**Ministry of Higher Education**

**and Scientific Research**

**University of Diyala**

**College of Medicine**

# A Review Article in:

# Dermatological manifestations of beta Thalassemia major

**Submitted to the Council of the College of Medicine, Diyala University, in Partial Fulfillment of Requirements for the Bachelor Degree in medicine and general surgery.**

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## Abstract

Thalassemias are a heterogeneous grouping of genetic disorders that result from a decreased synthesis of alpha or beta chains of hemoglobin (Hb). Thalassemias are a quantitative defect of hemoglobin synthesis. This is in contrast with hemoglobinopathies, such as sickle cell disease, which are structural or qualitative defects of hemoglobin. Beta-thalassemia refers to an inherited mutation of the beta-globin gene, causing a reduced beta-globin chain of hemoglobin. A diagnosis of beta thalassemia is based upon identification of characteristic symptoms, a clinical evaluation and a variety of specialized tests. The aim of our review is to discuss the dermatological manifestations of beta thalassemia major. We found that the pruritus, xerosis, hyperpigmentation, white streak and bronzy skin are the most common complications.

## Introduction

Thalassemias are a heterogeneous grouping of genetic disorders that result from a decreased synthesis of alpha or beta chains of hemoglobin (Hb). Hemoglobin serves as the oxygen-carrying component of the red blood cells. It consists of two proteins, an alpha, and a beta. If the body does not manufacture enough of one or the other of these two proteins, the red blood cells do not form correctly and cannot carry sufficient oxygen; this causes anemia that begins in early childhood and lasts throughout life. Thalassemia is an inherited disease, meaning that at least one of the parents must be a carrier for the disease. It is caused by either a genetic mutation or a deletion of certain key gene fragments [(1)].

Thalassemia are a quantitative defect of hemoglobin synthesis. This is in contrast with hemoglobinopathies, such as sickle cell disease, which are structural or qualitative defects of hemoglobin. Beta-thalassemia refers to an inherited mutation of the beta-globin gene, causing a reduced beta-

globin chain of hemoglobin. The highest prevalence of beta-thalassemia mutations is in people of Mediterranean, Middle Eastern, and Asian descent [2].

Thalassemia major is treated with red blood cell transfusion. The aim of transfusion is mainly to suppress erythroid expansion. It also serves to mitigate symptoms of anemia and to inhibit gastrointestinal iron absorption. Severe anemia and growth delays are indications for transfusions as well as clinical signs of erythroid expansion, including facial changes, bony expansion, and splenomegaly. The goal hemoglobin level for most transfusion regimens is pretransfusion hemoglobin of 9 to 10 g/dL and posttransfusion hemoglobin of 13 to 14 g/dL [3].

Complications are related to overstimulation of bone marrow, ineffective erythropoiesis, and iron overload from blood transfusions. Iron accumulates in the heart, causing heart failure with chronic anemia. Usually, these patients have dyspnea, with resting tachycardia, low blood pressure, high ejection fraction, and high cardiac output [4].

Other complications are chronic hepatitis (from blood transfusion infection of hepatitis B and C viruses), cirrhosis (iron overload), hypersplenism, HIV infection, osteoporosis and dermatologic manifestation which include pruritus, hyperpigmentation, bronzy skin, etc.

In this review, we will demonstrate the dermatological manifestations of beta thalassemia major.

## Literature review

- **Definition and pathogenesis**

Beta-thalassemia is an inherited disorder resulting from various mutations or, rarely, deletions of the beta-globin gene (HbB) on chromosome 11. Over 200 different thalassemia-causing mutations have been identified in the beta-globin gene, leading to the disease's wide genotypic and phenotypic variability. These mutations are primarily point mutations that affect transcriptional control, translation, and splicing of the HbB gene and gene product [(5)].

The pathogenesis of beta-thalassemia is two-fold. First, there is decreased hemoglobin synthesis causing anemia and an increase in HbF and HbA2 as there are decreased beta chains for HbA formation. Second, and of most pathologic significance in beta-thalassemia major and intermedia, the relative excess alpha chains form insoluble alpha chain inclusions that cause marked intramedullary hemolysis. This ineffective erythropoiesis leads to severe anemia and erythroid hyperplasia with bone marrow expansion and extramedullary hematopoiesis. The bone marrow expansion leads to bony deformities, characteristically of the facial bones which cause frontal bossing and maxillary protrusion. Biochemical signaling from marrow expansion involving the bone morphogenetic protein (BMP) pathway inhibits hepcidin production causing iron hyperabsorption [(6)].

- **Diagnosis**

  A diagnosis of beta thalassemia is based upon identification of characteristic symptoms, a clinical evaluation and a variety of specialized tests. With beta thalassemia major, initial symptoms often become apparent during the first two years of life and include failure to thrive, a swollen abdomen, and symptoms of anemia.

Any individuals suspected of having beta thalassemia will undergo blood tests such as a complete blood count (CBC) [17]. The complete blood count (CBC) of a patient with beta-thalassemia major will show microcytic hypochromic anemia with Hb levels less than 7g/dl, the mean corpuscular volume between (MCV) 50 and 70 fl, and mean corpuscular Hb (MCH) between 12 and 20pg [7]. A blood sample can be tested to measure the amount of iron in the blood, which is often elevated in individuals with beta thalassemia

Molecular genetic testing can confirm a beta thalassemia diagnosis. Molecular genetic testing can detect mutations in the HBB gene known to cause the disorder

- **Complications**

Possible complications of moderate to severe thalassemia include:

- ✓ **Iron overload**: People with thalassemia can get too much iron in their bodies, either from the disease or from frequent blood transfusions.
- ✓ **Infection**: People with thalassemia have an increased risk of infection. This is especially true if you've had your spleen removed
- ✓ **Bone deformities**: Thalassemia can make your bone marrow expand, which causes your bones to widen.
- ✓ **Enlarged spleen**: Thalassemia is often accompanied by the destruction of a large number of red blood cells. This causes your spleen to enlarge and work harder than normal.An enlarged spleen can make anemia worse, and it can reduce the life of transfused red blood cells.Slowed growth rates. Anemia can both slow a child's growth and delay puberty.
- ✓ **Heart problems**: Congestive heart failure and abnormal heart rhythms can be associated with severe thalassemia. [17]

- ✓ **Dermatological problem**: The cutaneous disorders are common among beta thalasemia patients, pallor ,xerosis and jaundice were the common skin changes, while white streak (leukonychia)and gingivitis are the most common nail and oral mucoasa changes respectivly. Xerosis is common in patients recieving desferoxamine, serum ferritin level was higher in patients with xerosis,hyperpigmentation and jaundice [(12)].

- **Dermatological manifestations of beta thalassemia major**

In this article I focused on the medical literature for published studies at cutaneous manifestations presented or seen in beta thalassemia major such as the study maid in Thalassemia Care Unit and Department of Pediatrics Medicine of North Bengal Medical College in July 2014 to June 2015 that show 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, acneform eruption, milliaria and pompholyx [(17)].

Pruritus is a very common complaint among general dermatology clinic patients. The prevalence of pruritus in a community-based study was found to be 8.4% [(8)]. The pathogenesis of pruritus is complex and has not been fully elucidated. A study investigating the relationship between stressful major life events and dermatologic symptoms in nonclinical

subjects found that the most commonly described symptom was pruritus [9].

A sample of 78 patients with β-thalassemia major was recruited and interviewed at the thalassemia clinic between April and June 2008. Sixty-five (83.3%) of the 78 patients examined had a diagnosed skin disease: pruritus (37.2%), xerosis (34.6%), scars (24.4%), ephelides (23.1%), skin irritation/erythema caused by deferoxamine pump (12.8%), idiopathic guttate hypomelanosis (6.4%), pityriasis alba (6.4%), tinea infections (5.1%), verruca vulgaris (5.1%), urticaria (3.8%), hyperhidrosis, contact dermatitis, and acne (2.6%), necrobiosis lipoidica (1.3%), melasma (1.3%), and others (14.1%). Pruritus and xerosis increased in frequency with age. The mean serum ferritin level was higher in patients with xerosis than in those without [10].

Table 1 show the results of the study.

**Table 1.**

| Dermatologic disease | Number of patients with dermatologic disease |
|---|---|
| Pruritus | 29 (37.2%) |
| Xerosis | 27 (34.6%) |
| Scars | 19 (24.4%) |
| Pigmentary disorders | |
| Ephelides | 18 (23.1%) |
| Idiopathic guttate hypomelanosis | 5 (6.4%) |
| Pityriasis alba | 5 (6.4%) |
| Melasma | 1 (1.3%) |
| Erythema, irritation caused by deferoxamine pump | 10 (12.8%) |
| Verruca vulgaris | 4 (5.1%) |
| Tinea infections | 4 (5.1%) |
| Urticaria | 3 (3.8%) |
| Hyperhidrosis | 2 (2.6%) |
| Contact dermatitis | 2 (2.6%) |
| Acne | 2 (2.6%) |
| Necrobiosis lipoidica | 1 (1.3%) |
| Others | 11 (14.1%) |

Community-based subjects from London, Ontario, Canada were recruited from the local university, schools and churches. The most frequently reported body region affected was the scalp (59.5%) and the most frequently reported symptom was itching (69.3%). The total number of major life events experienced over the previous 6 months correlated with the severity of the individual cutaneous symptoms. and with the total cutaneous symptom severity score (sum of all cutaneous severity ratings). This correlation remained significant after the possible confounding effect of psychological factors on cutaneous symptoms was partialled out statistically [(11)]. And in the beforementioned study it was the second in rank of prevalence.

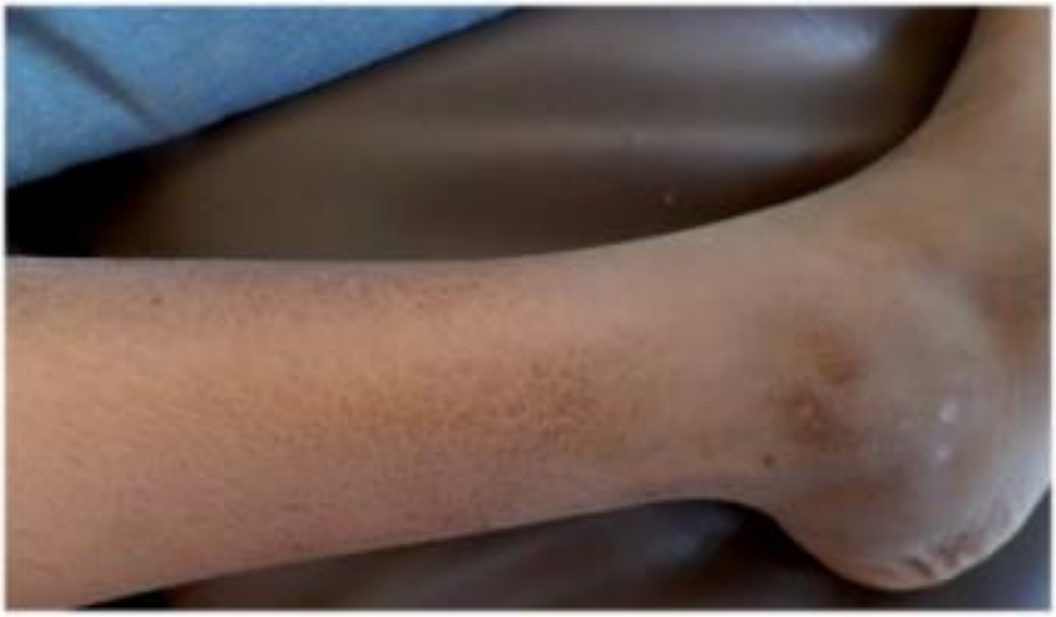

**Figure 1. Xerosis**

Study performed at Erbil Thalassemia center over a period extended from April, 2013 to January, 2014 it show All patients enrolled in this study had at least one cutaneous manifestation. The disorders are in decreasing order of frequency was pallor, xerosis, jaundice, bronze skin, hyperpigmentation

and the least frequent was vitiligo. Most of the of the findings (31.8%) were between (10-15) years age group. The mean age of patients, the mean duration of blood transfusion and the mean of serum ferritin level among patients with xerosis, pallor, hyperpigmentation and jaunduce was higher [(12)].

Researchers aimed to study the frequency and pattern of skin manifestations in Egyptian children with β-thalassemia. Fifty-four β-thalassemia major patients being followed at the Hematology Clinic of Beni-Suef University Hospital were selected to participate in this study. Pruritus (37%), scars (33.3%), hyperpigmentation (31.5%) and xerosis (22.2%) were the most common findings. We found significant relations between serum ferritin and the occurrence of scars, hyperpigmentation, xerosis and ephelides. Also, significant associations between use of deferoxamine and scars ($p$=0.004), hyperpigmentation, xerosis and ephelides were found [(13)].

This cross-sectional study included 105 Egyptian patients (50 female individuals and 55 male individuals) with transfusion-dependent β-thalassemia major in the period spanning from June 2017 to February 2018. The study was performed on child and adult patients of β-thalassemia who presented to the hematology clinic, Menoufia University hospital. The main skin disorders that were noticed in decreasing order of frequency were pruritus (34.4%), xerosis (24.8%), urticaria (21.1%), freckles (17.1%), tinea infections (11.6%), pitriasis alba reported in 10.5%, scars (10.5%), hypersensitivity to deferoxamine pump (9.5%), herpes simplex (9.5%), acne vulgaris (8.6%), miliaria (6.7%), contact dermatitis (4.8%). [(14)].

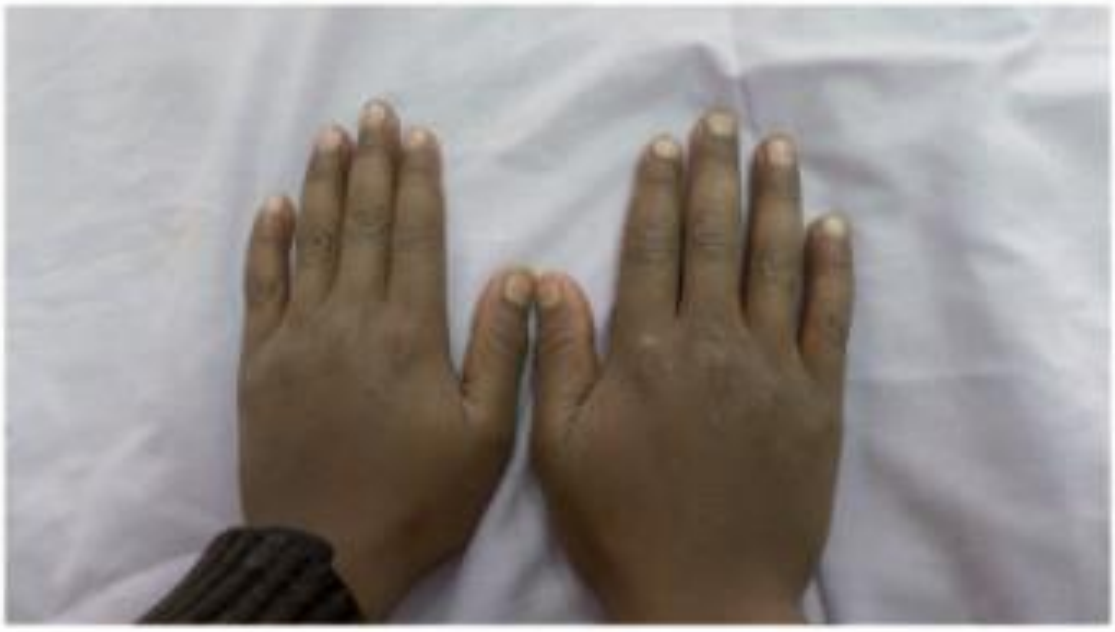

**Figure 2. Hyperpigmentation**

Patients with beta-thalassemia major attending the pediatric department of Fayoum University Hospital from April 2016 to October 2016 (n = 100) were compared with controls (n = 100). Children with thalassemia had a greater prevalence of xerosis (72%), pruritus (52%), idiopathic guttate hypomelanosis (22%), urticaria (16%), ephelides (freckles; 13%), and scars (13%) than controls. We detected a significant relationship between serum ferritin and pruritus, xerosis, ephelides, idiopathic guttate hypomelanosis, urticaria, and age of patients with thalassemia. Children without thyroid abnormalities were more likely to have xerosis, pruritus, idiopathic guttate hypomelanosis, urticaria, and ephelides (86%) than controls. Although there was no significant difference in skin findings between patients who did and did not receive chelating agents [(15)].

Reduction in serum zinc levels as a result of deferiprone therapy has been described by previous studies. This might be the cause of skin disorders found in thalassemia patients receiving deferiprone. Pruritus, scars,

hyperpigmentation and xerosis were the most commonly encountered cutaneous disorders in our patients receiving deferiprone [16].

A total 56 thalassemia children were examined for dermatological manifestatios 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 dermato-logical 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 foud to have isolated forehead hyperpigmentation. Less common dermatological changes noted were moluscum contagiosum, diffuse hair loss, nail brittleness, mucosal hyperpigmentation, freckles, acneform eruption, milliaria and pompholyx [17].

Cross-sectional study was conducted on 300 patients with beta major thalassemia in Zahedan. Data were obtained from medical records and questionnaires as well as through physical examination of patients. The data were statistically described and tested. Results: The mean age of patients was 17.9 ±6.3 years and 64.3% of patients were men and 35.7% were women. Among cutaneous lesions, freckles were the most common (70.7%) and the rarest one was peri orbital pigmentation (0.3%). Gingivitis (41.7%) and longitudinal lines on nails (72%) were the most common mucosal and nail manifestations. [18].

## Conclusion

The cutaneous manifestations studies regarding beta thalassemia major are still not enough to determine the actual prevalence of the skin disorders because of their limited number and different results.in interpretation of all these results show that the most common cutaneous manifestation among beta thalassemia patients are pallor, xerosis and jaundice, while white streak (leukonychia) and gingivitis are the most common nail and oral mucoasa changes respectivly. Xerosis is common in patients recieving desferoxamine, serum ferritin level was higher in patients with xerosis, hyperpigmentation and jaundice.

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