



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

Handoyo

General Practitioner, Landak General Hospital, Landak Regency, West Kalimantan, Indonesia

ABSTRACT

Background. Febrile seizure is the most frequent neurological disorder in childhood. 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 from May 2016 to April 2017. Hemoglobin level from first blood workup 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 ($p = 0.000$). Children with febrile seizure were more likely to be anemic compared to febrile children without seizure [OR 6.73 with 95% CI 3.18 to 14.26]. **Conclusion.** There is significant difference of mean hemoglobin among children with febrile seizure compared to febrile children without seizure. Children with febrile seizure were six times more likely to have anemia.

Keywords: Anemia, febrile, iron, seizures

ABSTRAK

Latar belakang. Kejang demam adalah gangguan neurologi yang paling sering ditemukan pada anak. Beberapa penelitian menemukan hubungan antara anemia dan kejang demam. Meskipun prevalensi anemia tinggi di Indonesia, hanya satu studi meneliti tentang hubungan ini. **Tujuan.** Untuk membandingkan kadar hemoglobin pada anak dengan kejang demam dan anak demam tanpa kejang, serta menilai hubungan antara anemia dan 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) dibandingkan dengan pemeriksaan 100 anak demam tanpa kejang (kelompok kontrol). **Hasil.** Rerata kadar hemoglobin lebih rendah pada kelompok kasus dibandingkan kelompok kontrol ($p = 0.000$). Anak demam dengan kejang cenderung dalam kondisi anemia dibandingkan anak demam tanpa kejang [OR 6.73, 95%K 3.18 - 14.26]. **Simpulan.** Terdapat perbedaan signifikan rerata kadar hemoglobin antara anak demam dengan kejang dibandingkan dengan anak demam tanpa kejang. Anak demam dengan kejang memiliki kecenderungan 6 kali lipat menderita anemia. **Handoyo. Asosiasi antara Anemia dan Kejang Demam episode Pertama: Studi Kasus Kontrol**

Kata kunci: Anemia, besi, kejang, demam

INTRODUCTION

The American Academy of Pediatrics (AAP) defined febrile seizure as brief (<15 minute) generalized seizure occurring once during 24-hour period in febrile children between the age of 6 and 60 months who do not have intracranial infection, metabolic disturbance, or history of afebrile seizures.¹ Febrile seizure is further classified into either simple or complex. Simple febrile seizure is defined as generalized, lasting less than 15 minutes, compromising tonic and clonic activities 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 duration longer than 15 minutes, and/or recurrence within 24 hours, and/or association with postictal neurological abnormalities.²

Population studies in Western Europe and USA report a cumulative incidence of febrile seizure in 2-5% children below 5 years old, most of them occur between 6 months to 3 years with 18 months as peak incidence. 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 risk factor of febrile seizure; some studies reported a statistical association between iron deficiency anemia and simple febrile seizure,^{6,7} while other cross sectional study⁸ has not found a significant association. Only one study⁹ on Indonesian children is found



HASIL PENELITIAN

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

This study was retrospective case-control using medical record data. The population was children aged 6 months to 3 years admitted at Landak General Hospital from May 2016 to April 2017. Children with first-time febrile seizure at admission were labeled as case group and children with fever without seizure, regardless the cause of the fever, were grouped into control. Fever was defined as axillar temperature over 38°C measured with electronic thermometer. Anemia data was collected from first complete blood count workup, and 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.

RESULT

Majority of subjects are male. More than half of cases are simple febrile seizure (**Table 1**). No statistical differences in gender and age in both groups. Most children with febrile seizure had acute respiratory infection (upper and lower) as the cause of the fever, while most control group enrolled with gastroenteritis ($p = 0.033$). Hemoglobin and hematocrit count were significantly different between two groups (**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%) were anemic. There was a significant association between anemia and febrile seizure (OR 6.73;

$p = 0.000$).

DISCUSSION

Febrile seizure is the most frequent neurological disorder in the pediatrics. It has been reported that one in every 25 children in the population will experience at least one febrile seizure during childhood.⁵ Most febrile seizures are simple and there is higher incidence in male children;^{6,8,9,12} findings in this study are similar.

Any febrile illness can provoke a seizure, 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 ($p = 0.033$) but it might be because of difference in sample size of each group.

Table 1. Case Group Characteristic

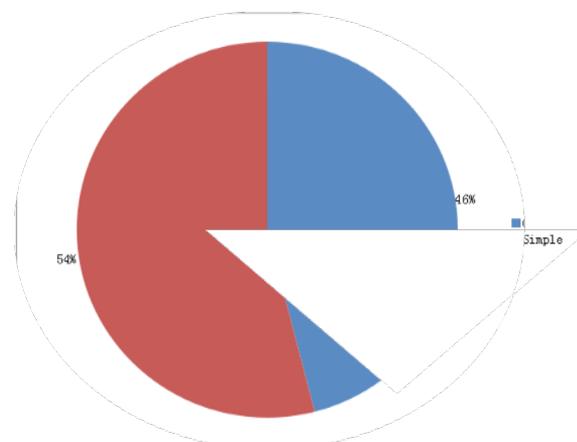
	Simple Febrile Seizure	Complex Febrile Seizure	
Male, n (%)	18 (36%)	11 (22%)	29 (58%)
Female, n (%)	9 (18%)	12 (24%)	21 (52%)
	27 (54%)	23 (46%)	50 (100%)

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		



Picture 1. Case Group Characteristic of Febrile Seizure

HASIL PENELITIAN



Generally children 6 months to 5 years of age are more prone to febrile seizure; peak incidence is 18 months which overlaps with the peak incidence of iron deficiency anemia (IDA) which is from 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. Mean age of febrile seizure group in this study is 16,38 ($\pm 7,96$) months compared to 19,33 ($\pm 8,83$) months in control group ($p > 0.05$).

This result is in accordance with other studies,^{6,7,9,15-6} that anemia is more prevalent in children with febrile seizure. Vaswani, *et al*,¹⁵ found 68% cases were iron deficient compared to 30% in controls, which is quite similar with 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 studies included by Habibian, *et al*,⁷ the severity of fever was not similar in the febrile seizure patients and controls. 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 FC children compared with the healthy ones; because ferritin is an acute phase reactor, it could rise in any inflammatory diseases.^{7,15} Consequently when a study included ferritin as a variable, severity of the fever as a marker of inflammation should be controlled to prevent fever became confounding factor.

Children with febrile seizure were 6.73 times more likely to have anemia compared to febrile

children without seizure [OR 6.73 with 95% CI 3.18 to 14.26]. This result is close to Malla, *et al*, study¹⁹ 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). On the whole, 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 (Survei Kesehatan Rumah Tangga) showed that prevalences 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 because the rapid phase of growth between 4 and 12 months, and by 4 months of age neonatal iron stores have been reduced by half, so exogenous iron is required to maintain haemoglobin concentration.¹⁸ Because anemia is the most common indicator for 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 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

Dallman²¹ 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.

This was a hospital based study, so the result might not be generalized. This study also didn't 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 febrile seizure were six times more likely to have anemia compared to febrile children without seizure.

REFERENCES

1. Steering Committee on Quality Improvement and Management; Subcommittee on Febrile Seizures American Academy of Pediatrics. Febrile seizures: Clinical practice guideline for the long-term management of the child with simple febrile seizures. *Pediatrics* 2008;121:1281-6.
2. Kimia AA, Bachur RG, Torres A, Harper MB. Febrile seizure: Emergency medicine perspective. *Curr Opin Pediatr*. 2015;27:292-7. doi:10.1097/MOP.0000000000000220.
3. Waruiru C, Appleton R. Febrile seizure: An update. *Arch Dis Child*. 2004;89:751-6. doi: 10.1136/adc.2003.028449.
4. Berg AT, Shinnar S, Hauser WA, Alemany M, Shapiro ED, Salomon ME, et al. A prospective study of recurrent febrile seizure. *NEJM*. 1992;327(16):1122-7.
5. Delpisheh A, Veisani Y, Sayehmiri K, Fayyazi A. Febrile seizures: Etiology, prevalence, and geographical variation. *Iran J Child Neurol*. 2014;8(3):30-7.
6. Gupta S, Argawal N, Maheshwari M. Iron deficiency as a risk factor for febrile seizure: A case control study. *PJSR*. 2015;8(2):37-40.
7. Habibian N, Alipour A, Rezaianzadeh A. Association between iron deficiency anemia and febrile convulsion in 3- to 60-month old children: A systematic review and meta-analysis. *Iran J Med Sci*. 2014;39(6):496-505.
8. Heydarian F, Vatankhah H. The role of anemia in first simple febrile seizure in children aged 6 months to 5 years old. *Neurosciences (Riyadh)*. 2012;17:226-9.
9. Dasmayanti Y, Anidar, Imran, Bakhtiar, Rinanda T. Hubungan kadar hemoglobin dengan kejang demam pada anak usia balita. *Sari Pediatri*. 2015;16(5):351-5.
10. Madiyono B, Moeslichan S, Sastroasmoro S, Budiman I, Purwanto SH. Perkiraan besar sampel. In: Sastroasmoro S, Ismael S, editors. *Dasar-dasar metodologi penelitian klinis*. 5th ed. Jakarta: Sagung Seto; 2014. p. 352-87.



HASIL PENELITIAN

11. Forsgren L, Sidenvall R, Blomquist HK, Heijbel J. A prospective incidence study of febrile convulsions. *Acta Paediatr Scand.* 1990;79:550–7.
12. Alvarez-Uria G, Naik PK, Midde M, Yalla PS, Pakam R. Prevalence and severity of anaemia stratified by age and gender in rural India. *Anemia.* 2014;ID 176182. doi:10.1155/2014/176182.
13. World Health Organization. Iron deficiency anemia: Assessment, prevention, and control. A guide for programme managers. Geneva: WHO; 2001.
14. Untoro R, Falah TS, Atmarita, Sukarno R, Kemalawati R, Siswono. Anema gizi besi. In: Untoro R, Falah TS, Atmarita, Sukarno R, Kemalawati R, Siswono, editors. *Gizi dalam angka sampai tahun 2003.* Jakarta: DEPKES; 2005. p. 41-4.
15. Vaswani RK, Dharaskar PG, Kulkarni S, Ghosh K. Iron deficiency as a risk factor for first febrile seizure. *Indian Pediatr.* 2009;47:437–9.
16. Sharif MR, Kheirkhah D, Madani M, Kashani HH. The relationship between iron deficiency and febrile convulsion: A case-control study. *Glob J Health Sci.* 2016; 8(2):185–9.
17. Helen Keller International (Indonesia). Iron deficiency anemia in Indonesia. Jakarta;1997 .p. 1-16.
18. Booth IW, Aukett MA. Iron deficiency anaemia in infancy and early childhood. *Arch Dis Child* 1997;76:549-54. doi: 10.1136/adc.76.6.549.
19. Malla T, Malla KK, Sathian B, Chettri P, Singh S, Ghimire A. Simple febrile convulsion and iron deficiency anemia: A co-relation in Nepalese children. *American Journal of Public Health Research.* 2015;3(5A):11-6. doi: 10.12691/ajphr-3-5A-4.
20. Scrimshaw NS. Functional consequences of iron deficiency in human populations. *J Nutr Sci Vitaminol.* 1984;30:47-63.
21. Dallman PR. Biochemical basis for the manifestations of iron deficiency. *Annu Rev Nutr.* 1986;6:13–40.
22. Youdim MBH, Sills MA, Heydorn WE, Creed GJ, Jacobowitz DM. Iron deficiency alters discrete proteins in rat caudate nucleus and nucleus accumbens. *J Neurochem.* 1986;47:794–9.
23. Beard JL, Wiesinger JA, Connor JR. Pre- and postweaning iron deficiency alters myelination in Sprague–Dawley rats. *Dev Neurosci.* 2003;25:308–15.