Published in final edited form as:

Ann Allergy Asthma Immunol. 2017 December ; 119(6): 548–552.e3. doi:10.1016/j.anai.2017.09.076.

Burden of skin pain in atopic dermatitis

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Abstract

Background—Atopic dermatitis (AD) is associated with itch, skin inflammation and barrier disruption, and scratching, all of which may be associated with skin pain.

Objective—To characterize the patient-burden of skin pain in AD.

Methods—We performed a prospective dermatology practice-based study using questionnaires and evaluation by a dermatologist (n=305).

Results—At baseline, 144 (42.7%) patients reported skin pain in the past week, with 42 (13.8%) reporting severe or very severe pain. Twenty four (16.8%) thought the skin pain was part of their itch, 16 (11.2%) from scratching and 77 (72.0%) from both. Patients with skin pain were more likely to describe their itch using terms resembling neuropathic pain. Prevalence of skin pain was increased in patients with vs. without excoriations (72.6% vs. 57.6%; Chi-square, P=0.02), but not other morphological characteristics. Skin pain severity was most strongly correlated with Patient Oriented Eczema Measure (Spearman rho=0.54), followed by ItchyQOL (0.52), 5-dimensions of itch scale (0.47), Dermatology Life Quality Index (0.45), Numeric rating scale for itch (0.43) and sleep (0.36), Patient Health Questionnaire-9 (0.36), patient-reported global AD severity (0.34), Eczema Area and Severity Index (0.23) and objective Scoring AD index (0.20) (P<0.0001 for all). Patients with both severe itch and pain vs. those with only one or neither symptom being severe had significant increases in all of these measures.

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Conflicts of interest: None

Trial registration: Not applicable

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Conclusion—Skin pain is a common and burdensome symptom in AD. Skin pain severity should be assessed with itch severity in AD patients and may be an important endpoint for monitoring treatment response.

Keywords

atopic dermatitis; eczema; pain; itch; pruritus; quality of life; burden of disease; patient-reported outcomes

Introduction

Atopic dermatitis (AD) is a chronic, inflammatory skin disease, associated with a heterogeneous presentation and highly symptomatic clinical course. The hallmark symptom of AD is itch or pruritus. However, recent studies demonstrated additional symptoms of AD, including increased sleep disturbance ^{1,2} and mental health symptoms ^{3–5}. These additional symptoms add to the patient-burden of disease and significantly worsen patients' quality of life (QOL).

Skin pain is yet another symptom that may play an important role in AD. AD patients with chronic itch may scratch their skin, resulting in skin-barrier disruption and painful erosions. In addition, recent studies suggested that AD patients have increased rates of skin pain and sensitivity to mechanical stimulation ⁶. Pain has been associated with profoundly harmful impacts on patients' mental health and all aspects of QOL in many disease states ⁷. In the present study, we sought to determine whether AD is associated with increased skin pain. Moreover, we sought to identify the predictors of skin pain and understand the impact of skin pain on patients' mental health and QOL.

Methods

Study design

We performed a prospective, dermatology practice-based, observational study to determine the impact of skin pain in AD. Self-administered questionnaires were completed by patients of the eczema clinic prior to their encounter. Patients were then evaluated with a medical history and total body skin examination by a dermatologist (JS). Subjects were enrolled between September, 2014 and January, 2017. The study was approved by the institutional review boards of Northwestern University and informed consent was waived.

Assessments for AD

The diagnosis of AD was confirmed using the Hanifin and Rajka diagnostic criteria⁸. The objective assessments of AD were the Eczema Area and Severity Index (EASI) [range: 0–72]⁹, objective-Scoring AD (oSCORAD) [range: 0–83], and SCORAD [range: 0–103]¹⁰. The Harmonizing Outcome Measures in Eczema (HOME) group found that only oSCORAD and EASI were adequately validated and assessed the four essential signs of AD, i.e. erythema, induration/papulation, lichenification and excoriation¹¹. Between these two assessment tools, EASI was preferred over oSCORAD for the assessment of AD signs in clinical trials¹².

Patients completed a questionnaire that included the questions: “Over the past week, did you have any pain of your skin?”, “How severe was the pain on a scale of 0–10?” and “Do you think the pain is part of the itch, from scratching, or both?”. Additional patient-reported outcomes (PRO) related to AD included: numeric rating scale (NRS) for itch and sleep loss in the past 3 days [range: 0–10], Patient-Oriented Eczema Measure (POEM) [range: 0–28]¹³ and Dermatology Life Quality Index (DLQI) [range: 0–30]¹⁴, mean ItchyQOL [range: 0–5]^{15, 16}, 5-D itch scale [range: 0–28]¹⁷, and Patient-Health Questionnaire-9 (PHQ9) [range: 0–30]¹⁸. POEM measures the frequency of patient-reported signs and symptoms of AD and is the preferred assessment of AD symptoms in clinical trials¹⁹. DLQI and ItchyQOL assess dermatology- and itch-specific QOL impairment, respectively. 5-D itch scale is a composite measure incorporating the different dimensions of itch and related QOL impairment. PHQ9 is a PRO for screening, diagnosing, and measuring the severity of depression.

Data processing and statistical methods

All data analyses and statistical processes were performed using SAS version 9.4 (SAS Institute). Complete data analysis was performed, i.e. subjects with missing data were excluded. Statistical significance was determined based on two-sided P-values ≤ 0.05 .

Associations of any skin pain with personal history of atopic disease, signs and symptoms of AD were tested using either Chi-square or Fisher’s exact tests. To determine potential predictors of skin pain, logistic regression models were constructed with skin pain as the binary dependent variable using stepwise selection from the following covariates ($\alpha < 0.1$): race/ethnicity (white/black/Hispanic/Asian/other), sex (m/f), alcohol consumption (yes/no), current smoker (yes/no), personal history of asthma, hay fever, food allergy or medication allergy, presence of excoriations, lichenification, dermatitis on the face, eyelids or conjunctivitis, lips or cheilitis, hands, feet, nipples, scalp, and/or posterior auricular area, nummular lesions, white dermatographism, clinical course worsened by environmental or emotional factors, pruritus when sweating and tendency toward cutaneous infections. Adjusted odds ratios (aOR) and 95% confidence intervals (CI) are presented. Models were also tested using backward and forward selection and the final models were identical as for stepwise selection.

Skin pain severity was not normally distributed. Therefore, non-parametric Spearman correlations were performed for overall comparisons of skin pain severity (continuous) and NRS-itch, NRS-sleep, POEM, DLQI, ItchyQOL, 5-D itch scale, PHQ9, patient-reported global AD severity²⁰, EASI and oSCORAD. Kruskal-Wallis tests were used to compare NRS-itch, NRS-sleep, POEM, DLQI, ItchyQOL, 5-D itch scale, PHQ9, EASI and oSCORAD scores (continuous) between no, mild, moderate, severe and very severe skin pain severity groups, as well between patients with or without severe itch and/or pain (binary). Chi-square tests were used to compare individual items from the DLQI questionnaire between patients with any vs. no skin pain (binary), and skin pain severity (ordinal). Chi square tests were performed and weighted kappa coefficients were determined for comparisons of concordance between patient-reported global AD severity (ordinal) with skin pain severity (ordinal) and patients with or without severe itch and/or pain (ordinal).

Results

Patient characteristics

Overall, 305 patients (ages 13–97 years) were included in the study, with 564 encounters. The cohort included 195 females (63.9%) and 193 whites (63.7%). The mean $\pm$ std. dev. age at enrollment was 42.3 ± 18.1 years and age of patient-reported AD onset was 29.6 ± 31.9 years (eTable 1).

At baseline, 144 (42.7%) of patients reported any skin pain in the past week, with 42 (13.8%) reporting severe or very severe pain. Twenty four (16.8%) thought their skin pain was part of their itch, 16 (11.2%) from scratching and 77 (72.0%) from both. Patients with skin pain were more likely to describe their itch as painful ($P < 0.0001$), throbbing ($P = 0.0007$), biting ($P = 0.01$), stinging ($P = 0.009$), burning ($P < 0.0001$), sharp ($P = 0.05$), tingling ($P = 0.03$), pinprick-like ($P = 0.01$), and a crawling sensation ($P = 0.007$), but not warm ($P = 0.24$), tight ($P = 0.41$), shooting ($P = 0.18$) or sensitive ($P = 0.24$) (Figure 1). In a sensitivity analysis of patients with no or only mild excoriations, the rates of use of the abovementioned pain-like descriptors were similarly increased in those reporting skin pain compared to those without skin pain (Figure 1).

Associations of skin pain in atopic dermatitis

Any skin pain was associated with increased personal history of hay fever ($P = 0.001$) and higher rates of conjunctivitis or eyelid dermatitis ($P = 0.05$) and cheilitis ($P = 0.002$), but not race/ethnicity, gender, alcohol consumption habits, current smoking status, personal or family history of other atopic disease, or other physical signs or symptoms of AD ($P = 0.11$) (eTable 2).

Prevalence of skin pain was also significantly increased in patients with vs. without excoriations (72.6% vs. 57.6%; Chi-square, $P = 0.02$), but was not associated with other morphological characteristics, such as lichenification (70.6% vs. 66.7%, $P = 0.57$), erythema (80.4% vs. 72.7%, $P = 0.53$), oozing/crusting (83.6% vs. 79.0%, $P = 0.43$), edema/papulation (79.5% vs. 80.6%, $P = 0.83$) or xerosis (78.6% vs. 87.0%, $P = 0.20$).

In multivariable logistic regression models with stepwise selection, only presence of excoriations (aOR [95% CI]: 3.47 [1.67 – 5.27]), cheilitis (2.49 [1.08 – 5.71]) and history of pruritus when sweating (3.29 [1.06 – 10.17]) were significantly associated with skin pain.

Skin pain severity and other AD assessments

Skin pain severity was most strongly correlated with POEM (Spearman rho = 0.54), followed by ItchyQOL (0.52), 5-D itch scale (0.47), DLQI (0.45), NRS-itch in the past 3 days (0.43), NRS-sleep in the past 3 days (0.36), PHQ9 (0.36), patient-reported global AD severity (0.34), EASI (0.23) and oSCORAD (0.20) ($P < 0.0001$ for all).

For each stepwise increase of skin pain from mild to very severe, there was a greater burden of disease with significant increases of skin symptoms (NRS-itch in the past 3 days, POEM) and poorer quality of life (ItchyQOL, DLQI, 5-D itch scale), as well as worsening sleep

(NRS-sleep in the past 3 days) and mental health symptoms (PHQ9) and greater AD severity (EASI and oSCORAD) (Kruskal-Wallis test, $P < 0.0001$ for all) (Figure 2).

The correlations between skin pain and the abovementioned objective assessments and PRO were similar in both men and women, whites and non-whites, ages < 40 and ≥ 40 years ($P < 0.01$ for all; data not shown).

Additive burden of itch and pain in atopic dermatitis

Skin symptoms (POEM), quality of life impact (ItchyQOL, DLQI, 5-D itch scale), sleep disturbance (NRS-sleep in the past 3 days), mental health symptoms (PHQ9) and AD severity (EASI and oSCORAD) were all increased in patients who rated both itch and pain as severe as compared to those who rated just one or neither of these measures as severe (Kruskal-Wallis test, $P < 0.0001$ for all) (eFigure 1).

In particular, skin pain was associated with increased self-consciousness and had a negative impact on ability to shop and perform other activities of daily living, to make clothing decisions, to socialize or pursue leisure activities, to play sports, to work or study, to have relationships with other, to have normal sexual function, and treatment burden ($P = 0.017$ for all) (eTable 3). Moreover, there was a significant dose-response effect with even more harmful impact on the above aspects of QOL with increasing severity of skin pain ($P < 0.0001$ for all) (eTable 4).

Skin pain and patient-reported global AD severity

Among patients reporting skin pain, there was moderate concordance between skin pain and patient-reported global AD severity (mild, moderate and severe) (weighted kappa = 0.31) (Chi square test, $P < 0.001$) (Table 1). The presence of both severe itch and pain vs. either alone or neither symptom being severe was associated with significant increases of patient-reported global AD severity ($P < 0.0001$).

Discussion

The present study found high rates of skin pain in patients with AD. Most patients reported that the pain was attributable at least in part to scratching (83.2%), but a substantial proportion reported that their pain was related to their itch. Patients with skin pain were more likely to describe their itch with distinct terms resembling neuropathic pain, even when no or only mild excoriations were present. In bivariable models and multivariable logistic regression models, skin pain was associated with excoriations, eyelid dermatitis, cheilitis, and/or pruritus when sweating, but not other symptoms or physical signs of AD. Skin pain, particularly severe pain, was associated with increased AD severity, poor sleep, depressive symptoms and poorer QOL. Combined severe skin pain and itch were associated with even poorer outcomes. Together, these results show that AD is associated with a profound burden of skin pain, in addition to itch.

Interestingly, a substantial proportion of patients reporting skin pain thought their pain was unrelated (16.8%) or only partially related (72.0%) to scratching and had no demonstrable excoriations on physical exam. A substantial proportion of AD patients described their itch

using pain-related terms, with even higher rates in those with no or only mild excoriations. It may be that some patients experience the sensation of pain secondary to cutaneous inflammation and/or neurosensory dysfunction. A case-control study of 25 patients with AD and 25 controls found that the AD patients had an average pain visual analog score of 39.7, increased sensitivity to mechanically induced pain both lesionally and extralesionally, and hyperknesis⁶. This suggests that sensitivity and pain may not be limited to sites of active skin lesions or excoriations. Another case-control study of 25 patients with AD, 9 with psoriasis and 20 controls found that noxious and chemical stimuli primarily triggered itch in AD patients, whereas pain was experienced in psoriasis patients and controls²¹. This suggests the perception of pain may be aberrant and overlap with itch in AD patients. Together, it appears that AD patients commonly experience skin pain and pain-like itch sensations, which may result from increased sensitivity.

The mechanisms of increased skin pain in AD are likely multifactorial. Two studies found increased density of dermal nerves in AD patients compared with controls^{22, 23}. In contrast, another study found that AD patients had *lower* nerve density than controls, but longer individual nerve fibers in lichenified and unlichenified lesions²⁴. Cutaneous nerve endings might be more vulnerable to exogenous stimuli secondary to impaired barrier function. There may also be increased and aberrant activation of cutaneous nerves to mechanical and other exogenous stimuli secondary to activation of transient receptor potential V1 and other receptors, which have been implicated in mouse models of AD^{25–27}. Future studies are needed to better understand these mechanisms, which may lead to improved treatments of itch and skin pain in AD.

This study has several strengths, including being prospective, and using validated objective assessments and PRO to assess the burden of skin pain. However, the study has limitations. In particular, the study was performed in an urban, academic, dermatologic setting and may not be generalizable to the entire US population. Future, larger-scale multicenter studies are needed to confirm the results of this study.

In conclusion, AD appears to be associated with increased skin pain. For most patients, scratching appears to be the major driver of pain. However, a subset of AD patients seem to experience pain-like itch resembling neuropathic pain without evidence of scratching. Skin pain was associated with increased AD severity and impacted all aspects of patients' QOL. We recommend that skin pain severity be routinely assessed along with itch severity in all AD patients. Moreover, skin pain severity may be an important endpoint for monitoring clinical response to treatment. Future studies are needed to determine the precise mechanisms and optimal treatment approaches for skin pain in AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Jl Silverberg had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

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Administrative technical or material support: None

Study supervision: None

Financial disclosures: None

Funding Support: This publication was made possible with support from the Agency for Healthcare Research and Quality (AHRQ), grant number K12 HS023011, and the Dermatology Foundation.

Abbreviations used

AD	atopic dermatitis
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
NRS	Numeric Rating Scale
POEM	Patient Oriented Eczema Measure
oSCORAD	objective Scoring Atopic Dermatitis
SCORAD	Scoring Atopic Dermatitis
5-D	5-dimensions

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Figure 1. Pain-like descriptors of itch in atopic dermatitis

Proportion of atopic dermatitis patients who described their itch using pain-like descriptors. Results are stratified by those with vs. without skin pain. Sensitivity analyses were performed in patients reporting skin pain, who did had either no or only mild excoriations on physical exam.

Figure 2. Associations of skin pain severity with itch, atopic dermatitis signs and symptoms and quality of life

Box-whisker plots and overlaid jitter plots of (A) NRS-itch, (B) POEM, (C) mean ItchyQOL, (D) DLQI, (E) 5-D itch, (F) NRS-sleep, (G) PHQ9, (H) EASI and (I) oSCORAD.

Table 1

Concordance between skin pain and patient-reported global AD severity.

Skin pain – freq (%)	Patient-reported global AD severity			P-value [#]
	Mild	Moderate	Severe	
Mild	34 (34.0%)	47 (47.0%)	19 (19.0%)	< 0.0001
Moderate	35 (28.5%)	53 (43.1%)	35 (28.5%)	
Severe / very severe	12 (10.3%)	22 (19.0%)	82 (70.7%)	
Severe pain and/or itch				
None	379 (53.1%)	239 (33.5%)	96 (13.4%)	< 0.0001
Either	42 (19.7%)	70 (32.9%)	101 (47.4%)	
Both	6 (8.8%)	7 (10.3%)	55 (80.9%)	

[#] Chi square test