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Original Research Paper

Pediatrics

FACTORS THAT RELATED IN INCIDENCE OF EPILEPSY IN CHILDREN WITH HISTORY OF FEBRILE SEIZURES

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ABSTRACT

Background: Febrile seizures(FS)are the most common neurological disorder in children ≤5 years old (90%) and 25-50% will experience recurrence of FS. History of FS is also associated with epilepsy in children and many factorshave related in the incidence of epilepsy.

Objective: To determine what factors have related in epilepsy in children with history of FS.

Method: A cross-sectional study was conducted at the Haji Adam Malik Hospital Medan from September-December 2019. The study sample was pediatric patients with FS in the emergency room and outpatient unit in neurology division of Department of Pediatrics SMF of Pediatrics Medan from 2014-2019 recorded in medical records and conducted interviews by mobile phone about the condition of children after experiencing FS (epilepsy).

Results: The study found 134 children who met the inclusion criteria, 17 children (12.69%) with epilepsy after experiencing FS and factors that related in incidence of epilepsy in children with history of FS are neurological/developmental disorders, frequencyof FS and gestational age, where each factor can increase risk of epilepsy by 4.02 times in neurological/developmental disorders, 6.41 times in FS frequency and 3.13 times in gestational age.

Conclusion: The most related factor in epilepsy in children with history of FS was neurological/developmental disorders and frequency of FS.

KEYWORDS : febrile seizures, epilepsy, children, factors

INTRODUCTION

Febrile seizures (FS) are seizures that occur in children aged 6 months to 5 years who experience an increase in body temperature (temperatures above 38°C with any temperature measurement method) that aren't caused by intracranial processes.[1,2] Many occur in children aged between 6 months to 22 months, the highest incidence of FS occurs at the age of 18 months.[2] The incidence of FS in the US and Europe between 2-5%.[2,3] In Asia has doubled when compared to Europe and US.[2,4]In Japan it's around 8.3-9.9% and Guam reaches 14%.[2,3,5] The incidence of FS in Indonesia reached 2-4% in 2008 with 80% caused by infection respiratory tract.[2,4]

Study in 2010, most children with FS were preceded by fever less than two hours and the age of first seizures in case group was mostly known less than 2 years.[2] The study found that children with FS that occurred within1 hour after fever was known (onset) has higher risk for subsequent epilepsy than children with FS associated with longer duration of fever.[2] Fever seizures have risk of causing delays in brain development, mental retardation, paralysis and can progress to epilepsy(2-10%).[3,5] One study found that patients with two complex features (prolonged and focal) can increase risk of becoming epilepsy, two other studies didn't detect this association.[3,5]

The incidence of epilepsy in children was reported from various countries with wide variations, around 4 to 6 every 1,000 children. In Indonesia, at least 700,000 to 1,400,000 cases of epilepsy with an increase of 70,000 new cases every year and an estimated 40-50% occur in children.[6] Literature studies find that children with cerebral palsy (CP) are often accompanied by several comorbidities including epilepsy.[6]

The results of preliminary study was found relationship between history of FS with incidence of epilepsy in children atthe regional public service institutionCut Meutia General Hospital North Acehin 2015.[7] Results of research conducted at dr. Moewardi Surakarta General Hospital found that there's relationship between history of FS with epilepsy rates.[8] The results of study in Makassar found that frequency of FS history was higher in the epilepsy group (50%) compared to the non-epilepsy group (17.5%). From dr. Kariadi Semarang showed relationship between history of FS and epilepsy in children aged 6-14 years old.[10]The purpose of our study was to determine factors that related in incidence of epilepsy in children with FS history in Neurology division of Department of Pediatrics the SMF of Pediatrics at the Haji Adam Malik (HAM) HospitalMedan, Sumatera Utara.

MATERIALS AND METHODS

Subject and Method

This study is a cross sectional study at the HAM Hospital Medan, Sumatera Utara. This research began in September-December 2019 after obtaining ethical approval. The sample were all pediatric patients with FS who came to the emergency room (ER)and outpatient unitof the Neurology division of the SMF Department of Pediatric in theHAMHospital Medan. From 166 children were found 134 children to meet the inclusion and exclusion criteria with age between 2 to 13 years old. Data was recorded through medical records from 2014-2019 and interviews by mobile phone about the child's current condition after experiencing FS (epilepsy). Data taken included the characteristics of the study subjects including age, gender, family history of epilepsy, neurological/developmental disorders, kind of FS, frequency of FS, duration of FS, gestational age, family history of FS, age of first FS, onset of seizures and type of FS. The inclusion criteria were all pediatric patients with FS who came in the ER and outpatient unit of the SMF Pediatric Neurology division in HAM Hospital Medan recorded in the medical record and exclusion criteria were pediatric patients who had history of trauma, central nervous system (CNS) infections, electrolyte disorders and congenital brain abnormalities, who experience FS for the first time at the age of>5 years, parents of the subject can't be contacted because there is nomobile phone number in the medical record and didn't answer.

Ethical Considerations

Our study was approve by Ethical Commision of Medical Faculty ofSumatera Utara University.

Statistic analysis

Data were analyzed statistically using SPSS software version 25.0 (Statistical Package for Social Sciences) for windows. Descriptive statistics are expressed in terms of mean ± standard deviation (SD); while for categorical data presented in the form of frequencies. Comparison of the proportion of the relationship of factors that influence the incidence of epilepsy in children with history of FS, performed with the Chi square test, but if requirements aren't met can be tested Fisher and continuity test, the P-value <0.05 is considered significant. Multivariate analysis was performed with simple and multiple logistic regression test.

RESULTS

During the study, we got 134 FS children, there were 76 boys (64.6%) and 41 girls (35.0%). The epilepsy children with history of FS was 17 children consisting of 7 boys (41.1%) and 10 girls (58.8%). The mean age of epilepsy children with history of FS was 7.2 years old and children without epilepsy with history of FS 6.6 years old**(table 1)**.

Factors that related in the incidence of epilepsy in children with history of FS

In our study, bivariate analysis was done between independent variables namely the factors that related in incidence of epilepsy children withhistory of FS and the dependent variable is epilepsy **(table 2)**.The FS group, 13 children (9.7%) had family history of epilepsy, while 4 children (30.8%) had family history of epilepsy in the epilepsy group (p=0.062). The FS group, 16 children (11.9%) with neurological/developmental disorders, which developed into epilepsy as many as 6 children (37.5%). There wassignificant relationship between neurological/developmental disorders and epilepsy in children with history of FS, where children with neurological/developmental disorders 4.0 times the risk of epilepsy (p=0.001). There're 2 types of FS in children, simple FS and complex FS, 66 simple FS children (49.3%) and 68 complex FS children (50.8%), 9 complex FS children (13.6%) and 8 simple FS children (11.8%) in the epilepsy group (p=0.745). The frequency of FS ≥4 episodes/year as many as 20 children (14.9%), which became epilepsy was 9 children (45.0%) and <4 episodes/year as many as 114 children (85.1%), which became epilepsy was 8 children (7.0%). There's significant relationship between the frequency of FS with epilepsy in children with history of FS, where children with FS frequency ≥4 episodes/year are 6.4 times at risk of becoming epilepsy (p<0.001). Twelve children (8.9%) had history of preterm birth in the FS group and 4 children (50.0%) in the epilepsy group. Children who have history of preterm birth are 3.1 times at risk for developing epilepsy (p=0.047). The FS duration was divided into two groups: <15 minutes and ≥15 minutes. There was no significant difference in FS duration between the FS group and the epilepsy group (p=0.136). Family history of FS found 36 children (26.9%) in the FS group, while 6 children (16.7%) had family history of FS in the epilepsy group (p=0.401). The FS group, 64 children (47.8%) FS were <2 years old, as many as 8 children (12.5%) in the epilepsy group (p=0.951). The onset of the seizure was divided into two groups, ≤24 hours and>24 hours. The onset of seizures didn't differ significantly between the FS group and the epilepsy group (p=0.358). In the FS group, 3 children (2.6%) with focal FS, while in the epilepsy group found 2 children (11.8%) with focal FS (p=0.121).

Classification of epilepsy incidence

In this study, we found that epilepsy consisted of 10 cases (58.8%) with symptomatic general epilepsy, 3 cases (17.7%) with idiopathic generalized epilepsy, 4 cases (23.5%) focal epilepsy and 4 cases (2.9%) FS plus.

Multivariate test of factors that related to epilepsy in children with history of FS

Multiple multivariate analyzes were done on the independent variables with incidence epilepsy in children with history of FS that were family history of epilepsy, neurological/ developmental disorders, frequency of FS, gestational age, duration of FS and type of FS. The factors analyzed were the factors with P value<0.25 in table 2.In step 1, family history of epilepsy, gestational age and type of FS didn't have significant relationship with epilepsy in children with history of FS **(table 3)**.

Significant variables were analyzed at step 2, which were neurological/developmental disorders, frequency of FS and duration of FS, were found significant relationship with epilepsy in children with history of FS **(table 3)**. In step 3, was found that neurological/developmental disorders factors (p=0.001) and frequency of FS (p<0.001) were the most influential factors in epilepsy in children with history of FS. Febrile seizures children with neurological/developmental disorders have 11.1 times risk of developing epilepsy. The frequency of FS has risk of 17.2 times becoming epilepsy later in life.

DISCUSSION

The research output obtained factors of neurological disorders and the frequency of FS was factor that related in the incidence of epilepsy in children with history of FS. Febrile seizures are the most common seizure disorders in children and defined as seizures accompanied by fever and no CNS infection, which occurs in infants and children aged 6-60 months old.[11]This study found that boys withFS 61.94% more than girls 38.1%. There's study are similar with research at Prof. Dr. RD Kandou Manado Hospital, that boys with FS are more with 66% compared to girls 34%.[4]In boys, FS are more frequent than girls with a ratio of 1:1.8, average age 19 months old and age between 2 to 60 months old.[12] This similar with research in Malang which found that FS occurred more in boys 68.4% compared to girls 31.6%.[13] This may be caused by cell maturation in girls faster than boys, including nerve cell maturation.[12,13]

Epilepsy is recurrent seizures without triggers (provocation) ≥2 with intervals>24 hours between the first and subsequent seizures.[14]In this study, the diagnosis of epilepsy was made based on history taking and physical-neurological examination by pediatric neurologist at HAM General Hospital Medan and recorded in medical record. Children who experienced epilepsy were more girls with 58.8% compared to 41.1% boys. The results of this study are consistent with the results of study at BLUD Cut Meutia Aceh Utara General Hospital in 2015, more epilepsy in girls 29% and boys 6.9%.[7] Steroid hormones in women produced by the ovaries will affect the severity and frequency of seizures epilepsy. Most women with epilepsy experience changes in phenotypic expenditure in response if epilepsy occurs during reproduction and the respiration cycle becomes excessive.[7,15] The frequency of seizure severity will increase during puberty, menstruation, pregnancy and menopause.[7] This increase occurs due to steroid hormones which was produced by the ovary affects the nerves in the central nervous system. Menstruation experienced in women is thought to play a role in epileptic seizures due to fluid and hormonal imbalances.[7,16]

This study found the incidence of epilepsy in children with history of FS was 12.7% consisting of 41.2% boys and 58.8% girls, with an average age of 7.2 years old. This wassame as retrospective study in Korea which found that the incidence of epilepsy after FS was 10%.[17] Prospective cohort studies in the Netherlands showed that risk of developing epilepsy after FS

was 2-5%.[18] Other studies found 7.2% of children with epilepsy with history of FS, where 8.7% of boys and 5.7% of girls.[19] In this study the incidence of epilepsy was higher than the previous study because the study site was a central public hospital in Medan. The HAMHospital Medan is a referral center, where patient visits to polyclinics and ER are quite high.

Studyresults from Korea show that frequency of FS during the first 2 years after onset of the initial seizure was associated with subsequent epilepsy.[17]The first FS in cases that later develop into epilepsy was after 2 years of age in 51.5% of cases and 35% of cases don't become epilepsy.[19] These findings support that high risk of developing FS into epilepsy, seizures are observed later in life. However, there's nosignificant correlation between age at first FS and it's development. Age at the first time FS in our study didn't have significant relationship to the incidence of epilepsy in children with history of FS, with the highest age of FS for the first time was 1 year to 2 years and 3 years to 4 years old. The results of this study are in line with other studies which state that age at onset of seizures has no effect on the level of risk of epilepsy after 2 or more years after first attack.[20] Children who have FS onset (<1 year) or late (>3 years) have risk of epilepsy higher in 2 years after FS compared to children whose onset occurs between the ages of 1 year and 3 years.[20] In infants the part of the brain that has developed is the hippocampus, lesions caused by FS at <1 year of age can become epileptogenic focus. The incidence of epilepsy in seizures is approximately 2-3 times more common in recurrent seizures.[21]

Study in Greece has shown that risk factors for seizures without provocation after FS were onset of FS at an early age, complex FS, neurodevelopmental abnormalities, abnormal EEG and family history of epilepsy.[22] The most important predictive risk factors for developing epilepsy were developmental delay/abnormal neurological examination before the onset of FS, history of complex FS (epilepticus fever status) and first generation family with epilepsy.[23] In literature, risk factors for epilepsy that develop after FS are body temperature below 39°C, complex FS, first EEG are pathological, seizures become focal and neurodeve lopmental abnormalities.[13] Logistic regression analysis shows risk of epilepsy 4.5 times greater in subjects with the first EEG after FS has become pathological and 21 times greater risk in those with neurodevelopmental disorders.[19] Other studies have found that the FS risk factors for epilepsy are age at first FS <12 months or>37 months old, history of epilepsy in the family, fever in progress <1 hour before seizure, APGAR score <4 in the first 5 minutes, history of at least 1 time complex FS, epileptic fever status, recurring seizures within 24 hours, focal seizures and neurological disorders.[24]

This study found that there's no relationship between the incidence of epilepsy with FS children who had family history of epilepsy. The results of this study found children with FS who had family history of epilepsy as much as 9.7%, which developed into epilepsy as much as 2.9%, where history of epilepsy in the family of parents (father) 75% and siblings 25%. This is in line with the results of other studies which show that there isn't established relationship between family history of epilepsy and epilepsy development.[25]This may be due to positive family history found in only one case with epilepsy after FS in this study group and for cases such as it doesn't adequately represent the study population. This study also emphasizes that the onset of FS after age of 3 years old increases risk of developing epilepsy.[25]Different from other studiesthere's relationship between epilepsy events with children with history of FS, which is 17.5% who have history of epilepsy in families. Logistic regression results show that family history of epilepsy 11 times risk of epilepsy.[26] Although FS has a good prognosis in most cases, the risk of becoming epilepsy in the presence of several risk factors including family history of FS and epilepsy can increase 9%.[27]

The types of FS in this study were 50.8% with complex FS and 49.3% with simple FS, and those that developed to FS plus were 2.9%. Study in Bali, complex FS was more dominant by 80% while simple FS was 20%.[28] Children who experienced FS as complex FS were around 58% and none had neurological abnormalities before the seizure. There're only 2 children with global developmental delayed (GDD) but both of them have been considered as simple FS in the study.[28] Risk of the development of epilepsy after simple FS was 1.5-2.4%, complex FS was 4-15%[11], and in focal FS it increases to 29%.[22] Fever causes faster body chemical reaction (oxidation reaction) which will result in oxygen intake run out quickly and cause hypoxia. Active transport that requires adenosine triphosphate (ATP) was disrupted so that intracellular Na ion levels and extracellular K ions increase which will cause membrane potential to decrease or nerve cell sensitivity to increase.[2,7] When FS will increase energy in the brain, heart, muscles, dang central temperature control. Fever will cause longer seizures so that brain damage increases. This is the risk of epilepsy in children with history of previous FS, both simple FS and complex FS.[2,7,29]

In Cohort study based on a population of more than 2 million children was found that history of FS was associated with an increased risk of epilepsy, especially between children with recurrent FS at an early age. This study observed at the relationship between recurrent FS and epilepsy risk, and the risk was very high for children who have more than 2 times FS.[30] This study found that boys compared with girls had higher risk of FS at all ages, but this gender difference didn't appear to be related to FS prognosis in terms of risk of recurrence and subsequent risk of psychiatric and neurological morbidity or mortality.[30] Previous study showed that risk of epilepsy after FS was very high in children with pre-existing neurodevelopmental comorbidities.[20]

In our study, 26.9% had family history of FS, consisting of 14.2% fathers, 3% mothers and 9.7% siblings. In line with other studies that found children with history of FS in the most families were parents (fathers) 15.3% and siblings with history of FS 11.3% and the lowest data were parents (mothers) with history of FS 4%.[28]Other studies found that about 26% were identified with positive history of FS or epilepsy in their first generation family.[4]The type of FS in this study was dominated by the general FS type rather than the focal type, which developed into epilepsy by 11.2% with the general type and as much as 1.5% for the focal type and there was no significant relationship to incidence of epilepsy. Other study, the prevalence rate of tonic-clonic seizures among other common types of seizures was 78.9% (95% CI: 68.80-89.20%) and was more prone to develop epilepsy.[31]

Genetic epilepsy syndrome clinically defined by FS plus (GEFS+). Mutations in subunit genes (SCN1A, SCN2A and SCN1B) that make up sodium channels that were given neuronal stress are reported to cause GEFS+. This study was found that FS children developed into FS plus as much as 2.9%.[32]Other studies found as many as 12% of children with history of FS becoming FS plus.[17] No single susceptibility gene for FS was known. Otherwise, gene identification has been successful in families with genetic epilepsy with FS plus abbreviated GEFS+ wasfamilial epilepsy syndrome with variety of fever-related epilepsy, especially FS plus (FS+), where FS can last up to 6 years.[33,34,35]

Our study found that speed of seizures and duration of FS had no significant relationship in epilepsy. This was in line with other studies which found no link between seizure duration and fever for seizures without provocation.[17] In large national cohort study, the incidence of epilepsy was 0.5% and

decreased with increasing gestational age to 41 weeks' gestation.[36] Preterm birth was associated with an increased risk of epilepsy and predicted to increase the risk of epilepsy (OR 1.76; 95% CI 1.30-2.38) and 0.7% of all groups have been hospitalized for lifelong epilepsy.[36] Our study found epilepsy incidence in children with history of FS and with preterm birth was 2.9%.

The weakness of this study, the incomplete initial data entered the patient and depend on parents' memories. Parents with anxiety can't remember the exact description of the focal sign and form of the seizure. The data obtained varies, the tools used are too subjective considering the age and education level of the patients interviewed.The strength of this research is that it was the first study conducted at the HAMHospital Medan, which can be used as a baseline for future research. In this study, significant factors were found in the incidence of epilepsy in children with history of FS, although further research is still needed.

Table 1. Characteristics of study samples

Characteristics	Epilepsy (n=17)	No epilepsy (n=117)
Age (years)		
Mean(SD*)	7.2(2.92)	6.6(2.99)
Gender, n(%)		
Male	7(41.11)	76(64.95)
Female	10(58.82)	41(35.04)

* SD: standard deviation

Table 2. Factors that related in the incidence of epilepsy in children with history of FS

Clinical factors	Epilepsy (n=17)	No Epilepsy (n=117)	p	PR(CI 95%)
Family history of epilepsy,n(%)			0.062[b]	2.9(1.09-7.51)
Yes	4(23.5)	9(7.7)		
No	13(76.5)	108(92.3)		
Neurological/developmental disorders,n(%)			0.001*	4.0(1.73-9.38)
Yes	6(35.3)	10(8.5)		
No	11(64.7)	107(91.5)		
Kind of febrile seizures,n(%)			0.745[a]	1.2(0.48-2.82)
Complex febrile seizures	9(52.9)	57(48.7)		
Simple febrile seizures	8(47.1)	60(51.3)		
Frequency of febrile seizures,n(%)			<0.001*	6.4(2.81-14.64)
≥4episode/year	9(52.9)	11(9.4)		
<4episode/year	8(47.1)	106(90.6)		
Gestational age,n(%)			0.047*	3.1(1.21-8.09)
Preterm birth	4(23.5)	8(6.8)		
Term birth	13(76.5)	109(93.2)		
Duration of febrile seizures,n(%)			0.136[a]	0.5(0.18-1.29)
≥15minutes	5(29.4)	57(48.7)		
<15minutes	12(70.6)	60(51.3)		
Family history of febrile seizures,n(%)			0.401[a]	1.5(0.59-3.72)
Yes	6(35.3)	30(25.6)		
No	11(64.7)	87(74.4)		
Age offirst febrile seizure,n(%)			0.951[a]	1.0(0.39-2.37)
<2years	8(47.1)	56(47.9)		
≥2years	9(52.9)	61(52.1)		
Onset of febrile,n(%)			0.358[b]	0.4(0.11-1.18)
≤24 jam	2(11.8)	29(24.8)		
>24 jam	15(88.2)	88(75.2)		
Type of febrile seizures,n(%)			0.121[b]	3.4(1.06-11.13)
Focal	2(11.8)	3(2.6)		
General	15(88.2)	114(97.4)		

* p<0.05 statistically significant with the chi square test
[a] Pearson chi-square
[b] fisher's exact

Table 3. Logistic regression test

Variable	P	OR(CI 95%)
Step I		
Family history of epilepsy	0.308	2.4(0.45-13.03)
Neurological/development disorder	0.002	17.7(2.93-107.22)
Frequency of febrile seizures	<0.001	16.7(3.95-70.18)
Kind of febrile seizures	0.715	0.7(0.12-4.24)
Duration of febrile seizures	0.037	0.2(0.05-0.91)
Gestational age	0.344	2.9(0.31-27.94)
Step II		
Neurological/development disorder	0.001	14.2(3.09-65.49)
Frequency of febrile seizures	<0.001	19.4(4.86-77.23)
Duration of febrile seizures	0.060	0.3(0.08-1.05)
Step III		

Neurological/development disorder	0.001	11.1(2.60-47.32)
Frequency of febrile seizures	<0.001	17.0(4.54-65.11)

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