RHEUMATOLOGY

Rheumatology 2012;51:157–168
doi:10.1093/rheumatology/ker310
Advance Access publication 10 November 2011

Original article

Factors and comorbidities associated with first neuropsychiatric event in systemic lupus erythematosus: does a risk profile exist? A large multicentre retrospective cross-sectional study on 959 Italian patients

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Abstract

Objective. To analyse risk factors and comorbidities potentially associated with CNS involvement in a large cohort of Italian patients affected by SLE.

Methods. A number of generic (not strictly SLE related) and specific (disease related) risk factors to which all patients have been exposed in the span of 5 years before the first neuropsychiatric (NP) event or before the last available observation were checked for and their distribution was analysed in 959 SLE patients with and without NP involvement; all the first NP events that occurred in a time frame of 10 years were recorded and categorized as SLE related or SLE unrelated.

Results. Three hundred and twenty-six SLE patients with and 633 SLE patients without NP manifestations were included in the study. A total of 469 NP events were recorded. Headache (26.1%), cerebrovascular events (22.7%), mood disorders (8.9%), seizures (14.4%) and cognitive dysfunctions (9.5%) were the most frequent SLE-related NP events. More risk factors [mean 4.52 (2.44) *vs* 3.73 (2.01); $P < 0.0001$] were observed in patients with than without NP involvement. Overall, aPLs, LA and APS were factors more strongly associated with NP involvement.

Conclusions. In SLE, NP involvement and aPLs were confirmed as closely related. Furthermore, other modifiable generic risk factors, such as hypertension, carotid vasculopathy and dyslipidaemia, appeared to be related to the occurrence of cerebral vascular accident (CVA) and cognitive dysfunctions, suggesting the need for a more intensive preventive strategy to optimize the management of NP lupus.

Key words: systemic lupus erythematosus, neuropsychiatric lupus, neurological involvement, anti-phospholipid antibodies, anti-phospholipid syndrome, cerebrovascular disease

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Submitted 4 February 2011; revised version accepted 2 August 2011.

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Introduction

Neuropsychiatric (NP) involvement represents an important cause of morbidity and mortality in patients with SLE [1, 2]. Therefore, an attempt to depict a clinical and serological risk profile for this complication is of utmost importance in daily clinical practice to allow a better prevention strategy.

Since studies on this topic are scant, in 2001, on behalf of the Italian Society of Rheumatology, a local task force (Italian Study Group on NPSLE) was established to study NP involvement in SLE. Eight Italian centres with long-standing expertise in SLE endorsed this initiative and developed a preliminary research programme. The primary aim of the present study was to analyse—in a large retrospective multicentric cohort of Italian patients affected by SLE—whether a panel of factors and comorbidities associated with NP involvement could be identified.

Patients and methods

Patient recruitment

Eight rheumatologic centres in different geographical areas of Italy (Fig. 1) were invited to participate in the study and provide data from patients with confirmed NPSLE involvement, observed from 1 January 2000 to 31 December 2009. SLE patients without NP involvement served as the disease-control group and were randomly selected from local databases using an alphabetical list. The ratio of NPSLE:SLE patients was approximately 1:2. All patients satisfied the revised ACR criteria for SLE [3] and were regularly followed at each centre by the same team. CNS involvement, and clinical and laboratory data were assessed by retrieving information from clinical documentation (hospital records, patient folders and clinical charts). In each centre, patient consent was obtained before storing data, in an anonymous format, in a dedicated database (Filemaker Pro 8.0), according to the Declaration of Helsinki; the study was approved by the local ethical committee (Comitato Etico della Provincia di Ferrara).

FIG. 1 Centres involved in the study. [a]Coordinator centre; [b]two centres.

Assessment of NP involvement

The identification of NP involvement and its attribution to the underlying disease, allowing the diagnosis of NPSLE, was performed by the local attending team according to the formal case definition nomenclature of the 1999 ACR criteria, after a careful exclusion of any other known cause of NP symptoms [4]. Cognitive function was usually assessed using the test battery proposed by the 1999 ACR criteria; alternatively, in a minority of patients, cognitive performance was assessed using short instruments such as the six-item screener test, mini mental state examination, the 7-min screen or questions based on common clinical symptoms, as suggested and summarized by Mosca *et al*. [5]. The application of these instruments varied across different centres in line with local availability and customs.

For this study, only the first SLE-related NP event emerging from the patient's history was considered. A final decision about attribution of each NP event to SLE was reached through a clinical judgement. To homogenize the NP event attribution, all participants agreed to take into account four items based on the recent experience of the SLICC group [6]: (i) exclusion and association factors reported in the ACR nomenclature and case definitions for NPSLE were referred to as non-SLE factors; (ii) time at onset: events occurring before ($>$6 months) the onset of SLE were considered to be not attributable to SLE; (iii) the occurrence of a minor NP event, as defined by Ainiala *et al*. [7], scored against the attribution to SLE; and (iv) the presence of other information [e.g. neuroimaging, cerebrospinal fluid (CSF) analysis, response to treatment] scored in favour of the attribution to SLE. Taking into account all of these items, and according to the local expertise, each participant centre assigned to each NP event an arbitrary score, ranging from 0 to 3, where 0 = unrelated, 1 = low, 2 = moderate, 3 = high probability of being disease related. Patients who had at least one NP event with score $\geqslant$2 were considered to have NPSLE; patients without NP events or with NP events with a score $\leqslant$1 were assigned to the SLE control group.

The NP events were categorized as focal or diffuse, single or multiple, at onset or after onset (within 6 months before or after the SLE disease onset), typical (i.e. included in the 1999 ACR list) or aspecific (i.e. included in the list proposed by Ainiala *et al*. [7]).

In all patients, a large panel of factors and/or comorbidities, routine laboratory tests and immunological parameters, as detailed in Table 1, were recorded at the time of their first access. Risk factors were categorized

Table 1 List of evaluated generic and specific (or disease-related) risk factors, comorbidities and immunological parameters

Generic risk factors	Specific risk factors	Immunological parameters
Hypertension	aPLs	Total serum gammaglobulins
Diabetes	aCLs	C3
Obesity	anti-β2GP1 antibodies	C4
Dislipidaemia	LA	ANA
Smoking	APS	ENA (Ro/SSA, La/SSB,Sm, RNP)
Valvular heart disease	Anti-Ro/SSA antibodies	Anti-dsDNA antibodies
Chronic atrial fibrillation	Anti-Sm antibodies	
Carotid vasculopathy	Livedo reticularis	
Contraceptive intake	RP	
GC cumulative dose >10 g	Cutaneous vasculitis	
Cranial trauma	SS	
Familiarity for epilepsy		
Familiarity for psychiatric disorders		
Familiarity for headache		
High-homocystein mean plasma levels		

Generic factors: hypertension [8], obesity [9], diabetes [10], dyslipidaemia [11], smoking habit (>10 cigarettes/day), previous head injury (patient's history), valvular heart disease and/or chronic fibrillation (based on electrocardiogram, echocardiogram, anti-arrhythmic drugs intake, history), high-cumulative dose of glucocorticosteroids (GCs) (defined as >10 g), oral contraceptives (taken continuously for at least 2 years), familiarity for epilepsy, headache or psychiatric disorders (history), carotid vasculopathy (assessed by US duplex examination and defined in presence of atherosclerotic plaques or stenosis >50 %). Homocystein plasma levels, when available, were also checked (assuming upper cut-off values of 13 μmol/l in men and 10.1 μmol/l in women as used in the majority of Italian laboratories). Anti-P-ribosomal antibodies were available in <10% of patients and thus not considered for analysis. Specific factors: aPLs including aCLs and anti-β2GP1 antibodies (both IgG and IgM isotypes) [12], LA [13], APS [12], RP, livedo reticularis, cutaneous vasculitis (registered in clinical charts and ascertained by history or by direct medical observation), anti-Ro/SSA and anti-Sm antibodies (ascertained as above mentioned) and SS (defined according to the criteria proposed by the American–European Consensus Group [14]). In a limited subgroup of patients, titres of aCLs were also determined and classified as low or high (the cut-off deemed as significant was 40 GPL/MPL units). Immunological parameters: total serum gammaglobulins (g/l); C3 and C4 (g/l) detected by nephelometry (hypocomplementaemia was defined as C3 <0.8 and C4 <0.11 g/l); ANAs tested by IIF, using Hep2 cell substrate (positivity was defined as a titre $\geqslant 1:160$); antibodies to ENAs and anti-dsDNA were analysed by each centre by validated assays routinely used (usually ELISA method for ENA and *Crithidia luciliae* IIF test, with a cut-off titre of 1 : 40 for anti-dsDNA). CSF examination data were taken into account, when indicated, only for diagnostic purposes and for the final assessment of the neurological pictures.

as generic (not strictly SLE related) or specific (SLE related), and each of them has been defined according to the corresponding references [8–14] or otherwise specified. Among SLE patients with NP manifestations, only the factors and/or comorbidities detected before the onset of the first NP event and to which the patients had been exposed in the span of 5 years before were taken into account. The same kind of exposure was considered for patients without NP involvement, at the time of their last evaluation. CSF examination, neuroimaging (MRI and/or SPECT) and electroencephalograms (EEGs) were also taken into account for diagnostic assessment.

Disease activity was assessed by ECLAM [15] and the accumulated multisystem chronic damage was measured by the SLICC/ACR damage index [16]. An ECLAM index >2 was assumed to be indicative of an active disease. In patients with NP involvement, ECLAM and SLICC/ACR were measured close to the time of appearance of the first NP manifestation without taking into account the NP items. In patients without NP manifestations, these scores were calculated at the time of the last available observation.

Statistical analysis

Data processing and statistical analyses were performed using MedCalc for Windows, version 9.5.0.0 (MedCalc Software, Mariakerke, Belgium). Risk factors, comorbidities, clinical and seroimmunological items were evaluated as categorical dichotomous variables (present/absent), with the exception of continuous variables (age, disease duration, age at disease onset, cumulative number of risk factors, ECLAM and SLICC/ACR scores). The Student's *t*-test was applied for unpaired, continuous variables, and chi-square with Fisher's correction was applied when percentages were compared. Spearman's rank correlation coefficient test was applied to evaluate relationships between individual NP clinical pictures and risk factors. Multiple stepwise logistic regression analysis was used to verify whether different risk factors could

be independently related to NP involvement overall or to different typologies of NP events. Overall, according to Hanly *et al*. [17], a missing data rate of ~25% was assumed as acceptable for these analyses. The corresponding odds ratios (OR) with a 95% CI were calculated. A statistical significance was assumed for $P < 0.05$.

Results

Demographic and clinical data

A total of 959 patients were included for analysis. Three hundred and twenty-six patients (36 males and 290 females) satisfied the above-mentioned criteria for the diagnosis of NPSLE. The disease control group (SLE) included 633 patients (51 males and 582 females), of whom 490 (47 males and 437 females) were free from NP events and 143 (4 males and 139 females) had only SLE-unrelated NP events. During the study period, 469 NP events were recorded: 326 were judged as SLE related (score $\geqslant 2$) and 143 as unrelated to SLE (score $\leqslant 1$). Demographic, clinical and laboratory data are reported in Table 2.

Headache was the most frequent NP event recorded (31.5%), followed by cerebral vascular accidents (CVAs; 17.9%) (multifocal encephalopathy, 17; stroke, 32; transient ischaemic attack, 34; and sub-arachnoid haemorrhage, 1), mood disorders (11.9%), seizures (11.1%), cognitive dysfunctions (9.8%), anxiety (5.1%) and psychosis (4.0%) (Table 3). The average age of patients with a CVA was 44.6 (12.8) years.

Overall, a complete ACR battery test for cognitive impairment was performed in 121 (12.6%) out of 959 patients. All patients classified as suffering with cognitive dysfunction underwent NP evaluation; 70% of them had a complete ACR NP battery. The average age

Table 2 Demographic, clinical and laboratory data according to revised 1997 ACR classification criteria for SLE

	NPSLE ($n = 326$)	SLE ($n = 633$)	*P*-value
Sex, F : M	290 : 36	582 : 51	–
Age, mean (S.D.), years	46.8 (14.0)	46.2 (14.8)	0.544
Age at first NP event, mean (S.D.), years	38.0 (13.0)	–	–
Age at disease onset, mean (S.D.), years	33.3 (13)	34.9 (14.7)	0.097
Disease duration at first NP event, mean (S.D.), years	4.9 (6.7)	–	–
Disease duration, mean (S.D.), years	14.3 (9.1)	12.1 (7.9)	0.0001
Illiterate, *n* (%)	0[a] (0)	3[b] (0.6)	0.390
Primary school, *n* (%)	32[a] (11.8)	91[b] (17.6)	0.024
Secondary school, *n* (%)	103[a] (38.1)	163[b] (31.4)	0.044
High school, *n* (%)	111[a] (41.1)	203[b] (39.2)	0.617
Degree, *n* (%)	24[a] (8.9)	58[b] (11.2)	0.320
1997 ACR criteria, no. of patients (%)			
Malar rash	126/326 (38.6)	270/633 (42.6)	0.261
Discoid rash	28/326 (8.6)	46/633 (7.3)	0.557
Photosensibility	160/326 (49.1)	296/633 (46.7)	0.524
Mucosal ulcer	48/326 (14.7)	93/633 (14.7)	0.923
Arthritis	216/326 (66.2)	466/633 (73.6)	0.020
Serositis	83/326 (25.4)	174/633 (27.5)	0.536
Nephropathy	83/326 (25.4)	189/633 (29.8)	0.174
Autoimmune haemolytic anaemia	30/313 (9.6)	64/622 (10.3)	0.825
Leucopenia	122/324 (37.6)	245/ 629 (38.9)	0.748
Lymphocytopenia	89/298 (29.8)	148/625 (23.7)	0.055
Thrombocytopenia	83/324 (25.6)	95/630 (15.1)	0.0001
Anti-dsDNA	201/325 (61.8)	397/631 (62.9)	0.793
Anti-Sm	34/325 (10.4)	81/619 (13.1)	0.271
LA	125/318 (39.3)	127/609 (20.8)	<0.0001
aPL (aCL or anti-β2GP1)	178/324 (54.9)	235/629 (37.3)	<0.0001
ANA	323/326 (99.1)	627/633 (99.0)	0.842
Other seroimmunological abnormalities, no. of patients (%)			
Low C3	181/311 (58.2)	336/628 (53.5)	0.196
Low C4	176/312 (56.4)	321/626 (51.3)	0.160
Hypergammaglobulinaemia	80/300 (26.6)	204/624 (32.7)	0.070
Anti-Ro/SSA	105/323 (32.5)	256/625 (40.1)	0.026
Anti-La/SSB	38/320 (11.9)	112/622 (18.0)	0.019
Anti-RNP	45/318 (14.1)	113/615 (18.4)	0.116

[a]Item evaluable for 270 patients. [b]Item evaluable for 518 patients. NPSLE: patients with NP involvement; SLE: patients without (disease related) NP involvement.

TABLE 3 Frequency of individual NP events

NP event	Overall, *n* (%)	SLE related, *n* (%) (score ⩾ 2)	SLE unrelated, *n* (%) (score ⩽ 1)
Headache[a]	148 (31.5)	85 (26.1)	63 (44.0)
CVA	84 (17.9)	74 (22.7)	10 (7.0)
Mood disorders[a]	56 (11.9)	29 (8.9)	27 (18.9)
Seizures	52 (11.1)	47 (14.4)	5 (3.5)
Cognitive dysfunctions[a]	46 (9.8)	31 (9.5)	15 (10.5)
Anxiety[a]	24 (5.1)	4 (1.2)	20 (14.0)
Psychosis	19 (4.0)	18 (5.5)	1 (0.7)
Dmyelinating disease	9 (1.9)	9 (2.7)	– (0)
Movement disorders	9 (1.9)	8 (2.4)	1 (0.7)
Optic neuropathy	8 (1.7)	8 (2.4)	– (0)
Acute confusional state	7 (1.5)	6 (1.8)	1 (0.7)
Myelopathy	4 (0.8)	4 (1.2)	– (0)
Aseptic meningitis	3 (0.6)	3 (0.9)	– (0)
Total	469 (100)	326 (100)	143 (100)

Score: 0 = unrelated; 1 = low; 2 = moderate; 3 = high probability to be disease-related. [a]NP events deemed as aspecific and included in the list proposed by Ainiala *et al*. [5]: headache, mood disorders, anxiety and mild cognitive dysfunctions.

of patients with cognitive dysfunction was 42.7 (14.7) years.

Both cognitive dysfunction and depression (or mood disorder) were classified according to the 1999 ACR nomenclature and definition for NP involvement in SLE. All patients included in the study and manifesting such disorders underwent a psychiatric consultation and an NP evaluation to define the type of NP event. For the purposes of the study, patients with both cognitive dysfunction and depression were classified as having the first event in the order of appearance.

All patients with cognitive dysfunction had a moderate to severe deficit with impairment in everyday functioning. Cognitive dysfunction could be limited to a profound disturbance in a single cognitive domain, or it could involve multiple cognitive deficits affecting at least two domains according to ACR classification criteria. Among the 326 SLE-related NP events, 156 (47.8%) were single and 170 (52.2%) multiple; 115 (35.3%) were focal and 211 (64.7%) diffuse; and 208 (63.8%) were typical and 118 (36.2%) aspecific. In one-third (33.1%) of cases, an NP event foreshadowed the manifestation of SLE.

Distribution of risk factors and associated comorbidities

SLE patients with and without NP involvement

At univariate analysis, generic and/or specific risk factors were more frequently observed in NPSLE (78.5%) than in SLE (66.7%) ($P = 0.0002$). NPSLE patients had a higher cumulative average number of associated factors and comorbidities than SLE patients [4.52 (2.44) *vs* 3.73 (2.01); $P < 0.0001$]. APS ($P < 0.0001$), aPL ($P < 0.0001$), aCL ($P < 0.0001$), LA ($P < 0.0001$), anti-β2GP1 ($P = 0.008$) and their different combinations were more frequently detected in NPSLE than in SLE patients, while anti-Ro/SSA antibodies were more frequent in SLE. Smoking ($P = 0.081$), cumulative dose of glucocorticosteroids (GCs) >10 g ($P = 0.0001$) and a history of psychiatric disorders ($P = 0.086$) were the generic risk factors more frequently observed in NPSLE than in SLE. In a smaller subgroup of patients, homocystein plasma levels were also available and the percentages of patients with elevated values proved to be similar in both groups (Table 4).

In multiple stepwise logistic regression analysis, APS (OR = 3.134; 95% CI 1.858, 5.287) and the simultaneous presence of both aCLs and LA (OR = 2.042; 95% CI 1.236, 3.371) proved to be independently related to NP involvement, while a lower cumulative dose of GC (OR = 0.514; 95% CI 0.350, 0.753) and age at disease onset (OR = 0.969; 95% CI 0.956, 0.983) were inversely related to NP involvement (see Appendix 1, available as supplementary data at *Rheumatology* Online).

Patients with and without NP events

The analysis stratified for NP events confirmed the above reported data with regard to specific risk factor distribution. Among generic risk factors, carotid vasculopathy was significantly more common in patients with SLE-unrelated NP events when compared with those without NP events ($P = 0.019$), but not when compared with patients with SLE-related NP events ($P = 0.551$); the percentage of patients with a cumulative dose of GC >10 g was higher in patients with SLE-related NP events than in patients with SLE-unrelated NP events ($P = 0.0001$) and those without NP events ($P = 0.021$). Finally, a history of psychiatric disorders was equally distributed in both SLE-related and -unrelated NP events ($P = 0.992$), but was more frequently detected among patients with

TABLE 4 Distribution of generic and specific or disease-related risk factors between patients with and without NPSLE

Risk factors (number and type)	NPSLE ($n = 326$)	SLE ($n = 633$)	*P*-value
Number of patients with RF (generic + specific), *n* (%)	256 (78.5)	422 (66.7)	0.0002
Number of RF (generic + specific)/patient, mean (S.D.)	4.52 (2.44)	3.73 (2.01)	<0.0001
Number of patients with specific RF, *n* (%)	297 (91.1)	546 (86.2)	0.036
Number of specific RF/patient, mean (S.D.)	2.68 (1.71)	2.13 (1.49)	<0.0001
Patients without specific RF, *n* (%)	29 (8.9)	87 (13.7)	0.039
Patients with one specific RF, *n* (%)	59 (18.1)	148 (23.4)	0.070
Patients with two specific RF, *n* (%)	73 (22.4)	163 (25.7)	0.296
Patients with three specific RF, *n* (%)	65 (19.9)	128 (20.2)	0.980
Patients with three or more specific RF, *n* (%)	100 (30.7)	107 (16.9)	<0.0001
Number of patients with generic RF, *n* (%)	280 (85.9)	490 (77.4)	0.005
Number of generic RF/patient, mean (S.D.)	1.83 (1.37)	1.60 (1.32)	0.0118
Patients without generic RF, *n* (%)	46 (14.1)	143 (22.6)	0.0023
Patients with one generic RF, *n* (%)	116 (35.6)	182 (28.7)	0.034
Patients with two generic RF, *n* (%)	70 (21.5)	167 (26.4)	0.112
Patients with three generic RF, *n* (%)	54 (16.6)	92 (14.5)	0.445
Patients with three or more generic RF, *n* (%)	40 (12.3)	49 (7.7)	0.027
Specific RF, no. of patients (%)			
aPL *(at least one)*	206/306 (67.3)	270/583 (46.3)	<0.0001
aCL + anti-β2GP1 + LA	40/275 (14.5)	39/536 (7.3)	0.0016
aCL + LA	97/318 (30.5)	82/609 (13.5)	<0.0001
Anti-β2GP1 + LA	40/275 (14.5)	45/536 (8.4)	0.010
aCL + anti-β2GP1	60/275 (21.8)	63/536 (12.1)	0.0004
aCL	178/324 (54.9)	218/628 (34.7)	<0.0001
anti-β2GP1	60/275 (21.8)	76/535 (14.2)	0.0082
LA	125/318 (39.3)	127/609 (20.8)	<0.0001
APS	104/324 (32.1)	59/629 (9.4)	<0.0001
Anti Ro/SSA antibodies	104/323 (32.2)	256/625 (40.9)	0.010
Anti-Sm antibodies	33/325 (10.1)	74/619 (11.9)	0.470
Livedo reticularis	60/325 (18.4)	98/612 (16.0)	0.399
RP	121/326 (37.1)	242/622 (38.9)	0.637
Cutaneous vasculitis	52/323 (16.1)	100/625 (16.0)	0.957
SS	42/326 (12.9)	103/619 (16.6)	0.159
Generic RF, no. of patients (%)			
Hypertension	86/326 (26.4)	193/627 (30.8)	0.180
Diabetes	9/326 (2.7)	16/631 (2.5)	0.975
Obesity	32/324 (9.9)	45/621 (7.2)	0.188
Dislipidaemia	82/323 (25.4)	164/623 (26.3)	0.825
Smoking	62/309 (20.1)	94/614 (15.3)	0.081
Valvular heart disease	41/318 (12.9)	61/621 (9.8)	0.182
Chronic atrial fibrillation	7/323 (2.1)	8/628 (1.3)	0.506
Carotid vasculopathy	15/274 (5.5)	19/512 (3.7)	0.318
Contraceptive intake (only females)	25/274 (9.1)	64/526 (12.2)	0.228
Steroid cumulative dose >10 g[a]	126/201 (62.7)	268/583 (45.9)	0.0001
Cranial trauma	11/323 (3.4)	12/587 (2.0)	0.283
Familiarity for epilepsy	5/311 (1.6)	6/550 (1.1)	0.755
Familiarity for psychiatric disorders	17/306 (5.5)	16/549 (2.9)	0.086
Familiarity for headache	17/307 (5.5)	27/534 (5.0)	0.878
High homocystein mean plasma levels[b]	30/167 (17.9)	24/196 (12.2)	0.169

[a]For this item, patients with NP events at disease onset were not taken into account. [b]Homocystein plasma levels were available in a limited number of patients and therefore this item was not included in the stepwise logistic regression analysis. RF: risk factors.

SLE-related NP events when they were compared with those without NP events ($P = 0.032$) (see Appendix 2, available as supplementary data at *Rheumatology* Online).

At stepwise logistic regression analysis, again, aCLs (OR = 1.855; 95% CI 1.113, 3.092) and APS (OR = 3.389; 95% CI 1.970, 5.829) proved to be independently related, while lower cumulative dose of GC (OR = 0.606; 95% CI 0.413, 0.890) and age at disease onset (OR = 0.966; 95% CI 0.952, 0.980) were retained in this model as independently, but inversely, related to the occurrence of SLE-related NP events (see Appendix 3, available as supplementary data at *Rheumatology* Online).

Different individual SLE-related NP events

Headache, CVA, seizures, cognitive dysfunctions, mood disorders and psychosis were the most frequently observed SLE-related NP events. The presence of aPLs (at least one out of aCL, LA or anti-β2GP1) was the most common specific risk factor associated with these NP events, with a clear prevalence for aCLs, except for psychosis, where LA positivity was dominant (60%). Among the generic risk factor, cumulative dosage of GC was the most prevalent risk factor, with the exception of psychosis, where smoking habit emerged as the most frequent (35.7%) (see Appendix 4, available as supplementary data at *Rheumatology* Online). No differences were observed between the two groups for titres and isotypes of aCLs (data not shown).

To check correlations between individual NP events and risk factors, the Spearman's rank correlation coefficient was calculated. Briefly, among specific risk factors, CVA was significantly related to LA ($P = 0.001$), APS ($P < 0.001$), cutaneous vasculitis ($P = 0.022$), cumulative number of risk factors ($P = 0.004$) and a higher mean age at disease onset ($P = 0.008$); seizures were related only to livedo reticularis ($P = 0.024$), and negatively associated with anti-Ro/SSA antibodies ($P = 0.026$) and age at disease onset ($P = 0.044$); cognitive dysfunctions were related only to cutaneous vasculitis ($P = 0.028$); mood disorders were associated with concomitant SS ($P = 0.013$); and headache was negatively associated with cutaneous vasculitis ($P = 0.023$). No significant associations were found for psychosis. Among generic risk factors, CVA was related to hypertension ($P = 0.042$), cumulative dose of GC ($P = 0.045$), carotid vasculopathy ($P = 0.006$), higher age at disease onset ($P = 0.008$) and the cumulative number of risk factors ($P = 0.016$); seizures were associated with chronic atrial fibrillation ($P = 0.025$), heart valvular disease ($P = 0.001$) and a history of epilepsy ($P = 0.002$); cognitive dysfunctions were related to hypertension ($P = 0.008$), dyslipidaemia ($P = 0.018$) and the cumulative number of risk factors ($P = 0.020$); mood disorders were related only to familiarity for psychiatric disorders ($P = 0.028$), while psychosis was associated with contraceptive intake ($P < 0.001$) and negatively correlated with a cumulative dose of GC$>$10 g ($P = 0.027$); headache was related only to female sex ($P = 0.030$) and negatively associated with hypertension ($P = 0.034$) and carotid vasculopathy ($P = 0.023$). No correlation emerged between each NP event and disease duration. In a subgroup of 167 patients, hyperhomocysteinaemia was associated with seizures ($P = 0.065$) and cognitive dysfunctions ($P = 0.001$), but was negatively related to headache ($P = 0.024$) (see Appendix 5, available as supplementary data at *Rheumatology* Online).

Different typologies of SLE-related NP events

Typical vs aspecific. Cutaneous vasculitis was more frequent among patients with typical events, while SS was more frequent in patients with aspecific events. Overall, aPLs were more frequently detected in patients with typical NP events, but only when their different combinations included anti-β2Gp1 antibody positivity. Among generic risk factors, hypertension ($P = 0.046$) and carotid vasculopathy ($P = 0.008$) were more frequent in patients with typical than in those with aspecific NP events. In the subgroup of patients with available homocystein plasma levels, hyperhomocysteinaemia ($P = 0{,}026$) was more frequent in patients with typical NP events.

Focal vs diffuse. LA ($P = 0.047$), the simultaneous positivity of aCLs and LA ($P = 0.008$), history of APS ($P = 0.006$) and livedo reticularis ($P = 0.028$) were significantly associated with focal events. Among generic risk factors, carotid vasculopathy was more frequently detected in patients with focal NP events ($P = 0.038$), while history of contraceptive intake was more frequent in patients with a diffuse pattern of NP involvement.

Single vs multiple. No significant differences were observed in specific risk factor distribution. Among generic risk factors, smoking habit ($P = 0.014$) and cumulative dose of GC >10 g ($P = 0{,}029$) were more frequent among patients with multiple NP events; hyperhomocysteinaemia ($P = 0.008$) was more frequently recorded in patients with multiple events.

At onset vs after disease onset. Among specific risk factors, a higher prevalence of aPLs ($P < 0.0001$) emerged in those patients with NP events that appeared after SLE onset. Among generic risk factors, a history of headaches was more frequent in patients with NP manifestation at disease onset ($P = 0.030$); a cumulative dosage of GC >10 g was more frequent in patients with NP events that occurred after disease onset ($P = 0.0003$) (see Appendix 6, available as supplementary data at *Rheumatology* Online).

In a stepwise logistic regression analysis, four different models were tested: β2GP1 antibodies positivity (OR = 2.517; 95% CI 1.222, 5.185) was the only specific risk factor retained as independently correlated with the occurrence of typical NP events (Model A). Cumulative dose of GC (OR = 0.376; 95% CI 0.201, 0.704) was independently and inversely related to the occurrence of multiple SLE-related NP events (Model B). Livedo reticularis (OR = 4.055; 95% CI 1.708, 9.626) was independently related to a focal pattern of NP involvement (Model C). Finally, age at disease onset was independently related to onset appearance of NP manifestations (OR = 1.037; 95% CI 1.017, 1.058) (Model D) (see Appendix 7, available as supplementary data at *Rheumatology* Online).

Relationship with disease activity and cumulative damage

The average ECLAM score was higher in NPSLE than in SLE patients [3.72 (2.38) *vs* 1.42 (1.61); $P < 0.0001$] and, more frequently, NPSLE patients had active disease (ECLAM > 2) (68.7 *vs* 19.1%). The average SLICC/ACR damage index was compared, excluding from the analysis those patient with NP involvement at onset; again, NPSLE patients had higher SLICC/ACR scores than SLE patients

($P = 0.021$) (Fig. 2 and Appendix 8, available as supplementary data at *Rheumatology* Online).

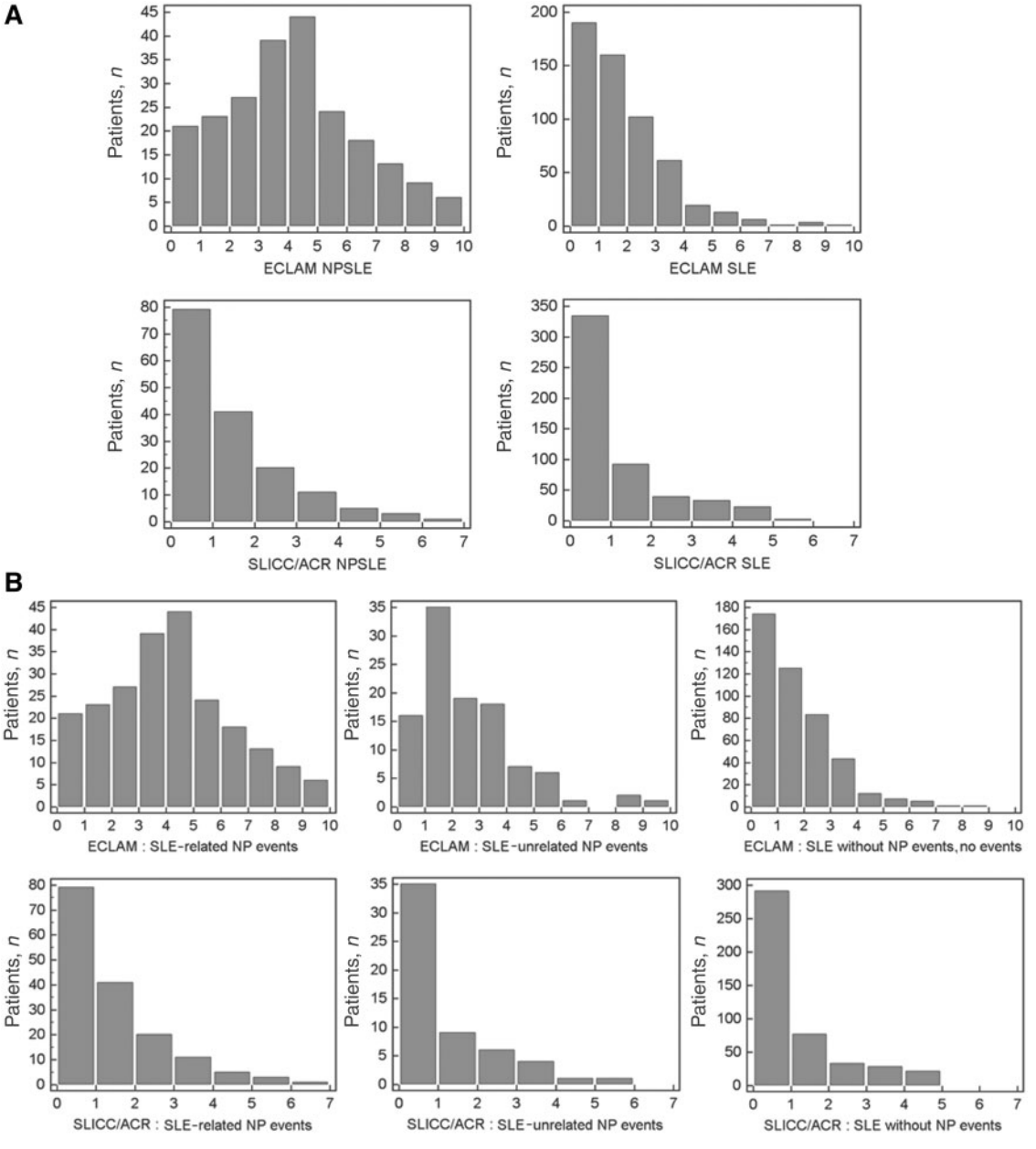
Treatment attitude

The treatment attitude recorded at SLE disease onset was compared between NPSLE and SLE patients, excluding from analysis those patients with NP onset. Although not significant, the only difference that was recorded refers to a less-frequent use of high-dose CYC i.v. boli administration in patients who, at follow-up, developed NP involvement ($P = 0.055$) (see Appendix 9, available as supplementary data at *Rheumatology* Online).

Discussion

Three major SLE-related risk factors have been reported as consistently linked to NPSLE [18]. First, generalized SLE disease activity and cumulative damage have been

FIG. 2 Relationships between disease activity, cumulative damage, NP involvement and NP events. (**A**) Disease activity (ECLAM) and cumulative damage (SLICC/ACR) profile, stratified in SLE patients with and without NP involvement. (**B**) Disease activity (ECLAM) and cumulative damage (SLICC/ACR) profile split for patients with SLE-related, SLE-unrelated and without NP events. SLICC/ACR distribution plot histograms were calculated excluding patients with NP events at onset.



shown to be associated with an increased risk of seizures and severe cognitive dysfunction [19]. Secondly, aPLs (aCL, anti-β2GP1, LA) have been associated with CVA, seizures, myelopathy, chorea and moderate to severe cognitive dysfunction [20–27]. Thirdly, previous or concurrent major NPSLE events, particularly stroke and seizures, have been shown to predict similar, future NP events [28, 29]. Other, non-SLE-related risk factors such as increasing age, hypertension and other traditional cerebrovascular disease risk factors have been associated with cognitive dysfunction and cerebrovascular disease [18].

In our study, the distribution of a consistent number of risk factors and comorbidities was analysed by comparing history, clinical and seroimmunological features, and therapeutic attitudes in a large multicentric cohort of SLE patients. Headache, cerebrovascular disease, seizures and cognitive dysfunctions were the individual NP events most frequently recorded. The comparison of patients with and without NP involvement showed that they differed for more frequent joint involvement, anti-Ro/SSA and anti-La/SSB positivity in SLE patients, while thrombocytopenia, LA and aCLs were more common among NPSLE patients. Altogether, these data agree with what has been previously reported by others [25–27, 30–32].

Overall, the strongest specific (disease-related) risk factor associated with NP involvement was the presence of aPLs (and their different combinations), with or without a history of APS. aPLs were more frequently observed among all the categories of individual NP events, although they were significantly associated only with CVA. A dominant role of aPLs and APS in NPSLE patients (especially those with a focal pattern of NP involvement) is well known [21, 33, 34]. In a prospective study, Karassa *et al*. [35] observed that aPLs, previous history of NP events and livedo reticularis were significantly correlated with the progression of neurological damage. In a retrospective study, quite similar to ours, but performed in a smaller group of patients, the NP involvement was found to be significantly associated with aPLs and some of their related clinical features [30]. In our study, livedo reticularis and cutaneous vasculitis have been found to be associated with CVA, seizures and cognitive dysfunction. These findings support a relevant role of aPLs in the pathophysiology of some NP pictures mediated by ischaemic/occlusive events or perfusion disturbances, even though aPLs may also directly interact with endothelium and neuronal tissue membrane components, impairing their integrity and functionality [36, 37]. This explains their potential role in other non-focal NP clinical pictures (i.e. psychosis, headache and mood disorders), where the pure ischaemic pathway seems less reasonable.

Other factors identified as related to NP involvement have been investigated and proposed by others, such as low levels of C3 and C4, high disease activity, Caucasian ethnicity, presence of anti-Ro/SSA antibodies, vasculitis, nephritis, and anti-dsDNA, LA and anti-Sm antibodies, but with conflicting results [30, 35, 38–40].

In our cohort, apart from aPLs, no other seroimmunological parameters proved to be associated with NP involvement. Interestingly, anti-Ro/SSA antibodies were more frequently detected among patients without NP manifestations. We do not have a clear explanation for this apparent protective effect of anti-Ro/SSA antibodies. In an SLE-related disease, such as SS, anti-Ro/SSA antibodies were found to be associated with more severe CNS disease and small-vessel vasculopathy [41, 42], but this finding has not been confirmed by us or others [43–44]. In SLE, the association between anti-Ro/SSA antibodies and skin involvement, rather than with SS, may partially account for a lack of correlation with NP involvement.

No generic risk factor was associated with the occurrence of NP events, with the exception of a history of psychiatric disorders and cumulative dose of GC, which were more frequently associated with patients with NP events compared with those without. A higher cumulative dose of GC was most frequently found in some of the individual SLE-related NP events (i.e. CVA, headache, seizures, cognitive dysfunctions, mood disorders, but not psychosis), whereas a significant correlation was found only for CVA. This last finding fits well with the suggested role of GC as a potentially independent risk factor related to an accelerated atherosclerosis [45]. Higher disease activity profile in patients with NP involvement, as reported by Karassa *et al*. [35], may further explain this finding.

Among some modifiable generic risk factors, hypertension was found to be negatively related to NP involvement. This unexpected result may be explained by taking into account the rigorous criteria for attribution of NP events that we have applied. However, when data were analysed considering individual NP manifestations, hypertension emerged as related to CVA and, along with dyslipidaemia and cutaneous vasculitis, to cognitive dysfunctions.

A correlation between cognitive impairment, aPLs, arterial hypertension and RP has been reported [19, 46]. In our study, we did not find this association, but this result should be regarded cautiously since it could have been underestimated due to the relatively low number of patients formally tested for cognitive dysfunction. The low prevalence of this pattern of NP involvement is probably due to the fact that, in our cohort, we considered only the first NP event.

Use of GC, diabetes, depression, disease-related cumulative damage and low levels of education have also been correlated with cognitive dysfunctions [21, 24, 47]. In our cohort, a lower percentage of high school-level education was found among patients with cognitive dysfunction (29.6%) than in patients without (39.2%), but the difference was not significant.

Our study has some limitations. First of all, it is retrospective and the factors that we have identified should be more appropriately considered as associated factors rather than true risk factors. Another limitation is that our results apply only to the first NP event in the clinical

history of the patients, thereby preventing us from ascertaining the role of an antecedent NP event as a risk factor *per se* for further NP events, as previously reported by others [35]. Furthermore, we did not extensively evaluate all patients for cognitive function, and conclusions about relationships between cognitive impairment and the examined risk factors should be made cautiously. Finally, our study applies only to CNS involvement.

Despite these limitations, this study provided some important confirmatory data in one of the largest cohorts of SLE patients studied to date, especially about the role of aPLs in NP involvement. In general, aPLs, higher disease activity, higher steroid intake and a younger age at disease onset (except for CVA) were associated with NP involvement. Other associations need further confirmations in properly designed prospective studies. A potential role played by certain modifiable cardiovascular generic risk factors, such as hypertension and carotid vasculopathy in CVA or hypertension and dyslipidaemia in cognitive impairment, suggests a more careful preventive approach to optimize the management of NPSLE. For the future, the study of risk factors associated with the time to develop an NP event might be even more informative from a clinical point of view. However, this issue was beyond the aims of our retrospective study and might only be assessed by an expressly designed prospective study.

If a risk profile is prospectively clearly defined and proven, it might translate into clinical and speculative information about the development of new preventive strategies for patients classified at higher risk of NP events (e.g. better control of risk factors and intensive follow-up) and properly designed studies on the potential effect of specific drugs (e.g. statin) in preventing NPSLE.

Rheumatology key messages

- aPLs are the most relevant risk factor for NPSLE.
- Modifiable risk factors such as hypertension, carotid vasculopathy and dyslipidaemia are related to CVA and cognitive dysfunctions.

Acknowledgements

Funding: This study has been supported with a grant provided by the Italian Society of Rheumatology.

Disclosure statement: M.R.T. has received research funding from Sanofi-Aventis and compensation for consultancy from Biogen, Sanofi-Aventis, Merk serono, Novartis and Sanofi-Aventis. All other authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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