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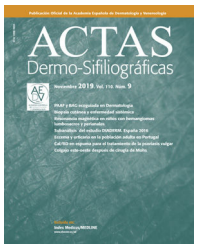

ORIGINAL ARTICLE

[Translated article] Chronic Nodular Prurigo: A Retrospective Study of 74 Cases

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Abstract

Background and objective: Chronic nodular prurigo (CNPG) is a recently defined and currently underdiagnosed disease with a variety of causes. It is associated with multiple comorbidities, and its management and treatment have improved with a better understanding of its pathogenesis. The aim of this study was to describe our experience with a series of patients with CNPG.

Material and methods: Single-center, observational, retrospective study of the sociodemographic and clinical characteristics of patients with CNPG seen at the dermatology department of a tertiary care hospital between 2009 and 2021.

Results: We included 74 patients, mostly women (63.5%), with a mean age of 57 years. Overall, 39.2% of patients had a concomitant skin condition, mainly atopic dermatitis (62%). Other comorbidities included endocrine disorders (54.1%), cardiovascular disease (44.4%), and psychiatric disorders (36.5%). Skin biopsy helped confirm the clinical diagnosis in 70% of cases. The mean immunoglobulin E level was higher than normal (516 IU/mL), regardless of atopic predisposition. On average, patients received three treatments, the most common choices being methotrexate, antihistamines, and topical and oral corticosteroids. Methotrexate was among the most effective options.

Conclusions: CNPG is a complex disease associated with multiple comorbidities. It requires a multidisciplinary approach, with the dermatologist at the center. Classical treatment approaches are probably insufficient.

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PALABRAS CLAVE
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Prurigo crónico nodular: estudio retrospectivo de 74 casos

Resumen

Antecedentes y objetivo: El prurigo crónico nodular (PCN) es una enfermedad recientemente definida, de etiología heterogénea e infradiagnosticado en la actualidad. Está asociado a múltiples comorbilidades y los avances en su patogenia han abierto puertas a un mejor manejo y tratamiento. Presentamos una serie de pacientes con PCN con el objetivo de aportar nuestra experiencia en el manejo de esta entidad.

Material y métodos: Se realizó un estudio observacional, retrospectivo y unicéntrico que incluye pacientes con PCN atendidos en el Servicio de Dermatología de un hospital terciario entre 2009 y 2021. Se recogieron variables sociodemográficas y clínicas.

Resultados: Se incluyeron 74 pacientes, mayoritariamente mujeres (63,5%), con una media de 57 años. La asociación del PCN con otras enfermedades cutáneas fue del 39,2%, sobre todo dermatitis atópica (62%). El 54,1% de los pacientes presentaron comorbilidad endocrina y el 44,4%, comorbilidad cardiovascular. La asociación con enfermedad psiquiátrica fue del 36,5%. La biopsia cutánea fue útil para confirmar la sospecha clínica en el 70% de los casos. El valor medio de la IgE fue superior a la normalidad (516 UI/ml), independientemente de la existencia de predisposición atópica. Se utilizó una media de tres tratamientos para el PCN por paciente. El metotrexato, los antihistamínicos y los corticoides tópicos y orales fueron los más empleados, estando el primero entre los más eficaces.

Conclusiones: El PCN es una enfermedad compleja asociada a un gran número de comorbilidades, que requiere una aproximación multidisciplinar con el dermatólogo como eje central. El manejo terapéutico clásico es probablemente inadecuado.

Introduction

The term *prurigo* is used both to refer to certain characteristic skin lesions and to denote certain specific clinical pictures.[1,2] To clear up this confusion, the consensus document of the European Prurigo Project was published in 2018, which establishes the definition of chronic prurigo as a ''distinct disease characterized by the presence of chronic pruritus for 6 or more weeks, and multiple localized or generalized pruriginous lesions''. It also defines the concept of pruriginous lesions as ''papules and/or nodules and/or excoriated, desquamative and/or crusted plaques''.[3] Furthermore, it classifies the different types of chronic prurigo by lesion morphology, into nodular, papular, plaque, umbilicate,[3] or linear.[4] Thus, the term chronic prurigo covers all classic variants, including nodular prurigo or prurigo nodularis. Moreover, the same patient may present pruriginous lesions of different morphologies at the same time, and these may change during the course of the disease.[5] Of all the variants of chronic prurigo, the most widely studied is chronic nodular prurigo (CNPG).

Another source of debate is its multifactor etiology.[6] According to the consensus document, CNPG may be of dermatologic, systemic, neurologic, psychiatric/psychosomatic, multifactor, or indeterminate origin. There is debate particularly regarding the perforating dermatoses associated with systemic disease (kidney failure, diabetes mellitus, etc.) and the prurigo-like lesions of atopic dermatitis.[3] Although no consensus exists, we agree with other authors that both entities should be considered within the spectrum of chronic prurigo.

CNPG occurs due to nerve sensitization to itching, i.e., an amplification of the pruriginous signaling in the peripheral and central nervous system, and the development of an itch-scratch cycle.[5,7] Considerable progress has recently been made in understanding the underlying pathophysiologic mechanism. Those pruriginous lesions show hyperplasia of the nerve endings in the papillary dermis that appear to be due to increased local inflammatory activity, promoted by certain proinflammatory substances secreted by those nerve endings.[7] These include both cytokines (IL-4, IL-13, and IL-22) and neuropeptides (substance P and the peptide associated with the calcitonin gene), which are considered to be potential therapeutic targets. These targets have made it possible to develop drugs aimed at them, such as dupilumab, which acts on IL-4, and nemolizumab, which acts on IL-13, with very positive results.[7–12] This is why it is essential to perform a correct diagnosis of the population with CNPG, so that they can benefit from an appropriate treatment.[13]

The objective of this study is to describe the sociodemographic and clinical characteristics of a series of 74 patients with CNPG.

Materials and methods

We performed a retrospective, single-center observational study. The clinical records of those patients with a clinical diagnosis of CNPG, from outpatient dermatology consultations of Hospital General Universitario, Alicante, Spain, between 2019 and 2021, or from the photographic archive of the same department between 2009 and 2018, were

Table 1 Sociodemographic characteristics of 74 patients with chronic nodular prurigo.

			n (%)
Sex			
Male			27 (36.5)
Female			47 (63.5)
Race			
Caucasian			71 (95.9)
Afro-American			2 (2.7)
Latin American			1 (1.4)
	Mean (SD)	Median (IQR)	Range
Age, years	57 ± 21		
Follow-up time, months		18.5 (51)	0–192

Abbreviations: IQR, interquartile range; *n*, number of patients; SD, standard deviation.

collected and reviewed. The only inclusion criterion was a clinical diagnosis of CNPG. All patients whose clinical records did not include a description of prurigo lesions or persistence of pruritus for more than 6 weeks were excluded.

Some sociodemographic and clinical variable, comorbidities, histopathology findings of the skin biopsy, immunoglobulin E (IgE) values, and information regarding treatment were recorded. Sociodemographic and clinical variables included age, sex, race, and location of the lesions. The comorbidities studied were psychiatric, endocrine, cardiovascular, cutaneous, autoimmune/autoinflammatory, hematologic, renal, infectious, allergic, and others. For allergic comorbidities, family history (FH) and personal history (PH) of atopic diseases (asthma, rhinitis, conjunctivitis, food allergies, and/or atopic dermatitis) were recorded. Levels of IgE in patients with and without atopic predisposition were compared. All treatments administered during the follow-up period and their efficacy in controlling the disease, indicated subjectively by the clinician, were recorded and efficacy was understood to be absent when the treatment administered had no effect, partial when the lesions and/or the pruritus did not resolve completely, and total when both resolved completely.

Statistical analysis was performed using the SPSS statistical package, version 25 (IBM Corp., Armonk, NY, USA). Using proportions and absolute frequencies to describe the qualitative variables, mean and standard deviation for quantitative variables with a normal distribution, and median and interquartile range for quantitative variables with a non-normal distribution. Between-group comparison of means was performed using the Mann–Whitney *U*-test.

Results

Seventy-four patients with a mean follow-up of 18.50 months were included. The patients' sociodemographic and clinical characteristics are summarized in Tables 1 and 2. Our patients were mostly women (63.5%), with a mean age of 57 years, and were caucasian. Distribution of the lesions was generalized in 45.9% of cases. The upper and/or lower limbs were involved in almost all patients, and involvement of the torso was always accompanied by lesions on the limbs. Only one patient presented lesions on the face.

Table 2 Clinical characteristics of 74 patients with chronic nodular prurigo.

	n (%)
Location of lesions	
Limbs	14 (18.9)
UL	4 (5.4)
LL	7 (9.5)
UL and torso	10 (13.5)
LL and torso	4 (5.4)
Torso and limbs	34 (45.9)
Face, neck, and chest	1 (1.4)

Abbreviations: LL, lower limbs; *n*, number of patients; UL, upper limbs.

Table 3 shows the principal comorbidities. The most notable data are that only 10.8% of patients presented no comorbidities and almost half of them presented three or more comorbidities. An associated cutaneous disease was present in 29 patients (39.2%); the most frequent of these was atopic dermatitis (62% of patients with cutaneous involvement). A total of 54.1% of patients had an endocrine comorbidity, especially dyslipidemia (DL) and diabetes mellitus (DM), which coexisted in 14.9% of patients. A cardiovascular comorbidity was present in 44.4%, principally hypertension (HT) (40.6%). An associated psychiatric disease was found in 36.5% of patients, mostly anxiety (27%) and depression (16.2%), which coexisted in 10.8%. Of these, 2.7% presented only a psychiatric disorder, whereas the rest had other associated comorbidities. Anxiolytics, antidepressants, and/or antipsychotics were used by 39.2% of patients for a reason other than CNPG. Finally, 9.5% presented a neoplasm, and almost all cases with a solid-organ tumor (4) had breast cancer.

The main histopathology findings and IgE determinations are shown in Table 4. A skin biopsy was performed in 60 patients. The histopathologic diagnosis was compatible with CNPG in 71.7% of cases. Levels of IgE were also determined in 43 patients. Those levels were compared in patients with atopic predisposition (median, 100; interquartile range, 334–335) and in patients without atopic predisposition (median, 280.5; interquartile range, 560), and no significant differences were found between the two populations ($P = .257$).

The treatments used and their efficacy are shown in Table 5. The mean (SD) number of treatments received by each patient was 3 ± 2. A total of 63.5% of patients received treatment exclusively with topical corticosteroids and/or antihistamines, with or without cycles of oral cor corticosteroids. A total of 54.1% receive both simultaneously as first-line treatment, which made it difficult to determine the real efficacy of each treatment separately. All cases in which total improvement was reported with topical corticosteroids and/or antihistamines were patients who did not receive other treatments, as these treatments had already proven efficacious. On the other hand, oral corticosteroids and phototherapy, despite their efficacy data, were always used in a self-limiting, as all patients relapsed. At the end of

Table 3 Principal comorbidities in patients with chronic nodular prurigo.

				n = 74
Comorbidities				*n (%)*
None				8 (10.8)
1–2				30 (40.5)
≥3				36 (48.6)
Type of comorbidity		*n* (%)	**Subtype of comorbidity**	*n* (overall %)
Skin		29 (39.2)	Atopic dermatitis	18 (24.4)
			History of insect bite	4 (5.4)
			Psoriasis	2 (2.8)
			Other (*bullous pemphigoid, lichen planus, Darier disease, morphea, toxic dermatitis, ACD*)	6 (8.4)
Allergy/atopic predisposition		20 (27)	Atopic dermatitis	18 (24.4)
			Personal history of atopy	11 (14.9)
			Personal history of environmental allergy	9 (12.2)
			FH of allergy	2 (2.7)
Systemic	Endocrine	40 (54.1)	DL	26 (35.2)
			DM	21 (28.5)
			Hypothyroidism	4 (5.4)
			Hyperthyroidism	2 (2.7)
	Cardiovascular	33 (44.6)	HT	30 (40.6)
			Ischemic heart disease (IHD)	7 (9.6)
			Cerebrovascular accident (CVA)	4 (5.5)
			Atrial fibrillation (AF)	3 (4.2)
	Hematologic	9 (12.2)	Iron deficiency anemia	3 (4.1)
			Other (*Waldenström macroglobulinemia, congenital hypoplastic anemia, ß-thalassemia, myelodysplastic syndrome, multiple myeloma, monoclonal gammopathy*)	6 (8.4)
	Renal	9 (12.2)	Chronic kidney disease (CKD)	9 (12.2)
	Neurologic	8 (10.8)	Dementia	3 (4.1)
			Epilepsy	3 (4.1)
		5 (6.8)	Others (*Parkinson disease, brachioradial pruritus*)	2 (2.8)
	Autoimmune	5 (6.8)	Rheumatic polymyalgia, vasculitis, Sjögren syndrome, hypothyroidism, hyperthyroidism, DM1	5 (68)
	Others	9 (12.2)	Fibromyalgia	3 (4.1)
			Alcoholic cirrhosis	2 (2.7)
			Others (*irritable bowel syndrome, bronchiectasis, chronic venous insufficiency, COPD*)	4 (5.6)
Psychiatric		27 (36.5)	Anxiety	20 (27)
			Depression	12 (16.2)
			Schizophrenia	2 (2.7)
			Personality disorder	1 (1.4)
Neoplasms		7 (9.5)	Breast cancer	4 (5.4)
			Other (*Waldenström macroglobulinemia, multiple myeloma, myelodysplastic syndrome*)	3 (4.1)
Chronic infection		1 (1.4)	HIV	1 (1.4)

Abbreviations: ACD, allergic contact dermatitis; COPD, chronic obstructive pulmonary disease; DL, dyslipidemia; DM, diabetes mellitus; DM1, type 1 diabetes mellitus; FA, family history; HIV, human immunodeficiency virus; HT, hypertension; *n*, number of patients.

Table 4 Histopathology findings and IgE determination in patients with chronic nodular prurigo.

Diagnostic test (*n*)		Result	*n* (%)	
Histopathologic findings (60)	Prurigo nodularis		43 (71.7)	
	Eczema		10 (16.7)	
	Rash		2 (3.3)	
	Other (bullous disease, bullous pemphigoid, lichen planus, bullous epidermolysis, toxic dermatitis, papular rash)		5 (8.5)	
		Mean ± SD Median (IQR)	Range	*P*
IgE determination (43)	Overall, (*n* = 43)	516 (1087) 130 (510)	0.01–6367	
	Nonatopic (*n* = 25)	550 (1338) 100 (334.5)	0.01–6367	
				.257
	Atopic predisposition (*n* = 18)	469 (623) 280.5 (560)	0.5–2490	

Abbreviations: IgE, immunoglobulin E; IQR, interquartile range; *n*, number of patients; *P*, level of statistical significance; SD, standard deviation.

Table 5 Principale treatments received in a series of 74 patients with chronic nodular prurigo and efficacy in control of the disease.

Treatment received	*n* (%)	Control of disease		
		Absent	Partial	Total
Topical corticosteroids	73 (98.6)	10 (13.9)	48 (66.7)	14 (19.4)
Antihistamines	64 (86.5)	27 (42.2)	31 (48.4)	6 (9.4)
Oral corticosteroids[a]	40 (54.1)	3 (7.5)	12 (30)	25 (62.5)
Phototherapy[a]	7 (9.5)	2 (28.6)	2 (28.6)	3 (42.9)
Pregabalin	4 (5.4)	3 (75)	1 (25)	0 (0)
Doxepin	8 (10.8)	7 (87.5)	1 (12.5)	0 (0)
Methotrexate	19 (25.7)	0 (0)	14 (73.7)	5 (26.3)
Ciclosporin	7 (9.5)	3 (42.9)	1 (14.3)	3 (42.9)
Azathioprine	2 (2.7)	2 (100)	0 (0)	0 (0)
Acitretin	1 (1.4)	1 (100)	0 (0)	0 (0)
Mofetil mycophenolate	1 (1.4)	1 (100)	0 (0)	0 (0)
Ustekinumab	1 (1.4)	1 (100)	0 (0)	0 (0)
Omalizumab	2 (2.7)	1 (50)	0 (0)	1 (50)
Dupilumab	4 (5.4)	0 (0)	2 (50)	2 (50)
Number of treatments received per patient	**Mean** ± SD	3 ± 2	**Range**	1–11

Abbreviations: *n*, number of patients; SD, standard deviation.
[a] Control of the disease with oral corticosteroids and phototherapy, despite the indicated data, was always self-limiting, as all the patients relapsed.

follow-up, a 70.3% control of the disease had been achieved with the treatments used.

Discussion

Existing data on the prevalence of CNPG are very limited, as the disease has been underdiagnosed or misdiagnosed. The 10th edition of the *International Classification of Diseases* (ICD-10) in 2016 and the consensus document of the European Prurigo Project in 2018 have made it possible to establish a genuine diagnostic code for this entity.[3,14,15] Recent studies in the US estimate a prevalence of 72 cases per 100,000 inhabitants and a mean age of 50.9 years, with increased frequency (though not significant) in women.[15] In Europe, a total of 1720 patients with CNPG were also recorded and a prevalence of 0.1% was estimated, with a slightly higher mean age.[16] Some of these studies exclude the very advanced age group, so that its prevalence may be underestimated.[6,15] Our series, which includes all age groups, presents a somewhat higher mean age (57 years) and predominance in women. Afro-American race is more frequently associated with CNPG and especially with coexistence with the human immunodeficiency virus (HIV), but caucasian race accounted for almost all cases in our series.[17]

The diagnostic approach to patients with CNPG must be multidisciplinary, as the origin of the prurigo may be highly heterogeneous, often multifactorial, and these patients tend to have many associated comorbidities.[15] The role of the dermatologist is essential for performing a correct differential diagnosis with other dermatologic diseases and for establishing the association of CNPG with

another cutaneous disease. We consider performing a skin biopsy to be essential. According to the 2020 guidelines of the International Forum for the Study of Itch (IFSI), it is indicated for recalcitrant or atypical CNPG or when data exist that suggest another skin disease.[13] This will allow us to confirm our suspected diagnosis and will provide us with information on potential associated diseases (30% of cases in our series). Atopic dermatitis (AD) is the skin disease most frequently associated with CNPG. It ranges between 10% and 50%, depending on the series (24.4% in our series).[16,18,19] This variability in frequency may be due to the fact that it is difficult to establish the diagnosis of CNPG in patients with AD who also present eczema lesions, as these cases are simply labeled as AD. If the patient presents only prurigo lesions, establishing the association with AD requires examining the patient's personal and family history for atopic diseases and the presence of elevated total serum IgE. We were, however, able to determine that the total IgE of our patients with CNPG is raised both in patients with atopic predisposition and in those without. This increase in IgE can probably be explained by taking a closer look at the pathophysiologic mechanisms involved in the production of these prurigo lesions.

Patients with CNPG have a greater risk of presenting multiple systemic comorbidities compared to the general population and it is difficult to discern how they contribute to perpetuating or triggering the disease.[20] An association has been found especially with DM, DL, HT, ischemic heart disease, anemia, and chronic kidney disease.[21] Approximately half of the patients observed had an associated endocrine and/or cardiovascular disease. Furthermore, many patients with CNPG had associated psychiatric diseases and/or were taking antidepressant or anxiolytic medication,[22,23] even more than in other skin diseases such as AD and psoriasis.[3,15] The association with neoplasms, especially blood cancers, is up to 4-fold that of the general population.[24–27] We believe that it is important to carry out a complete diagnostic study to screen for systemic disease and/or cancer, guided at all times by the clinical data in the patient's clinical records. We would like to highlight the important of multidisciplinary management of the endocrine-metabolic, cardiovascular, hematologic, and psychiatric disease with the help of the corresponding specialists, thus making it possible to contribute to some extent to controlling the pruritus by controlling the underlying disease, a practice that did not take place in our series.

Treatment of CNPG was recently updated by the 2020 IFSI guidelines.[13] The goal is to stop the itch-scratch cycle and reduce pruritus and the lesions.[7,13] This requires an individualized approach and, generally, the combination of topical and systemic therapy.[7,13] The former is based essentially on the combination of topical corticosteroids of moderate or very high potency and immune modulators, and the latter is based on the combination of drugs that act as immunosuppressants and neuromodulating agents.[7,13] The use of oral antihistamines and chronic use of oral corticosteroids is not recommended. Our data shows inadequate treatment of this disease, as these are the 2nd and 3rd most commonly used drugs and their efficacy is limited, which demonstrates the need to change habits in the consultation. Phototherapy has been shown to reduce pruritus due to its anti-inflammatory effect and it is useful in patients in whom certain treatments cannot be used due to their comorbidities and drug interactions.[7] Despite having achieved positive results, we believe that their use has a secondary role to play given their self-limiting efficacy over time. Neuromodulators, particularly antidepressants, have a strong degree of recommendation.[13] Their use as a treatment for CNPG, however, was rare in our series and their efficacy was limited, as more than two-thirds of the patients presented no response to these agents. The most efficacious immunosuppressants are methotrexate and ciclosporin,[28,29] and they were the most commonly used immunosuppressants. Treatments with azathioprine, mycophenolate, and acitretin were also tried but with no improvement. We have a particular experience in the use of methotrexate, and we have obtained very good results, helping to control the disease in all patients. The most commonly used biologic drug was dupilumab, which was administered to four patients and improvement was observed in all of them, in line with existing evidence regarding this drug.[10,11] We are convinced that the emergence of drugs such as dupilumab and JAK inhibitors and nemolizumeb[10–12] will change the therapeutic outlook of this disease.

The findings obtained in our series highlight the association of CNPG with a large number of comorbidities, which makes it necessary to perform a complete diagnostic study to identify possible systemic diseases and/or cancers, guided at all times by the data from the patient's clinical records and with the participation of a multidisciplinary team. This must especially include dermatology, endocrinology, cardiology, psychiatry, and other specialties, although this practice is rare in our experience. We have also seen that, contrary to the recommendations of the clinical guidelines,[13] the use of antihistamines and oral corticosteroids was very frequent, despite their limited utility. Immunosuppressants such as methotrexate and ciclosporin, and biologic therapy such as dupilumab demonstrated very good results.

Study limitations

All the data were obtained retrospectively from the information contained in the clinical records, which made it impossible to determine important variables in CNPG such as the number of lesions and their course per patient, as well as the time since onset of the disease at the moment of diagnosis.

The results regarding control of the disease are a subjective assessment by the clinician and the patient, as no standardized and dynamic severity scale exists to objectively report the course of the disease with the different treatments that, on many occasions, were also administered simultaneously with others. Nevertheless, we believe that our data may contribute to constructing an approximate idea of the efficacy of each treatment, which must be verified with further studies.

Conclusion

CNPG is a complex disease associated with a large number of comorbidities. Despite advances in the pathogenesis of the disease, the trigger or cause of the pruritus and the lesions

is still unknown, although everything appears to indicate that it obeys multiple factors, which requires individualized management. We present a series of 74 patients, in which we wish to show the importance of performing a skin biopsy that allows us to establish a more accurate diagnosis and rule out skin diseases with different treatments, the large number of associated comorbidities that requires multidisciplinary management, and the poor practice, still present in management of the entity, as antihistamines and oral corticosteroids continue to be widely used, while other alternatives with promising results exist.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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