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ORIGINAL RESEARCH

Evaluation of endocrinopathies among male thalassemic children attending a tertiary care centre in north India

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ABSTRACT

Introduction: Thalassemia is a group of disorders resulting from an inherited defect in the rate of synthesis of one or more globin chains. Endocrine abnormalities in thalassemia major are common alarmingobstacles which require prompt management.

Objective: To know the prevalence and pattern of endocrinopathies among thalassemicmale children (N=85) within 6months to 18 years of age attending thalassemia day care centre in department of paediatrics GMC, Jammu.

Results: All of the patients (98.8%) had thalassemia major; minor type of thalassemia was present in one patient only. Hypothyroidism and hyperthyroidism were present in 7% and 2% patients, respectively. Majority (69.41%)of the patients had lower Vitamin B12 level. Diabetes mellitus was absent. All patients had reduced haemoglobin level. Testosterone level was also normal. Among male children ≤ 10 years, only megaloblastic anaemia was present in 72.09% patients. In male children >10 years age, megaloblastic-anaemia and Hypothyroidism were noted in 66.66% and 7.14% patients respectively.

Conclusion: Our study throws some light on the endocrinal complications associated with thalassemia and adds to the already existing literature about the prevalence of endocrinopathies among thalassemic patients.

INTRODUCTION

Thalassemia refers to a group of genetic disorders of globin chain production in which there is an imbalance between the alpha globin and beta globin chain production **(DeBaun MR *et al.*, 2015).** In India the prevalence of gene varies between 1 - 7% in different regions(mean 3.3%) and nearly 8,000 to 10,000 new thalassemics (homozygous) are born every year.

Beta thalassemia is the best known and studied thalassemia. It is caused by a change in the gene for the beta globin component of haemoglobin. Thalassemia is not a single disease, but a group of disorders, each resulting from an inherited defect in the rate of synthesis of one or more globin chains. This spectrum of diseases is collectively known as *haemoglobinopathies* **(Weather all DJ *et al.*,2007).** In individuals with beta thalassemia there is either complete absence (**β^o-**thalassemia) or a partial reduction (β+ -thalassemia) of beta globin gene

production. In α-thalassemia, α- globin gene production is either absent or partially reduced **(Nelson text book of Pediatric, vol.2, 18th edition page no. 2033-2037).**The molecular basis of the β-thalassemia is very heterogeneous, with over 200 different mutations. Despite the marked heterogeneity, the clinical phenotype of these disorders is relatively homogeneous because of their common pathophysiology: deficiency of HbA tetramers and excess accumulation of free α-subunits incapable of forming haemoglobin tetramers because of deficiency of β-like globin subunits. Beta-thalassemia major is an inherited monogenic disorder that was first discovered by Cooley and Lee **(TheinSL, Clegg JB *et al.*, 1998).** It is caused by mutation at the Beta globin gene locus resulting in persistence of a globin chain that is precipitated with in erythroid precursors in the bone marrow associated with severe dyserythropoietic anaemia **(Olivieri NF, Nathan DG *et al.*, 1994).**

Thalassemia affects males and females equally.Foetal haemoglobin (HbF) concentration in blood decreases after birth by approximately 3% per week and is generally < 2 to 3 % of total haemoglobin by 6 months of age **(Surrey S *et al.*,1985).**Hb A2has not been detected in foetuses. Normal adult levels of Hb A2 are achieved by 4 months of age **(Gonzalez-Redondo JH *et al.*,1989).** Blood transfusion is mandatory for children with thalassemia major and thalassemia intermedia who cannot maintain Hb above 7gm/dl, or those who show evidence of growth retardation and hyper-spleenism.

Flynn DM *et al.*, (1976) conducted a study on Patients with severe thalassaemia major who suffer endocrine and other abnormalities before their eventual death from iron overload due to repeated blood transfusions. The endocrine status of 31 thalassaemic patients aged 2-5 to 23 years was investigated. Although the patients were euthyroid, the mean serum thyroxine level was significantly lower, and the mean thyrotrophic hormone level was significantly higher, compared with the values found in normal children. Forty oral glucose tolerance tests with simultaneous insulin levels were performed in 19 children, of whom 5 developed symptomatic diabetes and one had impaired tolerance. Previous tests on all 6 patients were available and some showed raised insulin levels possibly due to insulin resistance. 2 patients had clinical hypoparathyroidism. As evident from the above study and many other such studies, endocrine abnormalities in thalassemia major are common disturbing complications which require prompt management. Therefore, we designed this study to know the prevalence and pattern of endocrinopathies among thalassaemic patients attending thalassemia day care centre in department of paediatrics GMC, Jammu. This study will throw some light on the endocrinal complications associated with thalassemia.

SETTING AND DESIGN

One year Hospital based prospective study was conducted from 1st of November 2018 to 31st October 2019.

STUDY POPULATION

All male patients were diagnosed as Beta thalassemia major or intermedia between 6 months to 18 years of age under treatment at thalassemia day care centre, SMGS Hospital, GMC Jammu.This study was conducted over a period of one year at thalassemia day care centre in the Department of Paediatrics at Govt. Medical College, Jammu from Nov 2018 to Oct 2019 after getting approval from Institutional Ethical Committee, Government Medical Collge Jammu.A total of 85 males were selected for the study.All male patients diagnosed as Beta thalassemia major or intermedia between 6 months to 18 years of age under treatment at thalassemia day care centre, SMGS Hospital, GMC Jammu were included in the study. Detailed history and general physical examination of patient was recorded in prestructured proforma and their peripheral blood samples were analysed for complete blood count, serum ferritin, and hormonal assays which included (blood sugar, thyroid profile, Testosterone).

STATISTICAL ANALYSIS

Data was entered in Microsoft Excel spreadsheet. It was analysed in terms of numbers, means, standard deviations and proportions. Any apparent association or differences between variables was analysed and the statistical significance was derived using appropriate statistical technique. A p- value of < 0.05 wasconsidered as statistically significant.

RESULTS

This study was conducted over a period of one year at thalassemia day care centre in the **Department of Paediatrics at Govt. Medical College, Jammu from Nov 2018 to Oct 2019.** A total of 85 male children were selected for the study. About 98.8% of them had thalassemia major. Only 1 patient was detected with thalassemia minor.43 of the patients were less than 10 years old and 42 of them were greater than 10 years of age.

All the male patients within the age group (13-18) years had normal (4.94 - 32.01 nmol/l) testosterone level. The mean (SD) Testosterone was 20.73 (2.46) nmol/l. The haemoglobin level less than the lower limit of the normal range (13.5-17.5) in all the patients. The mean (SD) haemoglobin was 8.65 (0.75) g/dl. The blood sugar (random) was within the normal range (<150) in all the patients. The mean (SD) Blood sugar (Random) was 81.47(11.26)mg/dl.This is summarised in Table 1.

Table 1: Summary of a few study points with their findings

Study Point	Description/ Value (N=85)	Percentage/ Mean (SD)
Thalassemia Major	84	98.8%
Age ≤ 10 years	43	50.58%
Age > 10 years	42	49.41 %
Testosterone	Normal	M= 20.73 (2.46) nmol/l
Haemoglobin	Lower	M= 8.65 (0.75) g/dl
Blood Sugar Random	Normal	100%

Also, 100% of the patients had serum ferritin level greater than 204.00ng/ml. Serum ferritin values between 4.63 -204.00ng/ml was considered as normal as per the reference range of hospital's laboratory.

Majority of the patients had serum Ferritin level greater than the 2000 (ng/ml) as shown in Table 2.The mean (SD) serum ferritin of the 85 patients was found to be 2904.73 (1368.35).The levels are much higher than the normal. We also calculated correlation coefficient (R) between the ferritin and testosterone level in the above patients. The R value between the two variables was found to be 0.07, suggesting a very weak positive correlation between Ferritin level and the Testosterone level in the patients.

Table 2: Distribution of thalassemia patients with respect to different Serum Ferritin (ng/L) level.

Serum Ferritin (ng/ml) level.	Number of patients (N=85)
≤1000	4
1001≤2000	23
>2000	58

TSH (Thyroid Stimulating Hormone) was studied in thalassemia patients whose details are summarised in Table 3. The data shows that majority of the patients had normal TSH level yet approximately 7% had hypothyroidism and 2 percent had hyperthyroidism. Mean (SD) TSH was found to be 2.02 (1.16) µIU/ml.

Table 3: Distribution of thalassemia patients as per TSH level.

TSH level* (µIU/ml)	Number of patients (N=85)	Percentage (%)
<0.2700	2	2.35
0.2700 - 4.2000	77	90.58

>4.2000	6	7.05

* Reference value used in study Hospital laboratory.

Vitamin B12 level was checked in all the thalassemia patients. The data reveals that about two-third 69.41% patients had Vitamin B12 level less than the lower limit of normal range and about one-third 30 % of patients had VitaminB12 within the normal range. Mean (SD) Vitamin B12 was about 162.42(52.20)pg/ml.

Table 4: Distribution of Vitamin B12 level-wise thalassemia patients.

Vitamin B12 *(pg/ml) level	Number of patients (N=85)	Percentage (%)
<187	59	69.41
187-883	26	30.58
Total	85	100

* Reference value used in study Hospital laboratory.

The summary of the endocrinopathies based on the above data ispresented in Table 5. The data is divided in two age groups which is less than equal to 10 and greater than 10 years. We assessed endocrinopathies like hypothyroidism, megaloblastic anaemia, diabetes mellitus and hypogonadism.Majority of patients (72.09%) had Megaloblastic-anaemia in the age group (≤ 10 years). In the age group (> 10 years) patients had 7.14% hypothyroidism and 66.66% and Megaloblastic-anaemia. No other endocrinopathy was detected other than mentioned above in both the groups.

Prevalence of endocrinopathies based on the parameter like Ferritin, TSH, Vitamin B12, random blood sugar is defined in Table 6.

Table 5: Distribution of endocrinopathies at different age groups in patients

Endocrinopathies	Number of patients N=43(%)(≤ 10 years)	Number of patients N=42(%)(>10years)	Total Number of patients N =85(%)
Hypothyroidism	0	3(7.14)	3(7.14)
Megaloblastic-anaemia	31(72.09)	28(66.66)	59(69.41)
Diabetes Mellitus	0	0	0
Hypogonadism (Testosterone)	0	0	0

Table 6: Prevalenceof endocrinopathies in thalassemia patients.

Parameter	Prevalence %
Serum Ferritin(>204)	100
TSH(<0.27)	2.35
TSH(>4.20)	7.05
Vitamin B12(<187)	69.41
Blood Sugar(R)(>150)	0

DISCUSSION

The thalassemias are among the most common genetic disorders worldwide, occurring more frequently in the Mediterranean region **(Fawdry*et al.,* 1944)**,the Indian subcontinent, South-east Asia and West Africa. In Indian subcontinent, the average prevalence of the β-thalassaemia trait is about 3.5 %. Sindhis and Punjabis are known to carry the β-thalassaemia gene more commonly than other Indian populations. Most of the thalassaemic patients belonged to Jammu district of the state, this may be due to the fact that Jammu is the single largest city in the region with good medical facilities and the families of thalassaemic children have migrated to Jammu for the same reason. Clustering was also seen in Rajouri district of the state. Treatment facilities including transfusion, chelation and specialist should

be made available at district hospitals in regions where there is high incidence of thalassemia so that the families don't have to migrate to bigger cities for treatment.

We did this study at Department of Paediatrics, SMGS Hospital, GMC, Jammu. We aimed to study the prevalence and pattern of endocrinopathies among male thalassaemic patients attending thalassemia day care centre in department of paediatrics. We found that almost all of the patients (98.8%) were suffering from major type of thalassemia; only 1 patient was suffering from minor type of thalassemia. 7% patients were having hypothyroidism and 2% patients having hyperthyroidism. 69.41% patients had Vitamin B12 level less than the lower limit of normal range. Blood sugar random level was normal in all patients. All patients had low haemoglobin level. The male patients within the age group (13-18) years had normal testosterone level. The correlation coefficient between testosterone and serum ferritin was 0.07, suggesting a very weak positive correlation between the two variables.

Previous studies conducted on thalassemia patients to study the pattern of endocrinopathies reported similar demographic findings. **Upadya SH *et al.*, (2018)** included children aged 3 years and above and found that 43% belonged to the first decade and 47% to the second decade of life; 59% were boys and 41% were girls. They included children with beta thalassemia major only. **Soliman AT *et al.*, (2013a)** conductedstudy on patients with thalassemia major between 5 years and 18 years of age; there were 54.16% males and 45.84% females. **Soesanti*et al.*, (2013)** studied endocrinopathies profile in patients of thalassemia major and found mean age 16.7 years; out of 67 subjects (31 boys, 36 girls), 34% were diagnosed as β-thalassemia homozygote and the rest as β-thalassemia/HbE. Although a weak positive correlation was found between the testosterone and serum ferritin level, but **Harahap*etal*., (2021)** suggested negative correlation between them.

CONCLUSION

In present study, almost all of the patients (98.8%) were having major type of thalassemia; minor type of thalassemia was present in one patient only. Hypothyroidism and hyperthyroidism were present in 7% and 2% patients, respectively. Majority (69.41%) patients had Vitamin B12 level less than the normal range. Diabetes mellitus was absent. All patients had reduced haemoglobin level. All male patients within the age group (13-18) years had normal testosterone level. Among males ≤ 10 years, only megaloblastic anaemia was present in 72.09% patients. In male children >10 years age, megaloblastic-anaemia and Hypothyroidism were noted in 66.66% and 7.14% patients respectively. Our study throwssome light on the endocrinal complications associated with thalassemia and adds to the already existing literature about the prevalence of endocrinopathies among thalassaemic patients. Although being a single-centre hospital-based study, its results cannot be extrapolated to study the prevalence of endocrinopathies among thalassaemic patients in the general population.Lack of control population further posed limitations in studying the endocrinopathies among thalassaemic patients.

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