

FREQUENCY OF IRON OVERLOAD COMPLICATIONS IN BETA THALASSEMIA MAJOR PATIENTS

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ABSTRACT

Objective: To study the frequency of iron overload related complications in beta thalassemia major patients on chelation therapy in Fatimid Foundation, Peshawar.

Methodology: This cross-sectional study was conducted at Fatimid Foundation, Peshawar between June 2015 to August 2015. One hundred confirmed beta (β) thalassemia major patients were enrolled in this study. Their detailed history and physical examination including height and weight was recorded on pre-designed questionnaire. Blood samples were analysed for calcium and phosphorus. Levels of thyroid stimulating hormone (TSH) and thyroxin (free T4), random blood glucose, ECG, x-rays and echocardiography were all noted and positive cases of short stature, hypothyroidism, hypoparathyroidism, diabetes mellitus and cardiac dysfunction were recorded. Data were analysed using SPSS.

Results: Out of 100 patients, 53% were males and 47% were females. The age range of patients was 5 to 20 years (mean 13.62 ± 3.78 years). Short stature was seen in 89% patients, hypoparathyroidism in 26% patients, hypothyroidism in 10%, cardiac dysfunction in 9% and diabetes mellitus in 5% patients.

Conclusion: The frequency of frequency of iron overload related complications in beta thalassemia major patients was relatively higher in this study. Short stature was the most frequent complication while diabetes mellitus was the least common complication.

Key Words: Thalassemia major, Hypocalcemia, Hypothyroid, Short stature, Diabetes mellitus

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INTRODUCTION

Inherited hemoglobin (Hb) disorders rank first among the single-gene disorders¹. These are significant health problems worldwide with more than 330,000 infants born with these disorders annually; 17% of these infants are sufferers of thalassemia. Thalassemias are recessively inherited disorders of Hb synthesis where decreased synthesis of the β -globin chain occurs. The homozygous state leads to severe anemia requiring regular blood transfusion². When beta thalassemia major patients are transfused poorly or left untreated, they present as retarded growth, anemia, jaundice, weak musculature, knock-knee, liver and spleen enlargement, ulceration on the leg, development of masses from extramedullary hemopoiesis and changes in skeleton from bone marrow expansion³⁻⁵. Patients of this category

present usually in the first year of life and if left untreated they die within 5 years of life. Blood transfusions given at frequent intervals prolong the life of patients and are the mainstay of treatment. Although transfusions are life savers for such patients but at the same time lead to iron overload and expose the patients to many other complications like hypersplenism, chronic hepatitis, human immunodeficiency virus (HIV), venous thrombosis and osteoporosis⁶.

Iron overload is among the most serious issues of transfusion-dependent patients and its complications are the most significant cause of death. Iron overload in these children lead to retardation of growth and sexual dysfunction. Complications of iron overload later on include cardiac problems, hepatic dysfunction and endocrine problems. Many mechanisms have been proposed

so far for elaboration of glandular damage occurring via iron overload⁷.

This study was done to find out the frequency of iron overload complications like short stature, hypothyroidism, hypoparathyroidism, cardiac dysfunction and diabetes mellitus in beta thalassemia major patients on chelation therapy in our set up where data is scarce.

METHODOLOGY

This was a cross-sectional study done in Fatimid Foundation, Peshawar from June 2015 to August 2015. The population of this study comprised of 1500 patients of beta thalassemia major registered at Fatimid Foundation, Peshawar. Sample size was calculated to be 100 by Raosoft online sample size calculator with 7.95% margin of error, 90% confidence interval and 50% response distribution. Consequently, 100 patients of beta thalassemia major, aged 5-20 years whose diagnosis was confirmed by Hb electrophoresis and who were on regular transfusion and chelation therapy attending Fatimid Foundation, Peshawar were included in the study. Consecutive non-probability sampling technique was done. Ethical approval was taken for the study. Patients who were very ill, receiving calcium and vitamin D supplementation or drugs affecting calcium levels were excluded from the study.

Detailed history was taken, examination of the patients was carried out and 5ml of blood was taken from the patients in plain tubes with gel through venipuncture. Blood was allowed to clot and then centrifuged for separating the serum. Serum calcium and phosphorus levels were determined in the obtained sera on semiautomated analyser through commercially available kits. Hypoparathyroidism was labelled as positive in patients having serum calcium level below 8mg/dl and serum phosphate above 5mg/dl. Heights of patients were recorded and those 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 thyroid stimulating hormone (TSH) and thyroxin (free T4) using enzyme-linked immunosorbent assay (ELISA) on the obtained serum. Hypothyroidism was defined by a TSH level >8µU/ml, and T4 levels <4.5µg/dl. Blood glucose levels were determined on the sera. A random blood glucose level of ≥200 mg/dl was considered diabetes mellitus. ECG, x-rays and echocardiography of all patients were noted for any cardiac disease.

Data was analysed using SPSS version 19.0. Variables of interest were short stature, hypoparathyroidism, hypothyroidism, cardiac dysfunction and diabetes mellitus. Data were presented descriptively using mean, standard deviation and percentages.

RESULTS

Our study included 53(53%) males and 47(47%) females. Their age range was 5-20 years with the mean value of 13.62 ±3.78 years. Short stature was seen in 89% of patients. The frequencies of other iron overload related complications are given in Table 1.

DISCUSSION

The advent of transfusion therapy with adjuvant chelation has improved the life expectancy of thalassemic patients dramatically but at the same time have been associated with serum iron overload that leads to growth retardation, hypoparathyroidism, hypothyroidism, diabetes mellitus and cardiac complications⁸.

Short stature was the most frequent complication in our study and this may be explained by the fact that retardation of growth is also affected by other factors in addition to iron overload like chronic anemia, chelation toxicity, deficiency of zinc and social stress⁹. In our study 89% were short statured. Its frequency was very high as compared to other studies in different regions and this

Table 1: Frequencies of iron overload related complications (n=100)

Iron Overload Complication	Frequency	Percentage
Short Stature	89	89%
Hypoparathyroidism	26	26%
Hypothyroidism	10	10%
Cardiac Dysfunction	9	9%
Diabetes Mellitus	5	5%

might be attributed to suboptimal chelation due to unaffordability or genetic factors. The prevalence is 35.3% as reported in Greek patients, 37% in Italians, 54.5% in Malaysians and 53% in Romania¹⁰⁻¹³.

Hypoparathyroidism leading to hypocalcemia is considered a main complication of second decade of life in patients with thalassemia major who are on transfusion therapy⁹. In our study, 49% of patients were hypocalcemic. Hypocalcemia associated with hyperphosphataemia due to hypoparathyroidism was present in 26% of our subjects. Hypocalcemia was reported to be 16.6% by Dresner et al¹⁴, while Gulati et al¹⁵ reported it to be 13.5% and hyperphosphatemia was found in 60% of these hypocalcemics. Hypocalcemia and hyperphosphatemia were detected in 22% and 18% respectively by Mirrhosseini et al¹⁶. Hypocalcemia reported in Iraq was 21.7%, Saudi Arabia 20% and India 7.4%^{17,18}. In Pakistan hypocalcaemia in thalassaemic patients is reported to be 35.3% by another study¹⁹.

Cardiac dysfunction and specially left-sided heart failure are responsible for >50% of deaths in patients with thalassemia major and are therefore the main determinants of survival⁹. Cardiac dysfunction may present as hemosiderotic cardiomyopathy, cardiac failure, pulmonary hypertension, arrhythmias, systolic/diastolic dysfunction, pericardial effusion, myocarditis or pericarditis¹². Iron overload plays a main role in cardiac dysfunction; though genetics, immunologic factors, infections and chronic anemia are also responsible. Cardiac complications are reported to range from 4.5-23%^{5,12}. 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 is present in 13-60% of these patients but it is variable in its severity in different surveys. It was reported to be 7% in Shiraz by Karamifar et al²⁰ and 16% in Tabriz by Najafpour et al²¹ whereas De Sanctis et al²² reported 21.6% in Italy. A high prevalence of subclinical primary hypothyroidism (normal FT4, FT3; increased TSH) has been reported whereas prevalence of overt hypothyroidism (low FT4 and/or FT3; increased TSH) is relatively low²². The frequency of hypothyroidism in our study was 10%.

Although genetic predisposition was described, there was little data on its contribution to diabetes development in thalassemia major²³. The prevalence of diabetes mellitus in beta-thalassaemic patients is reported up to 24%²⁴. In our study, only 5% of patients were suffering from diabetes. This however may be due to the reason that age limit was 20 years in this study and diabetes is uncommon in beta-thalassaemics who are less than 16 years old according to a prior study²⁵.

LIMITATIONS

This study has several limitations. Data on direct measurement of hepatic iron or cardiac MRI was not available. Data on adherence to treatment was unavailable. Due to the fact that it was a single center study with a small sample size, the generalization of results to the whole population was restricted.

CONCLUSION

The frequency of iron overload related complications in patients of thalassemia major in our setting was different from their incidence reported internationally. Short stature was the most frequent complication in beta thalassemia major patients on transfusion therapy in our set up while diabetes mellitus was the least common complication.

RECOMMENDATIONS

It is important to determine the genetic status of thalassaemics of our region which will uncover the genetic modifiers responsible for iron overload mediated organ injury. This may explain the low cardiomyopathy rate and high short stature and hypoparathyroidism rate among our population. The high prevalence of complications in our set up also stresses the need for further improvements in the management of these complex patients.

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CONTRIBUTORS

SS conceived the idea, planned the study and drafted the manuscript. NF, AB, MS, SM and SF helped acquisition of data, did literature search & statistical analysis and critically revised the manuscript. All authors contributed significantly to the submitted manuscript.