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Correlation Between Brain-Derived Neurotrophic Factor Levels and Serum Iron Levels in Stunted Children Living in Malaria-Endemic Areas

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Abstract

BACKGROUND: Children who are living in malaria-endemic areas are highly vulnerable to malaria infections. The presence of malaria infection and low nutrient intake results in an increased incidence of stunting in children, especially those living in malaria-endemic areas. The stunting in children may reduce their cognitive functions.

AIM: This study aims to analyze the correlation between brain-derived neurotrophic factor (BDNF) levels and serum iron in stunted children living in malaria-endemic areas.

METHODS: The design of this research was a case-control study. The sample of this study was 60 elementary schoolchildren aged 9–12 years collected from five regencies in Bengkulu province. Among the samples, 30 of them were stunted and the remaining were non-stunted ones. The technique used to collect the samples was simple random sampling. Growth stunting was identified by calculating the Z-score of height-for-age (H/A). In addition, the whole blood of each research subject was drawn for the measurement of BDNF and serum iron levels. Serum BDNF level was measured using a method of enzyme-linked immunosorbent assay (ELISA), and serum iron level was measured using spectrophotometry. The characteristic data of the sample were collected from questionnaires. The obtained research data were then analyzed using the independent t-test and the Pearson correlation.

RESULTS: The levels of BDNF and serum iron in stunted children were lower than those in non-stunted ones (3.38 ± 1.05 vs. 4.16 ± 0.41 $\mu\text{g/dL}$ and 31.57 ± 9.88 vs. 52.99 ± 12.60 $\mu\text{g/dL}$). There was a significant difference ($p < 0.05$) in the mean level of BDNF and serum iron levels between stunted children and non-stunted ones. The results of the Pearson analysis of BDNF and serum iron levels indicated $p = 0.000$ and $r = 0.454$.

CONCLUSION: There was a significant correlation between BDNF levels and serum iron levels in stunted children living in malaria-endemic areas.

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Background

Malaria infection is one of the most contributing factors to the high rate of morbidity and mortality. Most of the areas in Indonesia are still endemic for malaria infection [1]. Children living in malaria-endemic areas are vulnerable to develop malaria infection. Seluma regency is one of the areas in Indonesia, which is endemic for malaria. Not only marked as one of the malaria-endemic areas but Seluma regency is also considered as an underdeveloped regency [2]. The presence of malaria infection and the lower intake of nutrition increases the incidence of growth stunting in children living in malaria-endemic areas.

Stunting is resulting from chronic undernutrition, and it is believed that stunting is triggered by poor dietary intake, infectious diseases, and environmental

problems [3]. The results of a similar study conducted by Pongou *et al.* and Ramli *et al.* stated that family socioeconomic, i.e., education, employment, and family income was the risk factors for stunting in children [4], [5]. Another similar study by Zere and Mc Indyre conducted in South Africa also proved that growth stunting was found higher in people with lower socioeconomic status [6]. Lower nutrient intake will lead to the lack of micronutrients needed by our bodies. One of the micronutrients closely associated with stunting is iron.

Iron is an essential nutrient not only for normal growth, health, and survival of children but also for their mental and motor development, and cognitive functioning [7]. Studies in animals proposed that iron deficiency causes epigenetic changes that change the structure of chromatin and the expression of BDNF genes. Iron deficiency lowers BDNF function and impairs

neuronal differentiation in the hippocampus. BDNF is a neurotrophin that is required for the development of synapses, synapse plasticity, and cognitive functions. The synthesis of BDNF requires some enzymes that depend on iron availability to work [8]. This study was to analyze the correlation between serum iron and BDNF levels in stunted children living in malaria-endemic areas.

Methods

This study was conducted in malaria-endemic areas [2] Seluma regency, Bengkulu province. The design of this study was a case-control study design that compared two groups of elementary schoolchildren, the first group was stunted and the second one was non-stunted. The study was conducted, in April 2019, involving a sample of 60 elementary schoolchildren taken by simple random sampling. The children came from elementary schools in five subdistricts, namely, Lubuk Sandi, Seluma Barat, Seluma Timur, Seluma Utara, and Talo. The growth stunting was determined by comparing the actual height values with the appropriate age. The Z-score was calculated by referring to anthropometric data of children and the WHO global database in terms of child growth and malnutrition using Anthro 1.02 software. The children who had a Z-score below or lower than -2 were determined as stunted [9]. After calculating and determining the children's status in stunting, 2 mL venous blood was taken from the children to measure the levels of serum iron and BDNF. The determination of serum iron levels was performed by spectrophotometric methods using the Iron Liq kit (Cat. No. 10230, human diagnostic), and that of BDNF levels by the enzyme-linked immunosorbent assay (ELISA) method using Human BDNF ELISA KIT (Cat. No. E-EL H0010, Elabsience). Then, all the data were computably analyzed using SPSS version 20 with the Chi-square and Pearson tests ($p < 0.05$). This study had received its ethical approval numbered 46/UN9.1.10/KKE/2019 from the Health Research Ethics Commission, Faculty of Public Health, Sriwijaya University.

Results

The results of this present study (Table 1) showed that 72.7% of the children aged > 10–12 years old were stunted, and 59.3% of the female students were stunted. Based on parental characteristic data, 60% of the mothers with low education background had stunted children, and 55.9% of those who did not work had stunted children.

Likewise, father's characteristic data showed that fathers with low education had stunted children,

Table 1: Frequency distribution of elementary school students' characteristics

Frequency distribution	Stunted		Non-stunted		Total	
	n	f (%)	N	f (%)	n	f (%)
1. Age						
a. 9–10 years old	14	36.8	24	63.2	38	100
b. >10–12 years old	16	72.7	6	27.3	22	100
2. Sex						
a. Male	16	59.3	11	40.7	27	100
b. Female	14	42.4	19	57.6	33	100
3. Malaria infection						
a. Positive	0	0	0	0	0	0
b. Negative	30	50.0	30	50.0	60	100
4. Mother's education						
a. Low	24	60.0	16	40.0	40	100
b. High	6	30.0	14	70.0	20	100
5. Mother's occupation						
a. Worker	11	42.3	15	57.7	26	100
b. Housewife	19	55.9	15	44.1	34	100
6. Father's education						
a. Low	20	54.1	17	45.9	37	100
b. High	10	43.5	13	56.5	23	100
7. Father's occupation						
a. Civil servant	2	40.0	3	60.0	5	100
b. Worker in the private sector	27	49.1	28	50.9	55	100
8. Economic status						
a. Low	26	59.9	18	40.1	44	100
b. High	4	25.0	12	75.0	16	100

and 49.1% of those who worked in the private sector had stunted children. Based on economic status, 59.9% of the families with low economic status had stunted children. The results of laboratory examination for BDNF levels (Table 2) showed that the mean level of BDNF of stunted children was lower than that of non-stunted ones (3.38 ± 1.05 vs. 4.16 ± 0.41 $\mu\text{g/dL}$).

Table 2: Comparison of BDNF mean levels between stunted and non-stunted children

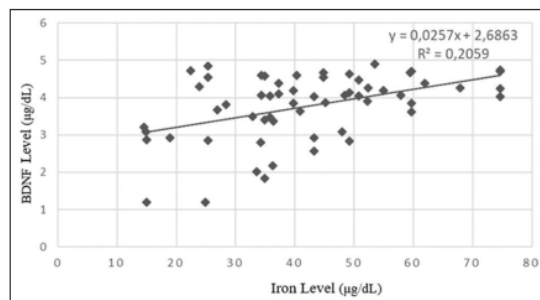
Status of H/A	BDNF Levels		
	N	Mean \pm SD ($\mu\text{g/dL}$)	p
Stunted	30	3.38 ± 1.05	0.001
Non-stunted	30	4.16 ± 0.41	

Similarly, the results of the examination of serum iron levels (Table 3) found that the mean serum iron levels in stunted children were lower than that of non-stunted ones (31.57 ± 9.88 vs. 52.99 ± 12.60 $\mu\text{g/dL}$).

Table 3: Comparison of serum iron levels between stunted and non-stunted children

Status of H/A	Iron Levels		
	N	Mean \pm SD ($\mu\text{g/dL}$)	P
Stunted	30	31.57 ± 9.88	0.000
Non-stunted	30	52.99 ± 12.60	

The results of the correlation test (Graph 1) between BDNF levels and serum iron levels showed that there was a significant correlation ($p = 0.0000$)



Graph 1: Correlation between BDNF serum levels and serum iron levels ($r = 0.454$, $n = 60$, $p\text{-value} = 0.000$)

between serum BDNF levels and serum iron levels with coefficient correlation in a moderate level ($r = 0.454$).

Discussion

Based on the data characteristics, 72.7% of the stunted children were in the age of > 10–12 years old, and 59.3% of them were male. According to Akombi *et al.*, stunting in infants is often not realized by parents, and it is more visible when they are growing older. In terms of gender, male students are said to have a higher risk of the developing stunting compared to girls. This is because in general male students are physically more active than girls and consuming more energy stores in their bodies [10]. From the examination of peripheral blood smear for plasmodium, none of the children (0%) was infected with malaria. Besides, clinical symptoms associated with malaria were not present in all research subjects. It can be assumed from these findings although malaria parasites were found negative, clinical history of having been infected with *P. vivax* may support the incidence of anemia in the children. The recurrence of *P. vivax* infection will contribute to structural and functional changes of red blood cells, and these hematological changes cause decreased hemoglobin levels and iron deficiencies. However, from the measurement of serum iron levels, it revealed that the stunted children had lower iron levels than compared with non-stunted children ($31.57 \pm 9.88 \mu\text{g/dL}$ vs. $52.99 \pm 12.60 \mu\text{g/dL}$). A similar study conducted by Damayanti *et al.* proved that there was a significant correlation between the level of iron stores and the incidence of stunting [11].

According to Petry *et al.*, iron deficiency in children can cause cognitive impairments and physical growth disorders [12]. Iron deficiency will inhibit neurogenesis in the hippocampus which results in morphological changes of the hippocampal neurons. The shape and size of the neurons are smaller and the number of branching neurons or synapses are reduced [13]. A study conducted by Brunette confirmed that in the mice with iron deficiency since they were intrauterine, the number of neuron branches was decreased, and the diameter of dendrite was smaller. This small diameter of dendrite decreases the speed of signal delivery [14]. Therefore, low nutrient intake, especially iron in stunted children, will give an impact on their low cognitive abilities and IQ scores which are characterized by low learning motivation and poor achievement in school [15]. The impaired cognitive development will result in the decreased performance of the nervous system which will lead to the low intelligence of children. Stunting in children can reduce their IQ scores by 5–11 points [16]. The incidence of stunting is closely related to the characteristics of

parents. In this study, 60% of mothers and 54.1% of fathers with low education, and 59.9% of the families with low economic status had stunted children.

The results of this study also showed that the mean level of serum BDNF in stunted children was lower than that in non-stunted children ($3.38 \pm 1.05 \mu\text{g/dL}$ vs. $4.16 \pm 0.41 \mu\text{g/dL}$). BDNF is a neurotrophin that plays a role in the development of synapses, synapse plasticity, and cognitive functions and contributes to the learning process and memory functions [17]. The decrease of BDNF expression is associated with impaired neuronal differentiation in several areas of the brain. Therefore, the low levels of serum BDNF will affect cognitive functions [18].

BDNF is produced by the brain, and the brain itself is the organ containing the highest concentration of iron. Iron plays a role in the formation of myelin, dopamine, and energy in the brain. Energy formation in the hippocampus of the brain requires sufficient iron to support the learning process and memory functions. If an iron deficiency occurs, there will be a reduction in BDNF expression in the brain which will then result in behavioral and cognitive changes. The results of several studies on animal suggest that iron deficiency that occurs early in life cause epigenetic changes that alter the structure of chromatin and expression of the BDNF genes and causes a decrease in the differentiation of neurons in the hippocampus. This is related to abnormalities of behavior and cognition, including decreased memory ability and increased anxiety. These abnormal behaviors and cognitions will persist into adulthood despite adequate treatment [18].

The results of the correlation test showed a significant correlation between the mean levels of serum BDNF and serum iron levels ($p = 0.000$, $r = 0.454$). This proves that the impact of stunting on cognitive function is caused by the low levels of BDNF and serum iron. Iron is one of the important micronutrients needed for the development and function of brain cells. BDNF synthesis depends on the availability of iron in the brain [18]. Iron deficiency results in a reduction in BDNF expression which further impacts cognitive impairment in stunted children.

Conclusion

There was a significant correlation between BDNF mean level and serum iron levels ($p = 0.000$, $r = 0.454$) in stunted children in malaria-endemic areas. Iron is required for the synthesis of BDNF. The low level of iron serum is responsible for the low synthesis of BDNF. These problems, in the long run, surely will affect cognitive functions of stunted children.

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