


Impact of the COVID-19 Pandemic on Diagnostic Frequency of Febrile Seizures: An Electronic Health Record Database Observational Study

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Katsiah Cadet, MS¹, Gary D Ceneviva, MD², Vonn Walter, PhD³, Neal J Thomas, MD^{3,4}, and Conrad Krawiec, MD² 

Abstract

Background and Purpose: Febrile seizures are common in children and are associated with viral infection. Mitigation strategies implemented during the coronavirus disease 2019 (COVID-19) pandemic have slowed the spread of all viral illnesses potentially impacting febrile seizure frequency. The objective of this study is to assess the impact of COVID-19 mitigation strategies on the diagnostic frequency of febrile seizures. **Methods:** This was a retrospective observational cohort study utilizing TriNetX[®] electronic health record (EHR) data. We included subjects aged 0 to 5 years of age reported to have a febrile seizure diagnosis. After the query, the study population was divided into 2 groups [pre-COVID-19 (April 1st, 2019 until March 31st, 2020) and COVID-19 (April 1st, 2020 until March 31st, 2021)]. We analyzed the following data: age, sex, race, diagnostic, medication, and procedural codes. **Results:** During the pre-COVID time frame, emergency or inpatient encounters made up 688,704 subjects aged 0 to 5 years in the TriNetx database, while in the COVID-19 pandemic time frame, it made up of 368 627 subjects. Febrile seizure diagnosis frequency decreased by 36.1% [2696 during COVID-19 vs 7462 during the pre-COVID-19] and a higher proportion of status epilepticus was coded [72 (2.7%) vs 120 (1.6%)] ($P < .001$) during the COVID-19 pandemic. Hospitalization, lumbar puncture, critical care services, mechanical ventilation procedural codes were similar between the 2 cohorts. Antimicrobial use was higher in the pre-COVID-19 pandemic group [424 (15.7%) vs 1603 (21.5%)] ($P < .001$). **Conclusions:** Less children were diagnosed with febrile seizures during the COVID-19 pandemic, but a higher proportion were coded to have the complex subtype. The medical interventions required with the exception of antimicrobial use was similar. Further study is needed regarding mitigation strategies and its impact on pediatric diseases associated with viruses.

Keywords

pediatrics, seizures, febrile, COVID-19

Introduction

Febrile seizures are a common neurologic disorder in children between the ages of 6 months and 5 years of age. The etiology is most likely multifactorial. Due to age, a developing nervous system, and underlying genetic susceptibility, when a child develops a fever (usually in the setting of viral illness), it may trigger a febrile seizure.¹ Seizure types range from simple (non-focal generalized tonic-clonic seizures lasting less than 15 minutes with spontaneous resolution) to complex (focal seizures that last longer than 15 minutes with possible recurrence within 24 hours that may require treatment with anticonvulsants and/or hospitalization).¹ In general, the outcomes in children with febrile seizures are favorable with a risk of recurrence in approximately one-third of children.²

In 2020, the United States was subjected to the coronavirus-19 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2

¹Penn State College of Medicine, Hershey, PA, USA

²Department of Pediatrics, Pediatric Critical Care Medicine, Penn State Hershey Children's Hospital, Hershey, PA, USA

³Department of Public Health Sciences, Division of Biostatistics and Bioinformatics, Pennsylvania State University College of Medicine, Hershey, PA, USA

⁴Department of Public Health Sciences, Pennsylvania State University College of Medicine, Hershey, PA, USA

Corresponding Author:

Conrad Krawiec, Department of Pediatrics, Pediatric Critical Care Medicine, Penn State Hershey Children's Hospital, Hershey, PA, USA.

Email: ckrawiec@pennstatehealth.psu.edu

virus).³ To conserve medical supplies and curb the spread of this virus (especially during a timeframe where there were no approved vaccines or treatments), preventive interventions were implemented.⁴ Schools were closed, face masks were mandated, social distancing guidelines were developed, frequent hand washing was encouraged, and non-essential medical areas were closed to reduce person-to-person spread.⁴ In the adult population, this has resulted in not only helping to decrease the spread of COVID-19, but other viruses as well.^{5,6} The same trend may be seen in pediatric populations including a decrease in viruses that are commonly associated with febrile seizures.⁷⁻⁹ It is possible that the frequency of febrile seizures has also changed secondary to the mitigation strategies implemented during the COVID-19 pandemic.

The objective of this present study is to evaluate if COVID-19 mitigation strategies impacted the frequency of febrile seizure diagnoses in children aged 0 to 5 years of age and the treatments applied. We hypothesized that the frequency of febrile seizure diagnoses would be reduced during the time period when mitigation strategies were implemented.

Methods

Study Design

This is a retrospective observational cohort study utilizing the TriNetX[®] electronic health record (EHR) database of pediatric subjects aged 0 to 5 years of age who had International Classification of Diseases, 10th edition, Clinical Modification (ICD 10-CM) diagnostic codes associated with febrile seizures (see [Table Supplementary 1](#)). TriNetX is global federated research network that collects EHR data elements (ie diagnoses, procedures, laboratory values) of approximately 68 million patients in 56 large health care organizations (HCOs) predominately in the United States. The data provided is aggregated and made available within a real-time user-friendly browser-based software in a de-identified fashion. No protected health information is provided. Thus, Penn State Health Institutional Review Board (IRB) pre-determined this study to be non-human research.

Data Collection

TriNetX provided a de-identified dataset of electronic medical records (diagnoses, procedures, medications, laboratory values) from 10 158 subjects from 46 HCOs in the United States. The data is de-identified based on standard defined in Section §164.514(a) of the HIPAA Privacy Rule. The process by which datasets are de-identified is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule.

After the dataset was received, we analyzed the following EHR data: age, sex, race, ethnicity, diagnostic, medication, and procedural codes. The dataset included all codes available for

each subject. If a code of interest was not present within the study time period, it was assumed the subject did not have the condition or therapy provided. For example, if a procedural code related to lumbar puncture was not present, the subject was classified as not having this procedure within their electronic medical record. Subjects with unknown race and ethnicity were included in the analysis. The data was de-identified and no date of birth was provided, therefore, ages are approximate for subjects older than 1 year of age. For example, a child born in 2019 with febrile seizure diagnostic code noted on January 1st, 2021, the subject was determined to be 2 years of age. Children less than 1 year of age, were given an age of 0. Laboratory data identifying specific viruses were not available due to database limitations. Clinical documentation was unable to be reviewed to ensure if the patient was correctly diagnosed with a febrile seizure and if the febrile seizure type was classified accurately. Thus, if a subject had a diagnostic code for febrile seizure, we relied on the clinician's judgement that the subject met the criteria for a febrile seizure (ie, having a convulsion in association with a fever, no previous history of afebrile seizures, absence of central nervous system infection, etc). A portion of subjects may have been diagnosed to have both simple and complex febrile seizures. Because an initial simple febrile seizure may be followed by complex seizure, in cases where both febrile seizure types were diagnosed, those subjects were analyzed as complex febrile seizure types. Because the TriNetX database undergoes continuous updates, the analysis for this study took place on April 8th, 2021 [Please see [Table Supplementary 2](#) for diagnostic, medication, and procedural code definitions that were analyzed in this present study].

The study population was divided into 2 cohorts [pre-COVID-19 (April 1st, 2019 until March 31st, 2020) and post-COVID-19 (April 1st, 2020 until March 31st, 2021)] and analyzed. These dates were chosen based on when mitigation strategies were approximately initiated. Due to database limitations, we were unable to determine the exact location of the HCO where subjects were diagnosed with febrile seizures.

Data Analysis

Summary counts and percentages were computed for categorical variables of interest and the results were displayed in contingency tables. Fisher's exact test was used to assess the statistical significance of associations between categorical variables of interest and pre/post-COVID status, except for Race and Ethnicity, where a Monte Carlo version of Fisher's exact test was applied (100 000 replicates, random seed used for reproducibility). All analyses were summarized in reports generated with R Markdown while running R 4.0.2 (R Core Team).^{10,11}

Results

Demographic Characteristics

A total of 10 158 subjects (n, %) were included in this study. During the pre-COVID time frame, emergency or inpatient

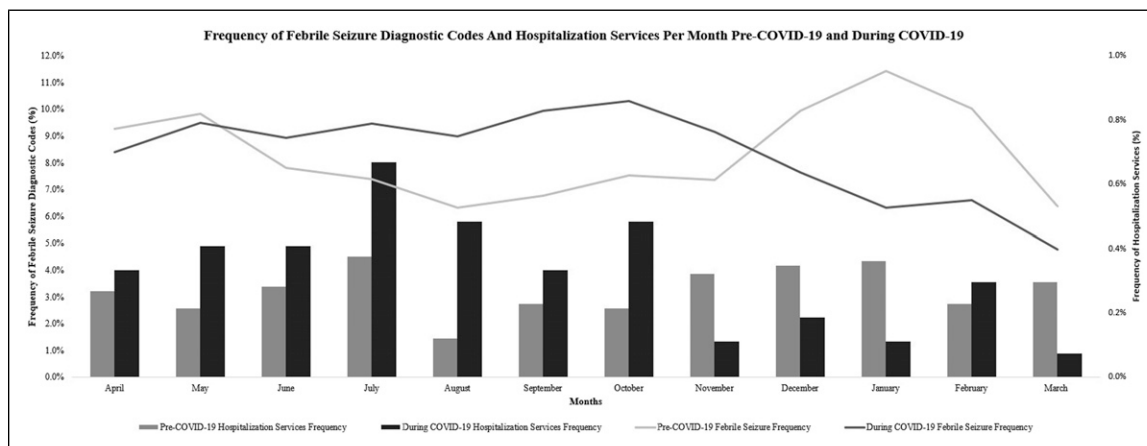


Figure 1. Frequency of febrile seizure diagnostic codes per month pre-COVID-19 and during COVID-19.

Table 1. Demographics of Pediatric Subjects Aged 0 to 5 years Diagnosed with Febrile Convulsions Pre-COVID-19 and During COVID-19 Pandemic.

	pre-COVID-19 Pandemic (n = 7462)	During COVID-19 Pandemic (n = 2696)	P-value
Sex			
Male	4290 (57.5%)	1551 (57.5%)	.802
Female	3125 (41.9%)	1143 (42.4%)	—
Age	2.0 ± 1.0	1.8 ± 1.1	<.001
Race			.004
American Indian or Alaska Native	34 (.5%)	12 (.4%)	—
Asian	318 (4.3%)	80 (3.0%)	
Black or African American	1722 (23.1%)	570 (21.1%)	
Native Hawaiian or Other Pacific Islander	33 (.4%)	19 (.7%)	
Unknown	1648 (22.1%)	615 (22.8%)	
White	3707 (49.7%)	1400 (51.9%)	
Ethnicity			<.001
Hispanic or Latino	1133 (15.2%)	406 (15.1%)	—
Not Hispanic or Latino	3618 (48.5%)	1444 (53.6%)	
Unknown	2711 (36.3%)	846 (31.4%)	
Febrile Seizure Type			
Simple	5955 (79.8%)	2097 (77.8%)	.029
Complex	1507 (20.2%)	599 (22.2%)	—
Deaths	4 (.05%)	1 (.04%)	1

encounters made up 688 704 subjects aged 0 to 5 years in the TriNetx database, while in the COVID-19 pandemic time frame, it made up of 368 627 subjects. Febrile seizure diagnosis frequency decreased by 36.1% [2696 during COVID-19 vs 7462 pre-COVID-19]. [Figure 1]

Subject ages were older in the pre-COVID-19 time period (2.0 ± 1.0 vs 1.8 ± 1.1 years, *P* < .001). Simple febrile seizures were more frequently diagnosed in both time periods when compared to complex febrile seizures. Subject characteristics are summarized in Table 1. [Table 1]

Viral Diagnostic Codes

Overall, 922 (12.4%) of febrile seizures were associated with a virus during the pre-COVID-19 period compared to 110 (4.1%) during the COVID-19 period (*P* < .01). Influenza [552 (7.4%)] and respiratory syncytial virus [101 (1.4%)] were the most frequent diagnostic codes noted in children with febrile seizures pre-COVID-19 pandemic. During the COVID-19 pandemic, the COVID-19 [48 (1.8%)] diagnostic code was the virus more frequently noted. [Table 2]

Table 2. Viruses Diagnosed During pre-COVID-19 and During COVID-19 Pandemic.

	pre-COVID-19 Pandemic	During COVID-19 Pandemic
Any Virus Present	922 (12.4%) ^a	110 (4.1%)
Adenovirus	54 (.7%)	16 (.6%)
Coronavirus	33 (.4%)	2 (.1%)
Coronavirus-2019	0 (.0%)	48 (1.8%)
Coxsackie Virus	6 (.1%)	1 (.0%)
Enterovirus	66 (.9%)	17 (.6%)
Human metapneumovirus	17 (.2%)	0 (.0%)
Influenza	552 (7.4%)	9 (.3%)
Parainfluenza	2 (.0%)	1 (.0%)
Pertussis	2 (.0%)	0 (.0%)
Rhinovirus	16 (.2%)	5 (.2%)
Respiratory Syncytial Virus	101 (1.4%)	2 (.1%)
Viral and Chlamydial	5 (.1%)	2 (.1%)
Virus – Other	137 (1.8%)	15 (.6%)

^aMultiple subjects noted to have multiple viruses present (62 pre-COVID-19 pandemic and 8 during COVID-19 pandemic)

Table 3. Selected Neurologic Diagnoses Reportedly Diagnosed Concomitantly with Febrile Convulsions pre-COVID-19 and During COVID-19 Pandemic.

	pre-COVID-19 Pandemic	During COVID-19 Pandemic	P value
Inflammatory diseases of the central nervous system	24 (.3%)	13 (.5%)	.263
Status Epilepticus Associated Diagnoses	120 (1.6%)	72 (2.7%)	<.001
Other Epilepsy Diagnoses	130 (1.7%)	86 (3.2%)	<.001

Table 4. Summary of Common Procedural Services.

	pre-COVID-19 Pandemic	During COVID-19 Pandemic	P value
Common Procedural Services (n,%)			
Critical Care Services	172 (2.3%)	60 (2.2%)	.88
Hospitalization	243 (3.3%)	105 (3.9%)	.123
Lumbar Puncture	72 (.96%)	38 (1.4%)	.065
Mechanical Ventilation	48 (.6%)	21 (.8%)	.494

Concomitant Neurologic Diagnoses

A higher frequency of status epilepticus associated diagnostic codes [120 (1.6%) vs 72 (2.7%), $P < .001$] were noted during the COVID-19 pandemic. Children with other epilepsy diagnostic codes also were noted to be present in a higher frequency during the COVID-19 pandemic time period [130 (1.7%) vs 86 (3.2%), $P < .001$]. There was no difference in the frequency of diagnostic codes of inflammatory diseases of the central nervous system between the 2 groups [Table 3].

Procedural Services

The frequency of lumbar puncture, critical care services, mechanical ventilation, and hospitalization were similar between the 2 groups. [Table 4]

Medication Usage

Subjects during the COVID-19 pandemic were noted to have a higher frequency of medication codes for anti-infectives for systemic use [1603 (21.5%) vs 424 (15.7%), $P < .001$], antiseizure medications [287 (3.8%) vs 128 (4.7%), $P = .047$], and benzodiazepines [918 (12.3%) vs 373 (13.8%), $P = .043$]. [Table 5]

Discussion

Mitigation strategies implemented throughout the United States during the COVID-19 pandemic assisted in reducing the spread of the SARS-CoV2 virus as well as non-SARS-CoV2 respiratory viruses. Because 1 potential trigger for febrile seizures are respiratory viruses, we hypothesized that the decrease in the prevalence of non-SARS-CoV2 viruses

Table 5. Selected Medication Classes Utilized Pre- and During COVID-19 Pandemic for Subjects Diagnosed with Febrile Convulsions for the First Time.

	Pre-COVID Pandemic	During COVID Pandemic	P-value
—	7462	2696	—
Anti-infectives for Systemic Use	1603 (21.5%)	424 (15.7%)	<.001
Antiseizure Medications	287 (3.8%)	128 (4.7%)	.047
Benzodiazepines	918 (12.3%)	373 (13.8%)	.043

would also decrease the frequency of febrile seizures. We found that overall, less children were reported to be diagnosed with febrile seizures during the COVID-19 pandemic within the TriNetX © database. It is expected that with the decrease in close contact with others, there is a decrease in the spread of viruses many of which may cause febrile illness and induce a febrile seizure in susceptible children.¹² Of the children diagnosed, however, a significantly higher proportion were coded to have status epilepticus. These findings may have important implications in future approaches to mitigation strategies.

The etiology of febrile seizures is multifactorial. In general, they are thought to be the result of a developing nervous system vulnerable to the effects of a high fever.² The trigger commonly associated with febrile seizures, however, are respiratory viral infections.¹³ It stands to reason, therefore, that mitigation strategies that limit the spread of respiratory viral illnesses may limit the frequency of febrile seizures.

The mitigation strategies included masking, social distancing, avoiding crowds, hand hygiene, and closures of schools as well as child-care centers. These measures were instituted as spread of SARS-CoV-2 is thought to be due to the direct person-to-person respiratory transmission.⁴ Limiting close-range contact and the use of face coverings limits the spread of respiratory particles through respiratory secretions, avoiding direct contact with the mucous membranes, and gaining host entry.¹⁴ As a result, there was also a decrease in non-SARS-CoV2 respiratory viruses due to a similar pathophysiology.⁸ While the impact of how non-SARS-CoV-2 viral illnesses are known from a respiratory standpoint, including need for hospitalization, it is unknown how children who developed neurologic diseases associated with respiratory viral illnesses, such as febrile seizures, were affected.¹⁵ An understanding of how mitigation strategies effected the frequency of febrile seizures could help us gain further understanding of why febrile seizures and if mitigation strategies could be of any benefit.

Febrile seizures, while potentially life-threatening, have a high survivability and favorable long-term prognosis.² Even so, these children may require critical care. Some may require aggressive antiepileptic medication administration to extinguish seizure activity,¹⁶ often resulting in airway control, invasive mechanical ventilation, and intensive care unit sources.¹⁷ Some of these patients may undergo further evaluation with lumbar punctures and others may receive

antimicrobials to rule out serious bacterial infections. Therefore, mitigation strategies may not only help us understand the impact of febrile seizure frequency, but the hospital resources needed to stabilize the patient.

Our study found that febrile seizure frequency reduced during the pandemic. Mitigation strategies likely reduced the spread of respiratory viral illnesses, the likelihood of the development of a higher fever, and subsequent occurrence of febrile seizures (especially in genetically susceptible patients). The implications are that use of routine masking and social distancing may be beneficial for this disease process from a health as well as a resource utilization standpoint.⁷ Justification for use of mitigation strategies to only reduce the frequency of febrile seizures, however, is limited. Prior to the COVID-19 pandemic, febrile seizures had a low occurrence with only a small use of hospital resources. Thus, while use of mitigation strategies likely limited the use of precious hospital resources during the early stages of the COVID-19 pandemic (thereby preserving mechanical ventilators and personal protective equipment), continuation of this strategy may not be feasible especially if only a small number of patients would be impacted.

These findings are in contrast to 1 other study conducted early in the COVID-19 pandemic. In an Italian institution, Smarrazzo et al reported that admissions for febrile seizures from March to May 2020 increased by 3-fold during the same period in 2019.¹⁸ There are many reasons for this difference. Our study was conducted over a one-year period vs a three-month period early in the pandemic. We included more subjects potentially resulting in significant differences. Our study included patients from multiple healthcare organizations. Thus, it is possible clinicians in some healthcare organizations had a higher index of suspicion for an alternative cause of a febrile seizure and documented it as such. Finally, some areas where these centers were located may have had more stringent mitigation strategies.

Despite a decrease in febrile seizure frequency, the diagnostic codes for status epilepticus were higher. It is unclear why this effect occurred. Mitigation strategies have increased the use of telehealth services with referral to in-person clinical evaluation when deemed absolutely necessary.³ It is possible that children during the COVID-19 pandemic, who developed a fever and secondary to an infection despite following mitigation strategies, had a delay in evaluation and treatment

likely to decrease progression to a febrile seizure (ie use of antipyretics).¹⁹ By reducing exposure to other individuals and thus common infections, the immune system may remain immature due to being infrequently activated. Thus, when exposed to a new infection, a more robust response such as febrile seizure may occur due to increased susceptibility.^{20, 21} Children who developed a febrile seizure during the COVID-19 pandemic may have had known risk factors that lowered the seizure threshold and when combined with a robust immune response (and high fever), increased the likelihood of a febrile seizure. The extent of medical intervention required, however, was similar when compared to before the pandemic. Finally, previous evaluations of status epilepticus have reported an incidence of approximately .02% in children and higher mortality rates.^{22,23} In our study, when evaluating children with febrile seizures, the overall incidence rate of status epilepticus was noted to be higher and the frequency of deaths were lower. It is possible because we included children less than 5 years of age, particularly infants who appear to be susceptible to developing status epilepticus, it may have confounded our overall incidence rate and our mortality findings.

Hospital resources used were similar between the pre-COVID and during COVID-19 groups. The use of antimicrobials was noted to be higher in the COVID-19 group. Mitigation strategies and reduced spread of viruses may have led to a higher index of suspicion for bacterial causes of febrile seizures. Lumbar puncture and use of antibiotics should be considered when there are symptoms of an intracranial infection (ie altered consciousness, nuchal rigidity, etc), in children 6 to 12 months of age with an unimmunized status, and if the patient was on antibiotics (as it can mask the signs and symptoms of meningitis).²⁴ Because these subjects also had a higher frequency of status epilepticus and may have had altered consciousness (at the very least), antimicrobials may have been administered empirically due to the presence of a presumed bacterial infection. The COVID-19 group was also younger, may have had delay in receiving immunizations due to social distancing, and may have been on antibiotics (due to the possibility of receiving telehealth services). Thus, a lower threshold for antibiotic administration may have occurred in these subjects.

There are several limitations of this study. Because this was a retrospective study utilizing an electronic health record database limited to HCOs in the United States there is a possibility of population bias. Due to the use of billing codes, there is a potential for measurement error, misclassification, and selection bias. We were only able to query for subjects when clinicians entered the diagnostic code for febrile seizures. It is possible that some subjects were diagnosed with these conditions without them being coded within the EHR. TriNetX © currently does not provide the precise date of birth (only the year of birth). Thus, we were unable to determine the ages of subjects less than 1 year. Clinical documentation was not available to review, thus we were unable to confirm how the febrile seizure diagnoses were made.

During the COVID-19 pandemic there were less children diagnosed with febrile seizures overall but a higher proportion were coded to have the complex subtype. The medical interventions required was similar. Further study is needed regarding mitigation strategies and its impact on pediatric diseases associated with viruses.

Declaration of Conflicting Interests

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ORCID iD

Conrad Krawiec  <https://orcid.org/0000-0001-7902-2568>

Supplemental Material

Supplemental material for this article is available online.

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