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Correlation between Serum Ferritin Level and Growth Disorders in Children with Thalassemia

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Abstract ***Background*** Children with thalassemia receiving regular blood transfusions without optimal iron chelation may experience high levels of iron. This condition can cause oxidative stress and affect the certain organs including endocrine organs leading to growth disorders. ***Objective*** To determine the correlation between serum ferritin levels and growth disorders in children with thalassemia. ***Methods*** This was a cross sectional study conducted during April-May 2015 at Children Thalassemia Clinic, Dr. Hasan General Sadikin Hospital, Bandung. The subjects were collected using consecutive sampling. The subjects were 93 children with thalassemia aged 10–14 years divided into several groups. The study used secondary data taken from the previous studies. The data were analyzed statistically using chi-square test to determine the correlation of both variables. The correlation between serum ferritin levels and growth disorders was examined by using point-biserial correlation and logistic regression models was used to determine the correlation between age and serum ferritin levels with short stature. ***Results*** The study included 46 boys (49%) and 47 girls (51%), 62% of which had short statures. The results revealed that the mean serum ferritin level (SD) was 4.355,9 (2.149) µg/L. The correlation between serum ferritin levels and growth disorders (r=-0.260;p=0.012) by ROC value was 3542 µg/L. There was a significant correlation between age and serum ferritin levels with short stature (OR=3.248, CI95%1.304–8.086; OR=3.964, CI95%1.192–13.190). ***Conclusion*** There was significant correlation between serum ferritin levels and growth disorders.

Keywords: *thalassemia, child, ferritin serum, growth disorder, short stature*

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1. Introduction

Thalassemia can impair growths in the period of fetus, infant, pre-puberty and puberty [1]. Increasing life expectancy in people with beta thalassemia major, regular blood transfusions can cause iron overload. Routine blood transfusions may lead to iron binding capacity of transferrin in body which increases reticuloendothelial system then entering into the parenchyma. This condition causes oxidative damages such as in the heart, liver and endocrine organs [2]. Inadequate iron chelating agent will worsen the iron overload [3].

The main cause of growth disorders in children with thalassemia major are influenced by many factors and still debated [4]. High serum ferritin levels in puberty were reported to cause short stature and delayed body growths in thalassemic major patients [5]. A study discovered a correlation between serum ferritin levels and growth disorders; higher ferritin levels were found in thalassemic children with short stature compare to those with normal bone [6]. Iron overload can prohibit bone metabolisms leading to growth disorders [7].

The serum ferritin levels in thalassemic children at Dr. Hasan Sadikin General Hospital, Bandung were still high. Meanwhile, a previous study described higher incidences of short stature were found in thalassemic children. Therefore, this study aimed to determine the correlation between serum ferritin levels and growth disorders in children with thalassemia at Dr. Hasan Sadikin General Hospital, Bandung.

2. Materials and Methods

This study used secondary data taken from the previous studies regarding the cognition in thalassemic children. This cross-sectional study was conducted in the period of April to May 2015. The subjects were measured by using consecutive sampling carried out from thalassemic children who met the inclusion criteria and regularly visited medical checkup at Children Thalassemia Policlinic Dr. Hasan Sadikin General Hospital, Bandung. The subjects who met the inclusion criteria were recorded into basic data of medical records. The inclusion criteria were children aged > 10 years, diagnosed with thalassemia and receive blood transfusion regularly, and have not hearing disorder and exclusion criteria was having congenital disease (Down's syndrome) and chronic illness other than thalassemia (such as malignancy, tuberculosis, chronic hepatitis, congenital heart disease, chronic renal failure, epilepsy, diabetse mellitus). Then, anamnesis,

physical examinations, and anthropometric status measurements were conducted.

Average hemoglobin (Hb) concentration before blood transfusion and serum ferritin levels for the last three months were recorded based on medical record data or data taken from Clinical Pathology Laboratory Dr. Hasan Sadikin General Hospital, Bandung. The subjects' height to the nearest 0.1 cm was measured using a mobile stadiometer (Seca 217[CE0123], USA). The subjects' body mass index (BMI) was calculated using the formula of weight/height^2 (kg/m^2). Then, the subjects were categorized based on World Health Organization (WHO) reference of Child Growth Chart which is recognized as z-scores (standard deviation scores).

In this study, the subject characteristics were descriptively described. The correlation between serum ferritin levels and growth disorders in thalassemic children was examined using point-biserial analysis. The study was approved by the Health Research Ethic Committee, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung.

3. Results

A total of 93 patients visited the Children Thalassemia Policlinic Dr. Hasan Sadikin General Hospital, Bandung in the period of April to May 2015. In addition, the study involved 46 boys and 47 girls as the subjects.

Table 1. Characteristics of thalassemic children (n=93)

	n	%
Sex		
Boy	46	49
Girl	47	51
Age (years)		
10-12	67	72
12-14	26	28
Child education (years)		
Mean (SD) =5.3		
Median = 5(1.57)		
Range = 0-9		
Parental Income		
Low	17	18
Middle	57	61
High	19	21
Anthropometric status		
Heigh-for-age		
Normal	35	38
Stunted	33	35
Severely stunted	25	27
Body mass index-for-age		
Median	84	90
<-2 SD	9	10
<-3 SD	0	0

Note: SD=standard deviation

There was no significant difference between boys and girls due to the number of the subjects as seen in Table 1. The subjects were classified into two groups, normal body height and short stature. In this study, there were 62% subjects with short stature.

The serum ferritin levels, hemoglobin level before transfusion, transfusion frequency, iron chelating agent and chelating iron therapy are described in Table 2. The study revealed that 77% serum ferritin levels were >2500 µg/L, 83% hemoglobin levels before transfusion were 5–8 g/dL, 56% were discovered in transfusion frequency every 4 week, and most frequently used chelating iron agent was deferoxamine. However, deferoxamine chelating agent was not optimally used for thalassemic children.

Short stature based on the study characteristics showed a significant correlation between short stature with parental income and serum ferritin levels ($p<0.05$) (Table 3). Furthermore, the serum ferritin level cut-off point and short stature incidences was evaluated by using receiver operating characteristic (ROC) curves. The examination was performed to obtain serum ferritin level cut-off point regarding to the incidences of short stature. The ferritin level cut-off point found in this study was 3342 ng/dL (Figure 1).

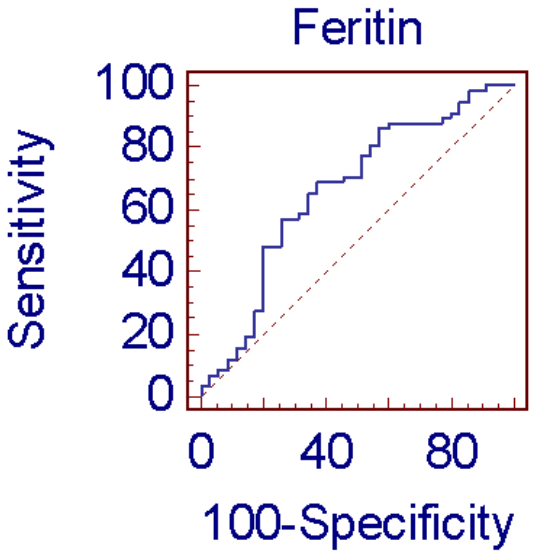

Figure 1. Receiver operating characteristic curve serum ferritin levels with short stature

As the serum ferritin level cut-off point was obtained, the subjects were divided based on serum ferritin level cut-off point. The analyses relating to the incidences of short stature were then performed. A significant correlation between serum ferritin levels and the incidences of short stature was found ($p=0.003$) (Table 4).

The correlation between serum ferritin levels and growth disorders was investigated by using point-biserial correlation test ($r=0.260$; $p=0.012$). Based on the multivariate analysis, age and serum ferritin levels influenced the incidences of short stature in thalassemic children.

The correlation between age and serum ferritin levels with short stature was considered statistically significant ($p<0.05$) as presented in Table 5.

Table 2. Variables characteristics

Variable	n	%
Ferritin level (µg/L)		
Mean (SD) = 4355.9(2149.3)		
Median = 3804		
Range = 698−9440		
<1.000	2	2
1000−2500	20	22
>2500	71	77
Hemoglobin level before transfusion (g/dL)		
<5	1	1
5−8	77	83
8–10	15	16
Transfusion frequency (per week)		
Every 2 week	14	15
Every 3 week	18	19
Every 4 week	52	56
>every month	9	10
Iron chelating agent		
Deferoxamine	5	5
Deferiprone	59	64
Deferasirox	27	29
Without therapy	2	2
Iron chelating therapy		
Optimally	45	48
Not optimally	48	52

Table 3. Short stature based on study characteristic

Characteristic	Interpretation		p Value
	Short stature (n=58)	Normal (n=36)	
Sex			
Boy	29	17	0.894*
Girl	39	18	
Age (year)			
10 - 12	36	31	0.06*
12 – 14	22	4	
Parental income (IDR)			
Low	14	3	0.044*
Middle	30	27	
High	14	5	
Average hemoglobin level before transfusio			
Mean (SD)	7.098(0.87)	7.232(0.58)	0.44**
Median	7.08	7.2	
Range	4.4-8.6	6.1-8.4	
Age when firstly diagnosed			
>2 year	22	18	
6 month – 2 year	26	9	0.183**
<6 month	10	8	
Frequency of blood transfusion			
Every 2 week	9	5	0.724**
Every 3 week	13	5	
Every 4 week	30	22	
>every 1 month	6	3	
Ferritin level			
Mean (SD)	4786.97(2059.22)	3641.49(2132.85)	0.009***
Median	4574.50	3305	
Range	1287-9440	2234-8062	

Note: SD = standard deviation
*The chi square analysis; **The t test analysis; ***The Mann-Whitney analysis

Table 4. Correlation between serum ferritin level and short stature by using receiver operating characteristic

Ferritin Level	Interpretation		p Value
	Short stature (n=58)	Normal (n=35)	
>3542	40	13	0.003
≤3542	18	22	

Table 5. Analysis between the variables and short stature

Variable	Koev (B)	SE (B)	p Value	OR (95%CI)
Age	1.377	0.613	0.025	3.248(1.304-8.086)
Ferritin	1.178	0.613	0.020	3.964(1.192-13.190)

* Logistic regression analysis backward stepwise

4. Disscussion

Thalassemia is still considered as one of several incurable diseases, however, quality of life (QoL) and life expectancy of thalassemia children might still be increased by optimal management [8]. Other risk factors that might affect growth disorders in thalassemia children are low hemoglobin level pre-transfusion, high ferritin level, not optimal used iron chelating agent, low social-economic level and increasing age of thalassemia children. [9]. Long-term blood transfusion and chelating agent administrations can improve QoL of the thalassemic children and decrease deaths due to heart failure [10]. Growth characteristics in children with thalassemia major commonly show normal condition in the first 10 years but growth retardation may occur after 10 years [11].

In West Java, Indonesia, 2,759 thalassemia major patients were reported (source: POPTI Bandung, 2014). Based on the data taken from Dr. Hasan Sadikin General Hospital, Bandung, 656 thalassemic patients visited thalassemia clinic regularly, therefore, 381 patients were reported 0–14 years old group. One of the main problems in the management of thalassemic children was unawareness in the early detection of growth disorders mostly found in thalassemia incidences.

A total of 93 subjects who met the inclusion criteria were involved in this study, 48% were boys and 52% were girls. In this study, the subject height and age was calculated based on the WCGS reference. The results showed that 62% subjects were reported stunted and severely stunted. The proportion of short stature in this study was similar to the previous studies conducted by Moayeri et al. [2] and Jana et al. [12] which discovered the incidences of short stature were 62% and 65.8%, respectively. These results was higher compared to a study by Shamshiraz et al. [13] which reports the incidences of short stature in thalassemic children is 39.3%. Short stature in thalassemia patients can be caused by several factors, including chronic anemia, hypersplenism and folate deficiencies [11].

This study discovered nutritional status values by using BMI based on age at which 90% of the subjects were in the median area. An alternative examination such as upper arm circumference-for-age measurement should be conducted to assess nutritional status in thalassemia patients who had enlarged organs.

Normal growths in thalassemic children in the first 10 years depend on hemoglobin levels which are maintained at above 10–11 g/dL. This condition can be caused by hypoxia as a major growth disorder factor [14]. In this study, the subjects who showed average hemoglobin level before transfusion 5–8 g/dL were 83%. There was no correlation between average hemoglobin level before transfusion and the incidences of short stature ($p=0.44$) in the study. However, a study conducted in Iraq revealed different results that the average hemoglobin level before transfusion was <9 g/dL which statistically increase the incidences of short stature in thalassemic children [14]. This is caused by a lack of compliance to attend regular blood transfusion. Low family income becomes a major factor which affect the compliance.

Serum ferritin levels can be influenced by several factors, such as the age when firstly diagnosed, the age when firstly having blood transfusion and the age when firstly treated with iron chelating agent. The height growth-for-age in thalassemic children is associated with higher serum ferritin levels [12]. Most of the subjects showed higher serum ferritin levels and needed iron chelation. The mean (SD) of serum ferritin levels in this study was 4,355.9 (2149) µg/L. More than 50% of the subjects did not receive optimal iron chelation which caused iron overload leading to higher risk of growth disorders.

In this study, a correlation was found between serum ferritin levels and the incidences of short stature ($p=0.003$). Based on the analysis using point-biserial correlation test, the correlation between serum ferritin levels and growth disorders revealed ($r=-0.260$; $p=0.012$). The multivariate analysis to examine the variables showed that age and serum ferritin levels influence the incidences of short stature in thalassemic children. Moayeri et al. stated that thalassemic children with serum ferritin levels above 2000 µg/L was those who had short stature. Therefore, these complications were mostly found in thalassemic patients without optimal iron chelating treatment and received late iron chelating agent than those who received treatment earlier [2]. Another study reported that short stature occured if ferritin levels were above 3000 µg/L, including at pre-puberty or the first years of life [15]. High serum ferritin levels in puberty may cause growth retardation [16].

In this study, there is a correlation between serum ferritin levels and the incidences of short stature. This was due to iron overload in endocrine glands producing growth organs will be impaired. This problem is considered as a factor which will influence the growth. Limitations of the study are the height measurement was only performed once and serum ferritin levels were analyzed instead of the actual serum ferritin levels at the exact assessment time of growth status but using serum ferritin levels in the last 3 months.

5. Conclusion

There was significant correlation between serum ferritin levels and short stature in thalassemic children. Another factor associated with growth disorders in thalassemic children was age in initial diagnosis.

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