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Endocrine dysfunction in transfusion dependent thalassemia patients from central India

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ABSTRACT

Background: Thalassemia refers to a group of genetically inherited diseases characterized by decreased or absent synthesis of normal globin chains resulting in defective globin chains. Most of the available studies in the literature have been done in adults and there is a paucity of studies highlighting the prevalence of hormonal dysfunction in transfusion dependent patients in pediatric age group. We conducted the present study with an aim to estimate the prevalence of hormonal dysfunction in transfusion dependent thalassemia (TDT) patients at a tertiary care center of Central India. **Aims and Objectives:** "The aim of the study was to estimate the prevalence of hormonal dysfunction in TDT patients at a tertiary care center of central India." **Materials and Methods:** It is descriptive cross-sectional study conducted at tertiary care hospital MGM Medical College, Indore, Madhya Pradesh, conducted over a period of 12 months (August 2021–July 2022). **Results:** Our study recruited a total of 100 children with age ranging from 9 year to 18 years with the mean age of 13.16 ± 2.86 years. Sixty percent (n = 60) of our study population were males and 40% (n = 40) were females. The prevalence of hypogonadism was 35.18% analyzed in 54 patients, hypothyroidism was 10%, and diabetes was 5%. Although serum ferritin was very elevated in all patients with endocrine dysfunction; statistically significant association was found between serum ferritin and hypothyroidism (P = 0.020). **Conclusion:** Patients with TDT are often associated with endocrinopathies; most commonly hypogonadism, followed by hypothyroidism and diabetes. Early screening and treatment is necessary to improve their outcome.

Key words: Endocrine dysfunction; Ferritin; Thalassemia

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INTRODUCTION

Transfusion dependent thalassemia (TDT) is the homozygous form of deficiency of beta globin chain synthesis which results in a severe transfusion dependent anemia and which becomes apparent in first 6 months.[1] Thalassemia also presents a substantial burden to patients and health-care system especially in the developing countries.[2] Endocrinopathies are among the most common complications in TDT patients resulting from the excess deposition of iron in the endocrine glands due to transfusion dependency. Hypogonadism is the most frequently reported endocrine complication, affecting 70–80% of TDT patients.[3] Hypothyroidism is the second most common endocrine disorder after hypogonadism, having been reported in 5.6–17% of patients. Iron deposition is the main cause of damage to the endocrine glands, directly or through the hypothalamic–pituitary axis.[4,5] Diabetes also represents a common endocrine complication in TDT patients.[6,7]

Aims and objectives

To estimate the prevalence of hormonal dysfunction in transfusion dependent thalassemia (TDT) patients at a tertiary care center of central India.

MATERIALS AND METHODS

Descriptive cross-sectional conducted over 1 year by the Department of Pediatrics, M.G.M Medical college,

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M.Y. Hospital, and CNBC Indore (M.P) after obtaining Institutional Ethics Committee clearance (EC/MGM/Dec-21/08 dated December 09, 2021).

Inclusion criteria

The following criteria were included in the study:

- Children diagnosed as TDT based on hemoglobin electrophoresis (by high performance liquid chromatography) report in the age group of 9–18 years
- Children who have been receiving regular blood transfusion for at least 5 years or more.

Exclusion criteria

The following criteria were excluded from the study:

- Children with any prior history of endocrine disorder
- Children on any hormonal therapy
- Children with any significant acute illness.

Study process

Children between 9 and 18 years of age with TDT confirmed by Hb electrophoresis were enrolled. Written informed consent/assent was taken from the parents/patient. During their admission for blood transfusion, their detailed clinical history was taken and physical examination done with particular attention to puberty and growth. The height, weight, and tanners staging was noted and interpreted as per the WHO growth charts. Patients underwent biochemical testing for blood samples for the evaluation of various endocrinopathies and tests such as thyroid-stimulating hormone, luteinizing hormone (LH), and fasting blood sugar (FBS) were done.

Girls with tanners' stage 1 after 13 years of age and boys with testicular volume <4 mL after 14 years of age were diagnosed to have delayed puberty.

Statistical analysis

Data were entered into Microsoft excel spread sheet and analyzed using open sources software. Continuous data were expressed in terms of mean and SD. Categorical data was expressed in the form of proportions and percentage. Appropriate test of significance such as t-test and Chi-square was applied wherever necessary and $P<0.05$ was considered statistically significant.

RESULTS

The baseline characteristics of patients are described in Table 1. Our study recruited a total of 100 children with age ranging from 9 year to 18 years with the mean age of 13.16±2.86 years. About 60% (n=60) of our study population were males and 40% (n=40) were females. Mean weight and height of children were 29.1 (±8.09) kg and 132 (±12.0) cm. Our patient shad very low mean transfusion hemoglobin (g/dL) of 5.8±1.12. Majority of the patient shad a frequency of transfusion every 2–3 weeks.

Table 2 describes the laboratory estimation of various hormonal levels, fasting sugars, and Ferritin levels in blood tests done in our patients. Hypogonadism was the most common endocrinopathy (35.18% analyzed in 54 patients) followed by hypothyroidism was 10% and diabetes was 5%. Serum ferritin was elevated in all patients with mean of 3552.48±2038.48 mg/L.

The mean ferritin levels were analyzed in all affected patients and compared statistically with those not affected (Table 3). In our study, among the 54 patients with hypogonadism had very high mean (SD) serum ferritin levels (3351±1983.428). However, statistically no significant difference was found among the two groups.

Patients with hypothyroidism also had elevated mean serum ferritin levels (4971.20±1705.73). There was statistically

Table 1: Baseline characteristics of children with transfusion dependent thalassemic patients (n=100)

Parameters	Frequency
Age (years) Mean±SD	13.16±2.86
Weight (kg) Range (Mean±SD)	15–55 (29.1±8.09)
Height (cm) Range (Mean±SD)	94–160 (132±12.0)
BMI Range (Mean±SD)	10.79–31.69 (16.61±3.57)
Pretransfusion hemoglobin (g/dL) Mean±SD	5.8±1.12
Frequency of blood transfusion	
Every 2 weeks	6 (6%)
Every 2–3 weeks	73 (73%)
More than 4 weeks	21 (21%)
Delayed puberty	
Delayed puberty (14 years for boys, 13 years for girls)	
Boys	11
Girls	07

Table 2: Laboratory parameters of transfusion dependent thalassemic patients and its prevalence

Parameters	Range mean±SD	Abnormal (%)	Normal (%)
LH (IU/L) (1.0–9.0)	0.1–8.0 4.08±2.47	19 (35.18)	35 (64.82)
TSH (mcg/mL) (0.5–5.5)	1.6–9.6 5.670.20	10 (10)	90 (90)
T4 (mcg/dL) (4.2–13.0)	1.2–12.0 5.97±2.57	10 (10)	90 (90)
FBS (mg/dL) (<125)	51–189 78.13±23.15	05 (05)	95 (95)
Serum ferritin (mg/L) (<500)	9580–600 3552.48±2038.48	100 (100)	00 (00)

TSH: Thyroid-stimulating hormone, LH: Luteinizing hormone, FBS: Fasting blood sugar

significant (P=0.020) co-relation of hypothyroidism with elevated ferritin levels.

Five percent of patients with TDT had diabetes (FBS ≥126 mg/dL). Mean and standard deviation of the serum ferritin levels in patients were 4011.80±3285.194. However, no significant difference was found among the two groups.

In the study, 27 patients either had at least 1 of the three endocrinopathies, two patients had hypogonadism with diabetes and hypogonadism with thyroid and only one patient had all the three disorders (Table 4).

Table 4 shows the association between hypogonadism and age of the beta thalassemia major patients. In middle adolescence patients, hypogonadism was present in 34% (n=17) while it was present in 50% (n=2) late adolescence patients. However, no statistically significant association was found between hypogonadism and age of the patients (P=0.519).

The second row shows association between hypothyroidism and age of the beta thalassemia major patients. In early adolescence patients, it was present in 4.3% (n=2), middle adolescence patients 14% (n=7) and late adolescence patients 25% (n=1). However, no statistically significant association was found between hypothyroidism and age of the patients (P=0.172).

The third row shows association between diabetes and age of the beta thalassemia major patients. In early adolescent patients, it was present in 4.3% (n=2), middle adolescence patients 4% (n=2), and late adolescence patients 25% (n=1). However, no statistically significant association was found between hypothyroidism and age of the patients (P=0.172).

DISCUSSION

Our study assessed the prevalence of hypogonadism, hypothyroidism, and diabetes in patients with TDT presenting at our center.

Our study recruited a total of 100 children with age ranging from 9 year to 18 years with the mean age of 13.16±2.86 years. About 60% (n=60) of our study population were males and 40% (n=40) were females. All our patients had clinical findings of pallor, hepatomegaly and splenomegaly, jaundice seen in 85% (n=85), hemolytic faces in 80% (n=80), and splenectomy in 2% (n=2). This clinical presentation is in agreement with study conducted by Hagag et al., where it was found that pallor was present in 100% (n=80), jaundice in 87.5% (n=70), splenomegaly in 82.5% (n=66), hepatomegaly in 93.75% (n=75), and with the exception of splenectomy in 17.5% (n=14) on patients.[8]

In our study, the most common endocrine disorder was hypogonadism. Out of the total study of 54 (Age >13 years) subjects, 35.18% (n=19) were found to have hypogonadism, which is higher than the study conducted by Al-Agha et al. who showed hypogonadism incidence to be 12.5% (n=15) and affected patients had serum ferritin levels more than 2000 ng/dL.[9] In our study, though no

Table 3: Comparing mean serum ferritin in transfusion dependent thalassemic patients with or without endocrine disorders

Disorder	Group	Frequency (%)	Ferritin mean±SD	Independent t-test	P-value
Hypogonadism	Yes	19 (35.18)	3351±1983.428	0.419	0.677
(No. analyzed: 54)	No	35 (64.82)	3610±2257.419		
Hypothyroidism	Yes	10 (10)	4971.20±1705.73	2.374	0.020*
(No. analyzed: 100)	No	90 (90)	3394.84±2019.11		
Diabetes	Yes	5 (5)	4011.80±3285.194	0.515	0.608
(No. analyzed: 100)	No	95 (95)	3528.31±1976.197		

*P<0.05 is significant

Table 4: Comparing various age groups in our transfusion dependent thalassemic patients with hormonal disorders

Disorders	Present (Yes/No)	Early adolescence (09–13 years of age) No. analyzed: 46 (%)	Middle adolescence (14–17 years of age) No. analyzed: 50 (%)	Late adolescence (17–18 years of age) No. analyzed: 4 (%)	P-value
Hypogonadism	Yes	NA	17 (34%)	2 (50%)	0.519
(No. analyzed: 54)	No		33 (66%)	2 (50%)	
Hypothyroidism	Yes	2 (4.3)	7 (14)	1 (25)	0.172
(No. analyzed: 100)	No	54 (95.7)	43 (86)	3 (75)	
Diabetes	Yes	2 (4.3)	2 (4)	1 (25)	0.172
(No. analyzed: 100)	No	54 (95.7)	48 (96)	3 (75)	

statistically significant association was found between the serum ferritin level and hypogonadism (P>0.05). Study conducted by Lee et al. had hypogonadism coming out to be 22.5% with mean ferritin level around 4000.[10] Study conducted by Shamshirsaz et al. also had lower prevalence of hypogonadism with prevalence of 17.5%.[11] In the above-mentioned studies, no correlation was found between serum ferritin and hypogonadism like our study. Lower prevalence of hypogonadism in above studies is due to better chelation and hyper transfusion. In our study, delayed puberty was found in 33.3% (n=18). Study conducted by Al-Agha et al. also had prevalence of delayed puberty of 68%. Yet another study conducted by Gulati et al., for endocrine dysfunction had pubertal delay as high as of 91%.

It is possible that this early appearance of endocrine complications is related to the poor chelation status of our patients. Although we did not find a correlation between endocrine dysfunction and serum ferritin, there may be many reasons for this. Ferritin measured during a year or two may not be representative of the ferritin maintained by the patient during the whole of childhood. Moreover, it is possible that damage to endocrine organs occurs at relatively lower levels of tissue iron, earlier in childhood, and the subsequent years of cumulative iron toxicity may have little role to play in comparison to tissue iron levels during a critical period of vulnerability.[12]

Iron deposition in the pituitary gonadotropes seems to be the main contributing factor to the development of hypogonadism. In our study, hypogonadotropic hypogonadism is the cause of hypogonadism. None of the patient had primary gonadal failure as evidenced by raised LH. Although, the incidence of hypogonadism has been decreasing during the past two decades, it is still the most common endocrine disorder in patients with beta thalassemia major.

We found the prevalence of hypothyroidism to be 10% with mean ferritin value of 4971.20±1705.73 ng/dL. Significant association was found between the mean ferritin value and hypothyroidism (P=0.020). Our study was similar to the study conducted by Sharma et al. with the prevalence of hypothyroidism coming out to be 9% with mean ferritin value coming out to be around 3000 ng/dL.[13] Our study was similar to the study conducted by Shamshirsaz et al. with the prevalence of 7.7%. However, in above-mentioned studies for hypothyroidism there was no correlation between serum ferritin and hypothyroidism. In our study, all cases had subclinical hypothyroidism; none had overt features of hypothyroidism, which is similar to the study conducted by Sharma et al. Some studies have reported high prevalence of primary hypothyroidism reaching up to 17–18%.[14,15] While, others reported low prevalence of 0–9%.[16,17] It is important to note that even in the studies, in which the prevalence of overt hypothyroidism as a complication of TDT is relatively low, milder forms of thyroid function are much more common.

The third most common endocrine disorder in our study was diabetes with prevalence of 5% (n=5) with mean serum ferritin value of 4148.40±1920.141 ng/dL. However, no significant association was found between serum ferritin and diabetes. Our study was similar to the study conducted by Bazi et al.[18] with the prevalence of diabetes 8.8% and Shamshirsaz et al. with the prevalence of diabetes 8.7% who also did not find statistically significant co-relation between serum ferritin levels and diabetes. In our study, none of the diabetic patient had family history of type 1 and type 2 diabetes in their siblings, parents, or grandparents. The reported prevalence of diabetes in thalassemic patients alone ranges between 4 and 26 in various studies. Previously, diabetes was thought to occur as a result of direct organ infiltration and iron deposition that destroys the function of pancreatic beta cells. More recently, it is now believed that the development of diabetes in patients with hemoglobinopathies complicated by hemosiderosis is preceded by a prolonged period of insulin resistance that eventually predisposes to the onset of diabetes. An appropriate chelation therapy is imperative to prevent impaired glucose metabolism and DM in TM patients.

Limitations of the study

Ours was a single center study of small population of TDT children. Multicenter studies with larger study population of TDT children are required to validate our findings. Many other hormonal dysfunctions such as hypoparathyroidism, growth hormone deficiency could not be assessed due to financial constraints.

CONCLUSION

The present study describes the prevalence of endocrine disorders in TDT presenting to tertiary care health institute in Madhya Pradesh and highlights the prevalence of hypogonadism followed by hypothyroidism and diabetes as endocrine dysfunction. Statistically significant association of serum ferritin was found only with hypothyroidism and not with hypogonadism and diabetes. Higher serum ferritin was responsible for endocrine disorders. Incidence of endocrine disorders increased as the age advanced.

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RS- Prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, and manuscript preparation; **AB-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **GSE**- Design of study and interpretation; **NJ-** Review manuscript.

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