Research Article

# Prevalence of hypothyroidism in children with β-thalassemia major in children coming to the New Civil Hospital, Surat, Gujarat

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**Abstract**

**Background:** Chronic blood transfusion therapy with iron chelation is only effective treatment for β-thalassemia major in India. This will increase the survival of patient but had a major drawback of endocrine complications such as hypothyroidism which is found more frequently in long-term survivors.

**Objective:** To study the prevalence of hypothyroidism in patients with β-thalassemia major.

**Materials and Methods:** A total of 100 cases of children with β-thalassemia major coming to NCHS from December 2013 to September 2014 were studied. All the cases were evaluated by clinical, demographical, biochemical analysis of each case with pedigree study to assess thyroid function.

**Result:** There were 67 males and 33 females with age ranging from 3 to 16 years and a mean age of 10.05 years. The mean pre-transfusion hemoglobin was 8.33 ± 0.62. Thyroid function as indicated by the level of thyroid hormones was impaired in 10 out of 100 patients (10%); all 10 patients (10%) had subclinical hypothyroidism (normal T4 with high TSH); no case of secondary hypothyroidism (low TSH, T4) was found.

**Conclusion:** Though thyroid dysfunction in thalassemia may start early in life, hypothyroidism is not clinically observed in most β-thalassemia major patients. Therefore, thyroid function should be followed periodically, particularly when other iron overload associated complications occur. Early recognition and hence prevention of these complications help to improve the quality of life of these patients.

**KEY WORDS:** Hypothyroidism, β-thalassemia, prevalence, children

## Introduction

Thalassemia is the most common monogenic single gene disorder in the world.[1] It is due to inherited impairment of hemoglobin production, in which there is partial or complete failure to synthesize a specific type of globin chains.[2] β-Thalassemias are widespread throughout many countries including India. India has 3.5 crores thalassemic carriers with about 10,000 thalassemic birth every year in India. In Gujarat, there are about 6000 thalassemic children. The prevalence of β-thalassemia trait (BTT) is not uncommon in India and its incidence is rising in certain states including Gujarat.[3] Every year around 100,000 children were born with β-thalassemia major in the world and about 10,000 were born in India alone. The carrier rate of β-thalassemia gene varies between 1%–3% in south India and 5%–15% in north India. The disease was previously considered fatal before second decade of life.[4] The combination of transfusion therapy and chelation therapy has dramatically extended the life expectancy of the children with β-thalassemia major who can now extend their life up to their third and fourth decades. The only curative treatment available is stem cell transplant which is not affordable in countries like India.[5] Due to the lack of physiological pathway for iron excretion, frequent blood transfusions and increased intestinal iron absorption will eventually lead to iron overload.[6] This iron overload may lead to many

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complications, including endocrine complications such as thyroid dysfunction.[7]

The iron burden on the body can be estimated by means of serum ferritin, iron, and TIBC levels. The estimation of serum ferritin levels is the most commonly employed test to evaluate iron overload in β-thalassemia major. The association between serum ferritin and levels of body iron are well-established and the test is easy to perform compared with other tests for iron overload.[8]

The most common form of thyroid dysfunction seen in thalassemia is primary hypothyroidism. Nonetheless, the frequency of hypothyroidism shows a discrepancy depending on the region, quality of management, and treatment protocols. Different studies suggest that thyroid dysfunctions appear with a frequency of 13%–60% in thalassemic patients after 10 years of age regardless of difference in the rate of prevalence, largely as in the form of subclinical hypothyroidism.[9]

Clinically overt manifestations of hypothyroidism occur late in life and most of the studies available are carried out on adults. Only a very few pediatric studies are available. In India, since β-thalassemia is found mostly in the poor and non-affordable patients, cost of chelation precludes ideal therapy for majority of the patients and the compliance with transfusion is often not optimal. Therefore, there is a possibility that there may be high prevalence of hypothyroidism in thalassemic children. In view of very few pediatric Indian studies, we therefore planned this study with the aim to assess thyroid function in children suffering from β-thalassemia major with iron overload and to evaluate its relation, if any, with serum ferritin levels.

## Materials and Methods

This is a cross-sectional study conducted at New Civil Hospital, Surat (NCHS) with 100 confirmed β-thalassemia major cases. Children who had received blood transfusion for at least 3 years, whose ferritin level is above 1000, and those > = 3 years up to 16 years where included for the study. Children with primary endocrinopathy, children on any hormonal therapy, and those with any other chronic illness were excluded from the study.

### Period of Study

Study was carried out from December 2013 to September 2014. Informed consent was obtained from all the parents. Patient history included demographic data; family pedigree and age of diagnosis; pre-transfusion Hb; immunization; ferritin level and initiation, duration, and frequency of blood transfusion as well as chelation therapy. Anthropometric data such as height, weight, BMI (body mass index) and head circumference were taken. All patients were being regularly transfused every 2–4 weeks with packed red cells since early years of life and were receiving suboptimal 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 splenectomised. 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, 3 mL 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

Hypothyroidism was defined by a TSH level >5.5 $\mu$IU/mL, T4 levels <10 pmol/dL and were defined as decreased. The thyroid function status of the patients was classified as compensated (increased TSH, normal T4) and uncompensated (increased TSH, decreased T4) primary hypothyroidism, euthyroidism (normal TSH, normal free T4). The normal range of S.TSH is 0.5–5.5 $\mu$IU/L and S.FT4 is 10.4–37.5 pmol/L.

Data were analyzed 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 $\chi^2$ (with 95% confidence interval). In all statistical analysis, only *p*–value < 0.05 was considered significant.

## Result

### Distribution of the Study Patients by Age and Gender

This study included 100 homozygous β-thalassemia patients; 67 males and 33 females with age group ranging between 3 and 16 years with a mean age of 10.05 years .The mean pre-transfusion Hb is 8.33 ± 0.62 [Table 1].

All patients have received multiple transfusions. All patients were iron overloaded, the mean S. ferritin level was 4434 ng/mL, values ranged between 1030 and 10,000 ng/mL. Transfusion therapy was optimal (hyper transfusion regimen) in 13 patients, when the steady state Hb was kept at 9.5 g/dL or more; the rest of the patients were transfused according to traditional method (transfusion is given when Hb drops to below 7–6 g/dL). Most patients were heavily iron overloaded,

**Table 1:** Statistical summary of patients' characteristics

| Male: Female | 67/33 |
|---|---|
| Age of diagnosis (months) | 10.04 ± 3.1 |
| Annual blood requirement | 177.32 ± 17.6 |
| Pre-transfusion Hb | 8.33 ± 0.62 |
| Ferritin level (ng/mL) | 4434.2597 ± 5984.60 |
| Weight (kg) ± SD | 25.56 ± 6.66 |
| Height (cm) ± SD | 128.09 ± 13.57 |

only in 10 (10%) patients S. Ferritin was 1500 ng/mL or less and in another 25 (25%) patients chelation was satisfactory (S. Ferritin < 2500 ng/mL) [Figure 1].

**Thyroid Function Status among Studied Patients**

Thyroid function as indicated by the level of thyroid hormones was impaired in 10 of 100 patients (10%); all 10 patients (10%) had subclinical hypothyroidism (normal T4 with high TSH) and no case of secondary hypothyroidism (low TSH, T4) was found.

**Degree of Association between Different Thyroid Hormones and Some of the Clinical and Lab Parameters**

The correlation between hormones level and some of clinical and hematological parameters including S. ferritin, age, height, weight, and the steady state Hb was studied. There was no significant correlation between T4 level and S. Ferritin. Also there was no significant correlation between TSH level and S. Ferritin.

**Comparison of Different Parameters between Euthyroid and Hypothyroid Patients**

Comparing different parameters among euthyroid and hypothyroid thalassemic, significance difference was not found [Tables 2 and 3].

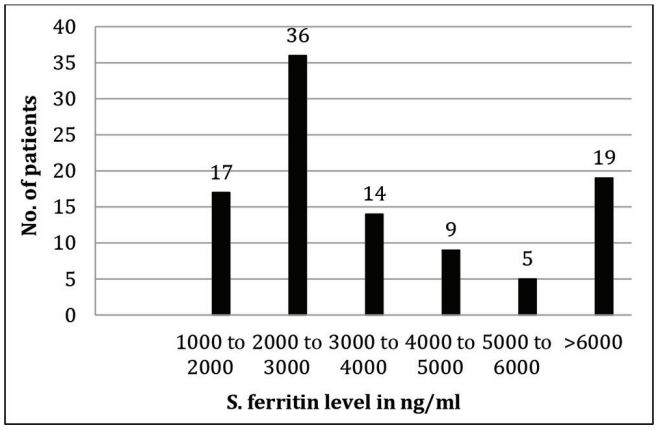


**Figure 1**: Distribution of S. Ferritin level among studied patients

**Table 3:** Group statistics

| | TSH | *N* | Mean | SD | SE |
|---|---|---|---|---|---|
| Annual blood requirement | Euthyroid | 90 | 177.24 | 17.58 | 1.85 |
| | Hypothyroid | 10 | 178.00 | 18.73 | 5.93 |
| Pre-transfusion Hb | Euthyroid | 90 | 8.35 | 0.63 | 0.67 |
| | Hypothyroid | 10 | 8.25 | 0.63 | 0.20 |

## Discussion

The two groups had no significant differences in age and gender. Compared to the euthyroid group, the studied patients had a lower mean height, weight, and Hb levels; the causes for this are multiple and include endocrinal impairment, chronic anemia, social, and nutritional reason. However, it is accepted that thalassemic patients have a delayed puberty and slower growth rate but ultimately the majority will catch up with their peers as age advances.[10]

Only 10 (10%) patients had ferritin levels below 1500 ng/mL; 25 had levels below 2500 ng/mL. This indicates that more than 70% thalassemic patients are poorly chelated. Poor chelation may be due to irregular supply of chelating agents, scarcity of infusion pumps, and poor compliance of patients.

In our study, 10% thalassemic children had subclinical hypothyroidism which is in good agreement with the study carried out by Sharma et al.[11] The reason for the lower frequency may be attributed to the fact that the majority of patients in this work were under 10 years. Not many studies are available from India and one among the very few studies carried out by Dr. N. K. Anand, Department of Pediatrics, Safdarjang, New Delhi said that 32% patients had subclinical hypothyroidism and 12% had clinical hypothyroidism.[12] This finding is comparable to our study in terms of subclinical hypothyroidism. Iron overload of tissue is the most important complication of β-thalassemia and is a major subject of management.[13] Although most clinical signs of iron loading do not appear until the second decade of life in patients with inadequate chelation, evidence from serial liver biopsies in very young patients present that the toxic effects of iron begins much earlier. After approximately 1 year of

**Table 2:** Demographic, hematological, and biochemical characteristics of study population

| Characteristics | Euthyroid | Hypothyroid | *p*-Value |
|---|---|---|---|
| Age | 10.06 ± 3.13 | 10.4 ± 3.167 | 0.638 |
| Annual blood requirement (ml/kg/year) | 177.24 ± 17.58 | 177.78 ± 19.68 | 0.639 |
| Height (cm) | 127.82 ± 13.52 | 133.78 ± 15.67 | 0.408 |
| Weight (kg) | 25.82 ± 6.01 | 28 ± 6.16 | 0.201 |
| Pretransfusion Hb (mg/dL) | 8.34 ± 0.63 | 8.23 ± 0.633 | 0.948 |
| S. Ferittin (ng/mg) | 6267.27 | 3550.21 ± 1852.51 | 0.442 |
| S.TSH (μU/L) | 2.82 ± 1.81 | 6.62 ± 1.59 | 0.000 |
| S. free T4(pmol/L) | 14.69 ± 3.33 | 13.93 ± 1.81 | 0.485 |

transfusions, iron starts accumulating in parenchymal tissues, where it may bring about substantial toxicity as compared with that within reticulo-endothelial cells. Despite the reports relating endocrine dysfunction with iron overload, it was recently demonstrated that the degree of iron overload, at least reflected by ferritin levels, was not associated with the development of endocrine complications.[8] Our results showed no association between S. ferritin level and the frequency of hypothyroidism among studied patients; this finding is in agreement with results of studies elsewhere. The absence of the relationship between ferritin and hypothyroidism may be explained by suggesting that the damage of endocrine glands caused by chronic hypoxia is more pronounced than that caused by hemosiderosis as a consequence of the collapse of iron. There was no correlation between thyroid dysfunction and gender and age. Similar results have been documented by Gathwala et al.[9]

## Conclusion

Though thyroid dysfunction in thalassemia may start early in life, hypothyroidism is not clinically observed and often go unnoticed in most thalassemia major patients. We have seen that thyroid function impairment was compensated (sub-clinical) in most patients. Also in India thalassemic patients have poor iron chelation; only the minority is adequately chelated. Transfusion is mostly suboptimal in most of the patients; the majority are on traditional regimens of transfusion. So iron overload is likely to be earlier. It is found that impaired thyroid function is more common in multiply transfused β-thalassaemia major patients in India. We also noticed that the frequency of hypothyroidism in transfusion-dependant β-thalassaemia is not related to serum ferritin level. One of the explanation is chronic hypoxia may cause thyroid function impairment in transfusion-dependant β-thalassaemia patients. Therefore, thyroid function should be followed periodically, particularly when other iron over load-associated complications likely to occur as in multiply transfused patients. Early recognition and hence prevention of these complications help to improve the quality of life of these patients.

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