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Original Article

Some aspects of thyroid dysfunction in thalassemia major patients with severe iron overload

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Abstract

Background Severe iron overload due to recurrent transfusions for chronic anemia and inadequate iron chelation therapy in thalassemia major patients result in various complications, including hypothyroidism. Currently, there has been no data on the prevalence of hypothyroidism in thalassemia major patients at the Thalassemia Centers, Department of Child Health, Cipto Mangunkusumo Hospital (DCH CMH).

Objective To study the prevalence of primary hypothyroidism in thalassemia major patients in the Thalassemia Center, DCH MCH.

Methods We performed a cross-sectional, descriptive study. All thalassemia major subjects aged 0-18 years with severe iron overload underwent thyroid function examination. Primary hypothyroidism was defined as either normal (compensated) or decreased (decompensated) free T4 (FT4) levels, along with elevated sensitive thyroid-stimulating hormone (TSH) levels.

Results 179 subjects enrolled this study with male: female ratio of 1:1.6. The prevalence of primary hypothyroidism in thalassemia major patients with severe iron overload was 26.8% (48/179). Of those 48, 45 had compensated hypothyroidism and 3 had decompensated hypothyroidism, 25.1% and 1.7% of the total subjects, respectively. Compensated hypothyroidism was observed in 17 subjects aged ≤10 years and in 28 subjects aged >10 years. All 3 decompensated hypothyroidism cases were >10 years of age. No relationship was found between the occurrence of primary hypothyroidism and mean pre-transfusion Hb levels (P=0.481, OR 1.30; 95% CI 0.63 to 2.68), elevated serum ferritin levels (P=0.74, OR 0.89; 95% CI 0.46 to 1.75), and compliance to iron chelation therapy (P=0.570, OR 0.76; 95% CI 0.35 to 1.65). Based on multivariate analysis, only age of < 10 year-old (P=0.029, OR 0.469; 95% CI 0.23 to 0.93) was significantly associated with primary hypothyroidism. Further analysis using receiver operator curve (ROC) technique found that age of 8.5 year-old was the cutoff value to predict the risk of hypothyroidism.

Conclusion The prevalence of primary hypothyroidism in our study is high. The occurrence of hypothyroidism is associated with age. **[Paediatr Indones. 2011;51:66-72]**.

Keywords: *thalassemia major, endocrine, primary hypothyroidism, iron overload, iron chelation therapy*

Increasing life expectancy in thalassemia major patients leads to various complications due to iron overload in some organs, including the thyroid gland, resulting in hypothyroidism.[1-9] Several studies have reported the prevalence of hypothyroidism in thalassemia major, ranging from 6% to 50%, depending on patients' age, age at iron chelation therapy initiation, and level of compliance to iron chelation.[2,10-14] Although there are now several options in forms of iron chelation therapy

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for thalassemia major patients, adherence to its use remains problematic. The clinical manifestations of hypothyroidism are nonspecific and patients are often unaware of their condition. Thus, early diagnosis of hypothyroidism could be more rapidly done through thyroid function tests.[8,15-17]

Despite the large numbers of new and returning patients in the Thalassemia Center, CMH, there has been no data collected on the prevalence of hypothyroidism in these patients.[18] In addition, there has been little research on primary hypothyroidism in the pediatric thalassemia major population in Indonesia. This study aims to determine the prevalence of thyroid dysfunction in thalassemia major patients using severe iron overload as one of the measures. It is hoped that this knowledge will help decrease morbidity and mortality of primary hypothyroidism as a treatment complication.

Methods

We conducted a cross-sectional, descriptive study at the Thalassemia Center, DCH CMH, Jakarta, from May to July 2010. Subjects were thalassemia major patients aged 0-18 years with severe iron overload, who underwent their last transfusion $\geq$ 2 weeks prior the study. The diagnosis of thalassemia major is established based on the need for regular transfusions, electrophoresis/Hb analysis examination, and the evidence of severe iron overload based on serum ferritin levels of >2500 ng/mL. We excluded patients with acute infections, goiters, and those whose parents had a history of thyroid disorders. This study was approved by the Research Ethics Committee of the Faculty of Medicine, University of Indonesia. All subjects' parents signed the informed consent.

Data regarding age, gender, type of thalassemia, disease duration, type of iron chelation therapy, adherence to chelation therapy, pre-transfusion Hb, and cumulative amount of transfused blood, were recorded. After conducting a patient history on the clinical symptoms of hypothyroidism, we obtained blood samples from the subjects and immediately sent them to the Clinical Pathology Laboratory of CMH for thyroid function tests (FT4 and TSH) and serum ferritin level measurement using electrochemiluminescence immunoassay (ECLIA) with a Roche Diagnostics Cobas E601 Analyzer.

Primary hypothyroidism was defined as the decrease in thyroid hormone production due to dysfunction of the thyroid gland itself, while secondary and tertiary hypothyroidism occurs due to dysfunction of the pituitary and hypothalamus. Primary hypothyroidism was established in patients with elevated TSH levels and normal (compensated) or decreased (decompensated) FT4 levels.[16,19,20]

Data was analyzed using the statistical package for the social sciences (SPSS) version 11.5. Subjects' characteristics were presented in percentages, means (standard deviation), and medians (range). The associations between variables and the incidence of hypothyroidism were analyzed using chi-square test or Fisher's Exact test. Mean differences were analyzed using Student's t-test or Mann-Whitney test, while the multivariate analysis was conducted using the Backward Stepwise Regression test. $P < 0.05$ was considered statistically significant.

Results

During study period, 179 subjects with thalassemia major fulfilled the inclusion criteria. There was a male:female ratio of 1:1.6. Patients with homozygous β-thalassemia accounted for 60.3% of the subjects, and the remainder had HbE-β-thalassemia. The mean age at diagnosis was 10.8 years (SD 4.1 years) with subjects ranging from 0 to 12.9 years old, while 31.8% of subjects were diagnosed before the age of 12 months. The average transfusion volume per year was 232.7 mL/kg/year (SD 63.6 mL/kg/year). The mean age of diagnosis was 1 year (0-12.9 years) for homozygous β-thalassemia, and 4.4 years (range 0-12 years, SD 2.8 years) for HbE-β-thalassemia. Other subject characteristics are shown in **Table 1.**

The majority of subjects received oral DFP iron chelation therapy, including most β-thalassemia major patients (47.0% of total) and HbE-β-thalassemia patients (30.2% of total). The number of subjects who adhered to the iron chelation therapy was less than those who did not. DFX and the combination of DFP and DFO were rarely used in our subjects. We observed primary hypothyroidism in 48 subjects (26.8%), as stated in **Table 2**. The youngest subject with homozygous β-thalassemia who developed

Table 1. Subjects' characteristics according to age and type of thalassemia

Characteristic	Total	homozygous β-thalassemia		HbE-β-thalassemia	
		≤10 yrs	>10 yrs	≤10 yrs	>10 yrs
Sex (male:female), n	83 : 96	24 : 32	25 : 27	14 : 16	20 : 21
Mean age, years (SD)	10.8 (4.1)	7.0 (2.2)	14.2 (2.1)	7.7 (2.1)	14.2 (2.4)
Mean duration of illness, years (SD)	8.1 (4.3)	5.5 (2.4)	12.3 (3.3)	4.0 (2.1)	9.3 (3.4)
Mean pre-transfusion Hb,g/dL	6.8 (0.7)	6.8 (0.5)	6.9 (0.7)	6.8 (0.5)	6.7 (0.8)
Age at diagnosis, yrs (range)		1.0 (0 to 12.9)		4.4 (0 to 12)	
Cumulative amount of blood, thousands of mL*	29.6 (1.4-231.0)	18.8 (1.4-42.8)	58.2 (11.2-97.9)	11.1 (2.8-120.1)	43.3(9.9-231.0)
Mean serum ferritin level, ng/mL (SD)	5,309 (2,886)	5,026 (2,171)	6,667 (3,824)	4,089 (1,499)	4,868 (2,546)
Type of iron chelation therapy, n (%)					
DFO	30 (16.7)	10 (5.7)	8 (4.4)	8 (4.4)	4 (2.2)
DFP	138 (77.1)	46 (25.7)	38 (21.2)	21 (11.7)	33 (18.4)
DFX	6 (3.4)	0 (0.0)	1 (0.6)	1 (0.6)	4 (2.2)
DFO+DFP	5 (2.8)	0 (0.0)	5 (2.8)	0 (0.0)	0 (0.0)
Adherence to iron chelation therapy, n, (%)					
Yes	60 (33.5)	21 (11.7)	18 (10.1)	6 (3.3)	15 (8.4)
No	119 (66.5)	35 (19.6)	34 (19.0)	24 (13.4)	26 (14.5)

*Median (range); DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox

Table 2. Thyroid function of subjects

Thyroid function	Type of thalassemia				Total (n=179)	(%)
	-β homozygous		-HbE-β			
	≤10 yrs	>10 yrs	≤10 yrs	>10 yrs		
Euthyroid	48	35	21	27	131	73.2
Hypothyroid	8	17	9	14	48	26.8
compensated	8	14	9	14	45	25.1
decompensated	0	3	0	0	3	1.7

Table 3. Differences in variables' means and thyroid status

Variable	Hypothyroid (n=48)		Euthyroid (n=131)		P	Compensated Hypothyroid (n=45)		Decompensated Hypothyroid (n=3)		P
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Mean age, years	12.5	3.9	10.3	4.1	0.001	12.4	3.9	15.0	2.6	0.256
Mean duration of illness, years*	9.3	4.8	7.7	4.1	0.042	9.2	4.8	10.7	5.5	0.606
Mean cumulative blood transfused, thousand of mL*	43.7	26.9	34.2	29.9	0.015	42.3	26.9	65.1	17.1	0.155
Mean transfusion/yr, mL/kg/year	247.7	74.2	227.2	58.6	0.056	242.2	49.9	200.0	0.0	0.154
Mean pre-transfusion Hb, g/dL	6.8	0.6	6.9	0.7	0.211	6.7	0.6	7.3	0.4	0.093
Mean serum ferritin level,thousands of ng/mL*	5.1	2.3	5.4	3.1	0.792	5.0	2.4	6.0	1.1	0.487

* Mann Whitney rank test; C: compensated; D: decompensated

primary hypothyroidism was 4.5 years old, while that for HbE-β-thalassemia was 5 years old.

In comparing the means of the variables listed in **Table 3** to thyroid status, there were significant differences in the hypothyroid group compared to the euthyroid group, for age, duration of illness, and cumulative amount of blood transfused. However, there were no significant differences between the the subjects' thyroid status and the mean transfusion volume/year, the mean pre-transfusion Hb levels and the mean serum ferritin levels. There was also no significant difference in subjects' characteristic based on type of hypothyroidism.

Table 4 shows significant risks for developing hypothyroidism based on age, duration of illness, and the cumulative volume of blood transfused. For subjects who had undergone regular iron chelation therapy, there was no significant risk difference for hypothyroidism between the subjects with disease duration of ≤ 8 years and > 8 years (P=0.451, OR 0.63; 95% CI 0.19 to 2.11). In addition, there were no significant hypothyroidism risk differences for the following variables: gender, pre-transfusion Hb levels, adherence to iron chelation therapy, and serum ferritin levels. The risk of hypothyroidism was also statistically insignificant when we compared the subjects with serum ferritin levels of < 5,000 and > 10,000 ng/mL (P=1.000, OR 1.18; 95% CI 0.30 to 4.61).

Further comparison of the hypothyroid C and D groups, revealed no statistically significant differences in the variables age, gender, duration of illness, cumulative blood volume transfused, adherence to iron chelation therapy, and serum ferritin levels. However, there was a significant risk difference in the association of mean pre-transfusion Hb levels of <7 g/dL and ≥7 g/dL to the occurrence of compensated and decompensated hypothyroidism. However, when we compared only subjects with hypothyroidism who used regular iron chelation therapy, there were no significant risk difference for the occurrence of compensated and decompensated hypothyroidism with their pre-transfusion Hb (P=1.000, OR 1.75; 95% CI 0.13 to 23.70).

Bivariate analysis showed that three independent variables (age, duration of illness, and cumulative volume of blood transfused) contributed to statistically

Table 4. Association of variables with hypothyroidism

Variable	Hypothyroid		P	OR	95% CI	Hypothyroid		P	OR	95% CI
	Yes	No				Decompensated	Compensated			
Sex										
Male	26	70	0.931	1.03	0.50 to 2.00	2	24	1.000	1.75*	0.15 to 20.71
Female	22	61				1	21			
Age (year)										
≤ 10	16	68	0.041	0.49	0.25 to 0.98	0	16	0.541	1.10*	0.991.23
> 10	32	63				3	29			
Pre-transfusion Hb (mg/dL)										
<7	30	71	0.481	1.30	0.63 to 2.63	0	30	0.047	1.20*	0.98 to 1.48
≥7	18	60				3	15			
Duration of illness (yr)										
≤8	21	81	0.030	0.48	0.25 to 0.94	1	20	1.000	0.63*	0.05 to 7.40
>8	27	50				2	25			
Cumulative blood transfused (mL)										
≤30.000	18	72	0.038	0.49	0.25 to 0.97	0	18	0.637	0.37*†	0.04 to 3.56
>30.000	30	59				3	27			
Serum ferritin level (ng/mL)										
2.500-5.000	28	80	0.740	0.89	0.461.75	0	28	0.149	6.44*†	0.676 to 2.31
>5.000	20	51				3	17			
Iron chelation therapy adherence										
Yes	14	46	0.570	0.76	0.35 to 1.65	1	13	1.000	1.23*	0.101 to 4.78
No	34	85				2	32			

* Fisher exact test; † corrected value.

Table 5. Logistic regression analysis of primary hypothyroidism

Independent variable	P	OR	95% CI
Cumulative blood transfused ≤30,000 mL*	0.741	0.83	0.28 to 2.51
Duration of illness ≤8 yrs*	0.585	0.74	0.25 to 2.18
Age ≤10 yrs*	0.417	0.65	0.23 to 1.83
Age ≤10 yrs¤	0.029	0.46	0.23 to 0.93

All significant independent variables included; * logistic regression analysis using enter method ; ¤ logistic regression analysis using Backward Stepwise Regression test

significant risk for the occurrence of hypothyroidism (**Table 5**). However, further analysis using Backward Stepwise Regression test revealed that only age less than 10 year-old was associated with the occurrence of primary hypothyroidism (P=0.029, OR 0.46; 95% CI 0.23 to 0.93). Using receiver operator curve (ROC) technique, we obtained that age of 8.5 year old (73% sensitivity, 43% specificity), duration of illness of 6.3 years (73% sensitivity, 43% specificity) and the cumulative amount of transfused blood of 22,000 mL (71% sensitivity and 41% specificity) was the cut-off point to predict the risk for the occurrence of hypothyroidism.

Discussion

Our study revealed a high percentage of hypothyroidism, 48/179 cases (26.8%), with 17 cases (9.5%) occurring at the age of ≤10 years. This percentage was quite high, compared with the results of other studies, which ranged from 6-20%.[11-14,21-29] The differences in prevalence may be caused by different protocols of therapy, namely the pre-transfusion Hb value used to warrant transfusion and patients' adherence to iron chelation therapy. In the Thalassemia Center, CMH, blood transfusion is carried out on patients when their Hb decreases to <8 g/dL, while in other studies, the pre-transfusion Hb levels were maintained above 8 g/dL. The protocol used in our Thalassemia Center led to higher hypoxia exposure. Hypoxia is one cause of thyroid gland impairment.[30] The euthyroid condition in the five subjects with mean pre-transfusion Hb >8 g/dL and the presence of significant risk differences between compensated and decompensated hypothyroidism with regards to mean pre-transfusion Hb, seem to support this hypothesis. In addition, the low adherence (33.5%) to iron chelation therapy also increased the risk of hypothyroidism. Regular and adequate use of iron chelation has been shown to decrease the chance of hypothyroidism due to iron overload. This therapy was even shown to restore thyroid function in 52% of the subjects in a study by De Sanctis *et al*.[31] In other words, adequate iron chelation therapy and blood transfusions at ideal pre-transfusion Hb to justify transfusing should be implemented to decrease thyroid gland damage due to iron overload and hypoxia and to restore thyroid function to its normal state.

Despite the high prevalence of hypothyroidism in this study, all subjects were clinically euthyroid, similar to previous study.[27] Complaints of lethargy and failure to thrive obtained from subjects with hypothyroidism could also be attributed to anemia as a part of thalassemia manifestation.

In this study, we found that subjects aged ≤ 10 years, cumulative volume of transfused blood ≤ 30,000 mL, and duration of illness of ≤ 8 years had statistically significant lower incidences of hypothyroidism. Similar to several other studies, we also did not find significant risk differences in hypothyroidism for the serum ferritin level variable.[11,12] This observation may be due to the nature of serum ferritin level as an overall indicator of iron accumulation in the body. However, serum ferritin level in itself cannot give a complete picture of the body's actual condition, because its level can be influenced by other factors such as inflammatory processes, liver abnormalities, and malignancies.[32,33] In addition, multifactorial etiologies from various endocrine abnormalities in thalassemia major, the difference of iron distribution in various organs, and the difference in sensitivity of various endocrine organs to iron cumulation are all possible reasons that we did not find associations between iron overload and thyroid dysfunction.[21]

This study was conducted in the Thalassemia Center, CMH, one of the referral centers for thalassemia patients in Jakarta and the surrounding

area, and involved only patients aged 0-18 years. Therefore, the subjects included in this study were assumed to represent the population of pediatric thalassemia patients in Indonesia. This study also included two types of thalassemia major most commonly found in Indonesia, homozygous β-thalassemia and HbE-β-thalassemia. To lower the chance of selection bias in this study, we excluded thalassemia patients with other conditions that could cause thyroid function impairment, such as goiter findings in clinical examination and a parental history of thyroid disorder.

One of the limitations of this study was that the measurement of variables was only conducted once, as it is a cross-sectional study. Another limitation was the consecutive sampling method that we used. In addition, the data on adherence to regular iron chelation therapy relied entirely on parents'/ guardians'/subjects'reports, making it prone to recall bias. The data on the cumulative volume of blood received by the subjects since they were first diagnosed was taken entirely from secondary data in the subjects' medical records in CMH. However, because CMH is a teaching hospital, the quality of its medical records is fairly reliable. The measurement for severity of iron accumulation entirely relied on the results of serum ferritin levels as up to this point, it was the most practical test available in Indonesia to measure the severity of iron accumulation in the body.

The fairly high prevalence of hypothyroidism in this study suggests the importance of regular thyroid function monitoring for pediatric thalassemia major patients, in order to detect and implement early treatment. Moreover, with the finding of subjects developing hypothyroidism before 10 years old, it is important to develop new recommendations for initiation of thyroid function screening on younger aged children in the Thalassemia Center, DCH CMH. Based on the analysis using ROC curves, the age 8.5 years can be recommended as the age to initiate thyroid function test in patients with thalassemia major. However, the clinical condition of thalassemia major patients aged 8.5 years may vary in terms of duration of illness, due to the differences in ages of diagnosis and according to the type of thalassemia. Consequently, for clinical application purposes, it may be better to use the cutoff point of 6.3 years duration of illness (to obtain 73% sensitivity and 43% specificity), as the recommended time to initiate thyroid function tests on thalassemia major subjects. Using the cutoff point of cumulative volume of transfused blood is not recommended as a guide for initiating thyroid function examinations, due to its impractical clinical application.

In conclusion, the prevalence of primary hypothyroidism in our study was high, higher than that of other studies. The high prevalence of hypothyroidism and the finding that many subjects develop hypothyroidism prior to 10 years old points toward the importance of conducting thyroid function screenings earlier in life compared to the currently used procedures. We recommend starting thyroid function evaluations on thalassemia major patients with > 6.3 years illness duration.

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