

Report

Skin diseases in patients with β -thalassemia major

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Abstract

Background β -Thalassemia major affects multiple organs and is associated with considerable morbidity and mortality. The goal of this analysis was to document the frequency of skin diseases among patients with β -thalassemia major.

Methods A sample of 78 patients with β -thalassemia major was recruited and interviewed at the thalassemia clinic between April and June 2008. A dermatologist completed a skin examination of each patient and recorded any skin disease present. The patients' laboratory results and treatment modalities were recorded from the charts.

Results 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 (5607.7 ± 2997.5 ng/mL and 4285.2 ± 4732.4 ng/mL, respectively) ($P = 0.005$). Moreover, xerosis was observed significantly more frequently in patients using deferoxamine and deferiprone than in those using deferasirox ($P = 0.047$, $P = 0.027$, and $P = 0.273$, respectively).

Conclusion Skin diseases, especially pruritus and xerosis, are observed highly frequently in patients with β -thalassemia major. Treatment is needed for these patients who already have other significant morbidities.

Introduction

β -Thalassemia major is endemic in the Mediterranean, Middle East, and South-East Asia, and is considered to be an orphan disease in the European Union and North America.¹⁻³ In β -thalassemia major, profound anemia and severe hemosiderosis cause functional and physiologic abnormalities in various organ systems.^{3,4} To our knowledge, no study has yet investigated the common dermatologic problems that coexist with β -thalassemia major. The purpose of this study was to determine the commonly seen dermatologic problems in patients with β -thalassemia major.

Materials and Methods

This was a prospective study in which patients with β -thalassemia major treated in the thalassemia clinic were included. A dermatologist completed a skin examination of each patient and recorded any skin disease present. The dermatologic diagnoses were classified into different groups based on the *International Classification of Diseases*, 10th edn.

(ICD-10). All the patients' laboratory results were recorded from the charts (i.e. complete blood test, ferritin level, urea, thyroid function tests). Skin scrapings for microscopy and fungal culture were obtained from suspected lesions. Direct microscopy was carried out with a 20% potassium hydroxide (KOH) preparation, and cultures were performed in culture tubes on Sabouraud dextrose agar. The collected data were obtained using SPSS descriptive statistics, Mann-Whitney *U*-test, and chi-squared (χ^2) test, and $P < 0.05$ was accepted as statistically significant.

Results

Seventy-eight patients with β -thalassemia major, aged from 10 months to 37 years (mean, 11.2 ± 7.6 years), treated in the thalassemia clinic, were recruited and interviewed between April and June 2008. Of these, 28 (35.9%) were female and 50 (64.1%) were male. The demographics, concomitant diseases, systemic medications, and laboratory findings of the patients are shown in Table 1. Systemic medications were defined as chelating therapy, such as deferoxamine (Desferal®, Novartis Pharma AG, Basle, Switzerland), deferiprone

Table 1 Detailed data of the study population

Findings	n (%)
Sex	
Male	50 (64.1%)
Female	28 (35.9%)
Family and sibling findings	
Parental consanguinity	
No relative	22 (28.2%)
First-degree relative	30 (38.5%)
Second-degree relative	4 (5.1%)
Distant relative	12 (15.4%)
Unknown	10 (12.8%)
Number of siblings with β -thalassemia	
None	4 (5.1%)
One	40 (51.3%)
Two	28 (35.9%)
Three	5 (6.4%)
Four	1 (1.3%)
Concomitant diseases	
Infections	5 (6.4%)
Osteoporosis	4 (5.1%)
Splenectomy	3 (3.9%)
Diabetes mellitus	2 (2.6%)
Hypogonadism	2 (2.6%)
Hypothyroid	2 (2.6%)
Mental retardation	2 (2.6%)
Systemic medications	
Deferoxamine	40 (51.3%)
Folic acid	29 (37.2%)
Zinc	27 (34.6%)
Deferiprone	25 (32.1%)
Drugs for osteoporosis	23 (29.5%)
Deferasirox	10 (12.8%)
Insulin	1 (1.3%)
Laboratory findings, mean $\pm$ SD (min–max)	
Hemoglobin level (g/dL)	25.2 $\pm$ 3.3 (15.5–32)
Hematocrit level (%)	8.9 $\pm$ 1.1 (5.3–10.7)
Ferritin level (ng/mL)	4781.1 $\pm$ 4190.5 (1231–30,000)

(Ferriprox®, Apotex, Toronto, ON, Canada), and deferasirox (ICL670; Exjade®, Novartis Pharma AG), zinc, folic acid, drugs for osteoporosis, and insulin.

Sixty-five (83.3%) of the 78 patients examined had a diagnosed skin disease. The dermatologic diagnoses were categorized into 28 different diseases. Twenty-seven patients were diagnosed with only one skin disease, whereas 38 patients had two or more. These diseases in decreasing order of frequency were pruritus (37.2%), xerosis (34.6%), scars (24.4%), epheides (23.1%), skin irritation/erythema caused by deferoxamine pump (12.8%), idiopathic guttate hypomelanosis (IGH) (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 (NBL) (1.3%), melasma (1.3%), and others (1.1%) (Table 2). The mean serum ferritin level was higher in the

Table 2 Dermatologic diseases seen in patients with β -thalassemia major ($n = 78$)

Dermatologic disease	Number of patients with dermatologic disease
Pruritus	29 (37.2%)
Xerosis	27 (34.6%)
Scars	19 (24.4%)
Pigmentary disorders	
Epheides	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%)

24 patients with xerosis than in the 44 without (5607.7 ± 2997.5 ng/mL and 4285.2 ± 4732.4 ng/mL, respectively) ($P = 0.005$) (Table 3). In addition, xerosis was found to be statistically more common in patients using deferoxamine or deferiprone than in those using deferasirox ($P = 0.047$, $P = 0.027$, and $P = 0.273$, respectively). There were no statistically significant differences between these three chelating drugs and the presence of pruritus ($P > 0.05$) (Table 3).

Discussion

β -Thalassemia major affects multiple organs and is associated with considerable morbidity and mortality. To our knowledge, this is the first report on the commonly seen dermatologic problems in patients with β -thalassemia major. In this study, a wide spectrum of skin diseases was identified, which were caused by both the hemoglobin disorder and the complications of treatment.

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%.⁵ 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.⁶ The results of a recent study revealed that patients with pruritic skin diseases have a high level of psychosocial morbidity.⁷ In our study, pruritus was the most common complaint among patients. This could be explained

Table 3 Relationship between ferritin levels, drugs, and dermatologic diseases

Dermatologic disease		Ferritin level (mean $\pm$ SD)	Drugs		
			Deferoxamine, n (%)	Deferiprone, n (%)	Deferasirox, n (%)
Xerosis	Present	5607.7 $\pm$ 2997.5	18 (46.2%)	13 (52%)	5 (50%)
	Absent	4285.2 $\pm$ 4732.4	21 (53.8%)	12 (48%)	5 (50%)
	<i>P</i>	0.005*	0.047†	0.027†	0.273†
Pruritus	Present	3740.1 $\pm$ 1622	10 (25.6%)	7 (28%)	2 (20%)
	Absent	5188.5 $\pm$ 4794.6	29 (74.4%)	18 (72%)	8 (80%)
	<i>P</i>	0.631*	0.895†	0.607†	1.000†
Ephelides	Present	7059.3 $\pm$ 8204.3	6 (5.6%)	4 (16%)	2 (20%)
	Absent	4359.3 $\pm$ 2878.1	33 (33.4%)	21 (84%)	8 (80%)
	<i>P</i>	0.149*	0.817†	1.000†	0.647†

*Mann–Whitney *U*-test.† χ^2 test.

partly because of the chronic nature of the disease, the xerotic skin of patients, and frequent blood transfusions.

It is well known that red blood cell transfusions are a vital, life-saving treatment for many patients with chronic anemias, including β -thalassemia. The drawback of this therapeutic gain, however, is the excessive accumulation of iron in vital organs, such as the liver, myocardium, and endocrine glands, leading to progressive organ dysfunction. Excessive iron in parenchymal tissues can cause serious clinical sequelae, such as cardiac failure, liver disease, diabetes, and eventual death.^{1,8–10} In this study, we observed that there was also a relationship between iron overload and xerosis. Xerosis (dry skin) is a common condition in which signs and symptoms, such as flaky skin, cracking, erythema, and pruritus, and overall visual appearance make patients highly desirous of relief. A lack of fatty acids in the skin that augment hydration and barrier function leads to the development of xerosis. The generalized itching that results can lead to anxiety or depression and, subsequently, progression to neurotic excoriations.¹¹ Xerosis provokes cutaneous discomfort and an unaesthetic appearance that justify appropriate treatment. Moisturizers and emollients represent a valuable first-line treatment option for xerosis.

It is well known that, in dark-skinned individuals, even small injuries have a tendency to produce scar formation.^{12,13} It is also known that patients with thalassemia have dark skin because of severe hemosiderosis. Therefore, it would not be surprising to find a high prevalence of scars in dark-skinned β -thalassemia patients. Indeed, we found that wound scars, especially on the face, were common in our study population.

Ephelides are a common problem in the dermatologic field. This term describes freckles that are flat, light brown or red, and fade in winter. Ephelides are more common in those with light complexions, and with the regular use of sunblock they can be suppressed. Although almost all of our patients had

dark skin, ephelides were the fourth most frequently observed problem seen in patients with β -thalassemia major.

Chelation therapy eliminates the complications of iron overload; the therapeutic management is based on the regular and accurate estimate of iron stores.^{1,10,14,15} Three iron chelators have been approved: deferoxamine, deferiprone, and deferasirox.^{14,15} Deferoxamine administration requires slow parenteral infusion over an 8–12-h period, five to seven times per week. Deferiprone is a three-times-daily oral iron chelator. It is the second-line treatment for iron overload in adult patients with thalassemia major for whom deferoxamine therapy is contraindicated or inadequate. Deferasirox, a tridentate oral iron chelator, demonstrates a manageable toxicity profile. It is important to note that deferasirox is able to provide 24-h chelation coverage with a single oral dose. The most common deferasirox-related adverse events are gastrointestinal disturbances and transient mild to moderate skin eruption (approximately 7% of patients).¹⁵ These events rarely require drug discontinuation and many resolve spontaneously. The present study revealed that patients using deferoxamine pumps had skin irritation and erythema over the area in which the pumps were placed. Furthermore, xerosis was more common in patients using deferoxamine and deferiprone than in those using deferasirox.

In this study, IGH was the sixth most frequently observed dermatologic disease among β -thalassemia patients. The etiology of IGH is unknown; however, solar exposure and genetic predisposition have been hypothesized as causative factors. It is usually associated with guttate hyperkeratosis, xerosis, and lentiginosis.¹⁶ As the study location was very hot and sunny, we conclude that both ephelides and IGH were affected by the climate.

Tinea infections are typically acquired directly from contact with infected humans or animals, or indirectly from exposure to contaminated soil or fomites. A diagnosis usually



Figure 1 Necrobiosis lipoidica in a patient with β -thalassemia major and diabetes mellitus

can be made with a focused history, physical examination, potassium hydroxide microscopy, and fungal culture. Four patients (none had diabetes) were found to have tinea infections (one tinea versicolor and three tinea pedis) in this study. On fungal culture from three patients with tinea pedis, *Trichophyton rubrum* strains were isolated. Microscopy (with KOH) of one patient revealed short sinuous hyphae and yeast clusters, indicating *Malassezia furfur*.

NBL is a chronic skin condition associated with dermal collagen degeneration, decreased collagen synthesis, granulomatous infiltrate, atrophy, and lipid deposition.¹⁷ The pathogenesis of NBL is largely enigmatic. Rarely, squamous cell carcinoma may arise *de novo* in an area of long-standing NBL.¹⁸ It has been suggested that the cause of NBL is microangiopathic, owing to the clear association with diabetes. About 0.7% of diabetic patients have NBL. Indeed, one of our diabetic patients, aged 37 years, had NBL on his left thigh of 9 years' duration (Fig. 1).

Several immunologic defects have been found in patients with thalassemia.¹⁹ Multiple blood transfusions and continuous immune stimulation may be responsible for this immune dysfunction. The reason for urticaria and contact dermatitis (3.8% and 2.6%, respectively), which were seen in our patients, could be explained in this way.

Acne and hyperhidrosis were also seen in the study group. We believe that this was a result of the age of the study subjects, rather than being caused by the thalassemia itself.

Some studies, for example those conducted by Baccarani-Contri *et al.*²⁰ and Aessopos *et al.*,^{21,22} have revealed that pseudoxanthoma elasticum (PXE)-like skin lesions are common in patients with β -thalassemia major. Nevertheless, we did not observe any patient with PXE-like lesions in our study group. This difference may be attributed to the ethnic and regional differences between the two study populations.

PXE-like clinical syndrome is age dependent, with a generally late onset, after the second decade of life; however, our study population consisted of patients usually in the first decade of life. Lotti *et al.*²³ reported leg ulcer in a patient with β -thalassemia and glucose-6-phosphate dehydrogenase deficiency, but we did not find any patient with a leg ulcer in our study group. Recently, Giordano *et al.*²⁴ presented a case with colloid milium and suggested that the lesion could be related to excess iron. Although all of our patients had iron overload, we did not observe any case with colloid milium.

In conclusion, skin diseases were frequent among patients with β -thalassemia who participated in this study, with pruritus and xerosis being the most prevalent. Further research is needed to delineate the specific factors causing the high levels of certain dermatologic problems in this population.

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