Impact of the COVID-19 Pandemic on the Distribution of Viral Pathogens Involved in Febrile Seizures

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ABSTRACT

Objective: To evaluate the impact of the COVID-19 pandemic on the distribution of viral pathogens responsible for febrile seizures (FS) in children.

Materials and Methods: This multicenter study reviewed cases diagnosed as compatible with FS between March 2018 and March 2022. Patients who underwent viral testing were included. Demographic and clinical data were reviewed from the system files.

Results: Laboratory tests targeting viral etiology were performed in 114 of 1683 patients with FS. The viral etiology of FS was consistent before and during the pandemic. The findings demonstrated a statistically significant increase in the number of patients who reported their first FS during the pandemic (81.3%) as opposed to before (63.6%) (p=0.041). There were no significant differences in viral test positivity rates before and during the pandemic (p=0.817). While influenza virus was mostly isolated in the pre-pandemic period, influenza and SARS-CoV-2 were almost equally isolated in the post-pandemic period.

Conclusion: Febrile seizures are usually benign, with no adverse events. However, this situation may be stressful for families, but identifying the cause can provide relief. The development of rapid diagnostic tests that simultaneously screen for both SARS-CoV-2 and influenza viruses could be valuable for efficient patient follow-up and treatment.

Keywords: Febrile seizure, pandemic, SARS-CoV-2

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for the Coronavirus Disease 2019 (COVID-19) pandemic, emerged in December 2019. After being recognized as a worldwide pandemic, the virus quickly spread to children, and the clinical course, with multiple system involvement, began to be defined for the pediatric population. Patients infected with SARS-CoV-2 initially presented to the pediatric emergency departments (ED) with fever, respiratory and gastrointestinal signs and symptoms. Soon after, pediatric cases presenting to EDs with central nervous system (CNS) signs and symptoms, such as acute altered mental status, febrile/afebrile seizures, encephalitis and meningitis were identified (1, 2).

The most prevalent seizure type during childhood is febrile seizure (FS). FS is characterized by fever-induced seizure in children aged 6–60 months. To be diagnosed with FS, the patient should not be diagnosed with CNS infection, should not have a history of afebrile seizures, and should not have an acute metabolic abnormality. This condition

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affects 2-5% of children in Western countries, with a slightly higher incidence in Asian children. If FS occurs only once within 24 hours, lasts less than 15 minutes, and is generalized, it is termed as simple FS. However, if it is focal, persists for more than 15 minutes, or recurs within 24 hours, it is classified as complex FS (3, 4). Viral infections are the most common cause of FS. Influenza virus and human herpes virus-6 (HHV-6) are the most frequently isolated viral pathogens in FS cases because of their potentially high febrile clinical course compared with other infectious agents (5-7). Although FS is most commonly encountered in the infant stage, some cases during the COVID-19 pandemic were diagnosed at an atypical age (8). Since some standardized information did not fully apply in the course of this infectious disease, protective measures have been taken, such as the obligation to wear surgical masks in closed areas, encouraging society to be more careful about hand hygiene, and activating remote working and online education options to reduce crowded environments as much as possible. These measures have decreased the incidence of COVID-19 and other infectious diseases (9).

Currently, information regarding FS in children with COVID-19 is limited, and studies addressing the actual prevalence, frequency, and characteristics of COVID-19-induced FS are scarce. Therefore, significant information gaps exist in this context. The primary aim of our study was to determine the influence of the COVID-19 pandemic on the prevalence of viral agents that contribute to the etiology of FSs. Our secondary objectives included examining the extent to which specific viral agents can be identified in children experiencing FS and delineating the clinical characteristics associated with particular pathogens.

MATERIALS AND METHODS

Study Group

The current multicenter study was conducted at the Pediatric Emergency Departments (EDs) of Marmara University and Medeniyet University, both of which are distinguished by their large tertiary care hospitals in Istanbul, Turkiye. These institutions recorded approximately 120,000 pediatric ED admissions annually. The study included patients with FS who underwent viral testing for respiratory or gastrointestinal infections between March 2018 and March 2022. Patients were grouped into those admitted before and during the pandemic according to the date of 11.03.2020 when the COVID-19 pandemic was declared in Turkiye.

We followed the definition of FS provided by the International League Against Epilepsy and the American Academy of Pediatrics (3, 4). In certain circumstances, FS may occur when body temperature starts to increase, but fever is not detected (10, 11). Therefore, during the admission of patients presenting with seizures, if their body temperature measurements are below 38℃, but they exhibit a fever pattern consistent with the FS definition during pediatric ED follow-ups, they are included in the FS category. Patients diagnosed with FS

(ICD-10 codes R56, R56.0, and R56.8) were reviewed. Eligible records from children aged 6–60 months who presented with FSs and underwent investigations for viral etiology were included. Demographic features, signs and symptoms, vital parameters, nasopharyngeal swab antigen / polymerase chain reaction (PCR) tests, and SARS-CoV-2 PCR results, detailed medical history, presence of FS or epilepsy in the family, fecal rotavirus and adenovirus antigen tests, length of stay (LOS) in the pediatric ED and pediatric ward, and emergency discharge status (discharge, ward admission, pediatric intensive care unit admission or exitus) were recorded for each patient. Patients with progressive chronic neurometabolic diseases or acute metabolic disorders and those aged <6 months or >60 months were excluded. Patients were divided into two groups as 6-24 months (group 1) and 25-60 months (group 2). We investigated whether there was a difference between these groups in terms of SARS-CoV-2 positivity in patients presenting with FS during the pandemic.

Viral Testing

The etiological agents were detected in the central laboratories of the hospitals using routine diagnostic protocols. This study was approved by the Marmara University, Clinical Research Ethics Committee, on July 22, 2022, with number 09.2022.949. In this study, 18 respiratory viruses (SARS-CoV-2, enterovirus, human paraechovirus, rhinovirus, bocavirus, adenovirus, human coronavirus [HKU1, NL63, 229E, OC43], human metapneumovirus, Influenza virus A and B, parainfluenza virus 1-2-3-4, respiratory syncytial virus [RSV]) and 2 gastrointestinal viruses (rotavirus, adenovirus) were studied. For the detection of respiratory viruses, CiTest® (Combo Rapid Test), Bio-Speedy® (Bioexen), TUSEB DiaKIT® SARS-COV-2, Coronex® (DS Bio and Nano Technology), and Microcult® (Tıpkimsan), rotavirus and adenovirus combo rapid test cassette (CiTest Diagnostics Inc.) kits for rotavirus and adenovirus antigens in stool were used. There were no restrictions in the continuity of viral testing for SARS-CoV-2 as well as other agents in our centers during the pandemic period.

Statistical Analyses

Statistical analyses were conducted using Jamovi (version 2.3.21.0). Categorical data are presented as numbers and percentages. To evaluate the impact of SARS-CoV-2 on patient distribution, patient data obtained before and during the pandemic periods were analyzed within their respective time frames, and percentages of patients were proportioned according to the number of patients in their period. Means and standard deviations were used for continuous data, whereas abnormally distributed data were depicted as medians (interquartile range [IQR] 25-75%). Nonparametric categorical data were compared using the chi-square test or Fisher's exact test, as required. Intergroup comparisons of non-normally distributed parameters were performed using the Mann–Whitney-U (MWU) test. A $p<0.05$ was considered significant.

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RESULTS

The records of 1683 patients who presented to our pediatric ED with FS were examined. Viral testing was performed in 114 of the patients. The remaining 1,569 patients did not undergo any virologic study. Table 1 presents the demographic and clinical traits of 114 patients. 66 (57.9%) patients were observed before the pandemic and 48 patients (42.1%) were observed during the pandemic. During the pandemic, 30 (62.5%) of the study participants were admitted before the emergence of the SARS-CoV-2 omicron variant. No statistically significant difference was observed in terms of age in the patient groups admitted to the pediatric EDs with FS before and during the pandemic (p=0.55, MWU test). In addition to the median age in Table 1, SARS-CoV-2-positive patients had a median age of 26 months (IQR: 15.5-28.5). No noteworthy difference was observed in the distribution of SARS-CoV-2 PCR positivity across age groups among patients monitored for FS (p=0.225). Before the pandemic, the median body temperature of patients was 37.8°C (IQR: 36.8-38.2°C), whereas during the pandemic, it was 38°C (IQR: 37.0-38.5°C). There were no significant differences in body temperature between the two periods (p=0.329).

Before the pandemic period, 42 patients (63.6%) presented to the ED with their first FS. During the pandemic, 39 patients (81.3%) presented with their first FS. The proportion of patients with first FS during the pandemic was significantly higher than that before the pandemic (p=0.041). Additionally, there was a marked increase in the prevalence of FSs with a familial history among patients before the pandemic (p=0.009). The present study investigated additional symptoms reported by patients upon admission to the ED. Notably, cough was the predominant symptom (n=43, 37.7%), followed closely by a runny/stuffy nose (n=41, 36%). Upon further analysis, we observed a shift in symptom prevalence during the pandemic:

Table 1. Demographic and clinical characteristics of the study population

	Total number of participants n (%)	Before the pandemic n (%)	During the pandemic n (%)	p value
Gender (girls/boys)	41/73 (36/64)	22/44 (33/66)	19/29 (39.5/48)	0.492
Median age, year (IQR)	19 (14–26)	18 (14–26)	21 (14.8–26.3)	0.55
FS type				0.362
Simple	72 (63.7)	44 (66.7)	28 (58.3)	
Complex	42 (36.8)	22 (33.3)	20 (41.7)	
FS, first time	81 (71.1)	42 (63.6)	39 (81.3)	0.041
Family history of FS	42 (36.8)	31 (47)	11 (22.9)	0.009
Family history of epilepsy	12 (10.5)	8 (12.1)	4 (8.3)	0.759
Chronic disease	4 (3.5)	2 (3)	2 (4.2)	1
Neurologic disease	2 (50)	1 (50)	1 (50)	
Cardiac disease	1 (25)	1 (50)		
Gastroenterologic disease	1 (25)		1 (50)	
Additional symptoms				
Cough	43 (37.7)	21 (31.8)	22 (45.8)	0.127
Sneezing	18 (15.8)	9 (13.6)	9 (18.8)	0.460
Runny/stuffy nose	41 (36)	22 (33.3)	19 (39.6)	0.492
Diarrhea	23 (20.5)	17 (25.8)	6 (13)	0.101
Vomiting	12 (10.5)	6 (9.1)	6 (12.5)	0.558
Rash	3 (2.7)	2 (3.1)	1 (2.1)	1
Fever etiology				
Acute upper/lower airway infections	79 (69.3)	46 (69.7)	35 (72.9)	0.695
Acute gastroenteritis	28 (24.6)	16 (24.2)	12 (25)	
Other	7 (6.3)	4 (6.1)	1 (2.1)	

IQR: Interquartile range

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while a runny/stuffy nose was the most common additional symptom before the pandemic (n=22, 33.3%), cough took precedence during the pandemic (n=22, 45.8%). However, no statistically significant difference was observed when comparing additional symptoms between different time periods.

Of the 68 tests to determine viral etiology before the pandemic, 44 (64.7%) were positive. During the pandemic, 31 (64.5%) of 48 tests were positive (Figure 1). There was no significant difference in the overall positivity rates between the two periods (p=0.817). Both respiratory tract viruses that could be tested in the laboratory and viral antigen (rotavirus and adenovirus) positivity in stool samples from patients with diarrhea were included in this group. Due to acute gastroenteritis, stool samples of 24 (36.3%) patients before the pandemic and 18 (37.5%) patients during the pandemic were

studied in the laboratory. The positivity rates of the stool test were 7/24 (29.1%) and 5/18 (%27.7), respectively. Research on viral respiratory tract infections was conducted for all samples, except those associated with fecal samples. SARS-CoV-2 PCR was performed on 28 (58.3%) patients admitted during the pandemic, and 10 (35.7%) of them were positive. During the pandemic, 22 (34.4%) of the tests other than SARS-CoV-2 PCR were positive. When comparing the positivity rates between the pre-pandemic and during-pandemic periods, the observed difference approached statistical significance (p=0.059).

The distribution of viruses detected in patients is shown in Figure 2. The influenza virus was the most frequently isolated virus in pre-pandemic tests (n=28, 24.6%). Of the 28 influenza-positive cases, 20 were Influenza A (71.4%), and 8 were Influenza B (28.6%). The most frequently isolated pre-pandemic viruses were enterovirus/rhinovirus (n=5) and rotavirus (n=4), followed by influenza. During the pandemic, Influenza and SARS-CoV-2 viruses were detected almost equally (n=12, 10.5% [Influenza A n=10, 83.3% and Influenza B n=2, 16.6%] and n=11, 9.6%, respectively). There were no statistically significant differences between the distribution of influenza subgroups before and during the pandemic (p=0.693). Rotavirus (n=4) was detected during the pandemic after influenza and SARS-CoV-2.

The median LOS in the ED was 7 h (IQR: 6–8) before and 6 h (IQR: 6–8) during the pandemic. There was no statistical difference between before and during the pandemic in terms of LOS in the ED (p=0.467). Before the pandemic, 17 (25.8%) patients required admission to a pediatric ward, whereas during the pandemic, 21 (41.8%) patients required admission from the ED to a pediatric ward. Accordingly, the hospitalization rate of children included in the study was significantly higher during the pandemic (p=0.044). When the LOS in pediatric EDs was compared, it was 6 h (IQR: 6) in SARS-CoV-2-positive patients and 7 h (IQR: 6–8) in other viral infections that could be detected. Patients with a viral infection other than SARS-CoV-2 positivity had a significantly higher ED LOS (p=0.03). None of
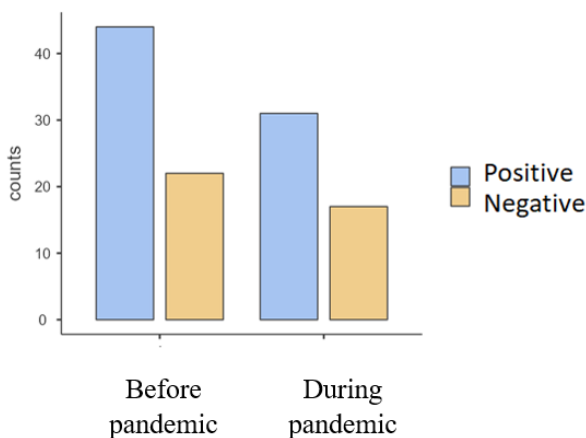

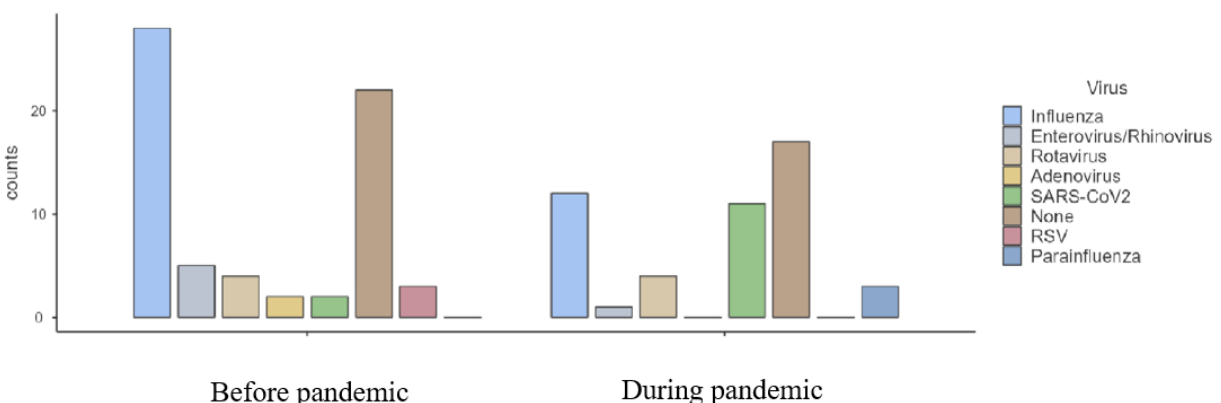**Figure 1.** Viral test positivity rates before and during the pandemic.

Figure 2. Distribution of viruses detected in patients with febrile convulsions before and during the pandemic (Note: SARS-CoV-2, detected before the pandemic, represents the old type of coronavirus.)

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the patients followed up during the study were hospitalized in the intensive care unit, and exitus was not observed.

DISCUSSION

When the demographic data of our study were analyzed, we observed that the median ages of patients with FS were similar before and during the pandemic. Similarly, the mean age of patients admitted with FS during the COVID-19 pandemic was close to the average age before the pandemic (12). However, some studies have shown that FS is also encountered in patients aged >60 months, defined as late-onset FS, especially in the SARS-CoV-2 omicron variant period (13). In our study, we did not encounter any patients with late-onset FS. Certain seizures classified as FS might not actually be FSs because the infection might have migrated to the central nervous system. This could explain how these seizures vary from typical FSs. Further research is needed to determine whether epileptic seizures caused by SARS-CoV-2 infection are truly FS or whether the central nervous system is involved.

In our investigation, in line with the study by Park et al. which explored the impact of the COVID-19 pandemic on respiratory viruses, the frequencies of individuals presenting with first-time FS during the pandemic exhibited a marked increase (14). The higher incidence of first-time FS during the pandemic may be due to strict isolation measures during the pandemic, which resulted in fewer human contacts and reduced the transmission of many infectious agents. Thus, SARS-CoV-2 may have been detected at a relatively higher rate among patients experiencing their first FS episode admitted to pediatric EDs with fever.

It has been reported that FS was more common during the SARS-CoV-2 omicron variant period (11, 15, 16). When we examined the FS admissions in our centers during the pandemic, we determined that there was an intensity of admissions in the time interval before the omicron variant period. For instance, a study by Han et al. in Korea found that 64 out of 33,457 patients diagnosed with COVID-19 had FS, all occurring during the omicron period (17). The discrepancy between our study and other studies during the admission period may be due to the prolonged home isolation practice in our country. Additionally, the extended closure of schools and preschools that provide care for children has contributed to a reduction in viral transmission.

It has been observed that most patients presenting to the pediatric ED with FS have simple FS. In our study, although the rate of patients admitted to the ED with complex FS during the pandemic was higher than that before the pandemic, this difference was not significant. In 2016, a prospective EFES study conducted in Turkiye indicated that a higher percentage of complex FSs were linked to the coronaviruses OC43 and 229 (18). This was also supported by the findings of a study conducted in China, in which complex FS affected 33% of patients, a larger percentage than previously documented. This could be connected to COVID-19's particular neurologic

effects. The fundamental process by which COVID-19 induces seizures may be associated with inflammation and direct viral damage to nerve cells. COVID-19 has a clinical course involving many systems. Being neurotoxic and neuroinvasive, it increases angiotensin-converting enzyme 2 (ACE2) and neuronal infection in cerebral vascular endothelial cells. Therefore, it initiates an inflammation cascade. Cytokines such as Interleukin (IL)-1β, IL-6, tumor necrosis factor-α, and IL-17 also play a role in inflammation. Children are more prone to FSs because of the hyperinflammatory response caused by the activation of glial cells by these cytokines, which raises nervous system excitability (19, 20).

When the signs and symptoms of the patients enrolled in the study were examined, the most frequent respiratory symptoms, such as cough, runny nose, and stuffy nose, occurred regardless of the time of admission. Most patients continued their follow-up and treatment with a diagnosis of upper or lower respiratory tract infection. Diagnosing patients with fever and FS in the pediatric ED is challenging. In a Korean study by Kim et al., 54.3% of patients reported no symptoms associated with fever. Therefore, to the extent necessary, it is important for patients to be monitored and treated by conducting viral screening according to their symptoms and findings to identify the infection that triggered FS (13).

Viral infections and FS are strongly related (21). A study conducted in Iran by Khiabani et al. revealed that approximately 3% of patients who presented with FS tested positive for SARS-CoV-2 (22). In contrast to this study, we found that during the pandemic, children with FS who were followed up in our pediatric ED had a high SARS-CoV-2 PCR positivity rate in appropriate cases. This high rate can be explained by prioritizing laboratory tests for other possible factors as a result of detailed anamnesis and physical examination before taking a test directly for COVID-19 in patients presenting with FS despite the pandemic period and applying the SARS-CoV-2 PCR test after ruling out other diagnoses for etiology.

Infectious gastroenteritis and influenza virus infections are two separate risk factors for FS in Japan (23, 24). Similar to this study, adenovirus was the most commonly found virus in the EFES study, followed by influenza virus (47.2%) (including influenza A and B, which were identified at 24.3% and 22.9%, respectively), and human RSV (16%) (18). Our study shows that in addition to these data, SARS-CoV-2 should be recognized as a leading infectious agent causing FS.

When the LOS in the pediatric ED was compared before and during the pandemic and according to the type of viral infection, it was found that patients who were SARS-CoV-2-positive and presented to the pediatric ED with FS had a shorter LOS. This may be because COVID-19 infections in children tend to cause milder clinical symptoms compared to adults (25). However, if the admission periods of the cases were considered rather than the viruses detected, the rate of hospitalization of patients in pediatric wards during the pandemic was significantly higher.

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This situation can be explained by the fact that, as a result of the measures taken during the pandemic period, there were more vacant beds in the wards of the hospitals as a result of the decrease in intra-community contact; thus, the number of infectious diseases and admission rates to EDs decreased. We can conclude that if there were more beds in the pediatric wards, the LOS in the EDs decreased, and more patients were transferred to the wards.

The current study has several limitations. Due to the retrospective nature of our study, patients lacking an ICD code corresponding to their diagnosis were excluded, potentially introducing selection bias. We did not have the results of the subgroup analysis in patients who were admitted with FS and were SARS-CoV-2-positive, so it was not possible to identify which variant of the virus was more likely to cause FS. Although publications in the literature support that the omicron variant is more associated with FS, we found that the patients in our study during the pandemic period were mostly referred to the pre-omicron.

CONCLUSION

In conclusion, most FS episodes are self-limiting and do not cause any problems. However, families may find them extremely upsetting. Parents tend to ask their children's physicians about the cause of FS, which is also a stressful event for them. When we encounter such a situation in pediatric ED, it is important that we perform etiological tests so that we can both know the disease course and provide the necessary detailed explanation to the family. During the pre-pandemic period, influenza virus was the most commonly detected pathogen in viral tests conducted on patients followed-up in pediatric EDs with a diagnosis of FS. However, during the pandemic, both influenza virus and SARS-CoV-2 played comparable roles in the etiology of FS. Given the urgency of diagnosing febrile illnesses in children, we propose developing rapid diagnostic tests that can simultaneously screen for both SARS-CoV-2 and influenza. Such tests could be valuable for efficient patient follow-up and treatment.

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