ORIGINAL ARTICLE

Prurigo as a symptom of atopic and non-atopic diseases: aetiological survey in a consecutive cohort of 108 patients

A. Iking†, S. Grundmann†, E. Chatzigeorgakidis†, N.Q. Phan†, D. Klein‡, S. Ständer†,*

†Department of Dermatology, Competence Center Chronic Pruritus, and ‡Department of Orthopaedics, University Hospital Münster, Germany

*Correspondence: S. Ständer. E-mail: sonja.staender@uni-muenster.de

Abstract

Background Prurigo nodularis Hyde (PN) is a highly pruritic condition due to a vicious circle of repeated itching and scratching. There are no representative clinical studies investigating comorbidities in a large collective of PN patients.

Objective This pilot study aimed to investigate the exact distribution of the coexisting diseases in a large representative consecutive cohort of PN patients.

Methods A total of 108 PN patients (36.1% male; mean age of 61.5 ± 16.7 years) were enrolled in the study.

Results In 87.0% of patients, diseases underlying PN could be established (18.5% skin disease, 7.4% systemic origin, 1.8% neurological diseases, 59.3% mixed origin). Due to several possible causative co-factors, the majority of patients were classified in the group of mixed origin (59.3%). In 53.1% of these patients, at least one dermatological factor was involved in the induction of PN. Interestingly, nearly half (46.3%) of all PN patients had either an atopic predisposition or atopic dermatitis as a single cause of PN (18.5%) or as one co-factor of PN of mixed origin (27.8%). Considering the different underlying diseases, there was no significant age or gender difference.

Conclusion PN does not seem to represent a characteristic symptom of one disease only. Multiple pruritogenic diseases are linked to evolution and improvement of PN upon treatment. Atopic predisposition is a major factor in nearly half of PN patients. The large collective of the present study helped detect a broad range of underlying diseases and thus to provide recommendations for rational diagnostics.

Received: 21 October 2011; Accepted: 27 January 2012

Conflict of interest

None declared.

Funding sources

None declared.

Introduction

Prurigo nodularis Hyde (PN) is defined by the presence of numerous, symmetrically distributed hyperkeratotic or erosive nodules.[1] The disorder is characterized by intense pruritus as the dominant symptom.[2–5] Both, the pruritus and the chronic persistent visible skin lesions, have a high influence on the quality of life.[3–6] It is still a matter of controversy if PN represents a separate entity or is a reaction pattern due to a vicious circle of repeated itching and scratching.[3,4,7] However, the latter hypothesis gained more and more acceptance during the past years. The pathophysiology of PN with evolution of circumscribed, therapy-refractory nodules is not yet understood but maybe related to altered skin nerve anatomy.[8,9] Multiple diseases ranging from dermatological to systemic or even psychiatric disorders have been assumed to cause PN. A broad variety of diseases such as gastrointestinal infections or Hodgkin's disease have been reported by case studies to underlie PN (Table 1). There are larger studies focusing on the point prevalence of single diseases such as cutaneous mycobacterial infection, HIV infection or gastric helicobacter pylori infection associated with PN, but no information is available on the total incidence of these diseases in a representative PN cohort.[10–12] For example, in French Guiana 36% of the selected PN patients have an underlying HIV infection.[11] Representative and systematic clinical studies based on a large collective investigating the distribution of underlying diseases for identification of the most frequent ones in Europe and to provide recommendations for diagnostics in PN

Table 1 Reported underlying diseases and number of patients with prurigo nodularis

Diseases	Number of patients	Reference
Dermatologic diseases		
Various dermatologic diseases	***n* = 46** (21 f, 25 m; 5–75 years old) with underlying disease in ***n* = 32** (**69.6%**): nummular eczema, *n* = 26; venous stasis, *n* = 4; psoriasis, *n* = 1; mycosis fungoides, *n* = 1	10
Cutaneous mycobacterial infection in PN nodules (different species, e.g. *M. avium*)	***n* = 43** (24 w, 19 m; 20–85 years old) mycobacteria in culture, *n* = 6 histopathological Ziehl-Neelsen staining positive; *n* = 12	31
Atopic dermatitis	***n* = 31** (15 f, 16 m; 11–68 years old) with underlying atopic dermatitis in ***n* = 20** (**64.5%**) ***n* = 1** (f, nine years old)	17 32
Epidermolysis bullosa acquisita	***n* = 1** (f, 30 years old)	33
Systemic diseases		
HIV infection	***n* = 154** (gender, age not provided) with ***n* = 55** (**35.7%**) being HIV positive	11
Metabolic diseases	***n* = 46** (21 f, 25 m; 5–75 years) with underlying disease in ***n* = 27** (**58.7%**) anemia, *n* = 10; diabetes, *n* = 5; alcoholics, *n* = 4; tumors (uterus, breast, esophagus), *n* = 3; hypothyroidism, *n* = 3; sarcoidosis, *n* = 1; hyperbilirubinemia, *n* = 1	10
Gastric *Helicobacter pylori* infection	***n* = 42** (27 f, 15 m; age range not provided) with ***n* = 40** (**95.2%**) being H. pylori positive	12
Uremia	***n* = 3** (3 m; 20–47 years old)	34
Gluten enteropathy	***n* = 2** (2 f, 37–41 years old) ***n* = 1** (f, 72 years old)	35 36
Intestinal *Strongyloides stercoralis* infection	***n* = 1** (m, 43 years old)	37
Pulmonary tuberculosis	***n* = 1** (m, 30 years old)	38
Tonsillitis	***n* = 1** (m, 42 years old)	39
Chronic HCV hepatitis	***n* = 1** (f, 52 years old)	25
Hodgkin's disease	***n* = 1** (f, 13 years old) ***n* = 1** (f, 24 years old)	40 41
Angioimmunoblastic T-cell lymphoma	***n* = 1** (m, 45 years old)	42
HTLV-1-positive adult T-cell leukemia/lymphoma	***n* = 1** (m, 52 years old)	43
Gastric cancer	***n* = 1** (m, 64 years old)	44
Metastatic bladder carcinoma	***n* = 1** (m, 84 years old)	45
Neuropathic diseases		
Prolapsed intervertebral disc	***n* = 1** (f, 66 years old)	46
Herpes zoster	***n* = 1** (f, 60 years old)	47
Psychogenic diseases		
Psychological disorder: depression, anxiety and other	***n* = 46** (21 f, 25 m; 5–75 years old) *n* = 14: major factor; *n* = 9: some influence on PN	10
Emotional stress and psychological disorders	***n* = 20** (14 f, 6 m, 42–80 years old) anxiety and depression	6

The total number of PN patients analysed and number/percent of affected patients in bold.

are pending. This study is the first to investigate the exact distribution of the coexisting and underlying diseases in a large representative consecutive cohort of PN patients.

Patients and methods

In this retrospective study, 108 patients encoded as PN in our multidimensional database for chronic pruritus patients were analyzed.[13] Previous to data entry into the local database, all patients were examined according to the current German Guideline for chronic pruritus using clinical and laboratory measures for detection of any underlying diseases.[14] The diagnosis of PN was confirmed clinically and histologically. The correlation between the underlying disease and PN was done by the history and course of the disease. We asked for the evolution of PN and for new and for known diseases. In addition, after the work-up and before entering the data into the database, the history and results of the work-up of patients with pruritus are again reviewed and diagnosis was refined. In the course of the medical care of patients in our specialized itch clinic, the database is updated after every visit. Only patients with a finalized diagnosis have been entered into this

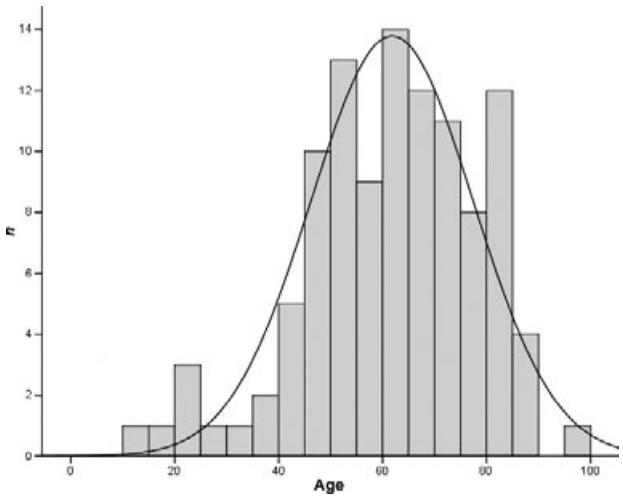

Figure 1 Age distribution in patients with prurigo nodularis. Age ranged from 11.9 years to 95.6 years with a median of 61.9 years.

study. Individual and clinical parameters such as age, gender, underlying origin of PN, diseases and comorbidities, pruritus localization, course, intensity and quality were extracted from the database and included into statistical analysis. The average intensity of pruritus was evaluated by an 11-point numeric rating scale (NRS-11). According to the position paper of the International Forum for the Study of Itch, patients were categorized according to the underlying disease (dermatologic, systemic, neurological, psychogenic, mixed, unknown).[15] In the German Guideline, only diseases known for their ability to induce pruritus and which were in close time correlation to PN were considered as origin of PN.[14] The study received approval from the local ethics committee and patients gave written informed consent.

Statistical analysis

Data were collected using Microsoft® Excel (Version 2003, Microsoft, Redmond, WA, USA). Statistical analysis was performed with the SPSS®-software package for Microsoft® Windows (Version 17.0, SPSS Inc., Chicago, IL, USA). Demographic and efficacy data were given as mean and standard deviation of the mean, or as median and range, as appropriate. To detect differences in success of categorized groups, depending on sample size Fisher's exact or chi-squared test was applied and $P \leq 0.05$ was considered statistically significant.

Results

Demographic data

A total of 108 patients (36.1% male; 63.9% female; mean age of 61.5 ± 16.7 years) were enrolled in the study (Fig. 1). The detailed demographic data are provided in Table 2. Mean duration of PN

Table 2 Demographic and clinical characteristics of 108 patients with PN

	Total	Dermatologic	Systemic	Neurologic	PUO	Mixed*	*P*-values
Sex							
n (%)	108 (100)	20 (18.5)	8 (7.4)	2 (1.9)	14 (13.0)	64 (59.3)	0.424
Male *n* (%)	39 (36.1)	6 (30.0)	2 (25.0)	1 (50.0)	8 (57.1)	22 (34.4)	
Female *n* (%)	69 (63.9)	14 (70.0)	6 (75.0)	1 (50.0)	6 (42.9)	42 (65.6)	
Age (years)							
Mean	61.54	58.85	64.68	68.95	58.88	62.34	0.956
SD	16.70	16.57	11.25	1.77	17.55	17.48	
Median	61.85	59.90	64.45	68.95	59.55	62.60	
Min	11.9	20.7	51.3	67.7	18.4	11.9	
Max	95.6	87.2	80.2	70.2	83.0	95.6	
Duration (months)							
Mean	77.48	86.15	151.50	107.50	44.69	70.82	0.130
SD	121.5	66.60	222.22	136.47	49.49	127.83	
Median	36.00	87.00	49.50	107.50	24.00	36.00	
Min	1	6	3	11	12	1	
Max	948	204	618	204	180	948	
Localization of PN – Begin							
Localized	74	19	7	1	8	39	
Generalized	34	5	4	1	3	21	
Localization of PN – Course							
Localized	13	5	1	1	2	4	
Generalized	95	19	10	1	9	56	

*Mixed: pruritus of multifactorial aetiologies.

PN, prurigo nodularis; PUO, pruritus of unknown origin, SD, standard deviation.

varied from 44.7 months in the group of PN of undetermined origin to 151.5 months in the group of systemic origin with a total mean duration of 77.5 months (SD 121.5, range 1–948 months). There was no correlation between underlying disease on the one hand and age-distribution, gender or duration of PN, on the other, though the majority of systemic diseases underlying PN were seen in the older patients (all patients in this subgroup were >50 years).

Diseases underlying prurigo nodularis

In 94 patients (87.0%), an underlying disease as the origin of PN could be established while in 14 patients (13.0%; 58.9 ± 17.6 years) no underlying disease was found. In 20 PN patients (18.5%; 58.9 ± 16.6 years) a skin disease (atopic diathesis, $n = 12$; atopic dermatitis, $n = 8$) was found to be the underlying disease (Table 3). A systemic origin was found in eight patients (7.4%; 64.7 ± 11.3 years) whereas two patients (1.8%, 69.0 ± 1.8 years) had an underlying neurological disease. No relevant monofactorial psychological disorder could be determined. Due to several possible causative co-factors, the majority of patients were classified in the group of PN of mixed origin (59.3%; 62.3 ± 17.5 years).

Underlying diseases in PN of multifactorial aetiologies

In the category of mixed origin, by definition, multiple diseases were found to be related to induction and maintenance of pruritus.[16] In our collective, 64 patients had PN of mixed origin, and a total 196 diseases were found as co-factors (Table 4). In the majority of patients, a combination of two (37.5%) or three (31.3%) co-factors was identified. More than three co-factors were noted as follows: four co-factors, $n = 14$; five co-factors, $n = 5$, seven co-factors, $n = 1$. Categorized in the same manner as in monofactorial prurigo, the majority of co-factors were internal diseases (70.9%) followed by dermatological diseases (19.4%). The leading systemic co-factors were food intolerances and malabsorption. In the group of dermatological co-factors, atopic diathesis was predominant and was observed in 46.9% of patients. A combination of dermatological and systemic factors as well as a combination of two or more systemic factors was observed most frequently (Fig. 2). In 53.1% of patients, at least one dermatological co-factor participated in the induction of PN.

.

Pruritus intensity and quality

Median pruritus intensity was NRS 8 with no significant differences in the diagnostic categories (dermatologic, median 7.25

Table 3 Underlying diseases in 108 patients with prurigo nodularis

Origin	Number of patients	Disease
Dermatological	20	Atopic diathesis/ dermatitis
Systemic	8	
	3	Sorbitol intolerance
	1	Lactose intolerance
	1	Hepatitis C
	1	Helicobacter pylori infection
	1	Iron deficiency
	1	Diabetes mellitus
Psychological	0	–
Neurological	2	Brachioradial pruritus
Mixed	64	
Unknown	14	–

Table 4 Co-factor analysis in the PN group of multifactorial aetiologies ($n = 64$). In the category of mixed PN origin, 196 diseases ('co-factors') were identified. More than one co-factor was identified in several patients

Dermatological factors	**38 (19.4%)**
Atopic diathesis	30
Venous insufficiency/ dermatitis	3
Allergic contact dermatitis	1
Cutaneous lymphoma	1
Dermatitis herpetiformis	1
Grover's disease	1
Lichen planus	1
Systemic factors	**139 (70.9%)**
Sorbitol intolerance	31
Lactose intolerance	21
Iron deficiency	15
Fructose malabsorption	13
Helicobacter pylori infection	13
Diabetes mellitus	8
Renal failure	8
Drugs	6
Zinc deficiency	4
Cobalamin deficiency	4
Hepatitis C	4
Carcinoma (renal cell carcinoma, bronchial carcinoma)	2
Colorectal cancer	1
Hepatic failure	2
Hyperuricemia	2
Hashimoto's thyroiditis	2
Chronic pancreatitis	1
Porphyria	1
Thrombocytopenia	1
Neurological factors	**8 (4.1%)**
Chronic pain syndrome	2
Neuropathy	2
PUVA-pain	2
Brachioradial pruritus	1
Restless legs syndrome	1
Psychological factors	**11 (5.6%)**
Psychological factors	10
Delusional parasitosis	1
Total	**196**

PN, prurigo nodularis.

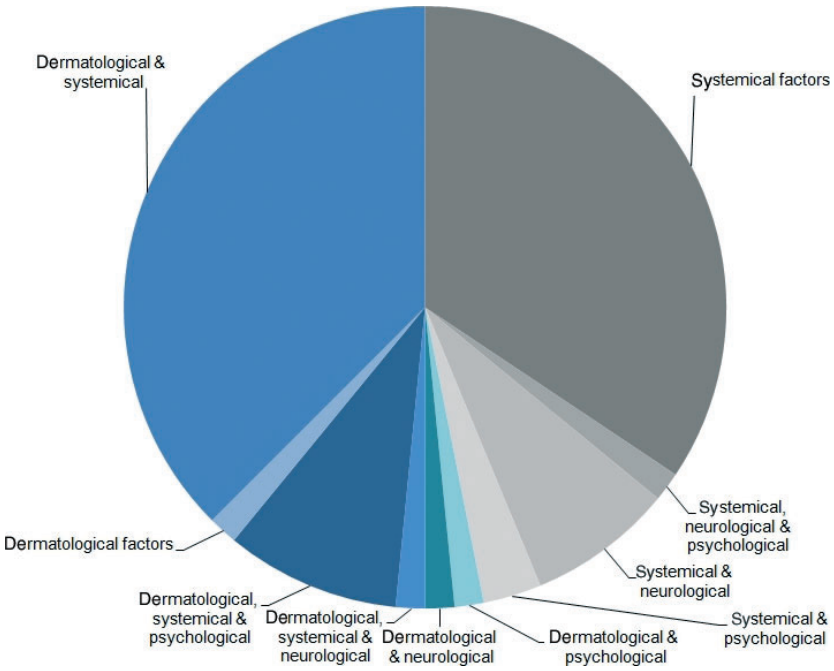

Figure 2 Distribution of co-factors in patients with multifactorial aetiologies of prurigo nodularis (n = 64, 196 contributing factors). The majority of patients had a combination of dermatological and systemic diseases or a combination of several systemic disorders. Derm, dermatological disease; Psych, psychogenic disease; Syst, systemic disease.

(range 1–10); systemic, 9 (5–10); neurologic, 7 (5–9); unknown, 7 (5–10); mixed, 8 (3–10); Fig. 3). Most patients mentioned more than one quality of pruritic sensation such as combination of pruritus and stinging (282/108, 2.6 different sensations per patient). Several subqualities have been reported such as burning (59.3% of all patients), stinging (47.2%), tingling (35%), heat (21.3%) and cold (2.7%). The subqualities were distributed among the different underlying disease groups without showing any statistically significant difference between groups with different aetiologies of PN and the quality of pruritus. Interestingly, stinging was not present in each PN diagnostic category (P = 0.074); however, both of the patients with PN of neurological origin stated that pruritus and stinging were present together.

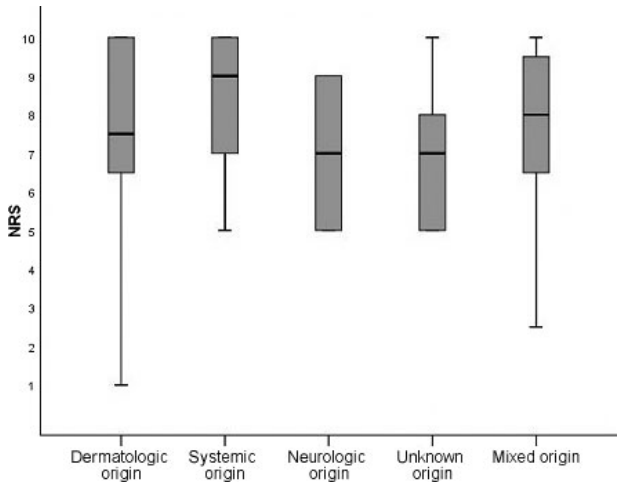

Figure 3 Pruritus intensity in patients with prurigo nodularis (n = 108, P = 0.792): self-report on the numeric rating scale (0–10).

Initial stages and course of PN

Initially, PN was localized in 68.5% of patients; only 31.5% had generalized PN at the onset. In the majority of patients (56.5%), a secondary generalization of PN was observed. In the course of PN, only 12.0% still suffered from a localized form of PN, including those with brachioradial pruritus but also PN patients with iron deficiency. In women, secondary generalization was more common (60.9% female); however, the gender-related effect was not statistically significant (P = 0.224).

Discussion

In this study, we analyzed the demographic and clinical parameters of a collective of 108 PN patients. Based on the clinical investigation, the associated diseases were categorized in dermatological, systemic, neurological, psychiatric, mixed and unknown ones according to the international classification of pruritic diseases.[15] A single uncontrolled study analyzing clinical and pathophysiological features of 46 patients with PN was published in 1985.[10] The authors focused on eczema and metabolic systemic diseases as well as concomitant psychosocial disorders. However, in this study, the subjects are not a representative collective and an all-embracing investigation of other potential diseases is missing. Moreover, several diseases were described to be present concomitantly

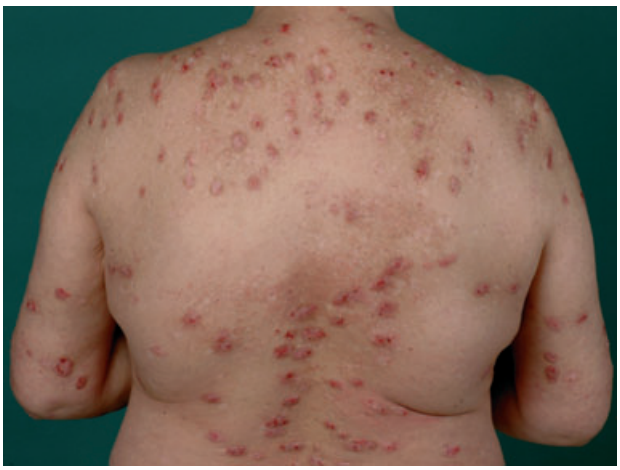

Figure 4 'Butterfly sign' on the back of 49 year-old-patients where they cannot reach with their hands.

but the authors did not comment on the relevant ones for the induction of PN.[10] With the help of precise diagnostic standards and follow-up, in our study, PN could be associated with an underlying disease condition in the majority (87%) of patients. Interestingly, nearly half (46.3%) of our PN patients had either an atopic predisposition or atopic dermatitis as the single cause of PN (18.5%) or as one factor of PN of mixed origin (27.8%). The large number of PN patients with atopy in our study is in agreement with a previous study of 31 PN patients of whom 64.5% had the same symptom constellation.[17] The authors differentiated atopic and non-atopic forms of PN and this distinction is confirmed by our findings. The presence of PN in atopic dermatitis (AD) is a well-known clinical observation designated as atopic prurigo nodularis.[18,19] A common pathogenesis of AD and PN was suggested by previous observations of dermal hyperplasia of nerve fibers or increased skin levels of interleukin 31 in both PN and AD.[20–22]

We could establish also other origins of PN such as systemic diseases in 7.4% of patients. The patients had, for example, gastric HCV infection, which have been described in single case reports before.[12,23] We found also some as yet unreported associations such as lactase deficiency that has recently been linked to chronic pruritus.[24] Interestingly, also sorbitol intolerance was found in association with PN which improved under sorbitol-free diet. However, monofactorial PN was rare and the majority of patients was classified in the group of mixed origin (59.3%) having a combination of two (37.5%) or three (31.3%) co-factors. These patients had an accumulation of many potentially pruritogenic diseases suggesting a multifactorial origin of pruritus (mixed pruritus/pruritus of multifactorial aetiologies). Previously our study group[16] and also Kantor & Lookingbill[25] found that several chronic pruritus patients had more than one underlying disease and a combination of, for example, kidney disease, liver disease, hypothyroidism and drug intake. Interestingly, in our previous

Table 5 Recommendations for diagnostics in PN based on underlying diseases reported so far (Table 1) and recent findings (Table 3, 4)

Investigation level	Investigations
Skin	Clinical examination: search for signs of atopic dermatitis, bullous pemphigoid, lymphoma or other skin diseases
	Skin biopsy: • H&E staining (routine histology) • Direct immunofluorescence to rule out autoimmune diseases (bullous pemphigoid, epidermolysis bullosa acquisita) if patient had reported blisters and/or if erythemas/blisters were found • PCR for mycobacteria if histological investigation finds granulomatous inflammatory infiltrate
	Allergy testing to rule our type I or type IV allergies
Laboratory – basic (frequent associations reported)	Erythrocyte sedimentation rate, differential blood cell count, glucose, IgE, HIV serology
Laboratory – advanced (rare associations reported)	Creatinine, urea, uric acid, alkaline phosphatase, y-GT, AP, bilirubin, AST, ALT, serum iron, ferritin, TSH, hepatitis C serology, gliadin antibody, zinc, cobalamin, total porphyrins, stool examination for *Strongyloides stercoralis*
Functional and radiological	• Chest X-ray (rule out sarcoidosis, neoplasm, lymphoma) • Ultrasound abdomen (rule out liver or kidney disease) • Ultrasound lymph nodes (rule out lymphoma; especially if patient reports weight loss, fever or night-time sweating) • Breath test for helicobacter, lactose and sorbitol intolerance • Magnet resonance tomography of cervical spinal column if patient has localized PN, for example, on lower arms • PN on the lower leg: phlebological investigation to rule our chronic venous insufficiency
Otolaryngology	Rule out tonsillitis
Psychosomatics/Psychiatry	Rule out anxiety, depression
Neurology	Rule out polyneuropathy, restless-leg syndrome

PCR, polymerase chain reaction; PN, prurigo nodularis.

study we found clinically 76.9% of patients in the group of mixed pruritus to have a PN.[16]

Previous reports (Table 1) together with the data of our study suggest that PN is not related to a single causative disease and can therefore not be considered as a part of a characteristic symptom constellation of one disease. Moreover, it is doubtful that PN presents a distinct disease entity. Given that multiple pruritogenic diseases are linked to evolution and improvement of PN upon treatment, it is more likely that PN presents a symptom related to long-lasting pruritus and repeated scratching. This is underlined by the frequent observation of the so-called butterfly sign (Fig. 4)[26] on the back of patients where they cannot reach with their hands. In line with this hypothesis is the observation that PN shows a common pattern in demographic and pruritus characteristics. No significant difference in age-distribution, gender, duration of PN, quality or intensity of pruritus could be observed in the different origin groups. Interestingly, the majority of patients (63.9%) were women. Previous studies had an equal gender distribution[17] or even a larger proportion of male patients[10] possibly due to study patients not forming a representative collective. Together, our study suggests that PN cannot be considered as a monofactorial disease, but rather a symptom of a variety of conditions. For a satisfactory therapy, a thorough workup of PN patients is necessary to determine underlying diseases or trigger factors. Atopic dermatitis seems to play a predominant role in the occurrence of PN as a symptom of pruritogenic conditions. Therefore, in atopic patients, an appropriate therapy of atopic dermatitis ameliorates PN, particularly if concomitant trigger factors and diseases are taken into consideration.[27,28] Patients benefit from therapeutic regimens adapted to associated skin or systemic diseases. Therefore, a standardized diagnostic workup, as established for chronic pruritus and applied for our multidimensional database, is helpful. A recommendation for the diagnostic work-up of PN patients is provided in Table 5.

This is the first study describing the different pruritus qualities in PN patients. We observed several subqualities of the itch sensation including tingling, burning, stinging, heat and cold sensations. Interestingly, in the group of dermatologic, mixed and unknown origin of PN, not all patients mentioned itching but rather other subqualities. This might be due to incompletely filled in itch questionnaires; it might also be speculated that patients with PN have a different experience of the unpleasant sensation, closely similar to a sensation of skin crawling and tingling than itching. However, the absence of a specific pattern of pruritus subqualities in PN patients argues again against PN being an independent disease entity.

Our study has some limitations. We aimed to include a representative cohort of PN patients without preselection in order to determine the underlying diseases. To rule out selection bias, we chose a retrospective design and screened our local database for those patients encoded as PN. All patients were subjected to thorough diagnostic work-up to establish presence of pruritus. Pruritus is the 'conditio sine qua non' to be included into the database of the pruritus network. The multidimensional database offers the opportunity to analyze a large collective of patients focusing on skin conditions, concomitant diseases and demographic data. A prospective design might have enabled inclusion of patients with PN not linked to pruritus. Our hypothesis of PN as a reaction pattern in pruritus is based on the presence of pruritus and has to be confirmed in a prospective study.

The previously reported finding of large numbers of cutaneous mycobacterial infection[10] is remarkable and could not be confirmed in this study. In a previous study we performed histological investigations of specimens from 136 PN patients and did not find signs of granulomatous inflammation as found in mycobacteriosis.[29] Another group focusing on the inflammatory infiltrate in subacute prurigo also failed to find granulomatous inflammation.[30] This might be due to a selection bias in patient recruitment in our and in the previous studies which leads to detection of different underlying diseases. For example, in our study, the mean age of patients was 61.5 years while in the study of Rowland Payne *et al.*[10] it was 39.5 years. In patients around 60 years, much more systemic diseases can be expected than in patients around 40 years of age. Failure to perform a broad range of investigations in all patients (for example, PCR analysis of skin samples) for many reasons including economic ones might lead to a failure to identify an underlying disease. In our study, we could not establish the origin of PN in 13% of patients despite comprehensive investigations. We suggest that the comprehensive diagnostic work-up as shown in Table 5 be carried out in order to identify the underlying disease/diseases and thus be able to offer appropriate therapy to PN patients.

Acknowledgements

We thank Rajam Csordas-Iyer for assistance in preparation of the manuscript.

References

1 Hyde JN (1883) *A Practical Treatise on Diseases of the Skin, for the Use of Students and Practitioners*, 1st edn. Lea & Febiger, Philadelphia.
2 Hammes S, Hermann J, Roos S, Ockenfels HM. UVB 308-nm excimer light and bath PUVA: combination therapy is very effective in the treatment of prurigo nodularis. *J Eur Acad Dermatol Venereol* 2011; **25**: 799–793.
3 Accioly-Filho LW, Nogueira A, Ramos-e-Silva M. Prurigo nodularis of Hyde: an update. *J Eur Acad Dermatol Venereol* 2000; **14**: 75–82.
4 Vaidya DC, Schwartz RA. Prurigo nodularis: a benign dermatosis derived from a persistent pruritus. *Acta Dermatovenerol Croat* 2008; **16**: 38–44.
5 Wallengren J. Prurigo: diagnosis and management. *Am J Clin Dermatol* 2004; **5**: 85–95.
6 Dazzi C, Erma D, Piccinno R, Veraldi S, Caccialanza M. Psychological factors involved in prurigo nodularis: A pilot study. *J Dermatolog Treat* 2011; **22**: 211–214.
7 Lezcano L, Di MartinoOrtizB, Rodríguez MasiM, Knopfelmacher O *et al.* Prurigo nodularis. *Arch Argent Pediatr* 2008; **106**: 446.
8 Schuhknecht B, Marziniak M, Wissel A, Phan NQ *et al.* Reduced intraepidermal nerve fibre density in lesional and nonlesional prurigo

nodularis skin as a potential sign of subclinical cutaneous neuropathy. *Br J Dermatol* 2011; **165**: 85–91.
9 Haas S, Capellino S, Phan NQ, Böhm M *et al.* Low density of sympathetic nerve fibers relative to substance P-positive nerve fibers in lesional skin of chronic pruritus and prurigo nodularis. *J Dermatol Sci* 2010; **58**: 193–197.
10 Rowland PayneCM, Wilkinson JD, McKee PH, Jurecka W *et al.* Nodular prurigo – a clinicopathological study of 46 patients. *Br J Dermatol* 1985; **113**: 431–439.
11 Magand F, Nacher M, Cazorla C, Cambazard F *et al.* Predictive values of prurigo nodularis and herpes zoster for HIV infection and immunosuppression requiring HAART in French Guiana. *Trans R Soc Trop Med Hyg* 2011; **105**: 401–404.
12 Neri S, Ierna D, D'Amico RA, Giarratano G *et al.* Helicobacter pylori and prurigo nodularis. *Hepatogastroenterology* 1999; **46**: 2269–2272.
13 Lotts T, Klein D, Chatzigeorgakidis E, Iking A *et al.* Multidimensional Database for Pruritus Patients – statistical evaluation of clinical characteristics. *Acta Derm Venereol* 2009; **89**: 691.
14 Ständer S, Streit M, Darsow U, Niemeier V *et al.* Leitlinie: diagnostisches und therapeutisches vorgehen bei chronischem pruritus. *J Dtsch Dermatol Ges* 2006; **4**: 350–370.
15 Ständer S, Weisshaar E, Mettang T, Szepietowski JC *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.
16 Sommer F, Hensen P, Barbara Böckenholt, Dieter Metze *et al.* Underlying diseases and co-factors in patients with severe chronic pruritus: a 3-year retrospective study. *Acta Derm Venereol* 2007; **87**: 510–516.
17 Tanaka M, Aiba S, Matsumura N, Aoyama H, *et al.* Prurigo nodularis consists of two distinct forms: early-onset atopic and late-onset non-atopic. *Dermatology* 1995; **190**: 269–276.
18 Feldmeyer L, Werner S, Kamarashev J, French LE *et al.* Atopic prurigo nodularis responds to intravenous immunoglobulins. *Br J Dermatol* 2012; **166**: 461–462.
19 Pugliarello S, Cozzi A, Gisondi P, Girolomoni G. Phenotypes of atopic dermatitis. *J Dtsch Dermatol Ges* 2011; **9**: 12–20.
20 Abadía MolinaF, Burrows NP, Jones RR, Terenghi G *et al.* Increased sensory neuropeptides in nodular prurigo: a quantitative immunohistochemical analysis. *Br J Dermatol* 1992; **127**: 344–351.
21 Sugiura H, Omoto M, Hirota Y, Danno K, Uehara M. Density and fine structure of peripheral nerves in various skin lesions of atopic dermatitis. *Arch Dermatol Res* 1997; **289**: 125–231.
22 Sonkoly E, Muller A, Lauerma AI, Pivarcsi A *et al.* IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol* 2006; **117**: 411–417.
23 Neri S, Raciti C, D'Angelo G, Ierna D *et al.* Hyde's prurigo nodularis and chronic HCV hepatitis. *J Hepatol* 1998; **28**: 161–164.
24 Grundmann SA, Stratmann E, Brehler R, Luger TA, Ständer S. Lactase deficiency: a potential novel etiological factor in chronic pruritus of unknown origin. *Acta Derm Venereol* 2011; **91**: 698–703.
25 Kantor GR, Lookingbill DP. Generalized pruritus and systemic disease. *J Am Acad Dermatol* 1983; **9**: 375–382.
26 Kimura T, Miyazawa H. The 'butterfly' sign in patients with atopic dermatitis: evidence for the role of scratching in the development of skin manifestations. *J Am Acad Dermatol* 1989; **21**: 579–580.
27 Siepmann D, Luger TA, Ständer S. Antipruritic effect of cyclosporine microemulsion in prurigo nodularis: results of a case series. *J Dtsch Dermatol Ges* 2008; **6**: 941–946.
28 Ständer S, Schürmeyer-Horst F, Luger TA, Weisshaar E. Treatment of pruritic diseases with topical calcineurin inhibitors. *Ther Clin Risk Manag* 2006; **2**: 213–218.
29 Weigelt N, Metze D, Ständer S. Prurigo nodularis: systematic analysis of 58 histological criteria in 136 patients. *J Cutan Pathol* 2010; **37**: 578–586.
30 Gambichler T, Skrygan M, Werries A, Scola N *et al.* Immunophenotyping of inflammatory cells in subacute prurigo. *J Eur Acad Dermatol Venereol* 2011; **25**: 221–226.
31 Mattila JO, Vornanen M, Vaara J, Katila ML. Mycobacteria in prurigo nodularis: the cause or the consequence?. *J Am Acad Dermatol* 1996; **34**: 224–228.
32 Amer A, Fischer H. Prurigo nodularis in a 9-year-old girl. *Clin Pediatr (Phila)* 2009; **48**: 93–95.
33 Furukita K, Ansai S, Hida Y, Kubo Y *et al.* A case of epidermolysis bullosa acquisita with unusual clinical features. *Clin Exp Dermatol* 2009; **34**: e702–e704.
34 Greer KE. Prurigo nodularis and uremia. *South Med J* 1975; **68**: 138–141.
35 McKenzie AW, Stubbing DG, Elvy BL. Prurigo nodularis and gluten enteropathy. *Br J Dermatol* 1976; **95**: 89–92.
36 Suárez C, Pereda JM, Moreno LM, García-González F *et al.* Prurigo nodularis associated with malabsorption. *Dermatologica* 1984; **169**: 211–214.
37 Jacob CI, Patten SF. Strongyloides stercoralis infection presenting as generalized prurigo nodularis and lichen simplex chronicus. *J Am Acad Dermatol* 1999; **41**: 357–361.
38 Saporito L, Florena AM, Colomba C, Pampinella D *et al.* Prurigo nodularis due to *Mycobacterium tuberculosis*. *J Med Microbiol* 2009; **58**: 1649–1651.
39 Katotomichelakis M, Balatsouras DG, Bassioukas K, Kontogiannis N *et al.* Recurrent prurigo nodularis related to infected tonsils: a case report. *J Med Case Reports* 2008; **2**: 243.
40 Shelnitz LS, Paller AS. Hodgkin's disease manifesting as prurigo nodularis. *Pediatr Dermatol* 1990; **7**: 136–139.
41 Seshadri P, Rajan SJ, George IA, George R. A sinister itch: prurigo nodularis in Hodgkin lymphoma. *J Assoc Physicians India* 2009; **57**: 715–716.
42 Khaled A, Sfia M, Fazaa B, Kourda N *et al.* Chronic prurigo revealing an angioimmunoblastic *T cell lymphoma*. *Tunis Med* 2009; **87**: 534–537.
43 Duval A, Rivet J, Moulonguet I, Cassar O *et al.* Atypical presentation of adult T-cell leukaemia/lymphoma due to HTLV-1: prurigo nodularis lasting twelve years followed by an acute micropapular eruption. *Acta Derm Venereol* 2010; **90**: 287–290.
44 Funaki M, Ohno T, Dekio S, Jidoi J *et al.* Prurigo nodularis associated with advanced gastric cancer: report of a case. *J Dermatol* 1996; **23**: 703–707.
45 Lin JT, Wang WH, Yen CC, Yu IT *et al.* Prurigo nodularis as initial presentation of metastatic transitional cell carcinoma of the bladder. *J Urol* 2002; **168**: 631–632.
46 Batta K, Foulds IS, Colloby P. Nodular prurigo occurring in the same distribution as sciatic pain from a prolapsed intervertebral disc. *Br J Dermatol* 1999; **141**: 170–171.
47 De D, Dogra S, Kanwar AJ. Prurigo nodularis in healed herpes zoster scar: an isotopic response. *J Eur Acad Dermatol Venereol* 2007; **21**: 711–712.