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PREVALENCE OF HYPOTHYROIDISM, DELAYED PUBERTY AND DIABETES MELLITUS IN PATIENTS OF B-THALASSEMIA MAJOR

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Abstract

Background: Beta-Thalassemia is a genetic disorder which is associated with a lot of complications. Frequent blood transfusions result in increased iron deposition in various tissues leading to dysfunction of many vital organs. Endocrine disorders constitute a major part of such complications increasing the morbidity of thalassemia manifold in the affected patients.

Methods: This is a descriptive cross sectional study carried out in 100 diagnosed patients of beta- thalassemia major who had visited the OPD/IPD of Subharti Medical College & affiliated Hospitals, Meerut for routine blood transfusion or for any other complication. Patients were clinically examined and investigated for presence of one or more endocrine disorders on their routine appointments.

Results: Endocrine disorders were detected in a total of 82 patients. Diabetes mellitus was detected in 12% patients, hypothyroidism in 36% patients and delayed puberty was found in 72% patients. Mean serum ferritin level was found to be 5831.0±2860.5 ng/ml in beta-thalassemia Major patients, while it was in normal range in control subjects.

Conclusion: Research concluded with finding of Delayed puberty (72%), Hypothyroidism (36%) and diabetes mellitus as (12%) in beta thalassemia patients who were on regular blood transfusion therapy. Iron overload as serum ferritin level was found to be highly raised in all study case. On the basis of our study we recommend that early detection and management protocols for these endocrinopathies may improve the life prospects of beta-thalassemia Major patients.

Keywords: Endocrine disorders, Hypothyroidism, Delayed puberty, Diabetes Mellitus Serum ferritin, Thalassemia Major.

Introduction

Thalassemia major is a genetic disorder of haemoglobin synthesis with defect in production of one or more hemoglobin chains. The homozygous state results in severe anaemia and is known to affect a significant population in Mediterranean countries, Middle East, northern India and parts of south East Asia. The combination of transfusion and chelation therapy has resulted not only in increased life expectancy of thalassemia patients but is also associated with various complications.

A number of these complications result from iron overload occurring due to repeated transfusions. (1) Excessive iron is deposited in most tissues of the body including the liver, heart and the endocrine glands.(2) Deposition of iron in tissues leads to endocrine dysfunction which is a well recognised complication in patients with transfusion dependent thalassemia.(3-5) The effect of iron toxicity on endocrine glands has been well proved in various histological studies.(6-7)

Endocrine complications in thalassemia patients: Delayed puberty, diabetes mellitus, hypothyroidism and hypoadrenalism are some of the most common endocrine complications found in thalassaemia patients.(8) Of all these complications delayed puberty due to hypogonadism is the most common occurring in upto 50-91% of patients.(8,9) Gonadal iron deposition resulting in primary gonadal failure is the most important cause of hypogonadism.[10]

Iron deposition in the pituitary gland can result in lowered Gonadotropin releasing hormone (GnRH) levels causing secondary hypogonadism.(11-13) The prevalence of diabetes is also very high and estimated to be between

2.3% to 24.1% in β-thalassaemia.(14,15) There are two main mechanisms resulting in glucose intolerance and subsequent development of diabetes mellitus. The first mechanism involves decrease in insulin production either by direct impairment of insulin excretory function by chronic iron overload or immune system activation against pancreatic cells in β-thalassaemia patients. (16)

The second mechanism involves decreased insulin sensitivity with reduced hepatic release of insulin. (8,18) Thyroid dysfunction is another frequently occurring endocrine complication. The natural history of thyroid dysfunction is not clearly understood and various studies have reported different incidences with almost 5 % thalassemia major patients having overt hypothyroidism and requiring treatment. (19, 20)

According to the development of therapeutic interventions and the increased lifetime of patients, complications such as endocrine disorders can be seen more frequently. As the complications treatment is expensive and time-consuming, early diagnosis can reduce the mortality rate and help patient's to experience the more active lives. The study focused to assess the prevalence of endocrine disorders in patients with β-thalassemia major who are regular blood transfusion leading to iron overload in Meerut district area.

Material and Methods:

We conducted this research on 100 diagnosed Beta thalassemia major patients as study cases, who had visited the OPD/IPD of Subharti Medical College & CSSH and Lokpriya Hospital, Meerut for routine blood transfusion or for any other complication. Total 100 healthy age and sex matched individual who volunteered themselves for study were included as controls.

Due Ethical clearance from IEC was obtained in advance and written informed consent was taken from patients/guardians/controls prior to include them as study population. A Questionnaire was framed covering the key points of clinical history of illness and treatment with family background. Relevant clinical examination and investigations were carried out to establish the diagnosis of delayed puberty, Hypothyroidism and Diabetes mellitus.

Inclusion criteria:
1. Age 10-25yrs
2. Confirmed cases of β-thalassaemia major.
3. Patients undergo regular blood transfusion.

Exclusion criteria:

1. Patients with primary endocrinopathy.
2. Patients with any other chronic illness.
3. Other type of haemoglobinopathies.

Hypothyroidism: Thorough clinical examination was done to look for signs and symptoms of hypothyroidism. Thyroid stimulating hormone (TSH) levels were done in all patients and full thyroid profile was done in patients with elevated serum TSH. A diagnosis of hypothyroidism was established with TSH >9.0mIU/L and free T4 <11.5 pmol/L. (9) Patients with established diagnosis of hypothyroidism on treatment were also included.

Delayed puberty: Pubertal stages were determined by both visual inspection and palpation, using the criteria and definitions described by James Tanner. It is a scale of physical development in children, adolescents and adults. The scale defines physical measurements of development based on external primary and secondary sex characteristics, such as the size of the breasts, genitalia, testicular volume and development of pubic and axillary hair. Delayed puberty was defined as the absence of breast enlargement in girls and testicular enlargement in boys by the age of 13 and 14 years respectively. Arrested puberty is defined as the absence of pubertal progression for more than one year after puberty onset, where testicular volume in boys is less than 6 to 8 ml and unchanged breast size in girls. (4).

Diabetes mellitus: As per ADA criteria Plasma Random blood glucose measurement was performed on two consecutive visits 24 hrs apart. The patient who had RBS level of ≥ 200 mg/dl was considered as diabetic. (21) Already diagnosed cases were also included.

Table 1: Details of Methods, instruments and reference range used for biochemical analysis

Sr. No	Name of Investigation	Normal Value	Method	Instrument
	Serum Ferritin	Male:12-322 ng/ml; Female: 12-290 ng/ml	Chemiluminescence Immunoassay	Siemens Advia Centaur-XP
	Free Triiodothyronine: (FT_3)	3.5 -6.5 pmol/L	Chemiluminescence Immunoassay	Siemens Advia Centaur-XP
	Free Tetraiodothyronine: (FT_4)	11.5-22.7 pmol/L	Chemiluminescence Immunoassay	Siemens Advia Centaur-XP
	Thyroid Stimulating Hormone: (TSH)	0.35-5.50 µIU/L	Chemiluminescence Immunoassay	Siemens Advia Centaur-XP
	Random Blood Sugar: (RBS)	< 200 mg/dl	Hexokinase	Siemens Dimension-RXL-max

Prevalence of hypothyroidism, diabetes mellitus and delayed puberty was reported using proportions and percentages. Statistical analysis was conducted with SPSS software.

Results

This study comprised of 100 cases and 100 controls. Cases included 39 female and 61 male patients. The mean serum ferritin level among cases was found 5831.00ng/ml. Data Analysis is done using SPSS software version 18. Results are specified in tables and graphs as below;

Table 2: Pubertal status in case & control subjects

Pubertal status	case	control	
Delayed puberty	72	0	p-value <0.001, Highly significant
Normal	28	100	
Total	100	100	
Chi square test applied			

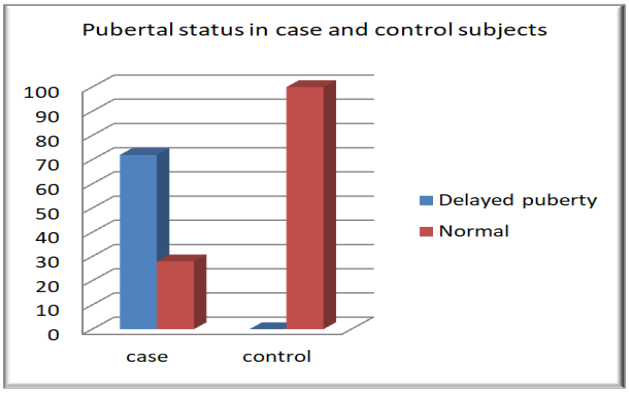

Figure 1: Pubertal status in case & control subjects

There were a total of 72% patients detected to be having delayed puberty. This included 43 males and 29females with delayed puberty; their mean serum ferritin level was above 3998.57±2573.90 ng/dl. As per tanner staging, stage 1 comprised of 38 cases that had not attained puberty and 27 cases were belonging to stage 2, furthermore in Stage 3 about 7 cases were classified and 28 cases in stage 4. Thus delayed puberty is found with equal preponderance in males i.e 43 out of 61 and females 29 out of 39 their mean age are 15 years. Thus more than fifty percent of the patients above 15 years of age are detected to have delayed puberty.

Table 3: Thyroid status of case & control subjects

Thyroid status	case	control	
Hypothyroidism	36	0	p-value <0.001, Significant
Normal	64	100	
Total	100	100	
Chi square test applied			

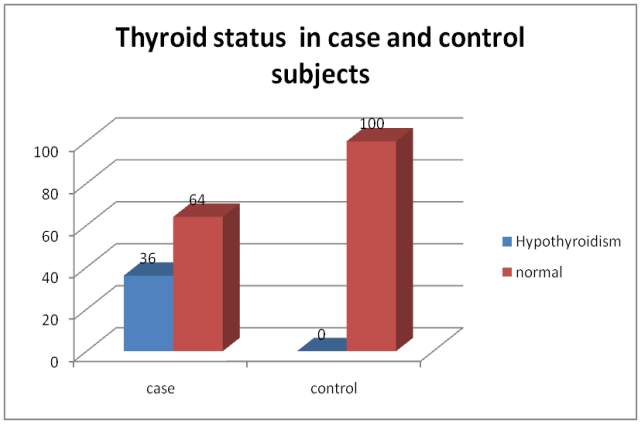

Figure 2: Thyroid status in case & control subjects

Of the 100 thalassemia major patients, 36 patients had hypothyroidism and 64 patients were not affected by this disorder. The Mean of the serum TSH and T4 levels in patients were 9.12µIU/ml and 5.81 pmol/L respectively. Among these 36 cases 27 patients were with overt hypothyroidism and 9 patients were diagnosed as subclinical Hypothyroidism. Mean and standard deviation of the serum ferritin levels was 5147.60±2356.8 ng/ml.

Table 4: Diabetic status of case & control subjects

Diabetic status	case	control	
DM	12	0	p-value <0.001, Significant
Normal	88	100	
Total	100	100	
Chi square test applied			

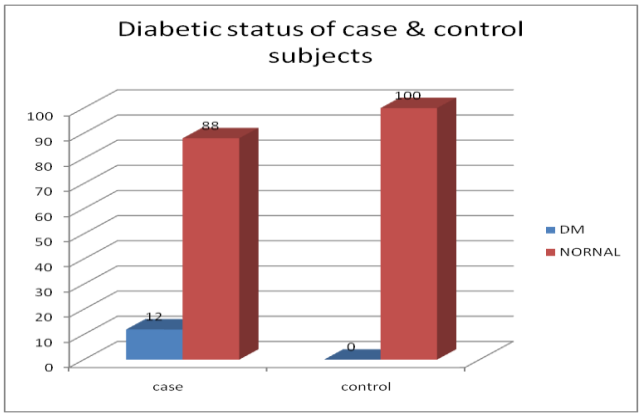

Figure 3: Diabetic status of case & control subjects

The Mean and standard deviation of the Random blood sugar (RBS) levels in patients were 185±89 mg/dl. 12% of patients with beta thalassemia major patients had diabetes mellitus (RBS ≥ 200 mg/dl), which includes 9 males and 3 females. 88% of cases were non diabetic as their random plasma glucose was less than 200 mg/dl.

Table 5: Demographic &biochemical characteristics of patients with thalassemia major

S. No	Parameter	Cases(n=100) Mean± SD	Controls(n=100) Mean± SD	P Value
1	Age (in years)	15±5.63	16 ±5.15	P>0.001
2	Serum Ferritin (ng /ml)	5831.0±2860.5	146.48±83.1	P<0.001
3	TSH (µIU/ml)	9.12±6.3	2.8±2.4	
4	T4(pmol/L)	5.81±1.76	13.25±3.71	
5	RBS (mg/dl)	218±39	95±18	

Comparing the mean ferritin levels in β- thalassemia major patients and healthy controls was highly significant (P<0.001).Table 5

Table 6: Classification of cases as per Tanner staging

Tanners Staging	Number of patient	Percent (%)
Stage 1	**38**	**38**
Stage 2	**27**	**27**
Stage 3	**07**	**7**
Stage 4	28	28

Table 7: Relation of serum ferritin levels with various endocrine abnormalities.

Serum ferritin (ng/ml)	1500-2500 ng/ml	2500-3500 ng/ml	>3500 ng/ml	Total
Disorder				
Delayed puberty patients	13	18	34	72
Hypothyroidism patients	03	12	21	36
Diabetic patients	0	03	09	12

Mean Serum ferritin levels of patients with diabetes (3972.62 ng/ml) and hypothyroidism (5147.60 ng/ml) were similar to those patients who had no diabetes and hypothyroidism whereas mean serum Ferritin levels of patients with delayed puberty (3998.57ng/ml) were found to be only slightly higher than those without delayed puberty. Furthermore 50% of patients with serum ferritin levels above 3500ng/ml had delayed puberty

Discussion

Repeated blood transfusions in patients of thalassemia major as obligatory requirement result in increased life expectancy. This management modality in thalassemia leads to variety of complications including endocrine abnormalities causing a lot of morbidity in these patients. The complications include hypo-gonadism, diabetes mellitus, hypothyroidism, delayed puberty and other endocrine abnormalities.(12)

In present study 12 (12%) patients were found to be suffering from diabetes mellitus. Previous studies have reported prevalence of diabetes from 2.3% to 24.1% in such patients (24, 25). **Ong et al (2008**) reported diabetes mellitus prevalence of 8% in these patients while **Jaruratanasiri kul et al. (2008)** found prevalence of diabetes mellitus as 12.5% in such patients. (26, 27) **Najafipour et al. (2008)** on the other hand reported prevalence of diabetes at 8.9% in Iran.(28) No correlation was found between serum ferritin levels of patients having diabetes and those without diabetes. The reason for this could be that in addition to chronic iron overload that result in diabetes, immune system activation against pancreatic beta cells also plays a significant role resulting in impaired insulin secretion. (17, 18)

Hypothyroidism was found in 36 (36%) of patients in our study. This was almost similar to the findings of **Zervas et al. (2002)** who reported prevalence of hypothyroidism in 34% of patients and **Karamifar et al. (2003)** who reported that 36% of patients had hypothyroidism.[29,30] Again in present study we found significant correlation of hypothyroidism with increasing levels of serum ferritin. There has been consistent occurrence of hypothyroidism in patients of thalassemia but still its causation is poorly understood and there is a lot of variation in its reported prevalence ranging from 4% to 60 %.(29, 31)

There is a high prevalence of endocrine abnormalities in multi transfused patients of beta thalassemia owing to direct deposition and toxicity of serum ferritin. (28,30) There were 72 (72%) patients in our study who had clinical evidence of delayed puberty as assessed by tanner staging chart which incorporated 59.17% of the males and 40.28% of the females in all delayed puberty cases. (With 100% of girls having primary amenorrhea).This percentage increased to 83% percent when patients younger than 15 years of age. Thus, more than half of the patients expected to have attained puberty had delayed puberty. High serum ferritin leading to gonadal iron deposition is thought to cause primary gonadal failure.(10) Iron deposition in pituitary gland can lead to secondary gonadal failure due to decrease in Follicle stimulating harmone (FSH) and Leutenizing harmone (LH) levels.(11,12) More commonly there may be both primary and secondary gonadal failure occurring together.(32)

Fatemeh Saffar, et al (2012) on their study group of 77 patients with β- thalassemia major (15-36 years old). Hypogonadism was the most common endocrine complication in 36 (46.8%) patients, 28 (36.4%) with delayed puberty and 8 (10.4%) with arrested puberty associated.(4)**Rashid H. et al (2011)** has studied 35 thalassemia major patients (16 females and 19 males), aged between 13 and 24 years found that 60% of the patients had not attained puberty. This group included 36.8% of the boys and 87.5% of the girls (with 87.5% of girls having primary amenorrhea).(2) **De Sanctis et al (2004)**, in a study group of 238 patients, aged 2-17 years, with beta-thalassemia major, regularly followed in 13 pediatric and hematological Italian centers, found delayed puberty in 18.4% of boys and 17.7% of girls.**(7) Shamshirsaz** et al(2003) evaluated 258 adolescent, homozygous, beta-thalassemia patients in Tehran; impaired puberty, which occurred in approximately 77% of their patients, was the most common endocrine abnormality and hypogonadism was seen in 22.9% of boys and 12.2% of girls in their study. (10).

Conclusion

Research concluded with finding of Delayed puberty (72%), Hypothyroidism (36%) and diabetes mellitus as (12%) in beta thalassemia patients who were on regular blood transfusion therapy. The Leading biochemistry indicator used to detect Iron overload is serum ferritin level which was found to be highly raised in all study case. In our research delayed puberty is chief endocrine disorder with highest prevalence as per Tanner's staging for puberty. Though, we were not able to support our finding with biochemical parameters for delayed puberty, we recommend them for future researchers. Hypothyroidism is fairly common in study cases which can be considered as contributing factor for high frequency of delayed puberty. Prevalence of Diabetes mellitus was detected at minimum and we were not able identify any specific pattern of its occurrence in our study population. We propose that early

investigation protocol to be prepared and applied for various endocrinopathies in patients of Beta thalaessemia Major who are on regular blood transfusion and chelation therapy. Early detection and management of these endocrinopathies will improve the life prospects of patients.

Ethical clearance: Granted by institutional ethical committee, SMC, SVSU Meerut

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