ORIGINAL ARTICLE

ASSOCIATION OF HYPOCALCEMIA WITH OTHER IRON OVERLOAD COMPLICATIONS IN BETA THALASSEMIA MAJOR PATIENTS

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ABSTRACT

Background: Multi-transfused ß-thalassaemia major patients, may develop severe endocrine complications due to iron overload. The anterior pituitary is particularly sensitive to iron overload which disrupts hormonal secretion resulting in hypogonadism, short stature, acquired hypothyroidism and hypoparathyroidism. Cardiac complications and diabetes mellitus are also common in thalassaemic patients.

Materials and methods: This cross sectional study was conducted at Fatimid foundation Peshawar from June 2015 to August 2015. One hundred diagnosed ß-thalassemia major patients were enrolled and blood samples were drawn to determine serum calcium and phosphorus levels using Microlab 200. Heights of patients were measured in centimeters. Levels of thyroid stimulating hormone (TSH), thyroxin (free T4), random blood glucose, ECG, X-ray and echo- cardiography were all noted and positive cases of short stature, hypothyroidism, diabetes mellitus and cardiac dysfunction were recorded and their association with hypocalcemia was observed. Data was analysed using SPSS.

Results: Short stature was observed in 39 hypocalcemics, hypothyroidism in 7, cardiac dysfunction in 5 and 4 patients had hypocalcemia along with diabetes.
Conclusion: Hypocalcemia is most frequently associated with short stature and least frequently with diabetes mellitus.

Key Words: Thalassemia Major, hypocalcemia, hypothyroid, short stature, diabetes mellitus.

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INTRODUCTION

Inherited hemoglobin disorders are the leading single-gene disorders[1]. These pose a significant health burden throughout the world with more than 330,000 infants being born with these disorders annually. Seventeen percent (17%) of these infants are struggling with thalassemia. Thalassemia is a broad group of disorders of hemoglobin synthesis with recessive inheritance, characterized by deficient synthesis of ß-globin chains due to a mutation. Homozygous state presents with severe anemia in first few months of life requiring regular blood transfusion[2]. Thalassemia is the most common monogenic disorder in the world[3]. Thalassemia major (ß-thalassaemia) affects a significant segment of the population in certain areas of the world.
Alterations in migration patterns have changed the geographic distribution of this disease and made it a worldwide health problem with a high frequency in Africa, India, Southeast Asia and the Mediterranean area[4].
When ß-thalassaemia major patients are transfused poorly or left untreated, they present with retarded growth, pallor, jaundice, poor musculature, hepatosplenomegaly, leg ulcers, development of masses from extra-medullary hemopoeisis and skeletal changes from bone marrow expansion[5]. Patients of this category usually present within first year of life and if left untreated they die within 5 years of life. Blood transfusions given at frequent intervals prolong the life- style of patient and are the mainstay of treatment. Al- though transfusions are life savers for such patients but at the same time lead to iron overload and expose the patients to multiple other complications like hypersplenism, chronic hepatitis, HIV, venous thrombosis, osteoporosis6. Iron overload is among the most serious concerns of hematologists regarding transfusion-dependent patients and its complications are the most significant

cause of death. Complications of iron overload in children are growth retardation and failure or delay of sexual maturation. Later on iron overload related complications include heart problems (cardiomyopathy or rarely arrhythmias), liver dysfunction (fibrosis or cirrhosis) and endocrine problems. Many mechanisms have been proposed so far for elaboration of glandular damage occurring via iron overload.
The purpose of this study was to find the association of hypocalcemia resulting from hypoparathyroidism with other diseases in such patients like short stature, hypothyroidism, cardiac dysfunction and diabetes.

METHODOLOGY

This was a cross-sectional study from June 2015 to August 2015. Hundred consenting beta thalassemia major patients diagnosed on hemoglobin electrophoresis and on regular transfusion and chelation therapy, attending Fatimid foundation Peshawar were included in the study. Only patients fulfilling the inclusion criteria were enrolled. Detailed history and physical examination was carried out. Approval was taken from ethical board of Khyber medical university. Non-probability consecutive sampling technique was used.

Using aseptic technique 5ml of venous blood was collected in plain gel tubes. Serum was separated by centrifugation. Serum calcium and phosphorus levels were measured in obtained sera using semi-automated analyzer microlab 200 through commercially available kits. Hypocalcemia was taken as serum calcium level <8 mg/dl. Serum phosphorus level above 5 mg/dl was taken as increased.

Height of patients was recorded and patients whose height was below the 5th percentile for their age as plotted on the Centers for Disease Control and Prevention (CDC) 2000 age/gender specific growth charts were labelled as short stature.

Thyroid function was evaluated by measurements of T4, and TSH using enzyme-linked immunosorbent assay (ELISA). Hypothyroidism was defined by a TSH level
>8μIU/ml, and T4 < 4.5μg/dl7. A random blood glucose level of ⩾200 mg/dL was considered diabetes mellitus7. ECG, X-rays and echocardiography of all patients was noted for any cardiac disease.

The prevalence of hypocalcemia came to be 49% in this study whereas 26% patients had hypocalcemia associated with hyperphosphatemia (suspected hypoparathyroidism).

Short stature was seen in 39 hypocalcemics, hypothyroidism in 7, cardiac dysfunction in 5 and 4 patients had hypocalcemia along with diabetes as shown in the table 1.

RESULTS

The prevalence of hypocalcemia came to be 49% in this study whereas 26% patients had hypocalcemia associated with hyperphosphatemia (suspected hypoparathyroidism).
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DISCUSSION

Hypoparathyroidism leading to hypocalcemia is considered a typical complication of second decade of life in transfusion-dependent patients of thalassemia major[8].
Hypocalcemia associated with hyperphosphataemia is most likely due to hypoparathyroidism and it was suspected in 26% of our subjects. Short stature was the most frequently associated complication with hypocalcemia in our study, while Fahim M et al from Egypt also reported short stature in 49% thalassemics[9]. This may be explained by the fact that retardation of growth is affected by other factors also in addition to iron overload like chronic anemia, chelation toxicity, deficiency of zinc and social stress[10].

Cardiac dysfunction and especially left-sided heart failure are responsible for more than half of the deaths in patients of beta thalassemia major and are thus the main determinants of survival[11]. Heart disease may manifest itself as hemosiderrotic cardiomyopathy, heart failure, pulmonary hypertension, arrythmias, systolic/diastolic dysfunction, pericardial effusion, myocarditis or pericarditis[12,13]. Iron overload is mainly implicated although genetic and immunologic factors, infections and chronic anemia also have important roles. The prevalence of cardiac dysfunction in our study was 9% and the heart diseases noted were heart failure, arrhythmias, pericardial effusion and pulmonary hypertension.

Thyroid dysfunction with high TSH level has been reported in 11.9% thalassemia major patients in a cross sectional study in Mashad Iran[14]. Most studies

report a high prevalence of subclinical primary hypothyroidism (normal FT4, FT3; increased TSH) whereas prevalence of overt hypothyroidism (low FT4 and/or FT3; increased TSH) is relatively low[15].The frequency of hypothyroidism in our study was 10 % where 70% of hypothyroid patients were also hypocalcemics.

The least association was seen with diabetes in our study which is mainly affected by iron overload.

LIMITATION

Serum parathyroid hormone levels could not be done, to confirm the presence of hypoparathyroidism.

CONCLUSION

Hypocalcemia is associated with many complications in transfusion-dependent ß-thalassaemia major patients. These include hypothyroidism, short stature, cardiac dysfunction and diabetes. The underlying cause is iron overload. Hypocalcemia was most frequently associated with short stature in our study and least frequently with diabetes.

Table 1: Association of hypocalcemia with other comorbidities in ß

	Low S. Ca	Normal S.Ca	Total	P value
Short stature				
Absent	10 (52.6%)	9 (47.4%)	**19 (100%)**	**0.725**
Present	39 (48.1%)	42 (51.9%)	**81 (100%)**	
Hypothyroidism				
Absent	42 (46.7%)	48 (53.3%)	**90 (100%)**	**0.161**
Present	7 (70%)	3 (30%)	**10 (100%)**	
Cardiac dysfunction				
Absent	44 (48.4%)	47 51.6%)	**91 (100%)**	**0.68**
Present	5 (55.6%)	4 (44.4%)	**9 (100%)**	
Diabetes				
Absent	45 (47.4%)	50 (52.6%)	**95 (100%)**	**0.155**
Present	4 (80%)	1 (20%)	**5 (100%)**	

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