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# Association between Microcytic-hypochromic Anemia and Simple Febrile Seizure in Children

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***Abstract---****Aims: This research aims to assess the impact of microcytic-hypochromic anemia on first febrile seizures in children, given its high incidence in developed countries like Indonesia. Settings and Design: This study was conducted in a regional general hospital setting. Methods and Material: We conducted a prospective cross-sectional study including 50 patients aged 6 months to 5 years old over 14 months. Patients were divided into 2 groups: Controls were the age and sex-matched febrile children without accompanying seizures, and the case group admitted with a first simple febrile seizure. Both case and control groups were normal in growth. To provide 95% confidence and 80% power in statistical analysis, a sample size of 25 for each group was calculated. Data including age, gender, body temperature, seizure characteristics, family history of febrile seizure, and laboratory findings consisting of hemoglobin, hematocrit, and mean corpuscular volume (MCV) were recorded. Anemia is defined as having hemoglobin level of less than 10.5 g/dl in children aged 6 months to 2 years old and less than 11.5 g/dl in 2 to 6-year-old patients. Simple febrile seizures were single, generalized convulsions lasting less than 15 minutes that occurred between the age of six and 60 months with a temperature of 38 degree centigrade or higher, that was not secondary to central nervous system infection or any metabolic imbalance and in the absence of a history of prior afebrile seizure. The inclusion criteria were patients aged 6 months to 5 years old with first simple febrile seizure and with normal growth and development. Exclusion criteria were neurodevelopment delay, previous history of febrile convulsion or epilepsy, complex febrile seizures, meningoencephalitis, metabolic disorders, moderate to severe dehydration, congenital heart disease, chronic renal failure, and incomplete data in the records. Statistical analysis used: The data was analyzed using SPSS Version 17 statistical software. The chi-square test was used for data analysis of qualitative variables, and mean values were compared using an independent T-test. Differences were considered significant at P-values of less than 0.05. Results: In the present study the median age of children with febrile seizure was 25.6±13.2 months. There were no significant differences between the sexes in both groups. The nutritional status of patients with febrile seizures was slightly worse than that of the control group with a higher presentation of patients with malnutrition (40% and 24%, respectively). The most frequent cause of fever in cases of febrile seizures was URTI (36%) while in the control group, gastroenteritis was the most common cause (32%). Anaemia was significant in febrile seizure cases as compared to control cases. Our study showed significantly low haemoglobin in the case group (mean 8.68±2.67) as compared to the control group (mean 11.17±1.12) which was significant. Other haematological indicators mean Haematocrit, MCV, MCH, and MCHC were significantly lower in the case group than control group. Conclusions: Microcytic-hypochromic anemia was not strongly associated with higher rates of febrile seizures. Anemia may be a risk factor for febrile seizures in children. Children with FS should be assessed and treated for anemia. Iron status workup and supplementation should be recommended for children in impoverished nations with a high prevalence of IDA, as well as those with established risk factors for febrile seizure.*
***Keywords---****anemia, children, febrile seizure, microcytic-hypochromic anemia.*

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## Introduction

Febrile seizures are generalized seizures, typically in children between the ages of 6 months and 5 years, that occur with a fever greater than 100.4 °F (38 °C) not associated with a central nervous system (CNS) infection, a known seizure-provoking etiology (eg, electrolyte imbalance, hypoglycemia, or substance abuse), or history of an afebrile seizure. Febrile seizures are categorized as simple febrile seizures, consisting of a single seizure lasting 15 minutes or less, or complex febrile seizures, characterized by multiple seizures occurring within 24 hours with focal neurologic features or a seizure lasting 15 minutes or more (Sawires et al., 2022).

A febrile seizure is further classified into either simple or complex. A simple febrile seizure is defined as generalized, lasting less than 15 minutes, compromising tonic and clonic activities without a focal component and recurrence within 24 hours. A 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 (Kimia et al., 2015). Children with simple febrile seizures usually have a good prognosis, with no evidence of increased rates of mortality, hemiplegia, or cognitive deficits (Jang et al., 2019).

The incidence of febrile seizures is estimated to be between 2% and 5% in the United States and Western Europe. Some studies have found a higher incidence of 8%–10% in Asian populations. The peak incidence of a first febrile seizure is in the second year of life, with 90% of children experiencing their first febrile seizure by the age of 3 years. Febrile seizures occur most frequently in the winter months, concurrently with febrile episodes. Some studies have found a higher incidence of febrile seizures in males, and others have found no significant difference based on gender (Eilbert & Chan, 2022).

The primary febrile seizure risk factors appear to include existing neurologic impairment, the presence of a viral infection, a family history of seizure, developmental delay, decreased serum zinc and iron levels, and maternal smoking and stress (Sawires et al., 2022).

Genetic factors seem to play a role in febrile seizures, with approximately one-third to one-half of children with febrile seizures having a family history thereof (Veisani et al., 2013). Viral infections, commonly influenza, adenovirus, parainfluenza, and herpesvirus-6 (roseola infantum), are the pathogens most often responsible for febrile seizures (Chung & Wong, 2007). Otitis media is the most common cause of febrile seizures caused by a bacterial pathogen (Teran et al., 2012). Febrile seizures may occur after the administration of certain vaccines, most commonly those containing measles (measles, mumps, and rubella), combined diphtheria-tetanus toxoids-pertussis, pneumococcal conjugate vaccine (PCV 13), and influenza vaccines (Li et al., 2018). Furthermore, infants generally have a lower seizure threshold, which may be modified by certain medications and water and electrolyte imbalances (eg, hyponatremia). Iron, zinc, vitamin B12, folic acid, selenium, calcium, and magnesium deficiencies increase the risk of febrile seizures (Leung et al., 2018).

Hemoglobin is a substance found in erythrocytes, which transport oxygen and nutrients throughout the body, including neurological tissue. If hemoglobin levels fall, the carrying capacity of oxygen to tissues decreases, resulting in hypoxia in bodily tissues. Oxygen is essential for maintaining nerve cell membranes during the transfer of Na+K+ ions. Unstable nerve cell membranes raise the intracellular concentration of Na+ ions, resulting in depolarization. When this condition is in permanent condition, it might cause febrile seizures when the body temperature rises if there is a fever (Tarhani et al., 2022).

Iron deficiency anaemia is the most common form of microcytic-hypochromic anemia and the most frequent micronutrient deficit worldwide (30%), particularly in developed countries (50%), and it is more prevalent in children aged 6 to 24 months. The prevalence of child anemia in Indonesia, based on 2013 Indonesian Basic Health Research (*Riskesdas)* data, is 28.1%. This figure increased from the previous year in 2007 to only 27.7%. Then it increased again in 2018 at Riskesdas showing a figure of 38.5%. Because it is a preventable cause, the frequency of febrile seizures can be reduced by addressing nutritional anaemia with diet and iron supplements. Iron deficiency decreases the metabolism of several neurotransmitters, including monoamine and aldehyde oxidase, which may modify a child's seizure threshold. In addition, the expression of cytochrome C oxidase, a measure of neuronal metabolic activity, is lowered in iron deficiency anemia (Thirupathi & Chang, 2019).

Iron is an essential trace element for the growth and development of humans. Iron compounds are also involved in other redox processes, including oxygen transport, the cellular oxidative respiratory chain, the tricarboxylic acid cycle, and DNA synthesis. However, in the neurological system, iron is strongly linked to myelin formation, catecholamine neurotransmitter metabolism, intellectual development, and neurodegenerative disorders (Chaudhary et al., 2021). Iron deficiency anemia was shown to be substantially linked with febrile seizures. Iron deficiency may be regarded as one of the risk factors for febrile seizures in children (Aziz et al., 2017).

This research aims to assess the impact of microcytic-hypochromic anemia on first febrile seizures in children, given its high incidence in developed countries like Indonesia. If there is an association between anemia and febrile seizures, it is advocated to do a complete blood count and screening for anemia in patients with febrile seizures, as well as children with risk factors (Sutarini & Windiyanto, 2023).

## Subjects and Methods

We conducted a prospective cross-sectional study including 50 patients aged 6 months to 5 years old over 14 months in Waikabubak General Hospital, Sumba, East Nusa Tenggara, and Lende Moripa Christian Hospital, Waikabubak, East Nusa Tenggara in Indonesia. Patients were divided into 2 groups: Controls were the age and sex-matched febrile children without accompanying seizures, and the case group admitted with the first simple febrile seizure. Both case and control groups were normal in growth. To provide 95% confidence and 80% power in statistical analysis, a sample size of 25 for each group was calculated. Data including age, gender, body temperature, seizure characteristics, family history of febrile seizure, and laboratory findings consisting of hemoglobin, hematocrit, and mean corpuscular volume (MCV) were recorded. Anemia is defined as having hemoglobin level of less than 10.5 g/dl in the 6 months to 2-year-old ones and less than 11.5 g/dl in the 2 to 6-year-old patients. Simple febrile seizures were single, generalized convulsions lasting less than 15 minutes that occurred between the age of six and 60 months with a temperature of 38 degrees centigrade or higher, that was not secondary to central nervous system infection or any metabolic imbalance and in the absence of a history of prior afebrile seizure. The inclusion criteria were patients aged 6 months to 5 years old with first simple febrile seizure and with normal growth and development. Exclusion criteria were neurodevelopment delay, previous history of febrile convulsion or epilepsy, complex febrile seizures, meningoencephalitis, metabolic disorders, moderate to severe dehydration, congenital heart disease, chronic renal failure, and incomplete data in the records.

The data was analyzed using SPSS Version 17 statistical software. The chi-square test was used for data analysis of qualitative variables, and mean values were compared using an independent T-test. Differences were considered significant at P-values of less than 0.05. This study was approved by the Study Ethics Committee of Waikabubak General Hospital, Sumba, East Nusa Tenggara.

## Results

In the present study, the median age of children with febrile seizures was 25.6±13.2 months. There were no significant differences between the sexes in both groups. The nutritional status of patients with febrile seizures was slightly worse than that of the control group with a higher presentation of patients with malnutrition (40% and 24%, respectively). The most frequent cause of fever in cases of febrile seizures was URTI (36%) while in the control group, gastroenteritis was the most common cause (32%). Anaemia was significant in febrile seizure cases as compared to control cases. Our study showed significantly low haemoglobin concentration in the case group (mean 8.68±2.67) as compared to the control group (mean 11.17±1.12) which was significant. Other haematological indicators mean Haematocrit, MCV, MCH, and MCHC were significantly lower in the case group than a control group

Table 1
General Characteristic (n=50)

| General Characteristics | Case (%) | Control (%) | Total |
|---|---|---|---|
| **Gender** | | | |
| Male | 16 | 15 | 31 |
| Female | 9 | 10 | 19 |
| **Age (in months)** | | | |
| Mean ± SD | 25.6±13.2 | 25.1±14.2 | |
| **Body temperature** | 39.63±0.83 | 39.30±1.46 | |
| **Nutritional status** | | | |
| Underweight | 10 | 6 | |
| Normoweight | 11 | 15 | |
| Overweight | 4 | 4 | |
| **Family history of febrile seizure** | 5 | 0 | |

| Etiology of fever | Case (%) | Control (%) | Total |
|---|---|---|---|
| Upper respiratory tract infection | 9 | 4 | |
| Acute gastroenteritis | 6 | 8 | |
| Lower respiratory tract infection | 3 | 3 | |
| Acute otitis media | 0 | 0 | |
| Urinary tract infection | 0 | 1 | |
| Pyoderma | 2 | 1 | |
| Dengue | 3 | 4 | |
| Fever without localizing sign | 2 | 4 | |

| Variables | Group | Mean | Std | P-value |
|---|---|---|---|---|
| **Hb** | Case | 8.68 | 2.67 | 0.0001 |
| | Control | 11.17 | 1.12 | |
| **Hct** | Case | 29.78 | 4.18 | 0.006 |
| | Control | 32.60 | 2.57 | |
| **MCV** | Case | 66.89 | 7.70 | 0.0001 |
| | Control | 75.06 | 5.39 | |
| **MCHC** | Case | 25.75% | 3.45 | 0.022 |
| | Control | 27.92% | 3.04 | |

| Group | Case | Control | OR | 95% CI | P-value |
|---|---|---|---|---|---|
| Anemia | 17 | 11 | | | |
| Non-Anemia | 8 | 15 | 2.89 | 0.92 – 9.10 | 0.068 |
| Total | 25 | 25 | | | |

**Discussion**

In the present study, the median age of children with febrile seizures was 25.6±13.2 months, which is following the literature. Simple febrile convulsions are common among 2–5% of children from 6 months to 5 years. Microcytic-hypochromic Anaemia is a major risk factor found aggravating febrile seizure in many studies. Some studies showed protective effects on it and others found no association with febrile seizure. In Pakistan, studies showed an association of iron deficiency which is a form of microcytic-hypochromic anaemia with febrile seizure as an aggravating factor (Soindemi et al., 2022).

First time, the association of microcytic-hypochromic Anaemia with febrile seizure was studied by Pisacaneet *et al*. In his study, microcytic-hypochromic Anaemia was significant in febrile seizure cases as compared to control cases. Our study showed significantly low haemoglobin in the case group (mean 8.68±2.67) as compared to the control group (mean 11.17±1.12) which was significant.

In this study, the incidence of microcytic-hypochromic anemia in the febrile convulsion group was higher than in the control group. Anemia was almost twice as common in children with febrile seizures compared with age-matched controls with fever. This is also following a previous study in a similar clinical setting by Sutarini and Windiyanto stating that there is a relationship between the incidence of febrile seizures and the incidence of microcytic hypochromic anemia (Zhang et al., 2023; Aroor et al., 2024).

In our study, other haematological indicators mean Haematocrit, MCV, MCH, and MCHC were significantly lower in the case group than the control group. In Egyptian children, Boshra et al showed mean haemoglobin, haematocrit and MCH significantly low in simple febrile fits case as compared to the control group. Similarly, an Indian study done by Srinivasa et al showed low Haemoglobin, MCV, and MCHC in febrile fit cases as compared to control.

Febrile seizure recurs in approximately 30% of children experiencing a first episode, in 50% after two or more episodes and 50% of children younger than one year at febrile seizure onset. There are many risk factors for the recurrence of febrile seizures such as younger age at onset, duration of fever < 24 hours, low-grade fever (38$^{o}$C to

39ºC), family history of febrile seizures or epilepsy, and maternal smoking and alcohol consumption during pregnancy.

The present study didn't show a significant difference in the association of microcytic-hypochromic anemia between the two types of febrile seizure: simple and complex febrile seizure. This finding is following a recent study done in South Korea where none of the hematological parameters showed any significant difference between simple and complex febrile seizures. Another study done in Jordan demonstrated significantly low Hb levels in complex febrile seizure as compared to simple febrile seizure (Millichap & Millichap, 2006).

The developing brain is more susceptible to febrile and other seizures. Experimental evidence has suggested that maturational changes of both inhibitory and excitatory neurotransmitters and other mechanisms influence the developing brain's susceptibility to seizure activity. Others have explored the role of viral infection in the etiology of febrile seizures. The mechanisms proposed include the generation of fever, the degree of fever, or an elevated/inappropriate response to cytokines generated in association with infection. With advances in molecular genetics, there are also attempts at identifying causative genetic mutations in family groupings responsible for febrile seizures. The effects of ID on the developing brain have been studied in a variety of animal models. Abnormalities in brain iron metabolism, myelination, and neurotransmitter activity have been demonstrated in ID. One may therefore hypothesize that the disruption of normal neurotransmitter activity caused by ID may be the mechanism that predisposes children with ID to febrile seizures. Further work in this area using an animal model of febrile seizure and ID to attempt to elucidate the mechanism is warranted (Zareifar et al., 2012; Kubota et al., 2020; Baumann & Duffner, 2000).

Iron is an essential micronutrient that affects the immunity, health, and nutritional status of children. Iron deficiency may alter the level of excitatory neurotransmitters like monoamine oxidase and aldehyde oxidase leading to decreased excitation of the neurons. Its deficiency may cause poor health and recurrent infections, which may lower the seizure threshold resulting in seizures, especially in children in developing countries. In our study, also, underweight, stunting, and wasting were associated more with febrile seizure than with controls. Another Nepalese study also showed that more cases (58.4%) were underweight than the controls (41.6%) but this was not statistically significant. The causes of microcytic-hypochromic anemia are very diverse, it can be caused by iron deficiency anemia, anemia due to chronic disease, and thalassemia. The limitation of this study, iron deficiency marker parameters (serum iron, TIBC, ferritin) were not examined so the exact relationship between iron deficiency anemia and the incidence of febrile seizures cannot be ascertained. For further study, iron status parameters should be assessed to determine the association between iron deficiency anemia and febrile seizure (Shah et al., 2010; Dutta et al., 2020; Pollitt, 2001).

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