Original Article

Comparison of sexual development with sociodemographic and hematological parameters in multi-transfused Patients of β-thalassemia Major

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Abstract

Background: β-thalassemia major encompasses a wide range of hematological and endocrinological complications. High levels of serum ferritin in individuals with β-thalassemia indicate transfusion-related complications including significant iron overload, which can contribute to endocrine disorders such as hypogonadism and subsequent sexual underdevelopment. Therefore, the aim of our study is to investigate the association of sexual development with sociodemographic and hematological parameters in multi-transfused Patients of β-thalassemia Major.

Materials and Methods: This multicentric cross-sectional study consisted of 147 β-thalassemia patients who got enrolled. The sexual development of the participants was evaluated utilizing the Patterson staging system. Data regarding hematological and other demographic variables were collected. Statistical analyses was done using SPSS version 26. Data analysis was done using independent-samples t-test, chi-square test was used for the analysis of collected data.

Results: Among the total of 147 patients, 79(53.74%) were males and 68(46.26%) were females. Based on the Patterson staging system, 63(42.85%) of the patients were in the pre-pubertal, early pubertal and mid pubertal/sexually under-developed stage, while 84 (57.15%) of the patients were in the pubescent and post-pubescent/sexually developed stage. Based upon serum ferritin level stratification there was a significant different in sexually developed and underdeveloped patients.

Conclusion: Increased **s**erum ferritin levels resulting from transfusion in β-thalassemia is significantly associated with hypogonadism in these patients.

Keywords: β-thalassemia, hypogonadism, blood transfusion, ferritin, iron overload.

Introduction

β-thalassemia, a genetic disorder involving the β-globin gene, presents with a wide range of hematological symptoms resulting in microcytic anemia.[1] Its high incidence is observed in regions such as the Indian subcontinent and Southeast Asia, as well as affecting large population of Middle East and Mediterranean countries, collectively referred to as the "World Thalassemia Belt".[2] Globally, approximately four out of every 100,000 live births are affected by β-thalassemia, and a significant number of individuals carry the gene without experiencing symptoms.[3] In Pakistan, statistics indicate that around 70,000 individuals are afflicted with β-thalassemia major, while 6,000 patients are currently under treatment as registered ones, with the number steadily increasing.[1]

Thalassemia is a condition marked by the spectrum ranging from partial impairment to complete dysfunction in the production of α and β-globin chain, which are essential components of adult hemoglobin (α2β2).[4] Individuals with a complete deficiency of α or β-globin chain rely on lifelong blood transfusions and are classified as transfusion dependent thalassemia(TDT) patients. With regular transfusions, the survival rates and life expectancy of individuals with thalassemia have shown significant improvements from the initial decade of life to the fifth decade. Historical data from the 1950s indicated that less than 9% of patients with β-thalassemia lived past the age of 6 years. By the 1970s, more than 50% of Italian thalassemic affected population had succumbed to the disease before turning age of 12.[5] However, significant advancements in treatment, including safe transfusions, regular chelation therapy, and bone marrow transplantation have led to a notable improvement in patient survival rates.

β-thalassemia patients are dependent on regular and multiple blood transfusions for their survival. Nevertheless, this condition leads to the accumulation of ferrous compounds in various tissues, including endocrine glands, which disrupts their normal functioning. Among the complications, gonadal dysfunction is the most prevalent. Patients who undergo 15-20 blood transfusions face a significantly increased risk of developing secondary hemochromatosis.[6] The excess iron overwhelms the binding and storing capability of serum ferritin and plasma transferrin, leading to the circulation of free unbound iron ions in the plasma. The presence of free iron ions contributes to the production of various radicals, causing various endocrine pathologies and complications[7].

Literature reveals a disturbingly higher mortality rates among beta-thalassemic patients with elevated ferritin levels.[1] In addition, β-thalassemia has been associated with several endocrine disorders, such as diabetes mellitus, hyperparathyroidism, hypopituitarism, hypothyroidism and hypogonadism.[8] Hypogonadism often results in delayed sexual development and is a frequent complication arising from ferrous compound deposits in the hypothalamus, pituitary gland, and gonads. While timely use of chelating agents including deferoxamine can improve survival rates, concerns remain for both patients and pediatricians alike.[9]

The Patterson staging system is employed as a tool for evaluating sexual development.[10] It is a simple and cost-effective method widely employed for documentation of progression in secondary sexual characteristics while patients are going through phase of puberty. In our study, we seek to investigate the impact of ferritin levels

on sexual underdevelopment in individuals with β-thalassemia, using the Patterson staging system as the standard measure. This paper aims to evaluate the comparison of hematological and sociodemographic parameters in patients with β-thalassemia major on multiple transfusions.

Materials and Methods

This cross-sectional study was conducted in Rawalpindi and Islamabad, a total of 160 patients diagnosed with β-thalassemia major and registered in Jamila Sultana Foundation, Holy Family Hospital, and Pakistan Institute of Medical Sciences were included. Data was collected from March 2018 to May 2019, employing convenience sampling method. The study included patients from both genders (male as well as female) with age range of 13 years to 30 years, while individuals with comorbidities such as diabetes, hypothyroidism, or metabolic disorders, as well as those with underlying infectious or inflammatory conditions, were excluded. Following the application of the exclusion criteria, the final analysis included 147 eligible patients.

The patients and their parents provided written informed consent, and the Patterson staging system was used to assess the sexual development of the patients. The pubertal staging on the Patterson scale[11] was used to classify the sexual maturation of the patients. Secondary sexual characteristics were assessed in patients, like growth of pubic hair, development of genitalia and breast. According to the Patterson staging, patients at stage 1 or stage 2 were judged as sexually underdeveloped (pre-pubescent), while those at stage 3, 4, or 5 were considered sexually developed (pubescent or post-pubescent). After obtaining consent from the patient and parents, a senior doctor conducted examinations to define the stage of secondary sexual development in the children. The ethical approval for this study was obtained from the institutional research review board Rawalpindi Medical University.

Comparisons were made between the results of Patterson staging and several laboratory values like hemoglobin level and serum ferritin level, as well as demographic variables (age, height, and weight). The comparison was conducted using an independent-samples t-test. Statistical significance was determined by a p-value of <0.05, and data analysis was performed using Statistical Package for Social Sciences (SPSS), version 23.0, developed by IBM in Armonk, NY, USA.

Results

Among the individuals who met the inclusion and exclusion criteria for the study, a total of 160 questionnaires were distributed. Out of these, 147 participants completed the questionnaire in its entirety, while 8 participants were unable to provide complete responses. Additionally, the data of 5 participants were excluded due to their inability to provide laboratory values for ferritin and hemoglobin during the follow-up. Therefore, the data from 147 patients were analyzed, resulting in a response rate of 91.87%.

For the interviews and examinations, they were done on all of 147 participants, consisting of 79 (53.74%) were males and 68 were females (46.26%). The mean age of the patients was 17.58±5.36 years, with the maximum age being 31 years, while the minimum 12 years. Using the Patterson staging system, it was determined that 63 (42.85%) of the patients were in the pre-pubertal, early pubertal and mid pubertal/sexually under-developed stage, while

84 (57.15%) of the patients were in the pubescent and post-pubescent/sexually developed stage. **(Table I)**

Table I: Patterson Staging among the participants**.**

Patterson Staging	Frequency	Percent
Pre-pubertal	8	5.44%
Early pubertal	13	8.84%
Mid pubertal	42	28.57%
Late pubertal	23	15.64%
Post-pubertal	61	41.49%
Total	147	100.0

Table II presents the statistically significant differences in the mean values of age, height, weight, serum ferritin levels and hemoglobin concentration levels between sexually underdeveloped and sexually developed individuals. The p-values indicate that there is no significant difference in gender distribution and age at the start of transfusion treatment between the two groups. **(Table II)**

In terms of gender (male), out of the total participants, 32 (40.5%) were sexually underdeveloped, and 47 (59.49%) were sexually developed, having p-value of 0.492. The mean age for sexually underdeveloped individuals was 13±2.3 years, while for sexually developed individuals it was 20±6.7 years, having p-value of <0.001. The mean height for sexually underdeveloped individuals was 139±11.45 cm, and for sexually developed individuals, it was 152±16.7 cm, with having p-value of 0.031. The mean weight for sexually underdeveloped individuals was 33.6±7.2 kg, and for sexually developed individuals, it was 42.78±6.3 kg, with having p-value of <0.001. The mean age at the start of transfusion treatment for sexually underdeveloped individuals was 10.78±4.3 years, while for sexually developed individuals, it was 12.9±1.8 years, with having p-value of 0.614. The mean recent ferritin level for sexually underdeveloped individuals was 4278±531 ng/mL, and for sexually developed individuals, it was 3089±489 ng/mL, with a p-value of 0.043. The mean current Hb level for sexually underdeveloped individuals was 7.67±1.9 g/dL, and for sexually developed individuals, it was 8.21±1.7 g/dL, with having p-value of 0.001.

Table II: Comparison between sexually under-developed and sexually developed participants

Variable	Sexually Underdeveloped		
	Yes Frequency/ Mean and Standard Deviation	**No** Frequency/ Mean and Standard Deviation	**P-value**
Gender (Male)	32 (40.5%)	47 (59.49%)	0.492
Age of the Patient	13±2.3	20±6.7	<0.001*
Height of the Patient	139±11.45	152±16.7	0.031*
Weight of the Patient	33.6±7.2	42.78±6.3	<0.001*
Age at Start of Transfusion Treatment	10.78±4.3	12.9±1.8	0.614*

Recent Ferritin Level	4278±531	3089±489	0.043*
Current Hb Level	7.67±1.9	8.21±1.7	0.001*

*Independent Sample T-test

**Chi-square Test

Discussion

Thalassemia, a hereditary disorder, is widely recognized as the most prevalent genetic condition worldwide. Individuals with thalassemia often experience various endocrine disorders that adversely affect their health.[1] Among these complications, hypogonadism is the most common in individuals with β-thalassemia major, affecting approximately 70-80% of patients.[12] The development of hypogonadism in thalassemia patients can be attributed to the accumulation of iron in the pituitary gland's gonadotrophic cells.[13] This iron deposition disrupts the normal production of gonadotropins, which are hormones responsible for regulating the functioning of the gonads (testes in males and ovaries in females). As a result of this disruption, hypo-gonadotrophic hypogonadism occurs, leading to impaired reproductive function and hormonal imbalances.

Out of 147 patients included in our study, 63 (42.85%) of the patients were in the pre-pubertal, early pubertal and mid pubertal/sexually under-developed stage, while 84 (57.15%) of the participants were having the pubescent and post-pubescent/sexually developed stage. This finding slightly coincides with previously performed studies as one study in Bangladesh showed prevalence of hypogonadism reaching 35.11%.[11] According to that study, among individuals with hypogonadism, 18.1% exhibited normo-gonadotropic characteristics, 11.7% displayed hypogonadotropic features, and 5.3% showed hypergonadotropic attributes. In contrast to that, a cohort study in Taiwan demonstrated lower rate of hypogonadism (23.1%), out of total studied 454 transfusion dependent thalassemia patients.

Our research reveals that individuals with incomplete sexual development have higher levels of ferritin compared to those with normal sexual development (4278±531 ng/ml vs 3089±489 ng/ml) with p-value of 0.043. This suggests that severe iron overload may contribute to hypogonadism. These findings align with previous studies that have established a direct correlation between serum ferritin levels and the presence of various endocrine disorders such as diabetes mellitus, hypoparathyroidism, hypogonadism and hypothyroidism.[1,14] In their study, Chowdhury R et al observed that hypogonadal patients had a statistically significant increase values of average serum ferritin level in comparison to eugonadal patients (2,174.79±749.12 ng/ml versus 3,572.59 ± 1,199.49 ng/ml).[11] Likewise, a study conducted in Turkey emphasized the importance of regular and frequent monitoring for diverse endocrinopathies in individuals with β-thalassemia who exhibit elevated serum ferritin levels.[15] By recognizing the correlation between elevated serum ferritin levels and the presence of endocrine disorders, the study highlighted the importance of proactive healthcare measures.

In our study, we were unable to find any statistically significant association between gender and hypogonadism (p-value=00.492). These findings align with previous studies conducted by Chowdhury R et al and Hamed AT et al with p-values of 0.125 and.833 respectively.[11,16] However, our results differ from Dumaidi et al.'s study, which reported a higher

prevalence of hypogonadism in males, suggesting that males are more susceptible to hypogonadism compared to females.[17]

In the existing literature, various approaches have been documented for assessing hypogonadism in individuals with thalassemia. These methods encompass the utilization of magnetic resonance imaging as well as measuring serum values of estradiol, testosterone, follicle-stimulating hormone and luteinizing hormone.[1] However, implementing these diagnostic techniques can be both time-consuming and costly, particularly within a resource-constrained health providing system of an underdeveloped nation like Pakistan, with the higher prevalence rate of β-thalassemia and is documented to be increasing. Consequently, there exists a pressing need to establish a prompt and cost-effective laboratory parameter for monitoring sexual underdevelopment in β-thalassemia patients.

Early assessment and prompt treatment of gonadal dysfunction in thalassemic patients through chelating regimen can bring down its occurrence, enhance the life quality, and prevent complications. However, base line data on functionality of gonads in this context is lacking. Hence, our study objected to determine the functional status of gonads in thalassemia patients dependent on transfusion and assess the predictive role of serum ferritin levels in hypogonadism. Hypogonadism secondary to hypogonadotropic chain disturbance can be effectively managed with iron chelating therapy and replacement of hormones alongside regularly performed monitoring, aiming to sustain achieved secondary sexual characters, fertility, and normal puberty onset. Combined use of deferiprone and deferoxamine has shown promising results in improving sexual development in thalassemia patients. Additionally, serum ferritin levels can serve as a useful indicator for monitoring of effectiveness of chelating regimen. However, replacement of hormones should be carefully employed in thalassemia patients due to associated complications.

Despite the limitations of our study being a cross-sectional and convenient sampling, our study emphasizes the conduction prospective studies in future to define and determine the exact association between serum ferritin value and underdevelopment of sexual characteristics. Exploring other markers of inflammation and hematological parameters, including C-reactive protein, in addition to ferritin, can provide a more comprehensive understanding of this association. The evaluation of the ratio between ferritin and CRP ratio may also be valuable in assessing sexual hypo-development. These efforts will contribute to the development of cost-effective laboratory tests for evaluating sexual hypo-development in individuals with β-thalassemia major, paving the way for further research in this field.

Conclusion

Delayed puberty, which indicates sexual underdevelopment, is a significant concern among individuals with β-thalassemia. Our study concluded that hematological and sociodemographic factors serve as a crucial parameters for assessing sexual underdevelopment. We suggest conducting additional case-control and prospective cohort studies to explore the relationship between serum ferritin, iron overload, and the prediction of sexual underdevelopment in individuals with β-thalassemia.

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