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Clinical profile of transfusion-dependent thalassemia major children with reference to serum ferritin and liver function: A prospective observational study

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ABSTRACT

Background: Thalassemia major is a genetic disorder characterized by severe anemia and the need for lifelong blood transfusions. **Aims and Objectives:** The aim of this study was to investigate the clinical profile of transfusion-dependent thalassemia major children with reference to serum ferritin levels and liver function. **Materials and Methods:** A prospective observational study included 100 children aged 1–12 years with beta-thalassemia major, who were receiving blood transfusions. Clinical data, including growth parameters, serum ferritin levels, and liver function tests, were collected. Descriptive and inferential statistical analyses were performed. **Results:** The study population predominantly consisted of children aged 1–5 years (54%) and males (51%). Hindu children accounted for 85% of the participants. Most children were diagnosed with thalassemia major before the age of 1 year (84%) and were diagnosed through Hb electrophoresis (77%). The majority of children received blood transfusions every 15–30 days (49%). Pre-transfusion hemoglobin levels ranged from <5 g/dL to 8.0 g/dL, while post-transfusion levels ranged from 7.1 g/dL to 10.1 g/dL. Liver function tests indicated the mean values for total serum bilirubin (0.81 ± 0.2), direct bilirubin (0.34 ± 0.10), indirect bilirubin (0.49 ± 0.10), aspartate transaminase (47.22 ± 11.06), alanine transaminase (45.45 ± 8.97), alkaline phosphatase (97.74 ± 4.39), total proteins (6.28 ± 0.29), and serum albumin (3.72 ± 0.2). No significant changes were observed in growth parameters over the 18-month study period. **Conclusion:** This study provides insights into the clinical profile of children with transfusion-dependent thalassemia major, emphasizing the significance of early diagnosis, regular transfusions, and monitoring of serum ferritin levels and liver function.

Key words: Serum ferritin; Liver function; Growth pattern; Iron overload; Blood transfusions; Pediatric population

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INTRODUCTION

Transfusion-dependent thalassemia major is a genetic blood disorder characterized by the absence or reduced production of functional hemoglobin, leading to severe anemia.[1] It requires lifelong blood transfusions to sustain the patient's life.[2] The accumulation of iron due to repeated transfusions poses a significant challenge in the management of thalassemia major.[3] Iron overload can result in organ damage, particularly in the liver, leading to impaired liver function.[4]

Understanding the clinical profile of transfusion-dependent thalassemia major children is essential for effective management and improved outcomes. This includes evaluating growth patterns, assessing iron overload through serum ferritin levels, and monitoring liver function through various laboratory tests.[5]

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Growth assessment is crucial in children with thalassemia major as growth failure is a common complication. Monitoring growth parameters using appropriate growth charts, like the Indian Academy of Pediatrics (IAP) growth charts, allows for early identification and intervention.[6]

Iron overload, resulting from chronic blood transfusions, leads to excessive accumulation of iron in various organs, especially the liver. Serum ferritin, a marker of iron stores, is commonly used to assess iron overload. Liver function tests, including serum bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), total proteins, and serum albumin, provide insights into liver health and potential damage.[7]

This study aimed to investigate the clinical profile of transfusion-dependent thalassemia major children with specific emphasis on serum ferritin levels, liver function, and growth patterns. By assessing these parameters, we can gain a comprehensive understanding of the disease presentation, iron overload, and liver involvement in this pediatric population.

Aim

Investigate the impact of early chelation therapy and specific chelators on growth parameters and liver function in transfusion-dependent thalassemia major children.

Objectives

Assess growth patterns, serum ferritin levels, liver function, and echocardiographic findings.

MATERIALS AND METHODS

Study design

This study employed a prospective observational design to investigate the clinical profile of transfusion-dependent thalassemia major children with respect to serum ferritin levels and liver function.

Study setting

The study was conducted at the Department of Pediatrics, Government Medical College, Nizamabad, Telangana, India.

Study duration

The study was conducted from May 2021 to October 2022.

Study population

The study included all patients with beta-thalassemia major who were attending the outpatient department of the Department of Pediatrics at GGH, Nizamabad.

Sampling technique

Convenient sampling was used to select the study sample.

Sample size

The sample size was calculated using the formula: n = (4pq/d^2), where p is the prevalence of beta thalassemia, q is 100-p, and d is the absolute precision.[8] Considering a prevalence of 1.5%, a 95% confidence interval, 80% power of the study, and 10% anticipated error, the sample size was calculated to be 100. To account for potential attrition and ensure an adequate sample size, the study aimed to enroll 100 participants.

Inclusion criteria

- Patients aged 1–12 years
- Patients diagnosed with beta-thalassemia major and confirmed through Hb electrophoresis or HPLC
- Patients receiving regular blood transfusions
- Patients willing to provide informed consent.

Exclusion criteria

- Patients aged <1 year or >12 years
- Children diagnosed with sickle-thal trait or any other hemoglobinopathies
- Children with a known case of primary endocrinopathy
- Children on hormonal therapy affecting growth
- Children with any chronic illness (e.g., tuberculosis, malignancy, congenital heart disease, chronic renal failure, chronic hepatitis, epilepsy, and diabetes mellitus)
- Patients who were unwilling to provide informed consent.

Data collection

- Patients who met the inclusion criteria were enrolled in the study after obtaining written informed consent from their guardians
- Detailed demographic data (gender, age of diagnosis, and age at the first transfusion) and anthropometric measurements (height, weight, and body mass index) were recorded for each participant
- Relevant clinical and laboratory details, including the frequency of transfusions and pre-transfusion hemoglobin levels, were documented
- Serum ferritin levels and liver function tests (serum bilirubin: Total, direct, indirect; SGOT, SGPT) were assessed using standard laboratory procedures
- Additional information, such as family history, allergic history, chelation therapy, and the number of drugs used, was collected through interviews and medical records
- Various examination findings, including pallor, hepatosplenomegaly, and splenomegaly, were noted during physical examinations.

Data analysis

Data entry and analysis were performed using appropriate statistical software (e.g., SPSS and R). Descriptive statistics were

used to summarize the demographic and clinical characteristics of the study population. Continuous variables were presented as mean±SD (min-max), and categorical variables were presented as numbers (%). Inferential statistical analyses, like the Chi-square test, were conducted to explore the associations between variables and determine any significant findings.

Ethical clearance

Ethical clearance for the study was obtained from the Institutional Ethical Committee of Government Medical College, Nizamabad.

RESULTS

The present prospective observational study was conducted at the Department of Pediatrics, GGH, Nizamabad. The results of the study are as follows:

Demographic characteristics

Age distribution

Among the study population (n=100), 54% belonged to the age group of 1–5 years, 25% were in the age group of 6–10 years, 12% were over 10 years, and 9% were less than a year old.

Gender distribution

Among the study population, 51% were male and 49% were female.

Religion distribution

The majority of the study population (85%) were Hindus, followed by Muslims (12%) and Christians (3%) (Table 1).

Clinical characteristics

Age at diagnosis

Most of the children (84%) were diagnosed with thalassemia major before the age of 1 year. A small proportion (6%) were diagnosed between the ages of 1–2 years and 2–3 years, while 4% were diagnosed at the age of 5 years.

Table 1: Demographic characteristics of transfusion-dependent thalassemia major children

Demographic characteristic	Frequency (n=100), n (%)
Age distribution (years)	
1–5	54 (54)
6–10	25 (25)
Over 10 years	12 (12)
<1	9 (9)
Gender distribution	
Male	51 (51)
Female	49 (49)
Religion distribution	
Hindus	85 (85)
Muslims	12 (12)
Christians	3 (3)

Method of diagnosis

Hb electrophoresis was the most common method of diagnosis (77%), followed by HPLC (23%).

Age at the first transfusion

The majority of the study population (84%) received their first blood transfusion before the age of 1 year. A small proportion (6%) received their first transfusion between the ages of 1–2 years and 2–3 years, and 4% received their first transfusion at the age of 5 years.

Frequency of blood transfusions

Most of the children (49%) received blood transfusions once every 15–30 days. The same proportion (49%) received transfusions once every 31–45 days, while a small percentage (2%) received transfusions every 46–60 days (Table 2).

Hemoglobin levels-pre and post transfusion

Pre-transfusion hemoglobin levels ranged from <5 g/dL to 8.5 g/dL. Post-transfusion targeted hemoglobin levels ranged from 7.2 g/dL to 10.3 g/dL. There was a statistically significant difference in hemoglobin levels at the end of the study (P<0.001) (Table 2).

Family history

Family history of thalassemia major was present in 33% of the study population.

Allergic history

Only 5% of the study population had a history of allergies.

Chelation therapy

The majority of the study population (76%) were on chelation therapy.

Table 2: Clinical characteristics of transfusion-dependent thalassemia major children

Clinical characteristic	Frequency (n=100), n (%)
Age at diagnosis (years)	
<1	84 (84)
1–2	6 (6)
2–3	6 (6)
5	4 (4)
Method of diagnosis	
Hb electrophoresis	77 (77)
HPLC	23 (23)
Age at the first transfusion (years)	
<1	84 (84)
1–2	6 (6)
2–3	6 (6)
5	4 (4)
Frequency of blood transfusions (days)	
15–30	49 (49)
31–45	49 (49)
46–60	2 (2)

Drugs used

Deferasirox was the most commonly used drug for chelation therapy (55%), followed by a combination of drugs deferasirox and deferoxamine (32%).

Growth parameters

Weight percentiles

The distribution of weight percentiles was as follows: <1st percentile (25%), 1st–3rd percentile (15%), 3rd–10th percentile (18%), 10th–25th percentile (17%), 25th–50th percentile (22%), and 50th–97th percentile (3%). (Table 3) The Chi-square test was used to examine the distribution of children across different weight and height percentiles.

Height percentiles

The distribution of height percentiles was as follows: <1st percentile (34%), <3rd percentile (10%), 1st–3rd percentile (8%), 3rd–10th percentile (20%), 10th–25th percentile (5%), and 25th–50th percentile (12%). (Table 3) The Chi-square test was used to examine the distribution of children across different weight and height percentiles.

Laboratory findings

Mean serum ferritin level

The mean serum ferritin level was 2060±1208 ng/mL.

Liver function tests

The mean values of liver function tests were as follows: total serum bilirubin (0.81±0.2 mg/dL), direct bilirubin (0.34±0.10 mg/dL), indirect bilirubin (0.49±0.10 mg/dL), AST (47.22±11.06 U/L), ALT (45.45±8.97 U/L), ALP (97.74±4.39 U/L), total proteins (6.28±0.29 g/dL), and serum albumin (3.72±0.2 g/dL) (Table 4).

2D echo findings

Among the study population, 13% had grade I diastolic dysfunction, 10% had grade II diastolic dysfunction, 19% had mild tricuspid regurgitation, 3% had pulmonary arterial hypertension, and 3% had dilated left ventricle/left atrium. The majority (62%) had normal findings (Table 5).

Table 3: Laboratory findings of transfusion-dependent thalassemia major children

Laboratory finding	Mean±SD (minimum–maximum)
Pretransfusion hemoglobin (g/dL)	7.4±0.8 (5.0–8.5)
Posttransfusion hemoglobin (g/dL)	9.0±0.7 (7.2–10.3)
Serum ferritin (ng/mL)	2060±1208
Total serum bilirubin (mg/dL)	0.81±0.2
Direct bilirubin (mg/dL)	0.34±0.10
Indirect bilirubin (mg/dL)	0.49±0.10
AST (U/L)	47.22±11.06
ALT (U/L)	45.45±8.97
ALP (U/L)	97.74±4.39
Total proteins (g/dL)	6.28±0.29
Serum albumin (g/dL)	3.72±0.2

AST: Aspartate transaminase, ALT: Alanine transaminase, ALP: Alkaline phosphatase

DISCUSSION

Thalassemia major is a hereditary blood disorder characterized by ineffective erythropoiesis, resulting in chronic anemia that necessitates lifelong blood transfusions for survival. This prospective observational study aimed to assess the clinical profile of transfusion-dependent thalassemia major children with reference to serum ferritin levels and liver function.

The age distribution of the study population revealed a significant proportion of children aged 1–5 years (54%), which is consistent with previous studies (Sharma et al.;[9] Harish and Pasha;[10] and Al-Kherbash et al.,[11]) This observation highlights the early onset of thalassemia major and the need for early diagnosis and management.

Regarding gender distribution, the present study showed a relatively equal distribution between males (51%) and females (49%). This finding is consistent with the study

Table 4: Growth findings of transfusion-dependent thalassemia major children

Weight percentiles	Percentage (%)
<1st percentile	34
1st–3rd percentile	10
3rd–10th percentile	8
10th–25th percentile	20
25th–50th percentile	5
50th–97th percentile	12
Height percentiles	
<1st percentile	34
<3rd percentile	10
1st–3rd percentile	8
3rd–10th percentile	20
10th–25th percentile	5
25th–50th percentile	12

The Chi-square test was used to examine the distribution of children across different weight and height percentiles

Table 5: 2D echo findings of transfusion-dependent thalassemia major children

2D echo findings	Frequency (n=100), n (%)
Grade I diastolic dysfunction	13 (13)
Grade II diastolic dysfunction	10 (10)
Mild TR	19 (19)
PAH	3 (3)
Dilated LV/LA	3 (3)
Normal findings	62 (62)

PAH: Pulmonary arterial hypertension, LV/LA: Left ventricle/Left atrium, TR: Tricuspid regurgitation

by Sharma and Bezboruah,[12] but differs from the study by Al-Kherbash et al.,[11] which reported a slight male predominance. The gender distribution may vary across different populations due to genetic and environmental factors.

Religion distribution revealed that the majority of the study population were Hindus (85%), followed by Muslims (12%) and Christians (3%). These findings reflect the demographic characteristics of the region where the study was conducted and may not be generalizable to other populations.

Early diagnosis of thalassemia major is crucial for the timely initiation of transfusion therapy. In this study, a significant proportion of children (84%) were diagnosed before the age of 1 year. This finding aligns with the recommended screening and diagnostic guidelines for thalassemia major (Weatherall et al.,[13]). Early diagnosis allows for early intervention and optimal management.

The most common method of diagnosis in the study population was Hb electrophoresis (77%), followed by HPLC (23%). These diagnostic methods are well-established and widely used for identifying hemoglobinopathies, including thalassemia major (Brancaleoni et al.,[14]). Hb electrophoresis is a cost-effective and accessible technique, making it the preferred choice in resource-limited settings.

The frequency of blood transfusions plays a critical role in managing thalassemia major. The majority of children in this study received transfusions either once every 15–30 days or once every 31–45 days (48% each). Regular and appropriately timed transfusions are essential to maintain hemoglobin levels and prevent complications associated with anemia.

Chelation therapy is an integral part of thalassemia management to prevent iron overload resulting from chronic transfusions. In this study, a substantial proportion of children (76%) were on chelation therapy. Deferasirox was the most commonly used chelating agent (55%), followed by a combination of drugs (32%). These findings indicate adherence to chelation therapy guidelines and the use of effective iron-chelating agents.

Assessment of growth parameters using IAP growth charts showed variations in weight and height percentiles among the study population. A considerable number of children had weight percentiles below the 1st percentile (25%), indicating growth impairment associated with thalassemia major. Similar findings were observed for height percentiles, with a significant proportion of children falling below the 1st percentile (34%). These growth impairments highlight the multifactorial nature of thalassemia major, involving not only anemia but also endocrine dysfunction and genetic factors (Skordis and Kyriakou,[15]).

Liver function tests, including serum bilirubin levels and transaminase enzymes (AST, ALT), provide valuable insights into liver involvement in thalassemia major. The mean values of liver function parameters in this study were within the normal range, indicating no significant liver dysfunction. These findings suggest an effective management of iron overload and the absence of significant hepatic complications in the study population.

Serum ferritin levels are widely used as an indicator of iron overload in thalassemia major. The mean serum ferritin level in this study was 2060±1208 ng/mL, indicating substantial iron burden. However, no significant change in serum ferritin levels was observed between the beginning and the end of the study. This finding may reflect the challenges of managing iron overload despite regular chelation therapy.

The examination findings revealed the presence of pallor in all children, indicating the chronic anemia characteristic of thalassemia major. Hepatosplenomegaly was observed in 67.74% of the study population, consistent with the literature on thalassemia major (Galanello et al.,[16] and Origa[17]). Splenomegaly was present in 32.26% of the children, suggesting the need for careful monitoring of splenic complications.

Limitations of the study

Blood samples were not collected at the same time for all investigations, which could have introduced bias in the results. Cardiac magnetic resonance imaging and liver biopsy could not be done due to a lack of resources, which limited the ability to assess the full impact of iron overload on the heart and liver. Siblings of the patients could not be sampled, which limited the ability to compare the clinical profile of patients with thalassemia major to their siblings.

CONCLUSION

Based on the study's results, there is evidence to suggest that early initiation of chelation therapy guided by serum ferritin levels, in combination with deferasirox and deferiprone, may have potential associations with improved growth parameters in children with transfusion-dependent thalassemia major. However, it is essential to consider that more than 34% of the study population exhibited weight and height centiles <1%, indicating that growth failure remains a prevalent issue despite chelation therapy. Maintaining target hemoglobin levels and receiving adequate chelation therapy resulted in stable

liver function. These findings highlight the importance of timely intervention and personalized treatment approaches for optimizing growth outcomes in thalassemia patients. Effective management of iron overload through chelation therapy plays a crucial role in preserving liver function.

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REFERENCES

1. Giardina PJ. Thalassemia syndromes. In: Hoffman R, Benz EJ Jr., Silberstein LE, Heslop HE, Weitz JI and Anastasi J, editors. Hematology: Basic Principles and Practice. 6th ed. Philadelphia, PA: Elsevier Saunders; 2013. p. 505-35.
2. Turner DA and Cheifetz IM. Shock. In: Kliegman RM and Behrman RE, editors. Nelson Textbook of Pediatrics. 21st ed. Philadelphia, PA: Elsevier; 2020. p. 2554-7.
3. Lokeshwar MR. Progress in the management of thalassemia. Indian Pediatr 2016;43:503-6.
4. Moiz B, Moatter T, Ansari SH and Bohra V. Anthropometric measurements in children having transfusion-dependent beta thalassemia. Hematology. 2018;23(4):248-252. https://doi.org/10.1080/10245332.2017.1395592
5. Sobhani S, Rahmani F, Rahmani M, Askari M and Kompani F. Serum ferritin levels and predicting liver iron load in patients with major beta thalassemia: A cross-sectional study. Croat Med J. 2019;60(5):405-413. https://doi.org/10.3325/cmj.2019.60.405
6. Cooley TB and Lee P. A series of cases of splenomegaly in children with anemia and peculiar bone changes. Trans Am Pediatr Soc. 1925;37:29-30.
7. Whipple GH and Bradford WL. Racial or familial anemia of children. Associated with fundamental disturbances of bone and pigment metabolism (Cooley-Von Jaksch). Am J Dis Child. 1932;44(2):336-365. https://doi.org/10.1001/archpedi.1932.01950090074009
8. Serdar CC, Cihan M, Yücel D and Serdar MA. Sample size, power and effect size revisited: Simplified and practical approaches in pre-clinical, clinical and laboratory studies. Biochem Med (Zagreb). 2021;31(1):010502. https://doi.org/10.11613/BM.2021.010502
9. Sharma S, Tikkas R, Uikey R and Kumar V. Clinico-pathological profile of pediatric patients with thalassemia major. Pediatric Rev Int J Pediatr Res. 2020;7(2):49-55. https://doi.org/10.17511/ijpr.2020.i02.01
10. Harish GV and Pasha SJ. Correlation of serum ferritin levels with liver function tests and anthropometric measurements in transfusion dependent beta-thalassemia major children: A cross sectional study. Pediatr Oncall J. 2019;16:101-104. https://doi.org/10.7199/ped.oncall.2019.33
11. Al-Kherbash HA, Al-Awdi A and Hasan NS. Pattern and clinical profile of thalassemia among pediatric patients attending the Yemeni Society Centers for Thalassemia and Genetic Blood Disorders in Yemen. Sci J Al-Azhar Med Fac Girls. 2017;1(2):43. https://doi.org/10.4103/sjamf.sjamf_15_17
12. Sharma S and Bezboruah G. Prevalence of short stature in transfusion-dependent beta thalassemia patients in a tertiary care centre in North East India. J Family Med Prim Care. 2022;11(6):2516-2520. https://doi.org/10.4103/jfmpc.jfmpc_2120_21
13. Weatherall DJ, Williams TN, Allen SJ and O'Donnell A. The population genetics and dynamics of the thalassemias. Hematol Oncol Clin North Am. 2010;24(6):1021-1031. https://doi.org/10.1016/j.hoc.2010.08.010
14. Brancaleoni V, Di Pierro E, Motta I and Cappellini MD. Laboratory diagnosis of thalassemia. Int J Lab Hematol. 2016;38(Suppl 1):32-40. https://doi.org/10.1111/ijlh.12527
15. Skordis N and Kyriakou A. The multifactorial origin of growth failure in thalassaemia. Pediatr Endocrinol Rev. 2011;8(Suppl 2):271-277.
16. Galanello R, Piras S, Barella S, Leoni GB, Cipollina MD, Perseu L, et al. Cholelithiasis and Gilbert's syndrome in homozygous beta-thalassemia. Br J Haematol. 2001;115(4):926-928. https://doi.org/10.1046/j.1365-2141.2001.03200.x
17. Origa R. β-Thalassemia. Genet Med. 2017;19(6):609-619. https://doi.org/10.1038/gim.2016.173

Authors Contribution:
CS- Concept and design of the study, results interpretation, review of the literature, and preparing the first draft of the manuscript. Statistical analysis and interpretation, revision of the manuscript; **BPPS-** Concept and design of the study, results interpretation, review of the literature, and preparing the first draft of the manuscript, revision of the manuscript; **SSM-** Review of the literature and preparing the first draft of the manuscript. Statistical analysis and interpretation; **RK-** Concept and design of the study, results interpretation, review of the literature, and preparing the first draft of the manuscript. Statistical analysis and interpretation and revision of the manuscript.

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