

Original research:**Dermatological manifestations in beta thalassemia major patients between 2 to 12 years and their relation with serum ferritine level****Koushik Roy***, **Sankar Kumar Das****, **Avijet Dutta*****, **Rajesh Kumar Mandal#**

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Received: June 1, 2018; **Reviewed:** August 7, 2018; **Accepted:** September 9, 2018.

Citation of article: Koushik Roy, Sankar Kumar Das, Avijet Dutta, Rajesh Kumar Mandal, Sankar Kumar Das, Dermatological manifestations in beta thalassemia major patients between 2 to 12 years and their relation with serum ferritine level, New Indian Journal of Pediatrics 2018;7(3): p.149-157

Abstract :

To describe the dermatological manifestations noted in multitransfused beta thalassemia major patients aged between two to twelve years and also to find out any correlation with their serum ferritine level, this study was done. A total 56 thalassemia children were examined for dermatological manifestations and their serum ferritin levels were measured. Amongst the patients, male to female ratio was 1:1. Most of the study subjects belonged to the Muslim community (64.3%). Dermatological changes were found amongst 94.6% study children and were more frequently seen in females (96.4%). Children belonging to older age group showed increased frequency (100% in >8years) of dermatological changes. Xerosis and Hyperpigmentation were the two most common dermatological changes noted in 66.1% and 53.6% study subjects. Pityriasis versicolor and alba (12.5%), urticaria (5.4%), acanthosis nigricans (8.9%) were other common dermatological manifestation. Besides generalised hyperpigmentation, some subjects (12.1%) were found to have isolated forehead hyperpigmentation. Less common dermatological changes noted were moluscum contagiosum, diffuse hair loss, nail brittleness, mucosal hyperpigmentation, freckles, acneiform eruption, miliaria and pompholyx. The study showed there was a statistically significant correlation between urticaria and the level of serum ferritin ($p < 0.05$). Hyperpigmentation and pityriasis (versicolor & alba) were also more frequent among study groups with higher level of serum ferritin level. However, the statistically significant correlation could not be established due to paucity of data.

Introduction:

Thalassemia is the commonest inherited autosomal recessive single gene disorder seen all over the globe^[1]. Beta-thalassemia results from mutation in the globin gene leading to deficiency, or absence of beta-globin chain synthesis of haemoglobin.

Three percent of world's population carries alleles for beta-thalassemia^[2]. High prevalence is present in Mediterranean, Middle East, Transcaucasus, central Asia and Indian subcontinent^[3]. In India, among all the hemoglobinopathies, beta-thalassemias are major health problem. Almost 10% of total thalassemic patients worldwide are born in India every year. Overall carrier frequency in India is 3% to 4%. Certain population in India like Sindhis, Gujratis, Punjabis and Bengalis are more commonly affected with beta thalassemia, incidence varying from 1% to 17%^[4].

Regular blood transfusion is the main modality of treatment for the correction of anemia of these patients. Repeated blood transfusion along with ineffective erythropoiesis and increased iron absorption leads to iron overload in the body.

Several literatures have been published on various systemic complications of beta-thalassemia major, but there is scarcity of literature regarding dermatological manifestations of these patients.

In the current study, we have described different dermatological manifestations noted in multi transfused beta-thalassemia major patients aged between 2 to 12 years attending the thalassemia care unit of North Bengal Medical College. We also tried to establish the correlation between dermatological manifestations with iron overload in the body (measured by serum ferritin level).

Materials and Methods :

Study type and design: Descriptive observational type with cross sectional design. Study area: Thalassemia Care Unit and Department of Paediatric Medicine of North Bengal Medical College. Study period: July 2014 to June 2015. Study population: Diagnosed cases of beta thalassemia major patients attended to Thalassenia Care Unit or admitted in the Pediatric Ward. Inclusion criteria: Beta thalassemia major patients between 2 to 12 years age already diagnosed by HPLC or Hb electrophoresis already transfused 10 units of blood.

Exclusion criteria: 1. Patients having other systemic diseases with dermatological manifestation. 2. Patients aged less than 2 years of age and more than 12 years. 3. Patients having pre-existing diagnosed skin disease. Sample size: All the diagnosed cases of beta thalassemia major patients visited Thalassemia care unit or pediatric outdoor or admitted in the pediatric ward during the study period aged between 2 to 12 years were included in the study keeping the inclusion and exclusion criteria in mind and the sample size ultimately became 56. Parameters to be studied: Dermatological examination and serum ferritin level. Plan for data analysis: Datas were entered in Microsoft excel sheet. Then it was analysed by SPSS version 20 software. Datas 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=56

Dermatological changes	Frequency	Percentage
Xerosis	37	66.1
Hyperpigmentation	30	53.6
Acanthosis nigricans	5	8.9
Pityriasis versicolor & alba	7	12.5
Urticaria	3	5.4
Others#	10	17.9

* Multiple responses found

Others include-moluscum contagiosum, diffuse hair loss, nail brittleness, oral mucosal hyperpigmentation, freckles, acneform eruption, milliaria, pompholyx.

Table 1 shows that, among all study subjects xerosis was the most common dermatological changes found followed by hyperpigmentation (includes both forehead 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=56

	Minimum	Maximum	Mean	Std. Deviation
Age (years)	2	12	6.45	3.080
Weight (kg)	8	40	17.21	6.806
Height (inches)	28	60	42.32	8.164
Last hemoglobin (gm/dl)	3	10	5.62	1.199
Serum ferritin (mcg/dl)	117	4060	1566.57	1009.127
Liver (cm)	5	10	6.544	1.255
Spleen (cm)	0	18	6.13	3.894

Table 2 depicts that, mean weight of the study children was 17.21 kg. Whereas, the mean age of the study children was 6.45 years, mean height was 42.32 inches. It is also seen that the mean level of serum ferritin was 1566.57 mcg/dl. Mean measurement of the liver span and spleen (below left costal margin) were 6.544 cm and 6.13 cm respectively.

Table 3 : Distribution of dermatological changes among study children in relation to their serum ferritin level. n=56

Serum ferritin(mcg/dl)	Dermatological changes		Total
	Present	Absent	
< 1000	15 (83.3%)	3 (16.7%)	18 (100.0%)
1000 – 2000	23 (100.0%)	0 (0.0%)	23 (100.0%)
> 2000	15 (100.0%)	0 (0.0%)	15 (100.0%)
Total	53 (94.6%)	3 (5.4%)	56 (100.0%)

Chi-Square value = 6.692, df = 2, p value = 0.035

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 83.3% 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=56

Age group (years)	Dermatological changes		Total
	Present	Absent	
< 5	18 (90.0%)	2 (10.0%)	20 (100.0%)
5 – 8	17 (94.4%)	1 (5.6%)	18 (100.0%)
> 8	18 (100.0%)	0 (0.0%)	18 (100.0%)
Total	53 (94.6%)	3 (5.4%)	56 (100.0%)

Chi-Square value = 1.871, df = 2, p value = 0.392

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 90% and 94.4% 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=56

Malnutrition	Dermatological changes		Total
	Present	Absent	
Present	48 (94.1%)	3 (5.9%)	51 (100%)
Absent	5 (100.0%)	0 (0.0%)	5 (100%)
Total	53 (94.6%)	3 (5.4%)	56 (100%)

Chi-Square value = 0.311, df = 1, p value = 0.577

Table 5 shows that, though most of the children under the study group were malnourished but all of the tiny group of well nourished children were found to have some dermatological changes amongst them(100%) but 94.1% 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=56

Hemoglobin level (gm/dl)	Dermatological changes		Total
	Present	Absent	
< 5	16 (94.1%)	1 (5.9%)	17 (100.0%)
5 – 7	32 (94.1%)	2 (5.9%)	34 (100.0%)
≥ 8	5 (100.0%)	0 (0.0%)	5 (100.0%)
Total	53 (94.6%)	3 (5.4%)	56 (100.0%)

Chi-Square value = 0.311, df = 2, p value = 0.856

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 94.1% of those who were having last 7 gm/dl or less had dermatological 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=56

Spleen size (cm)	Dermatological changes		Total
	Present	Absent	
Splenectomy done	4 (100.0%)	0 (0.0%)	4 (100.0%)
1 – 3	12 (85.7%)	2 (14.3%)	14 (100.0%)
4 – 7	19 (95.0%)	1 (5.0%)	20 (100.0%)
≥ 8	18 (100.0%)	0 (0.0%)	18 (100.0%)
Total	53 (94.6%)	3 (5.4%)	56 (100.0%)

Chi-Square value = 3.452, df = 3, p value = 0.327

Table 7 shows that, all those who had spleen size more than or equal to 8cm measured from left costal margin along the splenic axis amongst the study group, had dermatological changes and 95% and 85.7% 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	13 (72.2%)	5 (27.8%)	18 (100.0%)
1000 – 2000	15 (65.2%)	8 (34.8%)	23 (100.0%)
> 2000	9 (60.0%)	6 (40.0%)	15 (100.0%)
Total	37 (66.1%)	19 (33.9%)	56 (100.0%)

Chi-Square value = 0.558, df = 2, p value = 0.757

Table 8 shows that, amongst the study children 72.2% 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 65.2% and 60% 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	8 (44.4%)	10 (55.6%)	18 (100.0%)
1000 – 2000	12 (52.2%)	11 (47.8%)	23 (100.0%)
> 2000	10 (66.7%)	5 (33.3%)	15 (100.0%)
Total	30 (53.6%)	26 (46.4%)	56 (100.0%)

Chi-Square value = 1.655, df = 2, p value = 0.437

Table 9 shows that, Hyperpigmentation were found more commonly in those study children who had serum ferritin level in the higher side i.e. 66.7% who had serum ferritin level more than 2000 mcg/dl, 52.2% who had between 1000 to 2000 and 44.4% 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	1 (5.6%)	17 (94.4%)	18 (100.0%)
1000 – 2000	3 (13%)	20 (87%)	23 (100.0%)
> 2000	3 (20%)	12 (80%)	15 (100.0%)
Total	7 (12.5%)	49 (87.5%)	56 (100.0%)

Chi-Square value = 1.571, df = 2, p value = 0.456

Table 10 shows that Pityriasis were found more (20%) amongst the study children who had Serum Ferritin level more than 2000 mcg/dl than who had Serum Ferritin between 1000 to 2000 (13%) 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%)	18 (100%)	18 (100.0%)
1000 – 2000	4 (17.4%)	19 (34.8%)	23 (100.0%)
> 2000	1 (6.7%)	14 (93.3%)	15 (100.0%)
Total	5 (8.9%)	51 (91.1%)	56 (100.0%)

Chi-Square value = 3.885, df = 2, p value = 0.143

Table 11 shows that, Acanthosis nigricans were not present amongst the study children who had serum ferritin level <1000 mcg/dl, present amongst 17.4% who had between 1000 to 2000 and amongst 6.7% 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%)	18 (100%)	18 (100.0%)
1000 – 2000	0 (0%)	23 (100%)	23 (100.0%)
> 2000	3 (20%)	12 (80%)	15 (100.0%)
Total	3 (5.4%)	53 (94.6%)	56 (100.0%)

Chi-Square value = 8.664, df = 2, p value = 0.013

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 56 patients, male to female ratio was 1:1. Most of the study subjects belonged to the Muslim community (64.3%). Dermatological changes were found amongst 94.6% study children and were more frequently seen in females (96.4%). 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^[5].

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 $e^{-}8\text{gm/dl}$ had increased frequency of dermatological changes. Dermatological changes were also more common among study groups with more hepatic span ($e^{-}7\text{cm}$ liver span), as well as with large spleen size ($e^{-}8\text{cm}$ 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 (66.1%) dermatological change amongst the study subjects, followed by skin hyperpigmentation (53.6%). skin hyperpigmentation was noted as generalised hyperpigmentation (87.1%) as well as only forehead hyperpigmentation (12.9%).

Xerosis, the most common (64.1%) dermatological change among thalassemia major patients by Al-Rubiay KK et al. in Iraq, was comparable to our study^[5]. Bronzy coloured skin (54.9%) 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^[7]. 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.^[10]

Hyperpigmentation was found in 48.7% study subjects in the study done by Al-Rubiay KK et al. in Iraq^[5]. Momeni A et al. noticed hyperpigmentation at the injection site of desferal administration among 30% study subjects^[7]. Idiopathic 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^[11].

In the current study, generalised hyperpigmentation was more frequent (n= 27, 48.2%) 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 (7.1%) 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 8.9% patients, pityriasis versicolor and alba, accounted for 12.5% of all the skin changes seen. Urticaria was another important skin change noted in 5.4% study children.

Other less common dermatological changes included moluscum contagiosum, diffuse hair loss, nail brittleness, oral mucosal hyperpigmentation, freckles, acneform eruption, miliaria, pompholyx. The incidence of these skin changes comprised of 17.9% among total study subjects.

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 Iran⁶. 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^[8]. 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 5.4% 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^[9].

The average incidence of urticaria among Indian children is around 2.5%^[12]. The higher incidence of urticaria among our study groups may be due the allergic reaction in response to plasma proteins following repeated blood transfusion^[13].

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 8.9% of study subjects, and not correlated to the serum ferritin level.

Conclusion :

- ❑ Beta-thalassemia major is equally distributed amongst male and female subjects in the present study.
- ❑ Most of the patients belonged to the Muslim community.
- ❑ Dermatological manifestations were seen more among older multi-transfused beta-thalassemic children.
- ❑ Dermatological manifestations were more commonly seen in females.
- ❑ Common dermatological changes noted in our study were xerosis (66.1%), hyperpigmentation (53.6%), pityriasis versicolor & alba (12.5%), acanthosis nigricans (8.9%), urticaria (5.4%). Other less common finding were moluscum contagiosum, diffuse hair loss, nail brittleness,

mucosal hyperpigmentation, freckles, acneform eruption, miliaria, and pompholyx.

- ❑ Xerosis was the most common dermatological change noted in the study followed by Hyperpigmentation.
- ❑ A definite relationship between Dermatological change with serum ferritin level was noted in the present study, though it was statistically not significant.
- ❑ Relation between serum ferritin level and Urticaria was statistically significant.
- ❑ 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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