ORIGINAL ARTICLE

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

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KEYWORDS
Chronic nodular prurigo; Pruritus; Case series; Comorbidities; Skin biopsy; Immunoglobulin E; Multidisciplinary

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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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 comorbididades 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 comorbididades, que requiere una aproximación multidisciplinar con el dermatólogo como eje central. El manejo terapéutico clásico es probablemente inadecuado.

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a description of prurigo lesions or persistence of pruritus for
more than 6 weeks were excluded.

Some sociodemographic and clinical variable, comor-
dbidities, 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 his-
tory (PH) of atopic diseases (asthma, rhinitis, conjunctivitis,
 food allergies, and/or atopic dermatitis) were recorded.
Levels of IgE in patients with and without atopic predisposi-
tion were compared. All treatments administered during
the follow-up period and their efficacy in controlling the dis-
 ease, indicated subjectively by the clinician, were recorded
and efficacy was understood to be absent when the treat-
ment 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 sta-
tistical package, version 25 (IBM Corp., Armonk, NY, USA).
Using proportions and absolute frequencies to describe the
qualitative variables, mean and standard deviation for quan-
titative 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 1  Sociodemographic characteristics of 74 patients with chronic nodular prurigo.

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27 (36.5)</td>
</tr>
<tr>
<td>Female</td>
<td>47 (63.5)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>71 (95.9)</td>
</tr>
<tr>
<td>Afro-American</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Latin American</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td><strong>Mean (SD) Median (IQR) Range</strong></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>57 ± 21</td>
</tr>
<tr>
<td>Follow-up time, months</td>
<td>18.5 (51)</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Location of lesions</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limbs</td>
<td>14 (18.9)</td>
</tr>
<tr>
<td>UL</td>
<td>4 (5.4)</td>
</tr>
<tr>
<td>LL</td>
<td>7 (9.5)</td>
</tr>
<tr>
<td>UL and torso</td>
<td>10 (13.5)</td>
</tr>
<tr>
<td>LL and torso</td>
<td>4 (5.4)</td>
</tr>
<tr>
<td>Torso and limbs</td>
<td>34 (45.9)</td>
</tr>
<tr>
<td>Face, neck, and chest</td>
<td>1 (1.4)</td>
</tr>
</tbody>
</table>

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 cuta-
neous 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%, princi-
ially 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, antidepres-
sants, and/or antipsychotics were used by 39.2% of patients
for a reason other than CNP. Finally, 9.5% presented a neo-
plasm, 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
CNP 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,
334–355) and in patients without atopic predisposition
(median, 280.5; interquartile range, 560), and no sig-
ificant 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 corti-
costeroids. 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 pho-
thotherapy, despite their efficacy data, were always used in
a self-limiting was over time, as all patients relapsed. At the
end of follow-up, a 70.3% control of the disease had been
achieved with the treatments used.
<table>
<thead>
<tr>
<th>Type of comorbidity</th>
<th>n (%)</th>
<th>Subtype of comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>29 (39.2)</td>
<td>Atopic dermatitis, History of insect bite, Psoriasis, Other (bullous pemphigoid, lichen planus, Darier disease, morphea, toxic dermatitis, ACD)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>40 (54.1)</td>
<td>Personal history of atopy, Personal history of environmental allergy, FH of allergy, Hypothyroidism, Hyperthyroidism, HT, Ischemic heart disease (IHD), Cerebrovascular accident (CVA), Atrial fibrillation (AF)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>9 (12.2)</td>
<td>Iron deficiency anemia, Other (Waldenström macroglobulinemia, congenital hypoplastic anemia, β-thalassemia, myelodysplastic syndrome, multiple myeloma, monoclonal gammopathy)</td>
</tr>
<tr>
<td>Renal</td>
<td>9 (12.2)</td>
<td>Chronic kidney disease (CKD)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>8 (10.8)</td>
<td>Dementia, Epilepsy, Others (Parkinson disease, brachioradial pruritus)</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>5 (6.8)</td>
<td>Rheumatic polymyalgia, vasculitis, Sjögren syndrome, hypothyroidism, hyperthyroidism, DM1</td>
</tr>
<tr>
<td>Others</td>
<td>9 (12.2)</td>
<td>Fibromyalgia, Alcoholic cirrhosis, Others (irritable bowel syndrome, bronchiectasis, chronic venous insufficiency, COPD)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>27 (36.5)</td>
<td>Anxiety, Depression, Schizophrenia, Personality disorder</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>7 (9.5)</td>
<td>Breast cancer, Other (Waldenström macroglobulinemia, multiple myeloma, myelodysplastic syndrome)</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>1 (1.4)</td>
<td>HIV</td>
</tr>
</tbody>
</table>

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.
Our study included 74 patients with chronic nodular prurigo, which is a rare and chronic skin condition characterized by pruritic nodules on the skin. The main findings of our study are highlighted in Table 4, which shows the histopathology findings and IgE determination in patients with chronic nodular prurigo.

<table>
<thead>
<tr>
<th>Diagnostic test (n)</th>
<th>Result</th>
<th>n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histopathologic findings (60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prurigo nodularis</td>
<td>43</td>
<td>(71.7)</td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>10</td>
<td>(16.7)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
<td>(3.3)</td>
<td></td>
</tr>
<tr>
<td>Other (bullous disease, bullous pemphigoid, lichen planus, bullous epidermolysis, toxic dermatitis, papular rash)</td>
<td>5</td>
<td>(8.5)</td>
<td></td>
</tr>
<tr>
<td>IgE determination (43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall, (n = 43)</td>
<td>Mean (SD) Median, (IQR)</td>
<td>516 (1087) 130 (510)</td>
<td>Range</td>
</tr>
<tr>
<td>Nonatopic (n = 25)</td>
<td></td>
<td>550 (1338) 100 (334.5)</td>
<td></td>
</tr>
<tr>
<td>Atopic predisposition (n = 18)</td>
<td></td>
<td>469 (623) 280.5 (560)</td>
<td></td>
</tr>
</tbody>
</table>

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

In Table 5, we provide an overview of the principal treatments received by the patients with chronic nodular prurigo and their efficacy in controlling the disease.

<table>
<thead>
<tr>
<th>Treatment received</th>
<th>Absent</th>
<th>Partial</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical corticosteroids</td>
<td>73 (98.6)</td>
<td>10 (13.9)</td>
<td>48 (66.7)</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>64 (86.5)</td>
<td>27 (42.2)</td>
<td>31 (48.4)</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>40 (54.1)</td>
<td>3 (7.5)</td>
<td>12 (30)</td>
</tr>
<tr>
<td>Phototherapy</td>
<td>7 (9.5)</td>
<td>2 (28.6)</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>4 (5.4)</td>
<td>3 (75)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Doxepin</td>
<td>8 (10.8)</td>
<td>7 (87.5)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>19 (25.7)</td>
<td>0 (0)</td>
<td>14 (73.7)</td>
</tr>
<tr>
<td>Ciclesporin</td>
<td>7 (9.5)</td>
<td>3 (42.9)</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>2 (2.7)</td>
<td>2 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Acitretin</td>
<td>1 (1.4)</td>
<td>1 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mofetil mycophenolate</td>
<td>1 (1.4)</td>
<td>1 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>1 (1.4)</td>
<td>1 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>2 (2.7)</td>
<td>1 (50)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>4 (5.4)</td>
<td>0 (0)</td>
<td>2 (50)</td>
</tr>
</tbody>
</table>

Number of treatments received per patient | Mean | 3 (2) | Range | 1–11 |

Abbreviations: n, number of patients; SD, standard deviation.

Discussion

Existing data on the prevalence of CNP 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. 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. In Europe, a total of 1720 patients with CNP were also recorded and a prevalence of 0.1% was estimated, with a slightly higher mean age. Some of these studies exclude the very advanced age group, so that its prevalence may be underestimated. 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 CNP and especially with coexistence with the human immunodeficiency virus (HIV), but caucasian race accounted for almost all cases in our series.

The diagnostic approach to patients with CNP must be multidisciplinary, as the origin of the prurigo may be highly heterogeneous, often multifactorial, and these patients tend to have many associated comorbidities. The role of the dermatologist is essential for performing a correct differential diagnosis with other dermatologic diseases and for establishing the association of CNP with another cutaneous...
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 CNP or when data exist that suggest another skin disease. 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 CNP. 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 CNP 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 CNP 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 CNP 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 CNP 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 importance 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 CNP was recently updated by the 2020 IFSI guidelines.1 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 CNP, 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 nemolizumab10-12 will change the therapeutic outlook of this disease.

The findings obtained in our series highlight the association of CNP 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 CNP 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

CNP 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.

**References**


