

A Comparative Study to Assess Parathyroid Hormone Status in Different Age Groups of β -Thalassaemia Major Individuals from Eastern India

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ABSTRACT

Introduction: β -thalassaemia major, due to imbalance, missing or deficiency of β -globin chain synthesis pathway, is marked as a hereditary disorder. Homozygous state presents with severe anaemia. Regular blood transfusions and chelation therapy increase the life expectancy in thalassaemia patients. Due to recent advances in the treatment paradigm of β -thalassaemia major patients, there has been a significant increase in their lifespan but, due to the treatment related iron overload, endocrine defects like hypogonadism, diabetes mellitus, hypothyroidism and Hypoparathyroidism (HPT) have been seen to progress. Diverse studies state the occurrence of HPT to be from none upto almost 22.5% in patients. It has also been recognised that asymptomatic hypocalcaemia is much more common and can be overlooked unless precisely viewed.

Aim: To estimate and compare the biochemical parameters related to bone turnover in regularly transfused thalassaemia patients in different age groups and to find out significant correlation among the biochemical markers.

Materials and Methods: In this cross-sectional study conducted at Calcutta National Medical College, Kolkata, West Bengal, India, from January 2017 till January 2018, 100 β -thalassaemia major patients were enrolled. Serum Parathyroid Hormone (PTH), serum ferritin, ionic calcium (Ca^{2+}), Alkaline Phosphatase (ALP), phosphorus (P) and 25-Hydroxy vitamin D (25-OHD) levels were

estimated in these patients. Statistical evaluation was done by the Statistical Package for the Social Sciences (SPSS), version 12.0. Result was reported as mean \pm SD. Pearson correlation coefficient was used to determine the association of serum ferritin levels and parathormone levels. The p-value of <0.05 was considered as statistically significant.

Results: Out of 100 patients, 19 patients had HPT. The mean age was found to be 12.6 years on diagnosis, mean ionised calcium was 0.95 mmol/L, mean serum ferritin was 3045 $\mu\text{g/L}$ (range 1209-10,000 $\mu\text{g/L}$) and mean serum phosphate was 1.88 mmol/L (range 1.50-2.73 mmol/L). Serum PTH values of 7.04 pg/mL was found to be low. Negative correlation serum PTH and ferritin levels were found. Significant higher values of mean serum ferritin (2789 $\mu\text{g/L}$) and lower values of parathormone (17.13 pg/mL) was found in the age group of 11-18 years as compared to the other age group of ≤ 10 years with serum ferritin and parathormones values being 1648 $\mu\text{g/L}$ and 23.44 pg/mL, respectively.

Conclusion: Regularly transfused β -thalassaemia major patients, inspite of receiving chelation therapy tend to develop altered calcium and vitamin D homeostasis once they enter second decade of life. Thereby, biochemical parameters related to bone profile which includes ionic calcium, vitamin D, phosphate and parathyroid hormones levels should stringently monitored once the patient crosses first decade of life to prevent any development of hypocalcaemia or overt HPT.

Keywords: 25-hydroxy vitamin D, Hypocalcaemia, Hypoparathyroidism, Parathormone levels

INTRODUCTION

β -thalassaemia is one of the commonest heritable blood condition caused by a defect in the β globin gene. It is inherited in autosomal recessive manner. India is thalassaemia capital with millions affected across the world. Currently, it is estimated that there are 150,000 people living with a severe form of thalassaemia in India. The expected annual number of affected births estimated as 0.5/1000 live births for an average annual birth cohort of 25 million, predicted 12,500 thalassaemia major births per year. Over a period of 10 years, 125,000 more children will be added to the existing number of thalassaemia major cases [1].

Severe haemolytic anaemia is the commonest and the most significant characteristic of β -thalassaemia major which requires blood transfusion. In this study, mean Haemoglobin (Hb) was 8.5 ± 2.8 g/dL. Management of β -thalassaemia major which is based on periodic blood transfusions and iron chelation therapy with Desferrioxamine (DFO) has significantly enhanced the outcome of the disease [2]. Unfortunately, DFO is challenging to administer and hard to abide by, in view of its cost and side effects [3] and, patients are at a threat of emerging haemochromatosis of

the cardiac, hepatic and endocrine systems [4]. Iron excess results in certain endocrine defects such as hypogonadism, diabetes mellitus, hypothyroidism and HPT [5]. Regular blood transfusion leads to citrate toxicity and iron deposition in the parathyroid gland, which sequentially leads to decrease parathyroid level and thereby decreases calcium level. A few literature shows that few thalassaemia patients, who are on regular Packed Cell Volume (PCV) infusion develop HPT, particularly after 10 years of age [6]. Several researchers have found low levels of calcium and higher levels of phosphorus in β -thalassaemia major [7-9], while in contrary few researchers found out no change [10,11]. The authors come across several studies showing skeletal system problems like osteopenia, osteoporosis, scoliosis, spinal defects, nerve compression, and spontaneous fractures on a consistent basis [12,13]. Miscellaneous factors that add to skeletal deformities including medullary expansion, iron deposition, calcium phosphorus imbalance, increased bone turnover, hormonal inadequacy, and last of all hypoxia may effect skeletal complications [14].

The purpose of the study is to show changes in calcium and vitamin D homeostasis in a regularly transfused patients in spite of

the chelation therapy received, especially once the patient enters second decade of life. Monitoring of bone profile could prevent development of overt HPT.

MATERIALS AND METHODS

The present cross-sectional study was conducted at Calcutta National Medical College and Hospital, Kolkata West Bengal, India, period January 2017 to January 2018. Hundred patients with β -thalassaemia major were included in the study. After all required official consents and due ethical approvals having IEC no. CNMC/7 from Institutional Ethics Committee, research was completed following proposed ethical standards on human experimentation.

Inclusion criteria:

- Children in the age group of ≥ 2 -18 years of age with established diagnosis of β -thalassaemia major;
- Children with serum ferritin levels >1000 $\mu\text{g/L}$ on chelation therapy.

Exclusion criteria:

- Children with serum ferritin levels <1000 $\mu\text{g/L}$;
- Children with infection such as hepatitis or any on going bacterial and viral infections;
- Children with <10 blood transfusions.

Study Procedure

Informed consent was taken from parents/guardians of patients aged <18 years. All patients on regular blood transfusion were also being treated with chelation therapy using DFO/Desferal when their ferritin levels reached above 1000 $\mu\text{g/L}$. Serum intact Parathormone assay (Biomerica kit), 25-Hydroxy Vitamin D (25-OHD) and ferritin were done by Enzyme Linked Immunosorbent Assay (ELISA), ionic calcium (Ca^{2+}) was measured using ion selective electrode while rest of the parameters were measured in an autoanalyser (XL600).

Based on the fact that these patients started receiving transfusion from around 1.5-2 years of age and serum ferritin levels tends to rise above 1000 ng/mL only after 12-15 transfusions regardless of the chelation therapy they receive, the present study patients were categorised into two groups. First group belonging to patients aged ≤ 10 years having ≥ 15 transfusion and second group patients aged 11-18 years having ≥ 20 -25 transfusions, to determine the possible bone profile distinction with respect to age.

STATISTICAL ANALYSIS

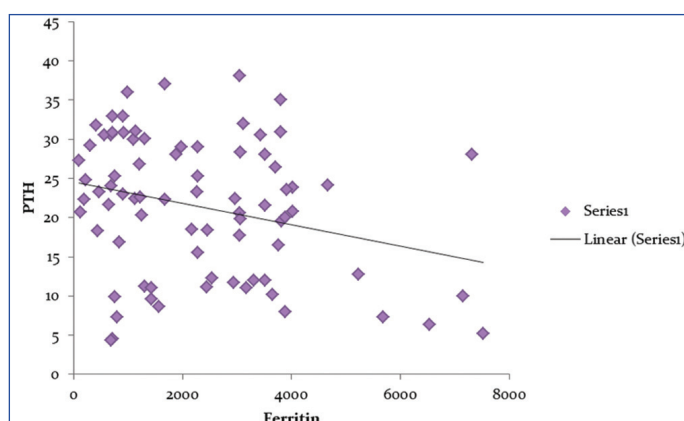
Statistical evaluation were done by the software packages SPSS version 12.0. Student's t-test was applied and result were reported as mean to compare both the groups. Pearson's correlation coefficient was used to determine the association of serum ferritin levels and parathormone levels. The p-value of <0.05 was considered as statistically significant.

RESULTS

The study included 100 homozygous β -thalassaemia major patients within the age group of >2 -18 years; 62 were males and 38 were female. The prevalence of HPT was 19% with Parathormone levels <10 pg/mL . Among this 19 HPT patients, 15 were males and four of them were females. All the β -thalassaemia patients who developed HPT ranged from 11 to 18 years (mean age=12.6 years). Their serum ferritin levels ranged from 1209 to $10,000$ $\mu\text{g/L}$ (mean 3045.2 $\mu\text{g/L}$). The mean serum PTH, ferritin, ionic calcium, phosphorus, ALP and vitamin D for different age groups as mentioned in [Table/ Fig-1]. The analysis revealed significant negative correlation between parathyroid hormone levels and serum ferritin as shown in [Table/ Fig-2]. The correlations were also calculated among variables. A negative correlation between serum ferritin and PTH levels was seen as depicted in [Table/ Fig-2].

Parameters (mean \pm SD)	≤ 10 years (having ≥ 15 transfusions) n=50	11-18 years (having ≥ 20 -25 transfusions) n=50	Student's t-test p-value (<0.05 statistically significant)
Ferritin ($\mu\text{g/L}$)	1648 \pm 232.28	2789 \pm 320.67	0.014*
Parathormone (pg/mL)	23.44 \pm 1.21	17.13 \pm 1.78	0.002*
Ionic calcium (mmol/L)	1.15 \pm 0.025	0.860 \pm 0.38	0.019*
Phosphorus (mg/dL)	4.35 \pm 0.238	4.81 \pm 0.227	0.037*
Alkaline phosphatase (U/L)	233.45 \pm 10.46	123.69 \pm 17.38	0.006*
25-OHD (ng/mL)	71.94 \pm 11.14	63.45 \pm 11.06	0.0002*

[Table/ Fig-1]: Showing comparison of biochemical parameters between two groups (aged ≤ 10 years and those aged 11-18 years). The p-value of <0.05 was considered as statistically significant.



[Table/ Fig-2]: Graph showing significant negative correlation between parathyroid hormone and serum ferritin levels.

Pearson's correlation coefficient value of serum ferritin and PTH is -0.385 and it is highly significant ($p < 0.004$)

DISCUSSION

The β -thalassaemia major (homozygous state) is characterised by severe haemolytic anaemia and requires blood transfusions on a regular frequency. Adjuvant chelation therapy and transfusion have resulted in enhanced life spans of these patients. HPT in β -thalassaemia major though a known complication, is believed to be uncommon and its frequency is declining with enhanced chelation treatment. Regardless of the finest management of thalassaemia major patients, some cases of HPT do continue to arise.

In the limited studies done, the occurrence fluctuates significantly from none to as high as 22.5% [10]. One of the leading study conducted till date on endocrine difficulties in thalassaemia comprised 1861 patients from 25 centres, and it documented HPT in 3.6% of patients (mean age at diagnosis 18.7 years), even though the percentage differed in different centres [11]. In the present study, the percentage of HPT is 19%, which is quite high, and the reason could be delay in the starting chelation therapy, as well as, non compliance with treatment. Endocrinopathies are known to be among the commonest adversities of thalassaemia but defining the exact occurrence is challenging because of dissimilarities in age of first contact to chelation therapy and the continuing progress in survival in well-chelated patients [15]. The HPT is not usually monitored due to lack of knowledge of its unusual clinical sequel. The intention behind the present study was to explicate the importance of monitoring serum calcium and parathormone levels and early recognition of HPT among thalassaemia patients, especially at the onset of second decade of life.

The anterior pituitary being more vulnerable to iron deposition with hormonal emission, causes several endocrine abnormalities. The endocrinological displays comprises of hypothyroidism, growth failure, HPT as well as, gonadal damage. HPT being evaluated

by parathormone levels, serum ionic calcium, and phosphate has been specified in numerous researchers with a prevalence of 4-40% [16,17]. The prevalence of HPT (19%) in the present study was comparable to numerous researches from different countries for example Iran (7.6-14.6%), Oman (19%), China (10.7%), and Greece (13.5%) [7,8,10,18,19].

Parathormone is principally accountable for the regulation of calcium balance in our body. Hypocalcaemia and osteoporosis can be caused due to HPT [13]. Calcium too has key part to play in skeletal mineralisation in human body [20]. Phosphorous along with calcium has an impact on bone growth and development, and osseous tissue comprises of 85% of total phosphorus content of our body [13]. Current study results revealed decreased level of ionic serum calcium and augmented inorganic phosphorus levels in β -thalassaemic patients. These conclusions are in accordance with both Adil A et al., and Mirhosseini NZ et al., [17,21].

The serum ionic calcium level was significantly low in our patients, decline being more in second decade (0.86 mmol/L). The present outcomes were in agreement with Aleem A et al., Fahim FM et al., in whom mean serum calcium was 1.88 mmol/L and 1.65 mmol/L (6.6 mg/dL) in patients respectively, who also noted substantial hypocalcaemia in the thalassaemia patient population [9,22]. Vogiatzi MG et al., results indicate a high prevalence of Lean Body Mass (LBM) among adolescents with (β -thalassaemia) Thal, regardless of adequate transfusion and chelation regimens [23]. On the contrary, some authors found insignificant variance in serum calcium level among the patients and controls [11,24]. The key reason of hypocalcaemia is endocrinopathy ancillary to haemosiderosis. Nevertheless, chelation therapy in advanced liver diseases too adds to hypocalcaemia.

In the present study, there is a tendency of phosphorus levels to rise in the beginning of second decade, and this finding being statistically significant (p -value=0.037). In patients below 10 years, the range is being toward lower normal or low. These findings were contrary to few researches that stated phosphorous levels to be within the normal limits in patients than in controls [5]. Few investigators also stated considerably higher serum phosphorous levels in thalassaemia patients than in control groups [25].

The mean 25-OHD levels were 71.94 ± 11.14 ng/mL and 63.45 ± 11.06 ng/mL for the two groups respectively and were statistically significant (p -value=0.002) in the present study. This was in accordance with studies that shows thalassaemia patients does exhibit noticeable deficit of 25-OHD [26,27]. The mean 25-OHD was significantly low ($p < 0.01$) with value 20.3 ± 0.7 ng/mL in Napoli N et al., study [26]; while it was 8 ± 4.5 ng/mL before vitamin D supplementation and after supplementation 21.3 ± 9.5 ng/mL in the study conducted by Soliman A et al., [27]. This dearth has been ascribed to improper absorption of vitamin D in addition to poor dietary consumption [15,22]. One more probable reason is hepatic dysfunctions which is responsible for faulty hydroxylation of vitamin D ensuing diminished levels [28]. Few authors also stated that the cause of 25-OH-vitamin D deficiency might be surplus iron rather than the inadequate functioning of endocrine tissues [22]. It was recognised that the role of osteoblast is diminished, which is thought to be the chief cause of osteopenia and osteoporosis in β -thalassaemia major. Osteoporosis is the most known bone complication in β -thalassaemia patients irrespective of steady transfusion and iron chelation treatment. The 25-hydroxyvitamin-D3 and bone mineral density were considerably reduced among patients with β -thalassaemia [29,30].

In the present study, all the thalassaemia patients had low serum calcium levels and normal to high serum phosphorus levels signifying impairment of parathyroid gland function. Also, there is negative correlation between serum ferritin and PTH levels (p -value < 0.004) which is consistent with the results of Belhou KM et al., [30]. Parathyroid hormones and calcitonin regulate the

calcium and phosphorus homeostasis in blood, and due to iron deposition these hormones are insufficiently produced [31,32]. The cause behind few patients developing HPT, while others not is still unknown. Several mechanisms have been accounted for glandular impairment due to iron excess. These comprise production of free radicals and lipid peroxidation ensuing in mitochondrial, lysosomal and sarcolemmal membrane destruction, and number of surface transferrin receptors in the cell, and the ability of the cell to shield itself against inorganic iron.

The present study reveals marked derangement of parathyroid hormone status and other biochemical markers related to calcium homeostasis in β -thalassaemia major patients with age-wise distinction. Thus, focussing on the fact that the toxicity caused due to iron deposition is not fully nullified or completely removed by chelation therapy. Therefore, the main cause of morbidity and mortality from second decade onwards remains iron toxicity with glandular damage.

Limitation(s)

The main limitation of the study was patient compliance. Also, the cost of chelating agents used as monotherapy was twice than that of combination therapy, revealing the scenario of utilisation of chelating agents among thalassaemia major patients on repeated transfusions.

CONCLUSION(S)

Regardless of the finest available treatment in thalassaemia major patients, few cases of HPT does arise. And as most patients are asymptomatic, it is vital to aggressively look for them, starting from the early second decade of life, so that the treatment can be introduced without delay. Screening of β -thalassaemia major patients should be done to look out for HPT, if any, especially after multiple transfusions, atleast once a year even if they are receiving chelation therapy to forestall hypocalcaemia associated complications. As a precautionary step youngsters with β -thalassaemia major in their second decade of life should be given calcium and vitamin D supplementation to avoid tetany due to hypocalcaemia, enable bone growth and to avert fractures. Also, screening for vitamin D deficit and hypocalcaemia should be done as a routine, in β -thalassaemia major children during second decade of their life.

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