Study of Prevalence of Hypoparathyroidism in Transfusion Dependent Thalassemia Patients Attending a Tertiary Care Hospital in West Bengal, Eastern India

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ABSTRACT

Aim: To determine the prevalence of hypoparathyroidism in transfusion dependent thalassemia patients and to correlate serum iPTH with serum ferritin level.

Material and Methods: This is a cross sectional study performed with 140 transfusion dependent thalassemia patients from February 2016 to July 2017. Diagnosis of Hypoparathyroidism was based on serum iPTH level < 10pg/ml, serum calcium< 8.5mg/dl with increased phosphorous (PO4) >5.5 mg/dl, normal alkaline phosphatase. Other parameters analyzed include age, sex, serum ferritin, fasting plasma glucose, 2 hours postprandial plasma glucose, TSH, FT4, any symptoms of hypocalcemia.

Results: The mean age of thalassemia patient was 16.16±3.10 yrs, In the present study out of 140 TDT patients 62 (44.3%) were female & 78 (55.7%) were male. Among 140 patients 21 patients were diagnosed with hypoparathyroidism. Only five patients (23.8%) were symptomatic for hypoparathyroidism, 16 (76.2%) are asymptomatic. Hypothyroidism was present in 16 patients (76.19%), Dysglycemia 3 patients (14.3%), and Cardiac diastolic dysfunction in 3 (14.3%) out of 21 Hypoparathyroidism patients. Mean age of diagnosis of hypoparathyroidism was 15.82 ± 2.76 yrs. out of 21 hypoparathyroid patients 8 patients (38.1%) were female, and 13 patients (61.9%) were male. Among hypoparathyroid patient 12 were E-ß thalassemia (57.1%), 9 were ß-major thalassemia (42.9%). A significant negative correlation was found between serum ferritin and iPTH (spearman’s correlation coefficient = -0.391, p=0.049) in the subjects with hypoparathyroidism.

Conclusion: Prevalence of hypoparathyroidism in transfusion dependent thalassemia was 15%. Among the hypoparathyroid patients, E-ßeta constituted most. In the present study a significant negative correlation was found between serum ferritin and intact PTH. So, we recommend that patients with transfusion dependent thalassemia should receive regular and continuous follow up for the early detection of hypoparathyroid.

Keywords: NIL

INTRODUCTION

Globally, β-thalassemia is considered as the most common autosomal recessive disorders. The condition is caused by the reduced or absent synthesis of the β globin chains of the haemoglobin tetramer. A high prevalence of thalassemic patients have been reported from Mediterranean, Middle-East, Central Asia, Indian subcontinent, and Far East. About 3% of the world’s population carries β thalassemia genes. Excess free alpha-globin chains become abnormal components in maturing red blood cells, which leads to their destruction with subsequent anemia.

Thalassemia major is usually treated via blood transfusion, 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. The patients with TDT (transfusion dependent thalassemia) require regular blood transfusion to survive and without adequate transfusion support, they would suffer several complications and a short life span. This category includes patients with β- thalassemia major, severe HbE/β- thalassemia, transfusion dependent HbH
disease or HbH hydrops and surviving HbBart’s hydrops. Excessive iron overload and suboptimal chelation, endocrine dysfunction is a common complication of βeta-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 management⁴.

Hypoparathyroidism secondary to siderosis in thalassemia was first described by Gabriele⁶. Prevalence of hypoparathyroidism in general population is 37 per 1 lac in US but in transfusion dependent thalassemia its prevalence is 3.6 to 10%⁵⁻¹¹. Cardiac diastolic dysfunction is a common non endocrine complication associated with hyperparathyroidism¹⁰⁻¹¹. Although various studies are thereto find out the prevalence of hypoparathyroidism in thalassemia patients, Indian study are less in this regard. Moreover there is increase in the prevalence of E/β thalassemia noted in our population. For this reason the study has been conceptualized to evaluate the prevalence of hypoparathyroidism in transfusion dependent thalassemia patients attending a tertiary care hospital in West Bengal, Eastern India.

Aims and objectives:
To determine the prevalence of hypoparathyroidism in transfusion dependent thalassemia patients and to correlate iPTH with serum ferritin level

Material and Methods

Study design: Cross sectional study.

Study duration: 18 months.

Sample size: 140 transfusion dependent thalassemia patients.

Study Population: All 140 transfusion dependent thalassemia patients with age >10 years attending department of Endocrinology and Metabolism (indoor and outdoor patients) & Institute of Haematology & Transfusion Medicine, Medical College, Kolkata

Inclusion criteria:

1. Confirmed diagnosis of TDT²¹ (Hb electrophoresis)
   • Clinical criteria²¹ irrespective of haemoglobin level: Haemoglobin >7gm/dl with any of the following
     - Facial changes
     - Poor growth
     - Fracture
     - Clinically significant extramedullary haemopoiesis
   OR
   • Laboratory criteria²¹
     - Haemoglobin level (Hb) <7gm/dl on 2 occasions, >2 weeks apart (excluding all other contributory causes such as infections)
2. Serum ferritin > 1000 ng/ml

Exclusion Criteria:

• Patients with chronic kidney disease with eGFR<60ml/min 1.73 m².
• Patient with decompensated liver disease (serum bilirubin> 3 mg/dl, serum albumin<3g/dl, INR>1.7, ascitis and encephalopathy).
• Patient with vitamin D deficiency (25 hydroxy vitamin D <20ng/ml)
• Patients with previous thyroid surgery.
• Patients with hypomagnesemia.

Statistical analysis:

Descriptive statistical analysis has been carried out in the present study. Results of continuous data were presented as Mean ±SD and results of categorical data were presented as Number (%). Statistical significance is assessed at a level of 5%. Normality of data tested by Anderson Darling test, Shapiro-Wilk, Kolmogorov-Smirnoff test and visually by QQ plot. ANOVA has been used to find the significance of study parameters between three groups of patients. Unpaired t test has been used to find the significance of study parameters between two groups of patients. Chi-square or Fischer exact test is used for categorical variables.

Results:
A total 140 transfusion dependent thalassemia (TDT) patients, age > 10 years were selected for the study. The mean age of thalassemia patient was 16.16±3.10 yrs, out of 140 TDT patients 62 (44.3%) were female & 78 (55.7%) were male mean Hb level was 6.31±0.52 gm/dl, mean serum ferritin value was 1780.25±1063.88ng/ml, mean serum calcium value was 8.49±0.72 mg/dl, mean serum i PTH was 37.89±17.25 pg/ml.

Out of 140 transfusion dependent thalassemia patients, hypoparathyroid was diagnosed in 21(15%)

<table>
<thead>
<tr>
<th>Prevalence of hypoparathyroid:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Absent</td>
</tr>
<tr>
<td>Present</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Out of 21 hypoparathyroid patients 8 patients (38.1%) were female, and 13 patients (61.9%) were male. Among hypoparathyroid patient 12 were E-ß thalassemia (57.1%), 9 were ß-major thalassemia (42.9%).

Prevalence Of Hypoparathyroidism by thalassemia type:

<table>
<thead>
<tr>
<th>Hypoparathyroidism</th>
<th>Total</th>
<th>E.ß</th>
<th>ß-major</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>119</td>
<td>82</td>
<td>37</td>
</tr>
<tr>
<td>Present</td>
<td>21</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>140</td>
<td>94</td>
<td>46</td>
</tr>
</tbody>
</table>

In hypoparathyroid patients mean age was 15.82±2.76yrs as compared to non hypoparathyroid patients where it was 16.23 ±3.17yrs & P value of both was (p<0.585) not statistically significant. Mean Hb in hypoparathyroid patient was 6.02 ± 0.61gm/dl & as compared to 6.37±0.59 gm/dl & P value of both were (p<0.003); statistically significant.

In the present study mean serum ferritin in hypoparathyroid patient was 2844.98±2111.24 ng/ml & mean ferritin in non-HPT was 1592.36±583.49 ng/ml & P value of both were (p<0.014; )

In the present study negative correlation was found between serum ferritin and i PTH (spearman’s correlation coefficient = -0.391, p=0.049) in the subjects with hypoparathyroid which was statistically significant.

Hypothyroidism was present in 16 patients (76.19%), dysglycemia in 3 patients (14.3%), and cardiac diastolic dysfunction in 3(14.3%) patients of hypoparathyroidism.
Discussion

Hypoparathyroidism is one of the most common endocrine manifestations in transfusion dependent thalassemia. In our study mean age of hypoparathyroid patients was 15.82±2.76 years, similar studies done by Shamsiraz¹² and Najafipour¹³ et al showed mean age of patients were 16.9 ±3.7 and 14.5±3.2 years respectively as compared to our study. In the present study majority of the subject were male ie. 55.7% Similar results are observed by Hamideh⁵ AA et al & Angelopo NG⁴ et al & Shamshirsaz ¹⁵ AA et al in their study. So, men are affected with hypoparathyroid more frequently.

In the present study out of 140 TDT patients 21 having hypoparathyroid. So prevalence of hypoparathyroid in transfusion dependent thalassemia in our study is 15%. Hamidieh ⁵ AA et al showed prevalence was 14.5%. Angelopoulos NG, et al studied 243 thalassemia patients, prevalence of hypoparathyroidism was 13.6%¹⁴. High prevalence of hypoparathyroid in our patients could be due to high ferritin level. In the present study out of 21 hypoparathyroid patient 12 were E-ß thalassemia (57.1%), and 9 were ß-major thalassemia (42.9%). Study done by Paramita Chowdhury⁹ et al showed hypoparathyroid prevalence (29.4%) in E-ß thalassemia patients. 21 hypoparathyroid patients symptomatic (23.8%) & 16 patients were asymptomatic (76.2%) similar to Aleem A, Al-Momen¹⁶ et al study where 75% also Asymptomatic hypocalcemia & Other study support most of hypoparathyroid in TDT patients are
asymptomatic. Mean serum ferritin level of hypoparathyroid patients 2844.98± 2111.24 ng/ml; Hamidieh\(^5\) AA et al in their study observed a mean serum ferritin level in hypoparathyroid patients were 2532.9 ng/ml. In the present study an weak negative correlation was found between serum ferritin and intact PTH (spearman’s correlation coefficient = -0.391, p=0.049). Adel A. Hagag et al\(^{17}\) studied there is a negative correlation between serum ferritin and PTH levels; disagrees with Sleem\(^{20}\) et al who found no correlation between these two parameters. In the preset study out of 21 hypoparathyroid patients 16 had hypothyroid (76.19%) & out of 119 non-HPT patients 10 had hypothyroid (8.41%), significant association was found between prevalence of hypoparathyroidism & hypothyroid, p= 0.002 as computed by chi-square test. Thyroid dysfunction is reported in 3-27% with thalassemia but its severity variable in different series\(^{12-13}\). In the present study out of 21 hypoparathyroidism patient 3 patents (14.3%) had dysglycemia. The prevalence of diabetes has been reported as ranging from 2.3% - 24.1% in ß-thalassemia\(^{18}\). In the present study cardiac diastolic dysfunction was found in 14.3% ; similar observation maid by Hamidieh AA et al\(^5\). The most plausible mechanism is iron overload and its associated tissue damage, in addition to, oxidative stress, lipid peroxidation and free radicals release. Mechanisms like increased collagen deposition secondary to increased activity of the iron-dependent proline hydroxylase enzyme, with subsequent disturbed microcirculation in the endocrine glands is possibly described to be responsible for glandular damage\(^{19}\).

**Limitations:**

Our study is a small cross-sectional study so its ability to infer causality is limited, more studies involving larger number of patients needed as also the prospective studies to elicit real prevalence of hypoparathyroidism in transfusion dependent thalassemia. For logistic and ethical constraints no control group were simultaneously studied. Further, the data regarding the duration of blood transfusion and chelation therapy, which could affect the status of hypoparathyroidism were not collected in the current study. We could not estimate liver iron concentration which is a better biomarker of tissue iron overload than serum ferritin.

**Conclusion:**

From this small cross sectional study the following observations have been unleashed; Prevalence of hypoparathyroidism in transfusion dependent thalassemia was 15%. E-Beta constituted significant proportion in hypoparathyroid patient. In the present study a significant negative correlation was found between serum ferritin and intact PTH. Diastolic dysfunction, dysglycemia and hypothyroidism is significantly higher in subjects with hypoparathyroid. So, we recommend that patients with transfusion dependent thalassemia should receive regular and continuous follow up for the early detection of hypoparathyroid.

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