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The Prevalence of Hypoparathyroidism in Group of Transfusion Dependent B-Thalassemia (TDT) and its Relation to Iron Chelation

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Abstract

Background: Hypoparathyroidism (HPT) due to siderosis in thalassemic patients was firstly described by Gabriele 1971. Hypoparathyroidism is a result of iron overload seen in transfused thalassemic major patients. It may cause a lot of neurological manifestations, including tetany, seizures, carpopedal spasms, paresthesia and even abnormal cerebral computed tomography findings have been reported

Objectives: To identify the prevalence of hypoparathyroidism among groups of patients with transfusion dependent B-thalassemia (TDT) and the associated risk factors.

Patients and Methods: Across sectional randomized study has been conducted at Thalassemia Center at Al-Zahraa Teaching Hospital in Al-Najaf City from the beginning of October 2016 to the end of May 2017. Eighty patients (49 male and 31 female) with transfusion dependent β-thalassemia involved in our study, they subdivided into two groups according to PTH level, and these two groups are thalassemic patients with hypoparathyroidism and thalassemic patients without hypoparathyroidism.

Result: The prevalence of hypoparathyroidism is 65% in the study population. We find that (older age patients, younger age at diagnosis, large number of transfusion per year, high serum ferritin, prolong duration of transfusion and chelation) are associated with significant risk. Patients that use oral deferasirox (Exjade) are significantly lower affected by hypoparathyroidism than that use mixed type (defirasirox and deferoxamine) chelation. Those with good compliance with chelation are significantly lower affected by hypoparathyroidism.

Conclusions: High prevalence of hypoparathyroidism 65% were found in transfusion dependent thalassemic major patients, mainly in the second decade of life.

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Introduction

Hypoparathyroidism (HPT) secondary to siderosis in thalassemia patients was firstly described by Gabriele in 1971 [1].

Thalassemia syndrome are inherited disorders characterized by absence or markedly decreased accumulation of one of the globin subunits of hemoglobin. In alpha α-thalassemias, there is absent or decreased production of α-globin subunits, whereas in beta β-thalassemias, there is absent or reduced production of β-globin subunits [2].

Thomas Cooley and Pearl Lee in 1925, describing a form of severe type of anemia occurring in Italian children and associated with splenomegaly and marked bone changes. Because all early cases were reported in children of Mediterranean origin, the disease was later termed thalassemia, from the Greek word for sea, thalassa and haima (blood) [3].

Hypoparathyroidisim is one of the most important endocrine complications of thalassemia major secondary to deposition of iron in parathyroid glands [4]. The parathyroid glands embryologically developed from the 3rd and 4th bronchial arches.Four parathyroid glands, lying behind each of the upper and lower poles of the thyroid gland [5].

Calcium control is driven by these four glands through parathyroid hormone. Iron overload and anemia affect parathyroids functions, resulting in hypoparathyroidism, which result in fall in calcium level in the body, which is in turn has effect on the level of phosphorous [6].

The major target end organs for parathyroid hormone (PTH) action are the kidneys, skeletal system, and intestine [7].

In most patients with ß-thalassemia major, hypoparathyroidism is asymptomatic and hypocalcaemia is detected only during routine laboratory examinations; however, in some patients hypocalcaemia can be sever and symptomaticn [8].

The initial manifestations are muscular pain and cramps; they

progress to numbness, stiffness, and tingling of the hands and feet. In patients with long time of hypocalcaemia, there is delay in teeth eruption. The skin may be dry and scaly, and the nails might show a horizontal lines [9-11].

A Hypoparathyroidisim patient with symptomatic hypocalcemia (eg, seizure, tetany, laryngospasm) requires intravenous calcium. Oral calcium and active vitamin D (calcitriol) should be initiated as soon the patient is tolerating oral feeds. Once serum calcium concentrations are in a safe range more than 7.5 mg/dl, intravenous calcium can be stopped. The active form of vitamin D, 1,25-dihydroxyvitamin D (calcitriol) of 0.25-1.0 μg, twice daily, is usually sufficient to normalize plasma calcium and phosphate [12,13]. Vitamin D supplementations in a daily dose of 400–800IU given to patients treated with activated vitamin D [13,14].

Management of thalassemia by two therapies

Long-Term Transfusion Therapy: The goal of long-term hyper transfusional support is to maintain the patient's hemoglobin level at 9-10 g/dL, transfusions are administered monthly in infancy and subsequently at 2 to 4 weeks [15].

Iron Chelation Therapy: In cases of ongoing transfusion therapy, with each RBC unit containing ~200 mg of iron, cumulative iron burden is an inevitable consequence [16,17].

Patients and Methods

A cross sectional randomized study has been conducted at Thalassemia Center at Al-Zahraa Teaching Hospital for Children and Maternity in Al-Najaf City from the beginning of October 2016 to the end of May 2017. Study done as part of regular follow up of patients.

This study includes 80 thalassemic major patients, diagnosis based on Hb-electrophoresis. Forty nine of them are males and another thirty one females. The cases were chosen randomly as one for each five – sequence of their files number.

Inclusion Criteria

- Age range from 1-18 years.
- Hemoglobin F more than 90%.
- Normal blood urea and serum creatinine.
- Normal total serum protein and albumin.
- Normal serum magnesium.

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 malabsorption and malnutrition. Patient with hypomagnesaemia also excluded from study.

After taking a history and clinical examination, the age, sex, weight, height, pre transfusion Hb, mean Hb of the last year, age at diagnosis, number of blood transfusions units per year and their compliance to transfusion, age of starting, and duration and compliance with chelation included in our parameters.

The patients who receive packed RBCs (8-15 ml/kg) every 2-4 weeks regarded as highly compliance for blood transfusion, aiming to maintain pre transfusion hemoglobin (Hb) levels above 9 g/dl.

All patients have received chronic chelation therapy either with oral Deferasirox (Exjade) single dose alone or with subcutaneous Deferoxamine (Desferal) according to the serum ferritin levels and patient tolerance. Regular chelation use for DFO defined when patient use the infusion device in pattern of five nights per week for at least eight hours of 40 mg/kg subcutaneously. Poor compliance patients for DFO use regarded when chelation used for less than four nights per week or improper dose. For those who were on Deferasirox (Exjade), good compliance patients were regarded when they are on single daily oral use of 20-30 mg/kg Deferasirox, 30 minutes before breakfast. Poor compliance for Deferasirox regarded when used with alternative day, improper dose or wrong time use.

Five ml of blood in serum tube taken to measure serum ferritin. The procedure consists of one-step enzyme immunoassay sandwich method with fluorescence detection as the final exam. All the steps are achieved automatically with Minividas machine. Also, two ml of blood was drawn with aplastic syringe and after centrifuged by 3000 cycle/minutes for 10 minutes, separated sera were kept frozen at 20□ and sample send to private laboratory, PTH were estimated by (ELIA) by using semi-auto chemistry analyzer. Serum calcium, phosphate, magnesium and serum alkaline phosphatase were determined by automated routine procedure. These Eighty patients with transfusion dependent thalassemia, after history, examination and biochemical parameters was taken, subdivided into two groups according to parathyroid hormone level, these two groups are thalassemic patient with HPT (that have low parathyroid hormone, low serum calcium, increased serum phosphate, Normal or decreased alkaline phosphatase levels), and thalassemic patient without HPT.

Statistical Analysis

The data were entered in the data base and analyzed using the statistical package for social sciences software SPSS program (version 20 of windows). Data were expressed as frequency and percentages; the chi-square test was used for categorical data. Independent t-test for comparison of mean. A P-value equal or less than 0.05 was considered as statistically significant. Lab observer and data analyzer has no idea about relation of patient's samples.

Results

Eighty patients with transfusion dependent thalassemia major that involved in our study subdivided into two groups according to parathyroid hormone level, these two groups are thalassemic patient with HPT (that have low parathyroid hormone, low serum calcium, increased serum phosphate, Normal or decreased alkaline phosphatase levels), and thalassemic patient without HPT. HPT presents in 52 patients (30 males and 22 females), with a prevalence of 65% in study population. Vast majority had PTH levels below 10 pg/ml.

Table 1 show the difference in these two groups, the age of the patients is higher in patients with HPT and is statistically significant p value = 0.001, the age of start blood transfusion is lower in patients with HPT and is statistically significant p value = 0.01. Number of transfusion per year is higher in patients with HPT and is statistically significant p value = 0.01. Duration of transfusion is longer in patients with HPT and is statistically significant p value = 0.0001. Duration of chelation is longer in patients with HPT and is statistically significant p value = 0.0001.

Biochemical parameters in these two groups, serum ferritin is higher in patients with HPT with significant p value = 0.0001, Pre transfusion hemoglobin is lower in patients with HPT and is statistically significant p value = 0.0001, PTH is lower in patients with HPT and is statistically

Table 1: Demographic characteristics biochemical and hormonal data.

	Normal PTH (n=28) mean±SD	Low PTH (n=52) mean±SD	P
Age (year)	9.8±3.7	13±3.3	0.001*
Age of start blood transfusion (year)	2.2±1.03	1.7±0.6	0.01*
Number of transfusion per year	16.9±3.02	19.5±4.9	0.01*
Duration of transfusion (year)	7.6±3.1	11.3±3	0.0001*
Age of start chelation(year)	3.9±0.9	4.5±1.7	0.09
Duration of chelation (year)	5.9±3.2	8.5±2.3	0.0001*
PTH pg/ml	18.3±7.6	5.6±2.7	0.0001*
Serum ALP (u/l)	417.9±143.7	372.4±228.3	0.3
Serum phosphate mg/dl	4.8±1.3	6.1±1.8	0.0001*
Camg/dl	8.4±1.6	6.5±1.8	0.0001*
Ferritin ng/ml	1950±440.1	4425.7±3212.9	0.0001*
Pre transfusion Hb g/dl	8.4±0.5	7.6±0.6	0.0001*

Where: *P< 0.05

Table 2: Comparison of type of chelation and compliance with transfusion and chelation in two groups.

Variable		Study group		Total	P
		Normal PTH (n=28) No. (%)	Low PTH (n=52) No. (%)		
Sex	Female	9(29%)	22(71%)	31(100%)	0.4
	Male	19(38.8%)	30(61.2%)	49(100%)	
Chelation	Oral Exgade	24(42.9%)	32(57.1%)	56(100%)	0.02*
	Mixed	4(16.7%)	20(83.3%)	24(100%)	
Compliance with chelation	Good	28(45.2%)	34(54.8%)	62(100%)	0.0001*
	Poor	0(0%)	18(100%)	18(100%)	
Compliance with blood transfusion	Good	28(37.8%)	46(62.2%)	74(100%)	0.06
	Poor	0(0%)	6(100%)	6(100%)	

significant p value = 0.0001. Serum calcium is lower in patients with HPT and is statistically significant p value = 0.0001. Serum phosphate is higher in patients with HPT and is statistically significant p value = 0.0001

Table 2 demonstrate that female 22 (71%) is more affected by HPT than male30 (61.2%) p-value is not significant. For chelation therapy, thalassemic patients use oral deferasirox (Exjade) 32 (57.1%) is lower affected by HPT than those on mixed therapy [oral deferasirox and injectable deferoxamine] 20(83.3%) and is statistically significant p value = 0.02. Those with good compliance for blood transfusion 46 (62.2%) lower affected by HPT than those with poor compliance 6 (100%) and statistically not significant p value=0.05. Those with good compliance with chelation 34(54.8%) is lower affected by HPT than those with poor compliance 18 (100%) and statistically significant p value = 0.0001.

Discussion

The prevalence of hypoparathyroidism in our study is 65% which is higher than 10% reported in recent study done in Iran by Azami M, et al. (2016) [18], Also higher than 19% in study done by Sleem GA, et al. (2007) [19] and 7% in study done by Al-Akhras A, et al. (2016) [20] in Egypt. This could be due to less cooperation of our patients in following the regimen of therapy, consequently, receiving less chelation therapy which lead to more iron overload.

Mean age of Hypoparathyroidisim in our study is (13±3.3) as shown in table 1, so Hypoparathyroidisim has generally been regarded as a typical complication of the second decade of life in transfusion dependent patients with β-thalassemia, this in accordance with study done in 2003 by Economou M, et al. (2003) [21] and study done in India 2017 by De Sanctis V, et al. (2013) [22].

The mean age of the thalassemic patients with HPT (13±3.3) years is higher than that of patients without HPT (9.8±3.7) years and is statistically significant as shown in table1. This could be due to longer duration of chronic anemia, hypoxia and iron overload (chronic anemia result in increased hematopoiesis that lead to bone resorption which induce suppression of parathyroid secretion), also longer duration and more blood transfusions, subsequently, a more iron overload .This result is in accordance with studies done in Iran by Hamidieh AA, et al. (2009) [23] and in Egypt by Sleem GA, et al. (2007) [19].

The median age of onset of transfusion therapy (1.7±0.6) years was lower and statistically significant in patients with HPT in comparison to age of thalassemic patients without HPT which is (2.2±1.03) years as shown in table 1, which may be due to longer duration of chronic anemia and blood transfusion, also longer period of unopposed iron overload that precipitate in parathyroid gland and cause damage to it, this result in accordance with study in Greece done 2006 by Angelopoulos NG, et al. (2006) [24].

The mean duration of transfusion is longer (11.3±3) years in thalassemic patient with HPT than thalassemic patient without HPT (7.6±3.1) years and it is statistically significant as shown in table 1, this in accordance with studies done by Hamidieh AA, et al. (2009) [23] and Angelopoulos NG, et al. (2006) [24], and this may be due to more blood transfusion and longer period of unopposed iron overload.

The numbers of transfusion per year in thalassemic patient with HPT is 19.5±4.9 which is higher than thalassemic patient without HPT 16.9±3.02 and is statistically significant as shown in table 1. This more numbers of blood transfusion result in more iron over load and more damage to parathyroid gland ,this agree with study done in Egypt 2016 by Al-Akhras A, et al. (2016) [20].

The mean age of start chelation in patient with HPT is (4.5±1.7) years which is higher than those without HPT (3.9±0.9) years, this may be due to longer duration of unopposed iron overload, but it is statistically insignificant as shown in table 1. This significance can be due to poor compliance with chelation in some patient although started with it at younger age, also younger age group at poor compliance with chelation therapy than older age and also still no enough time for chelation therapy to give its effect, or may be due to in effective dose. This result in accordance to studies done by Hamidieh AA, et al. (2009) [23] and Sleem GA, et al. (2007) [19].

The mean duration of chelation in thalassemic patient with HPT is (8.5±2.3) years which is higher than those without HPT (5.9±3.2) years which is statistically significant as in table 1. This may be due to longer duration of chronic anemia and hypoxia, also longer duration of blood transfusion with higher iron overload despite longer duration of chelation. While studies done Hamidieh AA, et al. (2009) [23] and Angelopoulos NG, et al. (2006) [24] also show mean duration of chelation in thalassemic patient with HPT also higher than those without HPT, but it is statistically insignificant.

Pre transfusion hemoglobin is (7.6±0.6) g/dl in thalassemic patient with HPT which is lower than (8.4±0.5) in thalassemic patient without HPT and statistically significant as shown in table 1, this may be due to chronic anemia, hypoxia and iron overload, Hypoparathyroidism is thought to be the consequence of iron deposition in the parathyroid glands or due to suppression of parathyroid secretion induced by bone resorption resulting from increased hematopoiesis secondary to the chronic anemia [25]. With low hemoglobin level the intestine will absorb more iron to compensate. Also low hemoglobin require more frequent blood transfusion and so more iron overload.

The mean serum ferritin in thalassemic patients with HPT is (4425.7±3212.9) ng/ml, which is higher than that of thalassemic patients without HPT (1950±440.1) and is statistically significant as shown in table 1; this could be due to higher iron deposition in parathyroid gland leading to gland dysfunction.

Our result agree with study done by Gamberini MR, et al. (2008) [26] and study done by Belhoul KM, et al. (2012) [27] in United Arab Emirates, but in contrast to studies done by Angelopoulos N et al [24] that show no significant difference in serum ferritin between these two groups, they found no clear relationship between HPT and serum ferritin levels in their patients, suggesting either an individual sensitivity to iron toxicity or early damage of the parathyroid gland before chelation had reduced the iron overload.

The mean level of parathyroid hormone is low (5.6±2.7) pg/ml in thalassemic patient with HPT and the mean level of parathyroid hormone is (18.3±7.6) in thalassemic patient without HPT and that is statistically significant as shown in table 1, this in accordance to the study done by Angelopoulos NG, et al. (2006) [24]. The mean serum Calcium level is low (6.5±1.8) mg/dl in thalassemic patient with HPT and (8.4±1.6) in those without HPT and is statistically significant as shown in table 1. This result is in accordance with study done by Angelopoulos NG, et al. (2006) [24], this may be due to that lack of parathyroid hormone is associated with lower levels of 1, 25-dihydroxyvitamin D, which reduced intestinal absorption of calcium, the hyperphosphatemia of hypoparathyroidism also limits the production of calcitriol. Also In the kidneys, PTH acts to reduce calcium clearance and stimulates synthesis of 1, 25-dihydroxyvitamin D, which stimulates absorption of calcium in the gastrointestinal tract. PTH also stimulates osteoclasts to resorp the bone and mobilizes calcium into the blood.

The mean serum phosphate level is high (6.1±1.8) mg/dl in thalassemic patient with HPT and (4.8±1.3) in those without HPT and is statistically significant as shown in table 1. While studies done by Angelopoulos NG, et al. (2006) [24] and Sleem GA, et al. (2007) [19] also show high serum phosphate but statistically insignificant.

In our study, we compare the relation between the thalassemic patient with HPT and the patient's use of deferasirox (exjade) alone and those that use both defersirox and deferoxamine. We found 32 (57.1%) of those used deferasirox have HPT which is lower than 20 (83.3%) of those use (both defersirox and deferoxamine) and have HPT, and it is statistically significant as shown in table 2. This may be due to, the use of two type of drugs result in less patients compliance, in addition, the deferoxamine requires intravenous or subcutaneous parenteral administration that may be bothersome to patients and so poor compliance. This in accordance to the study done in United Arab Emirates 2012 by Belhoul KM, et al. (2012) [27] which demonstrates that endocrinopathy is common in thalassemia major patients treated with subcutaneous deferoxamine therapy and is most probably due to poor compliance.

Also we compare the relation between the thalassemic patient with HPT and the compliance with blood transfusion. We found that 46 (62.2%) of those with good compliance with blood transfusion have HPT which is lower than 6 (100%) in those who are poor compliance and it is statistically insignificant $p = 0.006$ as shown in table 2. This may be due to that, those who are poor compliance with blood transfusion also poor compliance with chelation, also poor compliance with transfusion lead to low hemoglobin level, chronic anemia and hypoxia, and also the intestine will absorb more iron to compensate.

In comparison between thalassemic patient with HPT and the compliance with chelation, we found 34 (54.8%) of those with good compliance with chelation have HPT which is lower than 18 (100%) in those with poor compliance and it is statistically significant as shown in table 2. This result is in accordance with study done by Sleem GA, et al. (2007) [19].

Conclusion

- Hypoparathyroidism was found in significant proportion of patients with β-thalassemia major in the absence of obvious clinical signs of hypoparathyroidism.
- High prevalence of hypoparathyroidism 65% were found in transfusion dependent thalassemic major patients, mainly in the second decade of life.
- Most of the studied patients have low pre transfusion hemoglobin (mean pre transfusion Hb% level was (7.9±0.7), and those with lower pre transfusion Hb is more affected by HPT.
- Those that have high serum ferritin, poor compliance with transfusion and chelation therapy and those used mixed type of chelation were significantly affected by HPT.

Recommendation

- Health education of patients and their family about the importance of regular visit, transfusion program and iron chelation therapy.
- Regular evaluation of parathyroid hormone, serum calcium

and phosphate is recommended in all patients with β-thalassemia major since significant number of them has subclinical PTH.

- Improve the follow up of patients especially those with improper transfusion program and chelation therapy.

- Early start of iron chelation therapy improves out come and decrease risk of HPT.

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