Relationship between Short Stature and Serum Ferritin in Children with Beta Thalassemia Major

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Abstract: Short stature has been recognized in thalassemia major patients for many years and continue to be common problems despite regular transfusion and chelation therapy. The aim of this study was to determine the relationship between short stature and serum ferritin in children with beta thalassemia major. A cross sectional study was carried out in children with beta thalassemia major who met the inclusion criteria and selected based on consecutive sampling, aged less than 18 years, and regularly visited Thalassemia Day-Care Centre at H. Adam Malik and Universitas Sumatera Utara General Hospital. This study was conducted in March to May 2018. Data was collected through the questionnaire, anthropometric measurements, and blood test analysis. Descriptive statistics and chi-square test were performed, $p<0.05$ was considered as significant level. There were 56 children were recruited in this study, females and males comprised 27 (48.2%) and 29 (51.8%) respectively, 60.2% of subjects had short stature and 14.3% had severe thinness. The mean serum ferritin levels were 5081.41±4503.65 ng/mL. Age at diagnosis was 40±33.61 months. This study found there was no significant association between serum ferritin levels with short stature but significant association was identified between age at diagnosis and short stature.

1 INTRODUCTION

Thalassemia as the most common genetic disorder worldwide is regarded as a serious problem in public health issues especially in Asia region (Ansari Sh et al., 2014).Almost 100,000 patients with major thalassemia need regular transfusions. Regular red blood cell (RBC) expansion, permit normal development throughout childhood, and extend survival (Hashemi A et al., 2011). Transfusions result in iron overload, which is fatal without treatment in the second decade of life. Iron-chelating therapy for iron overload is one important part of major thalassemia treatment in last 20 years (Hashemi A et al., 2011).Although morbidity and mortality of the thalassemia major has been significantly in the light of modern medical treatment, however, it could influence various aspects of patients' life (Ansari Sh et al., 2014).

Many complications of beta thalassemia major are the result of increased iron deposition from repeated blood transfusion. The accumulation of iron in different tissues causes organ damage affecting mainly endocrine glands, heart, and liver. The most prominent endocrine complication is growth retardation and failure of normal pubertal development. Growth failure has been attributed to growth hormone (GH) hypothalamic and/or pituitary, insulin-like growth factor 1 (IGF-1), insulin-like growth factor binding protein 3 (IGFBP3) deficiency, hypothyroidism, delayed sexual maturation and to bone disorders caused by iron-chelating toxicity. Short stature in children with beta thalassemia major could be due to GH-IGF-1 axis dysfunction and iron-chelating induced bone dysplasia (Nasr MR., 2012).

Malnutrition is a significant cause of growth retardation in thalassemic children living in poor countries. In these children, inadequate nutrient intake (zinc, folic acid, vitamin D, carotenoids, and retinol binding proteins) contribute significantly to their growth impairment (De Sanctis V et al., 2014). The aim of this paper was to determine the relationship between short stature and serum ferritin in children with beta thalassemia major.

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2 METHODS

This cross sectional study was conducted in March to May 2018. Subjects were selected by using consecutive sampling that met the inclusion criteria and regularly visited Thalassemia Day-Care Centre at H. Adam Malik and Universitas Sumatera Utara General Hospital. The inclusion criteria were children with beta thalassemia major aged less than 18 years with regarding two years blood transfusion and received blood transfusion regularly, and exclusion criteria were having genetic disease such as Down syndrome and chronic illness (malignancy, tuberculosis, chronic hepatitis, congenital heart disease, chronic renal failure, primary skeletal disorders, diabetes mellitus). Serum ferritin level was measured using the chemiluminescentmicroparticle immunoassay (CMIA).

The study included a questionnaire for parents or guardians and anthropometric measurements. The questionnaires requested information about the age at diagnosis, history of thalassemia in family, get iron chelating agent, frequency of blood transfusion in a year, and social- economic data. Anthropometric measurements included body weight (in Kg), was measured to the nearest 0.1 Kg by digital machine. Height (in cm) was measured to the nearest 0.1cm by using stadiometer. All instruments were validated following the manufacturer's protocol. Body mass index (BMI) was calculated as weight (kg) /height (meter) (Ogden CL et al., 2010).Then, the subjects were categorized based on World Health Organization (WHO) reference of Children Growth Chart which is recognized as z- scores (standard deviation scores). Short stature was assessed by using Growth Chart Center for Disease Control (CDC) 2000 for boys and girls.

This study was approved by The Ethics Committee of The Medical School, Universitas Sumatera Utara, Medan, Sumatera Utara, Indonesia. All parents or guardians gave written informed consent that the results of this study would be used for scientific research purposes.

2.1 Statistical Analysis

Data were analyzed using SPSS software version 24 (SPSS Inc., Chicago, IL, USA). Quantitative variables were expressed as mean±standard deviation (SD). The descriptive statistics were used to analyze socio demographic characteristics of the subjects. The relationship between short stature and serum ferritin level was used chi-square test, $p<0.05$ was considered as significant level.

3 RESULTS

There were 56 children were recruited in this study, females was 27 (48.2%) and male was 29 (51.8%), respectively. Characteristics of children in this study are given in **Table 1**. Short stature was found in 34 (60.7%) and normal stature was in 22 (39.3%) subjects. Most thalassemia children had normal nutritional status, but 14,3% subjects were thinness (BMI <-2 SD) and 14.3% are severe thinness (BMI <-3 SD). Family history of thalassemia was found only in 12 (21.4%) subjects, but it is possible that the number of subjects who had a family history of thalassemia is actually more than that reported by parents in the questionnaire, because some are not diagnosed or have not screened. Most subjects were diagnosed with beta thalassemia major at over 2 years of age. Around 87.5% of subjects had parental income of 5-10 million rupiah in a month.

Table 1. Characteristics of Children in this Study

	n (%)
Age (years)	9.46±4.44
Age at diagnosis	
< 6 months	7 (12.5)
6 months to 2 years	12 (21.4)
>2 years	37 (66.1)
Sex:	
Male	27 (48.2)
Female	29 (51.8)

Table 1. Characteristics of Children in this Study (cont.)

Body weight (Kg)	23.63±8.77
Body height (cm)	121.41±19.07
BMI (kg/m^2)	15.50±2.16
Family history of thalassemia	
Yes	12(21.4%)
No	44(78.6%)
Father'sEducation level	
Elementaryschool	9 (16.1)
Middle school	11 (19.6)
Seniorhighschool	31 (55.4)
University	5 (8.9)
Mother's education level	
Elementaryschool	9 (16.1)
Middle school	14 (25.0)
Seniorhighschool	27 (48.2)
University	6 (10.7)
Parental income (Rupiah)	
< 5 million	49 (87.5)
5-10million	6 (10.7)
> 10million	1 (1.8)
Nutritional status (body mass index)	
Normal	40 (71.4)
Thinness (<-2 SD)	8 (14.3)
Severethinness (<-3 SD)	8 (14.3)
Stature	
Normal	22 (39.3)
Short stature	34 (60.7)

BMI: Body mass index. Data are means ± SD, or percentages.

Table 2 showed serum ferritin levels in most subjects were above 2000 ng/mL, hemoglobin levels before transfusion of most children between 5-7 g/dL, most subjects received blood transfussions every month, and 17 (30.4%) subjects did not use iron chelating therapy.

Table 2. Variables Characteristics

n(%)	
Ferritin Level (ng/mL)	
<1000	7 (12.5)
1000-2000	12 (21.4)
>2000	37 (66.1)
Haemoglobin level before transfussion (g/dL)	
<5	6 (10.7)
5-7	44 (78.6)

Table 2. Variables Characteristics (cont.)

>7	6 (10.7)
Transfussion frequency	
Every week	2 (3.6)
Every 2 weeks	19 (33.9)
Every 3 weeks	6 (10.7)
Every month	24 (42.9)
More than 1 month	5 (8.9)
Iron-chelating agent	
Deferiprone	21 (37.5)
Deferasirox	18 (32.1)
Without therapy	17 (30.4)

The relationship between short stature and serum ferritin levels and other variables characteristics can be seen in **Table 3**. There was no significant relationship between short stature and serum ferritin levels and with other characteristic variables, but this study reported a significant relationship between short stature and age at diagnosis.

Table 3. Association between short stature with serum ferritin and other characteristics

Normal	Short stature	*p*
Age		
<5	4	5	0.328
5-10	12	13	
>10	6	16	
Age at diagnosis			
< 6 months	6	1	**0.003**
6 months to 2 years	7	5	
>2 years	9	28	
Sex: Male	11	16	0.830
Female	11	18	
Family history of thalassemia			
Yes	18	26	0.634
No	4	8	
Parental income (Rupiah)			
< 5 million	19	30	0.440
5-10 million	2	4	
> 10 million	1	0	
Nutritional status (body mass index)			
Normal	15	25	0.799
Thinness (<-2 SD)	4	4	
Severe thinness (<-3 SD)	3	5	
Ferritin Level (ng/mL)			
<1000	1	6	0.296
1000-2000	6	6	
>2000	15	22	
Haemoglobin level before transfussion (mg/dL)			
<5	2	4	0.893
5-7	18	26	
>7	2	4	
Transfussion frequency			

Table 3. Association between short stature with serum ferritin and other characteristics (cont.)

Every week	1	1	0.062
Every 2 weeks	5	14	
Every 3 weeks	0	6	
Every month	14	10	
More than 1 month	2	3	
Iron-chelating agent			
Deferiprone	8	13	0.849
Deferasirox	8	10	
Without therapy	6	11	

Associations are considered significant when $p < 0.05$.

4 DISCUSSION

Beta thalassemia major is a severe early-onset form of beta-thalassemia characterized by severe anemia requiring regular red blood cell transfusions, it usually cause severe anemia with several health problems like enlarged spleen, bone deformities, short stature, diabetes, hepatitis infection, and requires regular life-long transfusion, therapy, and medical supervision. Thalassemia affects the growth of the thalassemic patients (Al-saleheQAA et al., 2015). 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. Long-term blood transfusion and chelating agent administrations can improve quality of life of the thalassemic children and decrease deaths due to heart failure. Growth characteristics in children with thalassemia major commonly show normal condition in the first 10 years but growth retardation may occur after 10 years (Al-salehe QAA et al., 2015; Fadlyana E et al., 2017).

A total of 56 subjects who met the inclusion criteria were involved in this study. The results showed that 60.7% subjects were reported short stature. The proportion of short stature in this study was similar to the previous studies that found the incidence of short stature,as in study that was conducted on Iranian thalassemic patients the incidence of short stature were 52.3% (Badfar G et al., 2017),and other countries reported the prevalence of short stature to be 30-60% (HamidahA et al., 2001; Shlomit et al., 2005; Borgna-Pignatti C et al., 1985; Gomber S, 2006). Butlower incidence was found in a study by Shamshirsaz et al that reported the incidence of short stature in thalassemic children was 39.3% (Shamshirsaz AA et al., 2003).Difference in prevalence of short stature in patients living in various countries could be due to genetic susceptibility to the toxic effects of iron overload in endocrine gland and serum ferritin. It may also indicate differences in quality of care, follow-up and treatment, quality of blood transfusion, chelation therapy type (regular or irregular) and beginning of iron chelating therapy.

Normal growth 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 (Al-(Wataify AS, 2014). In this study, most subjects showed average hemoglobin levels before transfusion was 5–7 g/dLthat foundin 78.6% subjects, this study also reported that there was no association between hemoglobin levels before transfusion and the incidence of short stature ($p>0.05$). However, a study that was conducted in Iraq revealed different results that the hemoglobin levels before transfusion was <9 g/dLwas statistically increase the incidences of short stature in thalassemic children (Wataify AS, 2014).Differences in results can be caused by a lack of compliance to attend regular blood transfusion. Low family income becomes a major factor that affect the compliance.

Ferritin is an iron storage form in the body, which releases the required iron when needed. All thalassemic patients using iron chelator should be monitored and evaluated regarding serum ferritin levels (Nesheli HM et al., 2016).Moayeri et al reported that short stature in thalassemic children was found with serum ferritin levels more than 2000 ng/mL.It can be caused by not optimal and delayed iron chelating treatment (Moayeri H et al., 2006).Another study reported that short stature was foundwith serum ferritin levels more than 3000 ng/mL (Shalitin S et al., 2005).While other study reported that high serum ferritin levels in puberty may cause growth retardation (Jahargidar R et al., 2017).Causes of growth retardation that usually becomes remarkable in puberty are chronic anemia-

related chronic hypoxemia, increased calorie need due to increased erythropoiesis, growth hormone deficiency that may develop as a result of toxicity on hypotalamo-hypophysial level caused by increased iron load, hypothyroidism, inability to make the growing spurt because of delayed puberty and hypogonadism, and psychosocial factors (Yaman A et al., 2013).

Unlike previous studies, in this study we did not find significant association between serum ferritin levels and short stature in our subjects.This can occur due to a small sample size, measurement errors, or chelating therapy type. Another possible reason to explaining the lack of significant association between serum ferritin levels and short stature is the possible serum ferritin tolerance. In this study, serum ferritin levels were measured at a given moment, and its changes at different times were not determined. However, short stature was seen in most our subjects with the serum ferritin levels more than 2000 ng/mL.

Some factors considered as risk factors for having complication in thalassemia patients were as follows: Sex, age at diagnosis, age at start of transfusions, age at start of chelation therapy, intensive and/or early chelation with desferrioxamine, use of oral chelators, chronic hepatitis C, and iron-related complications (Origa R et al., 2016).This study reported a significant association between age at diagnosis and short stature (p<0.05), it showed us that the rate of complications was increased in older patients. This phenomenon may be a result of early hypothalamic/ pituitary damage induced by iron overload, and/or by the toxic effects of iron deposition in tissues. As reported by a study conducted by Aydinok et al, although the risk of developing short stature was lower among children receiving the oral chelator, they reported decreased of stature in adolescent receive iron chelators after age 10 years for 3 years, therefore, an eventual positive effect of oral chelators on growth does not seem to be sufficient when started after age 10 years (Aydinok Y et al., 2012).Some of our subjects (30.4%) were without therapy of iron chelator treatment and maybe it may be caused by lack of parental or children compliance to protocol treatments that have been made to patients. Therefore, all thalassemia patients should be adherence to all treatments such as regularly transfusion and use iron chelation agents, and avoidance of iron chelator overdosage clearly reduced the risk for short stature and other thalassemia complications.

5 CONCLUSION

The results of this study demonstrated that there was nosignificant association between serum ferritin levels and short stature, but this result showed significant association between age at diagnosis and short stature, it means that they are suffering from growth disorder since the beginning of their life. Therefore, new planning and policies seem to be necessary to minimize the complications in patients with beta thalassemia major. Some of the recommended plans include improvement of blood transfusion protocols, chelation therapy, informing the parents and patients about the complications of iron overload in the endocrine glands. We suggest that all patients be examined at an early age in terms of growth every six months.

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