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Review

Peripheral nervous system involvement in systemic lupus erythematosus: Prevalence, clinical and immunological characteristics, treatment and outcome of a large cohort from a single centre

Pilar Toledano [a], Ramón Orueta [b], Ignasi Rodríguez-Pintó [a], Josep Valls-Solé [c], Ricard Cervera [a], Gerard Espinosa [a,*]

[a] Department of Autoimmune Diseases, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, Barcelona, Catalonia, Spain
[b] Primary Care, Sillería Health Center, Toledo, Spain
[c] Department of Neurology, IDIBAPS, Hospital Clínic, University of Barcelona, Barcelona, Catalonia, Spain

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ABSTRACT

Disorders of peripheral nervous system in patients with systemic lupus erythematosus (PNS-SLE) are a major cause of morbidity. The aims of the present study were to determine the prevalence of PNS-SLE involvement in a large cohort of SLE patients from a single centre, to characterize such involvement, treatment modalities and outcome, and to identify the possible variables that may be associated with its presence.

We performed an observational cross-sectional study that included all SLE patients being followed in our department between March and December 2015 who met at least one of the PNS-SLE case definitions proposed in 1999 by the American College of Rheumatology.

Overall, 93 out of 524 (17,7%) patients presented with PNS-SLE syndrome; 90 (96.8%) of them were women with a mean age at PNS-SLE syndrome diagnosis was 44.8 ± 14.1 years and the average time from diagnosis of SLE to PNS-SLE diagnosis was 88 (range, 541–400) months. The most frequent manifestation was polyneuropathy (36.6%), followed by non-compression mononeuropathy (23.7%), cranial neuropathy and myasthenia gravis (7.5%, each), and Guillain-Barré syndrome (1.1%). The most frequent electrodiagnostic tests (EDX) pattern was axonal degeneration, present in 49 patients that corresponded to 80.3% of the overall EDX patterns. Mixed sensory-motor neuropathy was the most common type of involvement accounted for 56% of cases. Thirty-six out of 90 (40%) received glucocorticoids and/or immunosuppressant agents. Overall, global response (complete and/or partial) to treatments was achieved in 77.4% of patients without differences between the types of PNS-SLE involvement. Older age at SLE diagnosis (37.3 ± 14.8 versus 30.8 ± 12; $p = 0.001$) and absence of hematologic involvement as cumulative SLE manifestation (11.8% versus 21.5%; $p = 0.034$) had independent statistical significant associations with PNS-SLE development.

The PNS-SLE involvement is not uncommon. Its most frequent manifestation is sensory-motor axonal polyneuropathy. The involvement occurs more frequently in patients who are diagnosed with SLE at older age. Prospective studies are needed to establish the incidence of PNS-SLE syndromes and the role of hematological manifestations in their development.

Contents

1. Introduction . . . 751
2. Material and methods . . . 751
   2.1. Design and target population . . . 751
   2.2. Study variables . . . 751
   2.3. Statistical analysis . . . 751
3. Results . . . 751

* Corresponding author at: Department of Autoimmune Diseases, Hospital Clínic, Villarroel 170, 08036 Barcelona, Catalonia, Spain.
E-mail address: gespino@clinic.ub.es (G. Espinosa).

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3.1. General characteristics . . . 751
3.2. Types of PNS-SLE involvement . . . 752
3.3. Treatment and outcome . . . 753
3.4. Factors related with the development of PNS-SLE syndrome . . . 753
4. Discussion . . . 753
5. Conclusions . . . 755
Take-home messages . . . 755
References . . . 755

1. Introduction

Neuropsychiatric involvement is one of the leading causes of morbidity and mortality in patients with systemic lupus erythematosus (SLE) [1–4]. In 1999 the American College of Rheumatology (ACR) defined 19 neuropsychiatric syndromes in SLE from which 12 involve the central nervous system (CNS-SLE) and 7 the peripheral nervous system (PNS-SLE) [5].

In the last decade, CNS-SLE involvement has been the focus of numerous studies, thus allowing to its clinical characterization, association with immunological markers or their relationship with SLE activity [6–11]. In contrast, PNS-SLE has been scarcely studied [12–15], despite its association with significant morbidity and a worsen quality of life [16]. Its prevalence is estimated to be between 5 and 27% [7–9,16–18] and it is fundamentally characterized by sensory or sensory-motor neuropathy. The pathogenesis is unclear, although it has been linked to vascular disease of the small arteries that supply the affected nerves [13,19]. However, PNS-SLE involvement has not been well characterized in terms of manifestations at onset, severity, and clinical and electrophysiological associations.

The present study aims to determine the prevalence of PNS-SLE involvement in a large cohort of SLE patients from a single centre, and to characterize such involvement regarding clinical features, serological markers and electrophysiological findings. In addition, we describe the different treatment modalities and the outcome, and study the possible variables that may be associated with the development of PNS-SLE.

2. Material and methods

2.1. Design and target population

This is an observational cross-sectional study that included all SLE patients with active monitoring between March 2014 and December 2015 at the Department of Autoimmune Diseases, Hospital Clínic, Barcelona, Catalonia, Spain. All patients fulfilled at least 4 of the 11 ACR criteria for SLE classification [20,21]. The case group target population included patients with PNS-SLE who met at least one of the PNS-SLE case definitions proposed in 1999 by the ACR [5]. Attribution to SLE was considered when PNS was present in the absence of other common etiologies. Those patients with PNS involvement that could be attributed to other diseases than SLE (diabetes mellitus, thyroid disease, primary vasculitis including anti-neutrophil cytoplasmic antibody-associated vasculitis, drugs or metabolic diseases with potential side effects on PNS) were excluded. Initially, compression neuropathy was not excluded due to the difficulty in consider its relationship with SLE activity. However, we performed the analysis taken and not into account this type of PNS involvement. The control group target population included SLE patients without PNS-SLE.

2.2. Study variables

The following variables were collected from medical records of each patient and entered into a database designed specifically for the present study by the same person (PT) to avoid bias in the collection: a) demographic variables such as sex and mean age at the SLE diagnosis and at the time of PNS-SLE appearance; b) time between SLE diagnosis and the appearance of PNS-SLE; c) time of follow-up defined as the time (in months) from the diagnosis of PNS-SLE to the last medical visit for the patients with PNS-SLE and from the SLE diagnosis to the last medical visit for the remaining SLE patients; d) associated SLE manifestations at the time of PNS-SLE development; e) characteristics of neurological involvement, including syndromic and topographic characteristics of the involvement; f) data from electrodiagnostic tests (EDX) in patients in which they were performed; g) immunological parameters, such as profile of antibodies against extractable nuclear antigens and antiphospholipid antibodies, from SLE diagnosis to the appearance of PNS-SLE, and anti-dsDNA antibody and complement levels at the time of PNS-SLE development; h) SLE disease activity index (SLEDAI) at the time of SLE diagnosis; i) SLEDAI and Systemic Lupus International Collaborating Clinics (SLICC) chronicity index at the time of appearance of PNS-SLE; and j) treatment at the time of PNS-SLE syndrome and treatment of PNS-SLE and outcome. Complete remission (CR) was considered when all the signs and symptoms had completely disappeared, partial remission (PR) when they had improved, but at least one persisted (sign and/or symptom), and no response (NR) when the clinical manifestations remained unchanged or deteriorating.

2.3. Statistical analysis

Categorical data are summarised as percentages; significant differences or associations were analysed using the χ^2 test or Fisher's exact tests. Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range, IQR) depending on normality demonstrated by Kolmogorov-Smirnov test.

Associations of quantitative data were analysed with Student's *t*-test and with the non-parametric Mann-Whitney *U* test. A two-tailed value of $p < 0.05$ was taken to indicate statistical significance. When independent variables appeared to have statistical significance in the univariate analysis ($p < 0.05$), they were included in a multivariate logistic regression analysis using a backward stepwise method. To avoid possible bias due to different follow-up time between two groups of patients, we included this variable in the regression model. The odds ratios (OR) and their 95% confidence interval (CI) obtained in the adjusted regression analysis were calculated. Statistical analysis was performed using the SPSS program (SPSS Statistics 22.0).

3. Results

3.1. General characteristics

The overall series comprised 529 SLE patients but 5 of them were excluded due to the lack of complete information. From 524 patients, 487 (93% [CI95 90.9%–94.8%]) were females and the mean age at SLE diagnosis was 31.9 ± 13.4 (range, 8–85) years and the median follow-up was 174 (1–570) months.

One hundred (19.1% [CI95 15.9%–22.7%]) patients developed some type of PNS-SLE syndrome. Seven of them were excluded due to other causes such as anti-neutrophil cytoplasmic antibody-associated vasculitis (n = 3), diabetic peripheral neuropathy (n = 3) and vitamin B12 severe deficiency (n = 1). Overall, 93 out of 524 (17.7% [CI95 14.7%–21.3%]) patients presented with PNS-SLE syndrome; 90 (96.8% [CI95 90.9%–99.0%])