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Original Article

Predictive factors for recurrent febrile seizures in children

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Abstract

Background One-third of children who experience febrile seizures have a recurrence, with rates of 75% in the first year, and 90% within the second year following the first febrile seizure. Predictive factors for recurrent febrile seizures have been reported in studies from other countries, but there have been few of these studies in Indonesia.

Objective To determine predictive factors for the recurrence of febrile seizures in children.

Methods Children with first-time febrile seizures were prospectively followed up, for at least 12 months. Subjects were recruited consecutively from August 2008 to April 2010 from two hospitals in Yogyakarta and one hospital in Klaten. We monitored recurrences of febrile seizure by telephone or home visits to parents every 3 months. Time to first recurrence of febrile seizures was analyzed using the Cox regression model.

Results There were 196 children with first-time febrile seizures who completed the follow up. Recurrent seizures were observed in 56 children (28.6%). Mean follow up time was 21.7 (SD 6.6) months. Temperature of <40°C at the time of seizure (RR=2.29, 95%CI 1.35 to 3.89, P=0.002), history of febrile seizures in first-degree relatives (RR=3.30, 95%CI 1.25 to 8.08, P<0.001), age at first febrile seizure of <12 months (RR=2.40, 95%CI 1.42 to 4.06, P=0.001) and duration of fever before the seizure of ≤1 hour (RR=4.62, 95%CI: 1.35 to 15.80, P=0.015) were significantly associated with recurrence of febrile seizures. Furthermore, Cox regression analysis revealed that the age of <12 months, history of febrile seizures in first-degree relatives and temperature of <40°C were significant predictive factors for the recurrence of febrile seizures.

Conclusion Age at first seizure of <12 months, history of febrile seizures in first-degree relatives, and seizure with temperature of <40°C were independent predictive factors for recurrent febrile seizures in children. **[Paediatr Indones. 2012;52:317-23]**.

Keywords*: febrile seizures, recurrence, predictors, prospective*

Febrile seizure is defined as seizure activity associated with fever of > 38ºC in a previously healthy child with no prior history of afebrile seizures, no evidence of intracranial infection, and no defined cause such as electrolyte imbalance or other metabolic abnormality.[1,2,3] Febrile seizures in children most commonly occur between ages of 6 months and 5 years, with a peak incidence at 18 months of age.[2,3] Although the occurrence may be benign, it can be frightening and anxiety-provoking for family or caregivers.[3,4] Reported prevalences vary in North America and Western Europe from 2-5%,[2,3,4] but in Asia the rate is higher.[1] In Japan the prevalence was reported to be 7%,[5] or higher at 9-10%.[6,7] The prevalence of febrile seizures in Guam was reported to be about 15%.[4] However, Chung *et al*. reported the incidence of febrile seizures as well as the incidence of recurrent febrile seizures in South China to be lower than that of Western countries, even though they had similar predictors.[5] Genetic predisposition and environmental factors may have influenced these results.[5, 8-12]

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Approximately one-third of children who have febrile seizures experience recurrent febrile seizures, with 75% doing so in the year following the first febrile seizure, and 90% within the second year following the first febrile seizure.[4] Numerous studies have examined the predictors of recurrent febrile seizures with incidences varying between 30-50%.[4,13,14] These predictive factors have been studied in other countries, but Indonesian data is limited. Incidence and predictive factors of recurrent febrile seizures in Indonesia may be similar to those in other populations. We performed this study to determine the incidence and predictive factors for recurrent febrile seizures in Indonesian population.

Methods

We undertook an on going cohort prospective study in subjects from three hospitals, Sardjito Center and Sleman District Hospitals in Yogyakarta and Suradji Tirtonegoro Central Hospital in Klaten from August 2008 to April 2010. Children with first-episode of febrile seizures were recruited consecutively and followed up for at least one year subsequently in order to determine febrile seizures recurrences.

Subjects were recruited by the resident-in-charge. We included the child in the study if the febrile seizure was the first-ever episode, the child was between 6 months and 5 years of age, did not have any pre-existing neurodevelopmental problem, and the parents agreed to participate in the study with a written informed consent. Information on possible predictive factors, such as age at onset of febrile seizure (< 12 months or ≥ 12 months), temperature at onset of febrile seizure (< 40ºC or ≥ 40ºC), history of febrile seizures in families [defined as first-degree (parents or siblings) or second-degree (grandparents, uncles/aunts or cousins], duration of fever before the seizure occurred (≤ 1 hour, >1 - 24 hours and > 24 hours), sex (male or female), family history of epilepsy (afebrile seizure or unprovoked seizure), type of seizure (generalized or focal), and type of febrile seizure (simple or complex febrile seizure) was compiled from interviews and medical records. Description of the seizures when the illness occurred was elicited from parents or witnesses. Information about the illness were collected included duration of fever before the seizure occurred, family history of afebrile seizure or unprovoked seizure, the highest temperature recorded before or just after the seizure, and if the child had a preexisting neurodevelopmental problem. All information was compiled from interviews and medical records including diagnoses, physical examinations and laboratory results. Temperature measured at the hospital was considered to be the most reliable. All information was recorded in a study form.

After the initial interview, parents were interviewed every three months by telephone, hospital visit, or home visit to determine whether the child had had reccurent febrile seizures. A recurrence of febrile seizure was defined as a subsequent febrile seizure during a new febrile period. Information about recurrences was based on parents' reporting, but when possible, documentation of recurrence was obtained from medical records. Follow up was done by the author and one assistant. Home visits were made if parents could not be contacted by telephone or hospital visit.

We excluded children with neurologic abnormalities, such as pareses, muscle weakness, uncoordinated movement, global developmental delay, impaired conciousness, hydrocephalus or other neurological deficits after the seizure. Children with long-term prophylaxis for seizure or those diagnosed with epilepsy or seizure without fever were also excluded. We concluded that a subject was lost to follow up if at one year of follow up, we could not obtain information as to whether the child suffered from recurrent febrile seizures. This study was approved by the Committee for Medical Research Ethics of the Gadjah Mada University Medical School.

Bivariate analysis was done using Chi square analysis and multivariate analysis was done using the Cox proportional hazards regression model. Magnitude of association between predictive variables and recurrent febrile seizures was expressed in hazard ratio (HR) and 95% confidence intervals (CI). All statistics were performed using SPSS 16.0 for Windows.

Results

During the study period, 226 children met the inclusion criteria. There were 196 children who completed the follow up for at least one year after their initial febrile seizures. Thirty children (13%) were lost to follow up (**Figure 1**).

The mean follow up time was 21.7 (SD 6.6) months, and 56 subjects (28.6%) had recurrent febrile seizures by the end of the study. Sixteen children (8.1%) experienced more than one recurrent febrile seizure. We assumed all participants were given diazepam prophylaxis according to our guideline though we did not control their compliance to prophylaxis. Baseline characteristics of subjects are depicted in **Table 1**.

Bivariate analysis revealed that there were no significant associations between gender, type of seizure, type of febrile seizure, and family history of epilepsy to the recurrence of febrile seizures. Age at onset of < 12 months, history of febrile seizures in first degree relatives, short duration of fever of ≤ 1 hour before the onset of febrile seizures and temperature of < 40°C at the onset of febrile seizure were all significantly associated with recurrent febrile seizures (**Table 2**).

Predictive factors with P < 0.25 in bivariate analysis were included in multivariate analysis. Multivariate analysis with the Cox regression hazard model revealed that the independent predictive factors for recurrent febrile seizures were age at onset of <12 months, history of febrile seizures in first-degree relatives, and temperature of <40°C at the onset of febrile seizure (**Table 3**).

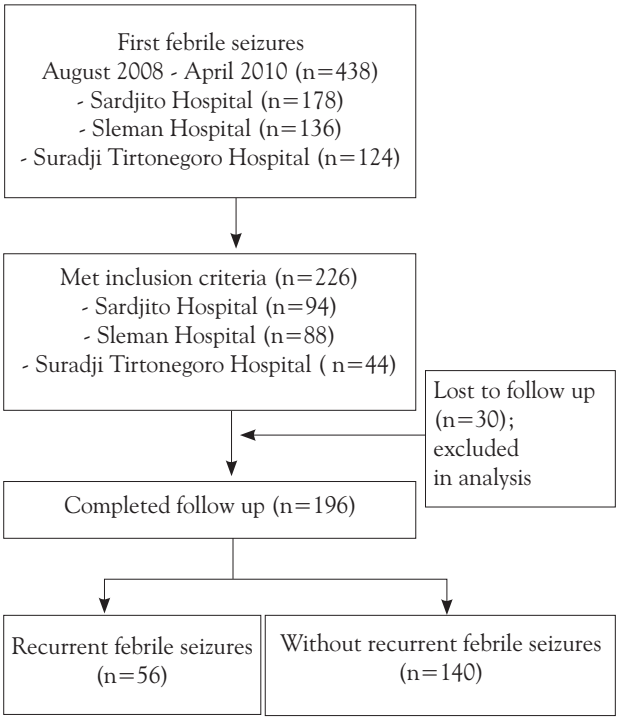

Figure 1. Flow chart of subject recruitment and follow up

Table 1. Baseline characteristics of subjects

Characteristics	n=196	
Male, n (%)	113	(57.7)
Mean age at onset, months (SD)	19.5	(11.3)
<12 months, n (%)	53	(27.0)
≥12 months, n (%)	143	(73.0)
Family history of febrile seizures		
First-degree relatives, n (%)	79	(40.3)
Second-degree relatives, n (%)	38	(19.4)
No family history, n (%)	79	(40.3)
Family history of epilepsy		
Yes, n (%)	9	(4.2)
No, n (%)	187	(95.8)
Type of seizure		
General, n (%)	189	(96.4)
Focal, n (%)	7	(3.6)
Type of febrile seizure		
Simple, n (%)	133	(67.9)
Complex, n (%)	63	(32.1)
Mean temperature at onset of febrile seizure, °C (SD)	39.8	(0.5)
<40°C, n (%)	77	(39.3)
≥40°C, n (%)	119	(61.7)
Mean duration of fever before onset, hours (SD)	14.2	(11.3)
≤1 hour, n (%)	12	(6.1)
>1-24 hours, n (%)	160	(81.6)
> 24 hours, n (%)	24	(12.2)
Incidence of recurrent febrile seizures, n (%)	56	(28.6)
Incidence of multiple recurrent febrile seizures, n (%)	16	(8.1)
Mean length of follow up, months (SD)	21.7	(6.6)
Children with recurrent febrile seizures	22.4	(6.8)
Children without recurrent febrile seizures	21.5	(6.5)

Table 2. Bivariate analysis of predictive factors for recurrent febrile seizures

Variables	Recurrent febrile seizures n=56		Without recurrent febrile seizures n=140		RR (95%CI)	P value
Male, n (%)	32	(57.1)	81	(57.9)	1.03 (0.61 to 1.74)	0.92
Age at onset < 12 months, n (%)	25	(44.6)	28	(20.0)	2.40 (1.42 to 4.06)	0.001
Family history of febrile seizures, n (%)						
1st degree relative	33	(58.9)	46	(32.8)	3.30 (1.25 to 8.08)	<0.001
2 ndegree relative	7	(12.5)	31	(22.1)	2.09 (0.92 to 6.40)	0.10
No history	16	(28.6)	63	(45.0)	1.0	
Family history of epilepsy, n(%)	2	(3.6)	7	(5.0)	0.78 (0.19 to 3.21)	0.73
Focal seizures, n (%)	3	(5.4)	4	(2.9)	1.62 (0.51 to 5.19)	0.42
Complex febrile seizures, n (%)	19	(33.9)	44	(3.1)	1.09 (0.63 to 1.89)	0.76
Temperature of < 40 °C at onset of febrile seizure, n (%)	31	(55.4)	46	(32.9)	2.29 (1.35 to 3.89)	0.002
Duration of fever before onset of seizure, n (%)						
≤ 1 hour	7	(12.5)	5	(3.6)	4.62 (1.35 to 5.80)	0.015
>1-24 hours	45	(80.4)	115	(82.1)	1.82 (0.66 to 5.09)	0.26
> 24 hours	4	(7.1)	20	(14.3)	1.0	

Table 3. Multivariate analysis with Cox regression model

Predictive factors	Hazard ratio (HR)	95%CI	P value
Age < 12 months	2.42	1.41 to 4.18	0.001
1 st degree relative with febrile seizures	2.73	1.59 to 4.70	< 0.001
Temperature of < 40 ºC	2.11	1.24 to 3.58	0.006
Duration of fever ≤1 hour	1.69	0.76 to 3.78	0.20

Discussion

The incidence of recurrent febrile seizures in this cohort prospective study was 28.6% (22.4% within the one year after the first febrile seizure). From a meta-analysis, Berg *et al*. reported the incidence of recurrent febrile seizures in a western population to be in the range of 29-55% (mean 34%).[15] In Japan, the incidence of recurrent febrile seizure was reported to be approximately 45%,[16] while a Chinese study reported approximately 12.7% in the first year of follow up and 20.5% after 3 years of follow up.[5] Our findings were similar to Western studies,[4] but higher than those of the Chinese study.[5] However, the higher incidence of recurrent fever in Japan may be due to genetic predisposition or environmental factors. Genetic susceptibility and epidemiological studies are needed to evaluate their influence in subjects.[5,8,9,12]

We found that 67.9% of children experienced simple febrile seizures, while the remainder (32.1%) had complex febrile seizures. Similarly, Karande reported that 9-35% of febrile seizures were complex.[6] Complex febrile seizure was not a significant predictor of recurrent febrile seizures in our study. In contrast, Chung *et al*. in China and Offringga *et al*. in the Netherlands reported that complex febrile seizure was an independent predictive factor for recurrence.[5,17] Nonetheless, this factor has been shown to be inconsistent as a significant predictive factor in several studies.[4,18] A later study by Offringa *et al*. of a pooled analysis reported that complex febrile seizure was not an independent predictive factor for recurrent febrile seizures.[19]

Family history of epilepsy and focal seizures were not significant predictors for recurrent febrile seizures in our subjects, consistent with previous studies.[13,14,15] However, this predictive factor was associated with the occurrence of later epilepsy in children with febrile seizures.[4,14]

Using Cox regression analysis, we found that history of febrile seizures in first-degree relatives and an age at onset of < 12 months were independent predictors for recurrent febrile seizures. These findings were consistent with previous studies.[4,5,13-15] However, we did not expect that history of febrile seizures in first-degree relatives would be the strongest predictive

factor in our subjects. This finding may suggest a genetic susceptibility in our population. Previous studies reported younger age to be the strongest predictor for the recurrence of febrile seizures, since there is a longer developmental window to develop a recurrence.[4,6,11,12] From two cohort prospective studies, Berg *et al.* reported that younger age, history of febrile seizures in first-degree relatives, short duration of fever before the seizure occurred and lower body temperature, as independent predictive factors for recurrent febrile seizures. A difference from our study was that they compared children aged < 18 months and > 18 months, as well as temperature classified into 4 ordinal categories from lowest to highest temperature of fever.[13,14] Nevertheless, we had similar conclusions and our findings support their previous findings, but with a stronger association. They also reported a lower relative risk of about two or less,[14] but we found the relative risks of history of febrile seizures in first-degree relatives and age of <12 months to be 2.73 and 2.42, respectively.

Berg *et al.* also reported short duration of fever before the onset of febrile seizure to be an independent predictive factor for recurrence of febrile seizures.[13,14] In contrast, we did not find this factor to be an independent predictor. In our study, duration of fever at the onset of febrile seizure of ≤ 1 hour was a significant predictor in bivariate analysis, but not in multivariate analysis. A Greek study reported that duration of fever of < 12 hours to be a significant predictive factor by univariate analysis, but not by multivariate analysis.[20] Duration of fever before the onset of febrile seizure is subject to errors in reporting. Most parents or caregivers become aware of fever some time after the fever has occurred.[4] In this circumstance, a modified calculation for the cutoff point for duration of fever before onset of febrile seizure may be needed for our population. However, we did not do this in our study.

Rosman *et al.* reported that intermittent prophylaxis with diazepam reduced the risk of recurrent febrile seizures by 44% [(diazepam (10%) vs placebo (19%), RR 0.56, 95%CI: 0.38 to 0.81, P=0.002)].[21] Similar findings were reported by Knudsen *et al.* in a study using rectal diazepam prophylaxis.[7] However, we still found a relatively high incidence of recurrent febrile seizures when giving intermittent diazepam prophylaxis, a guideline that applied to all subjects in our study.[1] But we could not control patient compliance to the prophylactic treatment, so this was a limitation of our study. In fact, findings have been inconsistent among studies on the effectiveness of intermittent prophylaxis. A meta-analysis by Masuko *et al.* did not conclude that intermittent diazepam prophylaxis was effective, due to heterogenicity among the studies.[22] A similar conclusion was reported by Rantala *et al.* who found that intermittent diazepam prophylaxis was not effective for preventing recurrent febrile seizures.[23] Noncompliance by caregivers may result in ineffective treatment, as reported by Autret *et al.*[24] Prophylaxis in children without good monitoring for more than a month was not effective in preventing recurrent febrile seizures.[19]

We did not consider number of fever episodes as a predictor for seizures. A child's risk for seizure would be higher if there were more opportunities for febrile seizures.[4,19,25,26] Pavlidou *et al.* reported in an univariate analysis that > 8 episodes of fever in a year was significantly associated with recurrent febrile seizure, but this association was not significant in a multivariate analysis.[20] However, Tarrka *et al.* found episodes of fever to be the only independent predictive factor for recurrence.[25] In addition, Stuijvenberg *et al.* (1999) reported that in a multivariate analysis, episodes of fever was an independent predictive factor for the recurrence of febrile seizures.[26] Since both groups (with and without recurrence) had similar mean ages, we suggest that the opportunity for febrile illness was the same.

Another limitation of our study was in controlling temperature measurements. Even when body temperatures were measured by medically-trained personnel, differences in thermometers may have affected the readings. Furthermore, body temperatures taken in the hospitals were often not performed when the seizures occurred. Therefore, the temperature measured in the hospitals was only an approximation of the subject's temperature at the time of seizure. In general, such errors attenuate the association between temperature and the risk of recurrence.[13] Since controlling temperature measurements is difficult, Chung *et al.* defined the temperature of the onset of febrile seizures to be the highest temperature measured during hospitalization.[5] A temperature at the onset of febrile seizure of < 40°C was an independent predictive factor for recurrent febrile seizures in our

study. This finding was consistent with the threshold model of febrile seizures that suggests that a seizure may occur above a threshold temperature. Different children have different thresholds.[4,13,14,19] The strength of association of this predictive factor is in a similar risk with other predictive factors. The lower temperature was also associated with later epilepsy occurrence.[4,5,16,18,27]

Sixteen subjects (8.1% of all subjects and 28.6% of those with recurrent seizures) had multiple recurrent febrile seizures. We found no significant predictive factor for multiple recurrent febrile seizures. A marginal statistical difference was found in subjects aged less than < 12 months (RR: 2.45, 95%CI: 0.85 to 7.08, P=0.09). Younger age was consistently the best predictive factor for multiple recurrent febrile seizures in many studies.[5,13,14,15,19] However, the short duration of our study prevents us from drawing a strong conclusion. A follow-up of the children should be continued until the age of five years, after which the risk of recurrent febrile seizures is considered to be very small or gone. This information is important for counseling to parents or caregivers. It has been estimated that 30-50% of those who have recurrences have more than one recurrence.[4,28]

Information on multiple recurrences of febrile seizures is also important to determine which subjects should be considered for long-term prophylaxis with valproic acid or phenobarbital, to add to our guidelines.[1] However, potential adverse effects may outweigh the relatively minor risks associated with febrile seizures, even if there are recurrences. The American Academy of Pediatrics recommends neither continuous nor intermittent anticonvulsant therapy for children with one or more simple febrile seizures. No study has demonstrated that treatment for simple febrile seizures can prevent the later development of epilepsy. Furthermore, there is no evidence that simple febrile seizures cause structural damage and no evidence that children with simple febrile seizures are at risk for cognitive decline.[2] Japanese studies further recommend a wait-and-see selective prophylaxis based on warning factors consisting of risks for recurrent febrile seizures and epilepsy.[16,27]

In conclusion, we found that a history of febrile seizure in first degree relatives, age at onset of febrile seizure of < 12 months and temperature at onset of febrile seizure of < 40ºC were independent predictive factors for recurrent febrile seizures in children. We can educate the parents or caregivers about the possibility of recurrent febrile seizure in children with these predictive factors. A longer study on children until they reach the age of five years is needed in order to draw a more comprehensive conclusion. Further study should consider for compliance to intermittent diazepam prophylaxis, episodes of fever, and temperature measurement in its methodology. We suggest adopting the Japanese recommendation for management of febrile seizures.

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