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ADVANCES IN PEDIATRIC RESEARCH

Parathyroid function in children with beta thalassemia and correlation with iron load

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Abstract

Background: Patients with beta-thalassemia present with severe anemia requiring regular red blood cell transfusions. This can lead to iron overload and its related complications including disorders of the endocrine systems. The aim of this work was to study parathyroid function in children with beta-thalassemia major in correlation with iron load.

Methods: 60 patients with beta-thalassemia major were included. The cohort included 32 males and 28 females with an age range of 6-10 years and a control group of 30 healthy children of matched age and sex. All patients underwent complete blood count, Hb electrophoresis, serum iron status, parathyroid hormone (PTH) levels, serum ionized calcium, phosphorus and alkaline phosphatase, and assessment of bone mineral density.

Results: Serum ferritin, iron, phosphorus and alkaline phosphatase were significantly higher in children with beta-thalassemia, while serum total iron binding capacity, PTH and ionized calcium were significantly lower in these patients compared to controls. A significant negative correlation was found between serum parathyroid hormone levels and ferritin. Reduced bone mineral density was present in 33 patients (55%), with osteoporosis in 21 patients (35%) and osteopenia in 12 patients (20%).

Conclusions: Parathyroid hormone levels are significantly lower in thalassemic patients, with a significant negative correlation with serum ferritin. Regular and continuous follow up of PTH, calcium, phosphorus, alkaline phosphatase, and 25-hydroxy vitamin D levels is recommended for early detection of hypoparathyrodism in thalassemic patients. Regular and continuous bone mineral density assessment is also recommended for early detection of osteoporosis or osteopenia.

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Introduction

Beta thalassemias are hereditary blood disorders caused by a defect in the beta-globin gene. Excess free alpha-globin chains become abnormal components in maturing red blood cells, which leads to their destruction with subsequent anemia**.** Phenotypes are variable, ranging from severe anemia to clinically asymptomatic individuals [1].

Thalassemia is usually treated via blood transfusion to provide the patients with healthy red blood cells containing normal hemoglobin. However, repeated blood transfusions can lead to iron overload, whereby excess iron accumulates in the body and is deposited in body organs such as the heart, liver and endocrine glands causing organ damage [2].

Attributed to excessive iron overload and suboptimal chelation, endocrine dysfunction is a common complication of beta-thalassemia. Disturbances in growth, pubertal development, abnormal gonadal functions, and impaired thyroid, parathyroid and adrenal functions are commonly encountered. Early detection and the implementation of an appropriate transfusion regimen and chelation therapy are essential for proper management [3].

Patients with beta-thalassemia major are prone to hypoparathyroidism; an irreversible and preventable disorder caused by iron overload [4]. This condition is asymptomatic in most beta-thalassemia patients, with hypocalcemia usually only detected during routine laboratory examinations. However, in some patients, it can be relatively severe with characteristic clinical signs of carpopedal spasm, tetany or seizures [5].

The aim of this work was to study parathyroid function in children with beta-thalassemia major in correlation with iron load.

Methods

Approval for this study was granted by the Ethical Committee of the Tanta University Research Center, and written consent was obtained from the parents of all children involved in this study. The study participants included 60 Egyptian children being followed up under the Hematology Unit of the Pediatric Department at Tanta University including 32 males and 28 females with an age range of 6-10 years and mean age value of 8±3.39 years, in the period from July 2012 to December 2013. Criteria for inclusion into the cohort were diagnosis of transfusion-dependent beta-thalassemia major with serum ferritin >1000ng/ml. This study also included 30 healthy children as a control group, including 16 males and 14 females with an age range of 5-10 years and mean age value of 8.17±3.02 years.

All study participants, in both the patient and control groups, were subjected to a thorough clinical examination, paying particular attention to pallor, jaundice, mongoloid facies, splenomegaly, hepatomegaly, and manifestations of hypoparathyrodism.

Study participants were also subjected to laboratory investigations. Six ml of venous blood was collected from each participant, using sterile needles through gentle venipuncture after sterilization of the puncture site with alcohol. One ml of each collected sample was mixed with 20 µL EDTA solution and used for a complete blood count, including a differential white blood cell count using a Leishman-stained peripheral blood smear and evaluated using an ERMA PCE-210 N cell counter [6]. The remainder of each blood sample was put into a plain tube and centrifuged to separate out the serum. This was used to estimate other values including Hb electrophoresis [7]; serum iron status including serum iron, serum total iron binding capacity (TIBC) and serum ferritin [8-10]; PTH levels using a direct label, two-site ELISA assay intended for the quantitative determination of PTH in plasma (PTH ELISA [Intact], Biomerica, USA; normal range: 10-65 pg/ml) [5]; serum calcium [11], phosphorus [12], alkaline phosphatase [13] and 25-hydroxy vitamin D levels in the blood plasma [14]. Bone mineral density (BMD) was determined by dual energy X-ray absorptiometry (DEXA) at two sites: the lumbar spine (L2-L4), and femoral neck. Patients with a Z-score <-2.5 were considered to be osteoporotic, and those with a Z-score between 1 and 2.5 as osteopenic. Z-scores were calculated according to bone density values based on age and sex [15].

Statistical analysis and presentation of the present study was conducted using SPSS V17 to calculate the mean, standard error, Student t-test, chi-square, and linear correlation coefficient tests.

Results

Pallor and jaundice were the most commonly presented signs, though on clinical examination, hepatomegaly and splenomegaly were most common in the cohort group. Most patients studied received a blood transfusion every four weeks, with the mean age of thalassemia diagnosis being 7.95±2.8 months. Reduced bone mineral density was present in the pelvis and spine of 33 patients (55%), with either osteoporosis in 21 patients (35%) and osteopenia in 12 patients (20%) (Table 1).

Table 1. Clinical data in studied patients

Clinical data	N (%)
Pallor	60 (100)
Jaundice	60 (100)
Hepatomegaly	48 (80)
Splenomegaly	42 (70)
Splenectomy	18 (30)
Mongoloid facies	24 (40)
Manifestation of hypoparathyroidism	
Tetany	3 (5)
Convulsion	2 (3)
Carpopedal spasm	2 (3)
Frequency of blood transfusion	
Every 2 weeks	6 (10)
Every 3weeks	12 (20)
Every 4 weeks	42 (70)
Bone mineral density in lumbar spine (L2–L4) and femoral neck	
Normal	27 (45)
Osteoporosis	21 (35)
Osteopenia	12 (20)

Compared to the control group, participants in the cohort group had significantly fewer red blood cells with lower mean corpuscular volume (MCV), lower levels of Hb and low mean corpuscular hemoglobin MCH), and significantly higher numbers of reticulocytes, platelets and white blood cells (Table 2).

Compared to the control group, patients had significantly lower levels of serum PTH, ionized calcium and 25-hydroxy vitamin D. They also had a lower serum total iron binding capacity, and significantly higher serum phosphorus, alkaline phosphatase, serum ferritin and serum iron levels (Table 3). The analysis revealed a significant negative correlation between parathyroid hormone levels and serum ferritin (Fig. 1).

Table 2. Comparison of cell blood count parameters between patients** and control groups

	Patients (n=60)	Controls (n=30)	X^2	p-value
Red blood cells (million cell/mm³)				
Range	3.3–4.0	4.5–5.5		
Mean±SD	3.20±0.69	5.35±0.55	10.780	<0.001*
Hb (g/dl)				
Range	4.9–9.0	11.0–12.6		
Mean±SD	7.61±1.27	11.79±-0.59	16.286	<0.001*
MCV (fL)				
Range	52.6–75.0	78.8–84.6		
Mean±SD	63.18±7.32	80.64±1.97	12.602	<0.001*
MCH (pg)				
Range	15.1–22.0	26.0–29.8		
Mean±SD	19.57±2.16	27.33±1.06	17.595	<0.001*
WBCs (thousand cell/mm³)				
Range	4.5–26.5	4.5–9.8	6.700	<0.001*
Mean±SD	13.81±5.49	6.79±1.65		
Platelets (thousand cell/mm³)				
Range	264.4–699.6	280.0–430.5	-3.500	<0.001*
Mean±SD	482.00±217.60	335.00±74.50		
Reticulocytes%				
Range	3.5–8.6	0.5–1.5		
Mean±SD	4.86±1.46	0.90±0.04	17.353	<0.001*

*Significant ($p<0.05$). ** Pre-transfusion complete blood picture for patients

Table 3. Comparison of calcium, phosphorus, alkaline phosphatase, PTH, 25-hydroxy vitamin D and serum iron status between patients and control groups

Parameters	Patients (n=60)	Controls (n=30)	t	p-value
Serum ionized Calcium (mmol/L)				
Range	0.60–1.23	1.17–1.30		
Mean±SD	0.96±0.13	1.20±0.15	6.320	0.001*
Serum phosphorus (mg/dl)				
Range	3.70–8.00	4.10–5.70		
Mean±SD	5.04±1.29	4.1±0.77	3.427	<0.001*
Serum alkaline phosphatase (U/L)				
Range	350.00–745.00	340.00–569.00		
Mean±SD	499.50±159.97	400.55±61.63	3.21	0.004*
Serum 25 hydroxy D3 levels (ng/ml)				
Range	14.00–118.00	62.00–158.00		
Mean±SD	55.60±27.74	96.80±29.38	-4.560	<0.001*
Parathyroid hormone (pg/ml)				
Range	8.90–64.00	23.10–64.80		
Mean±SD	32.89±15.77	44.18±5.124	3.720	0.004*
Serum ferritin (ng/ml)				
Range	501.00–20000.00	39.40–100.20		
Mean±SD	3253.70±707.10	203.00±56.70	12.520	0.001
Serum iron (µg/ml)				
Range	123.00–371.00	80.00–120.00		
Mean±SD	248.85±38.20	83.60±9.40	8.660	0.001
Serum IBC (µg/ml)				
Range	161.00–200.00	269.00–291.00		
Mean±SD	199.40 ±19.36	329.00±50.30	6.330	0.009

*Significant ($p<0.05$)

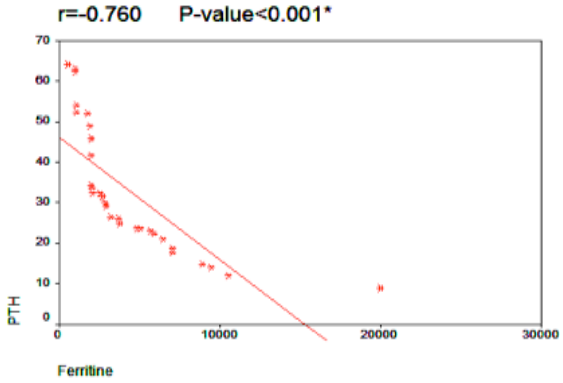

Figure 1. Correlation between parathyroid hormone and serum ferritin levels in studied patients

Discussion

In agreement with the work of Hagag *et al*. [2], this study found serum ferritin and iron levels in the patient group to be significantly higher than those in the control group, while TIBC was significantly lower in patients compared to healthy participants. This can be explained by repeated blood transfusions with resulting iron overload.

Like Saboor *et al*. [16], this study also found serum ionized calcium levels to be significantly lower in the cohort, and serum phosphorus and alkaline phosphatase levels to be significantly higher. However, our results do not concur with those of Napoli *et al*. [17], who found no alteration in calcium or phosphate levels in thalassemia patients.

In the current study, plasma 25-hydroxy vitamin D levels are found to be significantly lower in patients compared to controls. Fung *et al*. [18] also obtained this result in most of the patients they studied.

In this study, mean PTH levels are significantly lower in patients compared to the control group. This is in agreement with the recent work of Bash *et al*. [19], who explained this as a consequence of iron overload, whereby iron deposited in the parathyroid gland causes its damage. This is particularly observed in cases of suboptimal chelation therapy. Hypoparathyroidism was detected in 12 out of 60 (20%) thalassemic patients studied; this is nearly double that reported by Habeb *et al*. (11%), [20] and Chern *et al*. (10.7%) [21].

In the present study there is a negative correlation between serum ferritin and PTH levels. This finding agrees with results from Belhoul *et al*. [22], but disagrees with Sleem *et al*. [23] who found no correlation between these two parameters. As also found by Karimi *et al*. [24], reduced bone mineral density was present in the pelvis and spine of 33 patients (55%).

Variation between some of the results found in this study compared to others may be explained by variation in the number and age of patients studied, presentation of thalassemia, type and regulation of chelation therapy, and the degree of iron overload.

We conclude that bone mineral density and parathyroid functions are significantly lower in thalassemic patients, and that there is a significant negative correlation between levels of PTH and serum ferritin. Based on this conclusion, we recommend that patients with beta-thalassemia should receive regular and continuous follow up, to include assessment of levels of PTH, calcium, phosphorus, alkaline phosphatase and 25-hydroxy vitamin D for the early detection of hypoparathyrodism, and assessment of bone mineral density for the early detection of osteoporosis or osteopenia.

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