Neuropsychiatric Manifestations in Systemic Lupus Erythematosus: Prevalence and Association with Antiphospholipid Antibodies

GIOVANNI SANNA, MARIA L. BERTOLACCINI, MARIA J. CUADRADO, HANA LAING, MUNTHER A. KHAMASHTA, ALESSANDRO MATHIEU, and GRAHAM R.V. HUGHES

ABSTRACT. ***Objective.*** To apply the new American College of Rheumatology nomenclature for neuropsychiatric systemic lupus erythematosus (NPSLE), determine the prevalence of the different neuropsychiatric (NP) syndromes, and evaluate which of these manifestations correlates with the presence of antiphospholipid antibodies (aPL).

Methods. Clinical, serological, and imaging data of 323 consecutive patients with SLE were retrospectively reviewed. Neuropsychometric testing was applied by a neuropsychologist. Univariate and multivariate statistical analyses were applied to evaluate the association bewteen NP manifestations, magnetic resonance imaging (MRI) abnormalities, and aPL.

Results. In total, 185 patients (57.3%) had NP manifestations at any time during followup. Headache was the most frequent manifestation, present in 78 patients (24%). Cerebrovascular disease (CVD) was diagnosed in 47/323 patients (14.5%), with a total of 57 events. Mood disorders were found in 54 (16.7%), cognitive disorders in 35 (10.8%), and seizures in 27 patients (8.3%). Psychosis was diagnosed in 25 (7.7%), anxiety disorder in 24 (3.7%), and acute confusional state in 12 patients (3.7%). Less common manifestations were polyneuropathy, mononeuritis, myasthenia gravis, cranial neuropathy, myelopathy, chorea, demyelinating disease, and Guillain-Barré syndrome. The presence of aPL was associated with NP manifestations ($p < 0.001$). Multivariate analysis showed that aPL were independently associated with CVD (OR 6.17, 95% CI 2.94–12.9, $p = 0.001$), headache (OR 2.04, 95% CI 1.17–3.55, $p = 0.01$), and seizures (OR 2.89, 95% CI 1.18–7.10, $p = 0.02$). The presence of lupus anticoagulant (LAC) was independently associated with white matter hyperintensity lesions on MRI (OR 3.0, 95% CI 1.12–8.05, $p = 0.027$).

Conclusion. The new ACR criteria for NPSLE are useful to define NP manifestations in SLE with accuracy. NP manifestations are significantly associated with aPL. CVD, headache, and seizures were independently associated with these antibodies. (J Rheumatol 2003;30:985–92)

Key Indexing Terms:
ANTICARDIOLIPIN LUPUS ANTICOAGULANT CEREBROVASCULAR DISEASE
EPILEPSY HEADACHE MAGNETIC RESONANCE IMAGING

Nervous system involvement in patients with systemic lupus erythematosus (SLE) encompasses a wide spectrum of neurologic and psychiatric features. Clinical manifestations range from overt psychiatric or neurological dysfunction, such as psychosis or stroke, to more subtle and subclinical abnormalities in neurocognitive function, such as memory, intellect, and learning[1]. The frequency of neuropsychiatric (NP) manifestations in SLE patients has been estimated at around 25% to 70%[2], with a range of variability mainly due to the lack of standardized definitions and nomenclature until 1999, when the American College of Rheumatology (ACR) Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature developed case definitions for 19 different neuropsychiatric syndromes observed in SLE[3].

The association between antiphospholipid antibodies (aPL) and cerebral ischemia is well established, and thrombosis associated with these antibodies is thought to be the mechanism involved. The association between cerebrovascular disease (CVD) and aPL was reported in the original description of the antiphospholipid syndrome (APS)[4] and later confirmed by many other authors[5-7].

However, the association between other NP manifestations and the presence of aPL is still ill-defined. A number of other NP manifestations, including headache, seizures,

From the Lupus Research Unit, The Rayne Institute, and the Department of Psychology, St. Thomas' Hospital, London, UK; and the Centre for Systemic Rheumatic Diseases, Department of Medical Sciences, University of Cagliari, Cagliari, Italy.

Supported in part by Lupus UK.

G. Sanna, MD, PhD, Lupus Research Unit, The Rayne Institute, Second Chair of Rheumatology, Centre for Systemic Rheumatic Diseases, University of Cagliari; M.L. Bertolaccini, MD; M.J. Cuadrado, MD, PhD; M.A. Khamashta, MD, FRCP, PhD; G.R.V. Hughes, MD, FRCP, Lupus Research Unit, The Rayne Institute; H. Laing, PhD, Department of Psychology, St. Thomas' Hospital; A. Mathieu, MD, Second Chair of Rheumatology, Centre for Systemic Rheumatic Diseases, University of Cagliari.

Address reprint requests to Dr. M.A. Khamashta, Lupus Research Unit, The Rayne Institute, St. Thomas' Hospital, London SE1 7EH, UK. E-mail: munther.khamashta@kcl.ac.uk

Submitted April 26, 2002; revision accepted November 27, 2002.

chorea, cognitive dysfunction, psychosis, depression, and multiple sclerosis-like disease has been associated with aPL[8]. Many of these manifestations cannot be explained solely by hypercoagulability, and it is possible that some of them (e.g., chorea, headache) may have more complex causes.

We investigated the prevalence of NP manifestations in SLE applying the 1999 ACR criteria for the classification of NPSLE in a large cohort of patients attending the lupus clinic at St. Thomas' Hospital, and evaluated whether these manifestations correlate with the presence of aPL.

MATERIALS AND METHODS

Patients. This study included 349 consecutive patients attending our lupus clinic in the 8 months between September 1999 and April 2000. All of them fulfilled at least 4 of the ACR revised criteria for the classification of SLE[9]. Twenty-six patients were excluded because of insufficient information. From the remaining 323 patients, 265 (82%) were interviewed and examined for more precise data. We present data for 323 patients (308 female, mean age 41.9 ± 12.6 yrs, mean disease duration 10.9 ± 7.9 yrs, mean age at onset of disease 30.8 ± 11.3 yrs). Sixty-eight out of 323 patients (21%) fulfilled Sapporo criteria for the classification of definite APS[10].

Methods. Clinical details were reviewed retrospectively applying a specific 2-page questionnaire prepared with particular attention to history and objectively documented NP manifestations present at any time during followup (from the date of SLE diagnosis).

The first part of the protocol included demographic data, medical history, SLE classification criteria and other manifestations of the disease, current and previous treatment, and serologic and imaging results. The second part of the protocol was focused on NP manifestations. The definitions of the 19 syndromes provided by the panel of experts of the ACR Ad Hoc Committee, along with inclusion and exclusion criteria, were applied to classify the patients with NP manifestations in our series.

Patients with history, subjective complaints, or suspected cognitive dysfunction at study entry underwent a neuropsychometric evaluation to provide objectively verifiable information. As suggested by the ACR[3], we applied neuropsychological testing. A trained neuropsychologist applied the One-Hour Neuropsychological Battery for SLE proposed by the ACR, consisting of the following tests: Trail Making Test (Parts A and B), Wechsler Adult Intelligence Scale III Letter-Number Sequencing, Wechsler Memory Scale-Revised – Logical Memory, Rey-Osterrieth Complex Figure Test (copy, immediate recall, and delayed recall), Controlled Oral Word Association Test (COWAT/FAS), Animal Naming Test, Digit Symbol Substitution Test, and Stroop Color and Word Test in order to document deficits in any or all of the following cognitive domains: Simple attention, Complex attention/Executive functions, Memory, Visual-spatial processing, Language, Psychomotor speed, and Motor function. Premorbid IQ was estimated by means of the National Adult Reading Test[11].

Blood collection. Venous blood was collected in precooled tubes containing 0.105 M sodium citrate and centrifuged immediately at 4°C. Plasma samples were platelet-depleted by filtration then stored at –70°C until used.

Anticardiolipin antibodies (aCL). The aCL ELISA was performed according to the standardized technique[12].

Lupus anticoagulant (LAC). As many of the patients were taking warfarin at the time of the study, data regarding LAC were those in the patients' clinical records before starting anticoagulation therapy. LAC was screened using activated partial thromboplastin time and dilute Russell's viper venom time, and confirmed according to the guidelines recommended by the Subcommittee on Lupus Anticoagulant/Phospholipid Dependent Antibodies[13].

Other autoantibodies. Antinuclear antibodies (ANA) were determined by indirect immunofluorescence on HEp-2 cell slides. Anti-dsDNA were studied on *Crithidia luciliae* slides and by Farr assay (Orthoclinical Diagnostics Amersham, Buckinghamshire, UK). Antibodies against extractable nuclear antigens (anti-ENA) were tested by counterimmunoelectrophoresis.

Brain magnetic resonance. One hundred five of the 323 patients (32.5%) (102 female, mean age 43.1 ± 12.6 yrs, mean disease duration 11.5 ± 7.8 yrs) underwent brain magnetic resonance imaging (MRI) at any time of the disease during followup. Brain MRI was performed by standard spin-echo technique.

Statistical analyses. Data were stored in a database specifically designed using the program Microsoft Access 97. Statistical analysis was performed using SPSS v. 7.5 for Windows. For comparison of categorical data, chi-square test with Yates' continuity correction was applied. Fisher exact test was used when the expected frequency was small. Student's t test was used for continuous data with a normal distribution, otherwise Mann-Whitney U test was applied when appropriate. Univariate analysis was done using the chi-square test or Fisher exact test, while logistic regression was used for the multivariate analysis. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. Statistical significance was considered with 2-tailed $p < 0.05$.

RESULTS

Prevalence of NP manifestations. Demographic data on patients with SLE is depicted in Table 1. Both groups of patients had a comparable age and age at onset of SLE. Patients with NP manifestations were more likely to have a longer disease duration than those without NP manifestations (11.9 ± 8.1 vs 9.59 ± 7.5 yrs; $p = 0.009$).

Table 2 shows prevalence and type of the different NP syndromes in our SLE patients. Overall, 185/323 patients (57.3%) had NP manifestations at any time during followup, 94 (51%) presenting one syndrome and 91 (49%) more than one, ranging from 2 to 6 syndromes. Eighty-three of 323 patients (25.7%) had NP manifestations at the time of the visit.

Neuropsychometric testing was offered to 57/323 patients (17.6%) with clinical history suggestive of cognitive impairment; 10 of them declined to undergo the neuropsychometric assessment; 47 consented to be formally assessed and 35 were diagnosed with cognitive impairment (10.8% of the study population). From these, 31 also had other NP manifestations. Table 3 summarizes other NP manifestations present in patients with cognitive impairment.

aPL and NP manifestations. Prevalence of aPL is depicted in Table 4. A minimum of 2 positive tests (either aCL and/or LAC) were required to consider a patient as having a positive aPL status.

Patients with NP manifestations were more frequently positive for aPL than those without ($p < 0.001$). aCL of the IgG isotype and the LAC were more frequently found in patients with NP manifestations than in those without ($p = 0.0012$ and $p = 0.028$, respectively). Although the IgM isotype was more frequently found in patients with NP manifestations than in those without, this difference was not statistically significant.

Table 1. Demographic data on patients with SLE with/without neuropsychiatric (NP) manifestations

	NP Manifestations, n = 185	Without NP Manifestations, n = 138	p*
Female, n	176	132	
Age, †	43.1 ± 12.6	40.3 ± 12.5	NS
Disease duration†	11.9 ± 8.1	9.6 ± 7.5	0.009
Onset of the disease†	30.9 ± 10.9	30.6 ± 11.8	NS

† Mean years ± SD. * Student t test.

Table 2. Prevalence of neuropsychiatric (NP) manifestations in 323 patients with SLE according to ACR case definitions for NPSLE

Manifestations	n (%)
Headache	78 (24)
Tension-type	36 (11)
Migraine	33 (10)
Intractable/nonspecific	4 (1.2)
Cluster headache	3 (0.9)
Pseudotumor cerebri	2 (0.6)
Cerebrovascular disease	57 (17.6)
Transitory ischemic attack	24 (7.4)
Ischemic stroke	22 (6.8)
Chronic multifocal disease	6 (1.9)
Subarachnoid/intracranial hemorrhage	4 (1.2)
Sinus thrombosis	1 (0.3)
Mood disorders	54 (16.7)
Major depressive-like episode	37 (11.4)
Mood disorder with depressive features	15 (4.6)
Mood disorder with manic features	2 (0.6)
Cognitive dysfunction	35 (10.8)
Seizures	27 (8.3)
Partial or focal seizures	16 (5)
Primary generalized seizures	10 (3.1)
Under investigation	1 (0.3)
Psychosis	25 (7.7)
Anxiety disorder	24 (7.4)
Acute confusional state	13 (3.7)
Polyneuropathy	9 (2.8)
Mononeuritis	6 (1.8)
Myasthenia gravis	5 (1.5)
Cranial neuropathy	5 (1.5)
Myelopathy	4 (1.2)
Chorea	4 (1.2)
Demyelinating syndrome	3 (0.9)
Guillain-Barré syndrome	2 (0.6)
Total patients with NP manifestations	185 (57.3)

Table 3. Neuropsychiatric (NP) manifestations in 35 patients with cognitive impairment.

Manifestations	n = 35
Without other NP manifestations	4
With other NP manifestations	31
Cerebrovascular disease	15
Headache	13
Mood disorders	10
Seizures	8
Anxiety disorder	7
Psychosis	5
Acute confusional state	3
Cranial neuropathy	2
Demyelinating syndrome	1
Guillain-Barré syndrome	1
Polyneuropathy	1

Table 4. Prevalence of antiphospholipid antibodies (aPL) in 323 patients with SLE.

	n (%)
aPL	127 (39.3)
aCL	89 (25.7)
aCL IgG	61 (19)
aCL IgM	15 (4.6)
aCL IgG + IgM	13 (4)
LAC	69 (21.4)
LAC only	38 (11.8)
LAC + aCL	31 (9.6)

aCL: anticardiolipin antibodies, LAC: lupus anticoagulant.

Associations between aPL and specific type of NP manifestations. Results of the univariate analysis showed that patients with CVD presented aPL more frequently than those without, IgG aCL being the most strongly associated ($p < 0.001$).

IgG aCL was the only isotype significantly associated with headache as a whole ($p = 0.04$). However, we found no association between aPL and any specific subtype of headache.

Both IgG and IgM aCL were more frequently found in patients with seizures than in those without. Patients with partial seizures presented more frequently with IgM aCL ($p = 0.04$) and those with generalized seizures presented IgG aCL more frequently than those without ($p = 0.01$). After excluding 47 patients who had CVD, the association of partial seizures with IgM aCL and generalized seizures with IgG aCL remained significant (25% vs 7.8%, OR 3.90, 95% CI 1.16–13.03, $p = 0.04$; and 57.1% vs 16.8%, OR 6.57, 95% CI 1.42–30.40, $p = 0.02$, respectively).

aPL, particularly LAC, were also more frequently found in patients with cognitive disorders than in those without.

IgG aCL was the only aPL associated with cranial neuropathy (p = 0.001) as well as with chorea (p = 0.038).

Although the prevalence of aCL and LAC was high (ranging from 17% to 75%) in patients with demyelinating disease, myelopathy, Guillain-Barré syndrome, mononeuritis, myasthenia gravis, polyneuritis, acute confusional state, anxiety disorders, and mood disorders, the difference between subgroups was not statistically significant.

Multivariate analysis using logistic regression showed that the presence of aPL was independently associated with CVD (OR 6.17, 95% CI 2.94–12.9, p < 0.001), headache (OR 2.04, 95% CI 1.17–3.55, p = 0.01), and seizures (OR 2.89, 95% CI 1.18–7.10, p = 0.02). A further analysis showed that IgG and IgM aCL were both independently associated with CVD and seizures.

The associations between aPL and NP manifestations are shown in Table 5, along with the odds ratios and p values for the different covariates in univariate and multivariate analysis.

Other autoantibodies. ANA were found in 296/323 patients (91.6%). Anti-ENA were found in 132/323 patients (40.9%). One hundred out of 323 patients (31%) were positive for anti-Ro, 38/323 (11.8%) for anti-La, 32/323 (9.9%) for anti-Sm, and 41/323 (12.7%) for anti-RNP antibodies. Two hundred twenty-six out of 323 patients (70%) were positive for anti-dsDNA. No correlation was found between the presence of each of these antibodies and the presence of NP manifestations.

MRI studies. Of the 105 patients who underwent brain MRI, 94 had NP manifestations at some stage of the disease. White matter hyperintensity lesions (WMHL) were found in 33/105 patients (31%). Imaging findings are shown in Table 6. aPL were present in 63/105 patients (60%). aCL were present in 48/105 patients (46%) (35 had IgG, 6 IgM, and 7 IgG and IgM aCL) and LAC was detected in 33/105 patients (31%). Eighteen patients had both LAC and aCL. Patients with aPL presented WMHL more frequently than those without (36% vs 24%), but the difference was not statistically significant. aCL and its isotypes were also analyzed. The prevalence of IgG or IgM aCL did not differ between patients with/without WMHL (33% vs 30% and 31% vs 31%, respectively). Univariate analysis showed that patients with LAC presented WMHL more frequently than those without (45.4% vs 25%; OR 2.5, 95% CI 1.05–5.95, p = 0.044). Patients with WMHL were slightly older than those without (49.1 ± 12.6 vs 40.3 ± 11.6 yrs; p = 0.001). Multivariate analysis confirmed that the presence of WMHL was independently associated with the presence of LAC (OR 3.0, 95% CI 1.12–8.05, p = 0.027) and with older age of the patients (p = 0.001).

DISCUSSION

Neuropsychiatric involvement is a major cause of morbidity and mortality in SLE, and its prevalence, along with its pathogenesis, is still poorly understood. The lack of a standardized nomenclature has long been regarded as the main cause for the discrepancy between studies. The prevalence of NP manifestations applying the new ACR nomenclature for NPSLE was 57.3%, higher than reported previously. In 1995, our group reported that NP manifestations were present in 28% of 340 patients with SLE[14]. Due to the lack of guidelines in defining some psychiatric disorders, cognitive dysfunction, and mild-to-moderate migraine, these manifestations were excluded, leading to underestimation of the true incidence of NP manifestations in SLE. Mok, *et al*[15] found NP manifestations in 19% of 518 patients when applying the 1999 case definitions for NPSLE. In this series the presence of cognitive disorders was not evaluated, explaining at least in part the lower prevalence of NP manifestations.

However, Brey, *et al*[16] recently reported that 80% of their SLE patients had NP manifestations when applying this case definitions. The high prevalence of NP manifestations found in their and our series could be either: (1) because we classified and included patients with headache, mood disorders, cognitive dysfunction, psychosis, anxiety disorder, and acute confusional state; or (2) because they are referral centers, more severe cases are seen in our clinics.

Headaches are common in SLE and are a significant source of patient disability. The exact prevalence of headache in general and the prevalence of migraine in patients with SLE is unknown, and there is a large variability between studies depending on the classification criteria applied. Sfikakis, *et al*[17] found headache in 32% of their patients with SLE. Vazquez-Cruz, *et al*[18] studied 76 patients with SLE, diagnosing migraine in 31% of them. Montalban, *et al*[19] found migraine in 31% of 103 SLE patients and tension-type headache in 20% of them. Recently Glanz, *et al*[20] reported that 62% of their 186 SLE patients had headache and 39% of them had migraine. Mok, *et al*[15] found headache in 5% of 518 SLE patients, with a prevalence lower than those reported. Recently Omdal, *et al*[21] found 66% of 58 patients with SLE suffering from headache. They diagnosed migraine in 38% and tension-type headache in 36% of the patients. Estimates of the prevalence of migraine as defined by the International Headache Society in the general population range from 3.4% to 17.6%[22]. In our study headache was the most common NP manifestation, present in 24% of the patients, with tension-type and migraine being the most frequent types (11% and 10%, respectively).

CVD was found in 14.5% of the patients, transient ischemic attacks (TIA) being the most common manifestation, followed by ischemic stroke. This prevalence was similar to that reported by others[15,23,24] and also confirms the results of our previous study in which ischemic stroke and/or TIA were found in 16.4% of the patients[14]. The application of 1999 ACR criteria did not modify the definition of CVD in our cohort of patients.

Table 5A. Antiphospholipid antibodies (aPL) and neuropsychiatric (NP) manifestations in 323 patients with SLE.

NP Manifestations	aPL		Univariate Analysis		Multivariate Analysis	
	Positive, n = 127 n (%)	Negative, n = 196 n (%)	OR (95% CI)	p	OR (95% CI)	p
Patients with NP manifestations	90 (70.9)	95 (48.5)	2.58 (1.61–4.15)	< 0.001		
Headache	41 (32.3)	37 (18.9)	2.05 (1.22–3.43)	0.0088	2.04 (1.17–3.55)	0.01
Cerebrovascular disease	36 (28.3)	11 (5.6)	6.65 (3.23–13.67)	< 0.001	6.17 (2.94–12.9)	< 0.001
Mood disorder	19 (15)	34 (17.3)	0.84 (0.45–1.55)	0.68	—	—
Cognitive disorder	20 (15.7)	15 (7.6)	2.24 (1.10–4.56)	0.0369	—	—
Seizures	18 (14.2)	9 (4.6)	3.46 (1.50–7.97)	0.0043	2.89 (1.18–7.10)	0.02
Psychosis	11 (8.7)	14 (7.1)	1.23 (0.54–2.80)	0.77	—	—
Anxiety disorder	12 (9.4)	11 (5.6)	1.72 (0.74–4.04)	0.29	—	—
Acute confusional state	5 (3.9)	7 (3.6)	1.10 (0.34–3.56)	1.0	—	—
Polyneuropathy	4 (3.1)	5 (2.5)	1.24 (0.33–4.71)	0.74	—	—
Mononeuritis	2 (1.6)	4 (2)	0.76 (0.13–4.25)	1.0	—	—
Myasthenia gravis	2 (1.6)	3 (1.5)	1.02 (0.17–6.25)	1.0	—	—
Cranial neuropathy	5 (3.9)	0 (0)	1.04 (1.0–1.07)	0.0089	—	—
Myelopathy	1 (0.8)	3 (3.1)	0.51 (0.05–4.96)	1.0	—	—
Chorea	3 (2.4)	1 (0.5)	4.72 (0.48–45.85)	0.303	—	—
Demyelinating disease	3 (2.4)	0 (0)	1.02 (0.99–1.05)	0.059	—	—
Guillain-Barré syndrome	1 (0.8)	1 (0.5)	1.54 (0.09–24.9)	1.0	—	—

Table 5B. IgG anticardiolipin antibodies (IgG aCL) and neuropsychiatric (NP) manifestations in 323 patients with SLE.

NP Manifestations	IgG aCL		Univariate Analysis		Multivariate Analysis	
	Positive, n = 74 n (%)	Negative, n = 249 n (%)	OR (95% CI)	p	OR (95% CI)	p
Patients with NP manifestations	55 (74.3)	130 (52.2)	2.65 (1.49–4.72)	0.0012		
Headache	25 (33.8)	53 (21.3)	1.89 (1.06–3.33)	0.04	—	—
Cerebrovascular disease	24 (32.4)	23 (9.2)	4.71 (2.46–9.02)	< 0.001	4.15 (2.11–8.18)	< 0.001
Mood disorder	11 (14.9)	43 (17.3)	0.83 (0.40–1.71)	0.75	—	—
Cognitive disorder	13 (17.6)	22 (8.8)	2.18 (1.04–4.59)	0.057	—	—
Seizures	14 (18.9)	13 (5.2)	4.22 (1.88–9.44)	< 0.001	3.64 (1.53–8.63)	0.0033
Psychosis	6 (8.1)	19 (7.6)	1.06 (0.41–2.78)	1.0	—	—
Anxiety disorder	8 (10.8)	15 (6.0)	1.87 (0.76–4.61)	0.16	—	—
Acute confusional state	3 (4)	9 (3.6)	1.12 (0.29–4.27)	1.0	—	—
Polyneuropathy	3 (4)	6 (2.4)	1.71 (0.42–7.01)	0.43	—	—
Mononeuritis	2 (2.7)	4 (1.6)	1.70 (0.30–9.47)	0.62	—	—
Myasthenia gravis	0 (0)	5 (2.0)	0.97 (0.96–0.99)	0.59	—	—
Cranial neuropathy	5 (6.7)	0 (0)	1.07 (1.0–1.14)	< 0.001	—	—
Myelopathy	1 (1.35)	3 (1.2)	1.12 (0.11–10.96)	1.0	—	—
Chorea	3 (4)	1 (0.4)	10.48 (1.07–102.3)	0.038	—	—
Demyelinating disease	1 (1.35)	2 (0.8)	1.71 (0.15–19.18)	0.53	—	—
Guillain-Barré syndrome	1 (1.35)	1 (0.4)	3.39 (0.20–54.98)	0.40	—	—

The prevalence of mood disorders in patients with SLE is controversial. We found mood disorders in 16.7% of our patients. Among the different types of mood disorders, major depressive episodes were the most frequent, followed by depressive features and manic features. Anxiety disorders were found less frequently than mood disorders (7.4%), confirming the findings of Sabbadini, *et al*[23].

Psychosis was found in 7.7% and acute confusional state in 3.7% of our patients. The application of ACR criteria for NPSLE was useful in the classification of psychiatric manifestations and cognitive disorders.

Cognitive impairment in patients with SLE has been reported with a large range of variability of results. This may be explained by the different methods applied to select patients and different case definitions used. Carbotte, *et al*[25,26] found cognitive impairment in 66% and in 53% of SLE patients in 2 different studies. Hanly, *et al*[1,27] detected cognitive impairment in 21% of SLE patients at baseline evaluation and in 12% at one-year followup. Similar results were described by Hay, *et al*[28], who reported cognitive impairment in 23% of SLE patients at baseline screening and in 18% at 2-year followup. The lower prevalence found

Table 5C. IgM anticardiolipin antibodies (IgM aCL) and neuropsychiatric (NP) manifestations in 323 patients with SLE.

NP Manifestations	IgM aCL Positive, n = 28 n (%)	IgM aCL Negative, n = 295 n (%)	Univariate Analysis OR (95% CI)	p	Multivariate Analysis OR (95% CI)	p
Patients with NP manifestations	20 (71.4)	165 (55.9)	1.96 (0.84–4.61)	1.16		
Headache	5 (17.8)	73 (24.7)	0.66 (0.24–1.80)	0.55	—	—
Cerebrovascular disease	9 (32.1)	38 (12.9)	3.20 (1.35–7.59)	0.01	2.70 (1.10–6.60)	0.02
Mood disorder	6 (21.4)	48 (16.3)	1.40 (0.54–3.64)	0.43	—	—
Cognitive disorder	2 (7.1)	33 (11.2)	0.60 (0.13–2.68)	0.75	—	—
Seizures	6 (21.4)	21 (7.1)	3.54 (1.29–9.69)	0.02	2.9 (1.04–8.51)	0.04
Psychosis	1 (3.6)	24 (8.1)	0.41 (0.05–3.21)	0.70	—	—
Anxiety disorder	1 (3.6)	22 (7.4)	0.45 (0.05–3.51)	0.70	—	—
Acute confusional state	1 (3.6)	11 (3.7)	0.95 (0.11–7.69)	1.0	—	—
Polyneuropathy	0 (0)	9 (3.0)	0.96 (0.95–0.98)	1.0	—	—
Mononeuritis	1 (3.6)	5 (1.7)	2.14 (0.24–19.0)	0.42	—	—
Myasthenia gravis	0 (3.6)	5 (1.7)	0.98 (0.96–0.99)	1.0	—	—
Cranial neuropathy	1 (3.6)	4 (1.3)	2.69 (0.29–24.97)	0.36	—	—
Myelopathy	0 (0)	4 (1.3)	0.98 (0.97–0.99)	1.0	—	—
Chorea	0 (0)	4 (1.3)	0.98 (0.97–0.99)	1.0	—	—
Demyelinating disease	0 (0)	3 (1.0)	0.98 (0.97–1.0)	1.0	—	—
Guillain-Barré syndrome	0 (0)	2 (0.6)	0.99 (0.98–1.0)	1.0	—	—

Table 5D. Lupus anticoagulant (LAC) and neuropsychiatric (NP) manifestations in 323 patients with SLE.

NP Manifestations	LAC Positive, n = 69 n (%)	LAC Negative, n = 254 n (%)	Univariate Analysis OR (95% CI)	p	Multivariate Analysis OR (95% CI)	p
Patients with NP manifestations	48 (69.6)	137 (53.9)	1.95 (1.10–3.45)	0.028		
Headache	23 (33.3)	55 (21.6)	1.80 (1.01–3.24)	0.064	—	—
Cerebrovascular disease	16 (23.2)	31 (12.2)	2.17 (1.10–4.25)	0.035	—	—
Mood disorder	10 (14.5)	44 (17.3)	0.81 (0.38–1.70)	0.70	—	—
Cognitive disorder	13 (18.8)	22 (8.6)	2.43 (1.15–5.13)	0.029	—	—
Seizures	7 (10.1)	20 (7.9)	1.34 (0.54–3.32)	0.69	—	—
Psychosis	4 (5.8)	21 (8.3)	0.68 (0.22–2.05)	0.66	—	—
Anxiety disorder	6 (8.7)	17 (6.7)	1.32 (0.49–3.47)	0.59	—	—
Acute confusional state	4 (5.8)	8 (3.1)	1.89 (0.55–6.48)	0.29	—	—
Polyneuropathy	3 (4.3)	6 (2.4)	1.87 (0.45–7.71)	0.40	—	—
Mononeuritis	1 (1.4)	5 (1.9)	0.73 (0.08–6.37)	1.0	—	—
Myasthenia gravis	2 (2.9)	3 (1.2)	2.49 (0.41–15.25)	0.29	—	—
Cranial neuropathy	2 (2.9)	3 (1.2)	2.49 (0.41–15.25)	0.29	—	—
Myelopathy	0 (0)	4 (1.6)	0.98 (0.96–0.99)	0.58	—	—
Chorea	2 (2.9)	2 (0.8)	3.76 (0.52–27.19)	0.20	—	—
Demyelinating disease	2 (2.9)	1 (0.4)	7.67 (0.68–85.84)	0.22	—	—
Guillain-Barré syndrome	1 (1.4)	1 (0.4)	3.72 (0.23–60.25)	0.38	—	—

Table 6. Imaging findings in 105 SLE patients studied with brain MRI.

	n = 105 (%)
NP manifestations	94 (89.5)
Normal MRI	42 (40)
Abnormal MRI	63 (60)
WMHL	31 (29.5)
WMHL + infarct	2 (1.9)
Ischemic infarct	16 (15.2)
Multiinfarcts	5 (4.8)
Cortical atrophy	5 (4.8)
Subarachnoid hemorrhage	3 (2.8)
Sinus thrombosis	1 (0.9)

WMHL: white matter hyperintensity lesions.

in our study may be because we did not evaluate subclinical disturbances, since only patients with a history of cognitive disorders and/or patients with subjective complaints of cognitive dysfunction at the moment of the study underwent a formal neuropsychological evaluation administrated by a neuropsychologist, raising the possibility of a higher prevalence if neurocognitive assessment is also applied to asymptomatic patients. However, data for this are lacking in our study.

We also evaluated the associations between aPL and NP manifestations. Our earlier study[14] showed that 55% of patients with SLE and central nervous system involvement had aPL compared with 20% in the SLE control group (p <

0.001). Karassa, *et al*[29] also found that the presence of IgG aCL was strongly associated with NP manifestations in their series of 128 SLE patients. Mok, *et al*[15] also reported that IgG aCL was associated with NP manifestations in their cohort of 518 SLE patients. In our study, the association found between the presence of aPL — mainly IgG aCL — and NP manifestations confirms those previous results[14,15,29].

The pathogenetic mechanisms underlying the association with aPL are still uncertain. Some studies suggest an interaction between aPL and anionic phospholipid-protein complexes[30] or components of the coagulation cascade[31]. Recent studies show that aPL may activate vascular endothelial cells[32], leading to expression of various leukocyte adhesion molecules and generation of a prothrombotic state on the endothelial cell surface, resulting in vasoocclusive thrombosis[33]. The strong association between aPL and NP manifestations in our study supports the theory that an occlusive vasculopathy may be a major mechanism for NPSLE[6,34-36].

Early studies by Mackworth-Young and Hughes[37] found a higher prevalence of aPL in SLE patients with seizures, higher than the accepted prevalence of aPL in the common SLE population. In our 1994 study[38] describing 221 patients, seizures were also associated with IgG aCL, suggesting that aPL may play a role in the pathogenesis of seizures in SLE. Verrot, *et al*[39] found IgG aCL in 19% of their patients with epilepsy but no SLE. They speculated that a relationship between epilepsy and aCL is possible even in patients without SLE. We confirmed that aCL are independently associated with seizure disorders in patients with SLE.

Most studies looking for an association between aPL and headache have focused on migraine, probably because of accepted vascular mechanisms related with the development of migraine[40]. The results of these studies are controversial, with some authors confirming[41,42] and others rejecting[7,19] an association between aPL and migraine. Tietjen, *et al*[43] failed to observe an association between aCL and migraine in a large population of adult patients. Similar negative results were previously found by Montalban, *et al*[19] in 103 SLE patients. Migraine was present in 17% of the patients with aCL and in 37% of those without, emphasizing the lack of association between aCL and classical migraine.

The association between aPL and headache in our series can be explained by the fact that some chronic headache may actually have underlying ischemic mechanisms[44,45] and in this context aPL might play an important role.

WMHL are frequently found on brain MRI in patients with SLE. It was suggested that the presence of WMHL on MRI in patients with SLE could be due to small vessel thrombi[46]. Recently, we found WMHL on MRI in 54.2% patients with overt NP manifestations and in 38.6% of asymptomatic patients[47]. Our results confirmed those reported by Molad, *et al*[48], who found associations between MRI lesions and the presence of LAC in SLE patients, data that is so far not supported by others[49]. This association would support the thrombotic/ischemic origin of these lesions.

In summary, the new ACR criteria for NPSLE are useful to define NP manifestations in SLE with accuracy. We found that application of these criteria is useful for a better definition of each syndrome and for determining the prevalence of NP manifestations in a large series of patients with SLE. We found that aPL were associated with NP manifestations and in particular with CVD, seizures, and headache, suggesting that the presence of aPL may play an important role in determining at least these NP manifestations in patients with SLE. We also showed that brain MRI abnormalities are significantly more frequent in SLE patients with aPL than in those without aPL, suggesting that these lesions might be related to cerebral ischemia. Data from continuing prospective studies will aid in determining pathogenic disease mechanisms and developing appropriate therapy.

ACKNOWLEDGMENT

The authors are grateful to Dr. Pierpaolo Nurchis, Dr. Karla Strassburger-Lorna, and Sophie Gedda for their contribution during the early phases of the study.

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