Contact sensitization in prurigo patients

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Summary

Background. There are no studies on contact allergy in patients with prurigo. With itch being important in the pathophysiology of prurigo diseases and being a symptom of allergic contact dermatitis, we aimed to investigate contact allergy in patients suffering from prurigo.

Objectives. Exploratory analysis of patch test results in prurigo patients.

Materials and methods. A retrospective analysis of data of the Information Network of Departments of Dermatology, 2005–2014, was performed.

Results. Of 116 744 patch tested patients, 639 (0.55%) were diagnosed with prurigo. The median age was 61 years, 286 (45%) were pensioners, and 252 (39.5%) had generalized prurigo. The indication for patch testing was exclusion of contact allergy in 412 patients (64.5%), and 223 patients (35%) had at least one positive patch test reaction. There was no distinctive pattern of sensitization. Prurigo patients had significantly more (and stronger) reactions to the irritant control patch test with sodium lauryl sulfate than a control group (27.6% versus 21.0%).

Conclusions. Although prurigo is not a typical clinical manifestation of contact sensitization, our results indicate that patch testing in these patients may be helpful.

Key words: allergy; contact allergy; contact dermatitis; contact sensitization; itch; prurigo; pruritus.

Prurigo can be described as a chronic reaction pattern of the skin associated with severe itch (1, 2). Prurigo nodularis is characterized by the presence of numerous, frequently symmetrically distributed hyperkeratotic or erosive nodules on the skin of the whole body (3–6). The pathogenesis is not completely understood, and seems to be dominated by neuronal and immunological changes (2). Itch is the main and most persistent symptom of prurigo nodularis. Presumably, prurigo is a consequence of severe chronic scratching, leading to prurigo nodularis or prurigo papularis (1). It has been shown that hypoplasia of epidermal nerves is an important finding in lesional and interlesional areas that normalizes during healing, paralleling the reduction in itch (6). The origin of prurigo nodularis may be a dermatological, neurological or systemic disease, and it is frequently of multifactorial origin; however, atopic diathesis is reported to be a major factor in up to 50% of patients (3–5). The role of contact allergy in prurigo nodularis is unclear. Scarce case reports have shown that allergic contact dermatitis can present with prurigo nodularis-like lesions (7). To date, there is no knowledge on the occurrence and frequency of contact sensitizations in prurigo nodularis patients. However, with itch being an important symptom in allergic

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contact dermatitis, there might be some kind of correlation. On the other hand, one may assume that prurigo nodularis patients may have an increased risk of contact allergy caused by the use of topical preparations such as medicaments and emollients.

In the past, other clinical entities have been described as prurigo varieties, mostly on the basis of the clinical picture, and not on the above current definition of the International Forum for the Study of Itch (1). Some of these, for instance 'subacute prurigo', are still in use today. According to recent dermatology textbooks, subacute prurigo (prurigo simplex subacuta) clinically presents as intensely itching, excoriated papules, mostly in a symmetrical distribution on the extensor surfaces of the extremities, neck, lower trunk, and buttocks. Its aetiology is unknown; among other possibilities, hormonal or gastrointestinal disorders have been suspected, but never convincingly proved to be underlying diseases. The role of allergic reactions has also been discussed. Histopathological investigations have shown that the inflammatory cell infiltrate in subacute prurigo mainly consists of T lymphocytes, particularly $CD8^+$ cells, $CD15^+$ neutrophils, and $CD68^+$ macrophages (8–10).

Against the above background, we performed an exploratory analysis of data of the Information Network of Departments of Dermatology (IVDK). In the IVDK documentation, it is possible to code different forms of dermatitis in detail. However, for other diagnoses, in which patch testing is less frequently performed, a grosser classification is used; there is, for instance, only one category 'Prurigo', without further specification. According to additional information from the participating centres, the diagnostic category covers both prurigo nodularis and subacute prurigo patients.

Patients and Methods

For this retrospective data analysis, we selected data of the years 2005–2014 from the central database of the IVDK. The IVDK is a network of 56 departments of dermatology in Germany, Switzerland and Austria that are active in the investigation of contact allergy. Its structure and routine operating procedure are described in detail elsewhere (11). Briefly, anonymized clinical histories and data and patch test results of all patients tested in the participating centres are recorded in a standardized way by use of a uniform computer program (WINALLDAT/IVDK, developed and distributed to the partner clinics by the IVDK central office), and transmitted to the IVDK central office at the University of Göttingen twice yearly. Data are subjected to standardized quality control and analysed according to international standards (12, 13).

Among other items, one main diagnosis and one secondary diagnosis can be documented for every patient. We selected patients with the main diagnosis 'prurigo' from the IVDK database. As mentioned above, no further specification of prurigo is given in the IVDK documentation. However, from personal communications of the participating dermatologists, it is known that these patients suffer from prurigo nodularis or subacute prurigo.

Patch tests were performed and read according to internationally accepted guidelines, modified by the German Contact Dermatitis Research Group (DKG) (14). Patch test reactions to allergens were regarded as positive if they were characterized by erythema plus infiltration, papules, and/or vesicles (+, ++, or +++). Patch test reactions to the irritant control sodium lauryl sulfate (SLS) were coded according to the recommendations of Tupker et al. (15). All patch test preparations mentioned in this article were bought from Almirall Hermal (Reinbek, Germany). The patch test exposure time was 48 h in 538 patients (84%) and 24 h in 101 patients (16%). Analysis of the patch test results was performed on the basis of reactions on day 3 (D3). In a few exceptional cases, when a reading was performed on D4 instead, this reaction was selected.

Statistical analyses were performed with the software package SAS® (SAS Institute Inc., Cary, NC, USA), Version 9.4.

Results

Of the 116 744 patients patch tested during the years 2005–2014 in the departments of dermatology forming the IVDK, 639 (0.55%) had the main diagnosis 'prurigo'. Of these, 431 (67%) were women, and 208 (33%) were men. The age distribution is shown in Fig. 1; 561 patients (88%) were aged ≥40 years. Ages ranged from 14 to 93 years, with a median of 61 years, and quartiles of 49 and 71 years, respectively. Corresponding to this age distribution, 286 patients (45%) were pensioners. Sixty-six patients (10%) were housewives, and all other professions accounted for <5% each. The main affected body sites are shown in Table 1. A current secondary diagnosis was documented in only 42 patients (7%), with allergic contact dermatitis being the most frequent diagnosis (12 patients; 2%). Past or present atopic diseases were distributed as follows: atopic dermatitis in 50 patients (8%), allergic rhinitis in 98 patients (15%), and allergic asthma in 42 patients (7%). The indication for patch testing was exclusion of contact allergy in 412 patients (64.5%), and suspected contact allergy in 194 patients (30%). Possible allergen sources were leave-on cosmetics in 363 patients (57%), topical drugs in 142 patients

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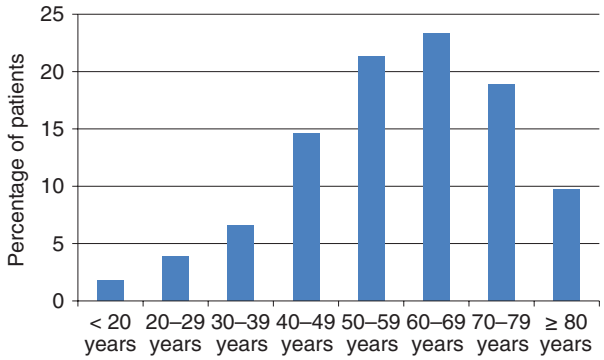

Fig. 1. Age distribution among 639 prurigo patients.

Table 1. Main affected body sites in 639 patients with prurigo

Site	Number	%
Generalized	252	39.5
Trunk	122	19
Arms	121	19
Legs	69	11
Head and neck	41	6
Hands	12	2
Feet	3	0.5
Missing/others	19	3

(22%), rinse-off cosmetics in 81 patients (13%), and textiles in 50 patients (8%). All other specified possible allergen sources accounted for <5% each. Aggravating factors were mentioned for 117 patients (18%), with heat being documented most frequently (20 patients; 17% of 117).

The most frequently tested DKG patch test series were the baseline series (606 patients; 95%), ointment base series (418 patients; 65%), preservative series (385 patients; 60%), and disinfectant series (136 patients; 21%).

Of the 639 prurigo patients, 223 (35%) had at least one positive patch test reaction. One hundred and seventeen patients (18%) reacted to one allergen only, 49 (8%) reacted to two allergens, 22 (3.5%) reacted to three allergens, and 35 (5.5%) reacted to more than three different allergens. SLS (0.25% aq.) has been patch tested as part of the baseline series as an irritant control since August 2008. Up to the end of the study period, 417 prurigo patients were tested with SLS. Of these, 115 (27.6%) had an irritant reaction, as compared with 21% of all other patients tested in the IVDK in this time period. The difference was significant at a 5% level. In particular, prurigo patients had significantly more strong irritant reactions of grade sls2 to sls4 (6.5% versus 3.0%; Table 2). Of the 417 prurigo patients tested with SLS, 33 (7.9%) had past or present atopic dermatitis, and, of these, 4 (12%) had an irritant reaction to SLS. Among those 384 patients without atopic dermatitis, significantly more [111 (28.9%)] reacted to SLS.

Table 3 shows the 30 allergens that elicited positive patch test reactions most frequently. *p*-Phenylenediamine (PPD) 1% pet. was removed from the DKG baseline series in 2005, owing to concerns about active sensitization (16). Only aimed patch testing was recommended. Of the 639 prurigo patients, 128 were patch tested with PPD 1% pet., and 3 of them (2.3%) reacted positively.

Some patch test preparations are well known for their irritancy, among them 1,3-diphenylguanidine (1,3-DPG) 1% pet.; weak positive reactions to such patch test preparations may be more often false-positive than usual. This may particularly occur in patients with increased skin irritability at the time of patch testing, as indicated by a positive SLS test result (17). As far from all patients were tested with SLS and these irritant patch test preparations, no reasonably complete analysis of our data in this regard was possible. However, it is remarkable that five of seven positive reactions to 1,3-DPG 1% pet. occurred in patients with positive reactions to SLS.

In view of the age distribution in the study group, with 88% of the patients being aged ≥40 years, we did not calculate the common age-standardized reaction frequencies. Instead, we divided the study group into two age classes, according to the median age (61 years), for further data analysis. The sex distribution was similar in these two subgroups, namely prurigo patients aged <61 years and ≥61 years, respectively. However, they differed to some extent concerning other items with possible influences on the frequency of reactions to allergens (Table 4). Among patients aged ≥61 years, more patients were patch tested in order to exclude contact sensitization (69% versus 60%). Consequently, there were more patients with at least one positive reaction in the younger group of patients (40% versus 30%).

As can be seen from Table 5, this difference was mainly attributable to nickel sensitization. Nickel sulfate was the only allergen to which significantly more patients of the younger subgroup reacted (18.3% versus 4.3%). For all other baseline allergens, the 95% confidence intervals of the percentages of positive reactions overlapped, indicating that there was no significant difference at a 5% significance level.

Discussion

Patch testing is not commonly performed in prurigo patients. Only 0.55% of the patients patch tested in the IVDK in 2005–2014 were diagnosed with 'prurigo',

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Table 2. Reactions to the irritant control sodium lauryl sulfate 0.25% aq.

	Prurigo patients		Other patients	
Reaction	Number	% (95%CI)	Number	% (95%CI)
sls0	302	72.4 (67.9–76.7)	54 196	79.0 (78.7–79.3)
sls1	88	21.1 (17.3–25.3)	12 312	18.0 (17.7–18.2)
sls2–4	27	6.5 (4.3–9.3)	2071	3.0 (2.9–3.2)
Total	417	100.0	68 579	100.0

CI, confidence interval.
Scoring of sls reactions according to Tupker et al. (15): sls0 – negative; sls1 – very weak erythema or minute scaling; sls2 – weak erythema, slight oedema, slight scaling and/or slight roughness; sls3 – moderate degree of erythema, oedema, scaling and/or slight roughness or minor degree of erosion, vesicles crusting and/or fissuring; sls4 – marked degree of erythema, oedema, scaling, roughness, erosions, vesicles, bullae, crusting and/or fissuring.

Table 3. The 30 most frequently observed contact allergens in 639 prurigo patients

Allergen	n tested	n positive	% positive (95%CI)
Nickel sulfate 5%	592	66	11.1 (8.7–14.0)
Myroxylon pereirae (Balsam of Peru) 25%	599	32	5.3 (3.7–7.5)
Fragrance mix I 8%	599	30	5.0 (3.4–7.1)
Cobalt chloride 1%	598	25	4.2 (2.7–6.1)
Methyldibromo glutaronitrile[a] 0.3%/0.2%	594	20	3.4 (2.1–5.2)
Potassium dichromate 0.5%	599	19	3.2 (1.9–4.9)
Fragrance mix II 14%	586	16	2.7 (1.6–4.4)
Colophonium 20%	600	14	2.3 (1.3–3.9)
Paraben mix 16%	599	11	1.8 (0.9–3.3)
Methylchloroisothiazolinone/methylisothiazolinone 0.01% aq.	602	9	1.5 (0.7–2.8)
Povidone iodine 10% aq.	134	9	6.7 (3.1–12.4)
Propolis 10%	599	9	1.5 (0.7–2.8)
Oil of turpentine 10%	599	8	1.3 (0.6–2.6)
Tolu balsam 20%	117	8	6.8 (3.0–13.0)
1,3-Diphenylguanidine 1%	154	7	4.5 (1.8–9.1)
Hydroxyisohexyl 3-cyclohexene carboxaldehyde 5%	598	6	1.0 (0.4–2.2)
Amerchol® L-101 50%	417	5	1.2 (0.4–2.8)
Cocamidopropyl betaine 1% aq.	429	5	1.2 (0.4–2.7)
Formaldehyde 1% aq.	599	5	0.8 (0.3–1.9)
Octyl gallate 0.3%	412	5	1.2 (0.4–2.8)
Propylene glycol 20% aq.	415	5	1.2 (0.4–2.8)
Ammoniated mercury 1%	137	5	3.6 (1.2–8.3)
Sorbic acid 2%	380	5	1.3 (0.4–3.0)
Thiomersal 0.1%	132	5	3.8 (1.2–8.6)
Benzoyl peroxide 1%	60	4	6.7 (1.8–16.2)
Neomycin sulfate 20%	183	4	2.2 (0.6–5.5)
tert-Butyl hydroquinone 1%	414	4	1.0 (0.3–2.5)
Methylisothiazolinone 0.05% aq.	312	4	1.3 (0.4–3.2)
Iodopropynyl butylcarbamate 0.2%	400	4	1.0 (0.3–2.5)
Evernia prunastri (Oakmoss absolute) 1%	117	4	3.4 (0.9–8.5)

CI, confidence interval.
The vehicle was pet. unless otherwise indicated.
[a]The test concentration was changed from 0.3% to 0.2% in August 2008.

meaning prurigo nodularis, prurigo papularis, or subacte prurigo. However, our results may indicate that patch testing in these patients is worthwhile, although prurigo is not a classic clinical manifestation of contact allergy/type IV sensitization, because prurigo patients may acquire secondary contact sensitization by using topical medicaments or emollients to treat prurigo.

Generally, the frequencies of reactions to baseline allergens were slightly, but not conspicuously, decreased in our study group as compared with other data analyses for the same time period (11, 18–20). This is not surprising

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Table 4. Comparison of prurigo patients aged <61 years and ≥61 years

	Patients aged <61 years (n = 319)		Patients aged ≥61 years (n = 320)	
	n	%	n	%
Women	212	66.5	219	68.5
Indication for patch testing: exclusion of contact allergy	192	60	220	69
Number of patients with ≥1 positive reaction	128	40	95	30

Table 5. The 10 most frequent contact allergens from the baseline series among prurigo patients aged <61 years and ≥61 years

Allergen	Patients aged <61 years (n = 319) % positive (95%CI)	Patients aged ≥61 years (n = 320) % positive (95%CI)
Nickel sulfate 5%	18.3 (14.0–23.2)	4.3 (2.3–7.2)
Cobalt chloride 1%	6.1 (3.6–9.4)	2.3 (0.9–4.7)
Myroxylon pereirae (Balsam of Peru) 25%	5.4 (3.1–8.6)	5.3 (3.0–8.4)
Fragrance mix I 8%	5.4 (3.1–8.6)	4.6 (2.5–7.6)
Potassium dichromate 0.5%	4.0 (2.1–7.0)	2.3 (0.9–4.7)
Colophonium 20%	3.4 (1.6–6.1)	1.3 (0.4–3.4)
Methyldibromo glutaronitrile[a] 0.2%/0.3%	3.0 (1.4–5.7)	3.7 (1.9–6.5)
Fragrance mix II 14%	2.7 (1.2–5.3)	2.7 (1.2–5.3)
Paraben mix 16%	2.4 (1.0–4.8)	1.3 (0.4–3.4)
Methylchloroisothiazolinone/ methylisothiazolinone 0.01% aq.	2.0 (0.7–4.3)	1.0 (0.2–2.9)

CI, confidence interval.
The vehicle was pet. unless otherwise indicated.
[a]The test concentration was changed from 0.3% to 0.2% in August 2008.

when we consider that approximately two-thirds of the patients were tested not because a contact sensitization was suspected, but in order to rule it out. Consequently, only one-third of the prurigo patients had one or more positive patch test reactions.

The qualitative spectrum of (frequent) allergens did not differ significantly from the spectrum found in the general patch test population (11, 18–20), with one exception. It is remarkable that 1,3-DPG is the only rubber ingredient among the top 30 contact allergens in prurigo patients. Normally, thiurams are the most frequent rubber allergens, followed by dithiocarbamates and mercaptobenzothiazole and its derivatives (11, 18–20). Of course, our finding that 7 of 154 prurigo patients reacted to 1,3-DPG should not be overinterpreted. 1,3-DPG 1% pet. often elicits doubtful or weak positive reactions, which are an expression of irritation rather than of true contact allergy (17). Considering that five of the seven positive reactions to 1,3-DPG occurred in patients with a positive SLS patch test reaction indicating increased skin irritability at the time of patch testing, one can assume that several reactions to 1,3-DPG were false-positive. To our knowledge, there is no evidence for a causative connection between contact sensitization to 1,3-DPG and prurigo. Moreover, we could not find an increased frequency of sensitization to allergens related to topical drugs or skin care products such as preservatives, fragrances, or active ingredients.

The finding of a more than fourfold increased frequency of nickel sensitization among prurigo patients aged <61 years as compared with older patients is impressive. This cannot be explained purely by differing proportions of women, or patients patch tested in order to exclude contact sensitization in both subgroups of patients, particularly because other allergens are not affected in the same way. It may simply be the well-known age effect, with younger people suffering from nickel allergy much more frequently (21–23), and an atopic predisposition and atopic dermatitis occurring in nearly half of prurigo patients, regardless of ethnicity and region (3–5). We are not aware of any proof of nickel allergy contributing causally to prurigo.

Case reports on prurigo and lichen simplex chronicus caused by sensitization to PPD have been published (7, 24). We found only 3 prurigo patients with PPD sensitization among 128 patients patch tested with PPD 1% pet. No far-reaching conclusions can be drawn from this finding. To our knowledge, there is no larger study on contact sensitization in prurigo patients and there are no special studies on PPD sensitization and prurigo.

The number of prurigo patients with an irritant test reaction to SLS and with strong irritant skin reactions was significantly higher than that among other patients tested in the IVDK. One explanation could be atopic skin diathesis, but this was less prevalent in our cohort than in the IVDK patients. In addition, prurigo patients with past or present atopic dermatitis had significantly fewer irritant reactions to SLS. Obviously, the comorbidity with atopic dermatitis did not increase skin irritability, as measured by patch testing with SLS, among prurigo patients. One may speculate that other changes in the skin of prurigo patients, for example inflammatory infiltrates,

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eosinophils, and neuroreceptors (2, 5), may contribute to this increased frequency of irritant reactions.

A general limitation of our study is that we had no reliable information on the individual clinical relevance of the sensitizations diagnosed. Hence, we cannot comment on the relevance of individual sensitizations for prurigo patients. However, our results may justify further prospective and systematic studies concerning the role of contact sensitization in causing or maintaining prurigo.

As compared with other groups of prurigo patients reported in the literature (3–5), the proportion of patients with past or present atopic dermatitis (8%) was remarkably low. This is probably attributable to patient selection for patch testing. Most dermatologists are probably aware of atopic dermatitis being a trigger for prurigo. Therefore, one may speculate that they see no need for patch testing in these patients. In contrast, if there is no history of atopic dermatitis, the physicians possibly tend to patch test more deliberately, in order to rule out or confirm contact sensitization as a prurigo trigger, which would lead to an over-representation of non-atopic prurigo patients. Also, one has to consider that previous studies investigated only a small number of prurigo patients (3–5). One has to be aware that our study is a retrospective analysis of routine patch test results focusing on the small subgroup of prurigo patients, and not an aimed patch test study in a defined group of prurigo patients.

In summary, we conclude that 35% of the prurigo patients had at least one positive patch test reaction but that there was no distinctive pattern of sensitization. Although prurigo is not a typical clinical manifestation of contact sensitization, the results indicate that patch testing in these patients is beneficial.

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