

High Prevalence of Hypoparathyroidism in Patients with beta-Thalassemia Major

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Abstract

Introduction: Hypoparathyroidism (HPT) is an irreversible but preventable disorder caused by an iron overload which can be considered a typical complication in patients with beta-thalassemia major.

Patients and method: Parathyroid function was evaluated in 130 patients in Qom, Iran, who suffered from beta-thalassemia major. Their serum ferritin levels were checked for monitoring of chelation therapy effects.

Results: The prevalence of HPT was 14.6% (19/130). The median age of patients with HPT was significantly higher than of patients without HPT (18 vs. 15 years; P=0.03). Serum ferritin levels was not significantly different between the two groups (median: 2709 vs. 1512; P=0.95). The prevalence of cardiac diastolic dysfunction in patients with HPT was significantly higher than in normal thalassemic patients (3.1% vs. 15.8%, P=0.04). Patients with hypoparathyroidism demonstrated abnormal glucose metabolism (0% vs. 15.8%; P=0.003).

Conclusion: the high prevalence of hypoparathyroidism demonstrated poor chelation therapy in these patients. Close monitoring of ferritin level was recommended. Also, the measurement of parathyroid hormone on a regular basis for all thalassemic patients was recommended.

Keywords: beta-Thalassemia major, Hypoparathyroidism, Ferritins

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Introduction

Beta-thalassemia major, a hereditary hemoglobin disorder was first described by Cooley and Lee,(1) and is characterized by a decreased synthesis of the β -globin chain. Regular blood transfusions and chelation therapy have considerably prolonged survival in thalassemic patients.(2) Despite a significant increase in the lifespan of these patients, many endocrine abnormalities such as hypogonadism, diabetes mellitus, hypothyroidism and hypoparathyroidism (HPT) develop due to an iron overload.(3) Even though HPT is thought to be a rare complication, it may cause various neurological manifestations such as tetany, seizures, carpopedal spasms, and paresthesia.(4, 5)

In different studies which have been performed, the incidence of hypoparathyroid dysfunction varies

from 0% up to almost 22.5% of patients.(6) This discrepancy can be attributed to the small number of patients in most studies, the different treatment protocols regarding transfusion rate and chelation therapy and the different nationalities of the patients studied. For this reason, we decided to assess parathyroid function within a large group of Iranian patients suffering from beta thalassemia major, who have been regularly followed in our department and undergoing similar regular blood transfusion.

Patients and Method

We studied 130 patients with beta thalassemia major from July, 2007 through February, 2008 at a thalassemia clinic in a central city of Iran, Qom. The diagnosis of homozygous thalassemia was based on the usual hematological criteria

Table 1- Patients' characteristics in each study group

	Patients without HPT (n=111)	Patients with HPT (n=19)	p-Value
Median age (years)	15 (1-30)	18 (2-42)	0.03
Gender			0.27
Male	49 (44%)	11 (58%)	
Female	62 (56%)	8 (42%)	
Median age at first blood transfusion	12 (2-168)	6 (1-144)	0.91
Median age of start iron chelation	29 (3-240)	33 (6-144)	0.15
Median duration of transfusion therapy	162 (6-402)	186 (24-295)	0.17
Median duration of chelation therapy	132 (2-396)	168 (60-240)	0.21
Median duration transfusion without	12 (1-144)	24 (4-114)	0.38
Median interval of transfusion therapy	25 (4-309)	25 (15-40)	0.70
Poor compliance with iron chelation	29(26%)	6 (32%)	0.62
Mean of Body Mass Index (kg/m ²)	19.3	18.4	

Table 2- Symptoms and co-morbidity in each study group

	Patients without HPT (n=111)	Patients with HPT (n=19)	p-Value
Symptoms			
Seizure	7 (6%)	4 (21%)	0.06
Tetanus	14 (13%)	6 (32%)	0.08
Paresthesia	16 (14%)	8 (42%)	0.09
Carpal spasm	8 (7%)	4 (21%)	0.08
Co-morbidity			
HBV infection	0 (0%)	0 (0%)	1.0
HCV infection	0 (0%)	0 (0%)	1.0
Cardiac dysfunction	3 (3.1%)	3 (15.8%)	0.04
Diabetes mellitus	0 (0%)	3 (15.8%)	0.003

(peripheral blood evaluation and hemoglobin electrophoresis). All patients were kept on a regular transfusion program in order to keep their hemoglobin levels at least 9.5 g/dL before each transfusion. In order to reduce the iron overload caused by frequent transfusions, desferrioxamine mesylate (Desferal; Novartis, Basel, Switzerland) at a standard dose of 40-50mg/kg, 4-6 days a week, was prescribed for the patients. The drug was given by subcutaneous infusion overnight, for 8-12 hours. Hypoparathyroidism was diagnosed if patients displayed all of the below criteria:

- 1- Intact parathyroid hormone (PTH) less than 10 pg/dl
- 2- Serum calcium less than 8.5 mg/dl
- 3- Increased serum phosphate
- 4- Normal alkaline phosphatase or decreased levels
- 5- Normal values for BUN, Cr, total protein, albumin levels and magnesium

In all patients who had been diagnosed as hypoparathyroidism, Blood Urea Nitrogen (BUN) and creatinine were checked to rule out any renal dysfunction. Also, total protein and albumin levels were checked to rule out malnutrition and malabsorption. Various data, including age, sex, age of starting the transfusions, age of beginning iron chelation therapy, a history of splenomegaly, mean serum ferritin levels, a history of diabetes mellitus

and liver dysfunction (as hepatitis) were obtained for each patient. A detailed neurological history and clinical examination was carried out in all patients.

Measurements: An Iron overload was determined by a measurement of serum ferritin concentrations using ELISA (Diaplus, USA; normal range: 50-150µg/l).

Plasma intact PTH levels were determined using a direct label, 2-site ELISA intended for the quantitative determination of PTH in plasma (PTH ELISA (Intact), Biomerica, USA; normal range: 10-65 pg/ml).

Serum concentrations of calcium, phosphorous, alkaline phosphatase and magnesium were measured by routine laboratory methods.

Statistical Methods: Quantitative data was summarized as a median level which was followed by minimum and maximum values as well as qualitative data expressed as raw numbers with related frequencies. The comparison of qualitative data between two study groups was performed by independent samples *t*-test and to compare the quantitative variables between the groups; a *chi* square test or related Fisher exact test (when appropriate) were used.

Results

In this cross-sectional study, we reviewed 130 thalassemic patients with a median age of 16 years (the range was 1 to 42 years). 47% of the patients were males and 53% were females.

HPT was diagnosed in 19 patients (11 males and 8 females), with a prevalence of 14.6% (95% CI, 9.03-21.9). The demographic characteristics of the two groups (with and without HPT) and related statistical comparisons are shown in Table 1.

The mean Body Mass Index (BMI) in both groups was almost in the same range (19.3 and 18.4 kg/m², respectively) (Table-1). Serum levels of ferritin, creatinine, and magnesium did not differ significantly between the two study groups. As expected, levels of PTH and calcium were significantly lower, while phosphorous concentration was significantly higher in thalassemic patients with HPT.

Even though, the prevalence of HPT in the male group was more than in the female group, this difference was not significant. The median age range in the group of patients without HPT showed a significant difference compared to the patients with HPT (P=0.03). Diastolic cardiac dysfunction in patients with HPT was significantly more than with thalassemic patients without HPT (P=0.04). Patients with HPT demonstrated abnormal glucose metabolism (P=0.003). (Table- 2)

Discussion

HPT has been considered as a typical complication of the second decade of life in transfusion-dependent patients with thalassemia major.(7-9)

To our knowledge, our study is one of the largest studies that have been conducted to evaluate parathyroid hormone secretion in thalassemic patients. The prevalence of HPT in beta-thalassemic patients in our study (14.6%) was higher than a recent study that evaluated 243 thalassemic patients with the prevalence of 13.6%.(10) This could be due to less cooperation of our patients and, consequently, receiving less chelation therapy.

The prevalence of HPT reported by other authors was in the range of 3.6%-10.7%.(7, 8, 11-14)

Even though more women participated in our study (60 males and 70 females), HPT seems to affect men more frequently (male/female ratio=1.37). This finding is in accordance with other studies.(10, 13)

It seems that most endocrine complications in thalassemic patients result solely from iron overload, and might be due to older age, creating an initiation of deferrioxamine.(10)

In our study, the mean age of the thalassemic patients with HPT was significantly higher than of patients without HPT. This could be due to more blood transfusions and, subsequently, a greater iron overload. It is noteworthy that the mean serum ferritin levels of our participating patients were 2532.9 ng/ml, which are lower than those observed in a larger population and lower incidence of HPT.(10)

Moreover, in accordance with the reports of a recent large study,(10) we found no significant difference in ferritin levels in the two groups (Table-1). Severe iron load before the initiation of the chelation therapy might attribute to the development of organ damage. In two studies, the mean age of deferrioxamine initiation was 6.9 ± 4.4 and 7.6±5.6 years, respectively. So, the increased prevalence of HPT could possibly be attributed to the older age of deferrioxamine initiation. Even though, in our study, the mean age of the initiation deferrioxamine in thalassemic patients with HPT, it was lower than the other two studies, but the prevalence of HPT (14.6%) was higher than the other two studies (10.7% and 13.6%, respectively).(7, 8)

It is interesting to note that, in our study, the thalassemic patients with HPT, began blood transfusions at an older age than in other studies indicated, with a lower prevalence.(7)

So, we can not explain the higher prevalence of HPT with a longer period of unopposed iron overload in our patients. Nonetheless, the age of onset of transfusion therapy was higher (but not statistically significant) in patients with HPT in comparison to thalassemic patients without HPT in our study.

Although the interval between the onset of transfusion and the onset of chelation therapy was longer in thalassemic patients with HPT, the difference was not statistically significant. Additionally, the mean duration of chelation therapy in thalassemic patients with HPT was longer (but not statistically significant) than with thalassemic patients without HPT.

Nevertheless, the mean duration of transfusion without chelation therapy was longer (but not statistically significant) in our thalassemic patients with HPT than with patients without HPT.

Taken together, the above data indicates that ferritin concentration is not an accurate indicator of tissue iron toxicity, at least regarding parathyroid hormone secretion. Other factors, like individual susceptibility to iron toxic effects and the hematological phenotype of the disease(15, 16)

could also play an essential role in the development of HPT.(17)

Regarding the other complications of the disease, our results clearly showed that patients with HPT usually exhibit glucose metabolism abnormality.(18) Further, our study confirmed that diastolic cardiac function seems to be the most common non-endocrine complication in this group of patients.(19)

In conclusion, further studies are required to evaluate the mechanism of HPT in thalassemia major patients. However, we recommend the continued measurement of parathyroid hormone on a regular basis in all thalassemic patients.

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