Hypocalcemia and hyperphosphatemia due to iron over-load in homozygous β-thalassemia patients in Mosul city

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Abstract

This study was conducted on 105 patients with homozygous beta-thalassaemia dependent blood transfusion children 62(59%) males and 43 (40.9%) females aged between 2.5-18 years were collected randomly from the thalassemic center in Ibn-Al-Atheer Teaching Hospital in Mosul City. Together with 54 healthy children have served as normal control group. The iron status in these patients was assessed. The mean value of serum iron (SI) was (183.4 ± 44.3 µg/dl), mean of total iron binding capacity (TIBC) was (239.2 ± 46.2 µg/dl) and transferring saturation (TS) was (79.1 ± 21.4%). The mean of serum calcium was (8.55 ± 1.00 mg/dl) and the mean of serum phosphate level was (6.01 ± 1.56 mg/dl). Serum calcium and phosphorus were found to be normal in 83 cases (79.04 %), while founds low value in the serum of 22 cases (20.96 %). It is concluded that many thalassemics have impaired cardiac function, and hypocalcaemia, in these patients can precipitate or aggravate cardiac failure. Therefore, it is very important to look for these patients, from the early second decade of life.

Introduction

Thalassaemia is a series of genetic disorders of haemoglobin synthesis characterized by reduced rate of production of one or more of the globin chains of haemoglobin(1, 2). β -thalassaemia major is the most important one characterized by progressive anaemia which manifests during the second month of life, and associated with marked splenomeglay and features of chronic haemolytic anaemia. So regular blood transfusion is required usually every three to four weeks to maintain minimal haemoglobin level and prevent complication (3, 4). The disease remains incurable with complications result from iron overload as result of blood transfusion and increase intestinal absorption of iron (5). This complication includes growth retardation, cephalofacial deformity, endocrine dysfunction, cardiac impairment, hypoparathyroidism, diabetes mellitus, and increase susceptibility to infections especially in splenectomized patients (6).

Calcium is an important ion for many vital processes including, bone formation, cell division and growth, blood coagulation hormone- response coupling, muscle contraction, cardiac action and activate some enzymes, regulation of serum calcium levels in some what complex. (7) The major control mechanism is PTH. In β-thalassaemia major hypoparathyroidism secondary to iron desposition in parathyroid glands it has also been documented that asymptomatic hypocalcemia is much more common (8).

Hypoparathyroidism which may lead to hypocalcemia due to secondary siderosis in thalassaemic patients. Thalassaemia throughout the world and is one of the major public health problems occur at high frequency in endemic regions as the Mediterranean countries, Middle East, North Africa and Asia (9, 10).

Survey in Iraq showed that β-thalassaemia trait is carried by 4.5-5% of the population (11). Since this inheritable disease is regarded as a dangerous social phenomenon, therefore researches on this disease have been focused. So the aim of this study is to show the effect of thalassaemia major on the iron, calcium and phosphorus levels.

Materials and Methods

Cross Sectional, Hospital based study was carried out on 105 thalassaemia dependent blood transfusion patients with a mean age of 8.91 years and a range 2.5-18 (62 males and 43 females) and fifty four healthy volunteers, with a mean age of 9 yrs and a range of 4 – 17 yrs were investigated to serve as a control group, This study was conducted during the period from the first of October 2001 till the end of May 2002. The study was performed in Ibn-Al-Atheer Teaching Hospital, in Mosul city. About 4 ml of venous blood was drawn from the cubital vein using disposable needles and syringes, without using tourniquet. In all the cases blood samples were collected in the morning

Four ml was put in a clean dry plain plastic tube and was allowed to clot at 37 °C for 10-25 minutes before centrifugation. The serum obtained was used for the estimation of serum iron, total iron binding capacity, calcium and phosphorus. It was essential to ensure that the serum did not show haemolysis. The clear serum was transferred to clean plastic tubes by disposable syringes. Serum iron level was measured by using SI kit (Randox) Bathophenanthroline method (12). It was expressed as μg / 100 ml. and TIBC was measured by using TIBC kit (Randox) magnesium carbonate absorption method by using the Spectrophotometer at a wave length of 540 nm. (12).

It was expressed in μg / 100 ml, Transferrin saturation TS was calculated by dividing SIL by TIBC and multiplying it by 100 to express the result as %. Serum calcium was measured by using serum calcium kit (Biomerieux). Using O-cresolphthalein complexone method (13). It was expressed as mg/100 ml while Serum phosphorus level was measured by using serum phosphorus kit (Biomerieux). Using a single reagent which forms a phosphomolybdate complex in the presence of a reducing agent (ferrous sulphate) (13). It was expressed in mg/100ml.

Statistical analysis used mean, standard deviation; correlation coefficient and Z-test were used. The differences were considered significant when $p < 0.05$.

Results

Table 1 show the serum iron status, calcium and phosphorus in 105 thalassemics patients and normal subjects. As show in this table, the mean of SI and TS in thalassemic patients are significantly higher than normal control subjects ($p < 0.001$).

Sex difference was found in iron parameters between male and female thalassemic patients. Mean SI in male thalassemics (192.1 ± 45.8 μg/dl) was significantly higher than in female thalassemics (169.8 ± 38.4 μg/dl; $p<0.001$) Fig. (1) shows the pattern of serum iron distribution among male and female patients.

In normal subjects, it was also higher in males (113.4 ± 21.4 μg/dl) compared to females (91.8 ± 20.8 μg/dl). Also the mean TS in both male thalassemics (82.9±20.04%) and normal control subjects (37.7 ± 9.1%) was significantly higher than in female thalassemics (73.2±22.5.7%; $p<0.001$) and normal (29.6 ± 7.1%; $p<0.001$) respectively. Fig. (2) Shows sex related distribution of TS levels in homozygous beta-thalassaemia.

No significant differences regarding age related to Hb, concentration has been shown ($r = 0.052$, $p=0.52$), the same is true to the PCV ($r = 0.065$, $p=0.42$). Serum calcium and phosphorus were found to be normal in 83 cases (79.04%), while low value of serum calcium (7.18 ± 0.64 mg/dl), and high value of serum phosphorus (7.84 ± 1.98 mg/dl) were found in 22 cases (20.96%).

The mean of serum calcium level in a total of 105 thalassaemic patients (8.55 ± 1.00 mg/dl) was lower than the normal control subjects (9.01 ± 0.68 mg/dl). The mean of serum phosphorus level in thalassemics (6.01 ± 1.56 mg/dl) was higher than normal (5.27 ± 0.97 mg/dl). Also the mean of Ca:P ratio in patients (1.27 ± 0.57) was lower than normal(1.78 ± 0.44). The results are summarized in Table (1) In homozygous thalassaemia patients, serum calcium levels are positively related to the age, decreased calcium level is the most common in older children and the common age group was above 10 years. Fig. (3) shown significant age related distribution of serum calcium in thalassemic patients (r= -0.54, p<0.01).

Also, serum phosphorus levels are positively related to the age, serum phosphorus levels significantly ($r = 0.47$, $p < 0.01$) increased with the age of thalassaemic patients. As, in Fig. (4) which shown the age related distribution of serum phosphorus in thalassaemic patients.

Discussion

Beta-thalassaemia is a common genetic disorder in the Mediterranean countries and throughout the Middle East (14). In Iraq, previous surveys showed that beta-thalassaemia trait is carried by (4.5-5%) of the population. There are about 2500-3000 known thalassemic in this country although this is most likely to be an underestimate (15). This is indicating that thalassaemia is not rare in Iraq.

In patients with thalassemia, the excess iron results not only from blood transfusion but also from increased iron absorption secondary to the ineffective erythropoiesis. The cause of the increased iron absorption is not certain (16). The mean value of serum iron in male thalassemic patients was higher than that in female thalassemics. In normal subjects it was also higher in males compared to females; also the mean of transferrin saturation in both male thalassaemics and normal was higher than that in female for both groups Fig. (2). It is obvious that thalassemic patients in our locality are iron overloaded and this load increase with transfusions frequency and age and since iron overload is the major limiting factor for the survival of these patients, chelation therapy is an important steps in the management of these patients. In this series none of the patients studied had received chelation therapy in optimal doses.

Hypoparathyroidism (HPT) is well known to occur in thalassaemia major patients, but it is thought to be uncommon and its incidence is considered to be decreasing with improvements in chelation therapy (8). The cause of HPT is assumed to be iron deposition in parathyroid glands, which cause hypocalcemia and hyperphosphatemia in these patients (17, 18).

The reason of why some patients develop HPT and others do not is not exactly known. A number of possible mechanisms have been described to be responsible for glandular damage through iron overload. These include free radical formation and lipid peroxidation resulting in mitochondrial, lysosomal and sarcolemmal membrane damage (18).

In all 22 thalassemic patients reported who developed hypocalcemia and hyperphosphatemia were above the age of 10 years. These findings are in agreement with finding of Zafeiriou DI (19). It is quite obvious that although optimal chelation therapy does reduce the incidence of HPT which lead to hypocalcemia and other endocrine complications, nonetheless some patients will continue to develop HPT (18, 19). It is important to note that HPT can give rise to cataract formation.

Many thalassemics have impaired cardiac function, and hypocalcemia in these patients can precipitate or aggravate cardiac failure.

As a recommendation; despite the best management of thalassemia major patients, some cases of HPT (which lead to hypocalcemcia) will continue to arise and as most patients are asymptomatic, it is very important to actively look for them, starting from the early second decade of life, so that the treatment can be initiated without delay (18).

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Table (1) Serum iron status, calcium and phosphorus levels in beta- thalassemia major and normal subjects

Groups	Sex	SI (μg/dl) Mean ± SD	TIBC μg/dl Mean ± SD	TS (%) Mean ± SD	S.Ca mg/dl Mean ± SD	S.P. mg/dl Mean ± SD	Ca/P ratio Mean ± SD
Patients	M	192.1 ± 45.8	237.4 ± 44.80	82.9 ± 20.04	8.51 ± 1.07	6.12 ± 1.56	1.26 ± 0.49
	F	169.8 ± 38.4	241 ± 48.8	73.2 ± 22.5	8.51 ± 0.90	5.92 ± 1.57	1.32 ± 0.61
	Total	183.4 ± 44.3	239.2 ± 46.2	79.1 ± 21.4	8.55 ± 1.00	6.01 ± 1.56	1.27 ± 0.57
Control	M	113.4 ± 21.4	296.8 ± 48.3	37.7 ± 9.1	9.04 ± 0.69	5.35 ± 0.97	1.76 ± 0.45
	F	91.8 ± 20.8	310.1 ± 42.1	29.6 ± 7.1	8.99 ± 0.68	5.17 ± 0.98	1.81 ± 0.45
	Total	101.5 ± 21.1	302 ± 45.1	32.7 ± 8.1	9.01 ± 0.68	5.27 ± 0.97	1.78 ± 0.44

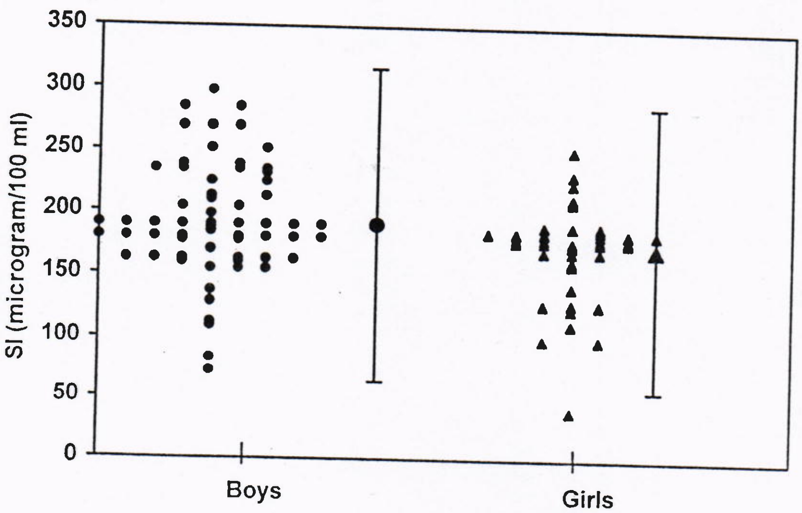

Figure (1) Sex related distribution of serum iron level in patients

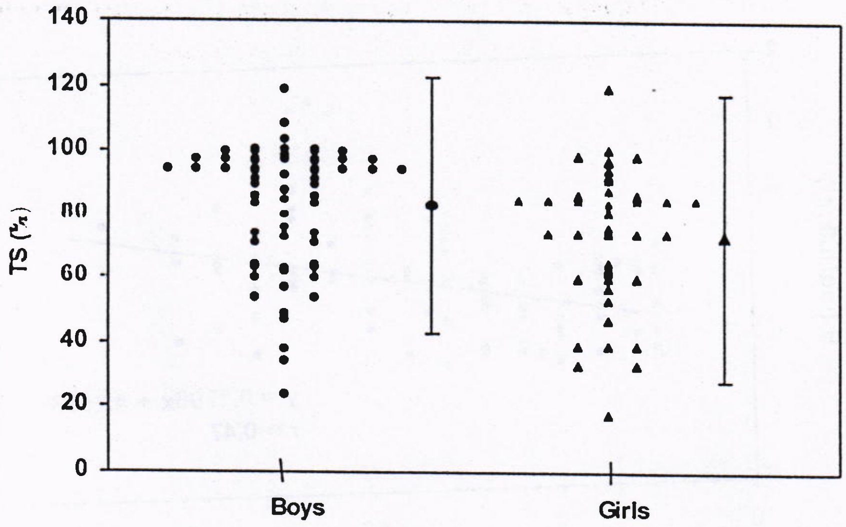

Figure (2) Sex related distribution of transferrin saturation in patients

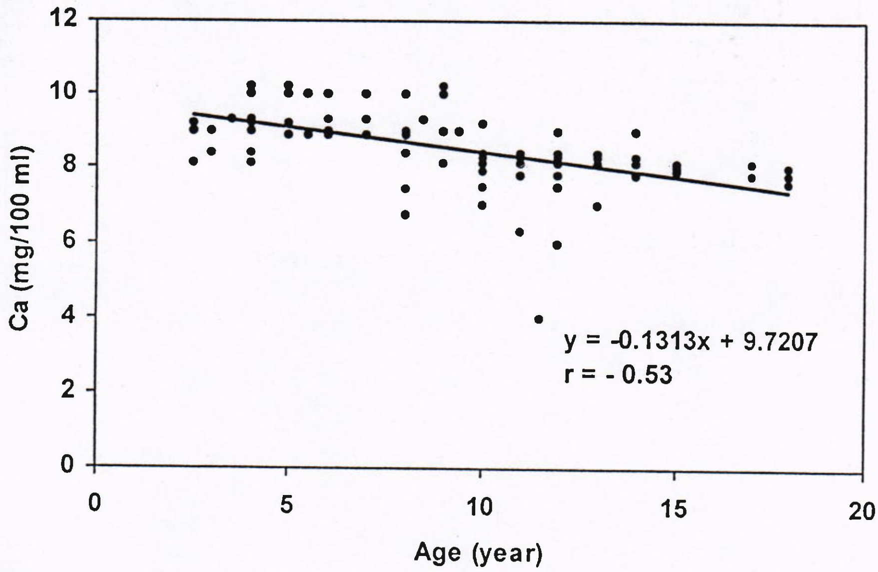

Figure (3) Age related distribution of calcium level in homozygous β-thalassaemia.

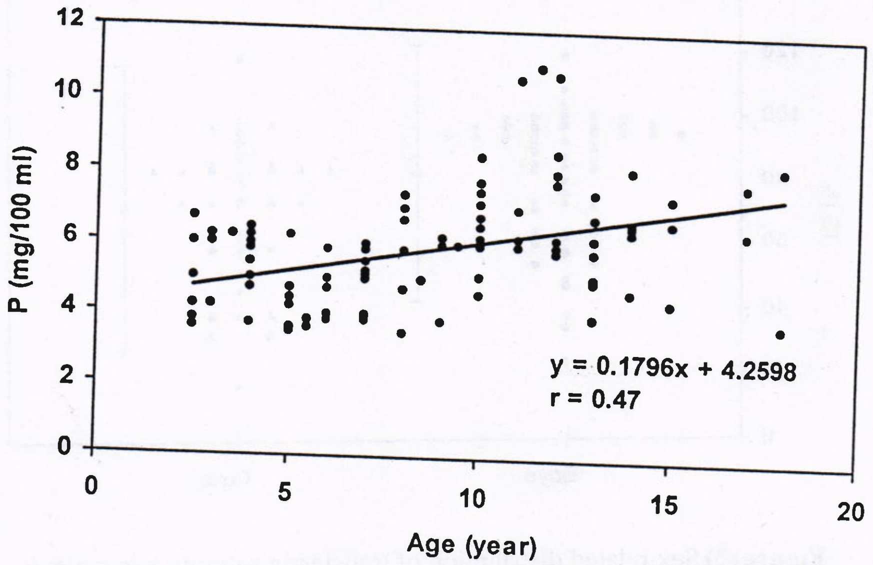

Figure (4) Age related distribution of phosphorus level in homozygous β-thalassemia.