Original paper

Assessment of the sensory threshold in patients with atopic dermatitis and psoriasis

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Abstract

Introduction: Atopic dermatitis (AD) and psoriasis are chronic inflammatory skin diseases frequently accompanied by itching. The exact pathogenesis of dermatological pruritus remains unknown, but it is believed that altered skin innervation may play a role.

Aim: The assessment of the sensory threshold in AD and psoriasis in relation to pruritus experienced by patients.

Material and methods: A total of 18 subjects with AD, 20 with psoriasis and 49 healthy controls were exposed to alternating current generated by the current source. A selected preset of current frequencies (ranging from 5 Hz to 2000 Hz) allowed a selective stimulation of different nerve endings (Aβ, Aδ and C-type). Pruritus severity was measured with visual analogue scale (VAS) and an itch questionnaire developed in house. All results were analyzed statistically.

Results: Sensory thresholds within the uninvolved skin of AD or psoriasis patients were significantly higher than in healthy volunteers ($p < 0.001$), and no significant differences were found between AD and psoriasis ($p > 0.05$). Similarly, sensory thresholds within the diseased skin of AD or psoriasis were significantly higher than in the normal skin ($p < 0.01$), and patients with psoriasis had also a significantly higher threshold than AD individuals ($p < 0.05$). The sensory threshold inversely correlated with pruritus severity in AD and psoriasis and the highest correlation was found for 5 Hz frequency predominantly stimulating C fibers (VAS: $R = –0.32$, $p < 0.05$; pruritus questionnaire: $R = 0.54$, $p < 0.001$).

Conclusions: Evaluation of the sensory threshold may be a valuable tool for pruritus assessment, but further studies are still warranted.

Key words: pruritus, itch, diagnostics, skin diseases.

Introduction

Chronic inflammatory skin diseases, like atopic dermatitis (AD) or psoriasis, are frequently accompanied by itching, a subjective sensation evoking a desire to scratch. In many patients it is an extremely distressing and bothering ailment, making it a very relevant clinical problem [1–3]. Due to its subjective nature, the objective and valid assessment of pruritus remains a significant challenge [4]. The pathophysiology of chronic pruritus in skin diseases is also still not precisely elucidated despite the fact that a number of substances have been postulated as possible itch mediators [5]. However, it was observed that patients with AD or psoriasis suffering from pruritus demonstrated increased nerve density within the epidermis and dermis [6–9]. Interestingly, asreported by Urashima and Nahara [6], the diameter of skin nerve fibers in AD was also much larger, because of the large number of axons in each nerve fiber. It was postulated that an abnormal skin innervation in patients with chronic pruritus might be responsible for their higher sensitivity to itchy stimuli due to lowering of itch threshold [10–13]. It was observed that tactile threshold in patients with nodular prurigo, a chronic itchy skin condition, was lower than in controls and this phenomenon was reversed by capsaicin suggesting neuropeptide involvement, mainly substance P [10]. Furthermore, the basal skin blood flow

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level was more fluctuating in itchy areas than in healthy skin areas in nodular prurigo patients suggesting an abnormal spontaneous activity of nociceptive peripheral nerve fibers and a consequent release of vasoactive agents from their terminals (axon reflex) [10]. People with chronic pruritus may be even prone to feel itch after stimuli that normally do not evoke pruritus. For instance, it was shown that painful stimuli evoked itch rather than pain in AD patients suggesting the presence of a central sensitization phenomenon [14].

Several studies demonstrated that electric stimulation might evoke pruritus in patients with chronic itch [15, 16]. It was also shown that different frequencies of electric stimuli may activate different nerves subtypes [17]. Many studies indicated the role of transcutaneous electrical nerve stimulation to specify nerve function in various types of peripheral neuropathies [18–23]. Taking into account the ease of evoking electric stimuli in clinical settings [16, 24], it seems interesting to test whether measurement of the threshold for electrical stimuli might be a helpful procedure in evaluating pruritus intensity.

Aim

To verify this hypothesis we performed a study to assess the sensory threshold for electric stimuli in AD and psoriasis in relation to perceived pruritus.

Material and methods

Patients

A total of 87 subjects including 18 patients with AD, 20 with psoriasis and 49 healthy volunteers were recruited into the study. Each participant after getting a detailed explanation about the study aim signed an informed consent form prior to any study procedure. Detailed demographic and clinical characteristics of the studied population are demonstrated in Table 1.

Study design

The study was approved by the Bioethical Committee of Wroclaw Medical University. All subjects underwent thorough anamnesis and physical examination. Atopic dermatitis severity was assessed according to Scoring of

Table 1. Demographic and clinical characteristics of studied subjects (results demonstrated as cardinality and frequencies or means ± standard deviations)

Parameter	Patients with atopic dermatitis	Patients with psoriasis	Controls	Value of *p*
N	18	20	49	–
Gender:				
Males	8 (44.4)	16 (80.0)	31 (63.3)	< 0.01
Females	10 (55.6)	4 (20.0)	18 (36.7)	
Age [years]	37.8 ±14.4	44.6 ±12.9	26.3 ±9.6	< 0.001
Education:				
Primary school	0 (0)	1 (5.0)	1 (2.0)	0.24
High school	14 (77.8)	13 (65.0)	43 (87.8)	
University	4 (22.2)	6 (30.0)	5 (10.2)	
Place of living:				
Village	2 (11.1)	0 (0)	9 (18.4)	< 0.001
Small town	10 (55.6)	14 (70.0)	6 (12.2)	
Big city	6 (33.3)	6 (30.0)	34 (69.4)	
Disease duration [years]	25.4 ±16.5	20.8 ±17.1	–	0.4
Duration of disease exacerbation [months]	3.1 ±3.1	8.3 ±8.9	–	0.03
Pruritus intensity:				
VAS currently	3.6 ±2.8	3.4 ±2.4	–	0.87
VAS_{max}	6.4 ±2.5	4.8 ±2.8	–	0.07
Pruritus questionnaire	15.2 ±3.8	12.0 ±4.4	–	0.02
Disease severity:				
SCORAD	50.8 ±16.6	–	–	–
PASI	–	19.6 ±10.0	–	

Results presented as mean ± standard deviation or n (%).

AD (SCORAD) [25], while psoriasis severity according to Psoriasis Area and Severity Index (PASI) [26]. Pruritus intensity was evaluated with the 10-point Visual Analogue Scale (VAS) [27, 28] and the validated itch questionnaire developed on site [29]. With VAS patients assessed pruritus intensity at the time of examination ($VAS_{current}$) and maximal itch intensity within the previous 3 days (VAS_{max}). Scoring of itch questionnaire with VAS ($VAS_{current}$ and itch questionnaire: $\rho = 0.45$, $p < 0.01$; VAS_{max} and itch questionnaire: $\rho = 0.47$, $p < 0.01$).

Assessment of the sensory threshold

Participants were exposed to the alternating square wave current of following frequencies: 5 Hz, 250 Hz, and 2000 Hz to obtain stimulation of unmyelinated C (C), small myelinated A (Aδ) and large myelinated A (Aβ) nerve fibres, respectively. Prior to measurements, the skin was degreased with ethanol and next the electrodes were attached to the palmar surface of the forearm. Both, involved and uninvolved skin was tested in AD and psoriasis patients. The alternating current of defined frequency was generated by the current source constructed by the authors (KC and AR) (Figure 1, pending patent application P. 400 563 (PK/1662/AW)). The current intensity was gradually increased with manual regulation. Patients were instructed to indicate the moment of the first current perception. Current intensity was measured with an ammeter integrated with the current source. Current frequencies were tested in a random order.

Statistical analysis

Each measurement was performed in triplicate and the mean value of these three measurements was used for further analysis. All results were analysed statistically using Statistica®10.0 (StatSoft, Cracow, Poland). The significance of the observed relationships of studied parameters were determined by the analysis of variance (ANOVA), with paired and unpaired Student's *t* test or Spearman's rank correlation test. A *p*-value lower than 0.05 was considered as statistically significant.

Results

Measurement of the sensory threshold in healthy controls

The mean sensory thresholds in healthy subjects at 5 Hz, 250 Hz and 2000 Hz current frequency were 118.1 ±25.5 µA, 192.9 ±24.5 µA and 687.1 ±86.0 µA, respectively. Women had a significantly lower sensory threshold at 5 Hz compared to men (Table 2). In addition, patients living in villages showed significantly higher mean sensory thresholds than people living in towns or cities. There was no significant relationship between the sensory threshold level and age of healthy volunteers (Table 2).

Sensory threshold in atopic dermatitisand psoriasis

Patients with AD demonstrated a significantly higher mean sensory threshold for electric stimuli when com-

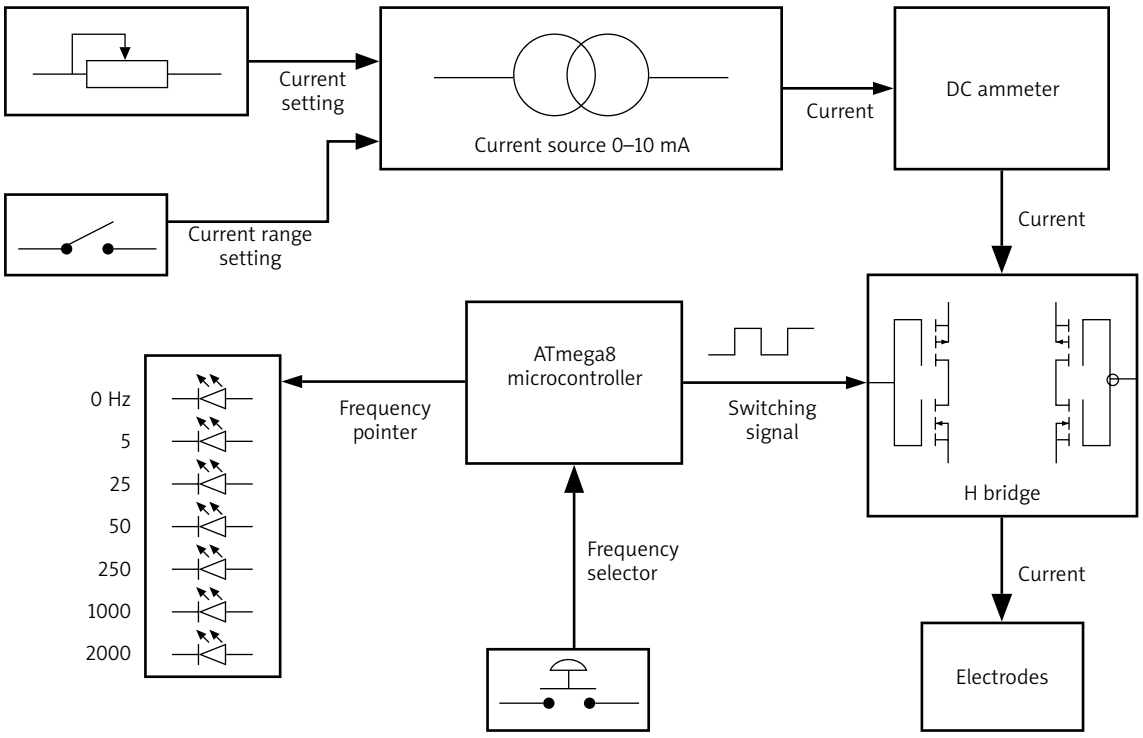

Figure 1. Schematic overview of the current source constructed for assessment of the sensory threshold

Table 2. Mean sensory threshold levels (μA) for different current frequencies in healthy subjects

Parameter	Current frequency		
	5 Hz	250 Hz	2000 Hz
Gender:			
Females	74.9 ±20.4	157.6 ±14.8	589.3 ±89.5
Males	192.6 ±56.7	253.7 ±59.9	864.2 ±175.2
	$p = 0.02$	$p = 0.47$	$p = 0.17$
Place of living:			
Village	292.0 ±108.1	318.9 ±98.1	906.5 ±234.5
Small town	100.7 ±31.5	206.4 ±28.3	985.0 ±148.7
Big city	75.2 ±16.9	157.2 ±21.2	561.7 ±99.4
	$p < 0.01$	$p = 0.04$	$p = 0.11$
Age	$\rho = 0.1$ $p = 0.48$	$\rho = 0.07$ $p = 0.63$	$\rho = 0.07$ $p = 0.64$

Results presented as mean ± standard error of mean, r – Pearson's correlation coefficient.

Table 3. Mean sensory threshold levels (μA) for different current frequencies in healthy subjects

Parameter	Current frequency		
	5 Hz	250 Hz	2000 Hz
Atopic dermatitis:			
Lesional skin	293.2 ±72.1	378.9 ±103.6	1129.8 ±171.7
Non-lesional skin	487.3 ±87.2	546.4 ±80.6	1584.9 ±193.8
	$p = 0.06$	$p = 0.14$	$p = 0.06$
Psoriasis:			
Lesional skin	693.1 ±161.2	887.5 ±182.2	2048.4 ±207.1
Non-lesional skin	681.1 ±192.3	586.6 ±153.4	1435.5 ±156.7
	$p = 0.92$	$p = 0.01$	$p = 0.001$
Healthy controls	118.1 ±25.5	192.9 ±24.5	687.1 ±86.0

Results demonstrated as mean ± standard error of mean, r – Pearson's correlation coefficient.

pared to healthy controls. Interestingly, a trend toward lower levels of sensory thresholds was observed in lesional AD skin compared to non-lesional one. Patients with psoriasis also showed higher sensory threshold levels when compared to the control group. They also demonstrated higher threshold levels within lesional psoriatic skin when compared to lesional AD skin ($p < 0.01$). In contrast to AD, patients with psoriasis demonstrated a higher sensory threshold level at 250 Hz and 2000 Hz within lesional skin compared to non-lesional one (Table 3).

Regarding patients with AD, there was no significant correlation between the sensory threshold level and disease duration, duration of the current AD exacerbation and disease severity according to SCORAD (Table 4). Similarly to AD, no significant correlations were found in psoriasis patients in regard to disease duration, duration of current disease exacerbation and psoriasis severity assessed with PASI (Table 4).

Relationship between sensory threshold and perception of pruritus

The intensity of pruritus at the time of examination was similar between AD and psoriasis patients (mean $VAS_{current}$: 3.6 ±0.7 points vs. 3.4 ±0.5 points, respective-

Table 4. Correlations between selected clinical parameters and sensory thresholds in patients with atopic dermatitis and psoriasis

Variables	Atopic dermatitis			Psoriasis		
	5 Hz	250 Hz	2000 Hz	5 Hz	250 Hz	2000 Hz
Disease duration:						
Lesional skin	$\rho = 0.01$; $p = 0.97$	$\rho = -0.07$; $p = 0.8$	$\rho = -0.01$; $p = 0.98$	$\rho = 0.3$; $p = 0.21$	$\rho = 0.14$; $p = 0.56$	$\rho = 0.14$; $p = 0.55$
Non-lesional skin	$\rho = -0.05$; $p = 0.85$	$\rho = -0.27$; $p = 0.27$	$\rho = -0.14$; $p = 0.58$	$\rho = -0.04$; $p = 0.87$	$\rho = -0.06$; $p = 0.79$	$\rho = -0.14$; $p = 0.54$
Duration of the current disease exacerbation:						
Lesional skin	$\rho = -0.34$; $p = 0.18$	$\rho = -0.36$; $p = 0.16$	$\rho = -0.2$; $p = 0.45$	$\rho = 0.02$; $p = 0.94$	$\rho = -0.07$; $p = 0.77$	$\rho = 0.12$; $p = 0.63$
Non-lesional skin	$\rho = -0.19$; $p = 0.47$	$\rho = -0.37$; $p = 0.14$	$\rho = 0.08$; $p = 0.77$	$\rho = -0.03$; $p = 0.91$	$\rho = -0.11$; $p = 0.63$	$\rho = 0.19$; $p = 0.42$
Disease severity (SCORAD/PASI):						
Lesional skin	$\rho = 0.15$; $p = 0.54$	$\rho = 0.1$; $p = 0.68$	$\rho = 0.4$; $p = 0.1$	$\rho = -0.1$; $p = 0.67$	$\rho = -0.14$; $p = 0.57$	$\rho = -0.22$; $p = 0.35$
Non-lesional skin	$\rho = 0.18$; $p = 0.48$	$\rho = 0.22$; $p = 0.38$	$\rho = 0.14$; $p = 0.58$	$\rho = -0.16$; $p = 0.5$	$\rho = -0.25$; $p = 0.28$	$\rho = -0.33$; $p = 0.15$

ρ – *Spearman's correlation coefficient.*

ly, $p = 0.87$). However, maximal itch intensity as well as pruritus scoring according to the itch questionnaire was slightly higher in AD patients than in psoriasis individuals (mean VAS_{max}: 6.4 ±0.6 points vs. 4.8 ±0.6 points, respectively, $p = 0.07$; mean itch questionnaire scoring: 15.2 ±0.9 points vs. 12.0 ±1.0, respectively, $p = 0.02$).

Regarding the sensory threshold for electric stimuli and intensity of pruritus we found that itch severity significantly correlated with the sensory thresholds for the current frequency of 5 Hz (Table 5). Significant correlations were also observed for itch questionnaire and sensory thresholds for 250 Hz and 2000 Hz, but the correlation coefficient was lower than for 5 Hz (Table 5).

Discussion

In this study we exposed 49 healthy volunteers, 18 patients with AD and 20 with psoriasis to alternating current stimulation with frequencies ranging from 5 Hz to 2000 Hz by using a current source constructed specially for this research. Based on achieved results it could be supposed that measurement of the sensory threshold might be a valuable, additional tool for the valid assessment of pruritus. However, several issues should be solved in the future prior to more widely employment of such devices in routine clinical settings. Unexpectedly, we found higher sensory thresholds in patients with AD or psoriasis than in healthy controls. These results are partly contradictory to some previously published reports. Kobayashi *et al.* [11] observed that patients with AD showed a lower barrier function and lower current perception threshold than normal individuals and the current perception threshold was found to be inversely correlated with transepidermal water loss levels. However, not all studies were able to demonstrate current threshold lowering in patients with AD and these discrepancies must be explained in the future. Ikoma *et al.* [16] did not find any difference between healthy subjects and AD patients regarding their response to electrical (0.08–8 ms, 2–200 Hz) and chemical (histamine iontophoresis; 100 microC) stimuli. Accordingly, Mori *et al.* [24] observed no statistically significant difference in the current perception threshold among extrinsic AD, intrinsic AD and normal controls. In contrast, our group found an even increased sensory threshold to current stimulation in patients with AD or psoriasis. Our findings are in accordance with the study by Yudina *et al.* [13] who documented elevated thermal thresholds in patients with AD. It is possible that the obtained results are influenced by the shape of the excitation current waveform. Other authors used sinusoidal [11, 24] or pulse [13, 16] excitation signal while in our study it was a bipolar square wave with duty cycle of 0.5. An increased threshold for electric stimuli in AD or psoriasis patients may be related to the thickening of epidermis, especially stratum corneum, a phenomenon frequently observed in these entities. This might cause that the current density varied in the subsequent layers of the electrically stimulated skin. Probably, majority of the current flew through upper epidermis layers while bypassing lower epidermis layers and dermis. As a consequence, a lower current perception threshold was observed in psoriasis and AD patients. Furthermore, patients with AD or psoriasis frequently apply various topical formulations to improve the skin condition. Although we have always cleaned the evaluated skin area prior to examination with alcohol, we cannot exclude that long-term application of emollients, which is frequently observed in this group of patients, might significantly alter the current conduction in the outer layers of epidermis.

One of the most relevant findings of our study was the significant correlation of the sensory threshold for 5 Hz with itch intensity. It is believed that the alternate current of 5 Hz mostly stimulates sensory C-fibres [30]. These nerve fibres are also thought to be the most important for conduction of itch stimuli. Having this in mind it could be supposed that with 5 Hz current we might test the excitation threshold of cutaneous C fibres. The lower the threshold is, the more severe pruritus the patient may experience. Thus, determination of the sensory threshold may be a valuable and objective examination

Table 5. Correlations between itch intensity and sensory thresholds in patients with atopic dermatitis and psoriasis

Variables	5 Hz	250 Hz	2000 Hz
$VAS_{current}$:			
Lesional skin	**$\rho = -0.33$, $p = 0.04$**	$\rho = -0.3$, $p = 0.06$	$\rho = -0.26$, $p = 0.12$
Non-lesional skin	$\rho = 0.05$, $p = 0.76$	$\rho = -0.02$, $p = 0.89$	$\rho = 0.05$, $p = 0.75$
VAS_{max}:			
Lesional skin	**$\rho = -0.32$, $p < 0.05$**	$\rho = -0.29$, $p = 0.07$	$\rho = -0.19$, $p = 0.26$
Non-lesional skin	$\rho = 0.09$, $p = 0.59$	$\rho = 0.05$, $p = 0.77$	$\rho = 0.21$, $p = 0.22$
Itch questionnaire:			
Lesional skin	**$\rho = -0.54$, $p < 0.001$**	**$\rho = -0.46$, $p < 0.01$**	**$\rho = -0.35$, $p = 0.03$**
Non-lesional skin	$\rho = -0.09$, $p = 0.57$	$\rho = -0.03$, $p = 0.84$	$\rho = 0.15$, $p = 0.38$

VAS – Visual Analogue Scale, r – Pearson's correlation coefficient; statistically significant results marked in bold.

during the assessment of pruritic dermatoses. Furthermore, it seems that at least some patients with chronic itch may demonstrate asmall nerve fibre dysfunction and measurement of the electric sensory threshold might be a valuable and promising adjunct diagnostic method for assessment of such patients. However, it should be underlined that a great variability of the sensory threshold between individual persons were also noted, which may hinder the proper interpretation of achieved results. Therefore, any reference ranges for sensory thresholds must be established with a great caution.

Interestingly, we also found that women had a significantly lower sensory threshold than men. Such finding might be explained by gender differences in the thickness of epidermis and, probably, by possible differences in cutaneous innervations. On the other hand, the differences between people living in the country and those living in the cities or towns can be caused by various work performed in different living places as well by different habits.

Conclusions

Our results confirmed previous suggestions that the most relevant population of nerve fibers conducting pruritic stimuli are unmyelinated C-fibers that are selectively activated by the 5 Hz alternating current. Measurement of current sensory perception might be a valuable tool for the assessment of patients suffering from dermatological pruritus.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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