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CLINICAL REPORT

Clinical Aspects of Itch in Adult Atopic Dermatitis Patients

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Although pruritus is an essential symptom of atopic dermatitis, its complex pathomechanism is not fully understood. The aim of this study was to characterize the clinical pattern of itch in adult subjects with atopic dermatitis. A total of 89 patients (59 females, 30 males) with atopic dermatitis, age range 18–60 years, were included in the study. Each patient completed a questionnaire about clinical features of itch. At the time of examination pruritus was present in 83.1% of patients. The majority of patients experienced itch in the evening (52.8%) and at night (38.2%). In 81% of patients itch caused difficulty in falling asleep. Twenty-five patients (28.1%) experienced itch every day. The main factors exacerbating pruritus were dryness, sweat, physical effort, food and hot baths. The most frequently used management regimes were topical emollients and oral antihistamines, but the long-term effects of these were very limited. There was a positive correlation between intensity of itch and age ($r = 0.3$, $p = 0.004$), and between disease duration and intensity of maximal itch ($r = 0.22$, $p = 0.04$). Patients with more severe disease reported more intense pruritus. *Key words: pruritus; itching; atopic dermatitis; eczema.*

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Itch is a cardinal symptom of atopic dermatitis (AD) and constitutes one of the major diagnostic criteria of this disease (1). Many authors have even suggested that it is present in every patient with AD. The skin of atopic patients, when compared with healthy individuals, is characterized by specific features that result in a lower itch threshold, prolonged maintenance of itch, and hypersensitivity to certain non-specific triggers (2, 3). Thus, pruritus in AD has a chronic and refractory character and can sometimes be very resistant to treatment. The itch-scratch vicious circle is frequently observed in patients with AD, being an important factor in the maintenance of AD symptoms. Furthermore, in a recently published study (4) more than 98% of AD subjects described their pruritus as annoying, bothersome, unpleasant or bothering and, importantly, as documented by our group, itch had a marked negative impact on various aspects of AD patients' well-being (5).

Although of great importance, clinical aspects of itching in AD have been poorly characterized in the literature. Most studies have concentrated mainly on sleep disturbance due to pruritus (6–8) and there are very few studies that have examined itching in AD more precisely (4, 9–11), with only one study that was performed on a European population (10). Thus, current knowledge about this symptom in AD is limited and further studies should be encouraged. We present here data about itch characteristics in patients with AD, in the hope that these results will improve our understanding of the pruritus that accompanies AD.

MATERIALS AND METHODS

Patient characteristics

A total of 89 adult patients with AD fulfilling the criteria of the Hanifin & Rajka classification (1) were enrolled in the study. All patients gave their written informed consent to be included. There were 59 (66.3%) females and 30 (33.7%) males, age range 18–60 years (mean age 31.6 ± 12.5 years). The patients were recruited from outpatient and inpatient clinics between September 2004 and December 2005.

Assessment of disease severity and itch

The study was approved by the local ethics committee. All patients underwent a careful dermatological examination. A specially designed questionnaire containing questions about demographic data (gender, age), atopic history (duration of AD, age at AD onset, personal and family history of atopy), clinical features of itching (frequency and diurnal/nocturnal variations of itching, presence of sleep disturbances, most common factors aggravating and alleviating itching) and administered therapy were completed by the dermatologists based on the anamnesis. Our questionnaire contained some elements that were patterned after the short-form McGill Pain Questionnaire (9, 12).

The severity of AD was assessed according to the SCORAD (SCORing of Atopic Dermatitis) index (13). Based on the SCORAD scores patients were classified as having mild (SCORAD scoring below 30 points), moderate (SCORAD scoring between 30 and 60 points) or severe AD (SCORAD over 60 points).

The severity of pruritus was evaluated with two different methods. The first was a visual analogue scale (VAS), in which patients were asked to estimate on the 10-cm long horizontal line the intensity of pruritus at the time of examination (VAS_{exam}) and at the time of maximal itching they had experienced recently (i.e. within the last two weeks) (VAS_{max}). The scores ranged from 0 (no itching) to 100 points (maximal itching). The second method was a validated 4-item questionnaire, which had been used successfully in our previous studies

on different pruritus types (14–16). The 4-item questionnaire consisted of evaluations of itching severity, frequency, localization and sleep disturbance, and the scale ranged from 0 (no itching) to 19 points (maximal itching).

Statistical analysis

All data were analysed statistically with Statistica® 6.0 software (Statsoft, Krakow, Poland). Student's *t*-test for independent variables, χ^2 test or univariate and multivariate analysis of variance (ANOVA/MANOVA) were used where appropriate. In addition, correlations between parameters were measured with Pearson's correlation test. Statistical significance was set at $p < 0.05$.

RESULTS

Characteristics of atopic dermatitis

Of the 89 enrolled subjects, 25 (28.1%) had mild, 38 (42.7%) moderate and 26 (29.2%) severe AD, as assessed by SCORAD (13). In the whole group, the results of SCORAD ranged between 4.7 and 84.7 points (mean: 46.0 ± 20.5 points) (Fig. 1). The age at onset of AD ranged from one month to 48 years (mean 8.7 ± 12.1 years); however, the majority of patients first developed AD before the age of 10 years (62 subjects, 69.7%). The mean disease duration was 22.8 ± 14.5 years (range one month to 59 years); most patients had had AD for more than 20 years (48 subjects, 53.9%). There was a positive family history of atopic disorders in 68 (76.4%) patients. In addition, 26 (29.2%) subjects also had other atopic diseases, such as asthma or hay fever. Most patients (61 subjects, 68.5%) were treated with antihistamines at the time of examination.

Frequency and character of itching

Seventy-four subjects (83.1%) experienced itch at the time of examination, and all patients had experienced pruritus in the past. The majority of patients had generalized pruritus. The itch was described as tickling by 48 (54.5%), burning by 43 (48.9%), stinging by 23 (26.1%) and pricking by 19 (21.6%) participants. One patient was not able to define the character of itch. Twenty-five (28.1%) patients reported experiencing itch every day, 34 (38.2%) had periods without itching lasting longer than one day but less than one week, 20 (22.5%) had itch-free periods that lasted up to one month and only 10 (11.2%) analysed subjects stated that the duration of periods without itching was longer than one month.

Intensity of itch

The intensity of itch at the time of examination (VAS_{exam}) ranged from 5 to 100 points (mean 31.3 ± 21.1 points) and at the time of maximal itch in the past (VAS_{max}) from 6 to 100 points (mean 79.2 ± 21.6 points). The itch scoring assessed with the 4-item questionnaire ranged from 5 to 19 points (mean 14.0 ± 4.4 points). A good correlation between VAS_{max} and 4-item questionnaire scoring was observed ($r = 0.56$, $p < 0.001$), whereas VAS_{exam} correlated with VAS_{max} and 4-item questionnaire to a lesser degree ($r = 0.36$, $p < 0.001$ and $r = 0.41$, $p < 0.001$, respectively). The most intense itching experienced by the majority of patients occurred in the evening ($n = 47$, 52.8%) or at night ($n = 34$, 38.2%). Only a small subgroup of AD patients reported the maximum severity of itch in the morning ($n = 10$,

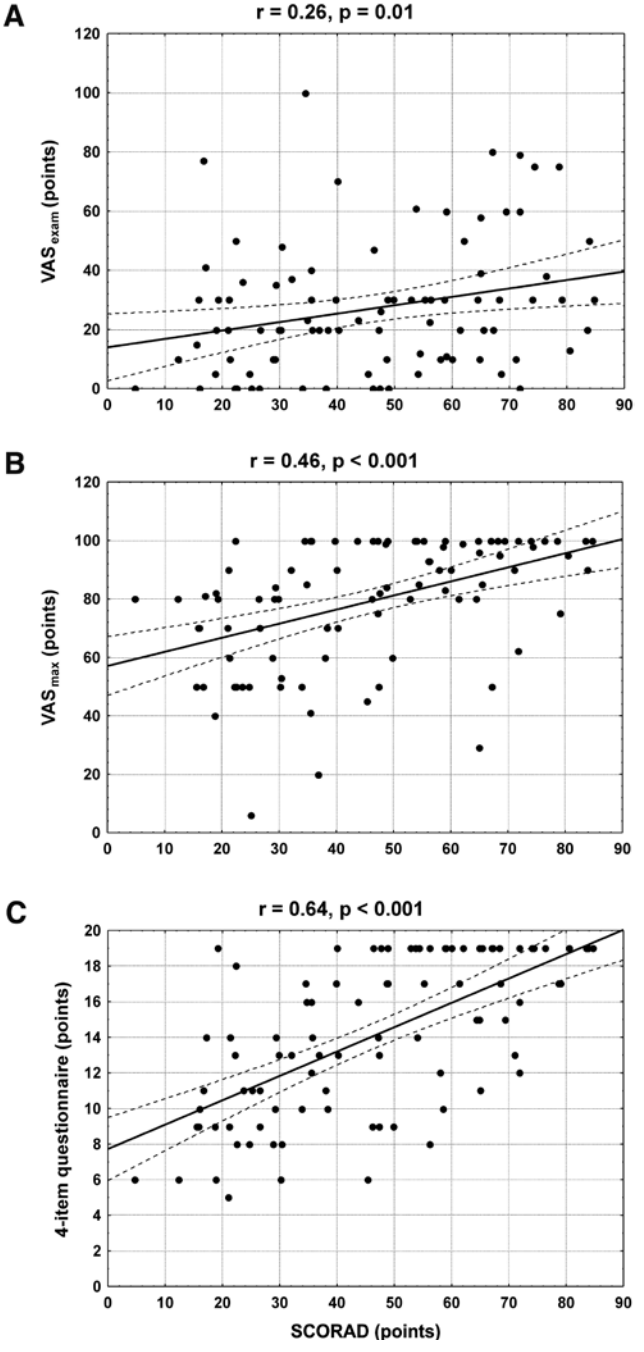

Fig. 1. Correlations between severity of atopic dermatitis (SCORAD) and pruritus intensity assessment. (A) VAS_{exam} vs. SCORAD; (B) VAS_{max} vs. SCORAD; (C) 4-item questionnaire vs. SCORAD.

11.2%). The remaining 13 atopic patients (14.6%) stated that the severity of the itch sensation was independent of the time of day.

Sleep disturbances

Itch caused significant difficulties in falling asleep in the majority of AD patients analysed ($n = 72$, 80.9%): 37 (41.6%) individuals reported severe and 35 (39.3%) mild sleeping problems. Moreover, 28 (31.5%) patients stated that they used sleep medication: 10 (11.2%) patients very often and the remainder (20.3%) from time to time.

Factors aggravating and alleviating itching

Major factors exacerbating itching were dryness of the skin ($n = 80$, 89.9%), sweating ($n = 78$, 87.6%), physical effort ($n = 58$, 65%), some foods ($n = 51$, 57.3%) and hot baths ($n = 49$, 55.1%). Interestingly, women stated significantly more commonly than men that diet might have a negative influence on their itch (72.9% vs. 26.7%, $p < 0.001$) (Fig. 2).

Various treatment modalities, including lubrication of the skin with topical emollients ($n = 72$, 80.9%), intake of oral antihistamines ($n = 69$, 77.5%), use of topical corticosteroids ($n = 61$, 68.5%), staying in a cool room ($n = 33$, 37.1%), taking a cool bath ($n = 21$, 23.6%), taking a rest ($n = 18$, 20.2%) and some others ($n = 10$, 11.2%) were applied by the surveyed patients to reduce itch. Among the two most commonly applied therapeutic options, topical emollients were considered by 23 (25.8%) individuals as providing long-term relief of itching, by 58 (65.1%) as providing short-term relief, and by 4 (4.5%) as being ineffective. Seven (7.9%) patients did not state an opinion about the usefulness of emollients. Antihistamines were assessed as providing long-term relief of itch by 12 (13.5%), short-term relief by 58 (65.1%) and having no antipruritic effect by 12 (13.5%) individuals. Similarly to emollients, 7 (7.9%) participants had no idea about the efficacy of antihistamines. Moreover, comparison of itch intensity between patients taking or not antihistamines during the examination revealed no significant differences (Table I).

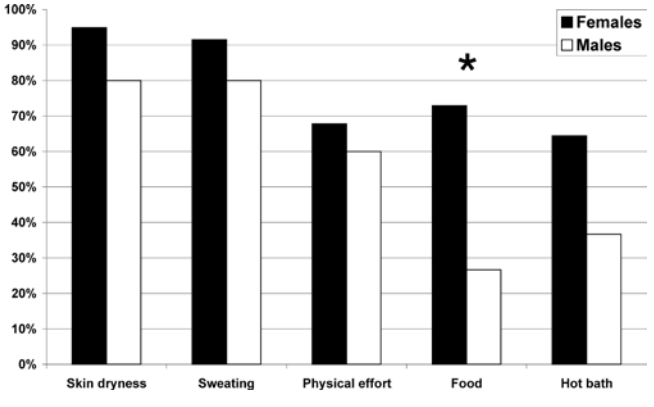

Fig. 2. Comparison of factors aggravating itching between females and males (*$p < 0.001$ according to χ^2 test).

Relationships between clinical parameters and itching intensity

We observed significant correlations between the values of SCORAD index and results obtained by all methods of itching measurements (Table II). Other clinical factors that might be relevant for determination of itching severity were patient age and disease duration (Tables II and III). However, these parameters appeared to be less important, as significant correlations were found only between patient age and the 4-item questionnaire scoring ($r = 0.3$, $p = 0.005$) and disease duration and VAS_{max} ($r = 0.22$, $p = 0.04$) (Table II). Furthermore, when age, disease duration and SCORAD were entered as covariates for MANOVA, SCORAD was found to be the only independent factor significantly influencing the severity of pruritus. In addition, no significant relationships were found between itch severity and other clinical parameters, such as gender, age at disease onset, coexistence of other atopic diseases and positive family history of atopy (Tables II and III).

DISCUSSION

Itch is an essential symptom of AD; however, its complex pathomechanism is still not fully understood. Our results seem to confirm previous suggestions that histamine, one of the major itch mediators, plays a minor role in atopic itch (2, 17, 18). Here, we found no difference in itch intensity between subjects taking antihistamines and those that did not. Furthermore, the majority of patients analysed claimed that antihistamines provided only short-term relief of itch, but were rather ineffective as long-term anti-pruritic therapy. These suggestions seem to be of importance and must be confirmed by prospective trials in the future, as antihistamines are currently often prescribed in AD, although they may be of very limited value.

Approximately 80% of the analysed population experienced pruritus at examination. However, as it was observed that AD patients frequently experienced the

Table I. *Comparison of SCORAD (SCOring of Atopic Dermatitis) and itch intensity in relation to treatment with antihistaminics*

	Antihistaminics (mean ± SD)	Non-antihistaminics (mean ± SD)	*p*
SCORAD (points)	48.5 ± 20.0	40.7 ± 20.9	0.09
VAS_{exam} (points)	26.3 ± 25.8	27.4 ± 20.8	0.83
VAS_{max} (points)	77.4 ± 22.3	80.1 ± 21.4	0.59
4-item questionnaire (points)	13.4 ± 4.4	14.3 ± 4.4	0.34

SD: standard deviation; VAS: visual analogue scale.

Table II. *Correlations between selected clinical parameters and pruritus intensity*

Clinical description		VAS_{exam}	VAS_{max}	4-item questionnaire
Age	r	0.12	0.18	0.3
	p	0.25	0.09	**0.005**
Disease severity	r	0.26	0.46	0.64
(SCORAD)	*p*	**0.01**	**<0.001**	**<0.001**
Disease duration	r	0.03	0.22	0.19
	p	0.77	0.04	0.07
Age at disease onset	r	0.09	– 0.07	0.08
	p	0.4	0.51	0.48

r-values according to Pearson's correlation test.
VAS: visual analogue scale; SCORAD: SCORing of Atopic Dermatitis.

most severe itching in the evening or at night, physicians must remember that the intensity of pruritus at the time of examination (usually performed in the morning or around noon) is frequently not the highest one. Moreover, it was reported that itching is not only most severe, but is also most frequent in the evening or at night (9). Therefore, in order accurately to assess the needs of the AD patient regarding anti-pruritic therapy it is crucial to ask at examination how the patient would rate the severity of pruritus within the last whole day or even couple of days. It is still not fully clear why patients experience itching in the evening or at night. However, it could be connected with tiredness in the evening or with decreased pruritus threshold in the warm atmosphere of the bed. Moreover, it could be supposed that while resting in the evening patients become more aware of pruritic sensations compared with other times of day, when they are more active. The phenomenon that itching is often most intense in the evening or at night is also connected with problems of falling asleep or awakening during the night, as is frequently reported in pruritic subjects (9, 19). As shown by Stores et al. (20) this could lead to a significant decrease in efficacy of sleep, especially among children. Thus, some patients with AD may require sleep medication to improve their functioning, even if they do not request it.

Table III. *Relationships between selected clinical parameters of atopic dermatitis and pruritus intensity (all results given as means ± standard deviations)*

Clinical description	VAS_{exam} (points)	VAS_{max} (points)	4-item questionnaire (points)
Age			
<30 years (*n*=53)	24.9 ± 21.6	76.9 ± 23.0	13.2 ± 4.2
≥30 years (*n*=36)	30.2 ± 23.4	82.7 ± 19.2	15.2 ± 4.5
	0.28[a]	0.21[a]	**0.03**[a]
Gender			
Females (*n*=59)	27.7 ± 23.7	80.5 ± 20.9	14.1 ± 4.7
Males (*n*=30)	25.8 ± 19.8	76.8 ± 23.1	13.8 ± 3.8
	0.72[a]	0.46[a]	0.74[a]
Disease severity			
Mild (*n*=25)	19.0 ± 19.0	66.5 ± 20.1	10.4 ± 3.5
Moderate (*n*=38)	26.1 ± 21.2	80.9 ± 21.4	14.1 ± 4.2
Severe (*n*=26)	36.2 ± 24.4	89.0 ± 17.7	17.3 ± 2.4
	0.02[b]	**<0.001**[b]	**<0.001**[b]
Disease duration			
<20 years (*n*=41)	27.1 ± 20.9	74.2 ± 22.9	13.1 ± 4.2
≥20 years (*n*=48)	26.9 ± 23.8	83.5 ± 19.7	14.8 ± 4.4
	0.97[a]	**0.04**[a]	0.07[a]
Age at disease onset			
<10 years (*n*=62)	28.6 ± 23.7	77.2 ± 21.3	14.4 ± 4.3
≥10 years (*n*=27)	26.4 ± 21.9	80.1 ± 21.9	13.9 ± 4.5
	0.68[a]	0.56[a]	0.62[a]
Coexistence of other atopic diseases			
Yes (*n*=26)	30.4 ± 20.7	82.6 ± 17.4	14.7 ± 4.7
No (*n*=63)	25.7 ± 23.0	77.9 ± 23.1	13.8 ± 4.3
	0.37[a]	0.35[a]	0.39[a]
Family history of atopy			
Positive (*n*=68)	27.1 ± 23.1	79.9 ± 21.3	14.3 ± 4.4
Negative (*n*=21)	26.7 ± 20.4	77.3 ± 23.1	13.0 ± 4.4
	0.94[a]	0.64[a]	0.22[a]

[a]*p*-values according to Student's *t*-test, [b]*p*-values according to analysis of variance.
VAS: visual analogue scale.

Itch in AD has a chronic and persistent character and the intervals that were free of this symptom were usually short. In our study more than 28% of patients experienced itch every day and, by contrast, only 11% had pruritus-free periods lasting longer than one month. This is in accordance with the results obtained in the study by Yosipovitch et al. (9), in which nearly all patients experienced pruritus at least every second week. Frequency of itching could be even higher, as shown by the study using a web-based questionnaire, that 91% of AD subjects reported pruritus on a daily basis, and 68% experienced itching at least five times a day (4). Furthermore, itching in AD seems to be very severe, when compared with other pruritic diseases (14, 15). Many AD patients also stated that pruritus is associated with pain (59%) and heat sensation (53%) (4). Thus AD must be considered as a disease with very frequently occurring, severe pruritus.

Regarding factors influencing the frequency of itching, skin dryness and sweating were the two most frequently mentioned parameters aggravating pruritus in our study. In another study (4) sweating was associated with itching in approximately 25% of patients. However, Yosipovitch et al. (9) found that sweat increased itch severity in 96% of AD individuals and it was the most frequent parameter exacerbating pruritus, followed by physical effort (73%), skin dryness (71%) and stress (71%). Although the problem of sweating has not been well investigated previously, it is worth mentioning that "presence of itch when sweating" belongs to the minor AD criteria proposed by Hanifin & Rajka (1). The mechanism of itch during sweating is unclear, but it seems probable that during water evaporation sweat becomes hypertonic. In subjects with an altered skin barrier, as in AD, changes in ion concentration on the skin surface might directly activate pruriceptive nerve endings, leading to pruritus. Interestingly, a significant number of patients with AD also regarded hot temperature as a provocative factor of itch; to prevent

or reduce pruritus they frequently used cool baths or avoided warm rooms and physical exercise (9). Another frequently applied treatment modality was emollients. Remarkably, they were considered as providing long-term relief of pruritus by 25% of studied subjects and as providing short-term reduction of itching by a further 65%. Recently we have also documented that, besides reducing pruritus and skin xerosis, emollients improved treatment results of AD with topical corticosteroids, being very important in maintaining AD remission (21). The significant importance of skin dryness may explain the high efficacy of emollients in the treatment of pruritus observed by our patients. Based on these observations it can be concluded that emollients play a crucial role in the proper therapy of AD individuals, also helping to reduce pruritus.

Furthermore, the proper treatment of AD is of key importance for controlling pruritus, as the disease severity was the major clinical parameter influencing itching intensity. It must be mentioned that our results might be influenced by the fact that the SCORAD index contains a VAS scale for itching evaluation as a part of AD severity assessment and it may produce some bias in the interpretation of the data. However, the strongest relationship was found between the SCORAD index and 4-point questionnaire scoring, suggesting that AD severity is indeed an important parameter influencing pruritus severity. In addition, Darsow et al. (10) also observed a significant correlation between pruritus intensity, as measured by the Eppendorf itch questionnaire, and AD severity evaluated by SCORAD ($r = 0.33$, $p < 0.05$). However, they noticed that the pruritus scoring was skewed to higher intensities compared with objective SCORAD (10). Moreover, some items defined as "compulsive, ecstatic component" (items of pleasure, loss of control, pulsating and a warm sensation in association with taking action against the itch by pinching or setting about it) were statistically independent from objective SCORAD (10).

Nevertheless, in our opinion, disease severity should still be considered as the major parameter determining itch intensity in AD. Other factors, such as age or disease duration, might also be of some importance, but this requires further investigation.

In conclusion, itch is one of the major problems experienced during the course of AD. It has a chronic and refractory character and may be intensified by many endogenous and exogenous factors. The effects of treatment are often partial and of short duration. Thus, further research is required to determine better therapeutic options for 10 patients.

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