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UNIVERSITE DE NICE SOPHIA-ANTIPOLIS

FACULTE DE MEDECINE DE NICE

Neuro-psychiatric manifestations in systemic lupus erythematosus: new concepts from a mono-center retrospective study

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A mon maître et Président du Jury

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Résumé

Contexte : En 1999, l'American College of Rheumatology (ACR) a défini 19 atteintes neuro-psychiatriques au cours du lupus systémique (LS). L'objectif de l'étude était d'étudier les paramètres cliniques, immunologiques et radiologiques, ainsi que les traitements et l'évolution de patients présentant un lupus neuro-psychiatrique.

Patients et méthodes : Nous avons mené une étude rétrospective, dans un centre spécialisé, de 2005 à 2018. Les patients étaient classés en 4 groupes selon le mécanisme physiopathologique supposé de l'atteinte : manifestations neuro-psychiatriques associées aux anticorps anti-phospholipides (APL), manifestations neuro-psychiatriques focales, manifestations neuro-psychiatriques diffuses, et manifestations neuro-psychiatriques mixtes (diffuses et focales).

Résultats : 81 patients (70 femmes), d'âge médian au diagnostic de LS de 27 ans [12 - 68], étaient inclus : 28 patients (34.6%) présentaient des manifestations neuro-psychiatriques associées aux APL, 8 patients (9.9%) des manifestations focales, 30 patients (37%) des manifestations diffuses et 15 (18.5%) des manifestations mixtes. L'activité du LS estimée par le Systemic Lupus Erythematosus Activity Index 2000 (SLEDAI-2K) était significativement différente entre les groupes au moment de l'atteinte neurologique (p=0.0001) tout comme les rechutes neurologiques et les séquelles neurologiques (p=0,038 et p=0,01 respectivement). Dans le groupe avec atteintes focales, 3/7 patients (43%) présentaient une rechute neurologique et 5/6 (83%) avaient des séquelles neurologiques. La corticothérapie et l'hydroxychloroquine étaient utilisés dans 91% et 95% des cas respectivement, et le cyclophosphamide dans 59% des cas.

Conclusion *:* La classification des lupus neuro-psychiatriques en 4 groupes selon le mécanisme physiopathologique supposé permet de séparer des patients ayant une présentation

clinique et une évolution distinctes. Cette classification pourrait aider à guider la prise en charge thérapeutique.

Mots-clefs : système nerveux central, système nerveux périphérique, lupus systémique, épilepsie, auto-anticorps.

Neuro-psychiatric manifestations in systemic lupus erythematosus: new concepts from a mono-center retrospective study

Running title: Neuropsychiatric manifestations in lupus

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Keywords: central nervous system, peripheral nervous system, systemic lupus erythematosus, psychiatric disorders, epilepsy, autoantibodies.

Authors contributions

F.C.A. and Z.A. designed the study.

D.R., A.M., M.M. and F.C.A. collected the data.

D.R. and F.C.A. conducted the statistical analysis.

D.R., A.M., J.H., M.M., Z.A. and F.C.A. analyzed and interpreted the data.

D.R., Z.A. and F.C.-A. wrote the manuscript.

All authors critically reviewed and approved the final version of the manuscript.

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Abbreviations

ACR	American College of Rheumatology
AQP4	Anti-aquaporine 4 antibodies
ANA	Anti-Nuclear Antibodies
APL	Antiphospholipid antibodies
AZA	Azathioprine
CNIL	Commission Nationale Informatique et Libertés
CNS	Central Nervous System
CSF	Cerebro-Spinal Fluid
CS	Corticosteroids
CYP	Cyclophosphamide
dsDNA	Double-stranded Deoxyribo-Nucleic Acid
ELISA	Enzyme-Linked Immuno-Sorbent Assay
ENMG	Electroneuromyogram
EULAR	European League Against Rheumatism
HCQ	Hydroxychloroquine
IS	Immuno-Suppressive drug
IV Ig	Intra-Venous Immunoglobulin
LN	Lupus Nephritis
MMF	Mycophenolate Mofetic
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NMDA	N-Méthyl-D-Aspartate
NMO-SD	Neuro-Myelitis Optica-Spectrum Disorders
NP	Neuro-Psychiatric
NPSLE	Neuro-Psychiatric manifestations in Systemic Lupus Erythematosus
PNS	Peripheral Nervous System
SLICC	Systemic Lupus International Collaborating Clinics
SLE	Systemic Lupus Erythematosus
SLEDAI- 2K	Systemic Lupus Erythematosus Activity Index 20

Abstract

Background: In 1999, the American College of Rheumatology (ACR) defined 19 syndromes of neuro-psychiatric manifestations occurring during systemic lupus erythematosus (NPSLE). The aim of this study was to describe the clinical, immunological, imaging presentations, treatments and outcomes of NPSLE 19 years later.

Patients and methods: We conducted a retrospective study between 2005 and 2018. Patients were classified in 4 groups: neuro-psychiatric (NP) manifestations related to antiphospholipid antibodies (APL), focal NP manifestations, diffuse NP manifestations and combined diffuse and focal NP manifestations.

Results: 81 patients (70 women, median age at SLE diagnosis 27 years [range: 12-68]) were included: 28 patients (34.6%) with NP manifestations related to APL, 8 patients (9.9%) with focal manifestations, 30 patients (37%) with diffuse manifestations and 15 (18.5%) with combined manifestations. Disease activity evaluated with Systemic Lupus Erythematosus Activity Index 2000 (SLEDAI-2K) was significantly different between groups (p=0.0001). The number of neurological relapses and neurological sequelae were significantly different between groups (p=0.038 and p=0.01 respectively): in the focal group, 3/7 patients (43%) had neurological relapses and 5/6 (83%) had neurological sequelae. Corticosteroids and hydroxychloroquine were prescribed in 91% and 95% of patients respectively, and cyclophosphamide in 59%.

Conclusion: This classification of NPSLE in 4 groups based on assumed pathogenic mechanisms enables to separate patients with different clinical presentations and different outcomes. It could help to guide therapeutic care.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease occurring in young adults, particularly women, and characterized by multi-systemic organ involvements. The most frequent manifestations are skin, joints, and kidneys involvements, hematological manifestations, and seritis. Neuro-psychiatric (NP) manifestations are common during SLE with a prevalence ranging from 37 to 95%, according to previous studies [1].

Neuropsychiatric SLE (**NPSLE**) refers to the neurologic syndromes of the central, peripheral, and autonomic nervous system and the psychiatric syndromes observed in patients with SLE in which other causes of neurologic manifestations have been excluded. NPSLE consists of heterogeneous clinical presentations, none of them being specific of SLE. NPSLE diagnosis requires excluding NP manifestations related to infections, treatments, atherosclerosis, metabolic abnormalities, or other neurological diseases. NPSLE can precede the onset of SLE or occur at any time during its course. Most of the time, NPSLE occurs within 2 years following SLE diagnosis [2]. The pathophysiology is not fully understood. Cerebro-spinal fluid (**CSF**) analyses and cranial magnetic resonance imaging (**MRI**) data are often normal in NPSLE patients (60 to 70% and 13 to 46% of cases, respectively), leading to diagnosis pitfalls [2]. Conversely, brain MRI may be abnormal in SLE patients without NPSLE (26 to 65% of cases) [2]. In 1999, an American College of Rheumatology (**ACR**) committee defined 19 NPSLE syndromes [3]: 12 central nervous system (**CNS**) and 7 peripheral nervous system (**PNS**) syndromes (Appendix). The CNS syndromes were defined as aseptic meningitis, acute confusional state, anxiety disorders, cerebrovascular disease, cognitive dysfunction, demyelinating syndromes, headache, movement and mood disorders, myelopathy, psychosis, and seizures. The PNS syndromes were acute inflammatory demyelinating polyradiculoneuropathy, autonomic disorders, cranial neuropathy, mononeuropathy, myasthenia, plexopathy, and polyneuropathy. However, this definition of

NPSLE has several limitations. First, it did not integrate the recent tools of inflammatory neurological diseases diagnoses, as anti-aquaporine 4 **(AQP4)** antibodies. Secondly, the heterogeneity of the 19 syndromes does not guide clinicians for treatments. Third, some NPSLE syndromes are frequent in the overall population, *e.g.* headache. Finally, the manifestations related to the 19 NPSLE as described by the ACR committee have distinct mechanisms (inflammatory, vasculopathy, others), although they are all referred to "NPSLE".

The aim of this study was to describe the characteristics of NPSLE 19 years after the ACR classification and to study 4 phenotypes based on assumed pathogenic mechanisms. Thus, we retrospectively studied clinical, biological, imaging characteristics, treatments and outcomes in NPSLE patients from a tertiary center, and compared 4 groups based on assumed pathogenic mechanisms.

Patients and methods

Patient selection

Patients with NPSLE were identified through the computerized database of 1300 SLE patients seen at least once in a tertiary center, which is the French National Reference Center for SLE, using the keywords "neuro-psychiatric", "neurologic", and "psychiatric" between 2005 and 2018. The medical charts were retrospectively reviewed.

The inclusion criteria were the following: (1) SLE according to the 1997 revised classification ACR criteria [4] or to the Systemic Lupus International Collaborating Clinics **(SLICC)** 2012 criteria [5], (2) at least one neuro-psychiatric manifestation according to the 1999 ACR commission [3]. We excluded patients with another neurologic diagnosis (including multiple sclerosis (**MS**) and neuro-myelitis optica (**NMO**)-spectrum disorders, using the recent criteria [6,7]) or an alternative cause for neuropsychiatric manifestations (infections, treatments, atherosclerosis, metabolic abnormalities or psychiatric diseases). Additionally, we excluded patients who had NP manifestations related to cryoglobulinemia

vasculitis. The medical files were reviewed by 2 independent experts (D.R. and F.C.-A) to classify the patients. In case of discrepancy between the 2 experts, a third opinion was searched (Z.A.) and considered as the final classification. Thus, the patients were classified into 4 groups based on pathophysiological mechanism of NPSLE: a group with neuro-psychiatric manifestations usually related to antiphospholipid antibodies **(APL)** (cerebrovascular disease, seizure disorders and movement disorders), regardless of positivity of these antibodies ; a group with focal neurologic manifestations (defined as myelopathy, cranial neuropathy, plexopathy, mononeuropathy or multiplex mononeuropathy, aseptic meningitis, demyelinating syndrome), a group with diffuse neurologic manifestations (including psychosis, mood disorder, cognitive dysfunction, acute confusional state, anxiety disorder, headache, myasthenia, Guillain-Barre syndrome or acute inflammatory demyelinating polyradiculoneuropathy, autonomic disorder, and polyneuropathy); and a group including patients who had combined diffuse and focal neurologic manifestations (mixed damage).

Data collection

The following data were collected: demographic characteristics, delay between the diagnosis of SLE and NPSLE, clinical characteristics of NPSLE, associated manifestations of SLE (cutaneous, articular, renal or lupus nephritis **(LN)**, seritis (pericarditis and pleurisy), pulmonary, digestive, haemophagocytic lymphohistiocytosis, hemolytic anemia, lymphopenia, leukopenia, thrombocytopenia, myositis, fever and adenopathy), blood test results during NPSLE (including anti-nuclear antibodies **(ANA)**, anti-double-stranded deoxyribonucleic acid (**dsDNA**) and anti-soluble antigen antibodies, complement fractions (C3, C4, and CH50), antiphospholipid antibodies), CSF analyses, cranial MRI data, electroencephalogram results, electroneuromyogram **(ENMG)** results, treatments, response to treatments (adverse events, worsening outcome or improved outcome) and outcomes. An

abnormal CSF was defined by elevated proteinorachy or aseptic meningitis. Response to treatment was defined by physicians' clinical examination which was recorded in hospital reports. Outcomes were classified as death, stay in intensive care unit, neurological sequelae (sensitive and/or motor deficiency, sphincter disorders or chronic tinnitus or persistent dizziness, secondary epilepsy, persistent cognitive dysfunction or psychomotor retardation) in clinical examination and lost to follow-up (no medical data since 3 years). Inactive NPSLE after treatment was defined by lack of clinical progression of NPSLE and biological activity of SLE (normal C3 level and decrease or absence of anti-dsDNA antibodies). The Systemic Lupus Erythematosus Activity Index 2000 (**SLEDAI-2K**) score was calculated at the time of the first flare of NPSLE according to the instructions [8], and missing data were not considered. Follow-up ended February 2018.

According to the French legislation, a **CNIL** (Commission Nationale Informatique et Libertés) declaration (MR-003) was made, and the physicians informed patients of the used data.

Statistical analyses

Descriptive statistics were undertaken for continuous variables. Chi2 test was used to compare qualitative variables and Kruskal & Wallis test (Mann-Whitney test-like with 3 samples or more), a non-parametric test, was used to compare quantitative variables when appropriate. All tests were 2-sided. A p value < 0.05 was considered as statistically significant.

Results

Patient population

Among the 1300 SLE patients of the French National Reference Center for SLE database, 117 (9%) were classified as "NPSLE". The flow chart is detailed in the **Figure 1**. Among them, 36 were excluded because they did not meet SLE criteria: 4 had MS without

SLE, 5 had NMO-SD without SLE, 4 had cryoglobulinemia vasculitis, 3 had insufficient data, and 20 had others diagnoses. Finally, 81 patients (6%) were included: 28 patients (34.6%) in the group with neuro-psychiatric manifestations related to APL, 8 patients (9.9%) in the focal group, 30 patients (37%) in diffuse group and 15 patients (18.5%) in combined group.

Demographic and clinical features

The demographic and clinical characteristics of the patients are detailed in **Table 1**. Seventy patients were women (86%). Median age at SLE diagnosis was 27 years [range: 12-68]. NPSLE occurred before 30-year-old in 43 out of 81 patients (53.1%), and before 40 years-old in 66 out of 81 patients (81.5%) **(Figure 2).**

NPSLE was the first manifestation of SLE in 39 patients (48%): 11 patients (39%) in the group related to APL, 2 patients (25%) in the focal group, 18 patients (60%) in the diffuse group and 8 patients (53%) in the mixed group. NPSLE occurred with a median time of 1 month [range: 0-263] after the diagnosis of SLE. The median number of neuro-psychiatric syndromes per patient was 2 [1-7]. The median number of neuro-psychiatric manifestations differed between the 4 groups, from 1 in focal group to 3 in diffuse and related to APL groups (p=0.001). There were 43 patients (53%) with psychiatric manifestations and up to 25 patients (83%) in diffuse group. Concomitant extra-neuropsychiatric manifestations of SLE were detailed in **Table 1**, for example no skin manifestation in focal group and 17 skin manifestations reported in diffuse and related to APL groups (57% and 61% respectively, p=0.005). The median number of all manifestations of SLE was significantly different in these 4 groups, and was the smallest in the focal group (p=0.011). The median SLEDAI-2K score at the time of NPSLE was 20 [range: 0-53]. The median SLEDAI-2K at the time of NPSLE was from 3 in focal group to 22 in group related to APL (p=0.0001). CNS syndromes were present in 76 patients (94%), PNS syndromes in 9 patients (11% of the cases), 5 patients having both PNS and CNS manifestations. Three patients (38%) of focal group had PNS

manifestations. The distribution of CNS manifestations between the group related to APL and those not related to APL including the 3 other groups is detailed in Figure 3.

The most frequent neuro-psychiatric events were headache (28 patients, 35%), psychosis (26 patients, 32%), anxiety disorder (24 patients, 30%), acute confusional state (23 patients, 28%) and mood disorder (21 patients, 26%). Aseptic meningitis was associated with another neuro-psychiatric event in 15 out of 17 patients (88% of cases; p=0.000002). Myelopathy were recorded in 5 patients (63%) of the cases of focal group, covering only 15% of all patients included (p=0.00002).

Immunological results

Positive ANA titers were found in 100% of cases, and anti-dsDNA antibodies were found in 69 patients (85%) **(Table 2).** Positive anti-ribosomal P antibodies titers were present in 9 patients (11%), never in the focal group, in 13% of the cases in diffuse and combined groups and in 11% of the cases with relationship with APL. Five patients (56%) with positive anti-ribosomal P antibodies titers had psychosis. Overall, APL titers were positive in 27 patients (34%) and APL syndrome was defined in 6 patients (7%).

Biological and radiological results

Overall, CSF and brain MRI were normal in 29 patients out of 61 (48%) and in 23 out of 73 patients (32%), respectively. The CSF was normal in 16 patients (70%) in the diffuse group while it was abnormal in 12 patients (80%) in the mixed group (p=0.02).

Treatments

Hydroxychloroquine (**HCQ**) and corticosteroids **(CS)** were used in 95% and 91% of patients, respectively. CS were given without immunosuppressive drug in 11 patients (14%). Immunosuppressive drugs, which were given mostly for NPSLE, were: cyclophosphamide (**CYP**) in 48 patients (59%), mycophenolate mofetil (**MMF**) in 36 patients (44%) and azathioprine (**AZA**) in 21 patients (26%). CYP was used in 22 patients (73%) in the group

with diffuse damage, in 3 patients (38%) in the group with focal damage, in 7 patients (47%) in the group with combined damage and to 16 patients (57%) in the group with manifestations related to APL. AZA was the first-choice immunosuppressive drug used in the focal group (4 patients, 50%). Plasma exchanges were used in 18 patients (22%): 10 patients (33%) with diffuse events, 11 patients (42%) with psychosis, 8 patients (36%) with mood disorder, 6 patients (30%) with acute confusional state and 8 patients (29%) with headache (Table 3). Four patients (5%) received IV Ig: 2 patients with an acute inflammatory demyelinating polyradiculoneuropathy, one patient with chorea and one patient who had an APL syndrome and a contraindication to carry on plasma exchanges because of infection.

Fifteen patients (19%) had renal impairment associated with NPSLE, which required an immunosuppressive treatment (MMF or CYP) too, 59 patients (73%) had received an immunosuppressive drug exclusively for NPSLE (none extra-neuropsychiatric manifestations of SLE associated), as it was for 7 patients out of 8 in focal group (88%).

Finally, immunosuppressive drugs associated to HCQ and CS were used in 59 patients (72.8%). CS were efficacious in 40 out of 43 patients (93% of cases) and CYC in 27 out of 28 patients (96.4% of case). Treatments according to CNS events are described in Table 3.

Outcome of NPSLE

Evolution after treatment of NPSLE is presented in Table 4. Thirty-two patients (40% of the cases) were lost to follow-up in the study. Overall, 11 patients out of 66 (17%) relapsed: 9 neurological relapses (82%) and 2 psychiatric relapses (18%). These 4 groups differed significantly about neurological relapses (p=0.038) and neurological sequelae in clinical examination (p=0.01): patients had the most of neurological relapses (43%) and the most neurological sequelae (83%) in the focal group.

Six patients (20%) in diffuse group and 10 patients (36%) in the group related to APL were hospitalized in intensive care unit, whereas none patient in focal group and only 2 patients (13%) in mixed group were hospitalized in intensive care unit.

Two patients died of NPSLE (multi-system organ failures): one in diffuse group and one in group related to APL.

We recorded that neuro-psychiatric conditions improved in 45 out of 48 patients (94%). At last visit, NPSLE was inactive in overall 42 out of 47 patients (89% of the cases), in 16 out of 19 patients (84% of the cases) for diffuse group, in 100% of the cases for focal group, in 5 out of 6 patients (83%) for combined group and in 15 out of 16 patients (94%) for group related to APL.

Adverse events were reported in 4 patients (5%), including 3 with infections.

Discussion

In this study, we found that NPSLE can be classified in 4 groups based on assumed pathogenic mechanisms. These groups are significantly different for the disease activity (p=0,0001), CSF abnormalities (p=0.02), skin manifestations (p=0.005), neurological relapses (p=0.038) and neurological sequelae (p=0.01). Patients with diffuse manifestations and those with manifestations related to APL appeared to have a more severe activity of extra neurologic SLE than those in focal group.

In this study, we used a classification of 4 groups of NPSLE, instead of 19 neurological syndromes. These 4 groups were based on pathogenic mechanisms. Indeed, different pathologic mechanisms were suspected [9]: inflammatory, vasculitic, and ischemic (with or without the role of APL) mechanisms. Inflammation would be mediated by injury with increased permeability of the blood-brain-barrier, involvement of intrathecal autoantibodies and immune complexes and production of inflammatory mediators (interferon alpha in particular) leading to diffuse NP manifestations [10]. This matched the diffuse group

in our study. Autoantibodies could play a role in mediating both ischemic and inflammatory disease mechanisms [9]. The anti-N-Méthyl-D-Aspartate (**NMDA**) receptors [11] and anti-ribosomal P antibodies may be involved in inflammatory mechanisms. The role of NMDA receptors was not well-defined, SLE antibodies could cross-react with DNA and NMDA receptors, gain access to CSF and mediate non-thrombotic and non-vasculitic abnormalities of the CNS [11]. Ischemic mechanisms were often caused by APL mediated by thrombosis, that is why we had classified all patients having NP events usually associated with APL in the same group regardless of their positivity. Besides, Govoni *et al.* [12] reported that APL antibodies were strongly associated with NP involvements during SLE. We assumed that in focal group the pathologic mechanism was the vasculopathy. However, Hanly *et al.* [9] proposed the hypothesis that ischemic injury mediated by APL, immune complexes and complement activation led to focal NP events (*e.g.* stroke) and diffuse NP events (*e.g.* cognitive dysfunction). Thus, it was needed to study precisely pathologic pathway with advances in neuro-imaging and use of specific biomarkers.

Similarly to previous studies, we found that headache was the most frequent NP manifestations in SLE [13,14,15]. Headache was not specific of SLE, not related to disease activity and not more frequent than in the overall population [16,17,18]. European League Against Rheumatism **(EULAR)** experts estimated the prevalence of headache between 10 and 20% [19], it varied from 3 %, in a Chinese cohort in which headache was infrequently reported since this population was known to report a lower rate of headache [20], to 87 % [21].

The anti-ribosomal P antibodies were associated with psychosis attributed to SLE [22]. In our study, 56% of patients having these antibodies had psychosis. Moreover, NPSLE was found to be associated with anti-ribosomal P antibodies and lupus anticoagulant [23].

This suggested that there were different autoimmune pathogenic mechanisms, although low sensitivity of these antibodies limited their clinical application.

Thirty-three patients were excluded in our study after review of medical files because they did not meet SLE criteria even if they were classified as "NPSLE" at first. Ainiala *et al.* [24] proposed to revise NPSLE criteria excluding the syndromes without neuronal damages evidence. It resulted in an improved specificity (93%). They also excluded anxiety and headache, as well as mild depression, mild cognitive dysfunction (with deficits in fewer than 3 dimensions) and polyneuropathy unconfirmed by ENMG. Moreover, Bortoluzzi *et al.* [25] have developed a new algorithm for attribution of NP events in SLE taking into account the time onset of NP events (it was the time of appearance of the NP events with respect to the time onset of SLE: before (>6 months), concomitant (within 6 months) or after, the presence or absence of minor or not specific NP events as defined by Ainiala *et al.* [24], the presence (absent, at least one and more than one) of confounding factors (*i.e.* associations as suggested by the 1999 ACR glossary) and favoring factors (not covered by the 1999 ACR classification [3], added and included both the specific SLE-related risk factors reported in the EULAR recommendations [19] and further information considered relevant for the attribution process by the expert panel). Thus, the optimal cut-off score to classify a NP event as related to SLE was higher than 7 and less than 3 to classify it as not related to SLE, with a positive predictive value of 100% and 86.3% in the training and validating cohorts, respectively. This algorithm will can be a useful tool to assist the clinician in attribution of NP events in SLE.

The CSF and brain MRI were not always abnormal in NPSLE [2, 3,19], we had the same results. Moreover, both asymptomatic patients (64.3%) and patients with neuropsychiatric manifestations (73.3%) had involvement of the CNS on brain MRI [26]. Lacking validated biomarkers and cerebral neuroimaging for an accurate attribution of the NP events occurring during the course of SLE, the clinical judgment of trained clinicians remains

the most reliable tool [10, 27, 28]. The association of clinical characterization, specific and non-invasive biomarkers and neuro-imaging could be a help to diagnose more easily NPSLE and to treat it [9, 29]. Several different magnetic resonance imaging techniques have identified microstructural or functional abnormalities. They used to determine central nervous system involvement in systemic lupus erythematosus [30].

Our study presented some limitations. First, it was a retrospective study, we also had several missing data. Probably, the prevalence of NPSLE and adverse events were underestimated since the data collection was declarative. The prevalence of NPSLE has been reported to range from 37% to over 95% [1]. It may be over-estimated, involving an over-treatment in some patients. We had only 6% of NPSLE, however this study was not designed to evaluate the prevalence of NPSLE. If isolated headache, anxiety, mild depression (no criteria for major depressive-like episodes), mild cognitive impairment (deficits in less than 3 of 8 specified cognitive domains) and polyneuropathy without electrophysiological confirmation, were not attributed to SLE, this prevalence ranged only between 19% and 38% [31]. Thus, NP events affected 6% to 12% of newly diagnosed SLE patients in the first year of disease [13], whereas we had 48% of inaugural NPSLE without these restrictions. Second, according cognitive dysfunction, formal neuro-psychological assessments were not performed on mostly patients. CSF analysis was not always done when the NP events affected only the PNS. Third, we noticed a lack of power about the focal group (only 8 patients), not enabling to conclude for some results. Next, we had an important number of lost to follow-up (40% of the cases), the patients preferring to follow-up near home. Finally, treatments are empiric and inhomogeneous, based on the knowledge about effective treatments of other serious organ damages in SLE (*e.g*. LN). We had not significant results about treatments, CYP and MMF were the more prescribed IS. In the group related to APL, 57% of patients have received CYP and 73% of patients have received it in diffuse group, we probably had an aggressive care in

our unit. Studies [32,33] showed that CYP was more effective in reducing symptoms of NP involvement in SLE compared with methylprednisolone. Besides, a low dose of intravenous CYP (200-400 mg per month) seemed to be also effective in NPSLE versus CS [34]. Catatonia was treated by plasma exchanges as it has been proposed by Marra *et al*. [35].

In conclusion, the NPSLE syndromes as defined by the ACR classification are heterogeneous and encompass a broad spectrum of pathogenic mechanisms. We showed that with a 4 groups classification based on suspected pathogenic mechanisms, we could define different clinical and outcomes profiles of patients. After confirmation of these results by replication cohorts and after studying pathogenic mechanisms of these 4 groups, this classification could help to use targeted therapies and to follow up patients according to pathogenic mechanisms.

Figures

Figure 1. Flow chart

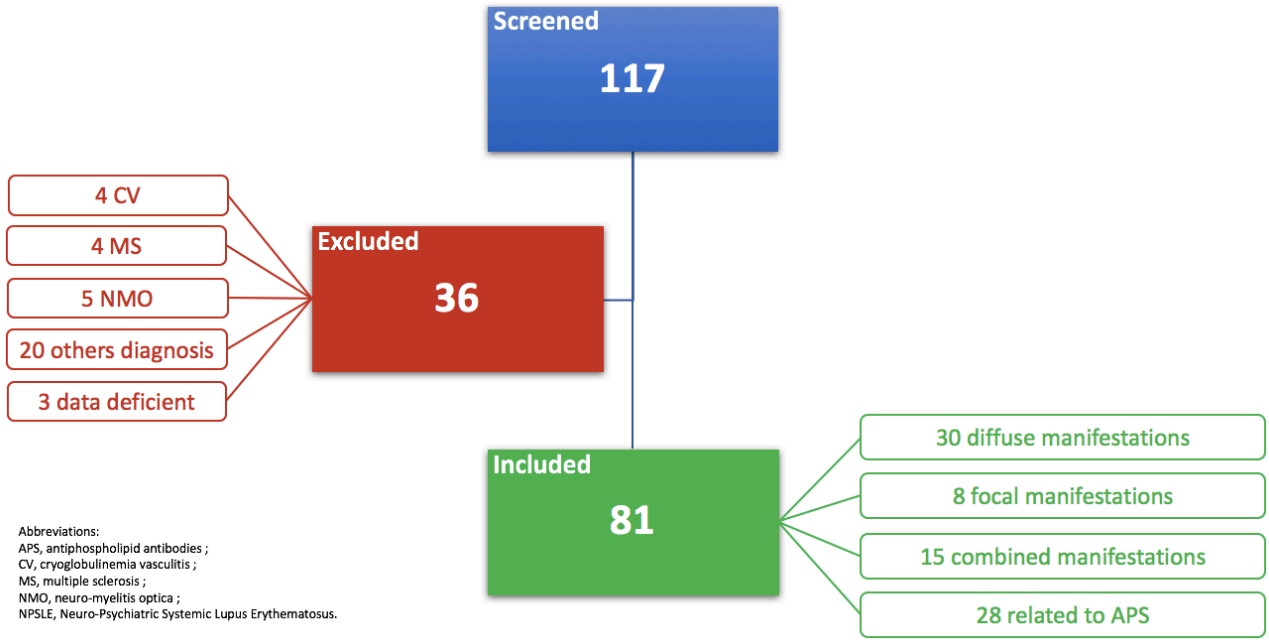


Figure 2. Age at NP manifestations of SLE by decile and sex

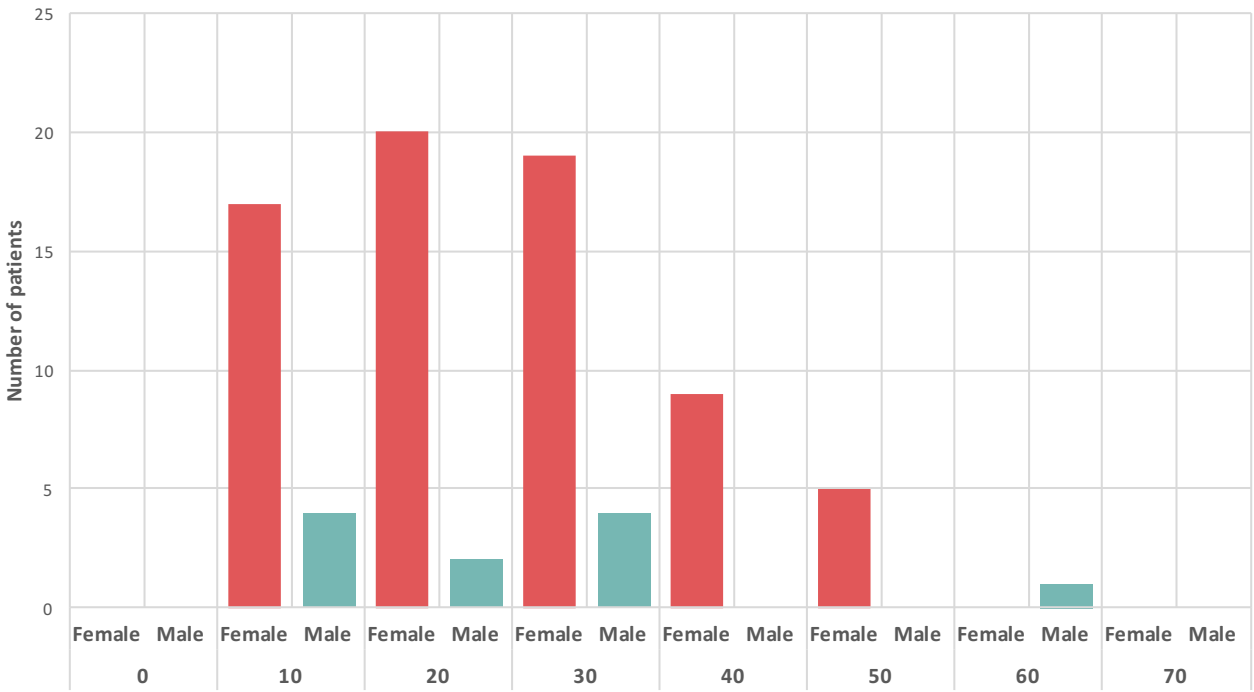
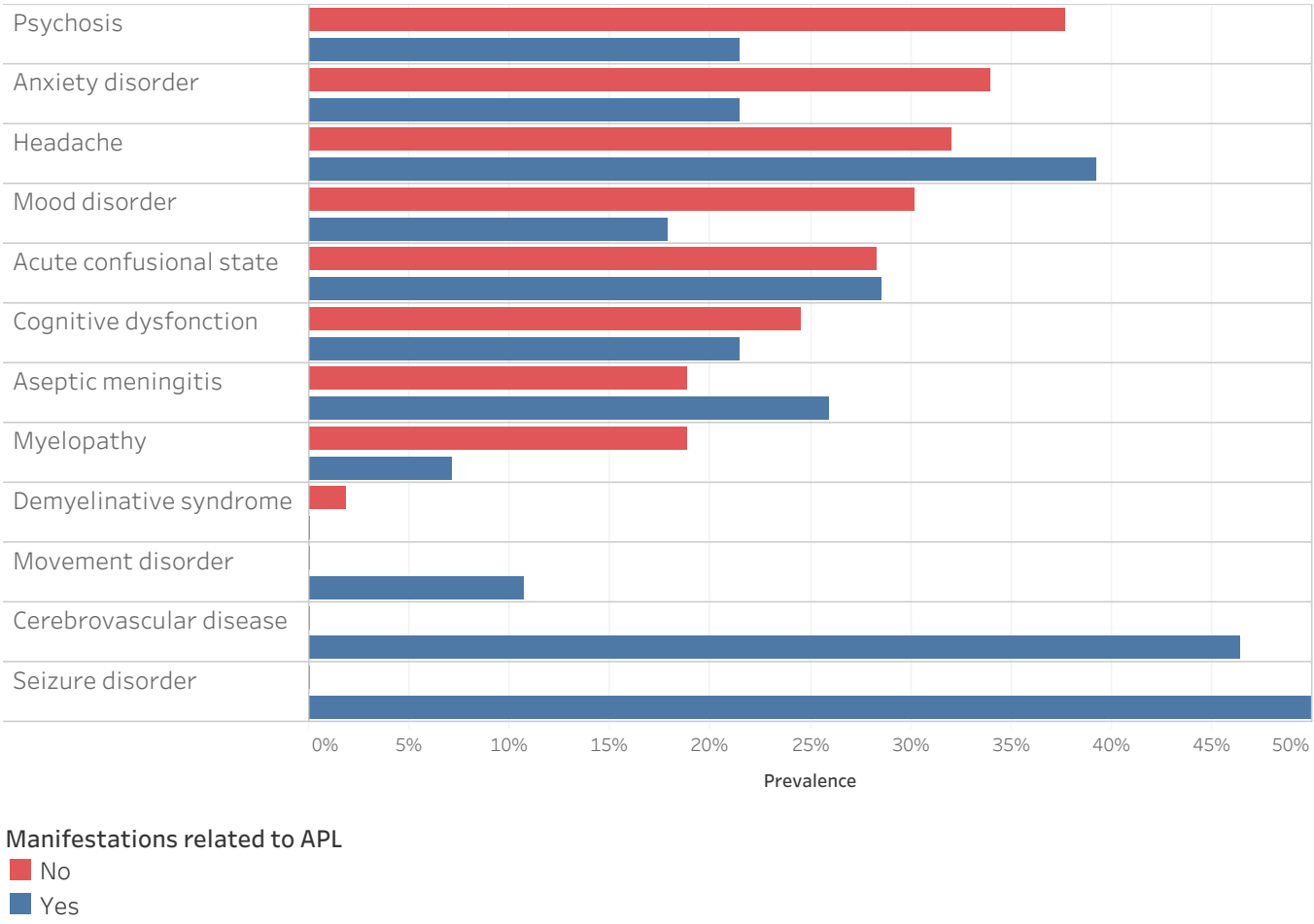


Figure 3. Distribution of CNS manifestations between the group related to APL and those not related to APL



Tables

Table 1. Demographic and clinical characteristics of patients with neuro-psychiatric systemic lupus erythematosus

Abbreviations: APL, antiphospholipid antibodies; NPSLE, Neuro-Psychiatric manifestations in Systemic Lupus Erythematosus; SLE, Systemic Lupus Erythematosus; SLEDAI, Systemic Lupus Erythematosus Activity Index. All manifestations of SLE: cutaneous, articular, renal, seritis (pericarditis and pleurisy), pulmonary, digestive, haematological (haemophagocytic lymphohistiocytosis, hemolytic anemia, lymphopenia, leukopenia and thrombocytopenia), myositis, fever and adenopathy. Mixed damages: diffuse and focal damages.

	All (n=81)	**Diffuse damage (n=30)**	**Focal damage (n=8)**	**Mixed damages (n=15)**	**Related to APL (n=28)**	**p**
Female	70 (86%)	26 (87%)	8 (100%)	11 (73%)	25 (89%)	0.303
Median age at SLE diagnosis (years) [range]	27 [12-68]	24.5 [13-55]	27.5 [15-49]	30 [16-68]	25 [12-48]	0.711
Median delay between SLE and NPSLE (months) [range]	1 [0-263]	0 [0-189]	88 [0-263]	0 [0-120]	1 [0-200]	0.060
Inaugural NPSLE n (%)	39 (48%)	18 (60%)	2 (25%)	8 (53%)	11 (39%)	0.217
Median number of all manifestations of SLE	3	3	1	2	3	0.011
Median number of neuro-psychiatric manifestations	2	3	1	3	2.5	0.001
Neurological manifestations	70 (86%)	19 (63%)	8 (100%)	15 (100%)	28 (100%)	0.00008
Psychiatric manifestations	43 (53%)	25 (83%)	0 (0%)	6 (40%)	12 (43%)	0.00006
Median SLEDAI at the time of NPSLE	20	18	3	18	22	0.0001
Skin manifestations	38 (47%)	17 (57%)	0 (0%)	4 (27%)	17 (61%)	0.005
Arthritis	34 (42%)	15 (50%)	3 (38%)	5 (33%)	11 (39%)	0.705
Lupus nephritis	21 (26%)	10 (33%)	1 (13%)	2 (13%)	8 (29%)	0.400
Pericarditis	11 (14%)	5 (17%)	0 (0%)	1 (7%)	5 (18%)	0.467
Seritis	13 (16%)	6 (20%)	0 (0%)	1 (7%)	6 (21%)	0.326

Antiphospholipid antibody syndrome	6 (7%)	1 (3%)	0 (0%)	2 (13%)	3 (11%)	0.461
Hemolytic anemia	8 (10%)	3 (10%)	0 (0%)	0 (0%)	5 (18%)	0.210
Haemophagocytic lymphohistiocytosis	10 (12%)	3 (10%)	0 (0%)	2 (13%)	5 (18%)	0.556
Peripheral nervous system (=PNS)	9 (11%)	2 (7%)	3 (38%)	2 (13%)	2 (7%)	0.080
Guillain-Barre syndrome	2 (2%)	2 (7%)	0 (0%)	0 (0%)	0 (0%)	0.323
Autonomic disorder	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	/
Mononeuropathy	2 (2%)	0 (0%)	2 (25%)	0 (0%)	0 (0%)	0.0003
Myasthenia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	/
Cranial neuropathy	5 (6%)	0 (0%)	1 (13%)	2 (13%)	2 (7%)	0.272
Polyneuropathy	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	/
Plexopathy	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	/
Central nervous system (= CNS)	76 (94%)	28 (93%)	5 (63%)	15 (100%)	28 (100%)	0.001
Aseptic meningitis	17 (21%)	0 (0%)	0 (0%)	10 (67%)	7 (26%)	0.000002
Cerebrovascular disease	13 (16%)	0 (0%)	0 (0%)	0 (0%)	13 (46%)	0.000002
Demyelinative syndrome	1 (1%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)	0.216
Headache	28 (35%)	9 (30%)	0 (0%)	8 (53%)	11 (39%)	0.068
Seizure disorder	15 (19%)	0 (0%)	0 (0%)	0 (0%)	15 (54%)	0.0000001
Acute confusional state	23 (28%)	9 (30%)	0 (0%)	6 (40%)	8 (29%)	0.240
Myelopathy	12 (15%)	0 (0%)	5 (63%)	5 (33%)	2 (7%)	0.00002
Movement disorder	3 (4%)	0 (0%)	0 (0%)	0 (0%)	3 (11%)	0.117
Cognitive dysfonction	19 (23%)	8 (27%)	0 (0%)	5 (33%)	6 (21%)	0.320
Mood disorder	21 (26%)	14 (47%)	0 (0%)	2 (13%)	5 (18%)	0.008
Anxiety disorder	24 (30%)	14 (47%)	0 (0%)	4 (27%)	6 (21%)	0.037
Psychosis	26 (32%)	16 (53%)	0 (0%)	4 (27%)	6 (21%)	0.009

Table 2. Biological, radiological characteristics, and treatments of patients with neuro-psychiatric systemic lupus erythematosus

Abbreviations: APL, antiphospholipid antibodies; CTS, corticosteroids; dsDNA, double stranded desoxyribonucleic acid; HCQ, hydroxychloroquine; IV Ig, intravenous immunoglobulins; IS, immunosuppressive drug; MRI, magnetic resonance imaging.

	All (n=81)	Diffuse damage (n=30)	Focal damage (n=8)	Mixed damages (n=15)	Related to APL (n=28)	p
Low C3 n (%)	39/79 (49%)	19/29 (66%)	3/8 (38%)	6/14 (43%)	11/28 (39%)	0.183
Positivity of anti-nuclear antibodies n(%)	80/80 (100%)	30/30 (100%)	7/7 (100%)	15/15 (100%)	28/28 (100%)	/
Positive dsDNA antibodies (radioimmunological assay) n (%)	49/72 (68%)	18/28 (64%)	3/7 (43%)	10/15 (67%)	18/22 (82%)	0.245
Positive dsDNA antibodies (ELISA assay) n(%)	69/81 (85%)	25/30 (83%)	6/8 (75%)	14/15 (93%)	24/28 (86%)	0.674
Positivity of anti-ribosomal P antibodies	9/81 (11%)	4/30 (13%)	0/8 (0%)	2/15 (13%)	3/28 (11%)	0.746
Positivity of APL	27/80 (34%)	8/30 (27%)	2/8 (25%)	5/15 (33%)	12/27 (44%)	0.507
Abnormal cerebrospinal fluid	32/61 (52%)	7/23 (30%)	2/5 (40%)	12/15 (80%)	11/18 (61%)	0.020
Abnormal brain MRI	50/73 (68%)	17/27 (63%)	6/8 (75%)	7/11 (64%)	20/27 (74%)	0.789
HCQ	77/81 (95%)	30/30 (100%)	8/8 (100%)	14/15 (93%)	25/28 (89%)	0.255
CTS	74/81 (91%)	27/30 (90%)	7/8 (88%)	15/15 (100%)	25/28 (89%)	0.617
With IS	62/81 (77%)	24/30 (80%)	6/8 (75%)	11/15 (73%)	21/28 (75%)	0.954
Alone	11/81 (14%)	3/30 (10%)	1/8 (13%)	4/15 (27%)	3/28 (11%)	0.437
Cyclophosphamide	48/81 (59%)	22/30 (73%)	3/8 (38%)	7/15 (47%)	16/28 (57%)	0.167
Mycophenolate mofetil	36/81 (44%)	16/30 (53%)	3/8 (38%)	5/15 (33%)	12/28 (43%)	0.595
Azathioprine	21/81 (26%)	8/30 (27%)	4/8 (50%)	4/15 (27%)	5/28 (18%)	0.337
Methotrexate	1/81 (1%)	0/30 (0%)	0/8 (0%)	1/15 (7%)	0/28 (0%)	0.216
IV Ig	4/81 (5%)	1/30 (3%)	0/8 (0%)	2/15 (13%)	1/28 (4%)	0.400
Plasma exchange	18/81 (22%)	10/30 (33%)	1/8 (13%)	2/15 (13%)	5/28 (18%)	0.311
Rituximab	0/81 (0%)	0/30 (0%)	0/8 (0%)	0/15 (0%)	0/28 (0%)	/
IS of renal impairment associated	15/81 (19%)	9/30 (30%)	0/8 (0%)	1/15 (7%)	5/28 (18%)	0.119
IS of neuro-psychiatric manifestation only	59/81 (73%)	19/30 (63%)	7/8 (88%)	12/15 (80%)	21/28 (75%)	0.441

Table 3. Treatments of central nervous system events

Abbreviations: CTS, corticosteroids ; IV Ig, intravenous immunoglobulins.

	Cerebrovascular disease (n=13)	Headache (n=28)	Seizure disorder (n=15)	Cognitive dysfonction (n=19)	Acute confusional state (n=20)	Aseptic meningitis (n=17)
CTS	11 (85%)	24 (86%)	14 (93%)	19 (100%)	19 (95%)	17 (100%)
Cyclophosphamide	8 (62%)	17 (61%)	9 (60%)	17 (89%)	16 (80%)	9 (53%)
Mycophenolate mofetil	6 (46%)	13 (46%)	6 (40%)	12 (63%)	8 (40%)	7 (41%)
Azathioprine	2 (15%)	8 (29%)	2 (13%)	4 (21%)	4 (20%)	3 (18%)
Methotrexate	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)
IV Ig	0 (0%)	1 (4%)	0 (0%)	1 (5%)	1 (5%)	1 (6%)
Plasma exchange	2 (15%)	8 (29%)	4 (27%)	5 (26%)	6 (30%)	4 (24%)
Rituximab	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Movement disorder (n=3)	**Myelopathy (n=12)**	**Psychosis (n=26)**	**Demyelinative syndrome (n=1)**	**Anxiety disorder (n=24)**	**Mood disorder (n=22)**
CTS	3 (100%)	11 (92%)	24 (92%)	1 (100%)	20 (83%)	20 (91%)
Cyclophosphamide	1 (33%)	7 (58%)	20 (77%)	0 (0%)	19 (79%)	17 (77%)
Mycophenolate mofetil	1 (33%)	4 (33%)	16 (62%)	0 (0%)	14 (58%)	13 (59%)
Azathioprine	1 (33%)	5 (42%)	6 (23%)	1 (100%)	3 (13%)	5 (23%)
Methotrexate	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
IV Ig	1 (33%)	1 (8%)	1 (4%)	0 (0%)	1 (4%)	0 (0%)
Plasma exchange	0 (0%)	2 (17%)	11 (42%)	0 (0%)	6 (25%)	8 (36%)
Rituximab	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 4. Outcomes of patients with neuro-psychiatric systemic lupus erythematosus

Abbreviations: APL, antiphospholipid antibodies; NPSLE, Neuro-Psychiatric manifestations in Systemic Lupus Erythematosus.

	All (n=81)	Diffuse damage (n=30)	Focal damage (n=8)	Mixed damages (n=15)	Related to APL (n=28)	p
Adverse events n (%)	4/80 (5%)	2/30 (7%)	0/8 (0%)	1/15 (7%)	1/27 (4%)	0.854
Infection	3/80 (4%)	1/30 (3%)	0/8 (0%)	1/15 (7%)	1/27 (4%)	0.878
Neuro-psychiatric relapse	11/66 (17%)	3/26 (12%)	3/7 (43%)	3/13 (23%)	2/20 (10%)	0.174
Neurological relapse	9/66 (14%)	1/26 (4%)	3/7 (43%)	3/13 (23%)	2/20 (10%)	0.038
Psychiatric relapse	2/66 (3%)	2/26 (8%)	0/7 (0%)	0/13 (0%)	0/20 (0%)	0.366
Only one relapse of NPSLE	6/66 (9%)	2/26 (8%)	1/7 (14%)	2/13 (15%)	1/20 (5%)	0.725
Two relapses of NPSLE	2/66 (3%)	0/26 (0%)	1/7 (14%)	1/13 (8%)	0/20 (0%)	0.144
At least three relapses of NPSLE	3/66 (5%)	1/26 (4%)	1/7 (14%)	0/13 (0%)	1/20 (5%)	0.534
Stay in intensive care	18/81 (22%)	6/30 (20%)	0/8 (0%)	2/15 (13%)	10/28 (36%)	0.111
Death	2/49 (4%)	1/21 (5%)	0/6 (0%)	0/6 (0%)	1/16 (6%)	0.867
Worsening outcome	2/49 (4%)	1/21 (5%)	0/6 (0%)	0/6 (0%)	1/16 (6%)	0.867
Improved outcome	45/48 (94%)	19/20 (95%)	5/6 (83%)	6/6 (100%)	15/16 (94%)	0.667
Neurological sequelea	15/57 (26%)	4/21 (19%)	5/6 (83%)	2/11 (18%)	4/19 (21%)	0.010
Inactive NPSLE after treatment	42/47 (89%)	16/19 (84%)	6/6 (100%)	5/6 (83%)	15/16 (94%)	0.615
Lost to follow-up	32/81 (40%)	11/30 (37%)	2/8 (25%)	7/15 (47%)	12/28 (43%)	0.739

Appendix

19 neuropsychiatric syndromes observed in systemic lupus erythematosus, ACR nomenclature of 1999

12 CNS syndromes	7 PNS syndromes
Aseptic meningitis	Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)
Cerebrovascular disease	Autonomic disorder
Demyelinating syndrome	Mononeuropathy, single/multiplex
Headache (including migraine and benign intracranial hypertension)	Myasthenia gravis
Movement disorder (chorea)	Cranial neuropathy
Myelopathy	Plexopathy
Seizure disorders	Polyneuropathy
Acute confusional state	
Anxiety disorder	
Cognitive dysfunction	
Mood disorder	
Psychosis	

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Serment d'Hippocrate

Au moment d'être admise à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admise dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçue à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonorée et méprisée si j'y manque.