Original Article

DOI: 10.7860/JCDR/2014/6672.3997

Prevalence of Hypoparathyroidism (HPT) in Beta Thalassemia Major

Biochemsitry Section

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ABSTRACT

Aim: This study was to assess the parathyroid functions and bone mineral density (BMD) in patients with beta thalassemia and to correlate them with serum ferritin, calcium, phosphorus and alkaline phosphatase levels.

Materials and Methods: This is a case control study which was done on 55 subjects (40 cases and 15 controls) in the age group of 2-18 years. The cases included were with confirmed diagnosis of beta thalassemia major, more than ten blood transfusions and serum ferritin levels >2000 µg/L irrespective of chelation therapy.

Results: Significant Hypoparathyroidism (HPT) observed along with low BMD levels in beta thalassemia patients ($p < 0.01$).

A significant decrease in serum calcium level was seen in cases when compared to controls, where as the levels of both serum phosphorus and alkaline phosphatase levels increased in cases when compared to controls.

Conclusion: BMD and PTH levels are very useful tools for diagnosing HPT. As a routine, in beta thalassemia major, screening for vitamin D deficiency and hypocalcemia should be done in second decade of life and as a preventive measure they should be supplemented with calcium and vitamin D to prevent hypocalcemic tetany, to facilitate bone growth and to prevent fractures.

Keywords: Bone mineral density (BMD), Parathyroid hormone (PTH), Dual energy X-ray absorptiometry (DEXA)

INTRODUCTION

HPT secondary to siderosis in thalassemia patients was first described by Gabriele [1]. Beta-thalassemia major is a fairly common and serious hematological problem that causes life threatening anemia by three to six months of life. 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 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]. The aim of this study was to assess the parathyroid functions and BMD in patients with beta thalassemia major and to correlate them with serum ferritin, calcium, phosphorus and alkaline phosphatase levels.

MATERIALS AND METHODS

Subjects

The present case-control study was conducted from January 2008 to September 2009 at Kasturba Medical College Hospital, Mangalore, India on 55 subjects (40 cases and 15 controls).

Inclusion criteria

1. Children in the age group of 2-18 years with confirmed diagnosis of beta thalassemia major .

2. Children with serum ferritin levels >2000 µg/L irrespective of chelation therapy.

3. Children with >10 blood transfusions.

Exclusion criteria

1. Children with serum ferritin levels <2000 µg/L

2. Children with infection.

3. Children with <10 blood transfusions.

After all necessary formal consents and due ethical clearances from respective concerned authorities, study was performed following proposed ethical standards on human experimentation. The informed consent was obtained from parents of the subjects.

Methods

1. Serum intact parathyroid hormone was estimated by fully automated chemiluminescent immunoassay. Elecsys 1010 [7].

2. Serum calcium was estimated by OCPC method. Kit by Aspen laboratories [8].

3. Serum phosphorus by molybdate/UV method. Kit by Aspen laboratories [9].

4. Serum alkaline phosphatase by enzymatic, diethanolamine buffer method. Kit by Aspen laboratories [10].

5. BMD estimated by dual energy X-ray absorptiometry.

Statistical analysis done by Mann - Whitney U-test.

RESULTS

A significant decrease in PTH ($p < 0.001$) was observed. As a consequence, serum calcium and BMD were also significantly low ($p < 0.001$). The levels of both serum phosphorus and alkaline phosphatase were significantly increased [Table/Fig-1].

Test	Cases (n =40)	Controls (n = 15)	p value
Serum parathormone (ng/L)	5.14±1.89	30.38±10.24	<0.001
Serum calcium (mg/dL)	5.534±1.11	9.28±0.63	<0.001
Serum phosphorus (mg/dL)	5.748±0.95	3.406±0.67	<0.001
Serum alkaline phosphatase(U/L)	444.175±181.49	308.533±75.42	=0.004
Bone mineral density	0.753±0.06	0.874±0.07	<0.001

[Table/Fig-1]: Comparison of mean ± S.D. values of various parameters between controls and cases

DISCUSSION

Statistics reveal that in India thalassaemia major affects over 1,00,000 people and over 8,000 reported thalassaemia births take place every year [11]. The total annual incidence of symptomatic individuals is estimated at 1 in 100,000 throughout the world [12].

Our study is based on the fact that despite the best management of thalassemia major patients, some cases of HPT 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. Inadequate chelation following frequent blood transfusions plays a key role in the development of HPT

We studied cases with high ferritin levels (>2,000 µg/L) leading to the deposition of iron on soft-tissues causing hemosiderosis thus resulting in damage to the parathyroid gland function [13]. As per previous studies, the prevalence varies greatly from low to as high as 22.5% [14]. HPT is well-known to occur in thalassemia major patients, but it is thought to be uncommon and its incidence is considered to be decreasing with improvements in chelation therapy. The cause of HPT in thalassemia is assumed to be iron deposition in parathyroid glands, but the reason why some patients develop HPT and others do not, is not exactly known [15]. A number of possible mechanisms have been described to be responsible for glandular damage through iron overload [16]. These include free radical formation and lipid peroxidation resulting in mitochondrial, lysosomal and sarcolemmal membrane damage, and a number of surface transferrin receptors in the cell, and the ability of the cell to protect itself against inorganic iron.

In our study it was observed that there is no clear relationship between HPT and serum ferritin levels. In an Italian study conducted by the department of pediatrics, observed 24 cases of HPT in beta thalassemia major [17]. HPT is thought to be mainly the consequence of iron deposition in the parathyroid glands. The age of their patients when HPT was diagnosed ranged from 11 to 24 years (mean 16.5 years). Their serum ferritin levels ranged from 810 to 15,200 ng/mL (mean 3,772 ng/mL). The severity of HPT varied widely. The onset of HPT was preceded or followed in most patients by other endocrine and/or cardiac complications. 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. It has been shown that prognosis for survival is best for those thalassemia patients in whom serum ferritin levels can be maintained below 2,500 µg/L, but at the same time some patients who receive ideal management in terms of present standards do develop significant endocrine damage. A multicenter study found that 22% of their thalassemia patients had endocrine complications, with a serum ferritin level below 2,000 µg/L. From the preceding discussion, it is quite obvious that although optimal chelation therapy does reduce the incidence of HPT and other endocrine complications, nonetheless some patients will continue to develop HPT [18]. We often find it very difficult to convince the parents to start chelation therapy. Since the concentration of ferritin is not a valuable tool in the prediction of the development of HPT, parathyroid function should be tested periodically, particularly when other iron overloaded associated complications occur.

In our study all the cases had low serum calcium levels and high serum phosphorus levels indicating damage to the parathyroid gland function. The maintenance of a normal serum calcium concentration depends on the balanced actions of PTH, vitamin D, and, to a lesser extent, calcitonin [19]. Vitamin D, the hallmark of therapy, is a long-acting drug with a narrow therapeutic range [20]. Current progress in the area depends on the development of procedures for the measurement of metabolites in plasma and assessing the role of the vitamin D in normal and abnormal physiology. The complications of the disease and therapy are irreversible.

In our study DEXA for the total BMD was done only on cases who were in their second decade of life and the BMD values were significantly low ($p < 0.01$). Ferritin levels were high but not relevant in this study as there is no clear relationship between serum PTH and ferritin levels. The cause of such alterations in ferritin values may be the regular blood transfusions. Another study was conducted in Greece to determine the prevalence of HPT in a large number of beta thalassemic patients, and its potential correlation with the presence of other endocrinopathies caused by iron overload [21]. Serum and urine biochemical parameters were measured in 243 thalassemic patients (136 females and 107 males) in order to determine the prevalence of hypothyroidism and evaluate bone turnover. The reduction in BMD was more prominent in normal thalassemic patients (Z score = -2.246 ± 0.97) compared with those with HPT (Z score =-1.975 ± 0.89), although the difference was not statistically significant.

LIMITATIONS

It is a small and one time study. Serial estimation of PTH and DEXA will help us to detect the early damage to the parathyroid gland before hypocalcemia manifests.

CONCLUSION

Screening of beta thalassemia major patients after multiple transfusions for the evidence of HPT must be carried out atleast once in a year to anticipate hypocalcemia related problems. As a preventive measure children with beta thalassemia major in their second decade of life need to be supplemented with calcium and vitamin D to prevent hypocalcemic tetany, to facilitate bone growth and to prevent fractures. As a routine, in beta thalassemia major children, screening for vitamin D deficiency and hypocalcemia should be done in second decade of life.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jun 10, 2013**
Date of Peer Review: **Nov 20, 2013**
Date of Acceptance: **Dec 19, 2013**
Date of Publishing: **Feb 03, 2014**