

Association between age and serum ferritin level with bone age deficit in children with thalassemia major

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Abstract

Background Multiple blood transfusions in thalassemia patients lead to iron overload in bone tissue. Iron overload can be determined by serum ferritin measurement. Several studies have evaluated association between serum ferritin level and growth, but without bone age examination.

Objective To determine the association between age and serum ferritin level with bone age in children with thalassemia major.

Methods This study was conducted at Hasan Sadikin Hospital Bandung during March-May 2007. We performed physical examination, serum ferritin measurement, and bone age examination. Data were analyzed with χ^2 to determine association between variables. The association between age and serum ferritin level with bone age deficit was analyzed with regression logistic model.

Results Subjects consisted of 49 patients with thalassemia major. All subjects had bone age deficit. Most boys were in age group of ≥ 10 years and had bone age difference ≥ 36 months, while most girls were < 10 years and had bone age difference < 36 months. Subjects with bone age difference < 36 months mostly had serum ferritin level $< 5,000$ ng/dL, while most subjects with bone age difference ≥ 36 months had serum ferritin level $\geq 5,000$ ng/dL. This was statistically significant ($\chi^2=4.573$, $P=0.032$). There was association between age and bone age deficit (OR=13.461, 95% CI 3.199;56.640), but not with serum ferritin level (OR= 2.199, 95% CI 0.532;9.095).

Conclusion In thalassaemic children, bone age deficit is associated with age, but not with serum ferritin level. [Paediatr Indones 2008;48:33-36].

Keywords: growth, serum ferritin level, bone age, thalassemia major

Thalassemia major is a chronic disease that leads to growth impairment such as short stature and delayed puberty.¹⁻³ Study in Malaysia shows that the prevalence of short stature in transfusion-dependent thalassemias was 54.5%,⁴ and was more prevalent in the age of 10 years.⁴ Thalassemia major causes severe anemia that needs regular transfusion with hypertransfusion method. This method leads to iron overload which may result in endocrine abnormalities and bone disturbance.⁵

Iron overload can be determined by direct and indirect methods. Direct method with liver biopsy is the most accurate one, but it is invasive. Indirect method with serum ferritin level measurement is reliable, easy to perform, low cost, and had no side effects.⁶ There were several studies evaluated the association between serum ferritin level and growth impairment,^{4,7,8} but they did not perform bone age examination.

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The aim of this study was to determine the association between age and serum ferritin level with bone age disturbance in children with thalassemia major that received repeated blood transfusions.

Methods

This cross sectional study design was conducted at the Pediatric Thalassemia Clinic of Hasan Sadikin Hospital Bandung during March-May 2007. The inclusion criteria were patients with thalassemia major that received repeated blood transfusions and had complete medical records. We excluded patients with infections by performing blood analysis (hemoglobin, WBC, platelet count, hematocrit, C-reactive protein), feces, and urine examinations. The patients were excluded if the results were abnormal.

Subjects were classified into two age groups: <10 years and ≥10 years. Patients with thalassemia can grow normally until 10-12 years, but after that, some of them can have growth impairment.⁹ We performed physical examination, serum ferritin measurement, and bone age examination. A child was diagnosed as short stature if the height was below third percentile on National Center for Chronic Disease Prevention and Health Promotion (CDC) 2000 curve.¹⁰

Serum ferritin level was examined by ECLIA methods,¹¹ then the results were classified into two groups: <5,000 ng/dL and ≥5,000 ng/dL.

Bone age was reviewed by one radiologist, from hand radiograph (including wrist), based on Greulich and Pyle's Radiographic Atlas of Skeletal Development.¹³ The chronological age was subtracted with the bone age result to get the bone age difference. The bone age difference was then classified into two groups: <36 months and ≥36 months. The association between each variable was analyzed with χ^2 . Association between age and serum ferritin level with bone age deficit was analyzed with regression logistic.

Results

There were 49 eligible subjects. There were no difference between the number of boys (51%) and girls (49%). Most boys were in age group of ≥10 years

and had bone age difference ≥36 months, while most girls were <10 years and had bone age difference <36 months, as seen in **Table 1**.

All subjects had bone age deficit. There were 25 (51%) subjects with bone age difference ≥36 months, while the rest had bone age difference <36 months. There was association between age and bone age deficit. This results were statistically significant ($\chi^2=17.308$; $P<0.001$).

Subjects with bone age difference <36 months mostly had serum ferritin level <5,000 ng/dL, while most subjects with bone age difference ≥36 months had serum ferritin level =5,000 ng/dL. This results showed that serum ferritin level was higher in patients with bone age difference ≥36 months compared with those <36 months. This was statistically significant ($\chi^2=4.573$, $P=0.032$), as seen in **Table 2**.

Table 1. Subjects' characteristics

Characteristics	Bone Age Deficit		Total
	<36 months n=24 (49%)	≥36 months n=25 (51%)	
Boys	11 (44%)	14 (56%)	25
<10 years	8	2	10
≥10 years	3	12	15
Girls	13 (54%)	11 (46%)	24
<10 years	12	8	20
≥10 years	1	3	4

Table 2. Distribution of subjects according to age and serum ferritin level

Variable	Bone age difference		Total	
	<36 months n = 24 (49%)	≥36 months n = 25 (51%)		
Age				
<10 years	20	6	26	$\chi^2=17.308$
≥10 years	4	19	23	$P=0.000$
Serum ferritin level (ng/dL)				
<5,000	15	8	23	$\chi^2=4.573$
≥5,000	9	17	26	$P=0.032$

Table 3. Logistic regression between age and serum ferritin level with bone age deficit

Variable	Koeficient β	SE (β)	P value	OR (95% CI)
Age	2.600	0.733	0.000	13.461 (3.199;56.640)
Serumferritin level	0.788	0.724	0.277	2.199 (0.532;9.095)

We analyzed association between age and serum ferritin level with bone age deficit, and there were association between age and bone age deficit, but not with serum ferritin level, as seen in **Table 3**.

Discussion

In this study, most boys were in the age group of ≥ 10 years, while most girls were in the age group of < 10 years. According to sex, this result was different than the other studies that found most of growth impairments occurs in girls aged 10-15 years.¹⁵

This study showed that bone age deficit that poor prognosis (≥ 36 months) mostly occurs in boys. A study in Italy also found that bone lesion is more severe in boys compared with that in girls.¹⁶

Most subjects with bone age difference ≥ 36 months were in the age group of ≥ 10 years. This result was similar with other studies who reported that growth retardation occurs in children > 10 years.^{4,17} Previous studies found that 64% boys and 35% adolescent girls had growth and sexual impairment during puberty.^{18,19} Another study in Italy showed that even in those who had received adequate desferoxamine, there were still bone lesions that mainly affecting long bone metaphyses.²⁰

Properly treated thalassemia patients can grow normally until 10-12 years, but a growth impairment can still occurs thereafter.⁹ This might be due to direct toxicity of iron overload to osteoblast.⁹

All subjects had bone age disturbance. This might be due to inadequate transfusion methods they got. All subject did not get hypertransfusion from the time of diagnosis (hypertransfusion is a method to maintain hemoglobin level 10.5-11 g/dL), so that they were in chronic anemia condition that leads to tissue hypoxia. Hypoxia leads to cells damage, so iron uptake in damaged cells will increase that leads to organ dysfunction.²¹

Four subjects that had bone age difference ≥ 36 months still had normal height. This is because they still had normal endocrine function.⁹

A group with bone age difference ≥ 36 months had higher serum ferritin level compared with that with bone age difference < 36 months. A study by Brook¹⁴ found that patients with bone age difference ≥ 36 months had poor prognosis compared with

patients with bone age difference < 36 months. Although the association between serum ferritin level and bone age deficit was not statistically significant, but serum ferritin level was not excluded because there was biological phenomenon that ferritin can impair bone metabolism by direct toxicity to osteoblast.⁹ This was likely occurred because the higher level of serum ferritin were not purely caused by regular transfusions, there were other factors that were not analyzed at the time of the study. There are several factors that influences serum ferritin level, such as acute infection due to bacterial or virus, or vitamin C deficiency.¹¹ Although this study had already tried to exclude patients with infection, but we could not perform other laboratory examination such as vitamin C level due to limited equipment availability.

More iron overload leads to more severe bone disturbance. Other studies also found that bone age disturbance in patients with thalassemia is caused by iron overload.²² Study that observed the association between serum ferritin level and growth retardation in thalassemic patients showed that mean serum ferritin level in group with short stature is higher than in those with normal stature.⁸ Other studies showed most children with growth impairment had serum ferritin level = 5,000 ng/dL.¹²

We can conclude that in children with thalassemia major, bone age deficit is associated with age, but not with serum ferritin level.

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