Association Between Anemia and First-time Febrile Seizure: A Case Control Study

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Abstract

Introduction: *Febrile seizure is the most frequent neurological disorder in children below five years old. The direct cause is unknown. Some studies report association between anemia and febrile seizure. Even though anemia is highly prevalent in Indonesia, only one study assessed this association.*

Objective: *To compare the hemoglobin level in children with febrile seizure and febrile children without seizure, and to assess the relationship between anemia and febrile seizure.*

Method: *This retrospective case control study used medical record of febrile children aged 6 months to 3 years old hospitalized at Landak General Hospital between May 2016 to April 2017. Hemoglobin level from first laboratory examination then compared between fifty children with first-time febrile seizure (case group) and a hundred febrile children without seizure (control group).*

Results: *Hemoglobin level was lower in case group compared to control group ($p<0,001$). Children with febrile seizure were more likely to be anemic compared to febrile children without seizure [OR 6,73; 95% CI 3,18 to 14,26].*

Conclusion: *There is a significantmean difference between hemoglobin level of children with febrile seizure compared to febrile children without seizure. Children with febrile seizure were six times more likely to have anemia.*

Keywords: *anemia, iron, seizures, febrile*

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Hubungan Anemia dengan Kejang Demam Pertama: Studi Kasus Kontrol

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Abstrak

Pendahuluan: *Kejang demam adalah gangguan neurologi yang paling sering ditemukan pada anakdibawah usia lima tahun. Penyebab langsung hingga saat ini belum diketahui. Beberapa penelitian menemukan hubungan antara anemia dengan kejang demam. Meskipun prevalensi anemia tinggi di Indonesia, hanya satu studi meneliti tentang hubungan ini.*

Tujuan: *Untuk membandingkan kadar hemoglobin pada anak demam dengan kejang dan anak demam tanpa kejang, serta menilai hubungan antara anemia dengan kejang demam.*

Metode: *Penelitian retrospektif kasus kontrol, menggunakan data rekam medis anak dengan demam berusia 6 bulan hingga 3 tahun yang dirawat di RSUD Landak dari Bulan Mei 2016 hingga April 2017. Kadar hemoglobin dari pemeriksaan sampel darah pertama pada 50 anak demam dengan kejang pertama kali (kelompok kasus) dibandingkandengan 100 anak demam tanpa kejang (kelompok kontrol).*

Hasil: *Rerata kadar hemoglobin lebih rendah pada kelompok kasus dibandingkan kelompok kontrol (p<0,001). Anak demam dengan kejang cenderung dalam kondisi anemia dibandingkan anak demam tanpa kejang [OR 6,73 denganIK 95% 3,18 – 14,26].*

Kesimpulan: *Terdapat perbedaan rerata kadar hemoglobin yang signifikan antara anak demam dengan kejang dibandingkan dengan anak demam tanpa kejang. Anak demam dengan kejang memiliki kecenderungan 6 kali lipat menderita anemia.*

Kata kunci: *anemia, besi, kejang, demam*

Introduction

The American Academy of Pediatrics (AAP) defines febrile seizure as a seizure occuring in febrile children between the age of 6 and 60 months withoutevidence of intracranial infection, metabolic disturbance, or history of seizure without fever.[1] Febrile seizure is further classified into simple or complex. Simple febrile seizure is defined as primary generalized seizure, lasted less than 15 minutes, without focal component and without recurrence within 24 hours. Complex febrile seizure is defined by having these features: partial onset or focal features, and/or lasted more than 15 minutes, and/or recurrent within 24 hours, and/or association with postictal neurological abnormalities.[2]

Population studies in Western Europe and USA report a cumulativeincidence of febrile seizure in 2-5% children below 5 years old, most of them occur between 6 months to 3 years with peak incidence of 18 months. The incidence elsewhere in the world varies between 5-10 % (India), 8,8 % (Japan), and 14 % (Guam). Data from developing country is still limited. [1-3]

The direct cause of febrile seizure is unknown, but the most important associated factors are fever, epilepsy, hypoglycemia, head injury, poisoning and drug overuse, respiratory infection, or gastroenteritis.[5]Numerous studies are looking for iron deficiency anemia as a risk factor of febrile seizure; some studies reported statistical association between iron deficiency anemia and simple febrile seizure[6,7], while other cross sectional study[8]did not found a significant association. Only one study[9] on Indonesian children is found through online literature search.

The aim of this study is to evaluate the association between anemia and febrile seizure in 6-month-old to 3-year-old children hospitalized at Landak General Hospital West Kalimantan, Indonesia.

Methods

The design of this study was retrospective case-control using data collected from medical record. The population were children aged 6 months to 3 years who were admitted at Landak General Hospital between May 2016 to April 2017. Children with first-time febrile seizure on admission were labeled as case group and children with fever without seizure, regardless cause of the fever, were grouped into

control. Fever was defined as axillar temperature more than 38^0C measured with electronic thermometer. Anemia data was collected from first complete blood count evaluationif there were several of them during hospitalization, defined as hemoglobin level below 11 g/dl without any signs of bleeding.

Sample size was estimated 150 to achieve power of 80% and alpha value 5%.[10]A sum of 55 children with febrile seizure and 104 children with fever without seizure were eligible for the study. Simple randomization was performed to acquire 50 children in case group and 100 children in control group. Data was analyzed descriptively and analytically using SPSS 17.0 for Windows software. Continuous variables were non-normally distributed and presented as mean then compared using Mann Whitney U test. Categorical data are presented as proportions and compared using Chi-square bivariate analysis.

Results

Majority of subjects are male. More than half of cases are simple febrile seizure (Table 1). No statistical difference was found in gender and age in both groups. The cause of the fever in case group was mostly acute upper and lower respiratory tract infection, while most of control group enrolled with gastroenteritis (p= 0,033). The difference between hemoglobin and hematocrit levels in both groups are statistically significant (Table 2). Table 3 gives detail of anemia proportion in both groups. Out of 50 cases, 34 (68%) children with febrile seizure had hemoglobin level below 11g/dL, while among controls 24 of 100 children (24%) had anemia. There was a significant association between anemia and febrile seizure (OR 6.73; p<0,001).

Table 1. Case Group Characteristic

	Simple Febrile Seizure	Complex Febrile Seizure	
Male, n (%)	18 (36%)	11 (22%)	29 (58%)
Female, n (%)	9 (18%)	12 (24%)	21 (52%)
Total, n (%)	**27 (54%)**	**23 (46%)**	**50 (100%)**

Table 2. Subject Characteristic

	Febrile Seizure (case)	Fever without Seizure (control)	p-value
Sex, n (%)			.562
Male	29 (58%)	53 (53%)	
Female	21 (52%)	47 (47%)	
Age, months			
Mean (SD)	16,38 (±7,96)	19,33 (±8,83)	.054
Diagnosis, n (%)			.033
Acute Respiratory Infection	23 (46%)	28 (28%)	
Gastroenteritis	14 (28%)	49 (49%)	
Other	13 (26%)	23 (23%)	
Hemoglobin, g/dL			
Mean (SD)	10,58 (±1,47)	11,33 (±1,24)	.000
Hematocrit, %			
Mean (SD)	32,73 (±4,55)	35,1 (±4,52)	.005

Table 3. Bivariate Analysis

	Febrile Seizure (case)	Fever without Seizure (control)	p-value	OR (95% CI)
Hemoglobin				
Anemia	34 (68%)	24 (24%)	.000	6.73 (3.18 to 14.26)
Normal	16 (32%)	76 (76%)		
Total	**50**	**100**		

Discussion

Febrile seizure is the most frequent neurological disorder in pediatrics. It has been reported that one in every 25 children in the population will experience at least one febrile seizure during childhood.[5]Our study found that most febrile seizures are simple and the incidence is higher in male children; similar to other studies.[6,8,9,12]

Any febrile illness can provoke a seizure. However, some studies report that febrile seizure is more likely to occur with respiratory illness[5,16] This study also found that respiratory infection (46%) is more common in case group, while gastroenteritis (49%) is predominant in control group. There is significant difference in group diagnosis between case and control (p = 0,033).

Mean age of case group in this study is 16,38 (±7,96) months and 19,33 (±8,83) months in control group (p>0,05). In general, children from 6 months to 5 years of age are more susceptible to febrile seizure, with peak incidence of 18 months. The incidence of febrile seizure overlaps with the peak incidence of iron deficiency anemia (IDA), which is 6 to 24 months.[3, 12] This fact, together with the important role of iron in neurodevelopment, gave rise to suspicion of iron deficiency anemia as a risk factor of febrile seizure.

The role of iron is presumably more than erythropoiesis; it is recognized that even without anemia, mild to moderate iron deficiency has adverse functional consequences, one of which is altered neurological function.[20]Dallman[21] proposed that reduced brain tissue iron concentrations altered cerebral energy metabolism through loss of cytochromes and inefficient ATP generation and electron transport. These findings are supported by regionally distributed losses of cytochrome *c* oxidase, a marker of neuronal energy status, particularly in the hippocampus and frontal cortex. Youdim *et al*[22] has established that iron deficiency has widespread short and long-term effects on dopamine metabolism that they postulate is due to the dependence of this neurotransmitter on the iron-containing enzyme tyrosine hydroxylase. These groups have documented significant acute effects not only

on the monoamine neurotransmitters themselves, but also on their receptors and re-uptake mechanisms. A third major neuropathology was defined by a number of investigators who noted altered fatty acid concentrations in the iron-deficient brain and postulated that iron-containing enzymes responsible for their synthesis into myelin were compromised.[23] These seminal findings laid the groundwork for the three major theories of why iron was needed for proper brain development and function in the child.

In our study, anemia is more prevalent in children with febrile seizure. This result is in accordance with other studies.[6,7,9,15-16] Vaswani *et al*[15] found 68% cases were iron deficient compared to 30% in controls, which is quite similarto this study (68% vs 24%). Some studies included in meta-analysis by Habibian et al[7] engage ferritin level as a variable to assess iron deficiency, but ferritin is an acute phase reactor that nonspecifically increases in response to any febrile illness.[7,15]In some of thosestudies[7], the severity of fever was not similar in thepatients and controls group. Consequently, ferritin level could not be compared between the two groups. Nonetheless, when groups with similar fever severity (temperature) were compared, ferritin level was found to be lower in the febrile seizure children compared with the healthy ones.

Children with anemia were 6,73 times more likely to have febrile seizure compared to non-anemic children [OR 6,73 with 95% CI 3,18 to 14,26]. This result is close to Malla *et al* study[19] in Nepalese children [OR 5,971 with 95% CI 2,938 to 12,137], while Gupta *et al*[6] and Habibian *et al*[7] reported smaller odds ratio of 2.34 and 1.52, respectively. The major causes that have led to different results between these studies may include difference in age, number of samples, and difference in the diagnostic criteria of anemia (Habibian et al is a meta-analysis study). Overall, all of studies mentioned above revealed a statistically significant relationship between febrile seizure and anemia.

The prevalence of iron deficiency anemia among children below 5 years old in Indonesia is about 40-45%.[17] The 2001 Household Health Survey (*Survey Kesehatan Rumah Tangga*) showed theprevalence of iron deficiency anemia were 61,3%, 64,8%, and 48,1% for baby 0-6 months old, 6-12 months old, and children below 5 years old, respectively.[14] This is due to the rapid phase of growth between 4 and 12 months. By 4 months of age, neonatal iron stores have been reduced by half, so exogenous iron is required to maintain hemoglobin concentration.[18]As anemia is the most common manifestation of iron deficiency, the terms anemia, iron deficiency, and iron deficiency anemia are sometimes used interchangeably. WHO proposed that anemia prevalence of more than 40% is severe public health significance.[13]

The limitation of this study is as a hospital-based study, the result might not be generalized. This study also did not assess the recurrence of febrile seizure after iron supplementation.

Conclusion

The difference of hemoglobin level between children with febrile seizure and febrile children without seizure is statistically significant. Children with anemia were six times more likely to have febrile seizure compared to non-anemic children.

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