ORIGINAL ARTICLE

Distinguishing features of COVID-19 and non-COVID-19 febrile seizures in hospitalised children

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ABSTRACT

Introduction: Febrile seizures in children can be associated with various underlying conditions, including COVID-19. Differentiating COVID-19 and non-COVID-19 related febrile seizures is crucial for tailored patient management and for implementing appropriate infection control measures to prevent nosocomial transmission. This study aimed to describe the clinical features of children hospitalised for COVID-19 and non-COVID-19 febrile seizures and to identify factors that differentiate between the two groups.

Materials and Methods: This retrospective cross-sectional study involved children aged 6 months to 6 years who were hospitalised for febrile seizures in Hospital Tuanku Ja'afar Seremban (HTJS) from January 2021 to June 2022. Descriptive statistics were used to summarise the differences in demographics and clinical presentations. Logistic regression analyses were performed to identify factors associated with COVID-19 and non-COVID-19 febrile seizures.

Results: Of the 345 patients (median age 22 months, IQR 15-32; 59.7% were males) included in the study, 130 (37.7%) tested positive for COVID-19, while 215 (62.3%) tested negative. There were no significant differences between both groups based on age, comorbidities, history of febrile seizures, seizure types, temperature on arrival, cough and rhinorrhoea. Multivariate analysis revealed that a family history of febrile seizures and leucocytosis were associated with increased odds of non-COVID-19 febrile seizures. In contrast, lymphopenia was associated with decreased odds.

Conclusion: The clinical presentation of COVID-19 and non-COVID-19 febrile seizures are remarkably similar, highlighting the importance of including COVID-19 screening in febrile seizures workup. Full blood count readings may be potentially useful for differentiating between these conditions.

KEYWORDS:
Febrile fit, febrile convulsions, SARS-CoV-2, paediatric

INTRODUCTION

Febrile seizures are the commonest cause of childhood seizures, affecting approximately 2-5% of children.[1] These seizures are typically brief, triggered by a febrile episode in children aged 6 months to 6 years in the absence of signs of central nervous system (CNS) infection. The aetiology of febrile seizures is multifactorial, including a combination of genetic and environmental factors.[2,3] The vulnerability of the developing CNS to fever, combined with a genetic predisposition and exposure to a diverse range of pathogens as children start interacting more with the outside world, contribute to the high incidence of febrile seizures within this age group.

During the global health crisis caused by coronavirus disease 2019 (COVID-19), severe acute respiratory coronavirus-2 (SARS-CoV-2) emerged as a novel etiological agent for febrile seizures in children.[4,5] The differentiation between COVID-19 and non-COVID-19 febrile seizures is vital not only for individual patient management, but also for effective infection control purposes. Furthermore, as SARS-CoV-2 is a novel virus, the outcomes for febrile seizures associated with it may differ from those associated with other aetiologies.

There is a paucity of studies that demonstrate the differences in clinical manifestations between these two conditions. To address this knowledge gap, our study aims to compare the clinical characteristics and outcomes between COVID-19 associated febrile seizures and non-COVID-19 associated febrile seizures.

MATERIALS AND METHODS

Design and Setting

This retrospective, cross-sectional study was conducted at Hospital Tuanku Ja'afar Seremban, Negeri Sembilan from January 2021 to June 2022. The hospital serves as the sole tertiary referral centre for the state of Negeri Sembilan, serving approximately 1,100,000 people including 215,000 children below 12 years. During the study period, the rollout of COVID-19 vaccinations for children over 5 years old in the country began in early February 2022.[6]

This article was accepted: 20 May 2024
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Data Collection and Study Definitions

The study included all children aged between 6 months to 6 years who were hospitalised with a diagnosis of febrile seizures (R56.00, R56.01), as classified by the International Classification of Diseases, 10th edition (ICD-10) codes. The exclusion criteria included patients with febrile seizures who were not within the age group of 6 months to 6 years old and those who were COVID-19 negative but had recent sick contact/epidemiological link with a confirmed COVID-19 case. This study focused solely on patients with an ICD-10 diagnosis of febrile seizures. Therefore, patients with afebrile seizures, breakthrough seizures with underlying epilepsy or central nervous system infection such as meningitis, encephalitis, and meningoencephalitis were also excluded as they do not meet the inclusion criteria for febrile seizures.

The medical record of patients fulfilling the study inclusion criteria were reviewed. Information collected and analysed included sociodemographic characteristics, comorbidities, presenting symptoms (fever, nature of the seizures, accompanying symptoms such as cough, rhinorrhoea, diarrhoea, rashes) and their duration. Additional data included admission temperature, COVID-19 vaccination status and results, full blood count results, treatment received (intravenous fluids, oxygen, antibiotics, need for phenytoin loading), paediatric intensive care unit (PICU) admission, total length of stay and outcomes.

During the study period, all patients hospitalised for febrile seizures underwent routine COVID-19 testing as part of the hospital's admission protocol for infection control purposes. COVID-19 positive patients were isolated either in a dedicated COVID-19 ward or in a negative pressure isolation room within the general paediatric ward to prevent nosocomial transmission of SARS-CoV-2. Testing for COVID-19 was initially carried out by a nasopharyngeal swab for SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) until 20 May 2021. As COVID-19 prevalence increased in the community during the delta and omicron wave, SARS-CoV-2 rapid antigen detection testing was subsequently employed.

A patient was categorised as COVID-19 positive if the nasopharyngeal swab for SARS-CoV-2 RT-PCR or antigen detection test was positive. Conversely, a negative swab result indicated COVID-19 negative status. We defined those having a sick contact/epidemiological link with a COVID-19 positive case as symptomatic household or social contact (spending face-to-face contact within 1 meter for ≥15 minutes) in the preceding two weeks prior to the patient's symptom onset, as described previously.[7,8] Fever was defined as a body temperature of ≥37.5°C, consistent with our previous studies.[9,10] Simple febrile seizures were defined as primary generalised seizures lasting for < 15 minutes without recurrence within 24 hours. Complex febrile seizures were defined as focal, prolonged (≥ 15 minutes), and/or recurring within 24 hours, and/or accompanied by residual neurological deficit postictally, such as Todd's paralysis.[1] Full blood count abnormalities were defined as follows:[11,12] Leucocytosis referred to an elevated white blood cell count >14 × 10^9/L in children under 2 years, and >12 × 10^9/L in children aged 2 years and above. Lymphopenia was defined as an absolute lymphocyte count <4.5 × 10^9/L in infants < 8 months, and <1.5 × 10^9/L in children aged 8 months and above. Thrombocytopaenia was defined as a platelet count of <150 × 10^9/L, whereas thrombocytosis was defined as a platelet count of >150 × 10^9/L.

Statistical Analysis

Categorical variables were presented as frequency (number) and percentages (%), and continuous data using median and interquartile range (IQR). Data were assessed for conformance to the normal distribution using the Shapiro-Wilk test. Given that all our continuous variables were not normally distributed, we used the Mann–Whitney U test for comparisons. For categorical variables, we used the Chi-squared test or Fisher's exact test as appropriate.

We performed univariate and multivariate logistic regression analyses to identify distinguishing factors between COVID-19 and non-COVID-19 febrile seizures. Statistical filter methods (Chi-squared test, Mann-Whitney U test) were used to select significant variables for the logistic regression model. Variables that were statistically significant ($p<0.05$) in the univariate logistic regression were included in the multivariate analysis. Full blood count results were not available for all the patients in the study; no attempt was made to impute these missing data. As such, our multivariate analysis was based on the patients who had complete data. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Any results with a two-sided p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

Ethical Considerations

The Medical Research and Ethics Committee, Ministry of Health Malaysia approved this study (NMRR-22-02432-REO [2]) and waived the requirement for informed consent. All patient data were de-identified prior to analyses.

RESULTS

Baseline Characteristics of Study Population

We identified 345 patients hospitalised for febrile seizures during the 18-month study period. The median age of the patients was 22 months (IQR 15-32), with 56.3% of patients aged below 24 months. Males constituted 59.7% of the study population, corresponding to a male to female ratio of approximately 1.5:1. At least one comorbidity was reported in 39 patients (11.3%), with developmental disorders being the most common (Table I). Of the 345 patients, 130 (37.7%) tested positive for COVID-19, and the remaining 215 (62.3%) were COVID-19 negative. Most of the seizures were categorised as simple febrile seizures (n=257, 74.5%), with generalised tonic clonic seizures being the most frequently observed semiology (n=238, 69.0%). The majority of patients (n=295, 85.5%) presented with their first-ever seizure. A family history of febrile seizures was present in 70 (20.3%) patients. None of the 360 patients had received COVID-19 vaccinations.

Table I: Baseline characteristics of the study population.

Baseline Characteristics of patients	Total (n=345)
Age in months, median (IQR)	22 (15-32)
6-12 months old	53 (15.4%)
12.1-24 months old	141 (40.9%)
24.1-72 months old	151 (43.8%)
Male sex	206 (59.7%)
Comorbidities[a]	
None	306 (88.7%)
Developmental	10 (2.9%)
Prematurity (if age <2 years old)[b]	9 (2.6%)
Neuromuscular	8 (2.3%)
Cardiovascular	7 (2.0%)
Genetic	5 (1.4%)
Respiratory	3 (0.9%)
Others	3 (0.9%)
COVID-19 status	
COVID-19 positive	130 (37.7%)
COVID-19 negative	215 (62.3%)
Type of febrile seizure	
Simple febrile seizures	257 (74.5%)
Complex febrile seizures	88 (25.5%)
Episode of febrile seizures	
First episode	295 (85.5%)
Recurrent episode	50 (14.5%)
Semiology of febrile seizure	
Generalized tonic clonic	238 (69.0%)
Generalised tonic	78 (22.6%)
Atonic	22 (6.4%)
Focal	7 (2.0%)
Received COVID-19 vaccination	0 (0%)

IQR Interquartile range
[a]A patient may have more than one comorbidity
[b]Gestational age <37 weeks at birth among children aged <2 years

Comparison of Demographic, Clinical Characteristics and Outcomes of Febrile Seizures Between the COVID-19 Positive and COVID-19 Negative Group

The demographic characteristics, such as the median age, proportion of males and prevalence of comorbidities were comparable between the COVID-19 positive and negative groups (Table II). However, a higher proportion of patients in the COVID-19 negative group had a history of past COVID-19 infection (8.8% vs. 2.3%, p=0.016). Likewise, a higher proportion of patients in the COVID-19 negative group had a family history of febrile seizures (26.0% vs. 10.8%, p=0.001).

There were no significant differences between the COVID-19 and non-COVID-19 groups regarding the proportion of patients presenting with their first febrile seizure, the day of fever which the seizure occurred, the type of febrile seizures and the semiology of seizures. Similarly, the frequency of accompanying symptoms such as cough, rhinorrhoea, and rashes did not differ significantly between both groups. However, gastrointestinal symptoms such as vomiting and diarrhoea occurred more frequently in the COVID-19 negative group (21.9% vs. 13.1%, p=0.042; 15.8% vs. 5.4%, p=0.004 respectively). Physical examination findings, including temperature on arrival, signs of respiratory distress and signs of shock were similar between both groups.

Full blood count findings revealed distinct patterns. Leucocytosis was significantly more common among the COVID-19 negative group (34.9% vs. 13.6%, p=0.002), whereas a greater proportion of the COVID-19 positive group demonstrated lymphopenia (23.7% vs. 9.7%, p=0.006). The proportion of patients with thrombocytopaenia was comparable between both groups.

In terms of treatment received, antibiotics were used more often in the COVID-19 negative group (11.2% vs 3.8%, p = 0.018). However, the need for oxygen therapy, intravenous fluid therapy and intravenous phenytoin as a loading dose were similar for both groups. The need for admission to the PICU and the median length of hospital stay were comparable between the groups. No mortalities were recorded throughout the study period.

Multivariate Analysis of Factors Differentiating non-COVID-19 from COVID-19 Febrile Seizures

Table III display the results from univariate and multivariate logistic regression analyses that aimed to identify factors differentiating non-COVID-19 from COVID-19 positive febrile seizures. All variables showed a significant association from the univariate analysis. However, following adjustment in the multivariate analysis, only three variables remained statistically significant. Specifically, a family history of febrile seizures (adjusted odds ratio, aOR: 2.77; 95% Confidence Intervals, 95%CI: 1.08, 7.07) and leucocytosis (aOR: 2.85; 95%CI: 1.24, 6.57) were significantly associated with non-COVID-19 febrile seizures. Conversely, lymphopenia (aOR: 0.40; 95%CI: 0.18, 0.93) was less likely to be present in non-COVID-19 associated febrile seizures.

Table II: Comparison of demographic, clinical characteristics and outcomes of febrile seizures between the COVID-19 positive and COVID-19 negative group.

	COVID-19 positive n=130 (%)	COVID-19 negative n=215 (%)	p-value
Demography			
Age in months, median (IQR)	24 (15-35)	21 (14-30)	0.137***
Male sex	76 (58.5%)	130 (60.5%)	0.713*
Any comorbidities	10 (7.7%)	29 (13.5%)	0.099*
Type of comorbidities			
Developmental	1 (0.8%)	9 (4.2%)	0·189*
Prematurity (if age <2 years)	1 (0.8%)	8 (3.7%)	0·400**
Neuromuscular	4 (3.0%)	4 (1.9%)	0.167**
Cardiovascular	2 (1.5%)	5 (2.3%)	1.000**
Genetic	2 (1.5%)	3 (1.4%)	0.587**
Past COVID-19 infection[a]	3 (2.3%)	19 (8.8%)	0.016*
Family history of febrile seizures	14 (10.8%)	56 (26.0%)	0.001*
First episode of febrile seizures	110 (84.6%)	185 (86.0%)	0.714*
Day of fever which seizure occurred	1 (1-2)	1 (1-2)	0.529***
Type of febrile seizures			
Simple febrile seizures	96 (73.8%)	161 (74.9%)	0.830*
Complex febrile seizures	34 (26.2%)	54 (25.1%)	
Semiology of seizures			
Generalized tonic-clonic seizures	93 (71.5%)	145 (67.4%)	0.425*
Non-generalised tonic-clonic seizures	37 (28.5%)	70 (32.6%)	
Accompanying symptoms			
Cough	25 (19.2%)	33 (15.3%)	0·350*
Rhinorrhoea	23 (17.7%)	40 (18.6%)	0·832*
Vomiting	17 (13.1%)	47 (21.9%)	0·042*
Diarrhoea	7 (5.4%)	34 (15.8%)	0·004*
Rashes	3 (2.3%)	6 (2.8%)	1.000**
Physical findings			
Temperature on arrival, °C	38.5 (37.9-39.0)	38.5 (38.0-39.1)	0.316***
Signs of respiratory distress	0 (0.0%)	4 (1.9%)	0.301**
Shock	0 (0.0%)	2 (0.9%)	0.529**
Abnormal neurological examination	0 (0.0%)	0 (0.0%)	-
Laboratory investigations[b]			
Leukocytosis	8 (13.6%)	61 (34.9%)	0.002*
Lymphopaenia	14 (23.7%)	17 (9.7%)	0.006*
Thrombocytopaenia	1 (1.7%)	2 (1.1%)	1.000**
Thrombocytosis	3 (5.1%)	12 (6.9%)	0.449
Treatment			
Oxygen therapy	3 (2.3%)	6 (2.8%)	1.0000**
Intravenous fluid therapy	28 (21.5%)	55 (25.6%)	0.395*
Antibiotics	5 (3.8%)	24 (11.2%)	0.018*
Phenytoin loading	3 (2.3%)	3 (1.4%)	0.676**
Outcomes			
Paediatric ICU admission	1 (0.8%)	2 (0.9%)	1.000**
Length of stay, days	2 (1 – 2)	1 (1 – 2)	0.193***
Mortality	0 (0.0%)	0 (0.0%)	-

IQR Interquartile range
[a]defined as a documented past history of COVID-19 more than a month prior to the current hospitalization
[b]Laboratory results were available for 59 COVID-19 positive patients and 175 COVID-19 negative patients.
*Chi square test **Fisher exact test ***Mann Whitney test

DISCUSSION

In this study of hospitalised children with febrile seizures, we analysed a cohort of 345 patients over an 18-month period. To the best of our knowledge, this is the largest study of febrile seizures in children in Malaysia to date. The demographic profile of our patients, such as the median age and sex distribution, were comparable with the patterns observed in both local and international studies.[13-15] Most febrile seizures in our study were categorised as simple febrile seizures (74.5%), with generalised tonic-clonic seizures being the most common semiology (69.0%). These observations are consistent with the usual presentation of paediatric febrile seizures reported in literature.[16,17]

Viral upper respiratory tract infections are a common trigger for febrile seizures.[16-18] In our study, we added to this knowledge by demonstrating a substantial proportion of febrile seizures were associated with SARS-CoV-2 infection, thereby highlighting the neurological implications of this novel virus. Febrile seizures are one of the well-recognized neurological manifestations of COVID-19.[4,5] Previous research has shown that SARS-CoV-2 tends to be more neuropathogenic in children compared to viruses like influenza and parainfluenza.[19] The ability to distinguish between febrile seizures related to SARS-CoV-2 and those not related to the virus is crucial for both effective patient management and the implementation of appropriate infection control measures.

Table III: Multivariate analysis of factors differentiating non-COVID-19 from COVID-19 positive febrile seizures.

Variable	Univariate logistic regression			Multivariate logistic regression		
	OR*	95% CI	p-value	aOR**	95% CI	p-value
Past COVID-19 infection	4.10	1.19 – 14.15	0.025	2.31	0.48 – 11.26	0.30
Family history of febrile seizures	2.92	1.55 – 5.49	0.001	2.77	1.08 – 7.07	0.03
Vomiting	1.86	1.02 – 3.40	0.044	2.03	0.89 – 4.64	0.09
Diarrhoea	3.30	1.42 – 7.69	0.006	2.30	0.75 – 7.13	0.15
Leukocytosis	3.41	1.52 – 7.65	0.003	2.85	1.24 – 6.57	0.01
Lymphopenia	0.35	0.16 – 0.75	0.008	0.40	0.18 – 0.93	0.03

* Odds ratio calculated using COVID-19 positive group as the reference
**The multivariate analysis was based on the 234 patients with complete FBC data (59 COVID-19 positive, 175 COVID-19 negative)
OR = odds ratio, aOR = adjusted odds ratio

Our study shares certain similarities to a study done in Korea by Seo et al,[20] but there are notable differences in patient selection criteria and diagnostic workup protocols. The Korean study included a wider age range and identified a substantial portion, 21% (39 out of 186 patients) who fell into an atypical age group of under six months or over five years. However, lumbar punctures were only performed on a minority of these patients (20%, n=8/39). In contrast, we adopted stricter inclusion criteria, focusing on the typical age group for febrile seizures. We excluded patients falling outside this typical age group to avoid potential misdiagnosis of other conditions such as aseptic meningitis due to SARS-CoV-2 or other viruses, which could be mistaken for febrile seizures. This was because not all these patients underwent comprehensive diagnostic workup, including lumbar punctures. This approach ensured our patients accurately represented febrile seizures within the typical age group.

In our study, the clinical features of COVID-19 associated with febrile seizures were largely similar to those of non-COVID-19 febrile seizures. There were no significant differences across a variety of parameters such as age, gender distribution, co-morbidities, past history of seizures, seizure types, seizure semiology or onset, temperature on arrival or accompanying symptoms such as cough, rhinorrhoea and rashes. However, gastrointestinal symptoms such as vomiting and diarrhoea were more frequently observed among the COVID-19 negative group. This could be potentially due to these symptoms being an uncommon manifestation of COVID-19,[9,10,21] and may suggest the involvement of other gastrointestinal pathogens such as rotavirus, norovirus and enterovirus in triggering the seizures.[22-24] Despite the initial significance of these symptoms in our univariate analysis, it was no longer significant after adjustment for confounders through the multivariate analysis. Therefore, these symptoms may not be reliable to distinguish between COVID-19 and non-COVID-19 febrile seizures.

Our multivariate analysis revealed that a family history of febrile seizures was a significant predictor for non-COVID-19 febrile seizures. This suggests that genetic predisposition to febrile seizures play a more significant role in the non-COVID-19 group. Children with a genetic predisposition for febrile seizures could experience them in response to any febrile illness. In contrast, the neuropathogenic properties of SARS-CoV-2 might trigger febrile seizures in children,[25] irrespective of genetic predisposition. Leucocytosis also emerged as an independent predictor for non-COVID-19 febrile seizures. This could be attributed to bacterial infections such as urinary tract infections or cellulitis triggering febrile seizures in the COVID-19 negative group, which might explain the higher usage of antibiotics observed in this group. Conversely, lymphopenia was more likely to be associated with COVID-19 positive febrile seizures. The presence of lymphopenia can be one of the haematological manifestations of COVID-19, although less commonly observed in children than in adults.[26,27]

While the full blood count results could be a useful tool to distinguish between both conditions, our findings are subject to a few limitations. First, not all patients underwent blood sampling, particularly at the peak of the pandemic due to resource and manpower constraints. This may have introduced bias and potentially affect the reliability of our findings. Second, we acknowledge the possibility of false negative COVID-19 test results. The sensitivity and specificity of COVID-19 testing can vary based on the timing of testing relative to symptom onset, quality of the collected specimen, and method of testing. Nevertheless, we mitigated this potential source of error by excluding children from the COVID-19 negative group who had known epidemiological links or close contact with confirmed COVID-19 cases. A third limitation arises from the lack of routine testing for other pathogens in the COVID-19 negative group. This leaves the exact cause of their febrile seizures unidentified, potentially confounding comparisons in both groups. Lastly our study was conducted at a single centre, which may limit the generalisability of our findings to other settings or populations. Further studies should address these limitations by testing a broader range of pathogens to determine the underlying causes of febrile seizures and expanding the scope to multicentre, prospective studies to improve the understanding of COVID-19 and non-COVID 19 febrile seizures.

CONCLUSION

In conclusion, the clinical presentation of febrile seizures in both COVID-19 positive and negative patients is remarkably similar. This highlights the importance for COVID-19 testing in the diagnostic workup for febrile seizures for both individual patient management and infection control purposes. A family history of febrile seizures was more prevalent in the COVID-19 negative group, suggesting a possible genetic predisposition for febrile seizures unrelated to COVID-19 infection. We also noted haematological

differences that may be potentially useful for differentiating between these conditions. Leucocytosis was more common in COVID-19 negative group, whereas lymphopenia was more prevalent among the COVID-19 positive patients.

Despite these differences, the outcomes of both groups were similar, demonstrating the typically benign nature of febrile seizures in children. Although these findings provide insights into the differences between COVID-19 and non-COVID-19 febrile seizures, future research is needed to validate our findings, while addressing our study's limitations and incorporating the recommendations provided.

ACKNOWLEDGEMENT

We thank the Director-General of Health Malaysia for permission to publish this article.

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