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Original Research Article

# An Observational Study to Evaluate Dermatological Manifestations of Beta Thalassemia Major Children Aged 2 to 12 Years and their Connection to Serum Ferritine Levels

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**Abstract**

**Aim:** The aim of the present study to evaluate the dermatological manifestations in beta thalassemia major patients between 2 to 12 years and their relation with serum ferritine level. **Methods:** The descriptive observational study was conducted in the Upgraded Department of Paediatrics, Patna Medical College and Hospital, Patna, Bihar, India for 12 months. 100 children with beta thalassemia between 2 to 12 years age already diagnosed by HPLC or Hb electrophoresis already transfused 10 units of blood were included in this study. **Results:** xerosis was the most common (67%) dermatological change amongst the study subjects, followed by skin hyperpigmentation (55%). Acanthosis nigricans was also found in 10% patients, pityriasis versicolor and alba, accounted for 14% of all the skin changes seen. Urticaria was another important skin change noted in 6% study children. dermatological changes were present in all children amongst the study group who were having a serum ferritin level more than 1000 mcg/dl and in 85.71% children having less than 1000mcg/ dl. This finding is found statistically significant ($p<0.05$). dermatological changes and amongst the age group of 5 to 8 years and <5years, dermatological changes were found in 93.33% and 92.5% cases respectively. dermatological changes amongst them (100%) but 94.44% children who were having malnutrition were found to have dermatological changes amongst them. amongst the study children 71.43% whose serum ferritin level were below 1000mcg/ dl had Xerosis and those children whose serum ferritin level were between 1000-2000 mcg/dl and more than 2000 mcg/dl, Xerosis was found in 64.44% and 55% respectively. Hyperpigmentation was found more commonly in those study children who had serum ferritin level in the higher side i.e. 65% who had serum ferritin level more than 2000 mcg/dl, 53.33% who had between 1000 to 2000 and 45.71% who had less than 1000 mcg/dl. Pityriasis were found more (15%) amongst the study children who had Serum Ferritin level more than 2000 mcg/dl than who had Serum Ferritin between 1000 to 2000 (13.33%) and who had less than 1000 mcg/dl. **Conclusion:** The Beta-thalassemia major is equally distributed amongst male and female subjects in the present study. A relationship also found between hyperpigmentation and Pityriasis with serum ferritin level, but it was statistically insignificant. Further study with larger sample size is needed.

**Key words:** serum ferritine level.

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## Introduction

Thalassemias are a group of disorders that are attributable to the defective synthesis of the a- and b-globin polypeptides of hemoglobin. In b-thalassemias, impaired synthesis of b-globin chains results in unpaired a-globin chains, which are unstable in erythroid precursors, where they precipitate and cause membrane injury. This in turn causes ineffective erythropoiesis, triggers erythroid apoptosis and, in turn, leads to anemia.[1] Patients suffering the most severe form, indicated as b-thalassemia major, require chronic blood transfusion for survival. Patients associated with a milder phenotype, non-transfusion-dependent thalassemia (NTDT), produce comparatively higher levels of hemoglobin and might require only sporadic transfusions.[2] NTDT comprises a range of disorders, including b-thalassemia intermedia, a-thalassemia (mainly HbH disease), HbE/b-thalassemia, HbS/b-thalassemia and HbC thalassemia.[3] b-thalassemia is the most common single-gene disorder worldwide, in which hemoglobin b-chain production is decreased. Today, the life expectancy of thalassemia patients is increased because of a variety of treatment methods; however, treatmentrelated complications have also increased.[4] Profound anemia and severe hemosiderosis cause functional and physiologic abnormalities in various organ systems.[5] Thalassemia syndromes are inherited disorders of alpha or beta globin biosynthesis. In beta thalassemia minor (TI) disease there is one defective beta-globin gene, and in beta-thalassemia major (TMJ) disease, there are two defective beta globin genes.[6] Clinical features of beta thalassemia vary between subgroups. Beta thalassemia minor is usually clinically asymptomatic, whereas infants with TMJ usually have anemia after three months.[7] It was seen growth retardation, ridging in the nasal root, prominence of maxillae, and Mongoloid facial appearance in patients without the appropriate transfusion. The dysfunctions of the organs are due to iron build-up and inadequate oxygenation, and the number of complications increases with age.[7]

## Material and methods

The descriptive observational study was conducted in the Upgraded Department of Paediatrics, Patna Medical College and Hospital, Patna, Bihar, India for 12 months after taking the approval of the protocol review committee and institutional ethics committee.

Methodology

### Inclusion criteria

100 children with beta thalassemia between 2 to 12 years age already diagnosed by HPLC or Hb electrophoresis already transfused 10 units of blood were included in this study.

### Exclusion criteria

- Patients having other systemic diseases with dermatological manifestation.
- Patients aged less than 2 years of age and more than 12 years.
- Patients having pre-existing diagnosed skin disease.

Dermatological examination and serum ferritin level were studied.

### Statistical analysis

Data's were entered in Microsoft excel sheet. Then it was analysed by SPSS version 20 software. Data's were further presented by using principles of descriptive statistics that is frequency and percentage. Categorical outcome variables

were tested using chi-square test and student t test.

## Results

**Table 1: Distribution of different Dermatological changes n=100**

| Dermatological changes | Frequency=100 | Percentage |
|---|---|---|
| Xerosis | 67 | 67 |
| Hyperpigmentation | 55 | 55 |
| Acanthosis nigricans | 10 | 10 |
| Pityriasis versicolor & alba | 14 | 14 |
| Urticaria | 6 | 6 |
| Others# | 20 | 20 |

**Others include:**

moluscum contagiosum, diffuse hair loss, nail brittleness, oral mucosal hyperpigmentation, freckles, acne form eruption, milliaria, pompholyx.

Table 1 shows that, among all study subjects xerosis was the most common dermatological changes found followed by hyperpigmentation (includes both fore head hyper-pigmentation and generalised hyperpigmentation), pityriasis versicolor & alba, acanthosis nigricans, urticaria and others in descending order.

**Table 2: Mean values of some important parameters of the study n=100**

| Variables | Minimum | Maximum | Mean | Std. Deviation |
|---|---|---|---|---|
| **Age (years)** | 2 | 13 | 7.02 | 3.11 |
| **Weight (kg)** | 7.5 | 40.5 | 18.22 | 6.23 |
| **Height (inches)** | 28.5 | 60.5 | 41.33 | 8.22 |
| **Last hemoglobin (gm/dl)** | 3.3 | 10.3 | 4.98 | 1.36 |
| **Serum ferritin (mcg/dl)** | 120 | 3987 | 1498.36 | 1125.02 |
| **Liver (cm)** | 5.2 | 10.3 | 7.66 | 1.32 |
| **Spleen (cm)** | 0 | 19 | 5.88 | 3.78 |

Table 2 depicts that, mean weight of the study children was 18.22 kg. Whereas, the mean age of the study children was 7.02 years, mean height was 41.33 inches. It is also seen that the mean level of serum ferritin was 1498.36 mcg/dl. Mean measurement of the liver span and spleen (below left costal margin) were 7.66 cm and 5.88 cm respectively.

**Table 3: Distribution of dermatological changes among study children in relation to their serum ferritin level. n=100**

| Serum ferritin(mcg/dl) | Dermatological changes | | Total |
|---|---|---|---|
| | Present | Absent | |
| < 1000 | 30 (85.71%) | 5 (14.29%) | 35 (100%) |
| 1000 – 2000 | 45 (100.0%) | 0 (0.0%) | 45(100%) |
| > 2000 | 20 (100%) | 0 (0.0%) | 20 (100%) |
| **Total** | **95 (95%)** | **5 (5%)** | **100(100%)** |

Chi-Square value = 6.74, df = 2, **p value = 0.041**

Table 3 shows that, dermatological changes were present in all children amongst the study group who were having a serum ferritin level more than 1000 mcg/dl and in 85.71% children having less than 1000mcg/ dl. This finding is found statistically significant (p<0.05).

**Table 4: Distribution of dermatological changes among study children in relation to their age group. n=100**

| Age group (years) | Dermatological changes | | Total |
|---|---|---|---|
| | Present | Absent | |
| < 5 | 37(92.5%) | 3(7.5%) | 40 (100%) |
| 5 – 8 | 28 (93.33%) | 2 (6.67%) | 30(100%) |
| > 8 | 30 (100%) | 0 (0.0%) | 30 (100%) |
| **Total** | **95(92%)** | **5 (5%)** | **100 (100%)** |

Chi-Square value = 1.78, df = 2, p value = 0.41

From the table 4 we came to know that, all the children amongst study who were above the age of 8 years had dermatological changes and amongst the age group of 5 to 8 years and <5years, dermatological changes were found in 93.33% and 92.5% cases respectively. The findings were found statistically not significant (p > 0.05)

**Table 5: Distribution of dermatological changes among study children in relation to their nutritional status. n=100**

| Malnutrition | Dermatological changes | | Total |
|---|---|---|---|
| | Present | Absent | |
| Present | 85 (94.44%) | 5 (5.56%) | 90 (100%) |
| Absent | 10(100%) | 0 (0.0%) | 10 (100%) |
| **Total** | **95 (95%)** | **5 (5%)** | **100 (100%)** |

Chi-Square value = 0.298, df = 1, p value = 0.514

Table 5 shows that, though most of the children under the study group were malnourished but all of thetiny group of well nourished children were found to have some dermatological changes amongst them (100%) but 94.44% children who were having malnutrition were found to have dermatological changes amongst them. The findings were statistically not significant (p<0.05).

**Table 6: Distribution of dermatological changes among study children in relation to their last hemoglobin level (Pretransfusion). n=100**

| Hemoglobin level(gm/dl) | Dermatological changes | | Total |
|---|---|---|---|
| | Present | Absent | |
| < 5 | 27 (93.10%) | 2 (6.90%) | 29 (100%) |
| 5 – 7 | 62 (95.38%) | 3 (4.62%) | 65 (100%) |
| “ 8 | 6 (100.0%) | 0 (0.0%) | 6 (100%) |
| **Total** | **95 (95%)** | **5(5%)** | **100(100%)** |

Chi-Square value = 0.298, df = 2, p value = 0.786

Table 6 shows that, all children who were having last hemoglobin (Pretransfusion) level more than or equals to 8 gm/dl had dermatological findings and 95.38% of those who were having last 7 gm/dl or less haddermatological changes. The findings were statistically not significant (p>0.05).

**Table 7: Distribution of dermatological changes among study children in relation to their spleen size. n=100**

| Spleen size (cm) | Dermatological changes | | Total |
|---|---|---|---|
| | Present | Absent | |
| Splenectomy done | 7 (100%) | 0 (0.0%) | 7 (100%) |
| 1 – 3 | 21 (84%) | 4 (16%) | 25(100%) |
| 4 – 7 | 36 (97.30%) | 1 (2.70%) | 37 (100%) |
| “ 8 | 31 (100.0%) | 0 (0.0%) | 31 (100%) |
| **Total** | **95 (95%)** | **5 (5%)** | **100 (100%)** |

Chi-Square value = 3.54, df = 3,p value = 0.339

Table 7 shows that, all those who had spleen size more than or equal to 8cm measured from left costalmargin along the splenic axis amongst the study group, had dermatological changes and 97.30% and 84% among those who had 4cm to 7cm and below 4cm spleen size respectively had dermatological changes. The findings was statistically not significant (p>0.05).

**Table 8: Relation between Serum Ferritin and Xerosis**

| Serum ferritin(mcg/dl) | Xerosis | | Total |
|---|---|---|---|
| | Present | Absent | |
| < 1000 | 25 (71.43%) | 10 (28.57%) | 35 (100%) |
| 1000 – 2000 | 29 (64.44%) | 16 (35.56%) | 45(100%) |
| > 2000 | 11 (55%) | 9 (45%) | 20 (100%) |
| **Total** | **65 (65%)** | **35 (35%)** | **100(100%)** |

Chi-Square value = 0.523, df = 2,p value = 0.697

Table 8 shows that, amongst the study children 71.43% whose serum ferritin level were below 1000mcg/ dl had Xerosis and those children whose serum ferritin level were between 1000-2000 mcg/dl and more than 2000 mcg/dl, Xerosis was found in 64.44% and 55% respectively. The finding was statistically insignificant (p>0.05).

**Table 9: Relation between Hyperpigmentation and Serum Ferritin level**

| Serum ferritin(mcg/dl) | Hyperpigmentation | | Total |
|---|---|---|---|
| | Present | Absent | |
| < 1000 | 16 (45.71%) | 19(54.29%) | 35 (100%) |
| 1000 – 2000 | 24 (53.33%) | 21 (46.67%) | 45(100%) |
| > 2000 | 13 (65%) | 7 (35%) | 20 (100%) |
| **Total** | **53 (53%)** | **47 (47%)** | **100(100%)** |

Chi-Square value = 1.721, df = 2,p value = 0.459

Table 9 shows that, Hyperpigmentation were found more commonly in those study children who had serum ferritin level in the higher side i.e. 65% who had serum ferritin level more than 2000 mcg/dl, 53.33% who had between 1000 to 2000 and 45.71% who had less than 1000 mcg/dl. The finding was not statistically significant (p>0.05).

**Table 10: Relation between Serum Ferritin and Pityriasis.**

| Serum ferritin(mcg/dl) | Pityriasis | | Total |
|---|---|---|---|
| | Present | Absent | |
| < 1000 | 2 (5.71%) | 33 (94.29%) | 35 (100%) |
| 1000 – 2000 | 6 (13.33%) | 39 (86.67%) | 45(100%) |
| > 2000 | 3 (15%) | 17 (85%) | 20 (100%) |
| **Total** | **11 (11%)** | **89(89%)** | **100(100%)** |

Chi-Square value = 1.397, df = 2,p value = 0.463
Table 10 shows that Pityriasis were found more (15%) amongst the study children who had Serum Ferritin level more than 2000 mcg/dl than who had Serum Ferritin between 1000 to 2000 (13.33%) and who had less than 1000 mcg/dl. The finding was statistically not significant (p>0.05).

**Table 11: Relation between Serum Ferritin and Acanthosis nigricans**

| Serum ferritin(mcg/dl) | Acanthosis nigricans | | Total |
|---|---|---|---|
| | Present | Absent | |
| < 1000 | 0(0%) | 35 (100%) | 35 (100%) |
| 1000 – 2000 | 10 (22.22%) | 35 (77.78%) | 45(100%) |
| > 2000 | 2(10%) | 18 (90%) | 20 (100%) |
| **Total** | **12 (12%)** | **88 (88%)** | **100(100%)** |

Chi-Square value = 3.726, df = 2,p value = 0.139
Table 11 shows that, Acanthosis nigricans were not present amongst the study children who had serum ferritin level <1000 mcg/dl, present amongst 22.22% who had between 1000 to 2000 and amongst 10% who had more than 2000 mcg/dl. The finding was statistically insignificant (p>0.05).

**Table 12: Relation between Serum Ferritin level and Urticaria**

| Serum ferritin(mcg/dl) | Urticaria | | Total |
|---|---|---|---|
| | Present | Absent | |
| < 1000 | 0 (0%) | 35 (100%) | 35 (100%) |
| 1000 – 2000 | 0 (0%) | 45(100%) | 45(100%) |
| > 2000 | 3 (15%) | 17(85%) | 20 (100%) |
| **Total** | **3 (3%)** | **97 (97%)** | **100(100%)** |

Chi-Square value = 9.01, df = 2,p value = 0.011
Table 12 shows that Urticaria was only present amongst the study children who had a serum ferritin level more than 2000 mcg/dl and the finding was statistically **significant (p<0.05).**

## Discussion

Amongst the total 100 patients, male to female ratio was 1.5:1. Dermatological changes were found amongst 94% study children and were more frequently seen in females (96%).Children belonging to older age group showed increased frequency (100% in >8years) of dermatological changes.

Similar related study by Al-Rubiay KK et al. conducted among 195 thalassemia patients in Iraq, noted dermatological changes among all subjects.[8]

Another study done by Dogramaci A.C. et al. in Turkey, among 78 thalassemic children dermatological changes were noted in 83.3% study subjects, and males showed much higher frequency (64.1%) than females (35.9%).[9] In the present study, subjects having pre- transfusion haemoglobin level e”8gm/dl had increased frequency of dermatological changes. Dermatological changes were also more common among study groups with more hepatic span (e”7cm liver span), as well as with large spleen size (e”8cm measured from left costal margin along splenic axis).

No relationship was found between nutritional status of the study subjects with dermatological change.

In the present study, xerosis was the most common (67%) dermatological change amongst the study subjects, followed by skin hyperpigmentation (55%). Xerosis, the most common (65%) dermatological change among thalassemia major patients by Al-Rubiay KK et al. in Iraq, was comparable to our study.[8] Bronzy coloured skin (53%) was the second most common dermatological change noted in their study, but similar skin changes was not found in the present study subjects. Another study by Momeni A et al. also showed xerosis as the most common (53%) dermatological change manifested among beta- thalassemia major subjects in Iran.[10] Dogramaci A.C. et al. noted xerosis in 34.6% study subjects in Turkey.[9] The cause of xerosis may be due to excess iron storage in the body.[11] Hyperpigmentation was found in 55% study subjects in the study done by Al-Rubiay KK et al. in Iraq.[8] Momeni A et al. noticed hyperpigmentation at the injection site of desferral administration among 30% study subjects.[10] Idiopathis Guttate Hypermelanosis was noticed amongst 6.4% subjects in the study done by Dogramaci AC et al.[9] The cause of hyperpigmentation may be due to cutaneous Iron deposition which subsequently damages the skin and also enhances melanin production.[12]

In the current study, generalised hyperpigmentation was more frequent (53%) as compared to most of the other studies. Higher incidence is probably due to irregular chelation therapy and higher iron overloaded state in our study subjects. Moreover, isolated hyperpigmentation on forehead was noted among four study subjects (7%) and such finding was not noted in any other earlier studies as per literature search in English language with the best of efforts. Cause of this isolated hyperpigmentation could not be explained.

Acanthosis nigricans was also found in 10% patients, pityriasis versicolor and alba, accounted for 14% of all the skin changes seen. Urticaria was another important skin change noted in 6% study children.

Other less common dermatological changes included moluscum contagiosum, diffuse hair loss, nail brittleness, oral mucosal hyperpigmentation, freckles, acne form eruption, milliaria, pompholyx. However, Naderi M. et al. in 2013, reported freckles (70.7%) as the most common dermatological finding amongst their patients with beta-thalassemia major, in Iran.[13] Another study by Dogramaci A.C et al reported pruritus (37.2%) as the most common dermatological changes followed by xerosis (34.6%) and scarring (24.4%) in their study subjects in Turkey.[9] The present study was aimed at elucidating the correlation between serum ferritin and skin manifestations in the patients suffering from beta thalassemia major, and to see if at all, a high serum ferritin level may preclude a skin manifestation or vice-versa.

Aessopos A. et al, found 26% of the study subjects had either angioid streaks or pseudoxanthoma elasticum skin lesions or both.[14] However, no relation was found between these skin lesions with serum ferritin levels. Dogramaci A.C et al. found higher mean serum ferritin level among patients with xerosis.[9]

In the present study, xerosis was the most common dermatological manifestation, but no relation between xerosis and serum ferritin level was found. Hyperpigmentation (generalised and isolated forehead), was the second most common dermatological change found in the present study and was directly proportional with serum ferritin levels. However, this finding was statistically not significant ($p>0.05$).

Urticaria was seen in 6% of study children. Moreover, urticaria was found only in those patient who had serum ferritin level more than 2000 mcg/ dl and the correlation was found to be statistically significant ($p<0.05$). Dogramaci A.C et al also found urticaria among 3.8% study population.

The average incidence of urticaria among Indian children is around 2.5%.[15] [The higher incidence of urticaria among our study groups may be due the allergic reaction in response to plasma proteins following repeated blood transfusion.[16]

Pityriasis versicolor and pityriasis alba was also found to be directly proportional with serum ferritin level, but the correlation was statistically insignificant ($p>0.05$).

Acanthosis Nigricans was found in 10% of study subjects, and not correlated to the serum ferritin level.

## Conclusion

The Beta-thalassemia major is equally distributed amongst male and female subjects in the present study. A relationship also found between hyperpigmentation and Pityriasis with serum ferritin level, but it was statistically insignificant. Further study with larger sample size is needed.

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