

Pain and Itch Are Dual Burdens in Atopic Dermatitis

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Background: Despite being widely reported by patients with atopic dermatitis (AD), pain symptoms, unlike itch, have not been widely assessed.

Objective: The aim of the study was to understand the distinct pain symptoms in patients with AD.

Methods: Responses from an anonymous questionnaire were collected from our eczema clinic (in-person survey) and collaboration with Global Parents for Eczema Research Group and the National Eczema Association (online survey) to assess skin pain among patients with AD 5 years and older. Eczema Area and Severity Index was measured in the clinic cohort to correlate with pain symptoms.

Conclusions: In our international cohort of 103 patients with AD, 78% reported concomitant pain and itch. The greatest pain burden occurred on the hands (odds ratio [OR], 0.77), perioral region (OR, 0.74), and toes (OR, 0.7), corresponding to regions with the greatest sensory nerve density. Pain was most commonly described as “burning” and “stinging,” particularly when lesions were red, cracked, and dry. Its presence significantly interfered with sleep, leisure activities, and activities of daily living. Among the clinic cohort, we observed a strong Spearman correlation between objective Eczema Area and Severity Index score and subjective skin pain. It is imperative that clinicians understand patients’ unique pain burden to best evaluate clinical severity and quality-of-life interference.

Atopic dermatitis (AD) is a chronic inflammatory dermatosis associated with a significant psychosocial burden.¹ Although itch is the most commonly implicated symptom, patients may also report pain that is independent of or overlapping with itch. Together, these symptoms greatly affect the quality of life (QoL) of patients with AD.² Although pain and itch can be induced by similar triggers, there are separate pathways and molecular markers that distinguish itch and pain processing.³ Both symptoms are difficult to assess because of their subjective nature and therefore may not be adequately acknowledged and subsequently managed by clinicians. In addition, current diagnostic and clinical evaluation tools such as the Eczema Area and Severity Index (EASI), SCORing Atopic

Dermatitis, Patient-Oriented Eczema Measure, and Patient-Oriented SCORing Atopic Dermatitis do not include assessment items designed to capture pain symptoms. In response to these observations, we aimed to identify the underreported pain symptoms that complicate successful AD therapy.

STUDY DESIGN

Between December 2016 and June 2018, we deployed an anonymous 7- to 10-minute online (RedCAP) and dermatology practice survey-based questionnaire. This study was exempted by the University of Arizona Institutional Review Board, and informed consent was waived.

The survey addressed prevalence, characteristics, trigger and relief associations, and QoL impairments associated with AD-related pain symptoms and included questions such as the following: Where do you have active eczema lesions? Where do you experience skin pain? How would you describe the quality, depth, and intensity of your skin discomfort/pain (ie, soreness, burning, cold/freezing, numbing, electrical, cramping, radiating, crawling, stabbing, pinching, throbbing, aching, dull, sharp, stiff, tight, pulling, heavy, pressure, stinging, tender, shooting, pins, and needles)? How would you describe the skin changes in areas that you have pain? How is your pain related to itching and scratching? What aspects of your life are affected by skin pain? What makes your skin pain worse/better?

A dermatologist (V.Y.S.) also assessed EASI scores for patients completing the in-clinic questionnaire. Pediatric patients were

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assisted by their caregivers, and those younger than 5 years were excluded, because young children may not accurately characterize their pain symptoms using our classification system. Odds ratios (ORs) were calculated to assess the likelihood of skin pain in areas with active eczema lesions. A Spearman rank-order correlation was calculated to assess the strength of the relationship between EASI scores and reported skin pain.

RESULTS

One hundred three patients with AD or their caregivers (mean age [SD], 36.0 [18.4] years; age range, 5–74 years) completed the international survey, representing patients from 12 countries including the United States, the United Kingdom (England, Scotland, Wales), Denmark, Canada, Germany, Spain, Australia, Israel, Dominican Republic, and Slovenia. Demographics are listed in Table 1. Participants experiencing eczema reported a mean (SD) of 234 (227) months, with current treatments consisting of topical medications only (64.4%) or both topical and oral medications (34.7%).

Region, Quality, and Intensity

Seventy-eight percent of the participants reported experiencing both skin pain and itch, whereas 20.6% complained of itch only, and 1.0% complained of pain only. Most participants (87%) described pain only where they had active lesions, whereas 14.6% of the participants described pain at locations with active lesions and clear skin. Among those who complained of concomitant pain and itch, pain was most commonly present in the evening (71%) and overnight (49%) and occurred simultaneously with itch (61%), when scratching with (51%) or without (60%) an open wound present, and after itch (54%). The hands, perioral region, toes, buttocks, feet, legs, neck, fingers, and forearm lesions have the highest pain burden (Table 2) and reflect regions with a greater cutaneous sensory

TABLE 2. Burden of Pain in the Most Common Eczematous Sites

Anatomic Region	% Active		OR
	Eczema Lesions	% Pain	
Hands	65.0	50.0	0.77
Perioral	33.0	24.4	0.74
Toes	24.3	17.1	0.70
Feet	42.7	28.0	0.66
Legs	65.0	42.7	0.66
Buttock	26.2	17.1	0.65
Neck	46.6	28.0	0.60
Fingers	52.4	30.5	0.58
Forearms	60.2	34.1	0.57
Lower back	36.9	20.7	0.56
Shoulders	44.7	23.2	0.52
Groin	16.5	8.5	0.52
Scalp	33.0	17.1	0.52
Armpits	28.2	14.6	0.52
Periocular	40.8	20.7	0.51
Upper back	41.7	20.7	0.50
Upper arms	47.6	23.2	0.49
Cheeks	31.1	14.6	0.47
Thighs	49.5	23.2	0.47
Forehead	29.1	13.4	0.46
Ears	37.9	17.1	0.45
Chest	34.0	12.2	0.36
Genitals	11.7	3.7	0.32
Abdomen	44.7	13.4	0.30

nerve density (Fig. 1). Pain is most commonly experienced as superficial burning (73%), stinging (57%), soreness (42%), tightness (42%), tenderness (39%), and throbbing (32%). The mean symptom intensities, defined by a 10-point Likert scale, were 6.4, 7.1, 6.3, 7.5, 7.1, and 5.3, respectively. Participants reported that painful areas are red (88%), cracked (73%), dry (72%), scaling (57%), crusting/scabbing (56%), swollen (54%), bleeding (51%), warm (51%), and weeping/oozing (42%).

TABLE 1. Demographics of Survey Participants

	n (%)	Mean (SD)
Sex		
Female	74 (72)	
Male	29 (28)	
Age, y		
5–13	10 (10)	7.5 (1.4)
13–18	4 (4)	15.0 (2.6)
19–74	89 (86)	40.5 (16.0)
Ethnicity		
White	71 (69)	
Hispanic	11 (11)	
African American	4 (4)	
East Asian	4 (4)	
Native American	3 (3)	
South Asian	2 (2)	
Pacific Islander	1 (1)	
Other	7 (7)	

Timing, Precipitating, and Alleviated Factors

Respondents reported skin pain occurring several times a week (30.9%), with a singular episode lasting minutes (28%) to days (31%) at a time. Participants were mostly burdened with sleep interference (80%), completing leisure activities (78%), or unspecified activities of daily living (63%). Participants pinpointed the most common aggravating factors as sweat (71%), warm ambient temperature (60%), emotional stress (60%), bathing in hot water (49%), rubbing (45%), and wearing wool or synthetic clothing (43%). Although not among the strongest aggravating factors, moisturizer (30%) or topical medication (21%) use was implicated as an aggravator of pain. Relief occurred with cool temperatures (64%), moisturizer use (49%), emotional stress reduction (48%), sufficient sleep (47%), cold pack/wet towel (43%), or topical corticosteroid use (43%).

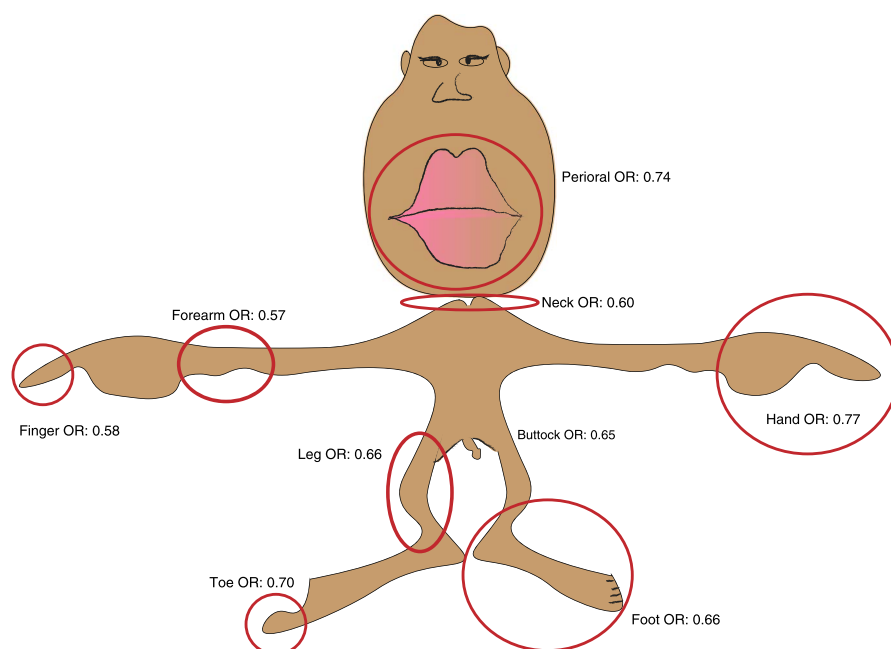


Figure 1. Homunculus identifies anatomic arenas of the greatest sensory density. Odds ratio assesses the incidence of pain in the most commonly involved AD regions.

Correlation Between Eczema Severity and Pain

The mean (SD) EASI score among the 23 patients who completed the in-clinic questionnaire was 17.34 (13.4). The average pain was 4.6 for mild (EASI, 0.1–5.9; $n = 6$), 5.8 for moderate (EASI, 6.0–22.9; $n = 13$), and 7.04 for severe EASI patients (EASI > 23, $n = 4$). Among the “mild” cohort, 66.7% had active lesions on the hands, toes, and buttocks, which were the sites reported as having the greatest active lesion presence at the time of survey completion. A Spearman rank-order correlation observed a large effect size for the correlation ($r = 0.53$, $P = 0.009$) between reported pain and EASI score (Fig. 2).

DISCUSSION

Although itch is commonly the distinguishing symptom of AD, our survey-based study found a near 4-fold prevalence of concomitant pain and itch sufferers compared with itch alone. In addition, there was a strong positive correlation between EASI score and subjectively reported pain. The AD pain was most commonly described as superficial burning (73%), stinging (57%), soreness (42%), and tightness (42%). Our findings are in parallel with a recent study conducted by Vakharia et al,⁴ where evidence was presented that the pain symptoms in patients with AD resemble neuropathic pain and are an important aspect of AD symptoms. The authors noted that skin pain was reported typically only when signs of excoriations were present.⁴ Our study consistently identified that pain is commonly experienced when the lesion is excoriated (red, cracked, or dry), although we found a larger effect size for the correlation between reported pain and EASI score ($r = 0.53$ vs 0.213). Although

the patient population in Vakharia et al's⁴ study was largely adults, we were able to capture responses from young children with the help of parents and caregivers. Through the feedback of caregivers from the Global Parents for Eczema Research Group, we determined that the age of 5 years was the lower limit that a child can reliably characterize pain. Our study was unique in associating specific areas of the body that correlated with the greatest pain burden, with the most pain experienced in the hands, perioral region, and toes.

Although EASI strongly correlated with pain intensity across all cases, some patients with mild and moderate EASI scores reported a relatively high pain burden, as identified by an average pain score of greater than 5. It is possible that clinically “mild” appearing lesions

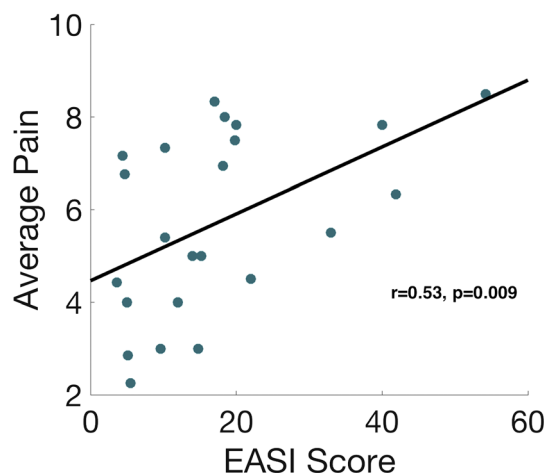


Figure 2. Spearman rank-order correlation between objective EASI and subjective average pain scores.

may still cause significant pain and itch affliction. This caveat reinforces the importance of quantifying the total disease burden in these individuals. More work is needed to update the current evaluation tools to include pain symptoms to more accurately capture disease severity and QoL interference.

In addition to insomnia and psychological stress,⁵ Chrostowska-Plak et al⁶ reported that the most commonly implicated exacerbating factors of itch in AD include skin dryness, sweat, physical effort, food, and hot baths. Similarly, in our cohort, pain was triggered by sweat, warm ambient temperature, emotional stress, bathing in hot water, rubbing the skin, wearing wool or synthetic clothing, and topical medication use. It is important to recognize that medications used to treat AD, particularly in our cohort, such as calcineurin inhibitors, topical corticosteroids, and topical crisaborole, may have excipients that cause skin burning and pain. Thus, pain symptoms should be considered when developing AD therapies. Furthermore, pain symptoms significantly interfere with QoL by disrupting sleep, leisure activities, and activities of daily living. Disruption of sleep is a predominant interference caused by itch in patients with AD.⁶ The similarities in triggers and interference suggest that, although pain and itch are closely related, current grading assessments do not accurately assess complete burden. Without taking pain into account, treatment goals may not target true clinical affliction. We propose that further investigation of pain in AD should pave the way for development of alternative assessments for AD symptoms beyond itch.

CONCLUSIONS

Pain is a frequent and prominent symptom in AD and most commonly occurs simultaneously with itch in approximately 80% of

our patients. Further studies are needed to elucidate mechanisms and transmission of skin pain in patients with AD, particularly in the pediatric population where communicating pain symptoms is more difficult. Development of an evaluation tool using these pain descriptors is imperative and can further classify disease severity, improve our understanding of triggers and disease burden, and allow tailored management of AD. This may additionally foster the development of therapeutics that control neurogenic and psychogenic pain in inflammatory dermatoses.

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