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Original Article

Prevalence of genetic variants in *SERPINB2* and *PKNOX1* genes in erythema nodosum leprosum patients from southern Brazil

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Abstract

Introduction: Erythema nodosum leprosum (ENL) is a humoral immune response to *Mycobacterium leprae* that is characterized by erythematous nodules, and may or may not be associated with systemic symptoms. Thalidomide is the primary treatment for ENL in Brazil, but peripheral neuropathy (PN) is a significant adverse effect. Genetic variants in *SERPINB2* and *PKNOX1* genes have been implicated in the predisposition to develop thalidomide-induced peripheral neuropathy (TiPN) in patients with multiple myeloma. This study evaluated the prevalence of the polymorphisms in *SERPINB2* and *PKNOX1* in ENL patients.

Methodology: A cross-sectional study was conducted in a sample of ENL patients from southern Brazil to assess the presence of genetic variants of *SERPINB2* and *PKNOX1*.

Results: Forty-seven patients with ENL were included. The prevalence of *SERPINB2* (rs6103) was 66% for the C allele and 34% for the G allele, and the prevalence of *PKNOX1* (rs2839629) was 75% for the A allele and 25% for the G allele. There was significantly relevant presence of the *PKNOX1* (rs2839629) A allele in patients with ENL ($p < 0.001$). In the case of patients with PN, the presence of the C genotype for rs6103 (*SERPINB2*) was 85% in homozygosity and 77.3% in heterozygosity; and the presence of the A genotype for rs2839629 (*PKNOX1*) was 84% in homozygosity and 80% in heterozygosity.

Conclusions: Polymorphisms in *SERPINB2* and *PKNOX1* were identified in patients with ENL, with emphasis on *PKNOX1*. If confirmed by more robust future studies, these findings may guide clinical decisions and treatment guidelines for ENL.

Key words: peripheral neuropathy; polymorphisms; thalidomide; leprosy; erythema nodosum leprosum.

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Introduction

Leprosy is an endemic infectious disease with a clinical course characterized by the development of several clinical immune reactions [1–5]. Erythema nodosum leprosum (ENL) is a humoral immune response to *Mycobacterium leprae* that is characterized by painful erythematous nodules located in the dermis and hypodermis, and these nodules may ulcerate. Systemic symptoms and inflammation of the nerves may be present, leading to a highly complex clinical condition [5–9]. The main drug used to treat ENL in Brazil is thalidomide [10–13], combined or not with other anti-inflammatory drugs [6,7,14,15]. Although it is effective, thalidomide has important adverse effects, such as teratogenesis and peripheral neuropathy (PN), which may be irreversible [1,8,13,16]. Little is known about the profile of patients with leprosy who are at increased risk of developing thalidomide-induced peripheral neuropathy (TiPN), and the influence of clinical and genetic factors is likely [17–20]. Genetic polymorphisms in the *SERPINB2* (rs6103) and *PKNOX1* (rs2839629) genes have been associated with TiPN in patients with multiple myeloma (MM) [17,19,21]; however, the effect of these polymorphisms

in patients with leprosy is unknown. In this study, we evaluated the presence of single nucleotide polymorphisms (SNPs) in *SERPINB2* and *PKNOX1* genes in patients with ENL at a leprosy referral center in southern Brazil.

Methodology

Sample

We conducted a cross-sectional study of patients with a diagnosis of ENL, whether clinically active or in remission, and followed up at the State Leprosy Referral Center in Rio Grande do Sul (Sanitary Dermatology Outpatient Clinic/Rio Grande do Sul State Department of Health), southern Brazil from 2021 to 2023. The study was approved by the institution's Research Ethics Committee (approval number 4.460.424).

The following variables were evaluated: age, gender, comorbidities, date of leprosy diagnosis, operational classification, clinical and immunological diagnosis of the disease, occurrence of reactional episodes, treatment of reactions, occurrence and characterization of neuropathy, and polymorphisms in *SERPINB2* and *PKNOX1* genes.

Genotyping to analyze polymorphisms

Blood samples were collected and processed in the Department of Genetics at the Federal University of Rio Grande do Sul (UFRGS). DNA was extracted using the Flexigene® Blood Kit (Qiagen™, Venlo, Netherlands). The quantity and quality of the extracted DNA were verified using a Nanodrop 1000 spectrophotometer (Thermo Fisher Scientific, Wilmington, DE, USA). Genotyping of polymorphisms was performed using the real-time polymerase chain reaction (PCR) technique, with TaqMan assays (Applied Biosystems, Foster City, CA, USA) on the StepOne™ system (Applied Biosystems, Foster City, CA, USA). The *SERPINB2*–rs6103 (C_11450583_30) and *PKNOX1*–rs2839629 (C_1605388_20) SNPs were analyzed. All analyses were performed at the UFRGS (Porto Alegre, Brazil), following manufacturer's instructions.

Statistical analysis

Descriptive statistics were used to describe the demographic and clinical variables of leprosy and ENL, where categorical data were expressed as relative frequencies and quantitative data as mean values. Hardy-Weinberg equilibrium was assessed for all polymorphisms using the Chi-square test. All tests were performed using SPSS, version 20 (IBM Corp. Released 2011. Armonk, NY, USA). The Chi-square test (or Fisher's exact test, when one or more events had a frequency of less than 5) was used to investigate the association between the presence of PN and the

Table 1. General characteristics of erythema nodosum leprosum (ENL).

Variables	Sample (n = 47)
Age	
< 35 years	7 (14.9%)
35–65 years	31 (66.0%)
> 65 years	9 (19.1%)
Gender	
Female	14 (29.8%)
Male	33 (70.2%)
Ethnicity	
White	21 (44.7%)
Black	6 (12.8%)
Mixed-race	17 (36.2%)
Indigenous	2 (4.3%)
Unknown	1 (2.1)
Comorbidities	
Systemic arterial hypertension	9 (19.1%)
Hypothyroidism	1 (2.1%)
Two or more comorbidities*	8 (17.1%)
Other**	9 (19.1%)
No comorbidities	20 (42.6%)
Alcoholism	
Yes	4 (8.5%)
No	42 (89.4%)
Unknown	1 (2.1%)
Operational classification	
PB (paucibacillary)	0
MB (multibacillary)	47 (100%)
Clinical classification	
Dimorphous	19 (40.4%)
Virchow's	28 (59.6%)
Multidrug therapy duration	
Treatment not completed	9 (19.2%)
12 months	19 (40.4%)
24 months	19 (40.4%)
Disability prevention (DP) at diagnosis	
Grade 0	4 (8.5%)
Grade 1	11 (23.4)
Grade 2	24 (51.1%)
Other	8 (17.0%)
DP at discharge	
Grade 0	8 (17.0%)
Grade 1	8 (17.0%)
Grade 2	17 (36.2%)
Other	14 (29.8%)
Leprosy reaction	
ENL	45 (95.7%)
Type 1 and 2 reactions	2 (4.3%)
Occurrence of type 2 reaction (ENL)	
Before treatment	13 (27.7%)
During treatment	27 (57.4%)
After treatment	4 (8.5%)
During and after treatment	3 (6.4%)
Thalidomide	
Yes	39 (83.0%)
No	8 (17.0%)
Peripheral neuropathy	
Yes	39 (83.0%)
No	8 (17.0%)
Neuropathy type	
Sensory	26 (55.3%)
Motor	1 (2.1%)
Sensory/motor	12 (25.5%)

*Three patients (6.4%) had systemic arterial hypertension (SAH) and type 2 diabetes mellitus (T2DM); 3 patients (6.4%) had SAH and other associated diseases, such as human immunodeficiency virus (HIV) infection, stroke, and hepatitis B; 2 patients (4.3%) had T2DM and other associated diseases, such as aortic stenosis and multiple myeloma. **Other: HIV infection, coronary artery disease, chronic obstructive pulmonary disease, epilepsy, anxiety, intellectual disability, chronic venous insufficiency, and chemical dependency.

Table 2. Allele and genotype frequencies of *SERPINB2 (*rs6103) and *PKNOX1* (rs2839629) variants and comparison with the database.

Gene	Variant	Genotype / Allele	Absolute number	Sample frequency (%)	ABraOM frequency (%)	*p* value	gnomAD frequency (%)	*p* value
		CC	20	42.6				
		CG	22	46.8				
SERPINB2	rs6103	GG	5	10.6				
		C	62	66.0	66.0	0.976	71.3	0.235
		G	32	34.0	34.0		28.7	
		AC	25	53.2				
		AG	20	42.6				
PKNOX1	rs2839629	GG	2	4.3				
		A	70	75.0	48.6	< 0.001	50.1	< 0.001
		G	24	25.0	51.4		49.9	

different genotypes, and to compare the frequency of variants in our study with that of two genetic databases (general population): Genome Aggregation Database (gnomAD) [22] and Online Archive of Brazilian Mutations (ABraOM) [23]. The estimated prevalence of the *SERPINB2* and *PKNOX1* variants in the Brazilian population were considered to be 34% and 48.6%, respectively. Based on these estimates, 43 patients would be required for the study (39 for *SERPINB2* and 43 for *PKNOX1*), assuming a 95% confidence level and a margin of error of 15 percentage points. Margins of error of 10 percentage points would require a sample size of 96 patients (87 for *SERPINB2* and 96 for *PKNOX1* variants).

Results

The main clinical characteristics of the patients included in the study are shown in Table 1. A total of 47 patients with ENL were included; 33 (70%) men and 14 (30%) women; and most (85.1%) were aged ≥ 35 years. All the patients had multibacillary leprosy, and the minority (8%) had grade 0 disability at diagnosis.

Of the 47 patients with ENL, 45 (95.7%) developed type 2 reaction alone, and 2 developed type 1 reaction concomitantly; 27 (57.4%) developed type 2 reaction during multidrug therapy (MDT), 13 (27.7%) before MDT, 4 (8.5%) after MDT completion, and 3 (6.4%) both during and after MDT. In addition, 83% had used or were using the thalidomide treatment of ENL.

Twenty seven patients (57.4%) had comorbidities, and systemic arterial hypertension and diabetes mellitus were the most frequent comorbidities; and 39 patients (83%) had PN (55.3% pure sensory; 25.5% mixed).

The main objective of this study was to determine the general prevalence of the polymorphisms in patients with ENL**.** We found that *SERPINB2* (rs6103) had a frequency of 66% for the C allele and 34% for the G allele, whereas *PKNOX1* (rs2839629) had a frequency of 75% for the A allele and 25% for the G allele (Table 2). We used population databases as comparative groups, and observed that the presence of the *PKNOX1* (rs2839629) A allele in patients with ENL was significant ($p < 0.001$).

The patients with PN had a higher frequency of homozygous and heterozygous genotypes C (85% and 77.3%, respectively) for rs6103 (*SERPINB2*), and homozygous and heterozygous genotypes A (84% and 80%, respectively) for rs2839629 (*PKNOX1*) (Table 3). However, these associations were not statistically significant.

Discussion

The prevalence of genetic variants can be variable among different populations. Their impact on the clinical outcomes can vary and can be modulated by other environmental and genetic factors. Johnson *et al.* were the first to propose the hypothesis that there are specific conditions and genetic predispositions for the development of post-thalidomide polyneuropathy and evaluated the presence of SNPs in the genetic material of patients with MM [19,24].

The primary objective of our study was to identify the presence of genetic variants in *SERPINB2* and *PKNOX1* in patients with ENL in a sample from Rio Grande do Sul, the southernmost state of Brazil. We identified statistical significance regarding the presence

Table 3. Comparison of *SERPINB2 (*rs6103) and *PKNOX1* (rs2839629) genotypes with the presence of peripheral neuropathy.

Gene	Genotype	Absence-Neuropathy (%)	Presence-Neuropathy (%)	*p* value[A]
	CC	3 (15.0)	17 (85.0)	
SERPINB2	CG	5 (22.7)	17 (77.3)	0.636
	GG	0 (0)	5 (100)	
	AC	4 (16.0)	21 (84.0)	
PKNOX1	AG	4 (20.0)	16 (80.0)	1.000
	GG	0 (0)	2 (100)	

[A] Fisher's exact test.

of the *PKNOX1* (rs2839629) A allele in patients with ENL (75%; $p < 0.001$).

As an additional objective, we evaluated the relationship between the genetic variants studied and the diagnosis of PN caused by thalidomide (TiPN). The C allele for rs6103 (*SERPINB2*) and the A allele for rs2839629 (*PKNOX1*) have already been identified as risk factors for TiPN (in other diseases, especially MM) in previous studies [17,19,25]. Our study demonstrated the same trend, without statistical significance, possibly due to the small sample size. To our knowledge, no study has been published to date that assesses patients with a diagnosis of ENL for genetic susceptibility to the development of TiPN in relation to the *SERPINB2* and *PKNOX1* genes.

SERPINB2 (also known as plasminogen activator inhibitor-2 or PAI-2) is a member of the serine protease inhibitor family [26,27]. It increases rapidly and significantly in acute brain injury models, and this overexpression mediates neuroprotection through undefined mechanisms [18,26,28,29]. Polymorphic variants in the *SERPINB2* gene have been reported to reduce the risk of neuronal damage and favor the resolution of TiPN, supporting the hypothesis that genetic susceptibility may contribute significantly to the natural history of TiPN [18,19,26,28,30]. Johnson *et al.* reported that the rs6103 G > C substitution variant was associated with the development of TiPN in the treatment of patients with MM [19]. Our findings are in agreement with the ABraOM database in that the risk allele C in the *SERPINB2* gene is present in 66%, and G in 34% of the population [23]. This polymorphism in the rs6103 gene results in an exchange of amino acids from asparagine to lysine; however, we did not find any functional evaluation of this polymorphic variation.

PKNOX1, also known as Pbx-regulating protein (PREP1), belongs to the three amino acid loop extension (TALE) superclass of proteins, and the gene encoding this protein (*PKNOX1*) is located on chromosome 21 [30–32]. *PKNOX1* is known to modulate the transcriptional activity of the *monocyte chemoattractant protein-1* (*MCP-1*) gene, an important mediator of macrophage-related neural damage in different animal models of hereditary neuropathies and acute inflammatory demyelinating neuropathy [17]. In the database, the frequency of the A allele in *PKNOX1* was 48.6% and of the G allele was 51.4% [23]. In our sample, the A allele was present in in 75% and the G allele in 25%. The *rs2839629* risk allele A was associated with high levels of *PKNOX1* expression, and these genes encode proteins that are involved in neuropathic and inflammatory pain [17,30].

In this study, most patients with ENL were men (70.2%), and this predominance has also been reported in previous studies [5,8,10,12,33,34]. Twenty-five patients (53.3%) self-reported as African Brazilian. In the study conducted by Chan *et al*., African Americans had a higher incidence of taxane-induced neuropathy than other racial groups [35]. Leprosy reaction occurred predominantly during treatment (57.4%), and this finding was also consistent with previous studies [3–5,8]. The most prevalent age range was 35–65 years (66%). Advanced age is associated with an increased risk of neurotoxicity, but previous studies evaluating chemotherapy-induced neuropathy did not confirm this association, and the conflicting results may be related to other comorbidities that cause PN [35–37]. Other factors that increase the risk of neurotoxicity include diabetes mellitus, alcoholism, and vitamin deficiencies; and a past history of neuropathy is the most important factor [17,38]. Our sample consisted of only 5 (10.6%) patients with diabetes and 4 (8.5%) with alcoholism. We could not attribute the occurrence of neuropathy exclusively to thalidomide in these patients.

Overall, 83% of our study patients developed PN; 26 with predominantly sensory PN and 12 with sensorimotor PN. A total of 32 patients (86.5%) were treated with thalidomide. The etiology of neuropathy may remain uncertain owing to other factors such as the disease itself, use of other medications, and associated comorbidities. This limitation was also reported in previous studies of patients with MM [38] and leprosy [10,16,39]. There is a higher likelihood of PN caused by the disease itself in patients with leprosy, which represents an important limitation of our study. We did not have complementary tests available in our service to conduct a longitudinal follow-up. In addition, the patients in our sample were retrospectively evaluated and were already receiving multiple drug therapy and/or thalidomide. Rates of TiPN vary widely across studies (10% to 83%), with the risk of neuropathy being related to the cumulative dose and duration of therapy [14,19,25,38], which may persist for some time after drug discontinuation [13,14,18]. Evaluating thalidomide dose and treatment duration related to the development of PN were not objectives of this study, and this shortcoming, along with the small sample size, may have limited the ability to identify the associations investigated in the study.

This study had additional limitations. First, due to the scarcity of information recorded in the medical records, it was not possible to accurately assess the total dose of thalidomide used or the duration of the treatment. Additionally, the irregularity of

consultations and the inappropriate use of thalidomide by some patients further complicated this assessment. Second, due to the study design, it was not possible to exclude other potential causes of neuropathy, considering the presence of confounding variables. Furthermore, the small sample size may have limited the statistical power necessary to detect meaningful associations between genetic variants and clinical outcomes, especially specific phenotypes observed in ENL patients. The limited number of patients and lack of control in our study can be attributed to the lower prevalence of leprosy in southern Brazil compared to other regions of the country. Furthermore, consultations were restricted during the data collection period due to the coronavirus disease 2019 (COVID-19) pandemic. Finally, the heterogeneity of ENL presentations among patients could introduce variability that obscures the relationship between the genetic variants and the observed clinical manifestations. These considerations underscore the complexity of drawing definitive conclusions from the findings of this study.

Despite these limitations, we believe that the present study successfully achieved its primary objective: to verify the prevalence of polymorphisms in the *SERPINB2* and *PKNOX1* genes that are known to increase susceptibility to TiPN in patients with ENL. If confirmed by other future studies, these results may drive changes in clinical practice, when opting for alternative treatments in patients with a predisposition to thalidomide neuropathy.

Conclusions

Polymorphisms in the genetic variants of *SERPINB2* and *PKNOX1* were found in patients with ENL, and the presence of the *PKNOX1* (rs2839629) A allele was statistically significant. Further studies analyzing the association of these genetic variants and comparing them with the occurrence PN should be carried out in larger samples to evaluate the role of those variants in ENL PN in the Brazilian population.

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Conflict of interests

No conflict of interests is declared.

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