

## Exclusive breastfeeding for 6 months is associated with reduced risk of febrile seizure

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### Abstract

**Background** Febrile seizure (FS) is the most common convulsion disorder without an intracranial abnormality in children aged 6 months to 5 years. Risk factors for FS vary from maternal illness during pregnancy to pediatric nutritional factors, such as micro-nutrient deficiency or history of exclusive breastfeeding (EBF). The WHO recommends breastfeeding for up to 6 months because breastmilk contains numerous protective factors that may influence immune system development.

**Objective** To analyze the relationship between FS and EBF and other potential risk factors in children aged 6-60 months.

**Methods** This paired case-control study used patient medical record data from Wangaya Hospital, Denpasar, Bali, from 2019-2020. Subjects were included by a purposive sampling technique, matched by age group. Children aged 6 to 60 months with fever  $>38^{\circ}\text{C}$  and seizures were allocated to the case group; those with fever but without seizures were allocated to the control group. Patients with intracranial disorders, born prematurely, or with incomplete medical record data were excluded. Data were analyzed using McNemar test, with P values  $<0.05$  deemed to be statistically significant.

**Results** Of 92 participants, 46 children were allocated into each group. There were no significant differences of gender, delivery method, or birth weight between the case and control groups. Febrile seizure was significantly greater in subjects with a family history of all seizures, overweight nutritional status, and who were non-EBF. McNemar analysis showed that EBF children had significantly lower risk of FS compared to non-EBF children (OR 0.74; 95% CI 0.15 to 3.55;  $P=0.017$ ). Additionally, positive family history of FS was also a significant factor (OR 4.33; 95% CI 0.25 to 76.04;  $P=0.021$ ), but not with the overweight nutritional status.

**Conclusion** Exclusive breastfeeding is associated with reduced risk of FS in children aged 6 months to 5 years. [Paediatr Indones. 2024;64:463-8; DOI: <https://doi.org/10.14238/pi64.6.2024.463-8>].

**Keywords:** febrile seizure; exclusive breastfeeding; risk factor

Febrile seizure (FS) refers to a seizures that begin with fever  $>38^{\circ}\text{C}$ , without central nervous system infection neither electrolyte imbalance.<sup>1,2</sup> Seizures usually occur among children aged 6-60 months,<sup>1-4</sup> as shown by several studies that demonstrated that most FS (65-85%) occurs in children aged 6 months to 3 years, with a peak at the age of 18 months.<sup>3,5,6</sup>

Febrile seizure is the most common type of seizure in children. In general, 2-5% of children under 5 years have experienced FS.<sup>2,4</sup> In East Asia, the prevalence of FS was reportedly 8-11%.<sup>7</sup> The prevalence in Japan ranged from 3.4-11%,<sup>8</sup> while India reported 10.1%.<sup>7</sup> The prevalence in Guam even reached 14%.<sup>4</sup> However, there is still a lack of data regarding the prevalence of FS in Indonesia.

Although most FS patients completely recover, and, thus, have a good prognosis, some patients may experience recurrence in as many as 1 out of 3 cases, leading to epilepsy in 2-7% of cases.<sup>4</sup> Parents, even though they understand that FS usually do not cause

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serious complications, are typically worried when their child has a seizure and are often concerned seizures will affect their child's growth and development.<sup>4,6,9</sup>

Risk factors of FS include maternal disease during pregnancy, difficulties in the birth process, premature birth, family history of seizures, persistent high-grade fever, and age at the first seizure episode.<sup>4,10</sup> In addition, nutritional factors also play a role in increasing the risk of FS, such as iron, zinc, calcium, and sodium deficiencies, hypoglycemia, and history of non-exclusive breastfeeding.<sup>3,4,5</sup>

Exclusive breastfeeding (EBF) is defined as no food or drink, not even water, other than breastmilk for the first 6 months of life.<sup>11,12</sup> Breastmilk contains macronutrients, vitamins, mineral growth factors, hormones, and protective factors which are components of the maternal immune system. The WHO recommends EBF for up to 6 months based on several studies that showed the practice to reduce the incidence of respiratory and digestive infections.<sup>13</sup> The Indonesian government also supports the EBF program to help protect infants from various infections.<sup>8</sup> However, according to the *Indonesian Ministry of Health*, the rate of EBF in Indonesia is still relatively low, at only 37.3%.<sup>11</sup> This rate is still far below the WHO recommendation of 50%.<sup>8,11,12</sup>

Several studies reported that EBF was protective against FS.<sup>14-16</sup> However, such studies have been limited in Indonesia. Because of the low rate of EBF in Indonesia and the general lack of Indonesian studies on EBF as a protective factor against FS, we aimed to analyze this relationship and other potential risk factors of FS in children aged 6 to 60 months.

## Methods

This case-control study was conducted at Wangaya Regional Public Hospital, Denpasar, Indonesia from November 2020 - January 2021, using medical record data of pediatric patients with FS who visited Wangaya Hospital in 2019-2020. Subjects were included by purposive consecutive sampling, which was carried out sequentially during the study period until the required number of subjects was fulfilled. In this study, the ratio between the case and control groups was 1:1, and subjects were age-matched by group (6 mo-1year, >1 to 3 years, and >3 to 5 years). The inclusion criteria

were (1) children aged 6-60 months (5 years), and (2) experienced fever > 38°C accompanied by seizures for the case group and fever > 38°C without seizures for the control group. The exclusion criteria were (1) patients with history of cerebral palsy, epilepsy, or other intracranial disorders, (2) premature birth, or (3) incomplete medical records. Medical records must have had the following information: age, gender, nutritional status, EBF status, family history of seizure, delivery method, and birth weight. The minimum required sample size was calculated based on the two-paired categorical group study formula, with type one error of 5% ( $Z\alpha=1.96$ ), type 2 error of 20% ( $Z\beta=0.84$ ), odds ratio (OR) of 0.5 considered to be significant,<sup>14</sup> and proportion of discordance of 0.4. Hence, a minimum sample size of 40 was needed for each group.

Univariate analysis was used to obtain characteristic distribution data. Data are displayed with sample frequency distribution table based on the characteristics of subjects. Bivariate analyses were done with McNemar test and Wilcoxon test using SPSS *version 25* software for Mac OS. The relationship between variables and outcome was shown by OR, with 95% confidence interval (CI). Results with P values <0.05 were considered to be statistically significant. This study was carried out with anonymity and confidentiality, and was approved by the Ethics Review Board of Wangaya Hospital, Denpasar, Bali.

## Results

A total of 92 children aged 6-60 months were enrolled, with 46 children allocated into each group. The distribution of subjects based on gender, age, nutritional status, delivery method, birth weight, breastfeeding status, and family history is shown in **Table 1**. Males comprised 62% of subjects, with 28 (60.9%) in the case group and 29 (63%) in the control group. There was no significant gender difference between groups ( $P=0.830$ ). Subjects were classified by age into 3 groups: 6 mo-1year, >1 to 3 years, and >3 to 5 years, with 21.7%, 52.2%, and 26.1% of subjects, respectively. There was no significant age difference between case and control groups because subjects were age-matched ( $P=1.00$ ). Based on the Waterlow classification for nutritional

status, 26.1% of subjects had malnutrition, 54.3% had good nutrition, and 19.6% subjects were overweight. There were significantly more overweight subjects in the case group than in the control group ( $P=0.014$ ). Both groups had similar rates of delivery methods, with vaginal delivery more common (58/92) than Caesarean section (CS), with 65.2% and 60.9%, respectively, for case and control groups. Most subjects had normal birthweight of 2,500-4,000g (82.6%); 3 subjects had low birth weight; and 13 subjects had birth weight >4,000 g. There were no significant delivery method or birth weight differences between groups. EBF was significantly higher in the control group (38 subjects; 82.6%) than in the case group (26; 56.5%) ( $P=0.007$ ). Most subjects had no family history of all seizures, with 80.4% in the case group and 100% in the control group, but this difference was significant ( $P=0.002$ ).

Bivariate analyses with McNemar test revealed that EBF was a significant protective factor against FS (OR 0.74; 95%CI 0.15 to 3.55;  $P=0.017$ ). The test also revealed that family history of all seizures was a

significant risk factor for FS (OR 4.33; 95%CI 0.25 to 76.04;  $P=0.021$ ). In the other hand, bivariate analyses with Wilcoxon test revealed that nutritional status was not significantly associated with FS ( $P=0.116$ ) (Table 2).

## Discussion

In our study, children with FS were predominantly male (60.9%), aged 1-3 years (52.2%), exclusively breastfed (56.5%), delivered vaginally (65.2%), and had normal nutritional status (41.3%), normal birthweight (84.8%), as well as no family history of seizure (80.4%). Similarly, a study in Manado, reported that children with FS were mostly male (66%), aged 1-3 years (50.6%), and had normal nutritional status (67.3%), vaginal birth (84.7%), normal birth weight (90%), and no family history for seizure (69.3%).<sup>16</sup> Our findings were also consistent with a study which subjects were 65.2% male, 94.9% normal birth weight (2,500-4,000g), and 92% with no

**Table 1.** Subjects' characteristics

Characteristics	FS (n=46)	Febrile without seizure (n = 46)	Total (N=92)	P value
Gender, n (%)				0.830
Female	18 (39.1)	17 (37)	35 (38)	
Male	28 (60.9)	29 (63)	57 (62)	
Age group, n (%)				1
6-12 months	10 (21.7)	10 (21.7)	20 (21.7)	
>1-3 years	24 (52.2)	24 (52.2)	48 (52.2)	
>3-5 years	12 (26.1)	12 (26.1)	24 (26.1)	
Nutritional status, n (%)				0.014
Malnutrition	13 (28.3)	11 (23.9)	24 (26.1)	
Good	19 (41.3)	31 (67.4)	50 (54.3)	
Overweight	14 (30.4)	4 (8.7)	18 (19.6)	
Delivery method, n (%)				0.666
Spontaneous	30 (65.2)	28 (60.9)	58 (63)	
CS	16 (34.8)	18 (39.1)	34 (37)	
Birthweight, n (%)				0.583
< 2,500 g	2 (4.3)	1 (2.2)	3 (3.3)	
2,500-4,000 g	39 (84.8)	37 (80.4)	76 (82.6)	
> 4,000 g	5 (10.9)	8 (17.4)	13 (14.1)	
Breastfeeding, n (%)				0.007
Exclusive	26 (56.5)	38 (82.6)	64 (69.6)	
Non-exclusive	20 (43.5)	8 (17.4)	28 (30.4)	
Family history <sup>a</sup> , n (%)				0.002
Yes	9 (19.6)	0 (0)	9 (9.8)	
No	37 (80.4)	46 (100)	83 (90.2)	

<sup>a</sup>family history of all seizures

**Table 2.** McNemar and Wilcoxon test on breastfeeding status, family history, and nutritional status associated with FS

Characteristics	FS	Febrile without seizure	OR (95%CI)	P value
Breastfeeding status, n (%)			0.74 (0.15 to 3.55)	0.017
Exclusive	26 (56.5)	38 (82.6)		
Non-exclusive	20 (43.5)	8 (17.4)		
Family history <sup>a</sup> , n (%)			4.33 (0.25 to 76.04)	0.021
Yes	9 (19.6)	0 (0)		
No	37 (80.4)	46 (100)		
Nutritional status, n (%)			-	0.116
Malnutrition	13 (28.3)	11 (23.9)		
Good	19 (41.3)	31 (67.4)		
Overweight	14 (30.4)	4 (8.7)		

<sup>a</sup>Family history of all seizures; McNemar test on breastfeeding status and family history; Wilcoxon test on nutritional status

family history of FS.<sup>14</sup> Furthermore, our results were also similar to a previous study in 2019, which noted that of 31 children enrolled, most were male (71%), aged 1-3 years (51.6%), and had good nutritional status (90.3%).<sup>18</sup>

Several studies reported that most FS (65-85%) occurred between the ages of 6 months to 3 years, with peaks at the age of 18 months.<sup>3,5,6</sup> In order to reduce bias in our study, we age-matched the groups. We found no significant relationships between the delivery method and FS, nor between birth weight and FS. Past studies noted that FS in children was associated with a history of difficult labor, but the specific type of delivery method did not increase the risk of FS in children.<sup>3,4,15,16</sup>

McNemar analysis revealed that EBF children had significantly lower risk of FS compared to non-EBF children (P=0.017). In addition, EBF was a protective factor against FS (OR 0.74; 95%CI 0.15 to 3.55). Similarly, a study reported that EBF for 6 months can be a protective factor against FS (OR=0.78; 95%CI 0.64 to 0.95).<sup>8</sup> Other studies had similar EBF findings. A previous study divided 120 children into case and control groups, then analyzed FS and duration of breastfeeding, but they did not mention EBF. The mean duration of breastfeeding was 5.95 months in the FS group, and 10.3 months in the control group (P<0.001). They concluded that children who were breastfed <6 months had a greater risk of developing FS (OR 9.56; 95%CI 2.47 to 36.9).<sup>15</sup> In 2020, a Chinese study also confirmed this conclusion. From a total of 336 children in case and control groups, there was a significant relationship between breastfeeding and FS (P=0.019), with EBF a protective factor against FS (OR=0.504; 95%CI

0.30 to 0.84).<sup>14</sup> To our knowledge, there have been no studies in Indonesia focused on the relationship of breastfeeding and FS.

Breastfeeding has many health benefits, including protection against gastrointestinal and respiratory infections in infants. The WHO initially recommended that solid foods be introduced at 4-6 months, but in 2001 that recommendation was changed to 6 months.<sup>17</sup> These changes were based on a systematic review comparing the effects of EBF for 6-7 months with EBF for at least 3-4 months and followed by mixed feeding (for example, breast milk plus solid foods and/or infant formula).<sup>17</sup> In 2012, the WHO updated their recommendations again, as studies from Belarus, Iran, and Nigeria reported that 6 months of EBF was associated with fewer gastrointestinal infections and fewer respiratory infections (in Iran and Nigeria) in infancy compared to EBF for 3-4 months.<sup>13</sup>

Several possible mechanisms of breastmilk's active role in protecting against FS have been suggested.<sup>7,8,15,19</sup> Breastmilk contains n-3 long-chain polyunsaturated fatty acids and lactose, which promote white matter growth, nerve myelin formation, and nerve excitability reduction which may prevent seizures.<sup>8,15</sup> Breastmilk is also rich in immunoglobulin A, which can increase a child's resistance to infectious diseases, thereby reducing the chance of fever and ultimately reducing the chance of seizures.<sup>19</sup>

The strength of this study was that it is possibly the first to evaluate and reveal a strong association between EBF and FS in Denpasar and in Indonesia. As such, this study can be used as a reference for further study and encouragement for mothers of newborns to breastfeed. However, there were several limitations

in our study, as other potential confounding factors were not analyzed further, so we cannot rule out that nutritional factors, such as hemoglobin levels in the blood, maternal illness during pregnancy, maternal parenting, and family socioeconomic conditions could have biased our results. In addition, the purposive consecutive sampling technique was not random, so patients did not have the same opportunity to be included. Finally, only one researcher was assigned to screening medical records, so there was a possibility of selection bias. Hence, subsequent studies should have a better study design, with random and blind sampling techniques, in order to avoid bias and obtain results that more accurately represent the population studied. We also suggest further study to analyze risk factors for FS in children using multivariate analysis.

In conclusion, EBF are protective factors against FS. In addition, family history of seizures also associated with higher incidence of FS. This information is useful, especially for clinicians to encourage parents to exclusively breastfeed their newborns for up to 6 months.

## Conflict of interest

None declared.

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