



Article

The Correlation between Hemoglobin Level, Age, and Family History of Febrile Seizure with The Incidence of Febrile Seizure in Children

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ABSTRACT

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Febrile seizure is a seizure that occur when the body temperature increases and is caused by an extracranial process. There are several risk factors of febrile seizure, including hemoglobin level, age, and family history of febrile seizure. The aim of this study was to analyze the relationship between hemoglobin level, age, and family history of febrile seizure with the incidence of febrile seizure in 6-60 months children in Fatimah Hospital of Mother and Child Lamongan. This study used a case control design through retrospective approach based on data of children's medical records in Fatimah Hospital Lamongan from January-November 2021. The sample was selected by consecutive sampling method. Data analysis were using the chi square test and continued with multiple logistic regression tests. The sample of this study was 80 children, consist of each 40 children as case and control group. Most of the febrile seizure occurred in children with a low hemoglobin level (85%), in age of 6-24 months (82,4%), and have a family history of febrile seizure (65%). The result of the bivariate analysis showed that there was significant correlation between hemoglobin level ($p = 0,022$), age ($p = 0,015$), and family history of febrile seizure ($p = 0,000$) with the incidence of febrile seizure. The result of the multivariate analysis showed that the most influential variable is family history of febrile seizure ($OR=13,670$). There was significant correlation between hemoglobin level, age, and family history of febrile seizure with the incidence of febrile seizure. Family history was the most influences factor for the incidence of febrile seizure.

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INTRODUCTION

A febrile seizure is a seizure that occurs when the body temperature increases (rectal temperature exceeds 38°C) and is caused by an extracranial process¹⁻². Cases of febrile seizures that occur in Europe and America, specifically in Western Europe, the United States, and South America, have been estimated to reach 2-4% of all neurological diseases in children. Reported cases in the United States have almost reached 1.5 million cases each year. Most cases are experienced by children aged 6 months to 36 months, and the majority of cases are in children aged 18 months. The World Health Organization (WHO) has released data stating that 80% of cases of febrile seizures occur in developing countries and 10-7% of cases of febrile seizures occur in developed countries³⁻⁴. The prevalence of cases in Indonesia is recorded at 2-4%. The 2012 Indonesian Health Profile states that 10 diseases are the most common causes of patients having to be hospitalized, one of which is febrile seizures. In East Java, 2-3% of 100 toddlers have febrile seizures⁵.

Febrile seizures have risk factors that can trigger seizures, including fever (body temperature), age, gender, genetics (family history of febrile seizures), Hb levels, LBW, birth trauma, and iron deficiency anemia⁶⁻⁷. Anemia is characterized by Hb levels below normal. It causes the ability of erythrocytes to bind O₂ to decrease. O₂ is an important component in the active transport process of sodium-potassium ions which plays a role in membrane stability in nerve cells. If the membrane in a nerve cell is disturbed, depolarization will occur. When depolarization occurs and is triggered by high fever, seizures are susceptible⁷⁻⁸. In research conducted in 2018, results showed that there was a relationship between Hb levels and febrile seizures⁹.

Age at the time of the first febrile seizure is one of the risks of febrile seizures. In children aged < 24 months, the brain is still immature, this has the potential to cause seizures if triggered by fever¹⁰. In research conducted in 2019, the results showed that there was a significant relationship between age and seizures in children¹¹.

The genetic pattern of inheritance of febrile seizures cannot be explained with certainty, whether it is autosomal recessive or dominant. Febrile seizure caused by autosomal dominant penetration is estimated at 60-80%¹². A study conducted in 2019 reported that one-third of febrile seizure patients had relatives who had also experienced febrile seizures before (first-degree relatives). Children with a history of febrile seizures have a risk level of 2 to 3 times for developing febrile seizures¹³.

This study aims to analyze the relationship between Hb levels, age, and family history of febrile seizures to febrile seizures in children 6-60 months at RSIA Fatimah Lamongan and analyzing the risk factors that most influence hemoglobin levels, age, and family history of febrile seizures to febrile seizures in children 6-60 months at RSIA Fatimah Lamongan.

METHODS

This research is a type of analytical-observational research that applies a case-control design through a retrospective approach. The research was conducted at RSIA (Rumah Sakit Ibu dan Anak/ Hospital of Mother and Child) Fatimah Lamongan on December 24, 2021. The research samples were children at RSIA Fatimah Lamongan that suitable with the inclusion-exclusion criteria and were determined using consecutive sampling techniques.

The sample consisted of 2 groups, the case group and the control group. The case group was children with febrile seizures at RSIA Fatimah Lamongan, while the control group was children with fever without seizures at RSIA Fatimah Lamongan. Inclusion criteria in this study include children aged 6-60 months who have complete medical record data including complete blood laboratory examinations, specifically examination of Hb, erythrocyte, leukocyte and electrolyte levels. The exclusion criteria for this study were children with a history of seizures without fever such as epilepsy, neurological development disorders (such as autism, cerebral palsy) and children with a history of LBW.

This study used secondary data from children's medical records at RSIA Fatimah Lamongan in the period January-November 2021. The data was analyzed using the chi-square test and multiple logistic regression test which had previously been carried out for candidate selection.

The research has received ethical approval from KEPK FK Muhammadiyah University Semarang with the issuance of letter number 119/EC/FK/2021 and research permission from RSIA Fatimah Lamongan with letter number 023/RSIA_FAT/E/XII/2021.

RESULTS

Table 1. The Characteristics of The Research Sample Who Experienced Febrile Seizure

Variable	Febrile Seizure n (%)	Without Febrile Seizure n (%)	Amount n (%)
Hemoglobin Level			
Low	34 (85)	25 (62,5)	59 (73,8)
Normal	6 (15)	15 (37,5)	21 (26,3)
Amount n (%)	40 (100)	40 (100)	80 (100)
Age			
6-24 months	33 (82,5)	23 (57,5)	56 (70)
25-60 months	7 (17,5)	17 (42,5)	24 (30)
Amount n (%)	40 (100)	40 (100)	80 (100)
Family History of Febrile Seizure			
Yes	26 (65)	6 (15)	32 (40)
No	14 (35)	34 (85)	48 (60)
Amount n (%)	40 (100)	40 (100)	80 (100)

Based on table 1, the majority of children with febrile seizures have low Hb levels (85%). The highest number of children with febrile seizures were children aged 6-24 months (82.5%) and children with a family history of febrile seizures (65%).

Table 2. Bivariate and Multivariate Analysis

Variable	Febrile Seizure n (%)	Without Febrile Seizure n (%)	p Value	OR (CI 95%)	p Value multivariate	OR multivariate (CI 95%)
Hemoglobin Level						
Low	34 (85)	25 (62,5)	0,022	3,400 (1,156- 9,996)	-	-
Normal	6 (15)	15 (37,5)				
Age						
6-24 months	33 (82,5)	23 (57,5)	0,015	3,484 (1,246- 9,747)	0,012	5,355 (1,451- 19,760)
25-60 months	7 (17,5)	17 (42,5)				
Family History of Febrile Seizure						
Yes	26 (65)	6 (15)	0.000	10,524 (3,559- 31,118)	0,000	13,670 (4,011- 45,595)
No	14 (35)	34 (85)				

Based on table 2, in the variable Hb levels, it was found that there was a significant relationship between Hb levels and febrile seizures in children 6-60 months at RSIA Fatimah Lamongan ($p = 0.022$). Children with low Hb levels have a risk level 3 times higher than children with normal Hb levels (OR = 3.400; 95% CI = 1.156 – 9.996). In the age variable, it was found that there was a significant relationship between age and febrile seizures in children aged 6-60 months at RSIA Fatimah Lamongan ($p = 0.015$). Children aged 6-24 months have a risk level 3 times greater than children aged 25-60 months (OR = 3.484; 95% CI = 1.246 – 9.747). In the family history of febrile seizures variable, it was found that there was a significant relationship between family history of febrile seizures and febrile seizures in children aged 6-60 months at RSIA Fatimah Lamongan ($p = 0.000$). Children with a family history of febrile seizures have a risk 10 times higher than children without a history family febrile seizure (OR = 10.524; 95% CI = 3.559 – 31.118). Selection of independent variables is carried out before carrying out multivariate analysis to determine variables that are suitable for the multivariate test. A suitable independent variable is an independent variable that has a p value <0.025 . The results of candidate selection showed that the Hb level was not suitable as a candidate for the multivariate test ($p = 0.026$). The variables age and family history of febrile seizures are suitable candidates for multivariate testing ($p = 0.017$; $p = 0.000$). In the results of the logistic regression test, the results obtained were that the variables age and family history of febrile seizures had a p value <0.05 . The age factor influences the incidence of febrile seizures ($p = 0.012$) and has a 5 times greater chance of causing febrile seizures in children aged 6-60 months at RSIA Fatimah Lamongan (OR = 5.355; 95% CI = 1.451 – 19.760). The family history of febrile seizures influences the incidence of febrile seizures ($p = 0.000$) and

has a 13 times chance greater cause of febrile seizures in children aged 6-60 months at RSIA Fatimah Lamongan. Febrile seizures in the family were the factor that had the most influence on the incidence of febrile seizures (OR = 13.670; 95% CI = 4.011 – 45.595).

DISCUSSION

Hb levels are related to the incidence of febrile seizures in children aged 6 months – 5 years. The results obtained following the percentage of children with febrile seizures with low Hb levels, namely 85%. Children with low Hb levels are 3 times more likely to suffer from febrile seizures than children with normal Hb levels. This has similar results to research carried out in 2020 by Anggreni and Suryawan, which stated that there was a significant relationship between Hb levels and the incidence of febrile seizures ($p = 0.026$)¹⁴. Research in South Korea by Jang, Yoon, and Lee in 2019 obtained similar results that children with low Hb levels had a 3.42 times higher risk of experiencing febrile seizures than children with normal Hb levels (OR = 3.42; 95% CI = 1.31 – 8.9)¹⁵.

Hb levels below normal result in a decrease in the ability of erythrocytes to bind O₂. O₂ is an important component in the active transport activity of sodium-potassium ions which has a function as a stabilizer in nerve cell membranes. If the nerve cell membrane is unstable, it causes intracellular sodium ions to increase and has an impact on the permeability of the nerve cells which change. This results in depolarization excessive⁸. When in a seizure state, the cause of excessive depolarization is the increase in excitatory neurotransmitters compared to inhibitory neurotransmitters. Inhibitory neurotransmitter levels have decreased due to low Fe levels which contribute to GABA synthesis activity as inhibition during febrile seizures¹⁶.

The age factor is associated with febrile seizures in children aged 6-60 months. Children aged 6-24 months have a 3 times higher risk of febrile seizures than children aged 25-60 months. This research is supported by research conducted in 2017 by Rohaiza, which states that there is a significant relationship between age and the incidence of febrile seizures and children aged less than 24 months have a 3.59 times higher risk of febrile seizures ($p = 0.018$; OR = 3,596)¹⁷. However, there are differences in research conducted in 2021 by Husodo, Radhiah, and Nugraheni, which found that the age variable was not related to the incidence of febrile seizures¹⁸. The causes leading to these different results may be the result of differences in amount of sample and differences in age classification criteria.

In children < 24 months old, the brain is still immature so the regulation of brain homeostasis is unoptimal. Brain homeostasis that is unoptimal will experience changes as the brain develops and ages. At this state, it is called the Developmental window. Neural excitability in the immature

brain is higher rather than in a mature brain, therefore in this phase, it is very susceptible to seizures¹⁹.

A family history of febrile seizures is associated with febrile seizures. The results obtained are following the percentage of children with a family history of febrile seizures (65%). Children who have a family history of febrile seizures have a 10 times higher risk of having febrile seizures than children who do not have a family history of febrile seizures. These results are similar to a study carried out in 2018 by Rimadhanti, Dewi, and Aulia, namely that there was a relationship between a family history of febrile seizures and febrile seizures ($p = 0.000$; 95% CI = 2.647 – 167.868)²⁰. A family history of seizures is a risk factor that can trigger febrile seizures. Based on a study conducted in Canada Bethune, et al., there was a significant relationship between a family history of febrile seizures (first-degree relative) and febrile seizures (OR = 4.5). The genetic inheritance of febrile seizures has not been determined. Autosomal dominant inheritance is predicted to reach 60-80%. Some studies show that febrile seizures are related to mutations in chromosome 19p and 8q13-21 genes; some of them are autosomal dominant²¹.

A history of febrile seizures is the risk factor that most influences the incidence of febrile seizures. The family history of febrile seizures referred to in this study is a history of febrile seizures owned by parents or first-degree relatives. This is similar to research conducted in 2016 by Chareunnisa, which stated that a family history of febrile seizures was the risk factor that most influenced the incidence of febrile seizures (OR = 47.47; 95% CI = 9.23 – 244.1)²². If a child's mother or father has had a febrile seizure, the child has a 20-22% chance of having a febrile seizure. If both of a child's parents have had a febrile seizure, then the possibility of the child experiencing a febrile seizure increases to 59-64%²⁰.

CONCLUSION

There is a significant relationship between Hb levels, age, and family history of febrile seizures on febrile seizures in children 6-60 months old at RSIA Fatimah Lamongan. A family history of febrile seizures is the most influential factor in febrile seizures.

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