COMORBIDITIES RELATED TO PRURIGO NODULARIS: A DESCRIPTIVE, RETROSPECTIVE, SINGLE-CENTRE TRIAL

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Summary

Introduction: *Prurigo nodularis (PN) is a rare pathology characterized by hyperkeratotic, intensely pruritic nodules appearing secondary to chronic scratching, being associated with multiple pruritus-generating conditions.*

Material and method: *Patients diagnosed with PN in the Dermatovenereology Clinical Department of the Mureș County Clinical Hospital between January 2017 and August 2024 were included in the trial. The purpose of this trial is to evaluate the profile of patients with PN, following clinical and paraclinical data.*

Results: *Of the total of 26 patients diagnosed with PN, the majority were women in their 6th and 7th decades of age. All patients presented at least one chronic systemic disorder, 61.53% of them being diagnosed with various non-malignant skin disorders. By analysing the laboratory parameters, an increase in inflammatory markers, a decline in renal function and an increase in basal plasma glucose were observed in most patients.*

Conclusions: *The long-term follow-up of patients with this condition requires vigilance in order to identify the pathologies that accompany PN and the early institution of specialized treatment.*

Key words: *prurigo nodularis, comorbidities, laboratory tests.*

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Introduction

Prurigo nodularis (PN) is a rare and severe form of chronic prurigo with little epidemiological data, with an estimated prevalence of 3.72 per 10,000 in the UK population [1]. It affects women more frequently, and it is more common in the 5th and 6th decades of life. Genetic differences are observed between the Caucasian, Asian and Black populations, the latter being more likely to develop PN [2].

PN occurs secondary to chronic scratching of the xerotic and intensely pruritic skin, and from a physiopathological point of view it is characterized by a hyperplasia of the nerve endings at the skin level and the increased expression of nerve growth factor (NGF) and some neuropeptides (substance P, calcitonin gene-related peptide CGRP) that promote a pro-inflammatory status [3].

Clinically, this pathology is characterized by multiple hyperkeratotic, pruritic nodules, distributed mainly on the extensor surfaces of the limbs, but the lesions can appear anywhere on the body [3,4]. This pathology has been associated with atopy, psychiatric conditions such as obsessive-compulsive disorder, affective dis-

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orders and psychotic disorders. Also, multiple systemic pathologies causing pruritus have been associated with the diagnosis of PN, among which chronic kidney disease, chronic liver diseases including viral hepatitis, thyroiditis, celiac disease, human immunodeficiency virus (HIV) infection, diabetes mellitus, cardiovascular diseases, various neoplasms, especially haematological ones. The diagnosis of this condition is generally based on clinical criteria, but paraclinical investigations can be useful in identifying a source of pruritus [3-5]. As for the treatment of this pathology, it is oriented towards the cause of the eruption and may consist of topical corticosteroids or calcineurin inhibitors for the inflammatory component, psychotropic medication for the neurogenic component or immunomodulatory therapies for the atopic component [6].

Material and method

This trial included patients diagnosed with PN in the Dermatovenereology Clinical Department of the Mureș County Clinical Hospital between January 2017 and August 2024. Adult patients diagnosed with PN, for whom there were comprehensive clinical and paraclinical data, were included in the trial. The online calculator provided by the National Kidney Foundation was used to estimate glomerular filtration rate (eGFR), taking into account the following parameters: serum creatinine, race, gender, and age. The data came from the hospital's electronic database. The purpose of the trial is to outline the profile of patients with PN, following demographic data, the patient's medical history, and the results of common laboratory tests. This paper aims to observe certain trends in the dynamics of paraclinical explorations and the prevalence of PN-related conditions, in order to contribute to a better understanding of the condition and improve individualized therapeutic strategies.

Results

26 patients were included in the trial. The majority were women (57.68%), with an average age of 68.11±12.92 years. The average duration of disease evolution calculated was 1 year and 4 months.

The most common associated conditions were cardiovascular diseases, present in over three quarters of patients. Obesity, diabetes, dyslipidaemia, and active infections were observed in about half of the patients, and chronic kidney disease (CKD), anaemia, and oncological conditions were identified in about a quarter of the cases (Table 1).

Table 1 – Comorbidities associated with PN

Comorbidities associated with PN	*n*	%
Cardiovascular diseases	20	76.92%
Diabetes	12	46.15%
Obesity	11	42.31%
Dyslipidaemia	10	38.46%
Chronic kidney disease (CKD)	7	26.92%
Secondary hyperparathyroidism	2	7.69%
Infectious outbreaks	13	50%
Neoplasm	5	19.23%
Anaemia	7	26.92%
Psychiatric conditions	4	15.38%
Chronic obstructive pulmonary disease (COPD)	3	11.54%
Chronic thyroiditis	2	7.69%
Chronic liver diseases	2	7.69%
Skin conditions	16	61.53%

Two of the seven patients with diagnosed CKD were on dialysis. Both cases of hyperparathyroidism occurred secondary to CKD. The most frequently identified infectious outbreaks were wound infections, cutaneous mycoses and urinary tract infections. In the case of oncological conditions, it was observed that 3 of the 5 patients were diagnosed with skin neoplasms, one patient was diagnosed with bladder neoplasm and one patient with ovarian neoplasm.

Sixteen patients had associated non-malignant skin conditions, most of whom had varying degrees of chronic venous insufficiency (CVI), followed by those with cutaneous mycoses (Table 2).

Laboratory parameters were analysed. The most common changes in the blood count were leucocytosis and neutrophilia. Inflammatory syndrome, defined by elevated values of ESR and C-reactive protein (CRP), was found in 80% of patients (Table 3).

Table 2 – Skin conditions associated with PN

Skin conditions associated with PN	*n*	*%*
Chronic venous insufficiency	8	30.77%
Mycotic infections of the skin and appendages	5	19.23%
Bacterial infections	1	3.85%
Bullous pemphigoid	2	7.69%
Pyoderma gangrenosum	1	3.85%
Nummular eczema	1	3.85%
Actinic keratosis	1	3.85%
Erythroderma	1	3.85%
Bowen's disease	1	3.85%
Basal cell carcinoma	2	7.69%
Squamous cell carcinoma	1	3.85%

Renal damage, demonstrated by the decrease in eGFR, was found in 19 cases, the majority of patients (n=12) presenting stage II CKD. Urea and creatinine had elevated values in 53.85% and 19.23% of cases respectively (Table 4).

Approximately half of the patients presented elevated basal glucose values, with a calculated mean value of 113.81 mg/dl, while hepatic cytolysis, defined by elevated AST and ALT values, was identified in approximately a quarter of cases. Glucosuria and leukocyturia were the most frequent changes in the urinalysis (Table 5).

Tabel 3 – Evaluation of leukocyte count, platelet count and inflammatory markers

Investigation	*Number of investigated patients*	*Mean value +/- DS*	*No. of patients with high values*	*%*
Leukocytes * $10^3/\mu L$	26	8.73 +/- 3.71	6	23.08%
Neutrophils * $10^3/\mu L$	26	5.99 +/- 2.96	7	26.92%
Lymphocytes * $10^3/\mu L$	26	1.92 +/- 1.2	9	13.85%
Monocytes * $10^3/\mu L$	26	0.56 +/- 0.28	1	3.85%
Eosinophils * $10^3/\mu L$	26	0.20 +/- 0.2	2	27.69%
Basophils * $10^3/\mu L$	26	0.05 +/- 0.0	4	27.69%
Platelets * $10^3/\mu L$	26	283.33 +/- 101.7	13	11.54%
VSH mm/h	20	36.95 +/- 30.23	16	80.00%
PCR mg/dL	10	13.76 +/- 16.98	8	80.00%

Discussions

In our study group, the most common comorbidities associated with PN were cardiovascular diseases, diabetes, obesity, dyslipidaemia. The data obtained are consistent with those in the literature, patients with PN having more comorbidities compared to the general

Table 4 – Evaluation of biochemical parameters

Investigație	*Nr. pacienți investigați*	*valoare medie +/- DS*	*Nr. pacienți cu valori crescute*	*%*
Urea (mg/dL)	26	62.44 +/- 43.58	14	53.85%
Creatinine (mg/dL)	26	1.86 +/- 2.62	5	19.23%
		>90 mL/min/1.73m²		
		60-89 mL/min/1.73m²	12	46.15%
		45-59 mL/min/1.73m²	2	7.69%
GFR (mL/min/1.73m²)	26	68.76 +/- 30.38	7	26.92%
		30-44 mL/min/1.73²	1	3.85%
		15-29 mL/min/1.73m²	1	3.85%
		<15 mL/min/1.73m²	3	11.54%
Uric acid (mg/dL)	10	5.88 +/- 0.96	3	30.00%
ALT (U/L)	25	25 +/- 18.25	5	20.00%
AST (UL)	25	21.36 +/- 10.9	3	12.00%
GGT (U/L)	24	37.25 +/- 28.7	9	37.50%
Fasting blood glucose (mg/dL)	21	113.81 +/- 53.13	9	42.86%
Total bilirubin -+ (mg/dL)	9	0.53 +/- 0.34	1	11.11%

Table 5 – Evaluation of urinalysis

Urinalysis	*No. of investigated patients*	*No. of patients with high (elevated) values (%)*			
		normal	+	++	+++
Urobilinogen (mg/dl)		20 (76.92%)	3 (11.53%)	3 (11.53%)	0
Ascorbic acid (mg/dL)		16 (61.53%)	10 (38.47%)	0	0
Nitrites		22 (84.61%)	4 (15.38%)		
Density		19 (73.07%)	7 (26.93%)		
pH	26	23 (88.46%)	3 (11.53%)		
Ketone bodies (mg/dL)		18 (69.23%)	7 (26.93%)	1 (3.84%)	0
Glucose (mg/dl)		15 (57.69%)	1 (3.84%)	4 (15.38%)	6 (23.07%)
Proteins (mg/dL)		21 (80.76%)	3 (11.53%)	2 (7.69%)	0
Erythrocytes / µL		19 (73.07%)	3 (11.53%)	3 (11.53%)	1 (3.84%)
Leukocytes / µL		15 (57.69%)	6 (23.07%)	0	5 (19.23%)

population, this fact drawing attention to the need for multidisciplinary management of patients with this diagnosis [7,8]. It was found that patients with PN have diabetes, cardiovascular, pulmonary, liver, and kidney diseases more frequently, compared to patients diagnosed with other chronic dermatoses such as atopic dermatitis or psoriasis [7]. Moreover, patients with PN use the services of cardiology and internal medicine more frequently than those mentioned above, with more frequent hospitalizations and longer durations of hospitalization [9].

A study conducted in Finland [8] observed that 72.9% of patients had at least one chronic systemic disease, the average age at diagnosis being 56 years, while another study conducted in Germany [10] observed the presence of comorbidities in 87% of the studied patients, the average age being 61.54 years. This trial found that all patients had at least one chronic systemic disease, a result that can be justified by the increased average age (68 years), as well as by the inclusion of several comorbidities in the analysis.

The present trial identified the presence of CKD in a significant percentage of patients. The association between PN and CKD is well known, with the skin condition being more frequently described in patients with end-stage CKD. A 2022 study conducted in Korea by Kim HS et al.[11] demonstrated that GFR decline and proteinuria are independent risk factors for PN, with the study authors noting that early initiation of angiotensin-converting enzyme (ACE) inhibitors as renoprotective therapy to ameliorate proteinuria could prevent not only decline in renal function but also the appearance of PN.

Patients with PN are 4 times more likely to be diagnosed with a neoplasm, the malignancies being most commonly detected within the first 3 months after diagnosis of the rash. Although leukaemia and lymphomas are traditionally associated with pruritus and the appearance of PN, an epidemiological study on this topic found that half of the tumours associated with PN are skin cancers, a result similar to that obtained in the present trial, where 3 out of 5 oncologic patients had associated skin malignancies. This association can also be motivated by the fact that patients with PN are followed by a dermatologist, maximizing the chances of diagnosis of skin tumours [12]. However, additional data in this regard can be obtained by enlarging the study group.

The association between psychiatric conditions and PN is known, our trial objectifying their presence in an important percentage of patients – 15.38% of patients associating anxiety-depressive disorders or psychotic disorders. Although some pathologies may contribute to the appearance of the rash, an increased frequency of sleep disturbances, anxiety, depression and suicidal ideation has been observed among patients secondary to the evolution and symptomatology associated with the disease, leading to a low quality of life. In this context, counselling

psychology often becomes an important step in the management of patients with PN [13-15].

In our group, 61% of patients associated another skin condition, a result similar to a study conducted on 228 patients with PN, which observed the presence of other dermatological conditions in 41.5% of the group [8]. In the cited study, nummular eczema, atopic dermatitis and contact dermatitis were the most frequently reported conditions, while in the present trial CVI and skin infections were the most frequently encountered. Although these differences may be motivated by the size of the group and the average age of the participants, the existing data in the literature regarding the association between PN and other skin conditions is limited, and further studies to evaluate the relationship between these and PN are needed to draw a conclusion.

Despite the established association between PN and atopic dermatitis, no patients with this diagnosis were identified in the studied group. This result can be motivated by the size of the group, as well as by the average age of the studied group. Previous research has observed the occurrence of PN in association with atopy in young patients, patients without atopic terrain developing PN at older ages, against the background of chronic systemic pathologies [3,16,17].

Multiple biomarkers have been studied to better understand this condition, but there is little information related to the relationship between the diagnosis of PN and the common laboratory tests. A single case-control study on this topic was found in the literature, a study by Cornman HL et al., published a year ago [18]. Similar to the results obtained by Cornman HL et al. [18] following the analysis of the group of PN cases, the presence of the inflammatory syndrome was objectified in approximately 57% of the patients, a lower percentage compared to the one obtained in this trial. However, considering the average age of the studied group (68 years) compared to that of the cited study (58.8 years), this difference can be attributed to advanced age and associated chronic conditions whose prevalence increases with age. Leucocytosis and neutrophilia were observed among patients with PN in both this trial and the cited study [18], in similar proportions.

Regarding kidney damage, the study by Cornman HL et al. [18] observed GFR decline in approximately three quarters of patients, similar to the results obtained in the present trial. In both studies, most patients had an eGFR between 60 and the normal value. Increased serum urea was observed in more patients with PN in this trial, increased serum creatinine being observed in fewer patients compared to the cited study.

Hepatocytolysis was observed in approximately equal percentages in both studied groups. The study by Cornman HL et al. [18] used glycated haemoglobin to quantify glycaemic control, and in the present trial, basal plasma glucose was used. Although both studies suggest poor glycaemic control among patients with PN, the results are difficult to compare because they use different parameters. However, glycated haemoglobin may be a more faithful marker in investigating the relationship with the diagnosis of PN, as it shows retrospective glycaemic control over a period of several weeks.

Compared to the study conducted by Cornman HL et al. [18], the presented trial did not evaluate the relationship between positive diagnosis and serum albumin, TSH and alkaline phosphatase, these parameters not being evaluated in enough patients. However, we believe that the inclusion of more laboratory parameters in the analysis is necessary to improve the accuracy and complexity of the results.

The presented trial has its limitations, the most important factor being the small group of patients selected from a single centre. Other limitations would be the lack of a standard investigation package and the performance of a limited panel of routine tests. Last but not least, only hospitalized patients were included, the study does not include patients diagnosed with PN following an outpatient presentation, an aspect that may influence some results. Also, paediatric patients with this diagnosis were not included, the distribution by age groups being affected, and the results obtained are difficult to generalize in this context.

Conclusions

The long-term follow-up of these patients requires vigilance in order to identify the pathologies that accompany PN and for the early establishment of secondary prophylaxis measures. Considering the multiple pathologies that can coexist with the skin condition, treatment customization and a multidisciplinary approach to the case become necessary to ensure a better quality of life for these patients.

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Conflict of interest
NONE DECLARED

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