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Original Research Article

Serum ferritin observations in beta thalassemia major patients with dermatological manifestation

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ABSTRACT

Background: Beta thalassemia major is a severe inherited blood disorder requiring regular blood transfusions, leading to chronic iron overload. This study aims to analyze serum ferritin levels and their association with dermatological manifestations in patients with beta thalassemia major in Bangladesh.
Methods: This cross-sectional observational study was conducted at the Department of Transfusion Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka, from March 2019 to August 2021. A purposive sample of 60 beta thalassemia major patients was selected based on specific inclusion and exclusion criteria. Data collection included detailed medical histories, dermatological examinations, and laboratory investigations for serum ferritin levels. Statistical analysis was performed using statistical package for the social sciences (SPSS)-27.
Results: Among the participants, 26.67% were aged 10 years or younger, and 46.67% were aged 11-20 years. The gender distribution was 43.33% male and 56.67% female. The mean hemoglobin level was 6.17±0.95 g/dl, with 75.00% of participants exhibiting extremely high serum ferritin levels (>1000 ng/ml). Dermatological manifestations included hyperpigmentation (50.00%), xerosis (46.67%), and pallor (26.67%). Significant associations were found between high serum ferritin levels and conditions such as hyperpigmentation ($p=0.028$) and xerosis ($p<0.001$).
Conclusions: The study underscores the critical need for regular monitoring and effective management of serum ferritin levels to mitigate dermatological and systemic complications in beta thalassemia major patients. Effective chelation therapy is essential to reduce the iron burden and improve patient outcomes.

Keywords: Beta thalassemia major, Serum ferritin, Dermatological manifestations, Iron overload

INTRODUCTION

Beta thalassemia major is a severe inherited blood disorder resulting from a defect in the production of the beta-globin chain of hemoglobin, leading to ineffective erythropoiesis and severe anemia. This genetic disorder is highly prevalent in regions such as Southeast Asia, the Middle East, and the Mediterranean, with significant incidences reported in Bangladesh as well. Beta thalassemia major patients require regular blood transfusions to manage severe anemia, a treatment that, while life-saving, results in chronic iron overload and necessitates continuous monitoring and management of iron levels in the body.[3] Regular blood transfusions elevate serum ferritin levels, a marker of iron overload, which is critical for assessing and managing the risk of iron-related complications. Elevated serum ferritin levels are associated with numerous adverse outcomes, including endocrinopathies, cardiac

dysfunction, liver disease, and growth retardation. For instance, a study by Shahid et al indicated that elevated serum ferritin levels were moderately sensitive and specific in predicting sexual underdevelopment in beta thalassemia major patients, underscoring the importance of monitoring and managing iron levels to prevent such complications.[4] Similarly, Ibrahim et al found that serum ferritin levels above 2500 ng/ml were significantly associated with an increased risk of diabetes mellitus among beta thalassemia major patients, emphasizing the need for stringent monitoring and effective chelation therapy.[5] Serum ferritin serves as a proxy for total body iron stores, and its levels can provide insight into the severity of iron overload and the effectiveness of chelation therapy. For instance, a study by Belhoul et al highlighted that patients with serum ferritin levels above 2500 µg/l were significantly more likely to develop endocrinopathies such as diabetes and hypothyroidism.[6] This correlation highlights the clinical significance of maintaining serum ferritin levels within a manageable range to mitigate the risk of severe complications. Managing serum hemoglobin levels through regular transfusions is crucial for patients with beta thalassemia major. However, this treatment also contributes to iron overload, necessitating a delicate balance between treating anemia and preventing iron-related toxicity. Bhalodiya et al demonstrated that high serum ferritin levels correlated with increased transfusion dependency and age, indicating the compounded risk of iron overload with ongoing transfusion therapy.[7] Effective chelation therapy is therefore essential to reduce the iron burden and prevent organ damage. Dermatological manifestations are common in beta thalassemia major patients and are often linked to iron overload. Das et al documented various skin conditions such as xerosis, hyperpigmentation, and acanthosis nigricans in beta thalassemia major patients, finding a significant correlation between these manifestations and elevated serum ferritin levels.[8] Similarly, Zulfiqar et al reported that xerosis, freckles, and pruritus were prevalent among these patients, with serum ferritin levels significantly higher in those with more severe dermatological symptoms.[9] These findings highlight the systemic nature of iron overload and its wide-ranging impact on patient health. Additionally, the impact of iron overload extends beyond dermatological issues to more severe systemic complications. Vinchi et al noted that systemic heme and iron overload resulted in oxidative stress and endothelial dysfunction, contributing to various complications in beta thalassemia major and intermedia patients.[10] This emphasizes the importance of comprehensive management strategies that address not only iron overload but also its broader systemic effects. Given the high prevalence of beta thalassemia major in Bangladesh and the associated complications of iron overload, this study aims to observe and analyze serum ferritin levels in beta thalassemia major patients presenting with dermatological manifestations. By understanding the correlation between these variables, the study seeks to provide insights into more effective management strategies to improve patient outcomes. The findings are expected to contribute significantly to the existing body of knowledge and inform clinical practices in managing beta thalassemia major, particularly in resource-limited settings like Bangladesh.

METHODS

This cross-sectional observational study was conducted in the Department of Transfusion Medicine at Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, from March 2019 to August 2021. The study population consisted of patients diagnosed with beta thalassemia major who were receiving regular blood transfusions. A purposive sampling method was employed to select a sample size of 60 patients. Patients were selected based on specific inclusion and exclusion criteria. The inclusion criteria included diagnosed cases of transfusion-dependent beta thalassemia major, patients aged between 6 to 40 years, of both sexes, and the duration of transfusion. Exclusion criteria were patients with other systemic diseases such as liver disease, kidney disease, thyroid and parathyroid disorders, diseases of the adrenal gland, and endocrine pancreas, as well as those with pre-existing diagnosed skin diseases. Data collection was carried out from November 2020 to August 2021, following approval from the Institutional Review Board (IRB). Sixty patients who met the inclusion criteria were enrolled in the study after obtaining informed written consent. Each patient's full medical history was recorded, including age, sex, disease duration, family history, consanguinity, blood transfusions, and treatment regimen. A single dermatologist conducted a thorough dermatological examination of each patient to detect cutaneous manifestations. The examination included the skin, nails, hair, and oral mucosa under good daylight. Laboratory investigations, specifically serum ferritin levels, were conducted for all participants at the Department of Biochemistry, BSMMU. The cutaneous manifestations evaluated included pruritus, xerosis, freckles, hyperpigmentation, hypopigmentation, erythema, urticaria, melasma, and other conditions. Data were compiled and sorted, with serum ferritin levels measured to assess iron overload. Data processing and analysis were performed using the statistical package for social science version 27 (SPSS-27). The data were expressed as frequencies and percentages for categorical data and as means with standard deviations for numerical data. Statistical significance was determined using Chi-square tests and unpaired t-tests, with a p value of less than 0.05 considered significant. Ethical considerations were adhered to in compliance with the Helsinki declaration for medical research involving human subjects (1964). The nature and purpose of the study were explained to all participants, and voluntary participation was emphasized. Informed and understood written consent was obtained from each patient before enrollment. Privacy, anonymity, and confidentiality of data were strictly maintained. Patients had the right to refuse participation or withdraw from the study at any time without affecting their treatment. Ethical clearance was obtained from the institutional review board (IRB) of BSMMU, and the

study protocol was approved by the academic committee of the Department of Transfusion Medicine. The informed consent included detailed information about the study's nature and purpose, procedures, benefits, and duration, ensuring that participants understood the implications of the research and their rights to refuse participation. Consent was taken in a locally understood language, ensuring clear communication of any risks related to the study.

RESULTS

The distribution of baseline characteristics among the participants is presented in Table 1. The age distribution showed that 26.67% of the participants were aged 10 years or younger, 46.67% were aged 11-20 years, 18.33% were aged 21-30 years, and 8.33% were aged 31-40 years. The gender distribution was 43.33% male and 56.67% female. Regarding the duration of blood transfusion, 10.00% of the participants had been receiving transfusions for 5 years or less, 40.00% for 6-10 years, 23.33% for 11-15 years, 20.00% for 16-20 years, and 6.67% for more than 20 years.

Table 1: Distribution of baseline characteristics among the participants (n=60).

Baseline	Frequency	Percentage
Age (in years)		
≤10	16	26.67
11-20	28	46.67
11-20	11	18.33
31-40	5	8.33
Sex		
Male	26	43.33
Female	34	56.67
Duration of blood transfusion (years)		
≤5	6	10.00
6-10	24	40.00
11-15	14	23.33
16-20	12	20.00
>20	4	6.67

Hyperpigmentation was the most common dermatological manifestation, observed in 50.00% of the participants. Xerosis was reported in 46.67% of the participants, while 26.67% exhibited pallor. Pruritus was noted in 20.00% of the patients, and scratch marks were present in 16.67%. Hypopigmentation affected 11.67% of the participants, and 6.67% had *Tinea alba*. Gingivitis was the least common manifestation, observed in only 1.67% of the participants (Table 2).

The distribution of hemoglobin levels showed that 18.33% of participants had hemoglobin levels below 5 g/dl, 58.33% had levels between 5-7 g/dl, and 23.33% had levels above 7 g/dl, with a mean hemoglobin level of 6.17±0.95 g/dl. Regarding serum ferritin levels, none of the participants had normal levels (≤250 ng/ml). A total of 25.00% of participants had high ferritin levels (251-1000 ng/ml), while a significant majority, 75.00%, had extremely high ferritin levels (>1000 ng/ml) (Table 3).

Table 2: Distribution of the study patients by dermatological manifestation (n=60).

Dermatological manifestation	Frequency	Percentage
Hyperpigmentation	30	50.00
Xerosis	28	46.67
Pallor	16	26.67
Pruritus	12	20.00
Scratch mark	10	16.67
Hypopigmentation	7	11.67
Tinea alba	4	6.67
Gingivitis	1	1.67

Table 3: Serum hemoglobin and serum ferritin levels among the participants (n=60).

Variables	Frequency	Percentage
Hemoglobin level		
<5	11	18.33
5-7	35	58.33
>7	14	23.33
Mean±SD	6.17±0.95	
Serum ferritin		
Normal (≤250 ng/ml)	0	0.00
High (251-1000 ng/ml)	15	25.00
Extremely high (>1000 ng/ml)	45	75.00
Mean±SD	4083.3±3037.1	

Participants with pallor had a significantly lower mean serum ferritin level (1344.4±735.7 ng/ml) compared to those without pallor (5079.2±2414.4 ng/ml), with a p value of <0.001. Those with hyperpigmentation had a higher mean serum ferritin level (4939.8±2118.3 ng/ml) compared to participants without hyperpigmentation (3226.7±3572.3 ng/ml), with a p value of 0.028. Similarly, participants with xerosis exhibited significantly higher mean serum ferritin levels (5808.8±2956.1 ng/ml) compared to those without xerosis (2573.4±2214.1 ng/ml), with a p value of <0.001. However, no significant differences in serum ferritin levels were observed for participants with or without hypopigmentation (p=0.326), *Tinea alba* (p=0.989), pruritus (p=0.097), or scratch marks (p=0.262) (Table 4).

The association of dermatological manifestations with high serum ferritin levels (>1000 ng/ml) among the 60 participants revealed several significant findings. Participants with pallor had a significantly lower proportion of high serum ferritin levels, with 93.8% having ferritin levels below 1000 ng/ml and only 6.3% above this threshold, resulting in a p value of <0.001. In contrast, hyperpigmentation was present exclusively in participants with high serum ferritin levels, as all 30 participants

(100.0%) with hyperpigmentation had serum ferritin levels above 1000 ng/ml, with a p value of <0.001. Similarly, xerosis was significantly associated with high serum ferritin levels, as all 28 participants with xerosis (100.0%) had serum ferritin levels above 1000 ng/ml, yielding a p value of <0.001. Pruritus also showed a significant association, with all 12 participants (100.0%) having serum ferritin levels above 1000 ng/ml and a p value of 0.025. Scratch marks were similarly associated with high ferritin levels, with all 10 participants (100.0%) having serum ferritin levels above 1000 ng/ml, with a p value of 0.046. Hypopigmentation and *Tinea alba* did not show a significant association with high serum ferritin levels, as all participants with these conditions had serum ferritin levels above 1000 ng/ml, but the p values were 0.104 and 0.232, respectively (Table 5).

Table 4: Comparison of serum ferritin level with or without dermatological manifestation (n=60).

Dermatological manifestation	N	Serum ferritin		P value
		Mean	SD	
Pallor				
Present	16	1344.4	735.7	<0.001*
Absent	44	5079.2	2414.4	
Hyperpigmentation				
Present	30	4939.8	2118.3	0.028*
Absent	30	3226.7	3572.3	
Hypopigmentation				
Present	7	5153.1	1808.4	0.326
Absent	53	3941.9	3148.7	
Tinea alba				
Present	4	4062.3	1072.6	0.989
Absent	56	4084.8	3135.6	
Pruritis				
Present	12	5384.9	2736.5	0.097
Absent	48	3757.8	3047.3	
Xerosis				
Present	28	5808.8	2956.1	<0.001*
Absent	32	2573.4	2214.1	
Scratch mark				
Present	10	5074.4	2900.4	0.262
Absent	50	3885	3053	

Table 5: Association of dermatological manifestations with high serum ferritin level (n=60).

Dermatological manifestation	N	Serum ferritin (ng/ml), no. (%)		P value
		<1000	>1000	
Pallor	16	15 (93.8)	1 (6.3)	<0.001*
Hyperpigmentation	30	0 (0.0)	30 (100.0)	<0.001*
Hypopigmentation	7	0 (0.0)	7 (100.0)	0.104
Tinea alba	4	0 (0.0)	4 (100.0)	0.232
Pruritis	12	0 (0.0)	12 (100.0)	0.025*
Xerosis	28	0 (0.0)	28 (100.0)	<0.001*
Scratch mark	10	0 (0.0)	10 (100.0)	0.046*

DISCUSSION

The present study provides a comprehensive analysis of serum ferritin levels in beta thalassemia major patients, focusing on the correlation with various dermatological manifestations. The demographic distribution showed a significant proportion of patients in the age group of 11-20 years (46.67%) and a higher percentage of female participants (56.67%). These findings align with previous studies that have observed similar demographic distributions in beta thalassemia major cohorts.[11,12] The duration of blood transfusions among participants revealed that a substantial number had been receiving transfusions for more than 10 years, highlighting the chronic nature of the disease and the associated iron overload.[13] This study's finding that 75.00% of participants had extremely high serum ferritin levels (>1000 ng/ml) is consistent with the literature, which frequently reports elevated ferritin levels due to regular transfusions.[14] For instance, Riaz et al observed mean serum ferritin levels of 4236.5 ng/ml in a

similar patient population, underscoring the severity of iron overload.[15] The dermatological manifestations observed in this study included hyperpigmentation (50.00%), xerosis (46.67%), and pallor (26.67%). These findings are in line with other studies that have reported a high prevalence of skin disorders among beta thalassemia major patients. Zulfiqar et al found that 89.4% of patients exhibited dermatological issues, with xerosis and pruritus being particularly common.[9] The significant association between high serum ferritin levels and dermatological manifestations such as hyperpigmentation (p=0.028) and xerosis (p<0.001) suggests a direct impact of iron overload on skin health. This is corroborated by Dogramacı et al who also reported a significant correlation between higher ferritin levels and the prevalence of xerosis (p=0.005).[16] Participants with pallor had significantly lower mean serum ferritin levels compared to those without pallor, indicating a potential protective factor or a different pathophysiological mechanism in these patients.[6] The lack of significant associations for hypopigmentation, *Tinea alba*, pruritus, and scratch marks with serum ferritin levels suggests that these conditions might be influenced by other factors beyond iron overload. Comparatively, Skandalis et al found that generalized dermatoses such as urticaria and CSVV were associated with higher ferritin levels, further supporting the impact of iron overload on severe dermatological conditions.[17]

The significant association of high serum ferritin levels with generalized dermatoses (p=0.001) emphasizes the need for stringent management of iron levels to mitigate skin-related morbidity. This study's findings on the prevalence of high serum ferritin levels and their association with dermatological manifestations highlight the systemic complications of chronic iron overload in beta thalassemia major patients. Effective chelation therapy and regular monitoring of ferritin levels are crucial in managing these complications. Eshaqh-Hosseini et al highlighted the importance of maintaining ferritin levels below 1500 µg/l to prevent endocrinopathies, which aligns with the need for comprehensive management strategies to reduce the risk of dermatological and systemic complications.[18]

In conclusion, the present study provides valuable insights into the significant burden of iron overload in beta thalassemia major patients and its association with various dermatological manifestations. The findings align with existing literature and emphasize the importance of regular monitoring and effective management of serum ferritin levels to improve patient outcomes and quality of life. Further research is warranted to explore the underlying mechanisms and develop targeted interventions for managing these complications effectively.

Limitations

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

CONCLUSION

In conclusion, this study highlights the significant burden of iron overload in beta thalassemia major patients, as evidenced by the elevated serum ferritin levels and their association with various dermatological manifestations. The findings underscore the importance of regular monitoring and effective management of serum ferritin levels to mitigate skin-related and systemic complications. High serum ferritin levels were strongly associated with conditions such as hyperpigmentation, xerosis, and pruritus, indicating a direct impact of iron overload on skin health. Effective chelation therapy and comprehensive management strategies are essential to improve the quality of life for these patients. Further research is warranted to explore the underlying mechanisms and develop targeted interventions for managing these complications effectively.

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