Exploratory Study of Intracutaneous Histamine Stimulation in Patient Populations with Chronic Pruritus

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Chronic pruritus can be a diagnostic sign of an underlying disease. In the intracutaneous histamine test, histamine (one of the best-known inducers of pruritus) may cause different reaction patterns depending on the underlying disease. The aim of this study was to determine if an intracutaneous injection of histamine can differentiate between the causes of chronic pruritus and thus be used as a diagnostic test in chronic pruritus of unknown aetiology. A total of 140 subjects with chronic pruritus with various dermatological, systemic or neurological diseases were included. The intracutaneous histamine test was performed once on each subject. Erythema, wheal and pruritus intensity were measured and analysed. Significantly greater wheal size was observed in patients with systemic or multifactorial causes. In general, there was a significant correlation between age and wheal size. Also, noticeable differences were found between males and females regarding pruritus and wheal size. In summary, the exact type of chronic pruritus could not be clearly determined based on the results of the intracutaneous histamine test. However, the results provide valuable insights into specific reaction patterns to experimental histamine-induced itch, e.g. sex-specific differences in the neurophysiology of pruritus, which should be considered in future studies.

Key words: chronic pruritus; itch; diagnostics; C-fibres; atopic dermatitis; neurophysiology.

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SIGNIFICANCE

Chronic itch (or pruritus) is a symptom of many underlying diseases, but clinically it is often not easy to determine the exact cause. The aim of this study was to determine whether a specific skin test, the intracutaneous histamine test, can differentiate between various potential causes of chronic itch. The results showed that the histamine test might indicate when there is a cause of chronic itch in the field of systemic, internal diseases. In addition, there were differences between male and female patients regarding the test reaction pattern.

Chronic pruritus is defined as itch that lasts for at least 6 weeks (1). There is a wide range of potential underlying diseases (German Guideline Chronic pruritus) (2). These diseases can be of systemic origin (e.g. chronic renal failure, hepatic failure, chronic hepatitis C, and cholestatic pruritus) or of dermatological origin (e.g. atopic dermatitis (AD) and cutaneous autoimmune diseases, such as bullous pemphigoid or dermatitis herpetiformis). Other causes can be neurological diseases, such as brachioradial pruritus, notalgia paraesthetica, post-herpetic neuralgia or multiple sclerosis. In addition, psychiatric diseases, such as depression or schizophrenia, can also cause chronic pruritus. Epidemiological studies have revealed that chronic pruritus has a point prevalence of 13.5% in the general population (3), among the working population point prevalence shows even higher values of up to 16.8% (4). Among elderly patients the values increase to 20.3%. Determining factors are female sex, low social economic status, mental distress and atopic background (5).

The most commonly known and studied mediator of pruritus is histamine (6–8). It is released by mast cells and causes pruritus by binding to the histamine 1-receptor on mechano-insensitive sensory afferents (mechano-insensitive-C-nociceptors) (9, 10). Abundant histamine release results in the clinical sign of a local wheal (urticaria) with a surrounding erythema in addition to the symptom of pruritus. The erythema is of neurogenic origin and reflects the peripheral release of neuropeptides from pruriceptors following their activation by histamine, and indicates the bidirectional interaction between neurones and innervated tissue. Accordingly, this reaction pattern is used as a positive control in allergological diagnostics where histamine is applied intracutaneously (11). During recent years many details of the underlying pathomechanism have been elucidated. Interestingly, histamine and the histamine 1 receptor expressed on mechano-insensitive-C-nociceptors were demonstrated to require the neuronal function of both PLCbeta3 and the TRPV1 channel to induce itch (12). Moreover, upon activation of the Toll-like receptor 4 (TLR4), expressed on sensory neurones, histamine-induced itch signal transduction is enhanced by potentiating TRPV1 activity (13,

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14). Interestingly, also, lipopolysaccharides (LPS) and μ-opioid receptor agonists, such as morphine, bind and activate TLR4 (15). This mechanism might be highly relevant in pruritic diseases that have increased endogenous production of opioids or show efficacy to an antipruritic therapy with μ-opioid receptor antagonists, such as certain dermatoses (AD, urticaria) and systemic diseases (cholestatic pruritus, nephrogenic pruritus) (16–18). It is important to understand these underlying mechanisms, since they can help to understand and correctly interpret specific results of an intracutaneous histamine test in various patient populations. With respect to the literature there is a large variety of studies investigating the symptoms pruritus, erythema and wheal induction by intracutaneous histamine testing, but focusing mainly on AD. On the one hand it was shown that patients with AD develop stronger pruritus and larger wheals than healthy controls after intracutaneous application of histamine (19, 20). On the other hand, Heyer et al. showed in 1995 and 1998 (21, 22) that intracutaneous application of histamine into non-lesional skin of patients with AD resulted in less pruritus and smaller erythema than in healthy controls. These results could be reproduced by several other authors, such as by Ikoma et al. in 2003 (23), Rasul et al. (24) Hawro et al. (25) and Wahlgren et al. (26).

In another study in patients with AD it could be shown that the patients' ability to discriminate 2 pruritic points (the so-called 2-point discrimination test) was better than in the group of healthy controls (27). To determine whether the onset of erythema and wheal are controlled independently from each other, Bjerring & Arndt-Nielsen measured histamine-induced wheal, erythema and pruritus after local analgesics in healthy controls (28). They found that the size of the wheal was not influenced by the application of local analgesics to the treatment area. However, the signs of erythema and the subjective symptom of pruritus were reduced after local analgesics. Stronger analgetics (infiltrative analgesic) worked better than topical ones to reduce erythema and pruritus. The symptom of (laser-induced) pain, however, was abolished by both methods, underlining the fact that pain and itch are transmitted separately.

Based on these complex findings regarding physiological reactions to histamine provocations, we wanted to clarify whether patients with different origins of chronic pruritus (dermatological diseases, systemic diseases, neurological diseases) show differences in the histamine intracutaneous test results. We hypothesized that patients with chronic pruritic dermatoses or systemic diseases might show enhanced responses to intracutaneous histamine with respect to wheal, erythema and pruritus severity, which could be explained by potential sensitization due to chronic and repeated H1 or TLR4 signalling. As the differential diagnostics of chronic pruritus (revealing the underlying disease) is still a challenge and requires an extended work-up programme (2), such an easy-to-perform histamine intracutaneous test could have the potential to become a valuable diagnostic tool in chronic pruritus if the various groups of patients with chronic pruritus show specific reaction patterns to the intracutaneous histamine test.

The primary aims of this study were to evaluate whether wheal size, erythema size and pruritus are different between the 5 main groups (healthy controls, atopic patients without dermatosis, patients with dermatosis, patients with systemic or multifactorial cause of pruritus, and those with a neurological cause of pruritus). A further aim was to compare pruritus intensity between the 9 different subgroups (**Table I**).

PATIENTS AND METHODS

Study population

In this descriptive study, 140 participants were enrolled with chronic pruritus of various causes. Included were patients with AD ($n=20$), urticaria ($n=20$), other dermatoses (subclassified to the group with ($n=20$) and the group without atopic predisposition ($n=20$)), patients with neurological ($n=20$), systemic ($n=20$) or multifactorial cause of pruritus ($n=20$). The defined reason for chronic pruritus results from prior standardized diagnostic procedures according to the German guidelines for chronic pruritus (2). In detail an extensive work-up programme, including laboratory and imaging diagnostic procedures, was performed in each patient to determine the exact cause of chronic pruritus. Only patients with clear association with one of the (sub)groups were included in the trial.

Table I. Overview of demographic data. Frequency of diagnosis and grouping of patients based on diagnosis

Group	Subgroup	Subgroup number	Age, years Median (min–max)	Sex Female/Male *n* (%)	Total *n* (%)
Healthy controls	Without atopy or pruritus	1	58 (22–74)	10 (6.1)/5 (3)	15 (9.1)
Atopic patients without dermatosis	Without pruritus	2	45 (21–56)	7 (4.2)/3 (1.8)	10 (6.1)
Patients with dermatosis	Atopic dermatitis	3	36 (19–89)	10 (6.1)/10 (6.1)	20 (12.1)
	Urticaria	4	41.5 (21–73)	14 (8.5)/6 (3.6)	20 (12.1)
	Other dermatosis with atopy	5	52 (19–92)	8 (4.8)/12 (7.3)	20 (12.1)
	Other dermatosis without atopy	6	62 (25–84)	11 (6.7)/9 (5.5)	20 (12.1)
Systemic or multifactorial cause of pruritus	Systemic one cause	7	55 (30–79)	9 (5.5)/11 (6.7)	20 (12.1)
	Systemic multifactorial	8	66 (20–81)	10 (6.1)/10 (6.1)	20 (12.1)
Neurological cause of pruritus		9	62 (41–78)	14 (8.5)/6 (3.6)	20 (12.1)
Total			53 (19–92)	93 (56.4)/72 (43.6)	165 (100)

Exclusion criteria were: the intake of drugs affecting pruritus, e.g. antihistamines, sleep aids, sedatives, antidepressants and the intake of neuroleptics, as well as the use of topical steroids, tacrolimus ointment, and pimecrolimus cream at least 14 days before study entry. Pruritus of psychogenic cause was also an exclusion criterion. Healthy volunteers ($n=15$) and healthy participants with atopic predisposition, but without pruritus ($n=10$) served as control groups.

Study design

The study was approved by the local ethics committee (ethics approval number 2007-413-f-S, date of approval 22 October 2007), and all subjects provided informed consent before the study start. The following data for the subjects were collected and compared: demographic information, manifestation of chronic pruritus including the duration, current intensity (visual analogue scale (VAS) 0–10) and underlying diagnosis. For patient-reported data, a pruritus-specific questionnaire (NeuroDerm questionnaire) was used (29). Atopic predisposition was assessed using the Erlanger Atopic Score Questionnaire (30).

Intracutaneous histamine injection

An intracutaneous injection of histamine, 1 mg/ml concentrated histamine solution (histamine hydrochloride solution; manufacturer Allergopharma GmbH, Reinbek, Germany) diluted 1:10 in NaCl 0.9%, was used as an established experimental model for allergy testing and experimental induction of pruritus. Twenty µl of the diluted solution was injected intracutaneously on a non-lesional skin area on the volar forearm using a 29 G needle. It was important to select a defined location, since it is known that various body sites show different reaction patterns to histamine provocation (31). Test results were observed and registered once 20 min after injection. Itch intensity in the injection area at the time point of 20 min after histamine injection was assessed using a visual analogue scale (VAS) from 0 to 10 (measurement in cm). Length and width of erythema and wheal were measured with a micrometric calliper in mm. Mean size of erythema and wheal formation was calculated from the sum of length and width divided by 2.

Statistical analysis

Statistical analysis was performed with software IBM SPSS Statistics for Windows (release 24; Chicago, IL, USA, 2016) and SAS (Version 9.4; SAS Institute Cary, NC, USA). Categorical variables are expressed as frequency and percentage, whereas continuous variables are presented as median, minimum and maximum.

Mann–Whitney *U* tests were used to compare continuous variables between 2 independent groups and Kruskal–Wallis tests for comparisons between more than 2 independent groups.

If a significant or noticeable difference was observed, subgroup analysis was performed in case of the Mann–Whitney *U* test and a *post hoc* analysis in case of the Kruskal–Wallis test. Only significant/noticeable results will be shown for subgroup and *post hoc* analysis.

Spearman correlations coefficient was used to calculate relationships between 2 continuous variables. Bonferroni correction was applied to the comparison of wheals size, erythema size and pruritus between the 5 main groups and the comparison of pruritus between the 9 subgroups ($p<0.0125$ were considered significant). All other analyses were considered explorative. No correction was applied for the explorative analysis and results were only considered noticeable ($p<0.05$ were considered noticeable).

Box-plots were used for graphical representation of the data. The box ranges for the 25%-quantile to the 75%-quantile. The horizontal line inside the box represents the median and the mean is indicated by either a circle, a cross or a diamond. The end of the whiskers indicated the largest/smallest values, which are not more than 1.5 times the box ranges removed from the box. Points above or below the whiskers are outliers. Significant/noticeable differences are marked by a horizontal bar.

The results are presented in tables and graphs created with and SAS (Version 9.4; SAS Institute Cary, NC, USA).

RESULTS

Participants

Participants were assigned to 5 main groups according to their diagnosis, and further subdivided into 9 subgroups (Table I). Patients with generalized pruritus due to AD, urticaria and various dermatoses with (e.g. dyshidrotic eczema) or without (e.g. bullous pemphigoid, psoriasis) atopic predisposition (subgroup number 3–6) were summarized to the main group of patients with a dermatosis. With 80 subjects they represent 48.5% of all involved individuals. All of the 20 patients with one systemic cause or systemic/multifactorial cause of pruritus had generalized pruritus. The fifth group comprised 20 individuals with mostly localized neuropathic pruritus (e.g. brachioradial pruritus) at the test location on the arms. A total of 165 participants (93 (56.4%) females and 72 (43.6%) males) were included in the study. Table I summarizes the participant characteristics. The median age of patients was 53 (19–92) years. A noticeable difference was found in patient age between the 5 main groups ($p=0.007$). Among the 5 main groups patients with dermatosis were the youngest (47 (19–92) years) and patients with systemic or multifactorial cause of pruritus were the oldest (63.5 (20–81)) (*post hoc* comparison $p=0.0362$). Similarly a noticeable difference was found between the 9 subgroups with regards to patient age ($p=0.0012$). *Post hoc* comparisons revealed a noticeable difference between patients with dermatosis (urticarial) (41.5 (21–73) years) and patients with multifactorial cause of pruritus (66 (20–81)) years ($p=0.0092$) and between patients with dermatosis (urticarial) and patients with neurological cause of pruritus (62 (41–78) years) ($p=0.0068$).

No difference in sex distribution could be found, although the percentage of female volunteers remains higher.

Primary goals

Table II shows the data for the 3 parameters: wheal size, erythema size and pruritus VAS according to the 5 groups (healthy controls, atopic patients without dermatosis, patients with dermatosis, patients with systemic or multifactorial cause of pruritus, and patients with neurological cause of pruritus). Significant differences were observed in both wheal ($p=0.0001$) (**Fig. 1**a) and erythema ($p=0.0011$) (Fig. 1b) size. *Post hoc* analysis revealed a significant difference between patients with

Table II. Summary of results. Values of Itch VAS, wheal size and erythema at the site of injection after intracutaneous test in all study groups

Group	Subgroup number	Subgroup	Sample size	Itch VAS, mm Median (min–max)	Wheal size, mm Median (min–max)	Erythema size, mm Median (min–max)
Healthy controls	1	Without atopy or pruritus	15	2 (0–5)	14 (10–20)	32.5 (14–75)
Atopic patients without dermatosis	2	Without pruritus	10	5 (0–10)	14.5 (10–19)	60.75 (43–150)
Patients with dermatosis	3–6			5 (0–10)	10.75 (1.4–20)	37.5 (1.45–145)
	3	Atopic dermatitis	20	2.5 (0–10)	10.25 (3–20)	24.25 (2.5–57.5)
	4	Urticaria	20	3 (0–6)	10 (5–20)	31 (10–145)
	5	Other dermatosis with atopy	20	5 (0–10)	11.75 (1.4–15)	37.5 (1.45–85)
	6	Other dermatosis without atopy	20	0 (0–10)	11.25 (3–15)	37.5 (4–65.5)
Systemic or multifactorial cause of pruritus	7–8			3 (0–10)	13.25 (1.45–20)	40 (2–80)
	7	Systemic one cause	20	2.25 (0–8)	13.25 (6–20)	42 (5–80)
	8	Systemic multifactorial	20	3.25 (0–10)	13.25 (1.45–15.5)	34 (2–59.5)
Neurologic cause of pruritus	9			3 (0–8)	12.75 (4.5–18)	42.5 (6–64)

VAS: visual analogue scale.

dermatosis and patients with systemic or multifactorial cause of pruritus (0.0012) with regards to wheal size. In addition, there were significant differences between healthy controls and atopic patients without dermatosis ($p=0.0113$), atopic patients without dermatosis and patients with dermatosis ($p=0.0008$), atopic patients without dermatosis and patients with neurological cause of pruritus ($p=0.0063$) and atopic patients without dermatosis and patients with systemic or multifactorial cause of pruritus ($p=0.0018$) when comparing erythema sizes. No significant difference could be found for pruritus VAS ($p=0.3785$) (Fig. 1c).

Similarly no difference was detected between the 9 subgroups with regards to the intensity of pruritus ($p=0.2165$) (Fig. 1d).

Correlation with duration of chronic pruritus

The mean duration of chronic pruritus was 43 (0–708) months for all subjects (**Table III**). For a more thorough assessment of the different study cohorts, groups with pruritus were divided into 3 categories: <18 months, between 18 and 48 months and >48 months (Table III). As depicted in Table III, we evaluated whether intensity of itching as well as size of wheal and erythema is associated with the total duration of pruritus.

No noticeable correlation was found between the 3 duration categories and wheal size ($p=0.8774$), erythema size ($p=0.3005$) and pruritus VAS ($p=0.1686$) (**Fig. 2**).

Correlation between pruritus and size of erythema and wheal

Spearman's correlation coefficient was used to assess the strength of a monotonic relationship between pruritus and size of erythema. Correlation between pruritus and size of erythema was r=0.264 ($p=0.0006$), and the correlation between pruritus and size of wheal was r=–0.027 ($p=0.729$).

Correlation with age

A noticeable correlation was found between age and wheal size (r=0.221; $p=0.0043$) and erythema size

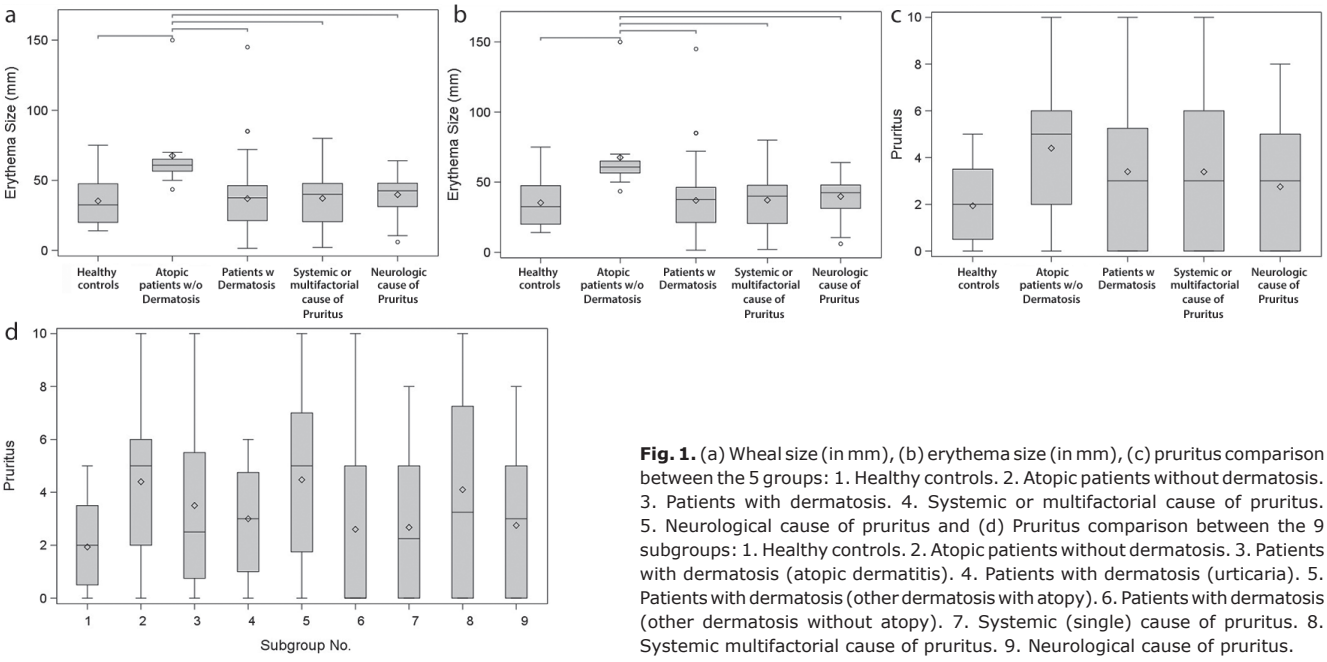

Fig. 1. (a) Wheal size (in mm), (b) erythema size (in mm), (c) pruritus comparison between the 5 groups: 1. Healthy controls. 2. Atopic patients without dermatosis. 3. Patients with dermatosis. 4. Systemic or multifactorial cause of pruritus. 5. Neurological cause of pruritus and (d) Pruritus comparison between the 9 subgroups: 1. Healthy controls. 2. Atopic patients without dermatosis. 3. Patients with dermatosis (atopic dermatitis). 4. Patients with dermatosis (urticaria). 5. Patients with dermatosis (other dermatosis with atopy). 6. Patients with dermatosis (other dermatosis without atopy). 7. Systemic (single) cause of pruritus. 8. Systemic multifactorial cause of pruritus. 9. Neurological cause of pruritus.

Table III. History of pruritus. Pruritus duration in patients with dermatitis, systemic or multifactorial and neurological cause

Group	Subgroup No	*n*	Median, months	Min–Max, months	Pruritus duration		
					< 18 month *n* (% within group)	18–48 month *n* (% within group)	> 48 month *n* (% within group)
Patients with dermatosis	3–6	80	41.5	2–708	27 (33.8)	21 (26.2)	32 (40.0)
Systemic or multifactorial cause of pruritus	7–8	40	36	5–564	11 (27.5)	10 (25.0)	19 (47.5)
Neurological cause of pruritus	9	20	60	15–240	2 (10.0)	7 (35.0)	55 (62.0)
Total		140	43	2–708	40 (28.6)	38 (27.1)	62 (44.3)

(r=–0.1749; p=0.0285). Pruritus, on the other hand, showed no noticeable correlation with age (r=0.0405; p=0.605).

Correlation with sex of the study population

A noticeable difference was found between male and female subjects regarding their response to intracutaneous injection of histamine (**Fig. 3**). Female patients had higher pruritus (4 (0–10)) than male patients (2 (0–10)) (p=0.0133). The opposite was found in relation to wheal size. Males displayed larger wheal size (13 mm (1.4–20)) than females (11.5 mm (3–20)) (p=0.0428).

Further subgroup analysis revealed that patients with a systemic multifactorial cause of pruritus showed a difference in pruritus between male (1.25 (0–10)) and female patients (6.5 (0–10)) (p=0.0458).

The difference in wheal size could also be found within patients with other dermatosis with atopy (male 12.5 mm (1.4–15) and female 10 mm (7.5–12.5)), (p=0.0147).

DISCUSSION

The aim of this study was to evaluate whether an intracutaneous injection of histamine has the potential to differentiate between the various causes of chronic pruritus and can thereby serve as an easy-to-perform diagnostic test in chronic pruritus of unknown aetiology. Itch VAS, wheal size and erythema size served as read-out parameters after intracutaneous injection of histamine. A prerequisite for a predictive diagnostic test is that it is applied in a standardized way, always using the same method, histamine concentration and skin area, independent of individual variables. Thus, we selected the ventral part of the lower arm, similar to the area used in allergological testing. Our results show, for the first time, that the patient group with a systemic or multifactorial cause of chronic pruritus developed larger wheals than patients with a dermatosis as cause for chronic pruritus (analysis of the subgroups did not show clear results, most likely due to too small patient numbers within the subgroups). Thus, development of a large wheal in intracutaneous histamine testing can be a justified indication for a thorough clinical investigation of the patient, searching for a potential systemic or multifactorial cause of chronic pruritus. However, it has to be considered that several studies have shown that wheal size increases with patient's age, so that in elderly patients a larger wheal should be interpreted with caution (32, 33).

With respect to the other test symptoms, such as erythema and pruritus (VAS), there are no differences among the various groups. Our test results give a first easy-to-read hint as to which group of diseases (dermatosis vs systemic/multifactorial cause of pruritus) might be responsible for the chronic pruritus. However, our groups contain only small numbers of patients; therefore the test results should be interpreted with caution. Future studies are needed to verify these initial results. With respect to the literature it is known that patients with AD already show larger wheals after intracutaneous histamine stimulation in comparison with healthy volunteers (19, 20). Our test results suggest that patients with systemic/multifactorial origin for chronic pruritus even show larger wheals than those. Due to the small number of patients it is too early to discuss a clear cut-off among the 2 groups. Although there was a significant difference with respect to wheal size there is a strong variability (wheal size in group of systemic/multifactorial origin was 13.25 mm (1.45–20)) compared with patients with dermatosis showing wheal size of 10.75 mm (1.4–20)).

These results show that the duration of chronic pruritus cannot be correlated with any of the 3 symptoms wheal, erythema and pruritus VAS after histamine stimulation. Therefore, any discussion about sensitization and influ-

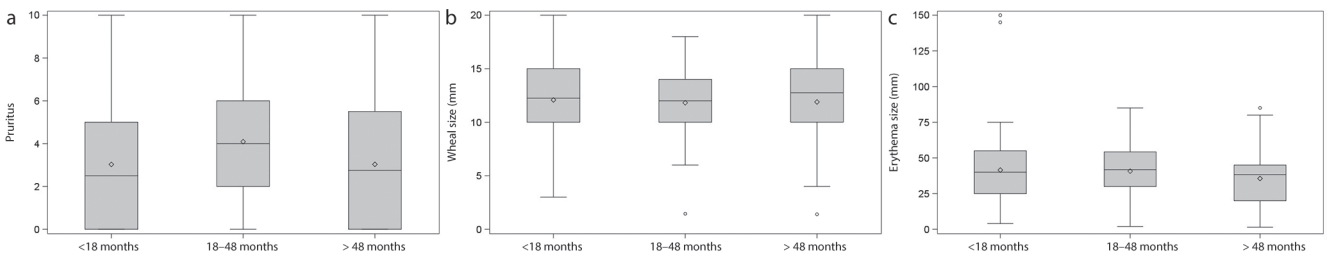

Fig. 2. (a) Wheal size (in mm), (b) erythema size (in mm), (c) pruritus, comparison between male and female patients. (d) Wheal size (in mm), (e) erythema size (in mm), and (f) pruritus comparison between male and female patients within the 5 different groups.

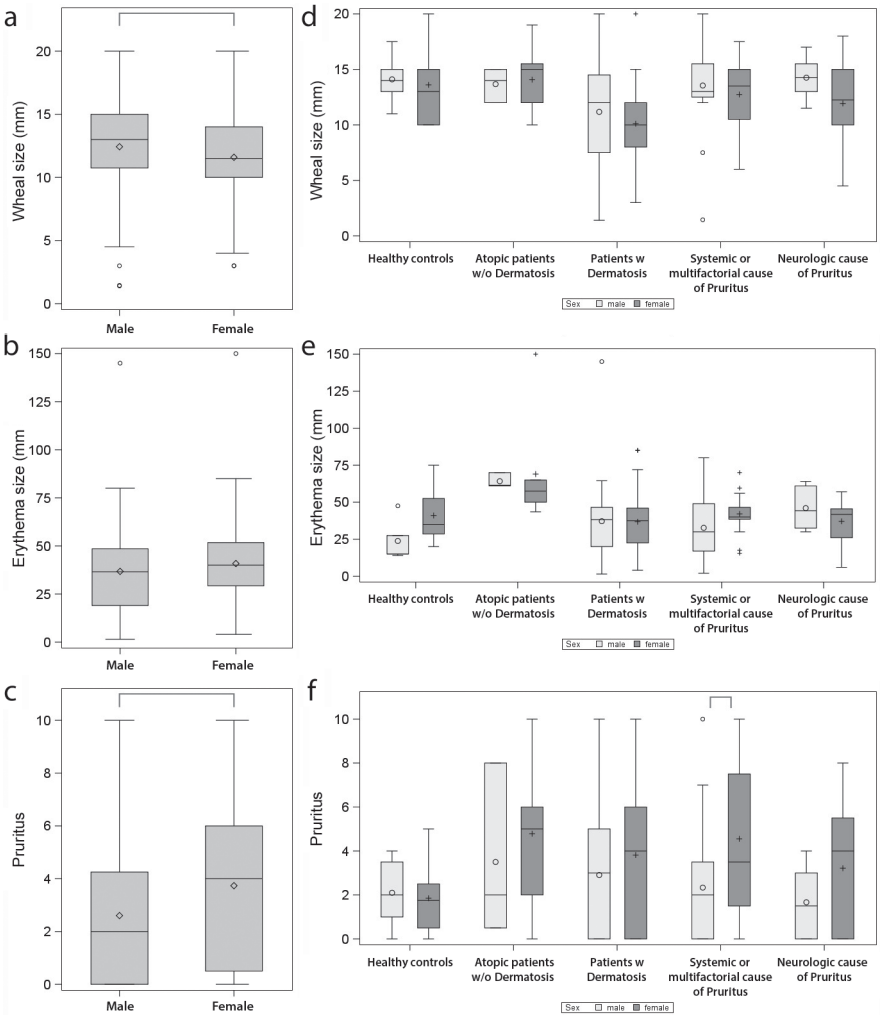

Fig. 3. (a) Pruritus, (b) wheal size (in mm) and (c) erythema size (in mm) comparison between the 3 duration categories: <18, 18–48 and >48 months.

ence of time on the (neurogenic) pathways of histamine stimulation in patients with chronic pruritus would be an over-interpretation at this time.

Further (sub)group analysis shows that the patients with multifactorial origin were older than all other groups. The group of patient with AD were the youngest. These results can be explained by the generally applicable fact that the amount of diseases within an individual increases with time. This explains the older population with multifactorial origin who, by definition, have more than one disease (as an origin for chronic pruritus). These multifactorial causes are often diseases that correlate with age (such as diabetes, renal deficiency, etc.). Since AD is a common disease in childhood and adolescence (34, 35), it is not surprising that the subgroup of patients with AD represents the youngest one.

Finally, the current study revealed several sex-dependent results. After histamine stimulation female patients showed higher values for pruritus, which could be most clearly pronounced in the subgroup of patients with multifactorial cause of chronic pruritus. In contrast to pruritus wheal size was generally decreased in females in comparison with males. To the best of our knowledge there are only a few reports by our group regarding differences in pruritus among males and females (36–38). We published the observation of higher perception values for pruritus in females in contrast to males in 2013 (32). Little is known about the pathomechanism of such phenomena. A first step towards a deeper understanding was the examination of central nervous reaction patterns to histamine stimulation by functional magnetic resonance imaging (fMRI) analysis (39). On histamine stimulation, females showed stronger activation of specific central nervous system (CNS) areas that are known for the integration of sensory, affective information as well as motor integration and planning (frontal brain areas including the prefrontal cortex and the secondary motor cortex region as well as the cerebellum and the lentiform nucleus). However, the decreased wheal size in females in our study cannot be explained by differences in CNS activation, and should therefore be clarified in future studies.

In conclusion, this study provides various insights into the reaction patterns to stimulation with intracutaneous histamine in patients with chronic pruritus. Although it is still not possible to clearly predict the exact cause of chronic pruritus using such an easy-to-read test, there is an indication that larger wheals might hint at a systemic or multifactorial cause of chronic pruritus. Interestingly, different reaction patterns were detected among females and males, and further research is needed to clearly understand the pathomechanism involved. Results such as these provide some preliminary aspects for the developing field of gender science.

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The authors have no conflicts of interest to declare.

REFERENCES

1. Ständer S, Weisshaar E, Mettang T, Szepietowski JC, Carstens E, Ikoma A, et al. Clinical classification of itch: a position paper of the International Forum for the Study of Itch. Acta Derm Venereol 2007; 87: 291–294.
2. Ständer S, Zeidler C, Augustin M, Bayer G, Kremer AE, Legat FJ, et al. Date of publication: 31-May-2016; Publisher: AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften; National League of Medical Guidelines) Available from: http://www.awmf.org/uploads/tx_szleitlinien/013-048l_S2k_Chronischer_Pruritus_2017-01.pdf.
3. Matterne U, Apfelbacher CJ, Loerbroks A, Schwarzer T, Büttner M, Ofenloch R, et al. Prevalence, correlates and characteristics of chronic pruritus: a population-based cross-sectional study. Acta Derm Venereol 2011; 91: 674–679.
4. Ständer S, Schäfer I, Phan NQ, Blome C, Herberger K, Heigel H, et al. Prevalence of chronic pruritus in Germany: results of a cross-sectional study in a sample working population of 11,730. Dermatology 2010; 221: 229–235.
5. Halvorsen JA, Dalgard F, Thoresen M, Thoresen M, Bjertness E, Lien L. Itch and mental distress: a cross-sectional study among late adolescents. Acta Derm Venereol 2009; 89: 39–44.
6. Schmelz M. A neural pathway for itch. Nat Neurosci 2001; 4: 9–10.
7. LaMotte RH, Shimada SG, Sikand P. Mouse models of acute, chemical itch and pain in humans. Exp Dermatol 2011; 20: 778–782.
8. Andersen HH, Elberling J, Arendt-Nielsen L. Human surrogate models of histaminergic and non-histaminergic itch. Acta Derm Venereol 2015; 95: 771–777.
9. Weinkauf B, Dusch M, van der Ham J, Benrath J, Ringkamp M, Schmelz M, et al. Mechano-sensitive nociceptors are required to detect heat pain thresholds and cowhage itch in human skin. Eur J Pain 2016; 20: 215–222.
10. Schmelz M, Hilliges M, Schmidt R, Ørstavik K, Vahlquist C, Weidner C, et al. Active "itch fibers" in chronic pruritus. Neurology 2003; 61: 564–566.
11. Ständer S, Steinhoff M, Schmelz M, Weisshaar E, Metze D, Luger T. Neurophysiology of pruritus: cutaneous elicitation of itch. Arch Dermatol 2003; 139: 1463–1470.
12. Imamachi N, Park GH, Lee H, Anderson DJ, Simon MI, Basbaum AI, et al. TRPV1-expressing primary afferents generate behavioral responses to pruritogens via multiple mechanisms. Proc Natl Acad Sci U S A 2009; 106: 11330–11335.
13. Min H, Lee H, Lim H, Jang YH, Chung SJ, Lee CJ, et al. TLR4 enhances histamine-mediated pruritus by potentiating TRPV1 activity. Mol Brain 2014; 7: 59.
14. Nakagawa H, Hiura A. Four possible itching pathways related to the TRPV1 channel, histamine, PAR-2 and serotonin. Malays J Med Sci 2013; 20: 5–12.
15. Hutchinson MR, Zhang Y, Shridhar M, Evans JH, Buchanan MM, Zhao TX, et al. Evidence that opioids may have toll-like receptor 4 and MD-2 effects. Brain Behav Immun 2010; 24: 83–95.
16. Fiedorowicz E, Kaczmarski M, Cieślińska A, Sienkiewicz-Szłapka E, Jarmołowska B, Chwała B, et al. β-casomorphin-7 alters μ-opioid receptor and dipeptidyl peptidase IV genes expression in children with atopic dermatitis. Peptides 2014; 62: 144–149.
17. Phan NQ, Bernhard JD, Luger TA, Ständer S. Antipruritic treatment with systemic μ-opioid receptor antagonists: a review. J Am Acad Dermatol 2010; 63: 680–688.
18. Mettang T, Kremer AE. Uremic pruritus. Kidney Int 2015; 87: 685–691.
19. Coulson IH, Holden CA. Cutaneous reactions to substance P and histamine in atopic dermatitis. Br J Dermatol 1990; 122: 343–349.
20. Heyer G, Hornstein OP, Handwerker HO. Skin reactions and itch sensation induced by epicutaneous histamine application in atopic dermatitis and controls. J Invest Dermatol 1989; 93: 492–496.
21. Heyer G, Ulmer FJ, Schmitz J, Handwerker HO. Histamine-induced itch and alloknesis (itchy skin) in atopic eczema patients and controls. Acta Derm Venereol 1995; 75: 348–352.
22. Heyer G, Koppert W, Martus P, Handwerker HO. Histamine and cutaneous nociception: histamine-induced responses in patients with atopic eczema, psoriasis and urticaria. Acta Derm Venereol 1998; 78: 123–126.
23. Ikoma A, Rukwied R, Ständer S, Steinhoff M, Miyachi Y, Schmelz M. Neuronal sensitization for histamine-induced itch in lesional skin of patients with atopic dermatitis. Arch Dermatol 2003; 139: 1455–1458.
24. Rausl A, Nordlind K, Wahlgren CF. Pruritic and vascular responses induced by serotonin in patients with atopic dermatitis and in healthy controls. Acta Derm Venereol 2013; 93: 277–280.
25. Hawro T, Lehmann S, Altrichter S, Fluhr JW, Zuberbier T, Church MK, et al. Skin provocation tests may help to diagnose atopic dermatitis. Allergy 2016; 71: 1745–1752.
26. Wahlgren CF, Hägermark O, Bergström R. Patients' perception of itch induced by histamine, compound 48/80 and wool fibres in atopic dermatitis. Acta Derm Venereol 1991; 71: 488–494.
27. Wahlgren CF, Ekblom A. Two-point-discrimination of itch in patients with atopic dermatitis and healthy subjects. Acta Derm Venereol 1996; 76: 48–51.
28. Bjerring P, Arendt-Nielsen L. A quantitative comparison of the effect of local analgesics on argon laser induced cutaneous pain and on histamine induced wheal, flare and itch. Acta Derm Venereol 1990; 70: 126–131.
29. Ständer S, Pogatzki-Zahn E, Stumpf A, Fritz F, Pfleiderer B, Ritzkat A, et al. Facing the challenges of chronic pruritus: a report from a multi-disciplinary medical itch centre in Germany. Acta Derm Venereol 2015; 95: 266–271.
30. Diepgen TL, Sauerbrei W, Fartasch M. Development and validation of diagnostic scores for atopic dermatitis incorporating criteria of data quality and practical usefulness. J Clin Epidemiol 1996; 49: 1031–1038.
31. Bin Saif GA, Alajroush A, McMichael A, Kwatra SG, Chan YH, McGlone F, et al. Aberrant C nerve fibre function of the healthy scalp. Br J Dermatol 2012; 167: 485–489.
32. Eriksson NE, Holmen A. Skin prick tests with standardized extracts of inhalant allergens in 7099 adult patients with asthma or rhinitis: cross-sensitizations and relationships to age, sex, month of birth and year of testing. J Investig Allergol Clin Immunol 1996; 6: 36–46.
33. Haahtela T, Burbach GJ, Bachert C, Bindslev-Jensen C, Bonini S, Bousquet J, et al. Clinical relevance is associated with allergen-specific wheal size in skin prick testing. Clin Exp Allergy 2014; 44: 407–416.
34. Williams H, Flohr C. How epidemiology has challenged 3 prevailing concepts about atopic dermatitis. J Allergy Clin Immunol 2006; 118: 209–213.
35. Bieber T. Atopic dermatitis. N Engl J Med 2008; 358: 1483–1494.
36. Steinke S, Bruland P, Blome C, Osada N, Dugas M, Fritz F, et al. Chronic pruritus: evaluation of patient needs and treatment goals with a special regard to differences according to pruritus classification and sex. Br J Dermatol 2017; 176: 363–370.
37. Ständer S, Stumpf A, Osada N, Wilp S, Chatzigeorgakidis E, Pfleiderer B. Gender differences in chronic pruritus: women present different morbidity, more scratch lesions and higher burden. Br J Dermatol 2013; 168: 1273–1280.
38. Stumpf A, Ständer S, Warlich B, Fritz F, Bruland P, Pfleiderer B, et al. Relations between the characteristics and psychological comorbidities of chronic pruritus differ between men and women: women are more anxious than men. Br J Dermatol 2015; 172: 1323–1328.
39. Stumpf A, Burgmer M, Schneider G, Heuft G, Schmelz M, Phan NQ, et al. Sex differences in itch perception and modulation by distraction – an FMRI pilot study in healthy volunteers. PLoS One 2013; 8: e79123.