children with febrile seizures following acute COVID-19 infection, we encountered six patients with complex febrile seizures. A positive reverse-transcriptase polymerase chain reaction assay using a nasopharyngeal swab confirmed COVID-19 in all patients. There have been similar reports of complex febrile seizures related to COVID-19 [7,8]. One study reported the case of a 2-year-old girl who presented with febrile status epilepticus and was diagnosed with COVID-19 [7]. Another study reported febrile status epilepticus in an otherwise healthy 5-month-old girl, suggesting that seizures may be an initial manifestation of COVID-19 in children [8]. These reports demonstrate that acute COVID-19 infection can cause sudden acute seizures, and prolonged febrile seizures are also possible.

The proportion of complex febrile seizures to total febrile seizures in COVID-19 patients (46%, 6/13 patients) was higher than that in the overall historical cohort, which was approximately 20% to 30% [5,6]. We also compared the data with the corresponding period in 2018—that is, a non-COVID-19 period—at the same institution. The complex febrile seizure proportion in the pandemic was also significantly higher than that of the corresponding pre-pandemic period (15.4%, 28/182 patients). This increased ratio is similar to that reported in a recent study, where an increase in complex febrile seizures in pediatric patients (88%, 14/16 patients) during the resurgence of COVID-19 was observed [9]. However, in two other studies, the proportion of complex febrile seizures to total febrile seizures was reported to be approximately 32% and 22%, respectively [2,10].

In conclusion, we reported a higher incidence of complex febrile seizures among children infected with COVID-19. Since this was a single-center retrospective study with a small sample size, it has a limited ability to establish the significance of the association between complex febrile seizures and COVID-19. Further studies with a larger number of patients are needed to support our findings and to evaluate the pathophysiology of febrile seizures in COVID-19.

**Conflicts of interest**

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

Conceptualization: HK. Data curation: LK, JYH, and HK. Methodology: LK, JYH, and HK. Project administration: JYH, AC, and HK. Writing-original draft: LK. Writing-review & editing: JYH, AC, and HK.

References