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Original Research Article

Endocrine impact of transfusion therapy: parathyroid status in pediatric thalassemia major

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ABSTRACT

Background: Thalassemia major, a severe form of inherited anemia, requires lifelong blood transfusions to manage the condition and sustain hemoglobin levels. However, these repeated transfusions often lead to iron overload, which can deposit in various organs, including endocrine glands and disrupt normal hormone production. One such affected gland is the parathyroid, responsible for regulating calcium and phosphate balance through parathyroid hormone (PTH) secretion. This study aimed to assess the parathyroid status in children with thalassemia major.
Methods: This case-control analytical study design was considered to assess the parathyroid status in children with thalassemia major. The study was carried out at the Department of Pediatric Hematology and Oncology, Dhaka Medical College Hospital, Dhaka, from July 2012 to June 2013. A total of 40 children with thalassemia major (termed as case) and another 32 normal children (termed as control) were included in the study. Data were analyzed using SPSS (Statistical Package for Social Sciences) version 16.
Results: The study found that children with thalassemia major had significantly lower parathyroid hormone (PTH) levels and higher phosphate levels compared to healthy controls, though calcium levels were similar between groups. Thalassemia patients, primarily receiving blood from professional donors, underwent transfusions for an average of six years, with limited use of chelation therapy (15%). Hypoparathyroidism was significantly more common in thalassemia patients (10%) compared to controls, with 25% also showing hyperphosphatemia. No significant differences were observed in age or sex distribution between the groups.
Conclusions: It can be concluded children with thalassemia possess significantly low serum PTH and high phosphate levels. The serum calcium level does not alter significantly compared to healthy children of similar age and sex. The findings call attention to the critical need for early intervention, regular endocrine screening and diligent chelation therapy in managing thalassemia major.

Keywords: Endocrine, Parathyroid, Transfusion, Thalassemia Major

INTRODUCTION

Thalassemia major, a severe form of beta-thalassemia, is a genetic disorder characterized by defective hemoglobin synthesis, leading to chronic anemia and a significant dependency on regular blood transfusions. This transfusion-dependent state, while life-saving, results in iron overload, which accumulates in various organs and causes multi-organ damage over time. One area

particularly affected by this iron overload is the endocrine system, with various hormonal deficiencies arising as a consequence. Among these, hypoparathyroidism is a prominent endocrine complication in children with thalassemia major, primarily due to iron deposition in the parathyroid glands, which disrupts their function.[1-3] Since the human body lacks an effective mechanism to excrete excess iron, it is stored in tissues and organs, including the liver, heart, pancreas and endocrine glands. Over time, iron deposition in the parathyroid glands can impair their function, leading to hypoparathyroidism, a condition characterized by low production of parathyroid hormone (PTH).[4]

The exact mechanism by which iron causes parathyroid dysfunction is complex and not entirely understood. It is believed that iron accumulation in the gland initiates a cascade of oxidative stress and cellular damage, eventually leading to fibrosis and atrophy of parathyroid cells. This process disrupts normal parathyroid function and reduces PTH secretion.[5]

Children with longer transfusion histories and insufficient chelation therapy are at a higher risk of developing hypoparathyroidism due to prolonged exposure to high iron levels. In addition to hypoparathyroidism, these children may suffer from other endocrine abnormalities, such as hypogonadism, diabetes mellitus and hypothyroidism, further complicating their clinical management.[6,7]

Clinically, hypoparathyroidism in thalassemia major presents with symptoms related to hypocalcemia, which can range from mild to severe. Early symptoms may include muscle cramps, numbness and tingling, especially in the hands, feet and around the mouth.

As hypocalcemia progresses, more severe manifestations such as tetany, seizures and cardiac arrhythmias can occur, posing a significant risk to the patient's health and quality of life.[8] In addition, chronic hypocalcemia can affect bone health, leading to an increased risk of osteoporosis and fractures, which are particularly concerning for growing children.[9]

However, the diagnosis can be challenging, as early symptoms may be subtle or misattributed to other causes. Furthermore, regular monitoring of these parameters is necessary for thalassemia major patients, as hypoparathyroidism may develop insidiously over time. Imaging studies such as ultrasound or MRI can be used to assess iron deposition in the parathyroid glands and other organs, providing additional insights into the extent of iron overload.[10]

Managing hypoparathyroidism in thalassemia major requires a multifaceted approach. The primary goal is to prevent iron overload and its complications, primarily through effective chelation therapy.

Chelating agents like deferoxamine, deferiprone and deferasirox are used to bind and remove excess iron from the body, reducing the risk of iron-induced organ damage.[11]

Regular monitoring and adjustment of chelation therapy are essential to maintain optimal iron levels and prevent further complications. In cases where hypoparathyroidism has developed, calcium and active vitamin D supplementation are necessary to maintain serum calcium levels and mitigate symptoms associated with hypocalcemia.[12] So, this study aimed to assess the parathyroid status in children with thalassemia major.

METHODS

Study design

This case-control analytical study design was considered to assess the parathyroid status in children with thalassemia major.

Study place

The study was carried out at the Department of Pediatric Hematology and Oncology, Dhaka Medical College Hospital, Dhaka.

Study duration

The study period from July 2012 to June 2013.

Children with thalassemia admitted to the above-mentioned hospital and normal children who visited the Pediatric Out-patient Department of Dhaka Medical College Hospital were the study population. Ethical clearance was taken from the Ethical Committee of the Dhaka Medical College, Dhaka.

Inclusion criteria

Age ranging from 6-15 years old of either sex, Children who received whole blood/packed cells transfusion more than 20 times to maintain hemoglobin levels between 9-10.5 g/dl.

Exclusion criteria

Very sick children, malabsorption syndrome, children suffering from disease of thyroid and parathyroid glands, those who receive long-term anticonvulsant therapy, parents of children refusing to give written consent.

Data collection

A total of 40 children with thalassemia major (termed as case) and another 32 normal children (termed as control) were included in the study. All necessary investigations were done. Data were collected using a structured

questionnaire (research instrument) containing the variables of interest.

Statistical analysis

Data were analyzed using SPSS (Statistical Package for Social Sciences) version 16. The test statistics used to analyze the data were descriptive statistics, Chi-square or Fisher Exact Probability Test (for comparison of data presented on the categorical scale) and Student's t-test (for comparison of data presented on a continuous scale). The level of significance was set at 0.05 and $p<0.05$ was considered significant.

RESULTS

Demographic characteristics of the case and control show that there was no significant difference between the groups in terms of age and sex (p=0.629 and p=0.956 respectively). The mean age of the cases and controls were 10.2 and 9.8 years respectively. A male predominance was observed in either group (Table 1).

Transfusion-related parameters are shown in Table 2. A majority (97.5%) of the children received blood from professional donors. Forty percent of their children received blood from two centers and 25% from multiple centers. In terms of the type of transfusion, 55% received PCV and the rest 45% received whole blood. Some 15% of children used chelating agents. The mean duration of transfusion was almost 6 years and the average number of transfusions was 13 (Table 2).

The level of serum PTH was significantly reduced and that of serum phosphate was significantly increased in the case group (thalassemia children) than those in the control group (p=0.049) and p=0.018 respectively), while the serum level of calcium was no different between groups (p=0.235) (Table 3).

Table 1: Comparison of age and sex between case and control groups.

Demographic variables	Group		P value
	Case (n=40)	Control (n=32)	
Age*(in years)	10.2±3.0	9.8±3.1	0.629
Sex#			
Male	26 (65.0)	21 (65.5)	0.956
Female	14 (35.0)	11 (34.4)	

Figures in the parentheses denote the corresponding percentage. *Data were analyzed using Student" 's t-test and were presented as mean±SD, #Data were analyzed using the Chi-square Test.

Table 2: Distribution of patients by transfusion-related parameters (n=40).

Transfusion-related parameters	Frequency (%)
Source of blood	
Voluntary	01 (2.5)
Professional	39 (97.5)
Transfusion received from	
One center	14 (35.0)
Two Centers	16 (40.0)
Multicenter	10 (25.0)
Type of transfusion received	
PCV	22 (55.0)
Whole blood	18 (45.0)
Chelating agent used	6 (15.0)
Years of transfusion	Mean±SD 5.95±2.84
No, transfusions received so far	Mean±SD 23.0±0.0

Table 3: Comparison of PTH, calcium and phosphate between groups.

Biochemical variables	Group		P value
	Case (n=40)	Control (n=32)	
PTH (pg/ml)	47.6±3.7	57.1±2.9	0.049
Calcium (mg/dl)	8.6±0.3	9.0±0.7	0.235
Phosphate (mg/dl)	11.1±2.4	6.3±0.5	0.018

Data were analyzed using an Unpaired t-test and were presented as mean±SD, 5.9 Comparison of parathyroid status and associated biochemical changes.

Table 4: Comparison of parathyroid status and associated biochemical changes.

Parathyroid status and associated biochemical changes	Group		P value
	Case (n=40)	Control (n=32)	
Hypoparathyroidism*			
Present	4 (10.0)	0 (0.0)	0.046
Absent	38 (90.0)	32 (100.0)	
Hypocalcemia#			
Present	14 (35.0)	7 (21.9)	0.223
Absent	26 (65.0)	25 (78.1)	
Hyperphosphatemia#			
Present	10 (25.0)	0 (0.0)	0.007
Absent	30 (75.0)	32 (100.0)	

Figures in the parentheses denote the corresponding percentage. *Data were analyzed using Student" 's t-test and were presented as mean±SD, #Data were analyzed using the Chi-square Test.

Four (10%) patients in the case group were hypo parathyroid as opposed to none in the control group (p=0.046).

While one-quarter (25%) of the children in the case group developed hypophosphatemia, none was found so in the control group than in the latter group, though the difference did not reach the level of significance (p=0.166) (Table 4).

DISCUSSION

Our analysis showed no significant differences in age and sex between the case and control groups (p=0.629 and p=0.956, respectively), suggesting that the groups were comparable demographically. The average age of cases was 10.2 years, while controls had an average age of 9.8 years. Male predominance was observed in both groups, which aligns with findings from other studies where a higher prevalence of thalassemia major was reported among males.[3,13] The majority of thalassemia patients (97.5%) received blood from professional donors and around 40% had received transfusions from two centers, with 25% receiving blood from multiple centers. This distribution highlights the frequent need for transfusions in thalassemia major and suggests potential exposure to varied transfusion practices. Most patients (55%) received packed cell volume (PCV) transfusions, while 45% received whole blood. Iron overload, an inevitable consequence of repeated blood transfusions, is a known risk factor for endocrine dysfunction, including hypoparathyroidism, as free iron accumulates in organs, including the parathyroid glands, leading to impaired function.[4] The mean duration of transfusion was approximately six years, with an average of 23 transfusions per patient. This duration and frequency of transfusion correlate with studies showing that endocrine dysfunction typically manifests after years of chronic transfusion therapy due to progressive iron overload.[2] Biochemical comparisons between the groups showed significant reductions in serum parathyroid hormone (PTH) levels (p=0.049) and significant increases in phosphate levels (p=0.018) in the case group compared to controls. The mean PTH level in thalassemia major patients was markedly lower than in controls (47.6 vs. 57.1 pg/ml), indicating parathyroid dysfunction likely due to iron deposition in the parathyroid glands. The incidence of hypoparathyroidism was significantly higher in the case group, with 10% of thalassemia patients showing evidence of hypoparathyroidism compared to none in the control group (p=0.046).

The findings are consistent with previous studies that documented a prevalence of hypoparathyroidism in 5-10% of thalassemia major patients, particularly in those with inadequate chelation therapy.[8,14] The findings reinforce the association between iron overload and parathyroid dysfunction in transfusion-dependent thalassemia major patients. Persistent iron overload, if not managed effectively through chelation, leads to endocrine gland toxicity, including the parathyroids. Iron deposits cause oxidative damage to parathyroid tissue, diminishing PTH synthesis and release, thereby predisposing patients to hypoparathyroidism and subsequent disturbances in calcium and phosphate homeostasis.[9] The findings of this study emphasize the need for early identification and regular monitoring of parathyroid function in thalassemia major patients, particularly those with a long transfusion history and inadequate chelation therapy. Current guidelines suggest initiating iron chelation therapy once serum ferritin levels exceed 1,000 ng/mL. However, due to the variability in iron deposition among organs, reliance solely on ferritin may not be sufficient for assessing iron toxicity risk. Advanced imaging techniques, such as T2 MRI, may provide more accurate insights into iron burden in tissues and should be considered in long-term management plans for transfusion-dependent patients.[15]

The present study was conducted on a small number of cases and as such the study findings cannot be generalized to a reference population. The study did not

collect intervention data to see the outcome of vitamin D and calcium supplementation in patients with thalassemia. Urinary calcium excretion was also not measured.

CONCLUSION

It can be concluded children with thalassemia possess significantly low serum PTH and high phosphate levels. The serum calcium level does not alter significantly compared to healthy children of similar age and sex. The findings call attention to the critical need for early intervention, regular endocrine screening and diligent chelation therapy in managing thalassemia major.

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