



## Recurrence Related Factors of Febrile Seizure



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### Abstract

Febrile seizure were the most common form of childhood seizures, affecting 2-5% of children aged 6 months until five years. They are considered benign and self-limiting, but some cases may recur up to 80%. Identified the recurrence related factors are important to determine prognoses and therapies. Aims of this study were to know the prevalence of febrile seizure in Sanglah hospital and it's recurrence related factors. A crosssectional study design to investigate febrile seizure cases in pediatric department, Sanglah Hospital. Five recurrent related factors were identified and analyzed, prevalently related counted. In this study, 100 subjects was enrolled. The prevalence was 1.5% in patients age 6 months until 5 years. Twenty-six subjects (26%) with a recurrent febrile seizure. Bivariate analysis obtained a recurrence febrile seizure occurred 1.5 (CI 95% 0.77-2.95) in patients suffering from first seizures at less than 12 month; 1.75 (CI 95% 0.9-3.38) in patient with temperature below 39°C; and 2.44 (CI 95% 1.3-4.57) occurred in patient with positive history of febrile seizure or epilepsy at 1st degree family. The significant related factor for recurrence is a positive history of febrile seizure or epilepsy at 1st-degree relative.

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## 1. Introduction

According to American Academy of Pediatrics (AAP), febrile seizures are a seizure occurring in children between 6 months until 60 months with an increased body temperature above 38°C (any method measurement) in absence of intracranial infection, metabolic disturbance, or history of afebrile seizure.[1] The incidence among those age 2-5%. [1,2] Febrile seizure are classified as simple and complex febrile seizure.[1,2]

The incidence of febrile seizure in India 5 to 10%, in Japan 8.8%, and in Guam 14%. [3] The peak prevalence is usually in the second year of life. [4] A national cohort study reported that 90% of children had their first febrile seizure before the age of 3 years, with the peak age being 18 to 24 months. There are only 6% of febrile seizures occur before 6 months of age and 4% after 3 years of age. [4,5] Most FS are simple; however, up to 30% might have some complex features. Febrile seizure considered benign and self-limiting, but in several cases are potential recurrent. [4]

The recurrence of FS is related to various factors. Younger age group, prolonged seizure duration, the degree of fever and positive personal and family history of febrile seizure, preexisting developmental delays, daycare attendance, stay in the neonatal nursery for more than 28 days, and various viral infection was predicted as factors related febrile seizure recurrence. [6, 7] Recent study at Nepal found that only male sex and age <1 year has significant risk factors for recurrence. [7] Indonesian Neurological Working Unit identified five factors which related to recurrence of febrile seizure are a family history of febrile seizure or epilepsy, age at first febrile seizure below 12 months, a temperature below 39°C when seizure occurred, the short time interval between onset of fever and seizure, first seizure's episode is a complex febrile seizure. [8] Febrile seizure without any of those factors estimated has recurrence rate 10-15%, the related increased up to 80% if all the factors fulfill. [8] Identified those factors are important to determine the need for prophylaxis therapy and prognoses.

Sanglah hospital is a 3<sup>rd</sup> level hospital referral center. Many neurologic cases admitted to Sanglah hospital but there are no data about febrile seizure until to date. Here we report the prevalence and the recurrence related factors for febrile seizure in Sanglah Hospital.

## 2. Research Methods

This was crosssectional study design to showed prevalence, characteristics and prove several factors influencing recurrence of febrile seizures. The data study was collected from inpatient and outpatient pediatric registers between May 2016 until April 2017 to calculate the prevalence, the characteristic and the related factors data were collected from inpatient data registers between May 2016 until February 2018, a period where complete data registers available. Sample size calculated according to  $\alpha$  0.05, power 80%, relative ratio 2, the proportion of recurrence febrile seizure 28%. The minimal sample size was 92 subjects. A patient who had a final diagnosis of meningitis, encephalitis, epilepsy and not complete data were excluded. A hundred (100) eligible subject's data were analyzed. The characteristic data were described in percentage for categorical data and in the median for numeric data. Chi-Square analysis and counted for prevalence ratio was conducted to determine each factor related to recurrence. The study protocol was approved by the local Committee for Research Ethics, Medical Faculty, Udayana University Denpasar.

### 3. Results and Analysis

#### 3.1 Results

We found the total patient who admitted pediatric division on May 1<sup>st</sup>, 2016 until April 30<sup>th</sup>, 2017 was 14.132 subject and 5.059 of them were age 6 months to 5 years. The total cases of febrile seizure age 6 month-5 years on that period was respectively: 3 outpatient cases from polyclinic (2 simple febrile seizure, 1 complex febrile seizure), 8 outpatient cases from emergency ward (all cases were simple febrile seizure), and 64 inpatient cases from pediatric wards. The prevalence was 1.5% from all children age 6 months until 5 years who admitted pediatric division, Sanglah hospital.

Table 1  
Characteristic of Febrile Seizures Patients

Characteristic	Simple FS n = 20	Complex FS n = 80
Male sex, n (%)	6/36	30/36
Age, month, median (minimum – maximum)	15.5(2-48)	19.5(6-60)
Age at first febrile seizure < 12 month, n (%)	6/26	20/26
Positive history of seizure in 1 <sup>st</sup> -degree relative, n (%)	3/26	23/26
Nutritional status, n (%)		
Obese	0	4 /4
Overweight	2/10	8/10
Well-nourished	15/66	31/66
Mild Malnutrition	3/20	17/20
Temperature at onset of FS < 39°C, n (%)	8/40	32/40
Seizure frequency > 1 time in first 24 hour episode, n (%)	NA	67/80
Febrile seizure's episode, n (%)		
First episode	16/74	58/74
Recurrent	4 /26	22 /26
Underlying disease, n=88 (%)		
Upper respiratory tract infection	10/63	53 /63
Lower respiratory tract infection	1 /4	3 /4
Gastrointestinal infection (with/without upper respiratory tract infection)	2 /12	10/12
Dengue infection	2/2	0
Others	2 /7	5/7

\*FS : febrile seizure, NA: not available

We did analyze the total of 100 subjects to show the character study and determine the recurrent related factors. We found that complex FS were dominant in our study (80%). In the group of complex FS, the seizure episodes occur up to 6 times (1% case). FS affected male more frequent than a female with ratio 1: 1.8. The median age enrolled was 19 months with the age range was 2 months until 60 months. Most of them were well-nourished status (66%). There were only 26% identified with the positive history of febrile seizure or epilepsy in their first degree relative family. Those who had their first seizure as a complex FS were about 58% and none of them had a neurological abnormality prior to seizure. There is only 2 sample with global delayed development but both had performed as simple FS in our study.

We found that the underlying disease that preexisting febrile seizure was 63% caused by upper respiratory infection, followed by gastrointestinal infection 12%, lower respiratory tract infection 4%, dengue infection 2%, others were viral infection related thrombocytopenia, varicella, and otitis media acute, they contribute 7% for causing fever.

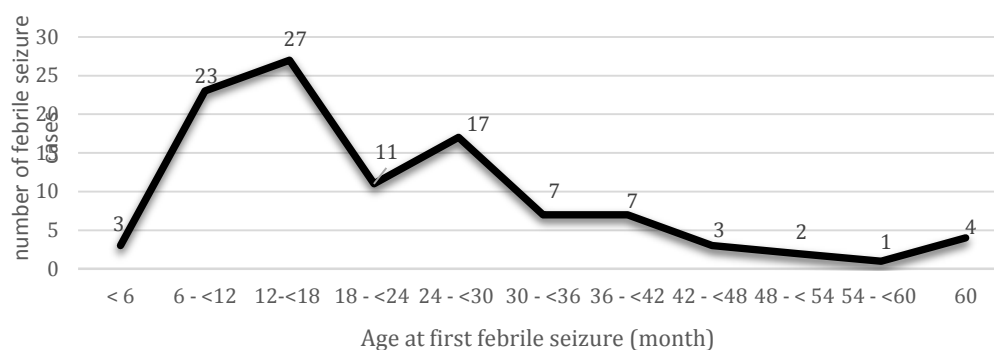


Chart 1. Febrile seizures frequency based on age at first febrile seizure

Chart 1 describe the natural course of age at first febrile seizure. It showed a rare frequency of FS below 6 months (3%) than increase after. The higher frequency occurred at 6 months until below 18 months (50%) with the peak frequency occurred at 12 months (19%). The frequency of FS decreases by the age of 3 years.

The temperature when the seizure occurred were categorized become  $<39^{\circ}\text{C}$  and  $\geq 39^{\circ}\text{C}$  group the number respectively 40% and 60%. Seventy-four percent (74%) of them had their first FS at the time sample enrolled. Others whose had the second episode of FS and more were categorized as recurrent group 26%.

Table 2  
Analysis bivariate of related factors related to recurrent febrile seizure

Variable	recurrence		P value	Prevalens ratio (PR)	95% confidence interval
	yes (n = 26)	no (n = 74)			
Male sex					
Yes	16	48	0.76	0.90	0.46-1.77
No	10	26			
Positive history of seizure in a 1 <sup>st</sup> -degree relative					
Yes	12	14	<0.01	2.44	1.30-4.57
No	14	60			
Age < 12 months at first febrile seizure					
Yes	9	17	0.24	1.50	0.77-2.95
No	17	57			
Temperature $<39^{\circ}\text{C}$ at the onset of FS					
Yes	14	26	0.09	1.75	0.90-3.38
No	12	48			
Complex febrile seizure					
Yes	22	58	0.49	0.72	0.28-1.87
No	4	16			

\*FS: febrile seizure

We identify 5 factors in our study who suggested as factors of recurrence FS. Male sex, positive history of seizure in 1<sup>st</sup>-degree history, age below 12 months at first febrile seizure, the temperature at the onset of FS, complex febrile seizure. We performed bivariate analysis of all factors with Chi-Square test and count the prevalence ratio. Table 2 showed the significant related factors for recurrence was a positive history of seizure in 1<sup>st</sup>-degree history family  $p=0.006$  with the prevalence ratio 2.44 (CI 95% 1.30-4.57).

### 3.2 Analysis

The prevalence of febrile seizure in RSUP Sanglah on a period of 1 year (May 2016 until April 2017) was 1,5 % on age 6 months until 5 years. In this study found that median age in our sample was 19 month, occurred male the dominantly 64% with a female: male ratio 1:1.8. This proportion was quite similar to Gunawan and friend in 2008, boys affected 63%. [8] This predominance may be explained that males are predisposed to infection for in males have an XY chromosome and in general condition, X chromosome is strongly related to the production of immunoglobulin. [9]

Most of our sample presented with well-nourished (66%), even in developed country malnutrition is the major cause or consequence of another disease, malnutrition increased host's susceptibility to infection while the infection is the main cause of fever leading to febrile seizure in predisposing children. In this study showed more than 75% of the Waterlow was to be above 90%. This result was consistent with Oseni study which included that febrile seizure was more prevalent in well-nourished children. [10]

There was a wide range variation of an age onset febrile seizure. Many studies shown the age range related febrile seizure onset was affected between 2 months until 11 years. However, our division of pediatric neurology adopted the AAP febrile seizure definition which determined the age range for febrile seizure between 6 months until 5 years. It's unusual for children younger than 6 months to have a febrile seizure, and it's rare for these seizures to occur after 3 years of age. [4,5] Only 6% febrile seizure occurs before 6 months the s. Our study found 3% indicating that the age at onset FS occur is a critical consideration in the further evaluation of children with febrile seizure. [4] This study found that the higher percentage of febrile seizure was between 6 months until below 18 months. It was parallel with a Lumbotobing study whose found that an age group below 1 year was the most frequent (56,7% ) had a febrile seizure. [11] At the age of fewer than 3 years, the state of the brain has not mature yet. The immature brain excitation is more dominant rather than inhibition. *Corta icotropin*-release sing hormone (CRH) is a neuropeptide excitation, potentially as *prokonvulsan*. In the immature brain CRH levels in the hippocampus are high, potentially a seizure arises when triggered by fever. Immature a brain neural Na ATPase is still lacking, causing Na<sup>+</sup> ion regulation, K<sup>+</sup>, and Ca not perfect, thus resulting in an increase in excitability neurons, susceptible to seizure generation. [12,13]

A febrile seizure is classified become simple and complex febrile seizure. Simple febrile seizure is usually general tonic-clonic, tonic or clonic, short lasting (duration <15 minutes), and does not recur within 24 hours. Complex febrile seizure characterises by focal or partial seizure or generalized seizure preceded by focal seizure, prolonged seizure (>15 minutes), recurring or more than 1 in 24 hours. The classification has major implication for the clinical course and prognosis of children presenting with this condition. Simple febrile seizure is by far the most common and usually isolated occurrence. Complex febrile seizures are associated with higher odds of recurrence, furthermore, the differential diagnosis of epilepsy and acute symptomatic seizure must be pursued more rigorously in these case. In our case complex, febrile seizure was more common (80%). This situation was held because of Sanglah hospital status as the third level hospital referral center so simple febrile seizure should be handled by the first level health service center, even though we had rest of 20% of them hospitalized as a simple febrile seizure. It's interesting that according to literature simple febrile seizure doesn't require hospitalization, based on our study this condition were describe on table 1 that showed the median age to date and onset of simple febrile seizure occurred at a lower age than a complex febrile seizure. First, we found 2 patient simple febrile seizure had their first seizure below 6 months on the time enrolled means indication for consideration to exclude other cause rather than a simple febrile seizure. Second, we found 2 patient with simple febrile seizure admitted with thrombocytopenia, the others admitted with diarrhoea, enteritis, bronchiolitis, and hyperpyrexia.

Febrile seizures most often occur within 24 hours of the onset of a fever and can be the first sign that a child is ill. In a Malayan study found the duration of fever prior to the onset of seizure ranged from 0 hours to 168 hours. [13] The short duration of onset *febris* to seizure is below 1 hour. [14,15] But in our study, the minimal duration between onset fever and seizure is 1 hour. The short duration of febrile onset to seizure was one of the recurrence factors. All cases of febrile seizure were general seizures. Seventy-four percent (74%) sample was the first episode of febrile seizure.

We found 26% patient with recurrence. Several cohort studies have found the same proportion. [4] We tried to analysis the related factors which contribute recurrences of febrile seizure, from various factors

identified 5 variable to analyze. Male sex, positive history of seizure in 1<sup>st</sup>-degree history, age below 12 months at first febrile seizure, temperature when the seizure occurred, and complex febrile seizure. We found there are significant prevalence ratio 2.44 times (CI 95% 1.30-4.57) become recurrences if there is a positive history of febrile seizure or epilepsy in their first-degree family. This result might be explained by a strong causation relation between related factors and outcome because the positive history of seizure had preceded before born. It was parallel with literature that said a history of febrile seizure in their 1<sup>st</sup>-degree family or higher was the most prediction power related factors for recurrence.[16,17] The recent retrospective study in Thailand presents similar result that positive history of febrile seizure in their family gave significant ratio odds 2.38 for being recurrent.[6][20][21][22]

The febrile seizure was induced by extra cranial infection process. The infection will increase body temperature above the limit (hyperpyrexia) lead to a seizure. In our study found that most common infection as *febris causa* in FS case was upper respiratory tract infection (63%); followed by gastrointestinal infection (12%); lower respiratory tract infection (pneumonia, laryngitis, bronchiolitis) about 2%; dengue infection; *trombositopenia* related viral infection (2%); varicella (1,4%); Otitis media acute. This parallel with Nelson and Ellenberg and Lewis study in Seidenberg had shown that the most common *febris causa* was respiratory tract infection (38%), followed by ear infection (23%), pneumonia (15%).[16] Specific infectious etiologies have been associated with febrile seizures, such as human herpes simplex virus-6 (*roseola infantum*), accounting for as much as 20% of children presenting with first febrile seizures, *shigella* gastroenteritis, and influenza A.[18,19]

Limitation of our study is difficult to collect complete data in identifying related factors of recurrent FS because some data was unrecorded properly effect to loss some sample.

#### 4. Conclusion

The prevalence of febrile seizure in Sanglah Hospital was 1.5% from all children age 6 months until 5 years. The febrile seizure was rare before 6 months, the proportion increased after 6 months to 18 months and decreased after 3 years. Male was dominant to female. Twenty-six percent experience recurrence. Positive history of febrile seizure or epilepsy in the first-degree family has 2.44 times become recurrence.

#### *Conflict of interest statement and funding sources*

The authors declared that they have no competing interest. The study was financed by personal funding.

#### *Statement of authorship*

The authors have a responsibility for the conception and design of the study. The authors have approved the final article.

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