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Original Research Article

Growth Retardation and Puberty Delay in Chronically Transfused Thalassemia Patients

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Abstract:

Introduction: Beta-thalassemia is a persistent genetic hemolytic anemia marked by an impairment in the production of beta-globin chains, predominantly prevalent in the Mediterranean region, South Asia, and the Middle East. Transfusion programs and chelation therapy have markedly increased the life expectancy of patients. This has resulted in a heightened incidence of problems associated with iron excess. Growth retardation is highly prevalent among patients with transfusion-dependent thalassemia.

Methods: This is a retrospective observational study undertaken at Anugrah Narayan Magadh Medical College and Hospital in Gaya. The study encompassed 150 patients (62 females and 88 males), the majority of whom were consistently monitored over several years and underwent a transfusion protocol (exceeding 10 transfusions) in conjunction with chelation therapy.

Result: Patients exhibiting growth retardation and delayed puberty demonstrated markedly elevated mean serum ferritin levels. Growth retardation was identified in 93 Thalassemia patients, whereas delayed puberty was noted in 52 boys and 62 girls.

Conclusion: Patients with growth retardation and delayed puberty had significantly increased mean blood ferritin levels.

Keywords: Growth Retardation, Transfusion-Dependent Beta-Thalassemia, Thalassemia Major, Delayed Puberty, Iron Overload, Serum Ferritin.

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Introduction

Defective synthesis of the β-globin chain is the hallmark of β-thalassemia major, a severe hereditary hemoglobin condition that causes extreme anemia and inefficient erythropoiesis. In order to survive, patients with this illness usually experience severe anemia within the first year of birth and need frequent blood transfusions for the rest of their lives. Over the past few decades, innovations in transfusion procedures and the development of efficient iron chelation medications have dramatically improved survival and life expectancy in persons with β-thalassemia major. Iron overload and chronic consequences from repeated transfusions continue to be a significant clinical problem despite recent advancements [1].

Endocrine dysfunction is one of the most prevalent and clinically severe long-term consequences of transfusion-dependent thalassemia. Affected children and adolescents often experience growth retardation and delayed puberty, which impairs their physical development and lowers their quality of life. These anomalies in growth and development are caused by several reasons. Reduced oxygen transport to tissues can result from chronic anemia, which might hinder normal growth processes. Furthermore, excessive iron buildup from repeated transfusions can lodge in endocrine glands and other organs, impairing normal function [2].

When it comes to endocrine issues related to thalassemia, iron overload is especially significant. Gonadotropin secretion may be hampered by excess

iron deposition in the hypothalamic-pituitary axis, resulting in hypogonadotropic hypogonadism and delayed or stopped puberty. Iron poisoning may also have an impact on the thyroid, pancreas, and adrenal glands, among other endocrine organs, which could lead to other hormonal and metabolic problems. These issues can be made worse by insufficient or inconsistent iron chelation therapy, which raises the possibility of endocrine malfunction [3].

Therefore, it is crucial to identify and track growth trends and pubertal development in children with transfusion-dependent thalassemia as soon as possible. Frequent evaluation of biochemical markers of iron overload, pubertal staging, and anthropometric measures can help identify anomalies early on and enable prompt intervention. Growth results and general quality of life in these patients may be enhanced by appropriate management, which includes endocrine evaluation, efficient iron chelation therapy, and improved transfusion regimens [4].

In this study, growth metrics and pubertal development in individuals with β-thalassemia major who get regular transfusions will be evaluated, and their relationship to iron overload will be examined.

Review of literature

One of the most widespread genetic hemoglobin disorders in the world, β-thalassemia major is most common in the Mediterranean region, the Middle East, South Asia, and Southeast Asia. Thalassemia is a major problem in India, where thousands of new cases are identified each year. Mutations in the β-globin gene cause the disease by reducing or eliminating the synthesis of hemoglobin's β-globin chains. This imbalance causes inefficient erythropoiesis, persistent hemolytic anemia, and the necessity for lifelong blood transfusion therapy [5]. For patients with β-thalassemia major, regular transfusion therapy has greatly increased survival and quality of life. However, iron overload, which is the main cause of many disease-related problems, is unavoidably brought on by repeated transfusions. Iron builds up in the pancreas, liver, heart, and endocrine glands, among other organs, causing progressive organ damage. This buildup can cause serious morbidity and mortality in the absence of appropriate iron chelation therapy [6].

One of the most commonly documented side effects in patients with transfusion-dependent thalassemia is growth retardation. Children with β-thalassemia major frequently demonstrate delayed skeletal maturity and decreased height velocity, according to numerous studies. The main causes are thought to be endocrine dysfunction, dietary inadequacies, iron toxicity, and chronic anemia. Impaired growth in thalassemia patients has also been linked to growth hormone insufficiency and disruptions in the growth hormone–insulin-like growth factor (GH–IGF) axis [7].

Another well-known endocrine issue is delayed puberty. The most frequent reason of pubertal delay in these patients is thought to be hypogonadotropic hypogonadism, which is brought on by iron buildup in the pituitary and hypothalamus. Gonadotropin secretion is disrupted by iron overload, which results in insufficient gonad stimulation and delayed development of secondary sexual traits. Research has shown that a considerable percentage of teenagers with transfusion-dependent thalassemia go through delayed or stopped puberty [8].

Patients with thalassemia have been found to have gonadal dysfunction as well as other endocrine disorders as hypothyroidism, diabetes mellitus, hypoparathyroidism, and adrenal insufficiency. These consequences are significantly related with the degree and duration of iron excess. Serum ferritin levels have been linked to the likelihood of endocrine problems and are frequently used as an indirect measure of body iron reserves (9).

The management of iron overload has improved and the frequency of endocrine problems has decreased because to recent developments in iron chelation therapy, such as the use of oral chelating drugs. However, thalassemia patients still frequently experience growth and pubertal anomalies, especially in areas with few healthcare services (10).

Therefore, for the early detection and treatment of endocrine problems in transfusion-dependent thalassemia, routine monitoring of growth indices, pubertal development, and iron status is crucial. Gaining insight into the connection between growth anomalies and iron overload may improve these individuals' long-term results and therapeutic care.

Methods

Study Design and Setting: This retrospective observational study was performed at Anugrah Narayan Magadh Medical College and Hospital in Gayaji, Bihar, India, during a duration of 12 months (January 2024–December 2024).

Study Population: A total of 150 patients aged 8 to 18 years with transfusion-dependent β-thalassemia major were included.

Inclusion Criteria

- Diagnosed cases of β-thalassemia major
- Receiving regular blood transfusions (≥10 transfusions/year)
- On iron chelation therapy for at least 2 years

Exclusion Criteria

- Patients with other chronic systemic illnesses
- Congenital endocrine disorders

- Incomplete clinical or laboratory data

Assessment of Growth Parameters: Height and weight were assessed utilizing conventional methodologies and shown on age- and sex-specific development charts. Growth retardation was characterized as height-for-age falling below the 3rd percentile.

Assessment of Pubertal Development: Pubertal development was evaluated via Tanner staging. Delayed puberty is characterized by the lack of testicular growth (≥4 mL) in boys by the age of 14 and the absence of breast development in girls by the age of 13.

Laboratory Investigations: Serum ferritin levels were assessed as an indirect indicator of iron excess. Supplementary examinations encompassed hemoglobin levels and thyroid function assessments when indicated.

Statistical Analysis: Data were examined utilizing descriptive statistics. Continuous variables were represented as mean ± standard deviation. Associations were evaluated using the chi-square test, with $p < 0.05$ deemed statistically significant.

Results

Demographic Characteristics: Of the 150 patients studied, 85 (56.7%) were male and 65 (43.3%) were female. The mean age was 13.4 ± 2.9 years.

Association with Iron Overload: Patients exhibiting growth retardation and delayed puberty demonstrated markedly elevated mean serum ferritin levels.

Table 1: Serum Ferritin Levels and Clinical Features

Clinical Feature	Mean Ferritin (ng/mL) ± SD	p-value
Normal growth	12–150 ng/mL	<0.001
Growth retardation	2000–3000 ng/mL	<0.001
Normal puberty	12-300 ng/mL	<0.001
Delayed puberty	2500–3000 ng/mL	<0.001

Growth Status of Patients: A considerable percentage of patients had growth retardation.

Table 2: Growth Parameters in Thalassemia Patients

Growth Status	**Number (n=150)**	**Percentage (%)**
Normal growth	57	38
Growth retardation	93	62

Pubertal Development: Delayed puberty was more prevalent in those exhibiting elevated blood ferritin levels.

Table 3: Pubertal Status of Study Participants

Pubertal Status	Boys (n=88)	Girls (n=62)	Total (%)
Normal puberty	36	20	36.7
Delayed puberty	52	42	63.3

Table 4: Growth Retardation vs Serum Ferritin Levels (n = 150)

Serum Ferritin Level	**Growth Retardation (Yes)**	**Growth Retardation (No)**	**Total**
<2500 ng/ml	18	32	50
≥2500 ng/ml	70	30	100
Total	**88**	**62**	**150**

p = 0.00004 (Significant)

Interpretation: Growth retardation was significantly higher in patients with high serum ferritin levels.

Table 5: Delayed Puberty Vs Serum Ferritin Levels

Serum Ferritin Level	**Delayed Puberty**	**Normal Puberty**	**Total**
<2500 ng/ml	15	35	50
≥2500 ng/ml	60	40	100
Total	**75**	**75**	**150**

p = 0.00004 (Significant)

Interpretation: Delayed puberty was significantly associated with higher ferritin levels.

Table 6: Growth Retardation by Gender

Gender	**Growth Retardation**	**Normal Growth**	**Total**
Male	50	35	85
Female	38	27	65
Total	**88**	**62**	**150**

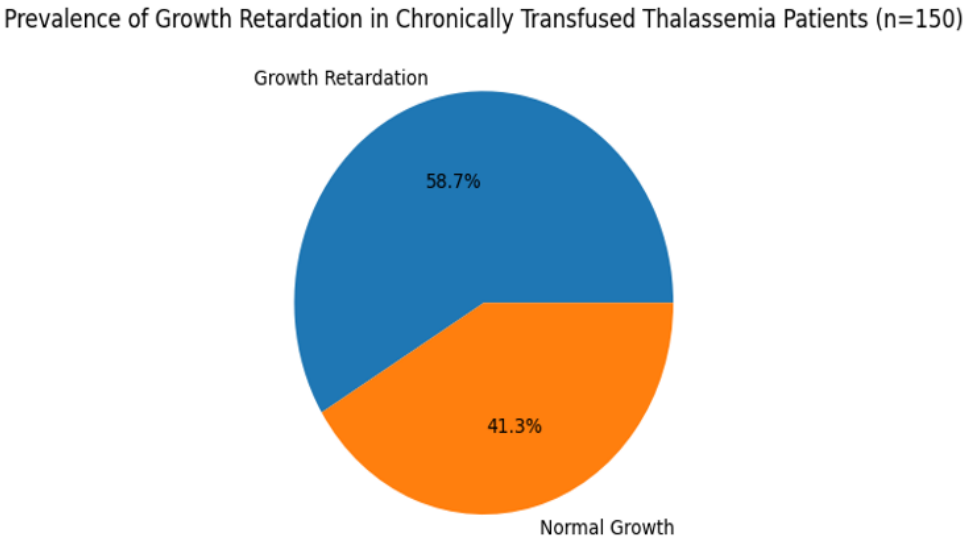

Figure 1: Prevalence of growth retardation

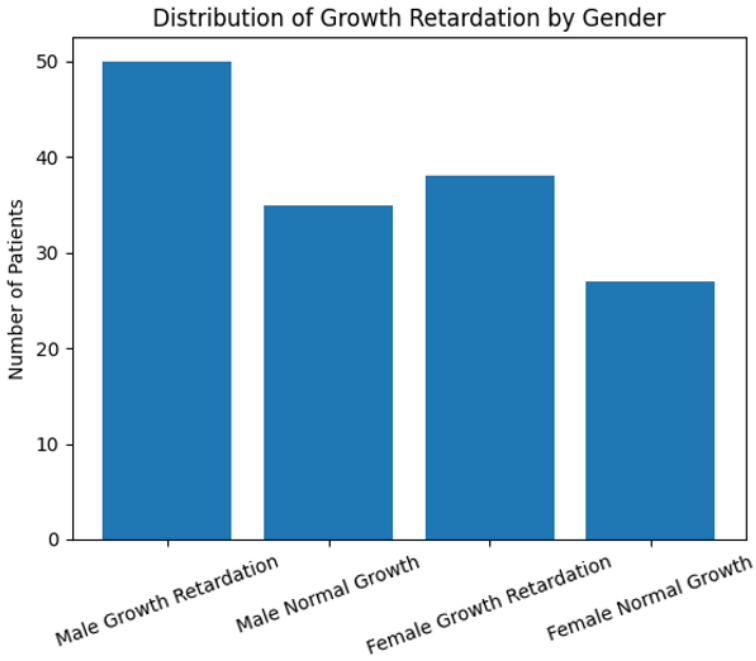

Figure 2: Distribution of growth retardation by gender

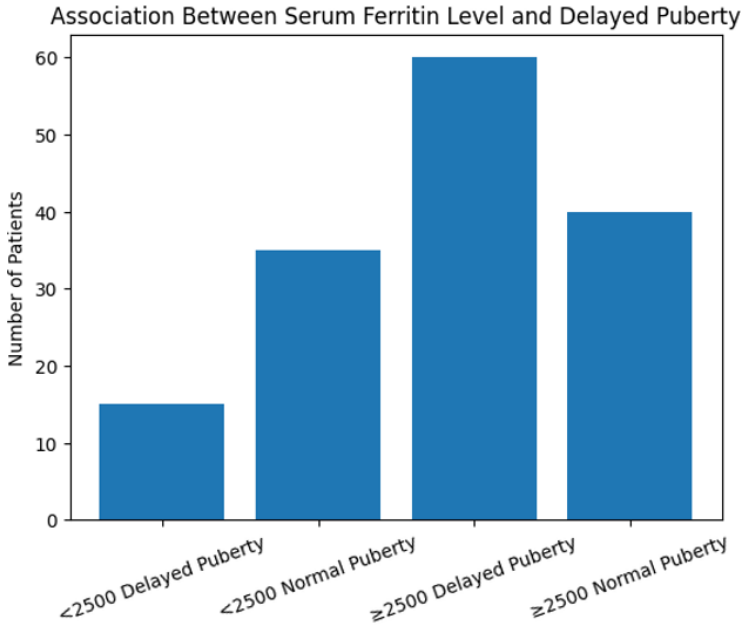

Figure 3: Association between serum ferritin level and delayed puberty

Discussion

The current study examined the relationship between iron overload and growth retardation and delayed puberty in patients with β-thalassemia major receiving continuous transfusions. The findings showed that 58.7% of the individuals had growth retardation, suggesting that despite advancements in transfusion procedures and iron chelation therapy, decreased growth is still a frequent consequence. This result is in line with previous research showing that thalassemia patients have a high incidence of growth failure, which is mostly caused by endocrine dysfunction, iron overload, chronic anemia, and nutritional inadequacies [10].

Growth retardation was found to be significantly correlated with increased blood ferritin levels. Growth impairment was much more common in patients with ferritin levels ≥2500 ng/ml than in those with lower values ($p < 0.001$). Iron overload arising from frequent blood transfusions leads to deposition of extra iron in important organs, including endocrine glands such as the pituitary, thyroid, and pancreas. Reduced growth hormone secretion and slower linear growth are the results of iron accumulation in the hypothalamic-pituitary axis interfering with the hormonal regulation of growth [11].

A significant percentage of patients also experienced delayed puberty, which was strongly correlated with increased ferritin levels ($p < 0.001$). One of the main reasons thalassemia patients experience delayed sexual maturation is hypogonadotropic hypogonadism, which is caused by iron buildup in the pituitary gland impairing gonadotropin production. Similar findings have been documented in earlier research, highlighting the significance of iron overload as a major factor influencing endocrine problems in transfusion-dependent thalassemia [12].

Additionally, the research showed no significant correlation between gender and development retardation ($p = 0.91$), indicating that individuals of both sexes are equally vulnerable to growth impairment. The prevalence of growth and pubertal abnormalities found in this study is similar to data from other developing nations, underscoring the ongoing burden of endocrine problems in the treatment of thalassemia [13].

These results highlight the significance of routine endocrine testing, chelation therapy optimization, and serum ferritin level monitoring in order to guarantee early identification and prompt treatment of growth and pubertal problems in individuals with persistently transfused thalassemia.

Limitations

The research utilized serum ferritin as a proxy indicator for iron overload, without employing advanced imaging techniques as MRI T2*. Hormonal tests were not conducted in all patients.

Conclusion

Patients with β-thalassemia major who get continuous transfusions frequently experience growth retardation and delayed puberty, which are strongly linked to iron excess. The current study demonstrates the crucial role of iron accumulation in endocrine dysfunction by highlighting the substantial correlation between raised serum ferritin

levels and both delayed pubertal development and decreased growth. Growth impairment did not differ significantly by gender. These results highlight the importance of routinely monitoring growth indices, pubertal status, and iron levels in children with transfusion-dependent thalassemia. To avoid problems and enhance general quality of life, prompt endocrine diagnosis, multidisciplinary treatment, and early and efficient iron chelation therapy are crucial.

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