



REPRODUCTIVE HORMONE IN TRANSFUSION DEPENDENT BETA THALASSEMIA MAJOR PATIENTS.

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ABSTRACT...Objective: To evaluate endocrine profile in transfusion dependent beta-thalassemia major patients. **Study Design:** Descriptive cross sectional study. **Setting:** Department of Pathology Liaquat University of Medical and Health Sciences, Jamshoro / Hyderabad and Thalassemia Centre Hyderabad. **Period:** 6 months from January 2018 to June 2018. **Material & Methods:** Cases already diagnosed with β -thalassemia major with recurrent blood transfusions (>20 transfusions or transfusion period over 2 years) both genders were included. All the patients went through routine laboratory checkups including Testosterone hormone, Luteinizing Hormone, and Follicle Stimulating Hormone. Data was recorded in preplanned proforma. **Results:** Overall 114 subjects were studied and their mean age was found to be 12.38 ± 5.71 years. Females remained in majority as 56.1%. Mean of follicle stimulate hormone (FSH) and luteinizing hormone (LH) level were 4.60 ± 4.88 and 5.39 ± 8.39 respectively. Most of the patients, 35.1% had >300 of transfusion rate. Ferritin levels were significantly correlated with patients with history of transfusion rate >300; p-value 0.003. Testosterone level's mean was considerably high among patients presented with transfusion rate of 201 to 300 and >300 transfusions; p-value 0.006. Likewise, mean of FSH and LH level was as well significantly high among the female subjects with history of transfusion rate of 201 to 300 and >300 transfusions; P-Values 0.019 and 0.026 respectively. **Conclusion:** Frequent hypogonadism was noted among thalassemia patients. Very low level average of FSH, LH and testosterone was seen.

Key words: Beta-thalassemia major, Endocrine Profile.

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INTRODUCTION

Beta-thalassemia denotes a set of recessively heritable hemoglobin disorders detected by decreased formation of β -globin sequence. It is believed to be the commonest genetic disorder aglobally.¹ β -thalassemia is a recessively heritable autosomal hemoglobinopathy and is highly prevalent in Pakistani nation.² Each year 4 to 9 thousand neonates with β -thalassemia (β -thal) major are becoming the part of current burden of this disease. The carrier rate is 5.0%- 8.0% in Pakistan and is noticed homogeneously distributed in all ethnic populations.³ The present cases of β -thalassemia-I carriers are around 240,000,000 globally. Each year around 100 thousand neonates enter this world with thalassemia.⁴ In Pakistan around 5 to 9 thousand

neonates are born with β -thalassemia yearly, though no records are available. The projected carrier rate is 5.0% to 8.0%, with 9800,000 carriers in the overall population of Pakistan.⁵ Even though blood transfusions are vital for anemia patients, chronic transfusions certainly result in iron overload, since human body is unable to actively eliminate excess iron. The increasing consequences of iron overload cause substantial mortality and morbidity, if remained intact.⁶ Excess iron is highly toxic to the body cells and can result in irreversible and serious organic destruction, such as hypogonadism, heart disease, diabetes, and cirrhosis.⁷ Many authors recounted a high rate of endocrine in patients of β -thalassemia major.^{8,9} Children, those have thalassemia, exhibit growth retardation in pre-pubertal, infantile, foetal

and pubertal times.

Sexual immaturity remains a serious problem of acute thalassemia. Numerous studies in gonads-related and pituitary-gonadal functions have started primary gonadal dysfunction in case of gonadal iron accumulation. Secondary hypogonadism is caused by iron accumulation on pituitary gland's gonadotrophic cells as presented by poor response of LH and FSH to GnRH stimulation or a group of both secondary and primary hypogonadism. Some studies reported the incidence rate of failure of puberty commencement up to 50.0% and could even reach 100.0%. Evidence suggest that individuals with further severe disorders have a higher rate of iron loading maybe due to high sensitivity to toxicity of free radicals. Iron toxicity on adipose tissues has also been shown to damage the formation of Leptin (a polypeptide hormone) and thus a delay in sexual maturation.¹⁰ Leptin is formed via adipose cells as a result of obgene expression and functions as a free signal to start puberty. Gross iron overload in pituitary, gonads and hypothalamus are ongoing yet with chelation therapy. Subjects with low gonadotropin have substantial insensitivity to gonadotropin hormones harmonizing with a pituitary and hypothalamic impairment. Delayed commencement of secondary amenorrhoea, oligomenorrhoea, menarche, diminished testicular size (of 6.0 – 8.0 ml) and size of breast at Tanner Stage-II or -III are frequent manifestations of considerably raised serum ferritin and iron levels. The total incidence was 72.0%, with 45.0% incidence in boys and 39.0% in girls. Adequate data mainly on local level was not found in literature. Hence this study has been carried out to assess the reproductive hormone in patients of β -thalassemia major.

MATERIAL AND METHODS

This descriptive cross sectional study was held at Department of Pathology Liaquat University of Medical and Health Sciences, Jamshoro/Hyderabad and Thalassemia Centre Hyderabad. Study duration was 6 months from January 2018 to June 2018. All the patients aged from 5 to 30 years and already diagnosed with β -thalassemia major with recurrent blood transfusion dependent.

(>20 transfusions or transfusion period >2 years), both of the male and female genders were enrolled in this study. Subjects with congenital hypothyroidism goiter and those who were taking prior medications related to endocrine function and annular pancreas/pancreatic tumors were excluded from study. All the subjects went through routine laboratory investigations together with Testosterone hormone, Luteinizing Hormone, and Follicle Stimulating Hormone. In male subjects serum testosterone, and among females serum LH and FSH were carried out by taking 6 ml of serum through standard sampling tubes and specimens were centrifuged for 10-15 minutes at 25 hundred round per minute (RPM) in HERAEUS LABOFUGE 400 (a thermostat scientific Machine). After centrifugation specimens were analyzed through Electrochemiluminescence immunoassay (ECLIA) achieved on Cobas e 6000 series (cobas e 601) or cobas e 411 analyzer by Roche Hitachi. All the data was collected on the proforma. Data was analyzed via SPSS version 16. Mean \pm standard deviation was computed for quantitative variables. Simple frequencies and percentages were calculated for categorical variables. Stratification in terms of gender, age and number of transfusion was carried out by chi square test and p-value ≤ 0.05 was taken as significant.

RESULTS

Overall 114 subjects were studied and their mean age was found to be 12.38 \pm 5.71 years with minimum and maximum age range of 5 and 35 years respectively. Females remained in majority 56.1% while males were 43.9%. Table-I: Average of testosterone levels was assessed among 50 male subjects and its mean was found to be 1.92 \pm 3.57, however this mean level was very low and this can possible be because of small age of most patients. 64 females were observed in terms of luteinizing hormone (LH) and follicle stimulate hormone (FSH). Mean of FSH and LH levels were found as 4.45 \pm 4.73 and 4.30 \pm 6.60 respectively. Table-II: Mean of FSH and LH levels were significantly high among the female subjects who had a history of 201 to 300 transfusion and >300 transfusions; p-values 0.019 and 0.026 respectively. This significant difference of FSH and

LH levels could also be because of lower rate of transfusions among females due to the lower age. Table-III: Likewise mean of testosterone levels was as-well significantly high among the patients presented with transfusion rate of 201 to 300 and >300 transfusions; p-value 0.006. This significant variance could also possibly be because of lower age of subjected who were presented with lower rate of transfusions. Table-IV:

Gender	Frequency	Percent
Female	64	56.1
Male	50	43.9
Total	114	100.0
Age		
Mean+SD	12.38±5.71	

Table-I. Patient distribution according to gender and age n=114

Variables	Mean±SD
Testosterone level n=50	1.92±3.57
FSH n=64	4.45±4.30
LH n=64	4.73±6.60

Table-II. Mean of Testosterone in males and FSH and LH level in females n=50

No. of transfusion	Frequency	Percent
>300	40	35.1
201-300	34	29.8
101-200	20	17.5
1-100	20	17.5
Total	114	100.0

Table-III. Patient distribution in terms of transfusion rates n=114

Variables	No. of transfusion				P-Value
	>300	201-300	101-200	<100	
LH level n=64	2.11 ± 3.40	9.0 ± 0.38	4.19 ± 3.39	7.18 ± 9.55	0.026
FSH level n=64	2.96 ± 1.71	1.24 ± 1.19	4.58 ± 3.30	6.45 ± 6.58	0.019
Testosterone level	0.84 ± 1.94	0.02 ± 0.03	1.17 ± 2.79	4.25 ± 2.79	0.006

Table-IV. Association of LH And FSH with No: of Transfusions in Female Patients n=64

DISCUSSION

Beta thalassemia major is a recurrent hereditary hemoglobinopathy. Growth retardation and excessive iron load are the frequent secondary complications among thalassemia cases those underwent multiple-transfusions. Thus, close monitoring of iron burden with effective iron chelation is necessary in these subjects. Regular erythrocytes transfusions being essential for survival of these subjects lead them to unavoidable excessive iron load, which is expressed by raised levels of ferritin. Progressive accumulation of iron results in failure and dysfunction of major organs. Current study intended to assess the reproductive hormone in β -thalassemia major subjects. In this study patients' mean age was 12.38±5.71 years with minimum and maximum range of 5 years and 30 years respectively. Females remained in the majority 56.1% in comparison to 43.9% males. Similar findings were reported by Karunaratna AM et al¹¹ where out of 40 patients of β -thalassemia major, females were 22 (55%) and males were 18 (45%) with a mean age of 10.97±5.9 years. In one more study by Sultan S et al¹² out of 36 patients of β -thalassemia major males were 17 and females were 19 with a reported mean age of 12.56 ± 5.9 years. In consistent, Hashemi A et al¹³ reported 34 males and 31 females out of 65 subjects. Consistent findings were reported in terms of age (mean age 10.30 years), with thalassemia major.

In present study total average of testosterone levels was lower which was observed among 50 male subjects with mean of 2.95±4.12 for testosterone levels. Mean of testosterone levels was considerably high among subject who were presented with transfusion rates of 201 to 300 and >300; p-value 0.006, this significant variance could possibly be because of lower aged patients presenting with lower rates of transfusions. Likewise mean of FSH and LH levels was also considerably high among the female subjects who had a history of 201 to 300 transfusions and >300 transfusions; p-value 0.019 and 0.026 respectively, this significant variance could also be justified by the lower rates of transfusions as the females had lower age. In contrast Vahidi AA, et al¹⁴ documented mean testosterone levels significantly depressed among thalassaemic

males than controls (p value 0.003) and Mean levels of LH and FSH were considerably lower among subject with β -thalassemia major ($p < 0.001$). In subjects with thalassemia major dwelling in underdeveloped nations, endocrine complications can possibly be frequent as a result of suboptimal iron chelation. In an earlier prospective study of Gulati et al¹⁵ from Indian, majority of the thalassaemic young adults or adolescents had hypogonadism. In one more study of Kiumarsi A et al¹⁶ the mean levels of FSH, LH and Testosterone were reported as 3.7 mIU/ml, 4.6 mIU/ml, and 4.8 ng/dl respectively. A few other studies as well reported that delayed puberty and hypogonadism are the commonest endocrinopathy among thalassaemic subjects (40–91%).^{17,18}

CONCLUSION

It was concluded that hypogonadism and hypothyroidism were most common. Very low level average of testosterone, FSH and LH were observed. More recent research is required on correlation of endocrine profile and ferritin level.

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2	Ikram Din Ujjan	Manuscript review.	<i>Ikram Din Ujjan</i>
3	Sadia Shahmeer	Data analysis and manuscript writing.	<i>Sadia</i>
4	Nazia Hafeez	Participation in data collection.	<i>Nazia Hafeez</i>
5	Kiran Amir	Participation writing and review.	<i>Kiran Amir</i>
6	Abdul Rehman	Participation in data analysis.	<i>Abdul Rehman</i>