Peripheral Nervous System Involvement in Systemic Lupus Erythematosus: prevalence, associated factors and outcome.

Target journal: Seminars in arthritis and Rheumatism

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Type of article: Original Clinical Research Studies Including Clinical Trials

Declarations of interest: none to declare.

Funding sources: none

Commento [A1]: Indicare email

ABSTRACT

In the past years, the peripheral nervous system involvement in systemic lupus erythematosus (PNSLE) has received little attention despite its potentially significant impact on health-related quality of life.

Objectives. To assess the prevalence and clinical features of PNS involvement in a large cohort of Systemic Lupus Erythematosus (SLE) patients.

Methods. SLE patients consecutively observed at two tertiary referral centres over a period of 14 years (from 2000 to 2014) were selected. PNS manifestations were ascertained according to the 1999 American College of Rheumatology case definitions and by using an attribution algorithm for neuropsychiatric (NP) events. Prevalence of PNSLE, demographic, clinical and laboratory data were assessed. Patients with PNS manifestations were compared with a control group of SLE patients without PNS involvement.

Results. In a retrospective cohort of 1,224 patients, the overall prevalence of PNS involvement was 6.9% (85 patients, 95% Confidence Interval (95%CI) 0.06-0.08), with 68% of the events attributable to SLE. Polyneuropathy was the most common manifestation observed (42 events, 43.3%), followed by cranial neuropathy in 30 cases (30.9%), 12 mononeuritis single (12.4%) or multiple (8 events, 8.2%). The average age of SLE onset was significantly higher in patients with PNS manifestations than in controls (mean ± standard deviation (SD): 45.9±14.8 vs 37.1±14.0) and they were more likely to have a higher SLEDAI-2K and SLICC/ACR Damage Index (SDI) scores and hypertension. A subgroup analysis for events deemed to be SLE-related provided similar results.

Conclusion. PNS involvement is an uncommon, but not so rare complication of SLE. A careful neurological evaluation for this manifestation should be included in the diagnostic workup, especially in patients with later onset and with higher damage and disease activity.

Keywords: Systemic lupus erythematosus, peripheral nervous system, neuropsychiatric lupus erythematosus, cranial neuropathy, polyneuropathy, mononeuropathy.

1.1 INTRODUCTION

Systemic lupus erythematosus (SLE) is an immune-mediated disease, characterized by the production of autoantibodies and immune-complexes deposition that can affect multiple organs and systems including both the central (CNS) and peripheral nervous system (PNS). The prevalence of neuropsychiatric lupus (NPSLE) widely varies across studies, depending on the type of manifestations, selection of inclusion criteria and the lack of standardized evaluation measures [1]. In 1999, the American College of Rheumatology (ACR) provided the definitions for 7 peripheral and 12 central NP clinical manifestations related to SLE [2].

Up to date, little is known about the actual prevalence of peripheral neuro-lupus (PNSLE) and the demographic and specific immunological factors related to this type of involvement [2]. Most of the studies evaluating NP involvement in SLE applying the 1999 ACR nomenclature are typically retrospective cohort studies and considered both peripheral and central involvement. The prevalence of PNS complications ranged between 2 and 10%, with a higher predominance of polyneuropathy (2-3%) and mononeuritis (single or multiple: 0.5-1%) compared to rare or unusual events as acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome (GBS), 0.1%), myasthenia gravis (0.1%) and plexopathy (<0.1%) [3–6]. For some Authors a revisiting of this classification seems advisable, for instance, including small fibers neuropathy among peripheral syndromes occurring in PNSLE [7–9]. In addition the diagnosis of PNSLE is a relevant and challenging clinical issue because up to one third of peripheral neuropathies (PN) recognizes a non-SLE etiology [7]; entrapment neuropathies, diabetes, infectious, endocrine, metabolic, critical illness, genetic, nutritional, traumatic, neoplastic and iatrogenic etiologies can represent alternative causes at any time [10].

The present study aims to estimate the prevalence of the PNS involvement in a large cohort of patients with SLE from two tertiary referral centres, distinguishing the proportion of events attributed to SLE and non-SLE causes. The secondary objective is to define clinical and serological characteristics, non-specific and specific risk factors, treatment approaches and short-term outcome with the final purpose to profile the patients with PNS involvement.

2.1 METHODS

2.1.1 Patients

We examined patients with SLE, evaluated over a 15-year period, between 1st January 2000 and 31st December 2014, at the Rheumatology Unit of the Ferrara University Hospital and at the Rheumatology Unit of the University Clinic of Cagliari, two tertiary referral centres for SLE. All patients had to be diagnosed with SLE according to the 1997 ACR revised classification criteria [11]. In all patients, signs or symptoms of PNS involvement have been evaluated by drawing the clinical and laboratory information from the available documentation (clinical hospital records, patient charts and lupus clinic database) and only patients with a clinical follow-up of at least one year were included in the study. As a disease-control group, patients evaluated during the same period and suffering from SLE but without NP abnormalities, matched for gender and disease duration, were randomly retrieved from the database by using an alphabetical list (1:3 ratio).

2.1.2 Case ascertainment

Each case of PNS involvement was further characterized at the time of neurologic diagnosis. For peripheral neuropathy, data included features of peripheral neurologic event. The electrophysiological study results were recorded when available, including the signs of neuropathic changes, denervation, axonal neuropathy or peripheral nerve demyelination. Pure compression neuropathy (e.g. the median nerve in the carpal tunnel) was not included in the analysis as not attributable to SLE. For cranial neuropathy, results of MRI examination were reviewed for evidence of nerve enhancement, as a marker of inflammation and to rule out nerve root compression [12].

The final neurologic diagnosis was also extracted from the chart review. We considered all the seven peripheral manifestations listed in 1999 ACR nomenclature and case definition, retrospectively attributed according to the attribution rules as explained elsewhere [13,14], considering (i) temporal relationship of NP events to the diagnosis of SLE; (ii) recognition of confounding factors (i.e. alternative causes or non-SLE contributing factors derived from the ACR case definitions for 19 NP syndromes); (iii) identification of minor or common NP events as described by Ainiala et al. [15]; (iv) favouring factors (i.e. clinical and non-clinical variables which support the attribution to SLE). Furthermore, besides cases defined by 1999 ACR nomenclature, we included in the study patients with small fiber neuropathy, diagnosed by biopsy "punch skin".

The outcome of PNS manifestations was generated from a physician's 7-point Likert scale (1=patient demise, 2=much worse, 3=worse, 4=no change, 5=improved, 6=much improved, 7=resolved) [16]. The outcome response for all PNS events was recorded after one year of follow-up and scored as “much improved or resolved” (score ≥ 5); “no change” (score = 4) or “worse” (score ≤ 3).

2.1.3 Associated factors

Disease activity was routinely assessed by the SLE Disease Activity Index 2000 (SLEDAI-2K) [17], measured at the onset time of the NP manifestation without taking into account the NP items. Damage was calculat-

ed by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index (SDI) [18].

In all patients, a large panel of factors and/or comorbidities was checked for. Risk factors were categorized as generic (not strictly SLE-related) or specific (SLE-related), and each of them has been defined elsewhere [19,20]. Generic factors included: hypertension, diabetes, dyslipidaemia, smoking habit (>10 cigarettes/day); specific factors were anti-phospholipid antibodies (aPLs) including anti-cardiolipin (aCLs) and anti-Beta2-glycoprotein I (aB2GP1) antibodies (both IgG and IgM isotypes), lupus anticoagulant (LA), anti-Ro/SSA and anti-Sm antibodies, anti-phospholipid syndrome (APS), Sjogren's syndrome (SS), Raynaud phenomenon (RP), livedo reticularis registered in clinical charts and ascertained by history or by direct medical observation. Immunological parameters were: total serum gammaglobulins (g/l); complement fractions C3 and C4 (g/l) detected by nephelometry (hypocomplementaemia was defined as C3<0.8 and C4<0.11 g/l); anti-nuclear antibodies (ANAs) tested by indirect immunofluorescence (IIF), using Hep2 cell substrate (positivity was defined as a titre $\geq$1: 160). aPLs, anti-Extractable Nuclear Antigen (ENAs) antibodies and anti-dsDNA were analysed by each centre by validated assays routinely used.

Treatment and medications recorded (ongoing at the time of the event and started/modified for new PNS manifestation) included: corticosteroids (CS), hydroxychloroquine, immunosuppressive drugs (cyclophosphamide (CYC), azathioprine (AZA), mycophenolate mofetil (MMF), cyclosporine A (CYA), methotrexate (MTX)), rituximab, intravenous immunoglobulins (IVIG), plasma exchange (PEX), neuroleptics, neurotrophics or other relevant treatments (e.g. anti-platelet therapy or anticoagulants). In the disease control group, we recorded ongoing treatment at the time of study inclusion.

2.1.4 Statistical analysis

Frequency calculations and descriptive statistics were used for the assessment of patient characteristics. Either the chi-square test or Fisher's exact test was used for group comparisons involving binary data, as appropriate. A normal distribution of continuous variables was estimated by Shapiro-Wilk test. For continuous variables, a two-tailed Student's t test or a nonparametric Mann–Whitney U test was used to perform comparisons between groups. The results were considered significant at $p<0.05$. Data processing and statistical analyses were performed using MedCalc for Windows, version 9.5.0.0 (MedCalc Software, Mariakerke, Belgium).

3.1 RESULTS

3.1.1 Demographic and clinical data

A total of 1,224 patients, 804 from Ferrara and 420 from Cagliari attended our lupus clinics for the indicated timeframe. Overall, 58 out of 804 patients (7.2%, 95% Confidence Interval (95%CI) 0.06 - 0.09) and 27 out of 420 patients (6.4 %, 95%CI 0.044 - 0.092), respectively, had at least one PNS event, for a total of 85 patients with PNS involvement (6.9 %, 95%CI 0.06 to 0.08) and 97 PNS events. Demographic, clinical and laboratory data are reported in Table 1. 85.9% of patients were female, mean age at SLE onset was 45.9 years (standard deviation, SD 14.8), mean (SD) disease duration at the time of the event occurrence was 5.8 years (9.2). In two cases the event has preceded the diagnosis of SLE and in 26 patients PNS involvement appeared at the onset of the disease, in the remaining 57 patients PNS involvement appeared after diagnosis of SLE.

3.1.2 Peripheral nervous system manifestations

Polyneuropathy was the most common manifestation (42 events, 43.3% of all PNS events recorded), followed by cranial neuropathy in 30 cases (30.9%), mononeuritis single in 12 (12.4%) or multiple in 8 cases (8.2%), small fibre neuropathy (4 events, 4.1%), myasthenia gravis (3 events, 3.1 %), plexopathy and autonomic neuropathy in 1 case (1%). Table 2 shows details of PNS involvement and electrodiagnostic features for polyneuropathy and cranial neuropathy. In our cohort, there were no cases of GBS or Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP). Using the attribution algorithm for NP events, applied as previously reported [13], 66 (68%) out of 97 PNS events in 61 patients reached the defined cut-point for a proper attribution to SLE (Table 2). Mononeuritis multiplex (85%, 17/20 events) and cranial neuropathies (93.3 %, 28/30) were more likely to be SLE-related.

3.1.3 Comparison between patients with and without PNS events

In our case-control study, we matched (by gender and SLE duration) SLE patients with PNS involvement to 243 control SLE patients without central or peripheral manifestations (1:3 ratio). In both groups, most patients were female, all Caucasian. The age at SLE diagnosis was significantly higher in patients with PNS involvement, and they were more likely to have higher SLEDAI-2K and SDI scores (Table 1). There was no significant difference in lupus serology between the two groups. Among clinical characteristics, an association was observed with concomitant Sjögren's syndrome in cases with PNS involvement, while malar rash and photosensitivity were more common in controls. Among generic risk factors, smoking habit, diabetes and hypertension were more often reported in patients with peripheral involvement, while livedo reticularis was the only specific risk factor related to PNSLE.

A subgroup analysis, including only the SLE-related PNS manifestations and their controls, gave similar results regarding significantly older age, higher SDI and SLEDAI-2K in cases compared to controls. Among generic and specific risk factors, concomitant hypertension showed a significant association with PNS events related to SLE.

Table 1. Demographic, clinical and laboratory data of SLE patients with peripheral nervous system involvement and disease control group.

	A SLE Control group	B SLE PNS (all)	A vs B	C SLE PNS related event	A vs C
Demographic characteristics	243 (74.1)	85 (25.9)		61 (18.6)	
Gender, F:M (%)	215/28 (88.5/11.5)	73/12 (85.9/14.1)	0.52	54/7 (88.5/11.5)	0.9
Age at disease onset, mean (SD) years	37.1 (14.0)	45.9 (14.8)	<0.0000	44.5 (14.7)	0.002
Disease duration at last assessment, mean (SD) years	13.1 (8.6)	13.9 (9.3)	0.4	13.1 (9.5)	0.9
Clinical and sero-immunological characteristics					
Central nervous system, N (%)	-	40 (47.1)	-	29 (47.5)	-
Sjogren's syndrome, N (%)	21 (8.6)	17 (20)	0.005	10 (16.4)	0.07
Malar rash, N (%)	89 (36.6)	14 (16.5)	0.001	11 (18.3)	0.006
Discoid rash, N (%)	15 (6.2)	7 (8.2)	0.51	7 (11.5)	0.15
Photosensitivity, N (%)	96 (39.5)	23 (27.1)	0.04	15 (24.6)	0.03
Mucosal ulcer, N (%)	22 (9)	6 (7.1)	0.57	22 (9.1)	1.0
Arthritis, N (%)	160 (65.8)	47 (55.3)	0.08	37 (66.7)	0.45
Serositis, N (%)	59 (24.3)	16 (18.8)	0.30	9 (14.7)	0.11
Nephropathy, N (%)	38 (15.6)	13 (15.3)	0.94	9 (14.7)	0.87
Haematological, N(%)	113 (46.5)	32 (37.6)	0.16	22 (36.1)	0.14
Hemolytic anemia, N (%)	12 (4.9)	3 (3.53)	0.77	2 (3.3)	0.74
Leucopenia/Lymphocytopenia, N (%)	96 (39.5)	28 (32.9)	0.28	20 (32.8)	0.33
Thrombocytopenia, N (%)	22 (9)	10 (11.7)	0.47	6 (9.8)	0.85
ANA, N (%)	240 (98.8)	81 (95.3)	0.08	57 (93.4)	0.03
Anti-dsDNA, N (%)	141 (58)	46 (54.1)	0.53	31 (50.8)	0.31
Anti-Ro/SSA, N (%)	90 (37)	35 (41.2)	0.49	26 (46.2)	0.42
Anti-Ro/SSB, N (%)	26 (10.7)	10 (11.8)	0.78	7 (11.5)	0.86
Antiphospholipid (LA, aCL or anti-β2GPI) , N (%)	89 (36.6)	40 (47.1)	0.09	24 (39.3)	0.69
Hypergammaglobulinaemia, N (%)	62 (25.5)	27 (31.8)	0.26	20 (32.8)	0.25
Hypocomplementemia, N (%)	136 (55.9)	52 (61.2)	0.40	37 (60.7)	0.51
Monoclonal component, N (%)	4 (1.6)	3 (3.5)	0.38	3 (4.92)	0.15
SLEDAI-2K at the first PNS event, mean (SD)	2 (2.3)	6.9°° (5.3)	<0.0000	7.7 (5.6)*	<0.0000
SDI	0.9 (1.1)	2.2 (1.9)	<0.0000	2.1 (1.8)	<0.0000
Risk factors					
Smoking, N (%)	43/224 (19.2)	8 (9.5)	0.04	6/60 (10)	0.09
Hypertension, N (%)	52/238 (21.8)	36/84 (42.9)	<0.0000	25/60 (41.7)	0.002
Diabetes, N (%)	7/238 (2.9)	14/84 (16.7)	<0.0000	5 (8.3)	0.07
Dislipidaemia, N (%)	59/238 (24.8)	25/84 (29.8)	0.37	15 (25)	0.97
Contraceptive intake, N (%)	25/237 (10.5)	0 (0)	0.001	0 (0)	0.004
Hypotiroidism, N (%)	23/239 (9.47)	12 (14.1)	0.28	8 (13.1)	0.43
Tiroiditis, N (%)	25/238 (10.5)	9 (10.6)	0.98	3 (4.9)	0.2
Raynaud's phenomenon, N (%)	60 (24.7)	20 (23.5)	0.83	11 (18.0)	0.27
Livedo reticularis, N (%)	14 (5.8)	13 (15.2)	0.006	9 (14.7)	0.02
Ongoing therapies					
Corticosteroids	205 (84.4)	83 (97.7)	0.001	60 (98.4)	0.002

Hydroxychloroquine	170 (70)	53 (62.3)	0.19	34 (55.7)	0.03
Immunosuppressants[§]	77 (31.7)	32 (37.6)	0.35	25 (41.0)	0.17
Rituximab	5 (2.1)	3 (3.5)	0.43	2 (3.3)	0.63
Anti-platelet therapy	72 (29.6)	39 (45.9)	0.006	27 (44.3)	0.03
Anticoagulant	13 (5.3)	12 (14.1)	0.009	8 (13.1)	0.03

**data available for 60/61 patients, °° data available for 84/85 patients. List of abbreviation: SLEDAI-2K, Systemic lupus erythematosus disease activity index 2000; SDI, systemic lupus international collaborating clinics/American college of rheumatology (SLICC/ACR) damage index; SD, standard deviation. [§] Immunosuppressants: Azathioprine, Methotrexate, Mycophenolate mofetil, Cyclosporine A).*

Table 2. Peripheral nervous system manifestations and electrodiagnostic studies observed in 85 PNSLE patients.

	All the events N° (%)	**Attributed events N° (%)**
PNSLE patients	**85 (100)**	**61 (71.8)**
Peripheral events	**97 (100)**	**66 (68)**
Polyneuropathy	**42 (43.3)**	**23 (34.9)**
Sensorimotor lower limbs	21 (21.6)	13 (19.7)
Pure sensitive lower limbs	10 (10.3)	5 (7.6)
Pure sensitive upper and lower limbs	2 (2.1)	1 (1.5)
Sensorimotor lower and upper limbs	2 (2.1)	1 (1.5)
Sensorimotor upper limbs	1 (1)	1 (1.5)
Pure sensitive upper limbs	1 (1)	1 (1.5)
Sensorimotor lower limbs and pure sensitive upper limbs	1 (1)	1 (1.5)
Small fibres neuropathy	4 (4.1)	NA
Cranial neuropathy	**30 (30.9)**	**28 (42.4)**
Optic neuritis	7 (7.2)	7 (10.6)
Trigeminal nerve	7 (7.2)	6 (9.1)
Vestibular nerve	7 (7.2)	6 (9.1)
Oculomotor nerve	4 (4.1)	4 (6.1)
Abducens nerve	3 (3.1)	2 (3)
Facial nerve	2 (2.1)	2 (3)
Mononeuropathy	**20 (20.6)**	**17 (25.7)**
Single	12 (12.4)	9 (13.6)
Multiple	8 (8.2)	8 (11.9)
Myasthenia gravis	**3 (3.1)**	**1 (1.5)**
Plexopathy	**1 (1)**	**0**
Autonomic neuropathy	**1 (1)**	0
GBS/CIDP	**0**	NA

PNSLE, Peripheral Nervous System manifestations in Systemic Lupus Erythematosus; GBS, Guillain-Barré syndrome; CIDP, Chronic Inflammatory Demyelinating Polyradiculoneuropathy.

3.1.4 Therapeutic approach and outcome

After PNS manifestations onset, pulses of CS were started in 10 cases of attributed polyneuropathies and in 3 cases of not-attributed ones, as well as in 6 attributed mononeuropathies and 8 attributed cranial neuropathies. A moderate to high dosage of background CS (0.5-1 mg/kg per day of prednisone equivalents) was started in 15 attributed cranial neuropathies, 12 attributed polyneuropathies and 9 mononeuropathies (8 attributed). Neurotrophic and neuroleptic agents were especially adopted in polyneuropathies (4 not-attributed and 17 attributed). Among immunosuppressants, 4 cases of attributed polyneuropathy and 3 cranial neuropathies received CYC, while mycophenolate mofetil (MMF) was used in 6 polyneuropathies (1 not-attributed) and 3 attributed mononeuropathies. Table 3 shows in detail the therapeutic approach.

Table 4 shows the short-term outcome for the most frequent PNS manifestations in our cohort. In 85 evaluable manifestations, the short-term outcome assessed 1 year after the onset of the PNS manifestation showed a resolution or a significant improvement in 56 cases (65.9%). 14/22 (63.6%) cases of attributed polyneuropathy and 11/18 (61.6%) cases of not-attributed polyneuropathy improved while only 4/22 (18.2%) attributed and 2/18 (11.1) not-attributed polyneuropathies became worse. All the not-attributed mononeuropathies and cranial neuropathies improved and only 1/14 (7.1%) attributed mononeuropathies and 1/26 (3.8%) attributed cranial neuropathies worsened. Myasthenias and plexopathy have shown an improvement during follow-up, autonomic neuropathy did not change.

Commento [A2]: Parte nuova con il dettaglio della terapia riportata in TAB 3, valutare se vale la pena tenerla o meno

Commento [A3]: Parte nuova con outcome dove disponibile

Table 3. Therapeutic approach for most frequent peripheral nervous system manifestations in SLE patients.

Commento [A4]: Valutare se eliminare

	Polyneuropathy		Mononeuropathy		Cranial Neuropathy	
	Not Attributed	Attributed	Not Attributed	Attributed	Not Attributed	Attributed
N° of events	19	23	3	17	2	28
Pulse CS	3	10	-	6	-	8
CS 0.5 -1 mg/kg/day	-	12	1	8	-	15
CYC	1	4	-	-	-	3
PEX		1	-	2	-	1
IVIG	1	2	1	2	-	1
RTX	-	-	-	2	-	2
CYA	-	1	-	-	-	-
MTX	1	2	-	1	2	1
MMF	1	5	-	3	-	-
AZA	1	2	2	3	-	2
Neurotrophics	2	9	1	1	-	3
Neuroleptics	2	8	1	1	-	3

CS, corticosteroids; CYC, cyclophosphamide; PEX, plasma exchange; IVIG, intravenous immunoglobulins; RTX, rituximab; CYA, cyclosporine A; MTX, methotrexate; MMF, mycophenolate mofetil, AZA, azathioprine.

Table 4. Short term (1-year) outcome of most frequent peripheral nervous system events in SLE patients.

	Polyneuropathy		Mononeuropathy		Cranial Neuropathy	
	Not Attributed	**Attributed**	**Not Attributed**	**Attributed**	**Not Attributed**	**Attributed**
N° of events	19	23	3	17	2	28
Outcome	18	22	3	14	2	26
Much improved or resolved, N (%)	11 (61.1)	14 (63.6)	3 (100)	8 (57.1)	2 (100)	18 (69.2)
No change, N (%)	5 (27.8)	4 (18.2)	0	5 (35.7)	0	7 (26.9)
Worse, N (%)	2 (11.1)	4 (18.2)	0	1 (7.1)	0	1 (3.8)

Short term outcome assessed according to a physician's 7-point Likert scale [16].

4.1 DISCUSSION

The final purpose of our study was to define the overall prevalence of PNS involvement and to profile the patient with SLE complicated by a PNS manifestation. The prevalence of PNS manifestations in our study is similar to that reported by Oomatia et al. [7] and by Hanly et al. [21] and slightly lower if compared to Florica's [22] and Toledano's et al results [23]. In the SLICC cohort, out of 843 NP events, 58 (6.9%) involved PNS [21]. In the study of Oomatia [7], in addition to classifying ACR criteria for NPSLE, patients had to meet the definitions of peripheral neuropathy provided by the Task Force of the American Academy of Neurology and the American Academy of Physical Medicine and Rehabilitation. The prevalence of peripheral neurological involvement was 6% (123/2097 of the patients), with 67% (82 of 123) attributable to SLE. In this study they excluded patients having cranial neuropathies and close attention was paid to small fibres involvement, not included in the original ACR nomenclature and more frequent than others, demonstrated in 17.1% of patients (14 of 82) by skin biopsy. Florica et al. found polyneuropathy in 207/1533 patients (14%). In this cohort, the authors also included chronic inflammatory demyelinating polyradiculoneuropathy, another manifestation not listed in the ACR case definition, that was more frequent (5.3% of the cases) than in other reports. Toledano et al. reported an overall prevalence of PNS involvement of 17.5% (93 out of 524 patients) and of 13.5% when excluding patients with carpal tunnel syndrome [23].

In our study the prevalence of individual PNS was very similar to the average prevalence observed in the literature meta-analysis carried out by Unterman et al., confirming that peripheral polyneuropathy is the most common manifestation across the studies, followed by cranial nerve neuropathy [24]. We have confirmed that GBS and plexopathy are extremely rare in SLE, suggesting, as already hypothesized, that they may reflect the manifestation of a distinct and coincidental neurologic syndrome [7]. Autonomic neuropathy was also very rare; however, the mild course and the not-specific and multifaceted character of this event, coupled with the lack of routine availability of identification tests, makes its recognition very tough in a retrospective study.

Like prior studies, our data emphasize the importance of a carefully diagnostic process of SLE related PNS manifestations. Regarding attribution, 71.8% of our patients experienced at least one PNS manifestation deemed as related to SLE (68% of all the events). Compared to other studies, Florica et al. [22] reported similar results with 39.6% of the whole PNS events registered and judged as not-SLE related (major causes were entrapment neuropathies, iatrogenic etiologies, hypothyroidism and diabetes mellitus; other causes were ethanol abuse, paraproteinemia, Sjogren's syndrome, uraemia, viral hepatitis). Similarly, Oomatia reported that out of total 123 PNSLE patients, 33.3% were not attributable to SLE due to other non-SLE etiologies, such as infectious or metabolic [7]. Analysing the type of the event, mononeuritis multiplex was more likely to be SLE-related, an observation confirmed again by Florica et al. [22] and in agreement with the new classification criteria for SLE that have seen the inclusion of this event, judged to be very specific.

In our series, cranial neuropathy was a very specific event as well, attributed to SLE in more than 93% of patients, making it a very evocative event for primary NPSLE.

Among clinical and demographic data, comparing patients with and without PNS involvement, an older age at onset of the disease, higher disease activity and SDI score are traits associated with PNS involvement attributed to SLE, data shared by different studies that have solely focused on the description of peripheral involvement in SLE and confirmed in our cohort [6,7,22,23]. Consistent with previous findings, even in our study signs of PNS involvement would seem to characterize a patient with different comorbidities or risk factors (Table 5).

Commento [A5]: Tabella nuova di analisi sintetica dei FdR di PNSLE

Table 5. Summary of the evidence of demographic and clinical items related to PNS involvement in SLE patients compared with SLE control groups.

PNSLE vs SLE control groups	Ferrara/Cagliari Lupus cohort	Beijing Lupus Cohort [6]	Hopkins Lupus Cohort [7]	Toronto Lupus Cohort [22]	Spain Cohort [23]
Mean age at SLE onset	45.9/37.1 (p<0.00001)	36.9/31,7 (p=0.007)	34.0/29.0 (p= 0.0031)	36.5/31.7 (p=0.0004)	37.3/30.8 (p=0.001)
Smoking habit (%)	9.5/19.2 (p=0.04)	-	-	-	-
Hypertension (%)	42.9/21.8 (p<0.00001)	-	-	-	-
Diabetes (%)	16.7/2.9 (p<0.00001)	-	8.5/9.1 (p=0.22)	-	-
Sjogren's syndrome (%)	20.0/8.6 (p=0.005)	-	-	-	-
aPLs (%)	47.1/36.6 (p=0.09)	-	-	22/20 (p=0.62)	-
Livedo reticularis (%)	15.2/5.8 (p=0.006)	-	-	-	-
Raynaud's phenomenon (%)	23.5/24.7 (p=0.83)	28.8/17.8 (p=0.063)	64.6/50.8 (p=0.012)	-	-
SDI (score)	2.2/0.9 (p<0.00001)	-	4.0/1.93 (p<0.0001)	1/0 (p=0.18)	-
SLEDAI (score)	6.9/2* (p<0.00001)	12.0/10.4 (p=0.02)	2.2/2.78** (p=0.013)	8/6 (p=0.01)	8/6 (p=0.006)
Photosensitivity (%)	27.1/39.5 (p=0.04)	-	-	-	48.4/41.5 (p=0.225)
Malar rash (%)	16.5/36.6 (p=0.01)	-	58.5/51.0 (p=0.14)	-	52.7/53.1 (p=0.947)
Kidney involvement (%)	15.3/15.6 (p=0.94)	53.4/64.4 (p=0.117)	-	41/46 (p=0.30)	24.7/38.4 (p=0.042)
Haematological involvement (%)	37.6/46.5 (p=0.16)	53.4/42.4 (p=0.125)	-	-	11.8/21.5 (p=0.034)

PNSLE, peripheral nervous system involvement in systemic lupus erythematosus; aPLs, anti-phospholipid antibodies; SDI, SLICC/ACR Damage Index; SLEDAI, SLE Disease Activity; 2K, Index 2000; SELENA, Safety of Estrogens in Lupus National Assessment.

**: SLEDAI-2K applied; **: SELENA-SLEDAI applied.*

If Oomatia et al. have reported an association with opportunistic infections and osteoporotic fractures [7], we investigated the association with general and specific risk factors, an aspect not covered by previous studies on PNS involvement in SLE. In our cohort, we find an association with Sjogren's syndrome, livedo reticularis, smoking habit and diabetes during PNS manifestations, but none of this sign has shown to have strong associations with events attributed to SLE, proving to be possible confounders. Only hypertension was confirmed as associated with SLE-related PNS involvement. Causes of the heterogeneity of acute and chronic immune neuropathies, despite significant advances in understanding pathogenesis, remain largely unresolved. Nevertheless, the vasculitic involvement of small vessels seems to be supported by the association of some definite conditions which may be associated with alterations in microcirculation (older age, smoking habits, hypertension) and the onset of an autoimmune disease like SLE acts a second hit to induce symptomatic peripheral manifestations.

In our study there was no significant association between lupus serology and peripheral manifestations. The role of autoantibodies in PNS involvement in SLE is still controversial; as contrasting data are present in literature; further studies are needed to clarify that.

In our retrospective cohort, patients were treated reflecting EULAR recommendations for the management of NPSLE [25]. Cranial neuropathies were managed with CS and immunosuppressants, while, in polyneuropathies, neurotrophic and neuroleptic agents were employed, as well, reserving PEX and IVIG for severe cases. The only controlled clinical trial designed in NPSLE patients [26] showed in severe peripheral neuropathies higher efficacy of intravenous CYC treatment compared with pulses of CS; however it included only 7 cases of polyneuropathy. In our cohort, most of the attributed events were treated with CS, while, among immunosuppressants used for severe polyneuropathies, MMF and CYC shared similar prescription rates. In our cases we confirmed the suggested and well-recognized treatment of mononeuritis (single or multiple) based on the use of CS, immunusuppressants and PEX/IVIG, reflecting a treatment strategy which aims to lower inflammation around the epineurium [27].

Regarding short-term outcome, our results depict a quite good prognosis for PNSLE. We found improvement in next-to 60% of polyneuropathies, while, among attributed ones, 18% worsened and a same percentage remained stable. Overall only 1 patient out of 14 mononeuropathies and 1 out of 26 cranial neuropathies got worse. The explanation of this favourable prognosis may lie in the presumptive inflammatory back-ground at the basis of these neurologic events that could have induced a more aggressive treatment behaviour.

Commento [A6]: Sezione nuova su terapia e outcome

A limitation of this study is its retrospective nature, which could have influenced the correct recognition of some PNS events such as small fibre neuropathy and autonomic neuropathy; secondly the evaluation of the evolution of the PNS events was only possible in a proportion of patients and has not been possible to assess the impact on quality of life perceived by the patient. Despite this, the use of stringent and validated criteria to determine whether peripheral manifestations were attributable to SLE is a strength of our study,

which provides a significant contribution to further knowledge of primary NPSLE, with special attention to peripheral pictures.

5.1 CONCLUSION

As we have recently reviewed [28] examining the peripheral involvement in SLE from epidemiological data to new pathogenetic and clinical evidence, to better characterize this complication it is still a priority in the approach to SLE. The goal of this study was to characterize clinical and demographic features related to PNSLE distinguishing between events deemed attributed or not to SLE. Higher age at SLE onset, higher disease activity and damage scores, hypertension were factors related to PNS events attributed to SLE, in line with previously reported literature date, while a global good outcome was enhanced for the majority of these manifestations. A careful clinical, instrumental and global assessment of the patient complaining PNS symptoms is mandatory to better and promptly recognize, attribute and manage such a neglect manifestation of the disease.

6.1 Key messages

Commento [A7]: Non servono per seminars

- Although to a lesser extent than CNS, PNS involvement is a ~~well recognized~~well-recognized but ~~also underestimated~~also underestimated manifestation of NPSLE.
- Polineuropathy is the most frequent PNS picture observed in SLE along with cranial neuropathies.
- Damage accrual, higher age, higher disease activity and concomitant hypertension are potential risk factors associated to PNS involvement attributed to SLE.

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