DOI: 10.1111/jdv.16309 JEADV

ORIGINAL ARTICLE

Chronic nodular prurigo: clinical profile and burden. A European cross-sectional study

M.P. Pereira,[1,*] V. Hoffmann,[1] E. Weisshaar,[2] J. Wallengren,[3] J.A. Halvorsen,[4] S. Garcovich,[5] L. Misery,[6] E. Brenaut,[6] E. Savk,[7] N. Potekaev,[8] A. Lvov,[8] S. Bobko,[8] J.C. Szepietowski,[9] A. Reich,[10] A. Bozek,[11] F.J. Legat,[12] M. Metz,[13] M. Streit,[14] E. Serra-Baldrich,[15] M. Gonçalo,[16] M. Storck,[17] I. Greiwe,[1] T. Nau,[1] S. Steinke,[1] M. Dugas,[17] S. Ständer,[1] C. Zeidler[1] on behalf of the EPP Consensus Conference Participants 2017[†]

[1]Department of Dermatology and Center for Chronic Pruritus, University Hospital Münster, Münster, Germany
[2]Occupational Medicine, Department of Dermatology, University of Heidelberg, Heidelberg, Germany
[3]Department of Clinical Sciences Lund, Dermatology and Venereology and Skane University Hospital, Lund, Sweden
[4]Department of Dermatology, Oslo University Hospital, University of Oslo, Oslo, Norway
[5]Institute of Dermatology, F. Policlinico A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy
[6]Department of Dermatology, University Hospital of Brest, Brest, France
[7]Department of Dermatology, Aydin Adnan Menderes University, Aydın, Turkey
[8]Moscow Scientific and Practical Center of Dermatovenerology and Cosmetology, Moscow, Russia
[9]Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland
[10]Department of Dermatology, University of Rzeszow, Rzeszów, Poland
[11]Department of Dermatology, School of Medicine, University of Information Technology and Management, Rzeszow, Poland
[12]Department of Dermatology, Medical University of Graz, Graz, Austria
[13]Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Berlin, Germany
[14]Department of Dermatology, Kantonsspital Aarau, Aarau, Switzerland
[15]Department Dermatology, Sant Pau Hospital, Barcelona, Spain
[16]Department of Dermatology, University Hospital and Faculty of Medicine, University of Coimbra, Coimbra, Portugal
[17]Institute of Medical Informatics, University of Münster, Münster, Germany
*Correspondence: M.P. Pereira. E-mail: manuelpedro.pereira@ukmuenster.de

Abstract

Background Chronic nodular prurigo (CNPG) is a condition characterized by chronic itch, a prolonged scratching behaviour and the presence of pruriginous nodules. A comprehensive understanding of this condition, especially regarding its clinical characteristics and impact on quality of life is still lacking.

Objectives Aim of this pan-European multicentre cross-sectional study was to establish the clinical profile of CNPG, including its associated burden.

Methods Fifteen centres from 12 European countries recruited CNPG patients presenting at the centre or using the centres' own databases. Patients were asked to complete a questionnaire in paper or electronic format. Demography, current co-morbidities, underlying disease, itch intensity, additional sensory symptoms, quality of life, highest burden and emotional experience of itch were assessed.

Results A total of 509 patients (210 male, median age: 64 years [52; 72]) were enrolled. Of these, 406 reported itch and CNPG lesions in the previous 7 days and qualified to complete the whole questionnaire. We recorded moderate to severe worst itch intensity scores in the previous 24 h. Scores were higher in patients with lower educational levels and those coming from Eastern or Southern Europe. Most patients experience itch often or always (71%) and report that their everyday life is negatively affected (53%). Itch intensity was considered to be the most burdensome aspect of the disease by 49% of the patients, followed by the visibility of skin lesions (21%) and bleeding of lesions (21%). The majority of patients was unaware of an underlying condition contributing to CNPG (64%), while psychiatric diseases were the conditions most often mentioned in association with CNPG (19%).

Conclusions This multicentre cross-sectional study shows that itch is the dominant symptom in CNPG and reveals that the profile of the disease is similar throughout Europe.

Received: 30 September 2019; Accepted: 27 January 2020

[†]See Appendix 1.

Conflicts of interest

MPP, VH, EW, JW, JAH, SG, LM, EB, ES, NP, AL, SB, FJL, MM, MS, ESB, MG, MS, IG, TN, SS, MD, CZ, FD, JE, CF, CR, GS and HS declare no conflicts of interest. MPP is an investigator in a clinical trial sponsored by Trevi and has received speaker honoraria from Galderma and Trevi. JCS is advisor for AbbVie, Almirall, Celgene, Dignity Sciences, LEO Pharma, Novartis, Pierre Fabre, Menlo Therapeutics, Sienna Biopharmaceuticals and Trevi, Toray Corporation, and has received speaker honoraria from AbbVie, Janssen-Cilag, LEO Pharma, Novartis, SunFarm, Sandoz and Eli Lilly; and clinical trial funding from AbbVie, Almirall, Amgen, Janssen-Cilag, Menlo Therapeutica, Merck, Novartis, Pfizer, Regeneron, Trevi and UCB. AR is a consultant or speaker for AbbVie, Bioderma, Celgene, Chema Elektromet, Eli Lilly, Galderma, Janssen, Leo Pharma, Medac, Menlo Therapeutics, Novartis, Pierre-Fabre, Sandoz and Trevi and a principal investigator or subinvestigator in clinical trials sponsored by AbbVie, Drug Delivery Solutions Ltd, Galderma, Genentech, Janssen, Kymab Limited, Leo Pharma, Menlo Therapeutics, MetrioPharm, MSD, Novartis, Pfizer and Trevi. AB is a subinvestigator in clinical trials sponsored by Drug Delivery Solutions Ltd, Genentech, Leo Pharma, Menlo Therapeutics and Trevi. SST is a consultant for Almirall, Bayer, Beiersdorf, Bionorica, Cara Therapeutics, Celgene, DS Biopharma, Galderma, Kneipp, Menlo Therapeutics, NeRRe Therapeutics, Novartis, Perrigo, Sienna Therapeutics, ACO HUD Nordic, Toray, Sanofi, Trevi Therapeutics, Bellus Health and an investigator for Dermasence, Galderma, Kiniksa, Menlo Therapeutics, Trevi Therapeutics, Novartis. TB is an advisor for Menlo Therapeutics (products may be related) and Novartis (unrelated).

Funding source

European Academy of Dermatology and Venereology (EADV, No. 2016-012 to MP).

Introduction

Chronic nodular prurigo (CNPG; synonym: prurigo nodularis) is a subtype of chronic prurigo, which is considered a disease characterized by chronic itch (i.e. itch lasting for 6 weeks or longer), a prolonged scratching behaviour and the presence of localized or disseminated pruriginous lesions.[1,2] CNPG develops in predisposed patients regardless of the aetiology of the underlying itch, which can be of dermatological, systemic, neurological, psychiatric/psychosomatic, multifactorial or unknown nature.[3] The pathophysiology of CNPG remains largely unknown, but neuronal sensitization mechanisms and a continuous itch-scratch cycle are thought to contribute to the chronicity of the disease.[4]

A comprehensive understanding of CNPG is still lacking. Establishing the clinical profile of the disease (demographic characteristics of the affected patient population, co-morbidities, itch intensity, concomitant sensory symptoms and secondary burden of the disease) is a major need for attending physicians. Even though no epidemiology studies have assessed the prevalence of CNPG, this condition is considered to be relatively rare. Therefore, multicentre studies are needed in order to explore this disease. We performed a prospective cross-sectional patient-reported questionnaire study, in which 15 centres across 12 European countries participated, with the aim of establishing the clinical profile and burdens of CNPG. This is an important step in order to gain a better understanding of the disease and consequently to provide a better care for affected patients.

Methods

In the frame of the European Prurigo Project (EPP),[1] we conducted a prospective, cross-sectional, cohort study in centres from Germany (Münster, Heidelberg and Berlin), Northern Europe (Sweden and Norway), Central Europe (Switzerland, France and Austria), Eastern Europe (Poland-Wroclaw, Poland-Rzeszow and Russia) and Southern Europe (Italy, Turkey, Spain and Portugal). Distribution of countries by regions was performed according to a historic widely accepted classification.

The study was approved by the local ethics committees corresponding to the study centres (main ethics committee: Medical Faculty of the University of Münster, nb.: 2017-168-f-S). Additionally, we registered the study at the German registry of clinical trials (DRKS00012876, registration date: 09.08.2017).

Subjects

Local investigators informed and invited adult CNPG patients, as defined by the European Academy of Dermatology and Venereology Task Force Pruritus[1], to participate in the study. Patients were either recruited at the centre when presenting to a routine appointment or were contacted via the centres' own databases. Patients with CNPG presenting to the centre in the previous 10 years were contacted. After signing the informed consent, patients received the questionnaire (Appendix S1) consisting of 37 questions either in paper or electronic format. Access to the mobile patient survey system (MoPat@Home) developed by the Institute of Medical Informatics at the University of Münster, Germany[5] was provided via a link sent by email. The patients' answers were automatically pseudonymized and sent SSL-encrypted to a central database in Münster, Germany. Data from paper questionnaires were entered in the database by the investigators. The database identified the country of origin and date of release by the patient.

Preparation of the questionnaire

In order to address the aims of the study, a steering committee (M. Augustin, C. Forner, F. Legat, M. Pereira, C. Riepe, S. Ständer, J. Sziepietowski, J. Wallengren, E.Weisshaar, C. Zeidler) prepared the scientific background and discussion on relevant aspects needed to be unveiled in respect to the clinical profile of CNPG, as well as a set of questions. This set of questions was discussed and refined and finally approved via voting using the Delphi method[6] in a consensus conference held on 3 February 2017 in Münster (Germany). The consensus conference was attended by 25 participants (24 dermatologists and one specialist for psychosomatics and psychotherapy) from 12 different countries and was moderated by an external neutral physician. Consensus was obtained when 75% or more of the participants agreed on the question being voted. Questions, for which no agreement could be reached during the consensus meeting, were further discussed and agreed upon using a postmeeting paper-based Delphi method (March 8–15th, 2017).

The questionnaire was translated and backtranslated by a professional translation agency involving also for quality checks the native investigators of all participating centres. The preliminary translated version was reviewed by each centres' principal investigator, and eventual corrections or adjustments were sent back to the professional translation office until a final version was agreed. A first translator performed the translation; a second and independent translator performed the back-translation of the questionnaire in order to compare it to the original version. If needed, additional adjustments were performed at this stage. The questionnaire was available both in electronic and paper format for every language.

Assessments

In this present paper, data from the first 26 questions of the questionnaire including demography (age, sex, height, weight, skin type, highest education, employment status and age of CNPG onset; questions 1–9), current co-morbidities (atopic eczema, asthma and rhinitis/conjunctivitis; questions 10–12), worst itch intensity in the past 24 h assessed by the verbal rating scale 0–4[7] (VRS 24 h; question 15) and by the numerical rating scale 0–10[7] (NRS 24 h; question 16), sensory symptoms (questions 17), quality of life (questions 18–22 corresponding to the 5-PLQ (pruritus life quality) questionnaire[8]), highest burden (question 23), emotional experience of itch (question 24) and underlying diseases (questions 25–26) are reported. Data from the remaining questions will be presented in a second paper.

Questions 13 (have you had itch within the last 7 days?) and 14 (have you had prurigo lesions within the last 7 days?) qualified the patients to continue completing the questionnaire, if both were positively answered.

Statistics

Data analysis was performed with IBM SPSS Statistics for Windows, v. 25.0 (Armonk, NY, USA). Analysis of normality was performed using the Kolmogorov–Smirnov test. The chi-squared test, Mann–Whitney *U* test and the Kruskal–Wallis test were used for group comparisons, as appropriate. Spearmans'rho was applied for correlation analyses. Data are shown as number of cases/total number of assessments (percentage) or as median [interquartile range]. Not all patients answered all items of the questionnaire. The total number of patients, who answered the question, is shown for each item. All statistical tests were two sided, and the significance level was set at $P < 0.05$.

Results

Demographics

Between March 2017 and June 2019, 509 patients (59% female, 41% male), aged 18–100 years (median 64 years [52; 72], $n = 498$), were enrolled in the various centres. Males (67 [54; 73], $n = 203$) were older than females (62 [50; 70], $n = 295$; $P < 0.001$). Demographics and co-morbidities for the whole population and by region are given in Table 1. Females reported more often suffering from rhinitis/conjunctivitis compared to men [$n = 97$ (34%) vs. $n = 46$ (22%), $P = 0.005$], while no sex differences were observed for atopic eczema or asthma. Patients reported a median duration of CNPG of 6 [3; 13] years ($n = 437$, only patients reporting disease begin in adulthood were considered, Table 1). The skin type distribution is displayed in Fig. 1. Concerning the educational level, 21.1% (104/494) of all patients finished school without further education, 32.2% (159/494) did an apprenticeship, 32.8% (162/494) had a graduate degree, 11.1% (55/494) had another education and 2.8% (14/494) abstained from answering. More than half of the patients (51.5%, 258/501) were retired, while 34.3% (172/501) were employed and 14.2% (71/501) unemployed at the time of questioning.

Of the 509 enrolled patients, 79.8% ($n = 406$) answered questions 13 and 14 both positively and completed the whole questionnaire (Germany: 137/185, 74.1%; Northern Europe: 69/92, 75.0%; Central Europe: 57/70, 81.4%; Eastern Europe: 76/84, 90.5%; and Southern Europe: 67/78, 85.9%). The data presented in the next sections refer to the 406 patients who answered positively to both qualification questions (questions 13/14).

Itch, sensory symptoms and underlying diseases

The median worst itch intensity in the previous 24 h assessed by the NRS was 7 [4; 8] (moderate intensity; $n = 393$), while the VRS self-categorization scale showed moderate to severe itch scores (Fig. 2). We recorded lower itch intensity scores in Germany compared to Eastern Europe (NRS: $P = 0.003$; VRS: $P < 0.001$) and Southern Europe (NRS: $P = 0.02$; VRS: $P = 0.003$), in Northern Europe compared to Eastern Europe (NRS: $P = 0.03$; VRS: $P = 0.002$) and Southern Europe (VRS: $P = 0.02$) and in Central Europe compared to Eastern Europe (NRS: $P = 0.04$). There were no sex differences in itch intensity assessed by the NRS (male: 7 [4; 8], female: 7 [4; 8]; $P = 0.62$,

Table 1 Demographics and co-morbidities of the enrolled patients in total (All) and by region i.e. Germany (Münster, Heidelberg and Berlin), Northern Europe (Sweden and Norway), Central Europe (Switzerland, France and Austria), Eastern Europe (Poland-Wroclaw, Poland-Rzeszow and Russia) and Southern Europe (Italy, Turkey, Spain and Portugal)

Characteristic	All	Germany	Northern Europe	Central Europe	Eastern Europe	Southern Europe
***N* (%)**	509 (100)	185 (36.3)	92 (18.1)	70 (13.8)	84 (16.5)	78 (15.3)
Age, years	64 [52; 72], *n* = 498	63 [52; 70], *n* = 182	69 [60; 75], *n* = 88	63 [50; 72], *n* = 66	65 [50; 70], *n* = 84	56 [42; 70], *n* = 78
Male, *n* (%)	210 (41.3),	79 (42.7)	42 (45.7)	26 (37.1)	43 (51.2)	20 (25.6)
Height, cm	168 [162; 175], *n* = 502	170 [164; 176], *n* = 183	171 [165; 178], *n* = 90	168 [163; 175], *n* = 68	167 [162; 173], *n* = 84	163 [158; 168], *n* = 77
Weight, kg	77 [65; 93], *n* = 500	79 [67; 95], *n* = 183	78 [68; 97], *n* = 88	75 [63; 88], *n* = 69	77 [65, 89], *n* = 82	73 [60, 88], *n* = 78
BMI (kg/m^2)	27.0 [23.7; 31.3], *n* = 496	27.0 [24.2; 31.1], *n* = 182	25.8 [23.3; 33.0], *n* = 87	25.7 [23.2; 30.0], *n* = 68	27.2 [23.8; 32.0], *n* = 82	27.5 [22.8; 32.7], *n* = 77
Disease duration (years)	6 [3; 13], *n* = 437	6.5 [3.3;13], *n* = 156	6 [11; 20.5], *n* = 77	6 [3; 13], *n* = 62	6 [3; 13], *n* = 70	3.5 [1; 9.8], *n* = 72
Co-morbidities, *n* (%)						
High blood pressure	217 (42.6)	82 (44.3)	34 (37.0)	32 (45.7)	39 (46.4)	30 (38.5)
Back pain	148 (29.1)	73 (39.5)	25 (27.2)	24 (34.3)	13 (15.5)	13 (16.7)
Heart disease	96 (18.9)	27 (14.6)	13 (14.1)	13 (18.6)	27 (32.1)	16 (20.5)
Depression	92 (18.1)	45 (24.3)	14 (15.2)	8 (11.4)	4 (4.8)	21 (26.9)
Diabetes	89 (17.5)	34 (18.4)	12 (13.0)	8 (11.4)	17 (20.2)	18 (23.1)
Lung disease	49 (9.6)	22 (11.9)	7 (7.6)	6 (8.6)	9 (10.7)	5 (6.4)
Arthritis	48 (9.4)	23 (12.4)	7 (7.6)	3 (4.3)	12 (14.3)	3 (3.8)
Ulcer/stomach disease	37 (7.3)	10 (5.4)	9 (9.8)	1 (1.4)	11 (13.1)	6 (7.7)
Kidney disease	33 (6.5)	16 (8.6)	3 (3.3)	2 (2.9)	6 (7.1)	6 (7.7)
Anaemia/blood disease	30 (5.9)	10 (5.4)	2 (2.2)	6 (8.6)	4 (4.8)	8 (10.3)
Liver disease	29 (5.7)	13 (7.0)	2 (2.2)	1 (1.4)	10 (11.9)	3 (3.8)
Rheumatoid arthritis	28 (5.5)	12 (6.5)	6 (6.5)	4 (5.7)	3 (3.6)	3 (3.8)
Cancer	20 (3.9)	5 (2.7)	4 (4.3)	6 (8.6)	1 (1.2)	4 (5.1)
Other	166 (32.6)	63 (34.1)	23 (25.0)	12 (17.1)	36 (42.9)	32 (41)
None	76 (14.9)	21 (11.4)	19 (20.7)	14 (20.0)	10 (11.9)	12 (15.4)
Atopy, *n* (%)						
Atopic eczema	163/492 (33.1)	76/180 (42.2)	45/90 (50.0)	15/68 (22.1)	11/78 (14.1)	16/76 (21.1)
Rhinitis/conjunctivitis	143/492 (29.1)	48/174 (27.6)	29/90 (32.2)	28/69 (40.6)	22/83 (26.5)	16/76 (21.1)
Asthma	103/594 (20.4)	47/185 (25.4)	20/91 (22.0)	17/69 (24.6)	7/82 (8.5)	12/77 (15.6)

Data are presented number of cases (percentage) or median [interquartile range].
BMI, Body Mass Index.

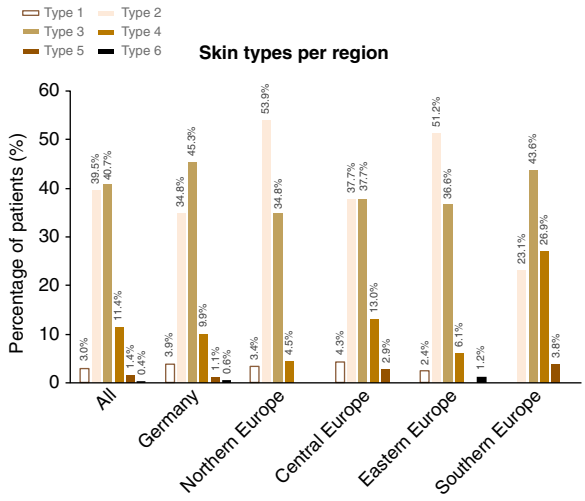


Figure 1 Proportion of patients per skin type (according to the Fitzpatrick classification) in the whole study population (All, $n = 499$; abstain: 3.6%) and by region i.e. Germany (Münster, Heidelberg and Berlin) $n = 181$; Northern Europe (Sweden and Norway) $n = 89$; Central Europe (Switzerland, France and Austria) $n = 69$; Eastern Europe (Poland-Wroclaw, Poland-Rzeszow and Russia) $n = 82$; and Southern Europe (Italy, Turkey, Spain and Portugal) $n = 78$.

$n = 393$), and age did not correlate with NRS scores ($r = 0.02$, $P = 0.67$, $n = 386$). We observed a negative correlation between NRS scores and height [$r = -0.101$ (low correlation strength), $P = 0.047$, $n = 390$], but not between NRS and weight ($r = -0.097$, $P = 0.057$, $n = 387$) or body mass index ($r = -0.070$, $P = 0.173$, $n = 385$). There were no differences in NRS scores from patients reporting having atopic eczema ($P = 0.79$, $n = 386$) or asthma ($P = 0.75$, $n = 392$) compared to those not suffering from these conditions, while a negative correlation between NRS scores and disease duration was recorded [$r = -0.116$ (low correlation strength), $P = 0.032$]. NRS scores did not differ across skin types ($P = 0.14$, $n = 388$) or according to employment status ($P = 0.21$, $n = 390$). As for educational degree, patients with lower educational level (regular school only) showed higher NRS scores (NRS: 8 [5; 9], $n = 84$) compared to those with an additional apprenticeship (NRS: 6 [4; 8], $n = 110$; $P = 0.001$) or a graduate degree (NRS: 6 [4; 8], $n = 136$; $P < 0.001$).

In addition to itch, the most frequently reported sensory symptoms were burning (39.9%), stinging (35.7%) and pain (32.5%). The distribution of the reported sensory symptoms by regions is presented in Table 2.

Over 30% of patients (141/395) indicated being told that their CNPG was related to an underlying disease (question 25). This disease was in most of the cases a psychiatric/psychosomatic disease (19.3%, 21/109), followed by diabetes (15.6%, 17/109) and allergy (9.2%, 10/109; Table 2).

Quality of life and Burden

The highest burden reported by patients was itch (49.3%), followed by visibility of skin lesions (21.4%), bleeding of skin lesions (14.1%), impact on everyday life activities (4.9%), sleep disturbance (4.3%), psychological consequences (3.3%) and pain (2.3%; $n = 304$; Fig. 3, Table 3). As for the emotional experience of itch, patients ($n = 406$) described their itch in various ways, with disturbing (55.2%), burdensome (50.7%), agonizing (46.6%) and intractable (35.0%) mentioned most often (Fig. 4, Table 3).

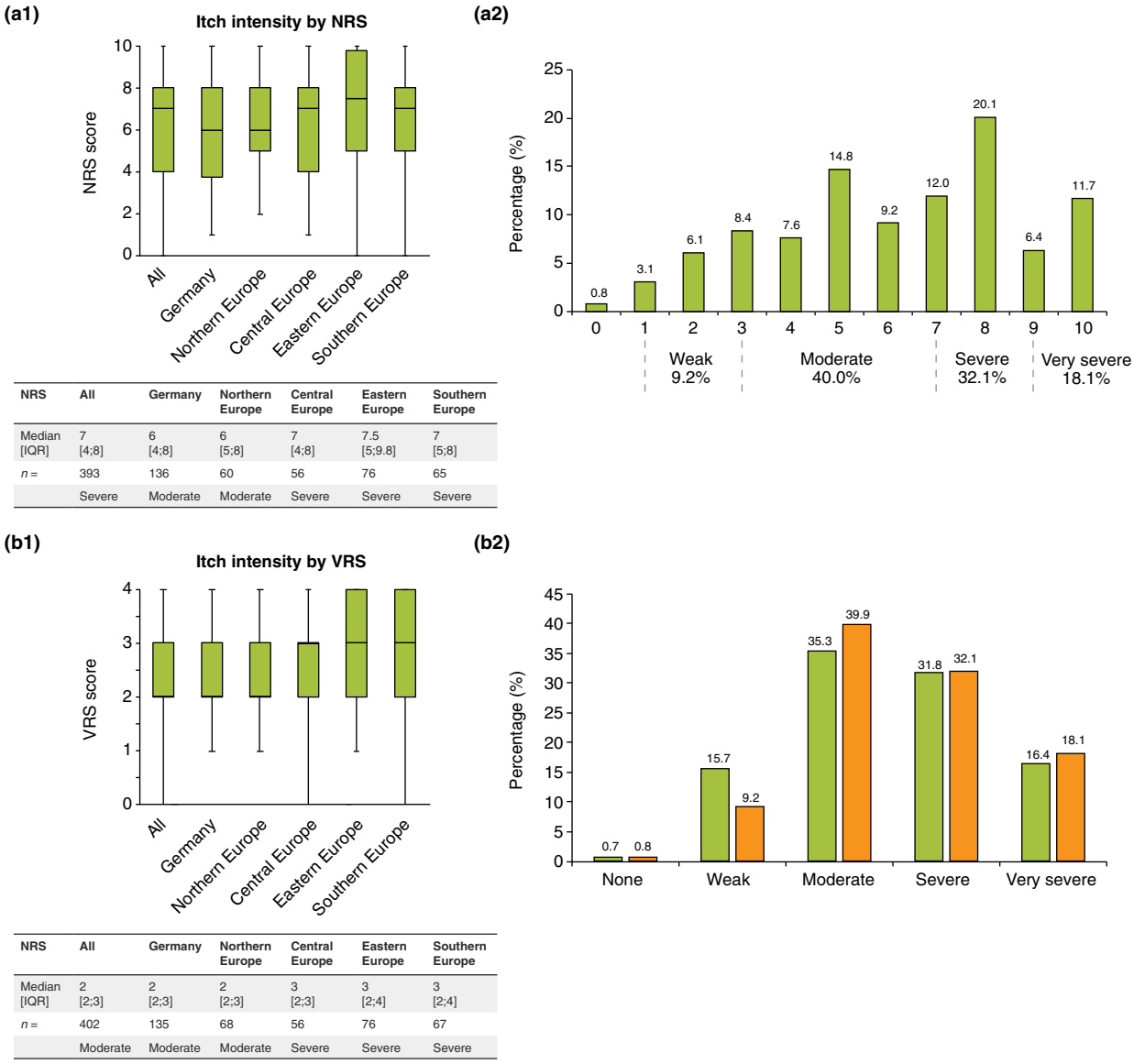
71.1% of patients reported experiencing itch often or always ($n = 402$). Their everyday life was negatively affected in 53.1% of the cases (very or rather affected, $n = 405$). The itch affected the interaction of the patients with others in 37.6% of the cases (very or rather affected, $n = 404$). Sleep was impaired in 42.5% of patients (very or rather affected, $n = 405$), while the joy and mood were negatively affected in 44.4% of patients (very or rather affected, $n = 403$). Figure 5 shows the results for all the patients and by region.

Quality of life as assessed by the 5PLQ scale was moderately impaired due to CNPG (2.4 [1.6; 3.0], $n = 405$; Fig. 6). The 5PLQ score correlated positively with the NRS score [$r = 0.62$ (moderate correlation strength), $P < 0.001$]. We recorded lower 5PLQ scores in Germany compared to Eastern Europe ($P = 0.01$) and Southern Europe ($P = 0.04$) and in Northern Europe compared to Central Europe ($P = 0.007$), Eastern Europe ($P < 0.001$) and Southern Europe ($P = 0.03$).

Discussion

This large European cross-sectional questionnaire study contributes to a better understanding of CNPG, providing comprehensive data on the clinical profile of the disease including associated dimensions of burden.

Itch was considered the highest burden of the disease by CNPG patients (49%). Using the NRS, we recorded a severe median worst itch intensity (7 [4; 8]), with 51.2% of patients rating the itch 7/10 or higher in the NRS scale (severe or very severe itch). The intensity showed only minor variations throughout Europe. It cannot be ruled out that seasonal variations or current treatments influenced itch assessments as we did not control for these factors. Interestingly, the assessment on the NRS correlated well with the self-categorization on the VRS. Only a small proportion of patients underrated the severity in relation to the intensity (Fig. 2). So, when asked to verbalize their itch intensity, almost half of the patients (48.2%) rated their itch as severe or very severe. The itch intensity recorded in our study is in line with previous reports. In a large multicentre European study analysing itch in patients with different skin diseases, itch intensity scores of CNPG patients were comparable to those from our study, however, only 17 prurigo patients were assessed (mean itch intensity 6.15 ± 2.98).[9] Lower itch intensities were recorded for other skin conditions such as atopic



NRS	All	Germany	Northern Europe	Central Europe	Eastern Europe	Southern Europe
Median [IQR]	7 [4;8]	6 [4;8]	6 [5;8]	7 [4;8]	7.5 [5;9.8]	7 [5;8]
n =	393	136	60	56	76	65
	Severe	Moderate	Moderate	Severe	Severe	Severe

NRS	All	Germany	Northern Europe	Central Europe	Eastern Europe	Southern Europe
Median [IQR]	2 [2;3]	2 [2;3]	2 [2;3]	3 [2;3]	3 [2;4]	3 [2;4]
n =	402	135	68	56	76	67
	Moderate	Moderate	Moderate	Severe	Severe	Severe

Figure 2 Worst itch intensity of the previous 24 h assessed by the NRS (scale 0–10, $n = 393$) and VRS (scale 0–4, $n = 402$). (a1) Median NRS worst itch intensity scores by region. (a2) Distribution of NRS scores for the whole study population. (b1). Median VRS worst itch intensity scores by region. (b2) Distribution of VRS (dark blue) and NRS (light blue) scores for the whole study population. NRS, numerical rating scale; VRS, verbal rating scale. Median [interquartile range] are shown in a1 (NRS) and b1 (VRS), while the distribution of scores is presented in percentage in a2 (NRS) and b2 (VRS, NRS) for all patients.

dermatitis, hand eczema, urticaria, psoriasis or bullous diseases.[9] Interestingly, itch intensity did not differ between patients with atopic conditions such as atopic eczema or asthma and those without them. Thus, atopic diathesis does not seem to be a relevant factor for the itch intensity in CNPG, as non-atopic patients are equally affected. Patients with lower educational levels reported suffering from higher itch intensities. This differs from patients with chronic pruritus, in which socioeconomic status does not seem to be an important factor.[10] CNPG patients with lower educational levels may have a lower level of health literacy and detrimental coping strategies for CNPG.

In addition to itch, CNPG patients also experience other sensory symptoms such as burning, stinging and pain. These sensations are typically found in neuropathic itch conditions,[11] which

Table 2 Chronic nodular prurigo related sensations and other contributing diseases for all patients (n = 406) and by region i.e. Germany (Münster, Heidelberg and Berlin) n = 137; Northern Europe (Sweden and Norway) n = 69; Central Europe (Switzerland, France and Austria) n = 57; Eastern Europe (Poland-Wroclaw, Poland-Rzeszow and Russia) n = 76; and Southern Europe (Italy, Turkey, Spain and Portugal) n = 67

Characteristic	All	Germany	Northern Europe	Central Europe	Eastern Europe	Southern Europe
Sensory symptoms						
Burning	162 (39.9)	53 (38.7)	20 (29.0)	23 (40.4)	31 (40.8)	35 (52.2)
Superficially localized	149 (36.7)	53 (38.7)	39 (56.5)	26 (45.6)	18 (23.7)	13 (19.4)
Stinging	145 (35.7)	59 (43.1)	19 (27.5)	17 (29.8)	28 (36.8)	22 (32.8)
Localized deep inside	136 (33.5)	54 (39.4)	30 (43.5)	17 (29.8)	12 (15.8)	23 (34.3)
Painful	132 (32.5)	59 (43.1)	23 (33.3)	21 (36.8)	17 (22.4)	12 (17.9)
Prickling	71 (17.5)	24 (17.5)	9 (13.0)	8 (14)	15 (19.7)	15 (22.4)
Spiky	70 (17.2)	16 (11.7)	16 (23.2)	10 (17.5)	6 (7.9)	22 (32.8)
Sharp	52 (12.8)	12 (8.8)	10 (14.5)	13 (22.8)	7 (9.2)	10 (14.9)
Stroking	34 (8.4)	10 (7.3)	15 (21.7)	1 (1.8)	4 (5.3)	4 (6)
Other	21 (5.2)	9 (6.6)	5 (7.2)	3 (5.3)	4 (5.3)	0 (0.0)
Suspected contributing disease	141/395 (35.7)	53/135 (39.3)	11/65 (16.9)	16/56 (28.6)	22/73 (30.1)	39/66 (59.1)
Psychiatric/Psychosomatic disease	21 (5.3)	4 (3.0)	2 (3.1)	5 (8.9)	0 (0)	10 (15.1)
Diabetes	17 (4.3)	4 (3.0)	0 (0)	2 (3.6)	2 (2.7)	9 (13.6)
Atopic eczema	10 (2.5)	6 (4.4)	0 (0)	0 (0)	1 (1.4)	3 (4.5)
Allergy	10 (2.5)	5 (3.7)	3 (4.6)	0 (0)	0 (0)	2 (3.0)
Liver disease	7 (1.8)	2 (1.5)	0 (0)	0 (0)	4 (5.5)	1 (1.5)
Iron deficiency	4 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (6.1)
Kidney disease	4 (1.0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (6.1)
Neurologic disease	4 (1.0)	1 (0.7)	1 (1.5)	1 (1.8)	0 (0)	1 (1.5)
Thyroid disease	4 (1.0)	2 (1.5)	0 (0)	0 (0)	1 (1.4)	1 (1.5)
Malignant neoplasm	3 (0.8)	1 (0.7)	0 (0)	2 (3.6)	0 (0)	0 (0)
Eczema (not atopic)	2 (0.5)	1 (0.7)	0 (0)	1 (1.8)	0 (0)	0 (0)
Atopic disposition	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.5)
Drug intake	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.5)
HIV	1 (0.3)	0 (0)	0 (0)	0 (0)	1 (1.4)	0 (0)
Skin infection	1 (0.3)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)
Skin lymphoma	1 (0.3)	0 (0)	0 (0)	0 (0)	1 (1.4)	0 (0)
Unknown	2 (0.5)	0 (0)	0 (0)	0 (0)	2 (2.7)	0 (0)
Other	16 (4.1)	6 (4.4)	1 (1.5)	4 (7.1)	3 (4.1)	2 (3.0)

Data presented as n (%).

support recent findings of altered epidermal neuroanatomy in patients with CNPG[12] and confirm previous reports.[13]

The humanistic burden of CNPG seems to be high according to available literature. Previous studies reported similar or even higher rates of clinical anxiety and depression (as assessed by the Hospital Anxiety and Depression Scale[14]) compared to patients with psoriasis or atopic dermatitis, while suicidal ideation was also more frequently reported in CNPG.[15,16] In a large retrospective study, significant associations between CNPG and anxiety and depression, as well as with the use of anxiolytics and antidepressants, were found.[17] The prevalence of current or past psychiatric co-morbidities was 48% in a small study including 50 patients with CNPG[18] and 65.9% in a sample of 44 inpatients with CNPG from a dermatological university ward.[19] Our study confirms previous reports pointing out a high burden in CNPG patients. Clinical depression was found in 18.1% of the patients, while 5.2% saw it as a contributing factor for CNPG. According to the 5PLQ, quality of life was moderately to severely impaired due to CNPG (5PLQ: 2.4 [1.6; 3.0], n = 405). This is in line with a previous study, in which a high Dermatological Life Quality Index[20] score was recorded in CNPG patients (12.4 $\pm$ 7.3), reflecting a severe impairment of the quality of life.[15] More than half of the patients reported their daily life being rather or very affected by CNPG. Particular aspects of daily life such as the interaction with others, sleep quality, mood and joy of life were substantially affected in a considerable number of patients (38–44%). The fact that symptoms are always or often present adds to the burden in the majority of the patients (71%). The highest burden associated with the disease was the itch, which was described as disturbing (55.2%), burdensome (50.7%) or agonizing (46.6%) by a substantial number of patients and has been shown to contribute substantially to psychological disease

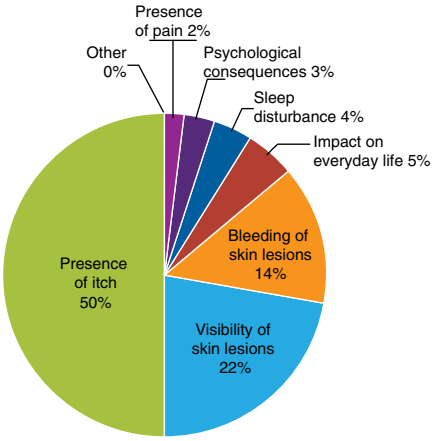


Figure 3 Highest burden of chronic nodular prurigo reported by patients (n = 304).

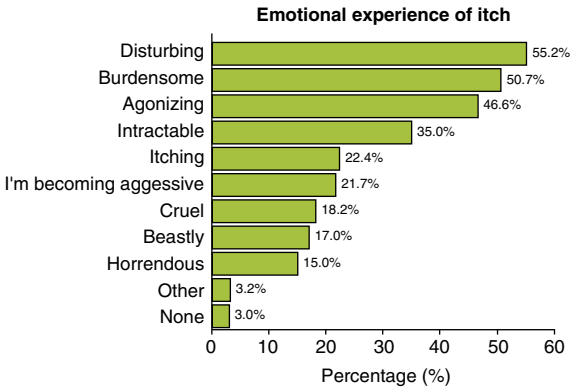


Figure 4 Emotional experience of itch and CNPG as reported by patients (n = 406).

burden.[21] Accordingly, the impairment of the quality of life correlated with itch intensity, as observed for other pruritic diseases.[22] Other aspects of the disease such as the visibility of the skin lesions and bleeding from the lesions were also mentioned as the highest burden, but only by a minority of the patients (14–21%) and thus seem to play a secondary role for patients.

Atopic eczema (33%), rhinoconjunctivitis (29%) and asthma (20%) were reported by a substantial number of patients, which is lower (possibly due to lack of self-reporting) compared to previous reports stating that an atopic predisposition is present in up to half of the patients with CNPG.[13] Moreover, patients from our cohort suffered from systemic conditions, which may lead to

Table 3 Highest burden and emotional experience of chronic nodular prurigo for all the patients and by region i.e. Germany (Münster, Heidelberg and Berlin); Northern Europe (Sweden and Norway); Central Europe (Switzerland, France and Austria); Eastern Europe (Poland-Wroclaw, Poland-Rzeszow and Russia); and Southern Europe (Italy, Turkey, Spain and Portugal)

Characteristic	All	Germany	Northern Europe	Central Europe	Eastern Europe	Southern Europe
Highest burden	n = 304	n = 91	n = 42	n = 54	n = 51	n = 66
Presence of itch	150 (49.3)	33 (36.3)	14 (33.3)	32 (59.3)	35 (68.6)	36 (54.5)
Visibility of skin lesions	65 (21.4)	19 (20.9)	16 (38.1)	9 (16.7)	11 (21.6)	10 (15.2)
Bleeding of lesions	43 (14.1)	15 (16.5)	6 (14.3)	5 (9.3)	4 (7.8)	13 (19.7)
Impact on daily activities	15 (4.9)	9 (9.9)	0 (0)	4 (7.4)	1 (2)	1 (1.5)
Sleep disturbance	13 (4.3)	9 (9.9)	2 (4.8)	1 (1.9)	0 (0)	1 (1.5)
Psychological consequences	10 (3.3)	4 (4.4)	2 (4.8)	1 (1.9)	0 (0)	3 (4.5)
Presence of pain	7 (2.3)	1 (1.1)	2 (4.8)	2 (3.7)	0 (0)	2 (3)
Other	1 (0.3)	1 (1.1)	0 (0)	0 (0)	0 (0)	0 (0)
Experiencing itch as:	n = 406	n = 137	n = 69	n = 57	n = 76	n = 67
Disturbing	224 (55.2)	91 (66.4)	37 (53.6)	30 (52.6)	23 (30.3)	43 (64.2)
Burdensome	206 (50.7)	97 (70.8)	28 (40.6)	34 (59.6)	31 (40.8)	16 (23.9)
Agonizing	189 (46.6)	88 (64.2)	42 (60.9)	22 (38.6)	24 (31.6)	13 (19.4)
Intractable	142 (35.0)	61 (44.5)	30 (43.5)	17 (29.8)	7 (9.2)	27 (40.3)
Only itching	91 (22.4)	35 (25.5)	7 (10.1)	10 (17.5)	21 (27.6)	18 (26.9)
I'm aggressive due to itch	88 (21.7)	33 (24.1)	6 (8.7)	17 (29.8)	9 (11.8)	23 (34.3)
Cruel	74 (18.2)	34 (24.8)	10 (14.5)	6 (10.5)	14 (18.4)	10 (14.9)
Beastly	69 (17.0)	33 (24.1)	8 (11.6)	6 (10.5)	9 (11.8)	13 (19.4)
Horrendous	61 (15.0)	26 (19)	3 (4.3)	7 (12.3)	17 (22.4)	8 (11.9)
Other	13 (3.2)	2 (1.5)	7 (10.1)	2 (3.5)	1 (1.3)	1 (1.5)
None	12 (3.0)	1 (0.7)	0 (0)	1 (1.8)	9 (11.8)	1 (1.5)

Data presented as n (%).

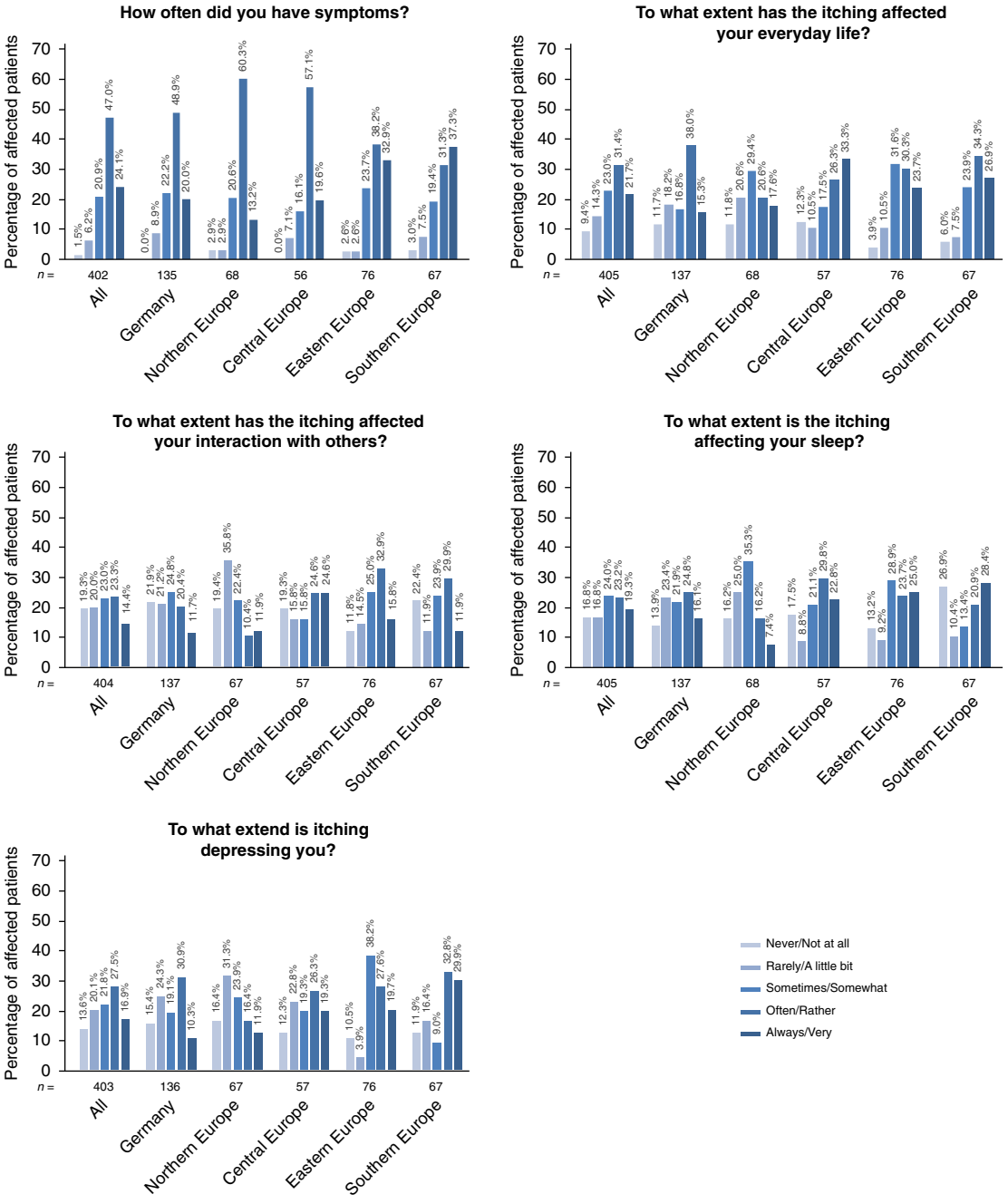
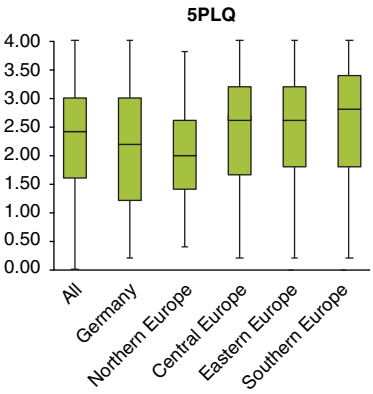


Figure 5 Percentage of patients affected in their quality of life by chronic nodular prurigo. Data presented for all patients and stratified by region i.e. Germany (Münster, Heidelberg and Berlin; DE); Northern Europe (Sweden and Norway; NRN EUR); Central Europe (Switzerland, France and Austria; CNTRL EUR); Eastern Europe (Poland-Wroclaw, Poland-Rzeszow and Russia; ERN EUR); and Southern Europe (Italy, Turkey, Spain and Portugal; SRN EUR).

itch and ultimately to CNPG, including diabetes (17.5%), kidney disease (6.5%), liver disease (5.7%) or cancer (3.9%). CNPG has been associated with systemic diseases such as chronic kidney disease, hepatitis C, chronic obstructive pulmonary disease, congestive heart failure, HIV infection[23] as well as solid tumours and malignancies of the hematopoietic system.[24]

Chronic nodular prurigo is considered a disease in its own right independent of the origin of the underlying itch.[1] The



NRS	All	Germany	Northern Europe	Central Europe	Eastern Europe	Southern Europe
Median [IQR]	2.4 [1.6;3.0]	2.2 [1.2;3.0]	2.0 [1.4;2.6]	2.6 [1.6;3.2]	2.6 [1.8;3.2]	2.8 [1.8;3.4]

Figure 6 Impairment of the quality of life assessed by 5-Pruritus Life Quality (5PLQ) for all patients (n = 405) and by region i.e. Germany (Münster, Heidelberg and Berlin) n = 137; Northern Europe (Sweden and Norway) n = 68; Central Europe (Switzerland, France and Austria) n = 57; Eastern Europe (Poland-Wroclaw, Poland-Rzeszow and Russia) n = 76; and Southern Europe (Italy, Turkey, Spain and Portugal) n = 67.

majority of patients in our study (254/395, 64%) were not aware of any condition contributing to the CNPG. More diagnostic efforts may be needed in order to find the underlying cause for the itch in these patients. Interestingly, of those reporting having a condition associated with their CNPG, psychiatric conditions were the most often mentioned (19%). This is in line with the studies cited above, which reported high levels of anxiety and depression or other psychiatric co-morbidities in patients with CNPG.[15,17–19] From our data, we cannot conclude, however, whether psychiatric co-morbidity is a consequence of CNPG or rather an etiological factor for the disease.

There were some small regional differences regarding the perception of itch intensity and impairment of the quality of life. In general, patients from Southern and Eastern Europe perceived itch slightly more intensely and reported a higher impairment of their quality of life compared to patients from Germany or Northern Europe. However, the magnitude of the recorded differences was small, and these findings were not controlled for possible treatment regimens. In line with our study, previous reports enrolling patients with pruritic dermatoses revealed regional differences in itch perception and quality of life across European countries.[25] For example itch intensity of patients with pruritic dermatoses was lower in Germany and higher in Turkey, while the impairment of the quality of life assessed using the ItchyQol was higher in Poland (but lower in Russia) compared to the other European centres.[25] There were no differences in NRS (P = 0.20) or 5PLQ scores (P = 0.16) across centres in Germany, the highest recruiting centres, suggesting that the observed regional differences are not centre dependent.

Academia has gained interest for CNPG in recent years. However, only limited data were available on the profile of the disease. This large multicentre European study addressed this issue by gathering data from a very large sample, contributing to a comprehensive understanding of the clinical profile and associated burdens of the disease. Our findings raise awareness for CNPG and highlight the urgency of developing standardized diagnostic and therapeutic guidelines in order to provide a better care for these patients.

Acknowledgements

We thank B. Pfleiderer M.D. for assistance in the study preparation and Galderma S.A., Kiniska Pharmaceuticals and Menlo Therapetics Inc. for the support of the study. This study was supported by the European Academy of Dermatology and Venereology (EADV, No. 2016-012 to MP).

References

1 Pereira MP, Steinke S, Zeidler C *et al.* European academy of dermatology and venereology European prurigo project: expert consensus on the definition, classification and terminology of chronic prurigo. *J Eur Acad Dermatol Venereol* 2018; **32**: 1059–1065.
2 Pereira MP, Zeidler C, Nau T *et al.* Position statement: linear prurigo is a subtype of chronic prurigo. *J Eur Acad Dermatol Venereol* 2019; **33**: 263–266.
3 Stander S, Weisshaar E, Mettang T *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.
4 Zeidler C, Stander S. The pathogenesis of Prurigo nodularis - 'Super-Itch' in exploration. *Eur J Pain* 2016; **20**: 37–40.
5 Storck M, Zeidler C, Rehr M *et al.* Validation of pruritus measures gathered with the electronic patient-reported outcome system MoPat. *Acta Derm Venereol* 2018; **98**: 38–43.
6 Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ* 1995; **311**: 376–380.
7 Phan NQ, Blome C, Fritz F *et al.* Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. *Acta Derm Venereol* 2012; **92**: 502–507.
8 Zeidler C, Stander S. Kurzfragebogen zur Lebensqualität bei chronischem Pruritus: ein neues Instrument zur Nutzung in der Praxis. 50 Tagung der Deutschen Dermatologischen Gesellschaft, Vereinigung Deutschsprachiger Dermatologen e.V. Berlin, 2019: 64–79.
9 Schut C, Dalgard FJ, Halvorsen JA *et al.* Occurrence, chronicity and intensity of itch in a clinical consecutive sample of patients with skin diseases: a multi-centre study in 13 European Countries. *Acta Derm Venereol* 2019; **99**: 146–151.
10 Carr CW, Veledar E, Chen SC. Factors mediating the impact of chronic pruritus on quality of life. *JAMA Dermatol* 2014; **150**: 613–620.
11 Misery L, Brenaut E, Le Garrec R *et al.* Neuropathic pruritus. *Nat Rev Neurol* 2014; **10**: 408–416.
12 Pogatzki-Zahn EM, Pereira MP, Cremer A *et al.* Peripheral sensitisation and loss of descending inhibition is a hallmark of chronic pruritus. *J Invest Dermatol* 2020; **140**: 203–211.
13 Iking A, Grundmann S, Chatzigeorgakidis E *et al.* Prurigo as a symptom of atopic and non-atopic diseases: aetiological survey in a consecutive cohort of 108 patients. *J Eur Acad Dermatol Venereol* 2013; **27**: 550–557.

14 Snaith RP. The hospital anxiety and depression scale. *Health Qual Life Outcomes* 2003; **1**: 29.
15 Brenaut E, Halvorsen JA, Dalgard FJ *et al*. The self-assessed psychological comorbidities of prurigo in European patients: a multicentre study in 13 countries. *J Eur Acad Dermatol Venereol* 2019; **33**: 157–162.
16 Schneider G, Hockmann J, Stander S *et al*. Psychological factors in prurigo nodularis in comparison with psoriasis vulgaris: results of a case-control study. *Br J Dermatol* 2006; **154**: 61–66.
17 Jorgensen KM, Egeberg A, Gislason GH *et al*. Anxiety, depression and suicide in patients with prurigo nodularis. *J Eur Acad Dermatol Venereol* 2017; **31**: e106–e107.
18 Dhawan L, Singh SM, Avasthi A *et al*. The prevalence of psychiatric comorbidity in patients with prurigo nodularis. *Indian Dermatol Online J* 2018; **9**: 318–321.
19 Schneider G, Driesch G, Heuft G *et al*. Psychosomatic cofactors and psychiatric comorbidity in patients with chronic itch. *Clin Exp Dermatol* 2006; **31**: 762–767.
20 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)–a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19**: 210–216.
21 Dalgard FJ, Svensson A Halvorsen JA *et al.* Itch and mental health in dermatological patients across Europe: a cross sectional study in 13 countries. *J Invest Dermatol* 2019; **140**: 568–573.
22 Zeidler C, Steinke S, Riepe C *et al*. Cross-European validation of the Itch-yQoL in pruritic dermatoses. *J Eur Acad Dermatol Venereol* 2019; **33**: 391–397.
23 Boozalis E, Tang O, Patel S *et al*. Ethnic differences and comorbidities of 909 prurigo nodularis patients. *J Am Acad Dermatol* 2018; **79**: 714–719.e3.
24 Larson VA, Tang O, Stander S *et al*. Association between itch and cancer in 16,925 patients with pruritus: experience at a tertiary care center. *J Am Acad Dermatol* 2019; **80**: 931–937.
25 Steinke S, Zeidler C, Riepe C *et al*. Humanistic burden of chronic pruritus in patients with inflammatory dermatoses: results of the European Academy of Dermatology and Venereology Network on Assessment of Severity and Burden of Pruritus (PruNet) cross-sectional trial. *J Am Acad Dermatol* 2018; **79**: 457–463.e5.

Appendix 1

EPP Consensus Conference Participants 2017: F. Dalgard (Department of Dermatology and Venereology, Skåne University Hospital, Lund University, S-20502 Malmö, Sweden), J. Elberling (Department of Dermatology, University Hospital Gentofte, Copenhagen, Denmark), C. Forner (Department of Dermatology and Center for Chronic Pruritus, University Hospital Münster, Münster, Germany), T. Leslie (St. John's Institute of Dermatology, Guy's & St Thomas' Hospital, London, United Kingdom), C. Riepe (Department of Dermatology and Center for Chronic Pruritus, University Hospital Münster, Münster, Germany), G. Schneider (Department of Psychosomatics and Psychotherapy, University Hospital Münster, Münster, Germany), H. Ständer (Dermatological Practice, Bad Bentheim and Department of Dermatology, Klinikum Dortmund GmbH, Germany).

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Questionnaire. Patients with CNPG were asked to fill out a questionnaire either in paper or electronic format. Data obtained from questions 1–26 are analysed in the present article.