International Journal of Biomedical and Advance Research
ISSN: 2229-3809 (Online); 2455-0558 (Print)
Journal DOI: https://doi.org/10.7439/ijbar
CODEN: IJBABN **Original Research Article**

Endocrine Manifestations in Thalassemia Intermedia

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Abstract

Background: Thalassemia intermedia are genetically similar to thalassemia major with homozygous β-globin chain defect. Transfusion-independence in such patients is not without side effects. The present study was undertaken to determine the prevalence of endocrine complications in patients of thalassemia intermedia.
Methods: Total 40 patients of thalassemia intermedia were enrolled in the study and divided into 2 groups. Group 1 consist of transfusion dependent (TD) patients (n=24) and group 2 consist of transfusion independent (NTD) patients (n= 16).
Results: Among group 1, commonest endocrine morbidity was short stature (85%), pubertal delay (57.5%), osteopenia (42.5%), osteoporosis (15%), hypothyroidism (15%) and diabetes mellitus (7.5%). While in group 2, short stature (70%), pubertal delay (55%), osteopenia (40%), osteoporosis (22.5%), no case of hypothyroidism and diabetes mellitus. Mean serum ferritin of group 1 was -3562.2 and group 2 was 913.2 and the difference between 2 groups being significant (p=0.0001) indicates that higher iron overload is correlating in group 1 patients having more incidence of endocrine manifestations.
Conclusions: There is significant difference in patients of non-transfusion dependent and transfusion dependent thalassemia intermedia in terms of endocrine manifestations with short stature being the most common manifestation.
Keywords: Thalassemia, β-globin, Transfusion, Endocrine, Osteopenia, Osteoporosis, Hypothyroidism, Diabetes, Iron.

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***Article History:**
Received: 02/09/2019
Revised: 27/09/2019
Accepted: 28/09/2019
DOI: https://doi.org/10.7439/ijbar.v10i9.5274

QR Code

How to cite: Khadse S, Sharma S and Shah N. Endocrine Manifestations in Thalassemia Intermedia. *International Journal of Biomedical and Advance Research* 2019; 10(9): e5274. Doi: 10.7439/ijbar.v10i9.5274
Available from: https://ssjournals.com/index.php/ijbar/article/view/5274

1. Introduction

β-thalassaemia intermedia (TI) is an inherited genetic disorder that affects haemoglobin chain synthesis, leading to ineffective erythropoiesis and anemia which does not or only occasionally requires transfusion [1]. Clinically it can be milder variant with age of onset>18months. Age of onset is late >18months. Blood transfusion and chelation are necessary in some patients, especially during childhood, in order to promote growth and prevent bone deformities. Usually frequent transfusion requirement is after 4 years of age [2].

The patients with TI are considered typically to have two β+ mutations. However, owing to the heterogeneity of the beta-globin mutations and the multitude of disease modifiers, difficulties remain regarding the prediction of phenotype from genotype. Thus, transfusion independence is still the best means of defining beta thalassemia intermedia [3]. Non-transfusion dependent thalassemia (NTDT) is a group of thalassemic disorders including patients who do not require frequent blood transfusions for survival [4].

Patients with NTDT may still require occasional or more frequent red blood cell (RBC) transfusion therapy in certain circumstances including but not limited to significant infection, pregnancy, periods of rapid growth, or

surgery [5, 6]. However, Transfusion-independence in such patients is not without side effects. Ineffective erythropoiesis, iron overload and chronic anemia, ultimately lead to a number of endocrine issues.

Although, being clinically heterogenous, beta thalassemia intermedia can range from a manifestation in which patients rarely, if ever, require transfusion to one in which individuals have chronic haemolytic anemia and in later life become transfusion dependent [3]. Over the years, many individual studies have showed a clear variation in the complications seen between transfusion dependent (TDT) and non-transfusion dependent (NTDT) thalassemic patients. In addition to the defining symptoms of TI, which are seen to a lesser or greater extent in other forms of thalassaemia, patients with TI experience a number of specific complications that are rare in thalassaemia major [7]. Hence the present study was carried out to determine the prevalence of endocrine complications in patients with thalassemia intermedia.

2. Materials and Methods

It was a retrospective comparative descriptive study conducted in Thalassemia Day Care Center and Pediatric Endocrine Clinic at Lokmanya Tilak Muncipal Medical College and General Hospital from February 2015 to January 2016.

This study enrolled total 40 patients with thalassemia intermedia in Thalassemia Day Care Center with clinically suspected endocrine morbidities.

Thalassemia Intermedia patients were divided into 2 groups. Group 1 consists of transfusion dependent patients (TD) (n=24) and group 2 consists of Non-transfusion dependent patients (NTD) (n=16) after treatment with hydroxyurea. Any patients already on hormonal treatment for endocrine problem were excluded from the study.

The demographic and biochemical characteristics, disease and treatment characteristics (e.g., Detailed history including age at first transfusion, total number of transfusions, frequency of transfusions, intake of any medicine for endocrine dysfunction, any chelation etc), growth percentiles and pubertal stages, and bone density, laboratory data including serum bilirubin was recorded.

a) Short Stature:

Short stature was considered as patient height < 3 percentile, as per IAP growth charts for boys and girls, Height below genetic potential: Midparental height = mothers's height + father's height+13 divided by 2. Height based on weight, length and head circumference.

b) Delayed puberty:

Delayed puberty was considered if no signs of sexual maturity by age of 13 years for girls and 14 years for boys, primary amenorrhoea by 16 years in females and sexual maturity rating (SMR). SMR- A scale used to classify the onset and progression of puberty in children and adolescents. The scale describes five stages of physical development on the basis of sex characteristics, such as pubic hair growth, development of genitalia in boys, and development of breasts in girls.

c) Osteopenia and Osteoporosis:

Osteopenia and osteoporosis was measure by Dual Emission X-ray, Absorbtiometry (DEXA). Lumbar spine bone mineral density Z-score of 1.5 to -2.5 was considered as osteopenia and Z score -2.5 and above as osteoporosis.

d) Diabetes mellitus (DM):

DM leading to polyuria, polydypsia, weight loss due to pancreatic damage was considered. A fasting blood sugar (FBS) level of ≥126 mg/dL or post prandial blood sugar (PPBS) level of ≥200 mg/dL was considered diagnostic of diabetes mellitus.

e) Hypothyroidism:

A detailed history followed by thorough clinical examination was done to look for signs and symptoms of hypothyroidism. Primary hypothyroidism considered as damage to thyroid gland and secondary hypothyroidism was damage to pituitary gland. Thyroid stimulating hormone (TSH) levels were done in all patients. A diagnosis of hypothyroidism was established in children with TSH >5.4mIU/L and free T4 <0.5ng/dl [8] or in children with diagnosed hypothyroidism and on thyroxin supplements or as per growth chart.

3. Observations and Results

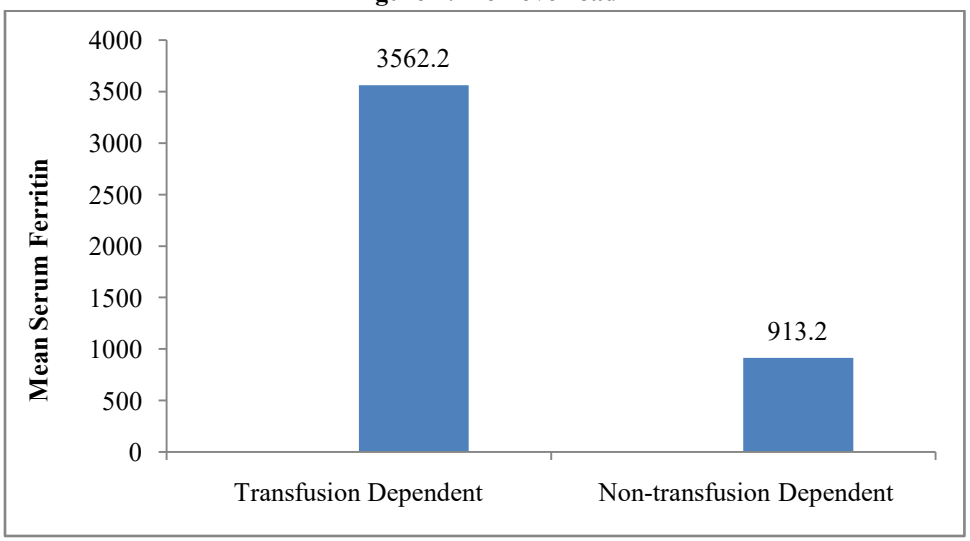
Total 40 patients of thalassemia intermedia were enrolled in the study, among them 30 (75%) were males and 10 (25%) were females. Group 1 (TD) had 24 patients with mean age of 15±3.12 years (range 8-20 years) and group 2 (NTD) had 16 patients with mean age of 13.1 ± 41.1 years (range 5-21 years). Demographic and biochemical characteristics of 40 patients with thalassemia intermedia are shown in table 1.

Table 1: Demographic and biochemical characteristics of patients

Parameters	Group 1		Group 2	
	Range	Mean ± SD	Range	Mean ± SD
Age in Years	8-20	15±3.12	5-21	13.1± 41.1
FBS (mg/dl)	62-269	94.0±35.5	70-190	75.2±24.5
TSH (Miu/l)	0.5-52	4.6±7.9	2-60	6.2±5.2
S. Ferritin (ng/ml)	983.7-5234.4	3562.2	945.9-4854.1	913.2

The comparison of iron overload between two groups depicted in figure 1. Group 1(TD) patients had mean serum ferritin 3562.2 ng/ml and group 2 (NTD) had mean ferritin value of 913.2ng/ml. p value for difference between serum ferritin of these 2 groups being significant (p=0.0001).

Figure 1: Iron overload



The comparison of various endocrine abnormalities such as short stature, delayed puberty, osteopenia, osteoporosis, hypothyroidism and diabetes mellitus among two groups is shown in figure 2.

Figure 2: Comparison of endocrine manifestation between two groups

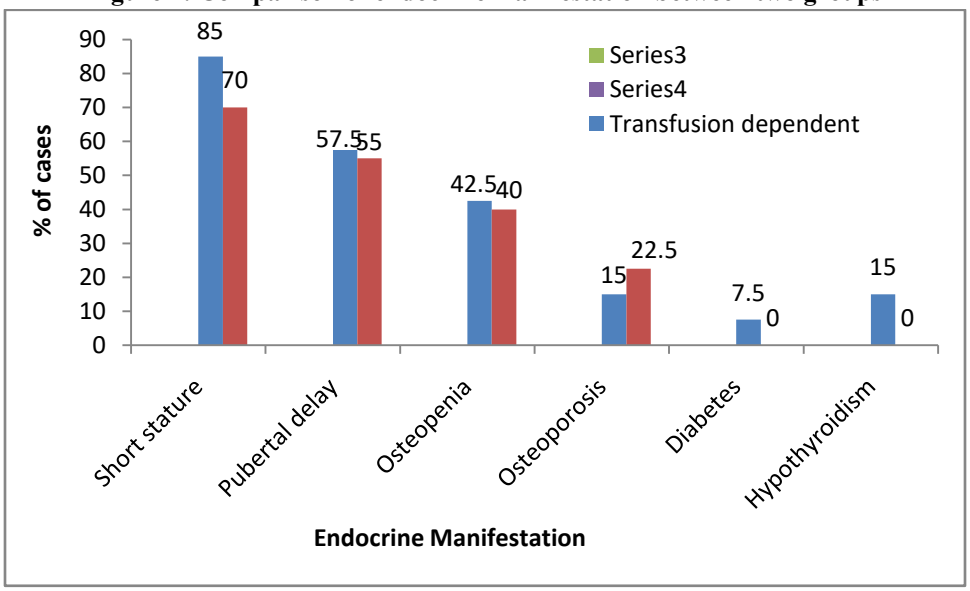


Table 2 show the correlation of serum ferritin levels with incidence of endocrine manifestations. 50% of patients with serum ferritin levels above 3500ng/ml had delayed puberty.

Table 2: Relation of serum ferritin levels with various endocrine abnormalities

Endocrine abnormalities	S. Ferritin (ng/ml)			
	500-1500 (n=2)	1500-2500 (n=11)	2500-3500 (n=19)	>3500 (n=8)
No. of Short stature patient	1 (50%)	2 (18.18%)	3 (15.78%)	1 (12.5%)
No. of patients with delayed puberty	1	4(36.36%)	5 (26.31%)	4 (50%)
No. of patient with Osteopenia	0	2 (18.18%)	3 (15.78%)	0
No. of patient with osteoporosis	0	1 (9.09%)	1 (5.26%)	1 (12.5%)
No. of diabetic patients	0	0	0	0
No. of Hypothyroid patient	0	0	1 (5.26%)	0

4. Discussions

In the present study, it is interesting to note that 2 groups based on transfusion requirement, had significant differences in endocrine manifestation except osteopenia and delayed puberty. In group 1, 85% of patients and in group 2, 70% of patients had short stature, (P<0.05). The difference in the prevalence of short stature may be due to several factors: gender, low fetal hemoglobin level [9] severity of anemia [9-11] treatment of iron overload and compliance to medical care [12-14]. Moayeri and Oloomi [15] reported that short stature was prevalent in 62% of patients. Delayed puberty was observed in 57.5% in group 1 and 55% in group 2, (p>0.05). Tiosano *et al* [16] reported prevalence of delayed puberty ranging from 50% to 100%.

Bone abnormalities in TI are quite frequent and range from a decrease in the bone mineral density (BMD) and consequent osteoporosis to spinal cord compression and increased risk of fractures [17]. Osteopenia occurred in 42.5% of cases in group 1 and 40% cases in group 2. In group 1, 15% and in group 2, 22.5% of patients had osteoporosis, (P<0.05). Other authors have reported a prevalence of bone disease in 53/70 (76%) patients, osteoporosis in 26/53 (49%), and osteopenia in 27/53 (51%) [17]. Relatively lower prevalence of osteopenia in our patients may be due to their young age, with high activity, regular intake of vitamin D, calcium and dairy products. The most recent guidelines by the Thalassemia International Federation (TIF) recommend that all patients >10 years of age be screened by yearly assessment of lumbar spine, femoral neck, and distal ulna BMD by DXA [18, 19].

Thyroid dysfunction is known to occur frequently in TI, but its prevalence and severity varies in different cohorts. In this study, hypothyroidism was observed in 15% of group 1 cases which is comparable with other studies that have reported prevalence of hypothyroidism ranging from 17–18% [20-22]. Diabetes mellitus is also a frequent complication later in life of thalassemic patients, mainly due to iron overload, chronic liver disease and genetic predisposition [23]. In the present study the prevalence of diabetes mellitus was 7.5% in group 1 patients. Similar to our study, Najafipour [24] reported that the prevalence of diabetes mellitus was 8.9%. Also, Ahmed Al-Akhras *et al* [25] reported prevalence of diabetes mellitus as 8%. In current study, diabetes and hypothyroidism was not seen in group 2 patients.

As per Inati *et al* [14], incidence of short stature was 31 %, delayed puberty 24%, hypothyroidism in 2-3 % , diabetes in 2% which is significantly lower than incidence reported in present study in both groups whereas osteoporosis in 81.6% patients unlike our study. Similarly according to study by Baldini *et al* [26], osteopenia was found in 38.5 %, osteoporosis in 37.1 % comparable to present study, whereas hypothyroidism in 14.2 %, delayed puberty in 4.2% and diabetes in 1.4% significantly lower than our study population.

Cut-offs of < 300 ng/mL for the absence of iron overload and > 800 ng/mL for the presence of clinically significant iron overload in TI has been suggested [27]. However, recent re-evaluation found that a considerable number of patients with SF levels between 300 and 800 ng/mL to have iron overload requiring management [17, 19]. Iron chelation therapy and hydroxyurea therapy have been associated with a lower frequency of endocrine complications [28]. In present study, patients on frequent blood transfusion (Group 1) had higher iron overload and higher FBG compared to the non-transfused group (Group 2) and difference between 2 groups being significant (p=0.0001), indicates that higher iron overload is correlating in group 1 patients having more incidence of endocrine manifestations.

5. Limitations of the study

This study is a retrospective comparative descriptive study with a small sample size. We need large-scale prospective observational and interventional studies to validate our observations.

6. Conclusion

There is significant difference in patients of non-transfusion dependent and transfusion dependent thalassemia intermedia in terms of endocrine manifestations with short stature being the most common manifestation. Early diagnosis with timely intervention can prevent morbidity and psychological impacts.

The present study emphasizes the need for long term surveillance for identification of organ-specific risk factors, early diagnosis, and treatment of growth and endocrine complications. We also recommend close monitoring of endocrine and other complications, according to the international guidelines.

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