Original Article

Frequency of hypothyroidism in patients of β-thalassaemia
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Abstract

Objective: To determine the frequency of hypothyroidism in patients suffering from homozygous β-thalassaemia.

Methods: This descriptive study included 70 diagnosed thalassaemia major patients aged 5-14 years. Demographic data as well as history of blood transfusion and chelation therapy was collected. Random blood samples were drawn and thyroid profile (serum thyroxine [T4], triiodothyronine [T3] and thyroid stimulating hormone concentrations [TSH]) was done by enzyme-linked immunosorbent assay (ELISA). Primary hypothyroidism was defined by a TSH level >4µIU/ml. Results were analysed by descriptive statistical methods.

Results: Primary hypothyroidism was seen in 18 (25.7%) patients. Of these, 17 had normal T4 levels with elevated TSH levels consistent with a diagnosis of compensated primary hypothyroidism whereas only one patient showed a decreased T4 level with elevated TSH (uncompensated primary hypothyroidism). Mean age of hypothyroid patients was 9.2 ± 2.6 years. Frequency of hypothyroidism was associated with increased serum ferritin levels.

Conclusion: Primary hypothyroidism occurs in a significant proportion of thalassaemia major patients in the absence of obvious clinical signs of hypothyroidism. Regular follow-up for early detection and timely treatment of such complications could improve the quality of life of these patients (JPMA 60:17; 2010).

Introduction

β-thalassaemia represents a group of recessively inherited haemoglobin disorders characterized by deficient synthesis of the β globin chain. The homozygous state results in severe anaemia in infancy which requires regular blood transfusion.1

Thalassaemia is the most common monogenic disorder in the world.2 In Pakistan, the gene frequency of β-thalassaemia is estimated to be 5-8%3 and it is present in all ethnic groups.4 Therefore it is estimated that each year more than 5000 children are born with transfusion dependent β-thalassaemia. In the last decade the average lifespan of these patients was not more than 10 years.5

The combination of blood transfusion and chelation
therapy has dramatically prolonged the life expectancy of these patients, thus transforming thalassaemia from a rapidly fatal disease of childhood to a chronic disease compatible with a prolonged life.6

On the other hand frequent blood transfusions, iron overload, poor compliance to therapy and chronicity of the disease have in turn contributed to a whole spectrum of complications including cardiac problems, hypogonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism and other endocrine and metabolic problems in adolescents and young adults suffering from thalassaemia major.7

The commonest form of thyroid dysfunction seen in thalassaemics is primary hypothyroidism due to abnormalities of the thyroid gland which, leads to insufficient production of the thyroid hormones. However, the frequency of hypothyroidism varies depending on the region, quality of management and treatment protocols.1

The main aim of this study was to determine the frequency of hypothyroidism in children suffering from thalassaemia major.

Patients and Methods

This descriptive study was conducted at the Haematology and Transfusion Medicine Division at The Children's Hospital and Institute of Child Health, Lahore from January, 2009 to April, 2009. Seventy patients of homozygous β-thalassaemia attending the Thalassaemia Clinic at The Children's Hospital on a regular basis were recruited, comprising 47 males and 23 females with an age range of 5 to 14 years (mean age 7.6 ± 2.5 years). The diagnosis of thalassaemia major was based on the usual haematological criteria i.e. peripheral blood evaluation and Hb electrophoresis.

Cases of β-thalassaemia minor and intermedia were excluded from the study as well as patients with acute illness or with a family history of hypothyroidism. Informed consent was obtained from the patients or the parents (if child was under age). Patient history included demographic data, initiation, duration and frequency of blood transfusion as well as chelation therapy. All patients were being regularly transfused every 2-4 weeks with packed red cells since early years of life and were receiving sub-optimal iron-chelating therapy. Chelation was started many months after the onset of blood transfusions and due to the expensive/complex protocol, the compliance was not good. None of the patients had been splenectomized.

Serum ferritin levels were obtained from the patients' medical records and the most recent values were recorded for analyses.

Random blood samples were drawn from the patients on the morning of attendance for regular blood transfusion and at least 2 weeks after the previous transfusion. In each case, 3ml of venous blood was drawn. After ultracentrifugation serum samples were analyzed. Thyroid function was assessed by thyroxine (T4), triiodothyronine (T3) and thyrotropin (TSH) assays using enzyme-linked immunosorbent assay (ELISA). Hypothyroidism was defined by a TSH level >4µIU/ml, T4 levels <4.5µg/dl and T3 levels <82ng/dl were defined as decreased. The thyroid function status of the patients was classified as compensated (increased TSH, normal T4, T3) and uncompensated (increased TSH, decreased T4 and/or T3) primary hypothyroidism, and euthyroidism (normal TSH, normal free T4).

Data was analyzed by using Statistical Package for Social Sciences (SPSS) software version 11.0. The results were computed as mean ± standard deviation for quantitative variables (age, duration of transfusion, thyroid profile and serum ferritin levels) using t-test. The results for categorical variables (gender) were computed as frequencies and percentages using Chi-square (with 95% confidence interval). In all statistical analysis, only p value<0.05 was considered significant.

Results

Of the 70 cases of β-thalassaemia, 47 (67%) were male and 23 (33%) female, with an age range of 5-14 years (mean age 7.6 ± 2.5 years).

Primary hypothyroidism was present in 18 (25.7%) patients. The mean age of hypothyroid patients was 9.2 ± 2.6years. Patients were divided into 2 groups on the basis of age. Group 1 had patients ranging from 5-9 years whereas group 2 patients were of ages between 10 and 14 years. The frequency of hypothyroidism was significantly higher in group 2 (47%) as compared to group 1 (20%) indicating an increase in the risk of this complication with advancing age.

Among the 18 hypothyroid patients, there were 11 (23%) males and 7 (30%) females. Thus, there was no significant difference in the frequency of hypothyroidism between boys and girls.

Mean ferritin level was 3924 ± 1247ng/ml in hypothyroid and 3136 ± 1387ng/ml in euthyroid patients indicating a significant difference in mean serum ferritin levels between hypothyroid patients and others (p=0.037).

Of the 18 patients who tested positive for hypothyroidism, 17 patients showed compensated subclinical hypothyroidism and only 1 patient showed uncompensated hypothyroidism. All patients were clinically euthyroid, none had a goiter. No case of central hypothyroidism was observed.

Discussion

Hyper-transfusion has improved the life expectancy of thalassaemic patients, over the decades. However, chelation
therapy is expensive, difficult to administer and not as readily available, hence the compliance is often poor despite regular transfusions\(^7\) resulting in iron overload.

It has been demonstrated that thyroid abnormalities in these patients are related to iron overload. Histological studies have supported this hypothesis.\(^8\) However, the serum ferritin is the most widely used test for assessment of iron status in these patients. In this study, a significant association was found between ferritin levels and thyroid functional status; the ferritin levels of hypothyroid patients being significantly higher than those of euthyroid patients. The precise mechanism by which iron overload causes tissue damage is not completely understood, though it is suggested that tissue iron deposits act at the cellular level causing damage via free radical formation and lipid peroxidation resulting in mitochondrial, lysosomal and sarcolemmal membrane damage. In the thyroid gland this affects the production of thyroid hormones and manifests as varying degrees of primary hypothyroidism. Hence, it is postulated that higher serum ferritin levels predispose to a greater risk of developing endocrinopathies like hypothyroidism and conversely, hypothyroidism. It has been suggested that thyroid dysfunction may be reversible by intensive chelation. Also, most complications can be avoided if serum ferritin levels are brought down to $<$1500ng/ml\(^9\) Apart from iron overload, other factors responsible for organ damage have been previously pointed out including anaemia and chronic hypoxia that may potentiate the toxicity of iron deposition in endocrines.\(^10\) Also, viral infections as well as individual susceptibility have been implicated in causing endocrine dysfunction.

The results of this study are comparable to the frequencies reported elsewhere. Thyroid dysfunction has been reported in 13-60% of patients with thalassaemia, but its severity is variable in different series.\(^1\) This variation has been attributed to difference in treatment protocols including different transfusion rates and chelation therapies in different centres. Prevalence of overt hypothyroidism as a complication of thalassaemia major is relatively low, milder forms of thyroid dysfunction are much more common.\(^11\) In this study too, the hypothyroid state was accompanied by a low T4 concentration in only 1 patient. Furthermore, as opposed to the gonadal axis, the thyroid gland appears to fail before the central components of the pituitary-thyroid axis, thus "primary" hypothyroidism is mostly seen. In several reports the TSH response to TRH stimulation has been tested and found to be normal, thus excluding the presence of pituitary hypothyroidism as a possible cause.\(^12\)

Thalassaemic patients having thyroid dysfunction have shown a greater incidence of other complications including multiendocrine dysfunction, worsening of already compromised cardiac function, more pronounced growth retardation, liver disease and need for splenectomy during the course of the disease.\(^13\)

Several studies have reported a lack of concordance of ferritin concentrations with the thyroid function status.\(^1,11,12\) This may be, in part, due to the fact that serum ferritin levels increase linearly with the transfusion load up to 100 units of transfused blood, but thereafter there is no simple relationship.\(^14\) Also, misleading ferritin levels can occur with chronic inflammatory disease\(^15\) as well as vitamin C deficiency.\(^16\)

The mean age of patients with hypothyroidism was lower than that reported in other studies which may be due to inadequate chelation therapy, chronic anaemia and malnutrition that is commoner in this part of the world.\(^17\)

**Conclusion**

A high prevalence of hypothyroidism noted in this study supports the rationale for regular follow-up of transfusion dependent thalassaemic patients to ensure early detection and timely treatment of associated complications. Early recognition and prevention of these complications could improve the quality of life of these patients.

**Acknowledgements**

The authors wish to thank all the thalassaemic patients who participated in this study and the Department of Haematology, Children's Hospital Lahore for their help and guidance.

**References**


