Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Pediatrics

Infections Associated with Febrile Seizure in Children in a Tertiary Care Hospital

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DOI: 10.36347/sjams.2023.v11i06.019 | **Received:** 12.04.2023 | **Accepted:** 20.05.2023 | **Published:** 16.06.2023

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Abstract **Review Article**

Background: A febrile seizure is the most common seizure disorder in the pediatric age group. Various extra cranial infections are associated with febrile seizures. For proper management, the underlying infection causing febrile illness has to be sorted out. This associated illness plays an important role in the outcome. ***Objective:*** The main objective of this study was to find out infections associated with febrile seizures in children and find out the common type and site of infection were also found. ***Method and Materials:*** It was a cross-sectional study. This study was carried out in Dhaka Medical College Hospital, Dhaka for 6 months from 1st January 2018 to 30th June 2018. This study included 60 patients with febrile seizures aged 6 months to 60 months. A detailed history was taken and a thorough clinical examination was done. Appropriate investigations were done to support or exclude other diagnoses and to find out associated infections. Twenty patients were excluded as their clinical features and laboratory findings were consistent with intracranial infections or metabolic abnormality. ***Results:*** Out of 60 patients, there were 68.33% male and 31.67% female. The male-female ratio was 2.15:1. The cause of FS was evident in 88.33% of cases; mostly resulting from respiratory tract infections (61.67%). Other causes were acute gastroenteritis (11.67%) and urinary tract infection (15%). No specific cause was found in 11.67% of cases. ***Conclusion:*** Associated infection was evident in most of the cases, mostly due to respiratory tract infection, urinary tract infection, and acute gastroenteritis in chronological order. The study has drawbacks of small sample size, short study period, and small study population. Study on a large scale and longer duration is awaited to find out the infections associated with FS in our country as there may be significant variation between developed and developing countries.

Keywords: Febrile Seizure, respiratory tract infection, urinary tract infection, acute gastroenteritis, chronological order.

I. INTRODUCTION

Febrile seizures (FS) are the most common neurological disorder observed in the pediatric age group. They were recognized as distinct from other seizures in the mid-nineteenth century [1]. It has been reported that one in every 25 children in the population will experience at least once at that time, treatment was redirected to the underlying causes of fever rather than the symptom of a seizure. With the introduction of the thermometer at the end of the 1800s, fever was understood to be the primary factor producing the convulsion. Until the early 20th century, infantile convulsions were thought to be severe and often fatal [2]. In the 1970s, two population-based studies formed the foundation of the current view of febrile seizures: they are common, many recur, the developmental outcome is not altered, and few children later develop epilepsy [3, 4]. There are two published operational definitions of FS. The National Institute of Health Consensus (NIH) statement defines an FS as "an event in infancy or childhood usually occurring between three months to five years of age, associated with fever but without evidence of intracranial infection or defined cause for the seizure"[5].

The International League against Epilepsy (ILAE) defines an FS as "a seizure occurring in childhood after one month of age, associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a

previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures" [6]. Most FS occurs between 6 months and 3 years of age with the peak incidence at 18 months [7-9]. Complex FS is defined by one or more of the following features during the seizure, prolonged duration (> 10-15 minutes), and recurrent within 24 hours or within the same febrile illness [4, 6, 10].

Febrile status epilepticus is an FS lasting longer than 30 min. Some use the term simple febrile seizure plus for those with recurrent FS within 24 hours. In cohorts of children with FS, the risk that siblings will have an FS is 10-45% [11]. Many studies have also found that the risk may be increased by an underlying brain disorder. Premature birth, delayed discharge from the neonatal intensive care unit, and developmental delay are potential markers for suboptimal brain function, but there is conflicting evidence definitively linking these factors and FS [12]. Causes of fever vary and remain the "everyday illnesses of childhood" including upper respiratory tract infection or pharyngitis (38%), otitis media (23%), pneumonia (15%), gastroenteritis (7%), roseola infantum (5%), and non-infectious illness (12%) [13].

There is evidence that human herpes virus-6 is linked with exanthem subitum, a condition that is frequently complicated by febrile convulsions. More recent work suggests that acute HHV-6 infection is a frequent cause of febrile convulsions in young children that do not have the signs of exanthem subitum [14, 15]. Bacterial infections may be associated with febrile convulsions- urinary tract infections, shigella, and pneumococcal bacteremia, for instance [16]. It has been shown that there are increased risks of FSs on the day of receipt of the DPT vaccine and 8-14 days after the MMR vaccine, apparently not associated with long-term adverse consequences [17]. A family history of FS (but not epilepsy) within first-degree relatives is associated with an increased risk of recurrence [18]. The prognosis of FS is generally extremely favorable [19, 20]. FS is one of the leading causes of doctor consultation on an emergency basis and hospital admission in the pediatric age group. Infections associated with FS are important for the physician to know. It will help in management and reduce hospital stays.

Rationale of the Study

Febrile seizure is one of the leading causes of doctor's consultation on an emergency basis. Parents become greatly panicked by the expression of the disease and its progress of it. Extensive research has been done in developed countries for clinical profiles and associated illnesses in simple and complex FS. But there are mere studies in developing countries like Bangladesh. The intention of this study is to find out the infections that are commonly associated with FS in our country. Early diagnosis and prompt treatment will improve outcomes, and reduce hospital stay.

II. OBJECTIVES

a) General Objective:

To find out the infections usually associated with febrile seizure in children.

b) Specific Objective:

To find out the common bacterial infection associated with FS.

To find out the common viral infection associated with FS.

To find out which type of infection is more common in FS.

To find out the common site of infection that is involved in FS.

III. LITERATURE REVIEW

History of febrile seizure:

Febrile seizures have been discussed in the medical literature since the time of Hippocrates, but it was not until the middle of the present century that they were recognized as a separate entity distinct from epilepsy [21]. With the introduction of the thermometer at the end of the 1,800s, fever was understood to be the primary factor producing the convulsion. Until the early 20th century, infantile convulsions were thought to be severe and often fatal. Unfortunately, few effective treatments were available. Sentinel studies in the 1940s by Lennox and Livingston investigated risk factors for recurrence and later Epilepsy [22].

Epidemiology of febrile seizure:

Variation in prevalence rates to differences in case definitions, ascertainment methods, geographical variation, and cultural factors [23]. In USA, South America and Western Europe, 2% - 5% of all children experience febrile seizure before 5 years. Frequency of febrile seizure is much higher in Japan (8%) and Mariana Island (15%) [24]. The cumulative incidence of FS by age 5 years was 4.47% over all; 5.14% in male; 3.17% in females [25]. The incidence is slightly higher in boys than in girls, but they tend to occur earlier in girls. Incidence in developing countries is likely to be higher because of increased frequency and severity of recurrent infections and perinatal insults [26].

Aetiology of febrile seizure:

Three features interact to bring on a febrile seizure: immature brain, fever, and genetic predisposition. Febrile seizures rarely occur before 6 months of age or 5 years of age, so there is a clear relationship with brain maturation. The nature of this maturation process is unclear and could be related to increasing myelination, normal dying back of excessive neurons, and/or increasing synaptic complexity [27, 28].

There is an increasing body of literature regarding viral pathogens in pediatric patients, and confirmed viral infections are far more commonly associated with FS than bacterial illnesses [13]. Sometimes FS is common after vaccination. FS occurring soon after immunization with whole-cell diphtheria – pertussis – tetanus and measles vaccines should not be regarded as a direct adverse effect of the vaccine. Such seizures are thought to be triggered by fever induced by the vaccine [17].

Pathophysiology of febrile seizure:

The mechanism mediating early life epileptogenesis remains unknown but might involve enduring changes in the expression of key molecules that govern neuronal network function. Temperature influences numerous cellular processes, including the electrical activity of neurons [29]. The functions of several neuronal ion channels are dependent markedly on the temperature in the physiological and fever ranges, approximately 36- 42^0celsius [30]. And temperature also modulates the amplitude and kinetics of major ionic channels [31] This notion is supported by the fact that, in children, hyperthermia induced by hot baths or anticholinergic medications might also provoke seizures [32].

Pyrogenic cytokines such as IL-2 have been reported to be associated with the pathogenesis of FS. A common viral component that induces host cell immune response, is double-stranded RNA. Research in the first two decades has indicated that both astrocytes and microglia secrete numerous cytokines, such as IL- 1, TNF alpha, and IL- 6, and that astrocytes and microglia participate actively in inflammation and infection [33]. Serum and CSF zinc levels are decreased in children with FS and zinc deprivation may play a role in the pathogenesis of FS [34]. Iron deficiency anemia has been found to be commoner in children with FS and may play a role in the pathogenesis of FS [35].

Types of febrile seizure: A febrile seizure is classified as

1. Simple
2. Complex

Febrile seizure plus:

Simple FSs are brief (lasting < 10-15 minutes), tonic-clonic in nature, and usually occur only once within a 24-hour period. There are no focal features and no postictal effect. Complex FSs are of prolonged duration (> 10-15 minutes), and focal and convulsion occur more than once within the same febrile illness. The majority of febrile illness is simple (70-75%), rest are complex (30-35%) [4, 6, 10].

Clinical features of FS:

In typical case, it is a tonic-clonic seizure, lasting < 15 min, and occurs only once in a 24-hour period. In atypical cases, it is focal, lasting > 15 min, and recurs within 24 hour period. Feature of associated illness e.g. cough or cold, draining ear, painful micturition, abdominal pain, loose stool etc.

Differential diagnosis of febrile seizure: Meningitis, electrolyte imbalance– hyponatremia, hypernatremia, hypocalcaemia, hypoglycemia.

Investigations in Febrile Seizure: Usually no investigations are required for diagnosis of FS. But some investigations are needed to find out associated illness and to exclude differentials.

To find out associated illness: Complete blood count, C-reactive protein, X-ray chest, Blood C/S, Urine R/E and C/S, Stool R/E and C/S.

To exclude differentials: CSF study, serum electrolytes, serum calcium, and random blood sugar.

IV. MATERIALS AND METHODS

Study Design- This was a cross-sectional study.

Place of Study- Dhaka Medical College Hospital, Bangabandhu Sheikh Mujib Medical University.

Duration of Study- The study was done in six months duration 1st January 2018 to 30th June 2018, on the children of febrile seizure, according to the following inclusion and exclusion criteria.

Inclusion Criteria: Age more than 5 months and less than 5 years and fever with convulsion.

Exclusion Criteria: Previous afebrile seizure. Children with neurologic deficits with febrile seizures. Hyponatremia and hypernatremia and hypocalcaemia and Hypoglycemia.

Operational Definitions: Febrile seizure: The International League against Epilepsy (ILAE) defines an FS as “a seizure occurring in childhood after one month of age, associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures”.

Simple FS: Generalized tonic-clonic in nature, brief (lasting < 15 min), usually occurs only once in 24

Hour Period: Complex FS: Complex FS is of longer duration (lasting >15 min), focal, and occurs more than once in 24 hour period. Possible bacterial infection- Raised CRP with neutrophilic leukocytosis, growth in blood culture Possible viral infection- CBC- lymphocytosis with normal CRP, no growth in blood culture.

Sample Size: The sample size has been determined to measure a given proportion with a given degree of accuracy at a given level of statistical significance by using the following formula

$N= z^2pq/ d^2$, Where n= the sample size

Z= the standard normal deviate, usually set at 1.96 at 5% level which corresponds to 95% confidence level. The target proportion is p to have a particular characteristics and q= 1-p. Here p= 0.04, prevalence of febrile seizure is 4.0%, according to Annual Yearbook 2011- 2012 of the Department of Pediatrics, Dhaka Medical College, d is the degree of accuracy which assume is 0.05.

Putting the values in the above equation the sample size n is estimated as -

$n = (1.96^2 \times 0.04 \times 0.96) / .05^2$

$= (3.8416 \times 0.04 \times 0.96) / .0025$

$= 0.1475 / .0025$

= 59 (Targeted sample size)

The sample size is 59 but I studied with a sample size of 60.

Patient Selection: All the children with fever and convulsion were enlisted. After taking brief history, careful clinical examination and some laboratory investigations, some patients were excluded. 60 patients fulfilling the criteria were enrolled for study population.

Procedure: A descriptive, observational study was performed with a sample size of 60. After enrollment in the study, a thorough history was taken to have a clue to the diagnosis and associated illness. History of febrile seizure was taken in separate column; it includes nature, duration and number of attack. Symptoms regarding associated infections were queried also. Information about birth history, family history and developmental history were taken. Careful examination was done and investigations were advised according to clinical suspicion of the associated infection. All data was recorded in a predesigned questionnaire.

Data Collection: Data were collected including investigation results and entered in a pretested questionnaire.

Statistical Analysis: Data recorded in questionnaires were compiled in computer and analyzed by using SPSS 15.0 statistical software.

V. RESULTS

Table- I. Demographical and socioeconomic data of the study sample (n=60)

Age Distribution	No. of patients	Percentage (%)
1>	18	30
1-2	24	40
2-5	18	30
Mean ± SD	1.80 ± 1.20	
Sex Distribution		
Male	41	68.33
Female	19	3.67
Distribution of cases by their residence		
Rural	10	16.67
Urban	50	83.33
Distribution of cases by monthly income		
<5,000	20	33.3%
5-10,000	20	33.3%
10-15,000	20	33.3%
>15,000	0	0.0%

Incidence was most common in 1-2 year age group (40%), other age groups constituted an equal amount of cases (30%). Most of the cases came from urban areas (83.33%) and from different socioeconomic conditions.

Table- II: Distribution of cases according to age

	Male	Female	Both Sex
Median	2.00	1.00	1.33
Interquartile range	4.00	0.17	2.00
Mean	2.55	1.21	2.12
Standard Error of Mean	0.29	0.19	0.22
Minimum	0.50	0.50	0.50
Maximum	6.00	3.00	6.00

A total of 60 patients were included in the study. Among the patients, 68.33% were male and 31.67% were female with a median age of 1.33 years, interquartile range was 2.00, minimum age of 0.5 years, and maximum age of 6 years.

Table- III: Duration and types of seizure (n=60)

		No. of patients	Percentage of the total number of patients
Duration of seizure	<5 minutes	30	50.0%
	5-15 minutes	20	33.3%
	>15 minutes	10	16.7%
Type of seizure	GTCS	50	83.3%
	Focal	10	16.7%

Table III shows that in most of the cases (50%) duration of the seizure was limited to less than five minutes, and in most of the cases (83.3%) it was GTCS in nature.

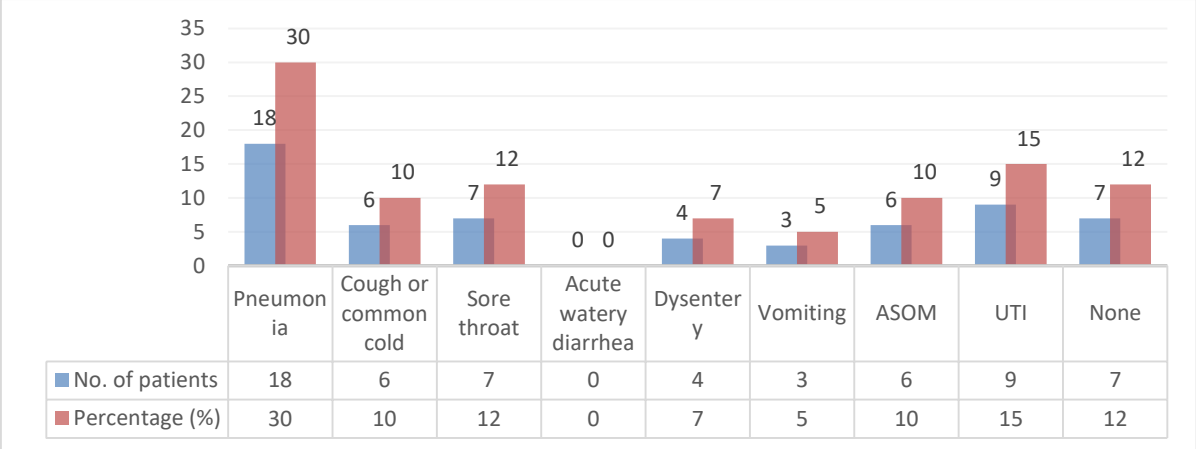

Fig.-1: Distribution of cases according to associated illness (n=60)

Table IV: Distribution of cases in relation to antenatal, peripartum, and family history (n=60)

		No. of patients	Percentage of the total number of patients
Term/Pre-term/Post-term	Term	30	50.0%
	Pre-term	30	50.0%
	Post-term	0	0.0%
Mode of delivery	NVD	40	66.7%
	LUCA	20	33.3%
	Instrumental	0	0.0%
Did the baby cry immediately cry after birth?	Yes	60	100.0%
	No	0	0.0%
History of trauma to head	Yes	0	0.0%
	No	60	100.0%
Milestones of development	Age appropriate	60	100.0%
	Not age appropriate	0	0.0%
Family history of febrile convulsion	Yes	20	33.3%
	No	40	66.7%
Family history of epilepsy	Yes	0	0.0%
	No	60	100.0%

Antenatal, peripartum, and family history are shown in Table IV. In most of the cases, the mother had regular antenatal checkups (83.3%). The mother had any instance of febrile illness with rash in the intrapartum period only in 33.3% of cases, and the mother had a history of PROM only in 16.7% of cases. There was not a single case found where the mother suffered from prolonged labor. The pregnancies were equally term or preterm, but no instance of post-term pregnancies was found. The most common mode of delivery was NVD (66.67%), and the baby cried immediately in all the cases, so, no instance of delayed crying was found. There was a past history of febrile seizure found only in 16.67% of cases, and no instance of head trauma was found. Immunization was up to date in most of the cases (83.3%) and milestones of development were age appropriate in all the cases. Family history of febrile convulsion was positive only in 33.3% of cases and consanguinity was found only in

16.67% of cases. A family history of epilepsy was absent.

Table -V: Distribution by Pattern of Investigation finding (n=60)

		No. of patients	Percentage (%)
CBC	Normal	33	55.0%
	Abnormal	27	45.0%
CRP	Negative	30	50.0%
	Positive	30	50.0%
Urine R/E	Normal	32	72.7%
	Abnormal	12	27.3%
X-ray chest P/A view	Normal	40	66.67%
	Abnormal	20	33.33%

Patterns of common investigation findings are shown in Table V. It is shown that CBC and urine R/E were normal in most of the cases, whereas CRP was normal in half of the cases. Chest x-ray was found abnormal in 20 cases (33.33%).

VI. DISCUSSION

The incidence of febrile seizure is 3-4% but varies according to geographical and ethnic distribution. In this study, FS started in the first year of life, peaked in the second year and the incidence declined with increasing age. There were 38.3% of children below 1 year, and 61.7% above 1 year of age. These findings correlate with the study conducted by Saidul Haque et al in 1981[36] where 39.5% of cases were below 1 year and 60.5% of cases were more than 1 year. In another study, 37% of children were below 16 months and 63% were above 16 months of age [37].

In this study, the first febrile seizure occurred at an average age of 15.95 months. Plochl and Laubichler et al in 1982 [29], reported the first FS at an average age of 22.20 months. Male suffered slightly more than females. The male female ratio was 2.15: 1 respectively, approximately the same result found in one study [8]. A positive family history of FS points to the importance of genetic factors and common environmental exposures. In this study, 33.33% of the children had a positive family history of FS. One previous study has shown 20% of children with positive family history [25] and another study reported positive family history in 29% of the cases [30]. A positive family history is associated with earlier age of onset.

In this study, the average age of onset was 16 months and in the case of positive family history of FS average age of onset was 13 months. These findings correlate with the results of another study, which reported an average age of onset of 18.2 months and in case of positive family history of FS 14.3 months [38]. In the present study, most of the children with a positive family history of FS had an initial simple type of FS. In a study conducted by Wallace in 1975, positive family history was also associated with decreased risk of complex FS [37].

In this study, 16.67% of children had recurrent FS during subsequent illnesses; approximately the same result shown by [9]. i.e. 20.5% in his article. Risk factors for recurrence include onset before 18 months, shorter duration of fever (<1 hour) before the seizure, and a family history of FS [13, 31]. In our study, 3.5% of children with FS had a family history of epilepsy and the finding is almost equal to another study that showed 4% [8]. The median age of onset is 16 months, and slightly less than half of children presented between 1-2 years; approximately the same observation by [25].

In the present study, complex FS occurred in 16.7% of cases, and simple FS in 83.3%.In a study by [34], 38% were of complex FS and 62% of cases were simple FS. However, another study has shown complex FS in 61.83% of cases [26]. The cause of higher incidence was as that study was done on hospitalized patients, where admission criteria were strictly maintained. The fever associated with an FS is usually defined by a temperature of at least 36^0 Celsius [4]. Seizures can occur at the time of the highest temperature or during defervescence. A seizure may be the first sign of illness and may occur even before the fever is noticed [35]. The rate of rise and the maximum temperature for the seizure to occur are also subject to debate. A child may have seizure at 38^0 celsius and the following week may have a temperature greater than 39 degrees Celsius without any convulsion. It was reported that higher fever from bacterial upper respiratory infections might not cause a seizure [28]. No evidence exists that FSs are more likely to occur with the maximal rate of temperature rise, although this is often quoted [8]. It has also been reported that in 25-42% of cases, seizure is the first symptom and fever appeared later [4, 11, 20].

In my study, temperature was not recorded by 80% of parents for being frightened by the horrible scenario of seizure, and they do not know how to record the temperature. Of the remaining 8.3% was low grade, 10% was high grade and very high grade was 1.7%. In our study and the study done by [38], there was no significant association between any adverse antenatal, natal, and postnatal events and there was also no significant association to any adverse neurological event. Seizure was predominantly brief, generalized tonic-clonic (83.3%) and a few had focal features (16.7%). The observation for focal one by other authors

was 4-16% [13, 24, 38]. Seizures last more than 15 minutes in 16.7% of children in this study.

The observation of another study was 10% [13]. The most common cause of fever in FS was respiratory tract infections (61.67%) which include pneumonia, bronchiolitis, pharyngitis, tonsillitis, otitis media, etc. [39] also reported in their study that respiratory tract infection was the most common cause of fever (67%) in FS. Other illnesses were acute gastroenteritis and urinary tract infection. In 11.67% of cases, the cause of fever could not be determined as there was no systemic symptom, sign, and positive investigations report. These cases may be due to a viral infection which has to be confirmed by PCR; an expensive test that is not feasible for our poor patient.

Limitations:

The sample size is small in relation to the overall incidence of the disease and the large size of the population of this country. This study was done in six months, so the duration may not be enough to make a conclusion. And the study does not represent the seasonal variation of associated illness. As the study was done in Dhaka Medical College Hospital, Dhaka; most of the patients were from urban areas which may not represent the villages of our country.

VII. CONCLUSION AND RECOMMENDATION

From the result of the present study, it can be concluded that febrile seizure is associated with various infectious causes. Associated infections were the most common respiratory tract infections, urinary tract infections, and acute gastroenteritis in chronological order. The causes were possible viral infections than bacterial ones. So, antibacterial medication was not needed and it reduces hospital stays. If the associated infection is diagnosed and treated properly, the outcome would be good. As the study was conducted on a small number of cases, a larger multicenter study is recommended. In addition the study, the microorganism causing infection should be isolated.

Conflict of Interests: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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