Measuring the impact of pruritus in patients with epidermolysis bullosa: evaluation with an itch-specific instrument

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Abstract

Pruritus is one of the most debilitating symptoms for patients with epidermolysis bullosa (EB). This study aimed to assess the burden of itch and to address its dimensions across patients with EB. Forty-six patients with EB were recruited from the Saudi EB registry to participate. All participants completed the Leuven Itch Scale. The sample included 5 patients with EB simplex (EBS), 3 with junctional EB (JEB), 34 with dystrophic EB (DEB), and 4 patients had unknown type. Overall, 97.8% patients reported itch. In patients with itch, 73.3% reported that it was often or always present, longer than 2h Itch episodes was reported by JEB (66.7%) and recessive DEB (3.2%). Itch, in all its dimensions, was worst in patients with JEB and DEB than EBS. Itch occurred mostly in a hot environment (80%), when sweating (71.1%), in healing wounds (40%), and during dressing change (35.6%) whereas cold environment resulted in itch in only (2.2%). The burden of pruritus increased with increasing age. This study highlights a challenging area in EB care with a need for specific treatments.

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Key words: epidermolysis bullosa, pruritus, itch, genodermatoses.

Contributions: AA, supervised the literature review, data collection, and analysis, contributed to the majority of the manuscript; RA, responsible for the conceptual design, writing of the proposal, data collection, and manuscript drafting; MA, NA, RA, contributed to the conceptual design, writing of the proposal, data collection, and manuscript drafting; PM, provided the questionnaire tool, translation, and analysis; TA, participated in data collection.

Conflict of interest: the authors declare no conflict of interest.

Availability of data and materials: data and materials are available by the authors.

Acknowledgments: the authors thank the patients and caregivers who participated in the survey.

Received: 26 February 2023.
Accepted: 3 April 2023.
Early view: 18 May 2023.

Dermatology Reports 2023; 15:9700
doi:10.4081/dr.2023.9700

Introduction

Epidermolysis bullosa (EB) is a heterogenous group of genetically inherited skin and mucosal fragility disorder. It is classified into four major classical EB types: EB simplex (EBS), Junctional EB (JEB), Dystrophic EB (DEB), and kindler EB.[1] There are multiple effects of EB on affected individuals including blistering, scarring, poor wound healing, pain and itch.[2] Itch (pruritus) was ranked as one of the major unmet needs in children with severe EB.[3]

In a prior study, itch was found to be common among all EB patients, especially in the more severe subtypes.[4] It was reported as the most bothersome symptom in patients with EB, even more than pain, oral or dental problems.[5] Pruritus can have a significant impact on patients' quality of life (QoL), daily activities, and contributes to increased mood disorders (*i.e.* anxiety and depression).[6,7] Proper recognition and understanding of the impact of pruritus on EB patients is crucial to ease this burden and improve patients' quality of life. In the current study, we aimed to assess the burden of itch and to address its dimensions across patients with EB.

Materials and Methods

Study population

This was a cross-sectional study in patients with EB. Patients from the Saudi EB registry was approached to participate in this survey. Patients were eligible for inclusion if they were diagnosed with EB of any age; if Arabic was their native language; and if they or, as appropriate, their caregivers, provided informed con-

sent. All participants were informed about the study objective, data confidentiality and were asked to indicate their understanding of the study conditions and agreement to participate. The study protocol was approved by the Institutional Review Board of Imam Mohammad Ibn Saud University.

Variables and measurement

We measured the impact of itch using the Leuven Itch Scale (LIS) patient questionnaire (Appendix).[8] The LIS is a validated and reliable itch specific tool consisting of an 11-item questionnaire.[8] The LIS has been tested in patients with different dermatological conditions, such as burns, atopic dermatitis, chronic urticaria, icthyosis and epidermolysis bullosa.[4,8,9] The LIS is a multidimensional patient reported instrument that evaluates the frequency, duration, severity and circumstances of itch symptoms as well as their location, management, distress, sensory perceptions and consequences over the preceding 4 weeks. Using specific algorithms, subscale scores on six domains (itch frequency, duration, severity, distress, consequences and surface area) can be calculated by summing the raw scores and transforming them to a scale ranging from 0 to 100. Higher scores represent more itching. The subscale scores allow the determination of a comprehensive profile of itch for individual patients or for groups of patients and can be expressed using radar graphs.[8] The LIS has been translated and validated into Arabic language.

Procedure

From the Saudi EB database, we retrieved a list of patients with severe EB who met the inclusion criteria. Patients and their caregivers were contacted for voluntary participation in this study and were also sent an invitation. A link to the questionnaire was sent via phone and/or email to participants. Data was collected from patients, or in the case of a minor, from their primary caregiver. Participants received the informed consent, the LIS and the clinical research form for demographic and clinical information. Data were collected between March 2022 and October 2022. This study was approved by the ethics committee of the Imam Mohammad Ibn Saud University Riyadh, Saudi Arabia (Reference 175-2021).

Statistical analysis

We performed data analysis using SPSS version 27 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean (standard deviation) and normally distributed variables were compared by independent samples Student's t test. Mann-Whitney U test and Kruskal-Wallis test were used, respectively, to compare medians of 2 and 3 or more groups of variables not normally distributed. The frequencies of categorical variables were compared using Pearson $\chi 2$ or Fisher's exact test, as appropriate. Spearman's rank correlation was used to assess the correlation among various LIS domains. All reported p values are two-sided and value of $p<0.05$ was considered statistically significant.

Results

A total of 46 EB patients aged 2 months to 37 years, with mean age of 9.8 years were enrolled. The gender distribution was similar, with 23 males (50%) and 23 females (50%). Table 1 provides information on the characteristics of the study patients and their itch profile. Most of the patients in the study had DEB (n=34), EBS (n=5), JEB (n=3), and 4 patients had unknown type. Out of the 34 patients with DEB, 2 had dominant DEB (DDEB) and the remaining had recessive DEB (RDEB).

Itch occurred in 97.8% of the participants, only one patient never experienced itch. Thirty-three out of 45 (73.3%) patients with itch reported to experience itch always or often. Majority of patients (59.1%) had itch episode lasting less than 30 minutes. Longer than 2 h Itch episodes was reported by JEB and RDEB (66.7%) and (3.2%) respectively. In fact, itch in all its dimensions, was generally worst in patients with JEB. Patients with EBS had a lower itch profile than JEB or DEB patients. The entire itch profile of the study groups is shown in a Figure 1.

In Table 2, the circumstances, consequences and sensory characteristics of itching are expressed. In the total sample of EB patients, itch occurred mostly in a hot environment (80%), and when sweating (71.1%), whereas cold environment resulted in itch in only (2.2%). Eighteen patients (40%) reported experiencing itch in healing wounds, and 16 (35.6%) during dressing change.

Most frequent consequences of itching included lesions from scratching, reduced quality of life, difficulties in falling asleep, bad mood, waking up at night and behavioral change. The differences between the groups were noticed. The most reported consequences for patients with EBS were lesions from scratching, difficulties in falling asleep and reduced quality of life. All JEB patients experienced lesions from scratching and reduced social contact. Patients with DEB suffered the most from scratch lesions, followed by difficulties in falling asleep, reduced quality of life, and bad mood (Table 2).

The most frequently described characteristic of itch was a burning sensation (n=24, 72.7%), then prickling by 11 (33.3%) participants. This was also the case for the JEB and DEB. However, it was observed that EBS patients frequently perceive itching as a prickling (80%), and less frequently as burning (40%) or tickling sensation (40%) (Table 2). One patient described pain accompanying with pruritus. Thirteen patients (28.3%) were unable to define the character of itch; the majority of these were caregivers' reports for children under 12 years of age.

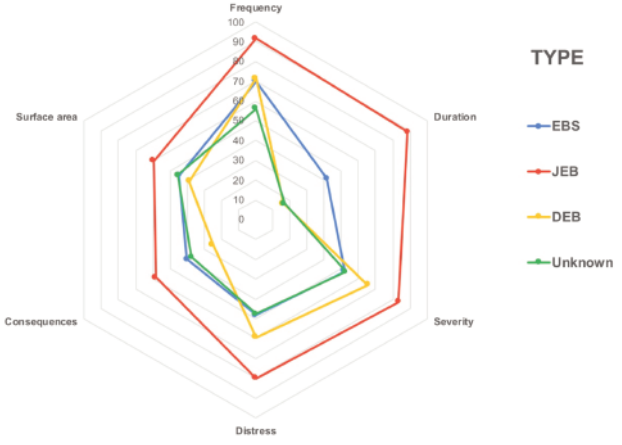

Figure 1. The itch profile of the epidermolysis bullosa subtypes. Six domains of itch were calculated by summing raw scores and transforming them to a scale ranging from 0 to 100. Higher scores represent more itching.

Table 1. Baseline characteristics and scale scores comparison among epidermolysis bullosa types.

Demographic and itch parameter (n=46)	Total sample (n=5)	EB simplex (n=3)	Junctional EB (n=34)	Dystrophic EB	p
Age (years)	9.8±8.7	15.8±12.4[a]	16.2±11.9	9.3±7.6	0.022
Gender					0.016
Male	23 (50%)	4 (80%)	0 (0%)	19 (55.9%)	
Female	23 (50%)	1 (20%)	3 (100%)	15 (44.1%)	
Frequency	71.2±22.3	70±27.4	91.7±14.4	71.3±19.6	0.301
Duration	23.5±32.6	41.7±31.9	88.9±19.2[b]	16.2±27.8[b]	0.009
Severity	64.1±24.9	52±30.3	83.3±5.8	65.6±23	0.273
Distress	58.4±26.7	48±31.1	80±10	59.4±25.6	0.303
Consequences	29.9±26.7	40±13.7	58.3±38.2	25±25.4	0.127
Surface area	41.3±27.3	44.8±38.2	59.7±33.3	38.8±24.3	0.781

EB, epidermolysis bullosa. All values are mean ± standard deviation. a,bDifferent letters mean significatively difference among values.

Table 2. Circumstances, consequences and sensory characteristics of itching in 45 patients with epidermolysis bullosa. Values are expressed in absolute numbers or percentages.

Total, n (%)	EB simplex, n (%)	Junctional EB, n (%)	Dystrophic EB, n (%)	Unknown, n (%)	p
Circumstances in which itch occurs					
During a change in the weather	12 (26.7)	1 (20)	2 (66.7)	7 (20.6)	2 (66.7)	0.084
During spells of pain	6 (13.3)	1 (20)	1 (33.3)	4 (11.8)	0 (0)	0.829
When making a movement	5 (11.1)	1 (20)	0 (0)	3 (8.8)	1 (33.3)	0.582
When sweating	32 (71.1)	3 (60)	2 (66.7)	24 (70.6)	3 (100)	0.855
In a hot environment	36 (80)	3 (60)	1 (33.3)	30 (88.2)	2 (66.7)	0.040
In a cold environment	1 (2.2)	0 (0)	1 (33.3)	0 (0)	0 (0)	0.133
When standing up after sitting or lying down	2 (4.4)	1 (20)	0 (0)	1 (2.9)	0 (0)	0.433
When I was stressed out	7 (15.6)	1 (20)	1 (33.3)	4 (11.8)	1 (33.3)	0.668
On contact with air	1 (2.2)	0 (0)	1 (33.3)	0 (0)	0 (0)	0.133
When touching the skin	1 (2.2)	1 (20)	0 (0)	0 (0)	0 (0)	0.244
Others						
New wounds	13 (28.9)	1 (20)	1 (33.3)	9 (26.5)	2 (66.7)	0.594
Wound healing	18 (40)	4 (80)	3 (100)	9 (26.5)	2 (66.7)	0.003
Dressing change	16 (35.6)	0 (0)	0 (0)	16 (47.1)	0 (0)	0.027
Consequences of itching					
Lesions from scratching	5 (100)	3 (100)	29 (90.6)	2 (100)	3 (75)	0.628
Reduced social contact due to itching	3 (60)	3 (100)	6 (18.8)	1 (50)	2 (50)	0.014
Reduced quality of life due to itching	4 (80)	2 (66.7)	10 (31.3)	1 (50)	3 (75)	0.133
Disturbed my routine activities due to itching	3 (60)	2 (66.7)	6 (18.8)	1 (50)	2 (50)	0.125
Difficulties in falling asleep due to itching	4 (80)	2 (66.7)	10 (31.3)	1 (50)	2 (50)	0.276
Waking up due to itching	3 (60)	2 (66.7)	8 (25)	1 (50)	3 (75)	0.131
Needed sleeping pills due to itching	1 (20)	1 (33.3)	4 (12.5)	0 (0)	0 (0)	0.730
Loss of appetite due to itching	2 (40)	2 (66.7)	4 (12.5)	1 (5)	0 (0)	0.078
Bad mood due to itching	2 (40)	2 (66.7)	9 (28.1)	2 (100)	3 (75)	0.079
Changes in behavior toward others due to itching	3 (60)	2 (66.7)	8 (25)	2 (100)	2 (50)	0.078
Loss of concentration due to itching	3 (60)	2 (66.7)	7 (21.9)	1 (50)	1 (25)	0.237
Sensory characteristics of itching					
A tickling sensation	7 (21.2)	2 (40)	0 (0)	4 (16.7)	1 (100)	0.160
A tingling sensation	1 (3)	1 (20)	0 (0)	0 (0)	0 (0)	0.273
A prickling sensation	11 (33.3)	4 (80)	1 (33.3)	5 (20.8)	1 (100)	0.027
A stinging sensation	5 (15.2)	1 (20)	2 (66.7)	2 (8.3)	0 (0)	0.127
A burning sensation	24 (72.7)	2 (40)	3 (100)	19 (79.2)	0 (0)	0.041

The correlation matrix of the dimensions of itch shows that itch frequency, duration, severity, distress, consequences and surface area are interrelated, with correlations ranging between 0.48 and 0.82 (Figure 2). We observed a significant correlation between distress and itch severity, showing that higher level of distress was noted in patients with severe itching.

An association was found between EB patient age group and the itch profile as shown in Figure 3. The burden of pruritus increased with increasing age of EB patients.

Discussion

Pruritus is one of the most common symptoms among all EB subtypes with a major impact on patients' QoL.[4-6,10] The present study shows that nearly all patients with EB reported itch, 73.3% experiencing this symptom as always or often. This in agreement with previous reports, in a study of 40 adults with EB, 85% of patients reported itch, a prevalence comparable to that found in atopic dermatitis.[4] In a study of itch in 13 patients with RDEB using the visual analog scale (VAS), the mean VAS score was 7.54±2.07, which is considered severe itch.[6]

We found burden of pruritus to be higher in severe subtypes (JEB, and DEB), and with increasing age. Higher level of distress was observed in patients with severe itching. The findings of our study are in line with a qualitative interview of 11 children with EB where itch was especially problematic in patients with severe disease.[3] Exposed wounds during dressing change, and healing wounds were the itchiest in our EB patients. Consistent with previous study in 146 EB patients of all ages and types, patients with RDEB had higher itch frequency than EBS, bandage change and healing wounds were significantly more itchy than intact skin.[5]

The pathophysiology of EB pruritus is not completely understood. It is likely that barrier dysfunction, and dysregulated activation of systemic proinflammatory cytokines are all involved.[10] There is evidence that sera of EB patients contain higher level of itch mediators particularly thymic stromal lymphopoietin (TSLP), interleukin (IL-6) and IFN-γ.[11]

Heat, and sweating provoked itch response in patients with EB. This is particularly an issue in the middle east countries where weather is extremely hot and can exacerbate itching in our EB patients. Lesions from scratching was the most frequent consequences of itching among all EB subtypes. This can induce a vicious itch–scratch cycle which irritate the skin and leads to new blisters.[12] The most frequently mentioned characteristic of itching was a burning then prickling sensation. However, our results suggest that the concept of sensory perceptions of itch may be difficult for young children to understand.

Furthermore, this and previous studies indicate that the itching associated with EB is prevalent and severe.[3-6,10] This study explored the itch in patients with EB using the LIS instrument. The LIS contains the most clinically relevant items to assess itching.[8] The LIS enabled pruritus assessments in patients with EB of all ages. Caregivers input was particularly useful for the younger patients who are too young to report their own outcomes. A version of the instrument for pediatric patients' assessment with minor modifications to the sensory perception of itch would be helpful.

This study had some limitations and highlighted challenges associated with measuring pruritus in a population with a rare disease. Although patient-reported outcome measures may be the preferred method for assessment of pruritus, however, some young patients may be unable to respond for themselves. Caregivers cannot directly describe the itch symptom, but they were able to assess its consequences through observable features such as scratching, mood and sleep disturbance. Despite our best efforts, the total number of patients with EBS and JEB is very low compared to the DEB. That may result from voluntary participation; perhaps patients with less severe itch did not feel compelled to participate.

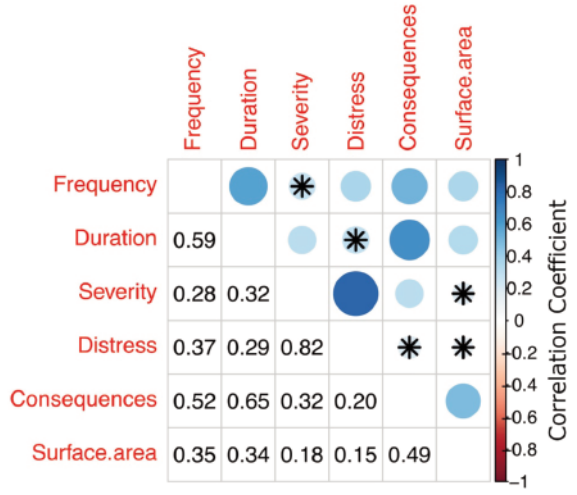

Figure 2. Correlation matrix of the dimensions of itch, reflecting the degree to which two variables are intercorrelated.

Figure 3. Itch profile of the epidermolysis bullosa according to age groups.

Conclusions

Controlling pruritus remains a research priority in EB and has been given substantial consideration in EB clinical practice guidelines.[13] With emerging clinical trials and targeted biologic therapies advances in symptomatic management of itch are expected.[14-17] There is still a desperate need for better ways to manage pruritus in individuals with EB.

Overall, this study demonstrated that itching is one of the most debilitating symptoms for patients with EB and specific treatments to control EB pruritus are necessary.

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Online supplementary material
Appendix: Leuven Itch Scale.