

# Analysis of 325 Patients with Chronic Nodular Prurigo: Clinics, Burden of Disease and Course of Treatment

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**Chronic nodular prurigo presents with multiple pruriginous nodules and severe pruritus. This study aims to explore the treatment course and regimens in patients with chronic nodular prurigo and to analyse predictive factors contributing to therapeutic success. A total of 325 patients with chronic nodular prurigo (male 37.5%) were analysed concerning demographic data, pruritus intensity, medical history, psychological impairment, quality of life, treatment duration, regimens and outcome. These parameters were compared with 325 sex- and age-matched patients with chronic pruritus on non-lesional skin. Treatment success was dependent on duration and regime of treatment and independent of age, sex and initial itch intensity. Non-responders displayed a higher percentage of inflamed nodules, a higher portion of excoriated nodules and a higher impairment of quality of life and mood factors before initiation of treatment. Gabapentinoids and immunosuppressants proved to be the most successful therapeutic agents. Compared with patients with chronic pruritus, those with chronic nodular prurigo needed longer duration of therapy.**

**Key words:** prurigo nodularis; chronic prurigo; pruritus; antipruritic therapy; treatment.

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Chronic prurigo (CPG) is defined as a disease of its own, which is characterized by the presence of chronic pruritus (CP), prolonged scratching behaviour and multiple pruriginous lesions (1). CPG is the umbrella term for several clinical subtypes, such as papular, nodular (synonymous: prurigo nodularis or chronic nodular prurigo (CNPG)), plaque, umbilicated or linear type of CPG (1, 2). The most common subtype is CNPG, which manifests with multiple hyperkeratotic nodules that can vary in quantity from a few to hundreds and is usually symmetrically distributed (3). Successful treatment of CNPG remains difficult. Currently, guideline recommendations include topical treatments with steroids, calcineurin inhibitors and/or capsaicin, and systemic therapy consisting of antihistamines, gabapentinoids, antidepressants (selective serotonin reuptake inhibitors), immunos-

## SIGNIFICANCE

Chronic nodular prurigo is an illness characterized by multiple nodules and severe itch (pruritus). The Center for Chronic Pruritus at the University Hospital Münster analyzed data of 325 patients with chronic nodular prurigo and compared them to patients with chronic pruritus on non-lesional skin. In this sample inflamed and excoriated nodules as well as a low quality of life at beginning of treatment were negative predictors for patient outcome. Chronic nodular prurigo patients suffer from higher itch intensity, depression and impairment of quality of life than patients with chronic prurigo on non-lesional skin. Treatment of chronic nodular prurigo is difficult and can take years, but medications like gabapentinoids and immunosuppressants could be beneficial.

uppressants (e.g. cyclosporine and methotrexate), opioid receptor antagonists and ultraviolet (UV) therapy (4). Recently, randomized controlled trials (RCTs) have been conducted in order to investigate the antipruritic effect of new substances, such as the neurokinin-1 receptor antagonist serlopitant (5) and the anti-interleukin-31 receptor A-antagonist nemolizumab in CNPG (6). Nemolizumab has been proven to significantly reduce CP (6).

However, there is a lack of systematic analyses regarding the treatment response and time until therapeutic success using the currently available drugs. It also remains unclear whether there are predictive factors for treatment response in CNPG.

The primary objective of this study was to explore the effect and duration of a sufficient treatment. This includes comparison of the different treatment regimens and identification of possible predicting factors for patients' therapeutic success. Furthermore, a comparison of the treatment response was performed between patients with CNPG and those with CP on non-lesional skin. It was hypothesized that CNPG is more difficult to treat.

## PATIENTS AND METHODS

### Data collection

Datasets were extracted from 325 patients with CNPG and 325 sex- and age-matched patients with CP on non-lesional skin, according to the international classification of the International Forum for the Study of Itch (IFSI) from the database of the Center for Chronic Pruritus, Department of Dermatology, University



**Fig. 1.** Example of the evaluation of the estimated number of nodules: (a) few, (b) moderate, (c) many.

Hospital Münster, Germany (7). This study was approved by the ethics committee of the Medical Faculty of the University of Münster (2007-413-f-S).

After obtaining oral and written informed consent, the patients' demographic and clinical data were collected and then pseudonymously transferred to the above-mentioned database. Demographic data (sex, age at first visit), comorbidities, atopic disposition (measured by the Erlangen Atopy Score (8)) and the origin of pruritus according to the IFSI classification (dermatological, systemic, neurological, psychological, multifactorial or unknown) were analysed. Furthermore, it was assessed via clinical presentation and medical history whether patients had a skin disease as part of the aetiology of the pruritus.

Pruritus intensity was assessed using the visual analogue scale (VAS; mean of the last 24 h, mean of the last 4 weeks and worst of the last 4 weeks, ranging from 0 to 10) and the numerical rating scale (NRS; mean of the last 24 h, ranging from 0 to 10) (9, 10). The impairment of QoL was analysed by the Dermatology Quality of Life Index (DLQI) (11) and the psychological impairment by the Hospital Anxiety and Depression Scale (HADS-A and -D) (12, 13). The course of pruritus was assessed with the Dynamic Pruritus Score (DPS), measuring the total change of pruritus from the initiation of treatment up to the present in percentage (range: +100%=almost no pruritus anymore; -100% pruritus strongly worsened) (14). To evaluate patient outcome, the following "response groups" were defined using the DPS: <30% (non-responders, NR), 30–49% (weak responders, WR), 50–69% (good responders, GR) and  $\geq 70\%$  (very good responders, VGR) (15).

With the exception of NR, the duration of therapy was determined by the time between the first consultation and the follow-up time-point with the highest response category. As for NR, treatment duration was defined as the interval between the first and the last consultations.

Treatment was considered as terminated when patients did not return for a follow-up appointment for more than 1.5 years.

#### *Dermatological examination at first visit*

Severity of CNPG was evaluated via digitized photographs taken prior to treatment. The number and severity of inflammation and

the proportion of excoriated vs non-excoriated nodules was assessed. The relative number of nodules was estimated in 3 categories: "few", "moderate" and "many" (Fig. 1). The nodules were categorized as either non-inflamed or inflamed (Fig. 2). The absence of an inflammatory dermatosis was verified. The presence of excoriations was described as "few (up to 1/3 of nodules excoriated)", "moderate (1/3 to 2/3 of nodules excoriated)" or "many (more than 2/3 of nodules excoriated)" of all of the patients' nodules (Fig. 3).

#### *Therapeutic regimens*

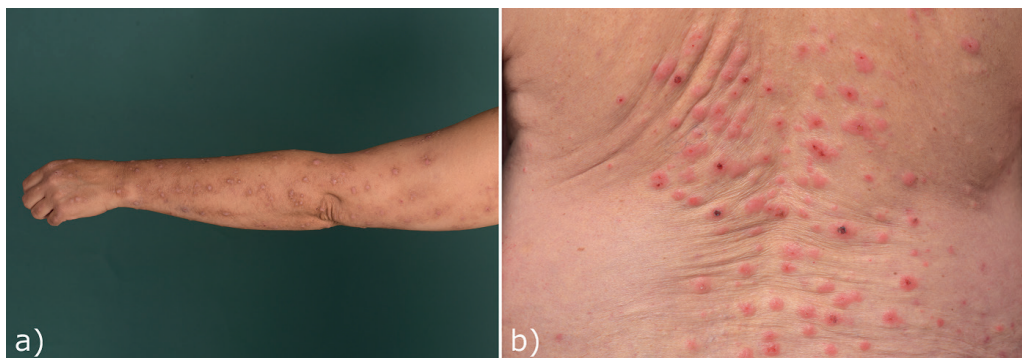
The antipruritic treatment was categorized into the following groups: antihistamines, gabapentinoids (gabapentin, pregabalin), antidepressants (e.g. selective serotonin reuptake inhibitors or tricyclic antidepressants) and immunosuppressants (e.g. cyclosporine A and methotrexate).

Other agents that were used less frequently (e.g. opioid receptors antagonists, such as naloxone and naltrexone, ursodeoxycholic acid and the neurokinin-1-receptor antagonist aprepitant) were summarized into the group "other therapies". If patients were treated with a combination of these groups the treatment was classified by the most potent substance used (antihistamines < gabapentinoids < antidepressants < immunosuppressants).

#### *Statistical analysis*

For every metric item median, mean, standard deviation (SD), minimum, maximum and range values were calculated. For categorical data frequencies and percentages were calculated. The Kolmogorov–Smirnov test was used to analyse variable distribution before statistical testing.

For normally distributed samples *t*-test was used to compare differences between 2 subgroups. For data that did not meet the criteria of normal distribution non-parametric tests were used (Mann–Whitney *U* test for analysis between 2 groups, Kruskal–Wallis test for more than 2 groups). Dunn–Bonferroni *post-hoc* test was used for pairwise multiple comparisons. Categorical parameters were analysed with  $\chi^2$  and Fisher's exact tests. Logistic and ordinal regression analyses were used to identify predictors of therapeutic success.



**Fig. 2.** Example of the evaluation of the inflammation of nodules: (a) non-inflamed, (b) inflamed.



**Fig. 3.** Example of the evaluation of the proportion of excoriated nodules vs non-excoriated nodules: (a) few, (b) moderate, (c) many.

All data analyses were performed with SPSS 25 (Statistical Package for the Social Science) and *p*-values <0.05 were considered significant.

**RESULTS**

*Patients with chronic nodular prurigo*

A total of 325 (median age 62.6 years; 122 males (37.5%), 203 females (62.5%)) patients with CNPG were included in the study (Table I). The main origin of CNPG was multifactorial (61.8%), followed by dermatological (20.9%), systemic (9.2%), unclear (4.6%), neurological (2.2%) and psychological (1.2%) diseases. Almost half of the patients with CNPG with an available Erlangen Atopy Score (EAS) had an atopic disposition (*n* = 116).

*Responder analysis*

Divided into the 4 response groups, *n* = 99 (30.5%) were NR, *n* = 17 (5.2%) WR, *n* = 58 (17.8%) GR and *n* = 151

(46.5%) VGR (Fig. 4). Treatment response was independent of age (*p* = 0.232; Kruskal–Wallis test) and sex (*p* = 0.575; Kruskal–Wallis test).

*Itch intensity, quality of life and mental impairment.*

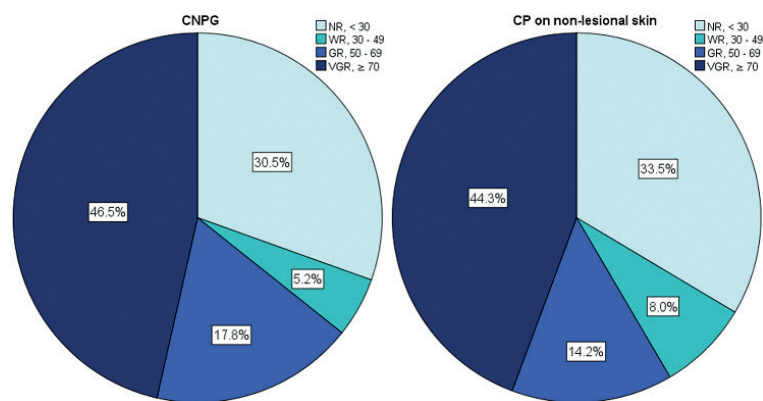
There were no significant differences in scores for VAS-average 24 h (*p* = 0.577, Kruskal–Wallis test), VAS-average 4 weeks (*p* = 0.319, Kruskal–Wallis test), VAS-worst 4 weeks (*p* = 0.305, Kruskal–Wallis test), NRS-average 24 h (*p* = 0.212, Kruskal–Wallis test) and HADS-A (*p* = 0.532, Kruskal–Wallis test) between the 4 response groups before initiation of treatment. However, there were overall significant differences in DLQI (*p* = 0.031, Kruskal–Wallis test) and HADS-D (*p* = 0.023, Kruskal–Wallis test) scores between the 4 response groups. NR showed significantly higher DLQI scores than GR (*p* = 0.017, Dunn procedure) and VGR (*p* = 0.008, Dunn procedure) before starting the therapy. Concerning HADS-D pairwise comparisons revealed higher scores for NR vs WR. (*p* = 0.002, Dunn procedure; Table I, Table SI<sup>1</sup>).

**Table I.** Sociodemographic data, pruritus intensity, quality of life and mental impairment before initiation of treatment in the total collective

	CNPG ( <i>n</i> = 325)	CP ( <i>n</i> = 325)	Statistics			<i>p</i> -value
			χ <sup>2</sup>	DF	T	
Sex, <i>n</i> (%)			0	1		1.0
Male	122 (37.5)	122 (37.5)				
Female	203 (62.5)	203 (62.5)				
Age, years, <i>n</i> , mean ± SD	325, 62.1 ± 13.3	325, 61.6 ± 13.2			0.556	0.578
Median (range)	62.2 (12.1–90.1)	59.9 (11.9–89.0)				
VAS-average 24 h, <i>n</i> , mean ± SD	306, 6.4 ± 2.7	319, 5.4 ± 2.7			4.771	<0.001***
Median (range)	7.0 (0.5–10)	5.5 (0–10)				
VAS-average 4 weeks, <i>n</i> , mean ± SD	290, 7.0 ± 2.2	319, 6.4 ± 2.2			2.948	0.003**
Median (range)	7.0 (0.5–10)	7.0 (0.5–10)				
VAS-worst 4 weeks, <i>n</i> , mean ± SD	289, 8.3 ± 1.8	318, 7.9 ± 1.9			2.500	0.013*
Median (range)	9.0 (0.5–10)	8.0 (1–10)				
NRS-average 24 h, <i>n</i> , mean ± SD	256, 6.1 ± 2.6	295, 5.5 ± 2.6			2.871	0.004**
Median (range)	7.0 (0–10)	6.0 (0–10)				
DLQI, <i>n</i> , mean ± SD	272, 12.1 ± 6.7	294, 9.2 ± 2.6			5.291	<0.001***
Median (range)	11.0 (1–30)	8.0 (0–30)				
HADS-A, <i>n</i> , mean ± SD	268, 7.7 ± 4.4	299, 7.9 ± 4.2			–0.604	0.546
Median (range)	7.0 (0–19)	8.0 (0–19)				
HADS-D, <i>n</i> , mean ± SD	270, 6.9 ± 4.3	300, 6.1 ± 4.2			2.328	0.020*
Median (range)	6.0 (0–20)	6.0 (0–22)				
EAS, <i>n</i> , mean ± SD	248, 9.5 ± 4.6	297, 7.9 ± 4.0			4.260	<0.001***
Median (range)	10.0 (0–25.5)	8.0 (0–18.5)				

\**p* < 0.05; \*\**p* < 0.01; \*\*\**p* < 0.001.

CNPG: chronic nodular prurigo; CP: chronic prurigo; SD: standard deviation; VAS: visual analogue scale, >7: severe pruritus; NRS: numerical rating scale, >7: severe pruritus; HADS: Hospital Anxiety and Depression Scale, >10 clinically significant depression/anxiety; DLQI: Dermatology Quality of Life Index (0–1=no effect at all on patient's life, 2–5=small effect on patient's life, 6–10=moderate effect on patient's life, 11–20=very large effect on patient's life, 21–30=extremely large effect on patient's life); EAS: Erlangen Atopy Score (0–3=no atopic disposition, 4–7=improbable atopic disposition, 8–9=unclear atopic disposition, 10–14=atopic disposition, 15–19=clear atopic disposition, 20 ≥strong atopic disposition).



**Fig. 4. Response to treatment, measured by dynamic pruritus score.** CNPG: chronic nodular prurigo; CP: chronic pruritus; NR: non-responders; WR: weak responders; GR: good responders; VGR: very good responders.

*CNPG severity before initiation of treatment.* No differences in the relative number of nodules were found between NR and VGR ( $p=0.202$ ,  $\chi^2$  test). However, NR had a significantly higher portion of inflamed nodules than non-inflamed nodules in comparison with VGR ( $p=0.002$ ,  $\chi^2$ -test). NR and VGR also differed in their number of excoriated nodules, with NR having more excoriations ( $p=0.049$ ,  $\chi^2$ -test) (Table II).

Independent  $t$ -test showed higher scores in VAS-average 24 h in patients with inflamed nodules before initiation of treatment (mean  $\pm$  SD  $7.11 \pm 2.22$  days) than in patients with non-inflamed nodules ( $6.14 \pm 2.91$  days;  $p=0.048$ ). Inflamed nodules ( $8.66 \pm 1.44$  days) were also associated with higher VAS-worst 4 weeks scores than non-inflamed nodules ( $7.91 \pm 2.23$  days;  $p=0.036$ , independent  $t$ -test). Patients with different degrees of excoriations differed in their DLQI scores at the first visit ( $p=0.046$ , Kruskal–Wallis test). Those who had excoriations on more than 2/3 of their nodules also had higher DLQI scores than patients who had less than 1/3 of their nodules excoriated ( $p=0.042$ , Dunn procedure). There were no significant differences in HADS-D scores ( $p=0.877$ , Kruskal–Wallis test).

<sup>1</sup><https://www.medicaljournals.se/acta/content/abstract/10.2340/00015555-3571>

**Table II. Severity of chronic nodular prurigo (CNPG) at the first visit**

Nodules	NR <i>n</i> (%)	WR <i>n</i> (%)	GR <i>n</i> (%)	VGR <i>n</i> (%)
Number				
Few	8 (18.2)	2 (40.0)	4 (16.0)	19 (27.1)
Moderate	21 (47.7)	2 (40.0)	9 (36.0)	22 (21.4)
Many	15 (34.1)	1 (20.0)	12 (48.0)	29 (41.4)
Inflammation				
Non-inflamed	19 (43.2)	3 (60.0)	21 (84.0)	51 (72.9)
Inflamed	25 (56.8)	2 (40.0)	4 (16.0)	19 (27.1)
Nodules affected with excoriations				
Few (<1/3)	10 (22.7)	2 (40.0)	5 (20.0)	28 (40.0)
Moderate (1/3–2/3)	12 (27.3)	0 (0)	9 (36.0)	21 (30.0)
Many >2/3)	22 (50.0)	3 (60.0)	11 (44.0)	21 (30.0)
Total	44	5	25	70

NR: non-responders; WR: weak responders; GR: good responders; VGR: very good responders.

Binary logistic regression analysis showed no effect of an inflammatory skin disease as a comorbid condition or aetiology regarding the inflammation of nodules ( $p=0.507$ ). Underlying autoimmune dermatoses were ruled out.

*Treatment duration and regimens.* Overall, the 4 response groups differed in their treatment duration ( $p<0.001$ , Kruskal–Wallis test). NR had a median treatment duration of 99 days (mean  $\pm$  SD  $218.7 \pm 305.8$  days). WR were treated for a median of 95 days ( $231.7 \pm 441.2$  days), GR for a median of 169 days ( $286.8 \pm 400.5$  days) and VGR for a median of 182 days ( $484.2 \pm 633.8$  days). VGR were treated significantly longer than NR ( $p<0.001$ , Dunn procedure) and WR

( $p=0.008$ , Dunn procedure). GR were treated significantly longer than NR ( $p=0.016$ , Dunn procedure) (Table III, Fig. 5, Fig. S1<sup>1</sup>).

Logistic regression analysis showed no significant effect of the origin of pruritus (pruritus category I–VI according to IFSI classification ( $p=0.735$ ) or the presence of atopic disposition on response to treatment ( $p=0.640$ ).

There was a significant difference in treatment regimens between the response groups ( $p<0.001$ ,  $\chi^2$ -test). VGR were more frequently treated with immunosuppressants (37.1%) than NR (6.1%). The treatment regimen did have an overall significant effect on response to therapy and accounted for 14% of variance of treatment response ( $R^2=0.144$ ) revealed by an ordinal regression analysis.

Out of all systemic antipruritic therapies, treatment with gabapentinoids ( $p=0.049$ ) and immunosuppressants ( $p<0.001$ ) was significantly associated with better response categories (Tables IV and V).

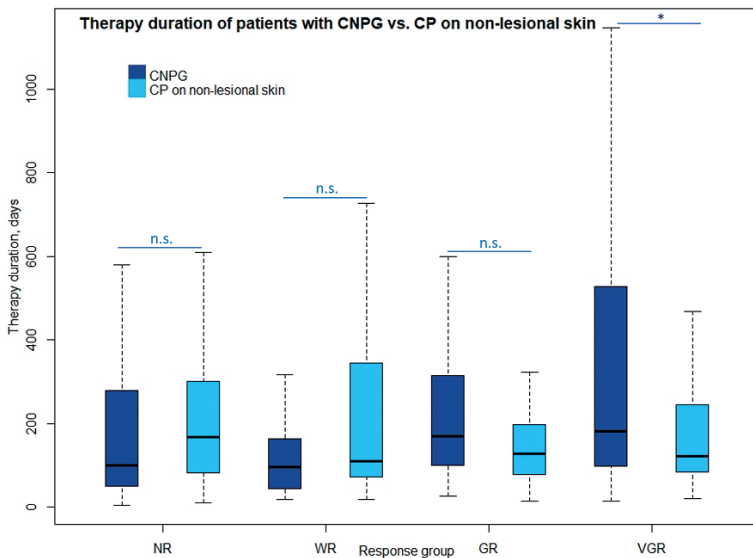
#### Comparison of patients with CNPG and those with CP on non-lesional skin

A total of 325 patients with CP on non-lesional skin (median 59.9 years, 122 males (37.5%), 203 females (62.5%)) were compared with the CNPG cohort. VGR in the CNPG group were treated significantly longer

**Table III. Treatment duration of the total collective**

	<i>n</i>	Treatment duration, days			
		Median	Mean $\pm$ SD	Range	Min–Max
CNPG					
Response group: DPS					
NR: <30	99	99	218.7 $\pm$ 305.8	1,945	5–1,950
WR: 30–49	17	95	231.7 $\pm$ 441.2	1,864	19–1,883
GR: 50–69	58	169	286.8 $\pm$ 400.5	2,568	26–2,594
VGR: $\geq$ 70	151	182	484.2 $\pm$ 633.8	3,696	15–3,711
CP on non-lesional skin					
NR: <30	109	168.0	238.4 $\pm$ 269.3	1,571	11–1,582
WR: 30–49	26	109.5	288.0 $\pm$ 387.0	1,680	19–1,699
GR: 50–69	46	127.5	214.2 $\pm$ 249.7	1,106	14–1,120
VGR: $\geq$ 70	144	122.0	232.1 $\pm$ 281.3	1,816	20–1,836

SD: standard deviation; CNPG: chronic nodular prurigo; CP: chronic prurigo; DPS: Dynamic Pruritus Score; NR: non-responders; WR: weak responders; GR: good responders; VGR: very good responders.



**Fig. 5. Comparison of treatment duration between patients with chronic nodular prurigo (CNPG) and chronic pruritus (CP) on non-lesional skin (non-responders (NR) < 30% pruritus improvement; weak responders (WR) 30–49%; good responders (GR) 50–69%; very good responders (VGR) ≥ 70%).** Outliers were excluded for better visualization. \**p* < 0.001.

than the VGR in the group of CP on non-lesional skin (*p* < 0.001, Mann–Whitney *U* test) (Table III, Fig. 5). For NR (*p* = 0.065, Mann–Whitney *U* test), WR (*p* = 0.333, Mann–Whitney *U* test) and GR (*p* = 0.115, Mann–Whitney *U* test), there was no significant difference in treatment duration between the 2 cohorts.

Aetiological categories between the 2 groups overall differed significantly (*p* < 0.001,  $\chi^2$ -test).

Patients with CNPG significantly more often had a multifactorial origin of pruritus than the control group (*p* < 0.001,  $\chi^2$  test). Patients with CP on non-lesional skin more often had a neurological origin than patients with CNPG (*p* < 0.001,  $\chi^2$ -test). There was no significant difference in the distribution of treatment responders between the CNPG cohort and the CP on non-lesional skin cohort based on the DPS (*p* = 0.271,  $\chi^2$  test) (Fig. 4).

## DISCUSSION

The aims of the retrospective study were to explore the treatment response in CNPG and to analyse predictive factors contributing to therapeutic success.

Age, sex, itch intensity before initiation of treatment and the aetiology of the underlying pruritus had no

significant effect on therapeutic success and treatment duration. The same applies to atopic disposition. Over 50% of our sample had an atopic disposition, a proportion that is consistent with previous literature (16–18). Patients with CNPG showed significantly more often an atopic disposition compared with healthy individuals and even patients with CP. Although this high proportion of patients with CNPG with atopic disposition suggests it could be a contributing factor for the onset of CNPG, it has no effect on the therapeutic success. These data lead to the hypothesis that once CNPG has been developed, intrapersonal factors, such as age, sex and the presence of atopic disposition, do not have an influence on treatment outcome. This supports the current assumption that CPG is a disease in its own right (1). The itch-scratch cycle appears to be a self-perpetuating process that is triggered by multiple factors and even identifying such factors and approaching them

individually is not a guarantee of satisfactory therapeutic outcome. Since the origin of pruritus and the treatment regimens administered might be interdependent, e.g. immunosuppressants primarily used for dermatological diagnoses, it remains unclear whether aetiology has no effect on patient outcome. RCTs could provide clarity on that matter.

The mean duration of a successful treatment of CNPG (=DPS ≥ 70) in this study was approximately 6 months, with a considerable range of 2 weeks to 10 years, showing great inter-individual diversity and the

**Table V. Ordinal regression analysis of treatment regimens used in the chronic nodular prurigo (CNPG) cohort**

	$\beta$	Z	df	<i>p</i> -value	OR	95% CI
<b>Threshold</b>						
NR-WR	-0.109	0.114	1	0.735	0.897	0.48–1.69
WR-GR	0.153	0.227	1	0.634	1.166	0.62–2.19
GR-VGR	0.973	8.855	1	0.003	2.647	1.39–5.02
<b>Treatment</b>						
Antihistamines	0.27	0.54	1	0.461	1.31	0.64–2.68
Gabapentinoids	0.75	3.88	1	0.049*	2.13	1.00–4.50
Antidepressants	0.50	1.09	1	0.297	1.65	0.64–4.24
Immunosuppressants	2.13	25.53	1	< 0.001***	8.43	3.69–19.27
Other therapies	1.34	3.06	1	0.080	3.81	0.85–16.99

\**p* < 0.05; \*\**p* < 0.01; \*\*\**p* < 0.001.

OR: odds ratio; CI: confidence interval; NR: non-responders; WR: weak responders; GR: good responders; VGR: very good responders.

**Table IV. Treatment regimens used in the chronic nodular prurigo (CNPG) cohort**

	<i>n</i>	No systemic treatment <i>n</i> (%)	Antihistamines <i>n</i> (%)	Gabapentinoids <i>n</i> (%)	Antidepressants <i>n</i> (%)	Immunosuppressants <i>n</i> (%)	Other therapies <i>n</i> (%)
Non-responders	99	15 (15.2)	46 (46.5)	23 (23.2)	9 (9.1)	6 (6.1)	0 (0)
Weak responders	17	5 (29.4)	4 (23.5)	3 (17.6)	2 (11.8)	2 (11.8)	1 (5.9)
Good responders	58	5 (8.6)	17 (29.3)	18 (31.0)	5 (8.6)	10 (17.2)	3 (5.2)
Very good responders	151	9 (29.4)	38 (25.2)	34 (22.5)	10 (6.6)	56 (37.1)	4 (2.6)
Total	325	34 (10.5)	105 (32.3)	78 (24.0)	26 (8.0)	74 (22.8)	8 (2.5)

Antihistamines: hydroxyzine cetirizine, loratadine, desloratadine. Gabapentinoids: gabapentin, pregabalin. Antidepressants: SSRI, SNRI. Immunosuppressants: Cyclosporine, methotrexate. Other therapies: neurokinin-1-antagonists, opioid-antagonists, ursodeoxycholic acid.

difficulty to treat CNPG. While almost two-thirds of the CNPG cohort (64.3%) experienced a good or very good improvement of symptoms, 30% of these patients remained non-responders. Although there is a consensus of CNPG being difficult to treat (19), this study confirms this expert opinion for the first time.

Analysis of the most effective therapeutic regimen showed that high responders were treated more frequently with immunosuppressants than were the other response groups. In contrast, almost half of NR were treated with antihistamines. Ordinal regression showed that gabapentinoids and immunosuppressants were most likely to provide a successful therapeutic outcome, while antihistamines and antidepressants were not beneficial. Antihistamines are currently recommended as the first step in the guideline and are prescribed very frequently (4, 19). Previous studies showed that antihistamines are not more effective than a placebo, either as monotherapy (20) or as add-on therapy (21) in treating atopic dermatitis. The current study suggests that the lack of effectiveness also extends to patients with CNPG. Although antihistamines are cost-effective and well tolerated, starting treatment of CNPG with antihistamines could cause a delay in administering more potent and effective medication and therefore should no longer be recommended.

Recently, the significance of neuromodulation in treating CNPG has been discussed. Gabapentinoids and cyclosporine both have neuromodulatory effects (22). Gabapentin has been predominantly evaluated as an antipruritic agent for patients with uraemic or neuropathic/neurogenic CP and has also successfully been used in patients with CNPG (23–25). Cyclosporine is used mostly for patients with inflammatory dermatoses, but has also been proven to be beneficial for patients with CNPG (26, 27).

Since patients with CNPG in this sample also profited most from the use of gabapentinoids and immunosuppressants, we suggest that these agents are beneficial for the treatment of CNPG. To confirm this observation, RCTs addressing this issue are needed.

With regard to novel drugs for treatment of CNPG the neurokinin-1 receptor antagonist serlopitant (5) and the anti-IL-31 receptor A-antagonist nemolizumab reduced pruritus in patients with CNPG in phase II trials (28).

$\kappa$ -opioid receptor agonists (KOR) and  $\mu$ -opioid-receptor agonists (MOR) are currently being tested in clinical trials (29). The anti-IL4 receptor  $\alpha$ -antagonist dupilumab is a drug approved for treating atopic dermatitis, but it has also been proven to be beneficial for patients with CNPG in several case reports (30, 31). These findings may give a new perspective on how to treat CNPG more proficiently. In the current study we could not take these novel drugs into account, due to the small number of patients in our sample receiving them.

Identifying factors that contribute to therapeutic success and minimize treatment duration is crucial in order

to optimize the treatment of patients with CNPG. In our cohort, patients with a great impairment of QoL and depression scores before initiation of treatment were more likely to be NR. Patients with CNPG often are severely affected by depression, anxiety and reduction of QoL compared with healthy control groups and to patients with other dermatological diagnoses (32, 33). Schneider et al. showed that patients with psychosomatic comorbidities report higher pruritus intensities and impairment of QoL than patients without a psychosomatic diagnosis (34). This raises the question as to whether a higher pruritus intensity before initiation of treatment leads to prolonged treatment. While this did not apply to our cohort, the high burden caused by an impaired QoL and higher depression could also alter the patient's perception of improvement.

In addition, the severity of CNPG could provide insight into further prognostic factors. NR's skin significantly more often displayed a large portion of excoriated nodules and more often showed inflamed nodules in comparison with VGR. In contrast, VGR were therefore more prone to non-inflamed nodules and showed a smaller portion of excoriations. Patients with inflamed nodules also had higher pruritus intensity than patients with non-inflamed ones. These findings suggest that inflammatory processes and immune response within the pruriginous nodules can cause higher pruritus intensity and delay therapeutic success. While scratching is considered to be one of the main factors contributing to the onset of CPG, there is no data on how the extent of scratching relates to therapeutic response (1, 35). The higher number of excoriated nodules among NR in this study suggests that frequent and harsh scratching is linked to a worse therapeutic outcome.

There were no differences in the response group distribution between patients with CNPG and those with CP on non-lesional skin. However, a successful treatment needed longer time in the CNPG group, suggesting that CNPG is a more stubborn disease.

This study has some limitations because of its retrospective design. There was a great variance in the patients' observation periods and number of visits. In addition, not every patient had a complete dataset, especially those who were treated years ago. For the most part this affected the analysis of the photographic material. The 4 response groups were not balanced with regards to the number of patients. Treatment regimens were not administered at random; hence any conclusions regarding the most beneficial drugs must be treated with caution.

Not every patient had their blood drawn and tested for total IgE, hence this parameter was not always included when calculating the EAS score. This may have resulted in underestimating patients' atopic disposition.

In conclusion, the majority of patients with CNPG experienced relief of pruritus under treatment, but reducing symptoms can take years and a third of patients were NRs. Physicians should be aware of patients with

a great impairment of QoL and presence of mental disorders, since these factors seem to negatively influence the therapeutic outcome. Patients who show psychological impairment should be offered counselling in order to increase their chances of therapeutic success. Practitioners should also pay attention to inflammation and excoriations of nodules, as they coincide with worse therapeutic outcome. Gabapentinoids and immunosuppressants remain the best therapeutic agents among the established drugs used in this study. However, there will be great demand for novel drugs in treating CNPG in the future.

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