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Original Article

Delayed puberty in thalassemia major patients

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ABSTRACT

Background Delayed puberty is the most common endocrine complication in thalassemia major. The main cause of delayed puberty in thalassemia major is the failure of the hypothalamic-pituitary axis due to iron accumulation in the pituitary.

Objectives The purpose of this study was to determine the prevalence of delayed puberty in β-thalassemia major patients in the Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta. This study also evaluated the adequacy of chelation therapy and determined serum gonadotropin and sex hormone levels in these patients.

Methods Seventy-two patients with β-thalassemia major aged 13-18 years old who visited the Thalassemia Outpatient Clinic of Cipto Mangunkusumo Hospital during February-July 2003 were included in the study. Each subject underwent examinations to determine the body weight and height, pubertal status, serum iron level, total iron binding capacity, and the levels of serum LH, FSH, estradiol (in girls) or testosterone (in boys).

Results Delayed puberty occurred in 40 of 72 patients (56%). The majority of patients with delayed puberty showed low levels of serum LH, estradiol, and testosterone whereas low levels of serum FSH only occurred in 6 of 21 boys and 11 of 19 girls. Most of the patients without delayed puberty had normal levels of serum LH, FSH, and estradiol, but 8 of 16 boys showed decreased serum testosterone levels. Only 3 patients used chelation therapy adequately, all of them showed normal puberty.

Conclusions The prevalence of delayed puberty in β-thalassemia major patients in this study was still high (56%). Periodic examination and recording of pubertal stage need to be done in girls who have reached 8 years old and boys who have reached 9 years old so that early detection and management of delayed puberty can be done. **[Paediatr Indones 2004;44:143-147].**

Keywords: *delayed puberty, endocrine complication, thalassemia major, chelation therapy, serum gonadotropin, sex hormone*

Thalassemia is a hemolytic disease that gives many problems to the patients. Patients with severe thalassemia who do not receive blood transfusions die at an early age due to complications of anemia.[1] With regular transfusions, survival rate increases but as a consequence, iron overload occurs in various tissues and organs including the endocrine glands which can lead to organ dysfunction.[1-4] As the survival rate of thalassemic patients increases, endocrine complications due to iron overload become more common. Failure of puberty, which occurs in 50% of patients, is the most common endocrine complication, followed by secondary amenorrhea, primary hypothyroidism, diabetes mellitus, and hypoparathyroidism.[5]

The main purpose of this study was to determine the prevalence of delayed puberty in thalassemia major patients in the Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta. This study also aimed to evaluate the adequacy of chelation therapy in thalassemia major patients with delayed puberty and to determine serum gonadotropin and sex hormone levels in these patients.

Methods

This was a cross-sectional descriptive study conducted

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at the Thalassemia Outpatient Clinic, Department of Child Health, Cipto Mangunkusumo Hospital during February-July 2003. The subjects consisted of 72 β-thalassemia major patients who were selected by consecutive sampling method. Patients were eligible for the study if they were β-thalassemia major patients aged 13-18 years old (girls) or 14-18 years old (boys) and their parents agreed to participate in the study. Subjects were excluded if they had received hormonal replacement therapy (such as testosterone, estrogen, progesterone, human chorionic gonadotropin, or human menopausal gonadotropin) or had accompanying disease that could cause delayed puberty.

Data regarding identity, date of birth, age at the time of diagnosis of thalassemia established, the amount of blood transfusions received, and the use of chelation therapy (adequate chelation therapy if >3 times a week[6]) were obtained from the patients' medical records. Each subject was examined to measure the body weight and height and to assess the pubertal stage according to Tanner. In this study, delayed puberty was defined as the absence of any breast development at the age of 13 years in girls or the absence of increase in testicular volume (<4 mL) at the age of 14 years in boys.[7] The average level of hemoglobin prior to transfusion was obtained from the medical records. Blood samples were taken to determine serum iron (SI) level, total iron binding capacity (TIBC), serum luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol (in girls) or testosterone levels (in boys). Iron overload was defined as transferrin saturation (SI/TIBC x 100%) of >55%.[8]

The study protocol was approved by the Committee of the Medical Research Ethics of Medical School, University of Indonesia. Data collected were processed using SPSS 11.0 computer program.

Results

During February-July 2003, 72 patients with β-thalassemia major aged 13-18 years old participated in the study. The characteristics of subjects can be seen in **Table 1.**

Delayed puberty occurred in 40 patients (56%) consisting of 21 boys and 19 girls. The number of patients with delayed puberty who have received more than 20 liters of blood transfusions were 39 (98%), who had an average hemoglobin level of >6-9 g/dL were 36 (90%), and who experienced iron overload were 36 (90%).

TABLE 1. SUBJECTS' CHARACTERISTICS

Sex:	Male	37 (51%)
	Female	35 (49%)
Age at the time of diagnosis		2 months–13 years
Nutritional status		
	Normal	30 (42%)
	Underweight	42 (58%)
Amount of blood transfusions (liters)		
	<20	3 (4%)
	>20-40	7 (10%)
	>40-60	28 (39%)
	>60	34 (47%)
	Average (SD)	56.9 (17.9)
Range		15-96
Transferrin saturation (%)		
	<55	11 (15%)
	>55	61 (85%)
	Average (SD)	75.3 (20.1)
	Range	5.5-99.4
Average hemoglobin level (g/dL)		
	Average (SD)	7.2 (0.7)
	Range	5.0-8.9
Chelation therapy		
	Adequate	3 (4%)
	Inadequate	69 (96%)

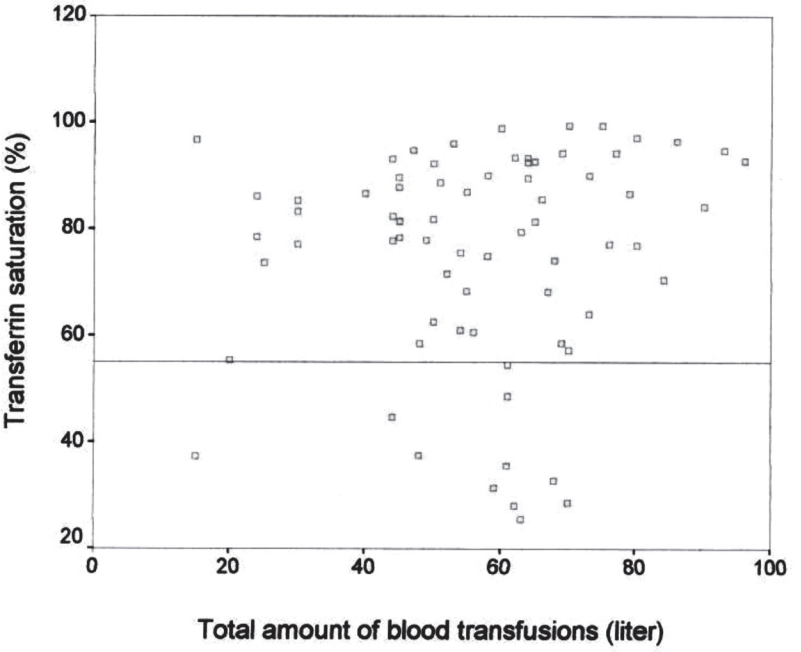

Figure 1. Distribution of transferrin saturation according to total amount of blood transfusions

Malnutrition occurred in 24 patients (62%) with delayed puberty. Adequate chelation therapy only occurred in 3 patients; all of them had normal puberty.

Figure 1 shows that most of the patients who had elevated transferrin saturation had received more than 20 liters of blood transfusions. On the other hand, several patients who had more than 20 liters of blood transfusions did not show elevated transferrin saturation.

Table 2 shows serum LH, FSH, and estradiol levels in female patients with delayed puberty, while **Table 3** shows serum LH, FSH, and testosterone levels in male patients.

Discussion

In this study, delayed puberty occurred in 40 out of 72 (56%) patients. This result was very different from that studied by Wahidiyat *et al*[9] in 1983, where 36 of 40 patients (90%) did not experience puberty. Several factors could be responsible for this difference such as the average of hemoglobin level prior to transfusion, nutritional status, and the presence of accompanying disease, which were not included in the latter study. Nevertheless, it seems that during the past 20 years, there has been an improvement in the management of thalassemic patients so that more patients could reach pubertal age.

Pubertal development itself is influenced by many factors such as genetics, nutrition, chronic anemia, and systemic disease.[10] In thalassemia major, aside from iron overload, those factors contribute to the occurrence of delayed puberty. In this study, malnutrition was found in 24 out of 40 patients (60%) with delayed puberty. Chronic anemia was also common in our patients who had delayed puberty with an average hemoglobin level of 7.1 g/dL.

As mentioned previously, iron overload is the main cause of delayed puberty in thalassemia major. Transferrin saturation is one of the methods that can be used to detect iron overload.[8] In this study, iron overload occurred in 36 patients (40%) with delayed puberty. However, 25 of 32 patients with normal puberty also showed iron overload. It is possible that iron overload had not occurred when these patients developed secondary sex characteristics.

TABLE 2. SERUM LH, FSH, AND ESTRADIOL LEVELS IN FEMALE PATIENTS

	Normal puberty	Delayed puberty
	n	n
LH		
Low	0	15
Normal	16	4
Total	16	19
FSH		
Low	2	11
Normal	14	8
Total	16	19
Estradiol		
Low	4	14
Normal	12	5
Total	16	19

TABLE 3. SERUM LH, FSH, AND TESTOSTERONE LEVELS IN MALE PATIENTS

	Normal puberty	Delayed puberty
	n	n
LH		
Low	2	18
Normal	14	3
Total	16	21
FSH		
Low	0	6
Normal	16	15
Total	16	21
Testosteron		
Low	8	21
Normal	8	0
Total	16	21

Figure 1 shows that the amount of blood transfused was not directly proportional with transferrin saturation level. There were 2 patients with blood transfusions <20 liters who had elevated transferrin saturation. This might be caused by the increase of gastrointestinal iron absorption due to ineffective erythropoesis which led to iron accumulation. On the contrary, 10 patients who had more than 20 liters of blood transfusions did not show elevated transferrin saturation even though they did not use adequate chelation therapy. The exact explanation was not known but certain conditions are believed to cause a decrease in transferrin saturation, such as chronic inflammation or infection, uremia, and malignancy. But unfortunately, such data were not available in this study.[11,12]

In this study, only 3 patients used chelation therapy adequately and they all had normal puberty whereas none of the patients with delayed puberty used adequate chelation therapy. Bronspiegel-Weintrob *et al*[13] reported that 90% of thalassemic patients who used chelation therapy adequately from an early age experienced normal puberty. While if therapy was given at older age, only 38% experienced normal puberty.

Although the exact mechanism in which iron overload causes tissue damage is not completely understood, there are evidences that free radical formation and lipid peroxidation can lead to the damages of mitochondrial, lysosomal, and sarcoplasmic membranes.[14,15] The presence of iron deposits and oxidative damage by free radicals affects the pituitary, ovarian follicles, and testis.[6] As the result, the hypothalamic-pituitary-gonadal axis function is disturbed which eventually leads to delayed puberty. In this study, most patients with delayed puberty had low levels of serum LH, estradiol, and testosterone while low serum FSH level was found in 11 of 19 female patients and 6 of 21 male patients. This showed a failure in the hypothalamic-pituitary-gonadal axis so that gonadotropin secretion decreased. Consequently, gonadal stimulation was reduced which caused estradiol and testosterone secretion decrease. This result was in accordance with those studied by others who found that pituitary gonadotropin defficiency is the main cause of delayed puberty in thalassemia major.[3,16] Actually, in order to differentiate hypothalamic from pituitary defects, determination of LH and FSH responses to gonadotropin-releasing hormone (GnRH) stimulation is needed. Moreover, in this study, it was not known whether the low serum levels of estradiol and testosterone were also caused by gonadal failure because stimulation tests with human chorionic gonadotropin (HCG) or human menopausal gonadotropin (HMG) were not performed.

Several patients with delayed puberty showed normal serum LH and FSH levels but low serum estradiol and testosterone levels. This inferred that the defect was located in the gonad. To confirm this, a stimulation test with HCG (in males) or HMG (in females) should be conducted.

A portion of patients with normal puberty had low serum estradiol level (4 of 16) and low serum testosterone level (8 of 16). It seemed that these patients started to experience derangement in sex hormone secretion sometime after pubertal onset which could be caused by inadequate gonadotropin secretion or gonadal failure. Such condition can lead to secondary amenorrhea in

females[5,17,18] and secondary hypogonadism[5] in males so that long-term monitoring is needed.

This study had several limitations. The definition of delayed puberty was based on the absence of breast development in girls and no increase in testicular volume in boys. This study did not include patients who needed more than 5 years to complete pubertal development. Therefore, there was a possibility that the prevalence of delayed puberty in this study was lower than the actual case. The measurement of serum LH, FSH, estradiol, and testosterone levels was only performed once. Ideally, the measurement should also be performed after stimulation with GnRH, HCG (in boys), and HMG (in girls) to evaluate the hypothalamic-pituitary-gonadal axis more accurately. Data regarding accompanying disease were not always available in the medical records.

In conclusion, the prevalence of delayed puberty in β-thalassemia major patients in this study was still high (40 of 72 or 56%). For that reason, periodic examination and recording of pubertal stage need to be done in girls who have reached 8 years old and in boys who have reached 9 years old so that early detection and management of delayed puberty can be done.

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