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CONCISE REPORT

Conventional brain magnetic resonance imaging in the longitudinal evaluation of newly diagnosed systemic lupus erythematosus patients: a retrospective analysis from a single-centre cohort

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Introduction: Neuropsychiatric (NP) manifestations occur mostly in the early phases of the systemic lupus erythematosus (SLE) course. Nonspecific alterations are evident in conventional brain magnetic resonance imaging (MRI), regardless of clinically overt NP symptoms. The main aims of this study were to assess the prevalence of MRI abnormalities in newly diagnosed SLE, and to evaluate the impact of MRI changes during follow-up (FU) and the clinical course of NP symptoms. **Materials and methods:** Newly diagnosed SLE patients with a baseline brain MRI and with available repeated MRI during FU were retrospectively evaluated. White-matter lesions and atrophy were recorded, comparing NPSLE and non-NPSLE patients. Cox proportional hazard models were used to compare NP events during FU with MRI data. **Results:** Forty-four patients were included, 22 with NP events attributed to SLE. The baseline MRI scan was abnormal in 21 patients (47.73%). New NP events occurred in 17 patients, and worsening was found in repeated MRIs in 12 (27.27%). A worsening of MRI was associated with higher occurrence of new NP events during FU (adjusted hazard ratio 3.946 (1.175–13.253)). **Conclusion:** Baseline MRI is useful in patients with an early diagnosis of SLE, allowing comparison with subsequent scans. In our study, radiological worsening of repeated brain MRI was associated with new NP events. *Lupus* (2020) **0,** 1–6.

Key words: Systemic lupus erythematosus; neuropsychiatric lupus erythematosus; brain magnetic resonance imaging; early lupus; longitudinal evaluation; white-matter lesions

Introduction

Systemic lupus erythematosus (SLE) is a disabling systemic autoimmune disease, with multi-organ involvement and potential life-threatening complications.[1] Neuropsychiatric (NP) involvement is among the most troubling manifestations of the disease,[2,3] with different clinical syndromes affecting both central (CNS) and peripheral nervous systems.[4] Brain magnetic resonance imaging (MRI) is the method of choice in the clinical evaluation of patients with NP syndromes (NPSLE).[5] Approximately half of the clinical manifestations occur in the early phases of the disease,[6] with no predictive neuroradiological or immunological biomarkers to antedate the occurrence of such events. Fifty per cent of patients with long-standing SLE display MRI abnormalities,[2] whereas newly diagnosed SLE subjects, even in the absence of overt NP clinical symptoms, display several nonspecific alterations at conventional MRI, with up to 25% of subjects showing white-matter hyperintensities (WMHIs) or different degrees of cerebral atrophy[7]; however, the specific clinical significance of such alterations is unclear. In addition, most neuroimaging studies focus on patients with established SLE or past NP manifestations, making unclear the clinical significance of nonspecific WMHIs and other alterations detected on MRIs in patients with newly diagnosed SLE. The role, timing and usefulness for patients and clinicians of sequential instrumental examinations during follow-up (FU) is questionable. Therefore, we have undertaken a retrospective analysis of a single-centre cohort of SLE patients, longitudinally evaluated at the lupus clinic

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in Ferrara, Italy, with the main aims (i) to evaluate the prevalence of nonspecific brain MRI abnormalities (namely WMHIs and atrophy) in patients with an early diagnosis of SLE, depending on the presence or not of clinically overt NP manifestations; and (ii) to evaluate the impact of MRI changes during FU and the clinical course of NP symptoms.

Materials and methods

Study design and setting

This is a retrospective analysis of a single-centre cohort. The database population was defined as the whole SLE cohort of the lupus clinic at the Rheumatology Unit of the University of Ferrara, Italy, a tertiary referral centre with over 550 SLE patients. The Ethics Committee of the Province of Ferrara approved the study protocols.

Participants and variables

Inclusion criteria were the following: patients meeting the revised American College of Rheumatology (ACR)[8] or Systemic Lupus International Collaborating Clinics (SLICC)[9] classification criteria for SLE; aged less than 55 years old; and having undergone a baseline brain MRI within 24 months of SLE diagnosis, with at least one available FU MRI evaluation within the following 36–48 months. Patients followed between 1 January, 1995 and 31 December, 2013 were included. A detailed history from all participants prior to MRI examination was obtained (see Supplementary Material). NP events already present at baseline and those occurring during FU were collected and defined according to the 1999 ACR nomenclature.[4] A complete diagnostic work-up was performed according to European League Against Rheumatism (EULAR) recommendations.[5] Attribution of NP events was based on physician judgement and considered attributed to SLE (NPSLE group), according to the validated algorithm of the Italian study group on NPSLE.[10]

Brain MRI analysis

Patients were imaged with a conventional brain MRI (1.5 Tesla GE Signa HDX scanner) at baseline and during FU (the MRI analysis performed after the first evaluation acquired at baseline was taken into account, irrespective of the relationship with subsequent NP symptoms). Each MRI dataset was blindly evaluated by an experienced neuroradiologist (MB) who considered the absence or presence of WMHIs (scoring 0–3 if WMHIs were none, 1, 2–4, or >5 respectively) and atrophy (scoring 0–3 if absent, mild, moderate, or severe respectively), according to a modified semiquantitative scoring system derived from Petri et al.[7] (Table S1).

Statistical analysis

For the primary aims of our study, statistical analyses were performed by comparing mean (standard deviation, SD) and median (interquartile range, IQR) values for normally distributed and skewed variables, respectively, between NPSLE and non-NPSLE groups. Occurrence of new NP events during FU in SLE patients was compared with MRI data using Cox proportional hazard models, crude and adjusted for pre-specified confounders (age, sex, baseline attributed NP symptoms, and antiphospholipid (aPL) antibody positivity). Censoring date was defined according to one of the following conditions: occurrence of a new/first NP event during FU after baseline MRI, death, last rheumatological available visit for loss-to-FU or at the end of an established FU (31 January 2015), whichever came first. All the analyses were performed using Stata14 software (STATA Corporation, Texas, USA).

Results

Descriptive analysis

Forty-four patients met the inclusion criteria (mean (SD) age 33.9 years (10.7)), 22 (50%) with attributed NP events. Thirty-one baseline NP events were evaluated, 23 attributed to SLE (Table S5). No meaningful differences regarding demographic and clinical variables were retrieved between NPSLE and non-NPSLE patients (Table 1, Table S2), apart from a higher prevalence of serositis in the NPSLE group. Glucocorticoids (GCs), hydroxychloroquine (HCQ), antiplatelets, and anti-coagulants were similarly distributed, whereas the NPSLE group received more immunosuppressants than the non-NPSLE (15/22 (68.18%) vs. 3/22 (13.64%), $p = 0.001$).

Baseline brain MRI data analysis

The baseline MRI scan was performed after a mean (SD) period of 242.6 (215.0) days from SLE diagnosis. An altered baseline MRI scan was demonstrated in 21 patients (47.73%): 14 (63.64%) NPSLE and 7 (31.82%) non-NPSLE ($p = 0.0350$) (Table 2, Table S3)). Six cases showed cerebral atrophy (13.64%), and WMHIs were present in

Table 1 Descriptive analysis in newly diagnosed SLE patients with and without attributed NP events.

Variables	*NPSLE (N = 22)*	*Non-NPSLE (N = 22)*	p	*Total (N = 44)*
Gender (F)	20 (90.91)	21 (95.45)	0.550	41 (93.18)
Age at baseline, mean (SD)	33.5 (11.2)	34.3 (10.3)	0.7924	33.9 (10.7)
Presence of comorbidities,[a] *N* (%)	8 (36.36)	6 (27.27)	0.517	14 (31.82)
Malar rash, *N* (%)	3 (13.64)	2 (9.09)	1.000	5 (11.36)
Discoid rash, *N* (%)	3 (13.64)	0 (0)	0.233	3 (6.82)
Photosensitivity, *N* (%)	15 (68.18)	12 (54.55)	0.353	27 (61.36)
Oral ulcers, *N* (%)	3 (13.64)	1 (4.55)	0.607	4 (9.09)
Serositis, *N* (%)	5 (22.73)	0 (0)	*0.048*	5 (11.36)
Renal involvement, *N* (%)	0 (0)	4 (18.18)	0.108	4 (9.09)
Haematologic disorders, *N* (%)	11 (50.00)	7 (31.82)	0.220	18 (40.91)
Anti-dsDNA, *N* (%)	13 (59.09)	15 (68.18)	0.531	28 (63.64)
ENA, *N* (%)	9 (40.91)	10 (45.45)	0.761	19 (43.18)
Low complement levels, *N* (%)	15/18 (83.33)	17/19 (89.47)	0.585	32/37 (86.49)
aCL, *N* (%)	15 (68.18)	10 (45.45)	0.128	25 (56.82)
aB2GPI, *N* (%)	6 (27.27)	3 (13.64)	0.457	9 (20.45)
LAC, *N* (%)	12 (54.55)	5 (22.73)	0.062	17 (38.64)
APS, *N* (%)	7 (31.82)	3 (13.64)	0.210	10 (22.73)
GC,[b] *N* (%)	20/20 (100)	21/21 (100)		41/41 (100)
Cumulative GC dosage[b] (mg), mean (SD)	3665.6 (5298.5)	1823.3 (1286.0)	0.4021	2604.9 (3631.9)
HCQ,[b] *N* (%)	18/19 (94.74)	15/19 (78.95)	0.150	33/38 (86.84)
Immunosuppressants,[b] *N* (%)	15 (68.18)	3 (13.64)	*0.001*	18 (40.91)
Antiplatelet therapy,[b] *N* (%)	15/21 (71.43)	12/22 (54.55)	0.252	27/43 (62.79)
Anticoagulant therapy,[b] *N* (%)	5/21 (23.81)	2/22 (9.09)	0.240	7/43 (16.28)
SLEDAI-2K, mean (SD)	5.95 (4.30)	6.73 (3.89)	0.5385	6.35 (4.06)
SDI, mean (SD)	0.38 (0.67)	0.18 (0.39)	0.3553	0.28 (0.15)

[a]Presence of comorbidities: hypertension, diabetes, obesity, dyslipidemia, smoking habits were evaluated. [b]Treatment at baseline evaluation.
List of abbreviations: NPSLE: neuropsychiatric systemic lupus erythematosus (patients with NP events attributed to SLE); SD: standard deviation; anti-dsDNA: anti-double stranded DNA antibodies; ENA: anti-extractable nuclear antigen antibodies; aCL: anti-cardiolipin antibodies; aB2GPI: anti-beta-2 glycoprotein I; LAC: lupus anticoagulant; APS: antiphospholipid antibodies syndrome; GC: glucocorticoids; HCQ: hydroxychloroquine; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; SDI: Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index.

21 patients (47.73%). Mean WMHIs and mean atrophy semiquantitative scores between NPSLE and non-NPSLE were similar.

Follow-up brain MRI data analysis

The FU MRI scan was performed after mean (SD) 1163 (160) days from baseline. Worsening in semiquantitative MRI scores was documented in 12 patients (27.27%): 7 (31.82%) NPSLE and 5 (22.73%) non-NPSLE ($p = 0.4980$). Patients with lupus anticoagulant (LAC) positivity tended to display a higher rate of MRI worsening compared with patients with a stable/ameliorated MRI; ongoing treatment and relevant comorbidities did not effect meaningful changes (Table S4). During FU, 17 new NP events were found in 11 patients after mean (SD) 1272 (1087) days: 7/11 (63.64%) patients with new NP events had previously attributed NP manifestations, while 4 (36.36%) did not, $p = 0.296$ (Table S5). MRI worsening was associated with a higher risk of occurrence of new NP events during FU (crude hazard ratio (HR) 4.029 (95%CI 1.216–13.344), adjusted (i) HR 3.946 (1.175–13.253)) (Figure 1, Figure S1). The inclusion of aPL positivity in the model was associated with a lower (not statistically significant) HR. Worsening in the semiquantitative atrophy score was similarly associated with the occurrence of new NP events, whereas worsening in WMHI score was not.

Discussion

This retrospective analysis of a tertiary referral lupus clinic has demonstrated the usefulness of baseline conventional brain MRI when compared with FU evaluations in patients with a recent diagnosis of SLE. Conventional MRI abnormalities were common in newly diagnosed SLE subjects, even in the absence of overt NP manifestations, and MRI worsening was found to correlate with the occurrence of new NP symptoms throughout the clinical course of the disease, regardless of age, gender or baseline NP manifestations.

We confirmed evidence of abnormal baseline conventional MRI scans in patients with early

Table 2 Brain MRI data at baseline and follow-up.

Variables	*NPSLE (N = 22)*	*Non-NPSLE (N = 22)*	p	*Total (N = 44)*
Time interval between diagnosis and first MRI (days), mean (SD)	213.2 (198.4)	272.0 (231.3)	0.5184	242.6 (215.0)
Time interval between MRI scans (days), mean (SD)	1225.0 (1187.2)	1102.1 (947.1)	0.7063	1163.6 (160.3)
Baseline atrophy score: 0, *N* (%)	18 (81.82)	20 (90.91)	0.521	38 (86.36)
Baseline atrophy score: 1, *N* (%)	3 (13.64)	2 (9.09)		5 (11.36)
Baseline atrophy score: 2, *N* (%)	0 (0.00)	1 (4.55)		1 (2.27)
Baseline atrophy score: 3, *N* (%)	0 (0.00)	0 (0.00)		0 (0.00)
Baseline mean atrophy score, mean (SD)	0.23 (0.53)	0.09 (0.29)	0.3646	0.16 (0.43)
Baseline WMHIs score: 0, *N* (%)	8 (36.36)	15 (68.18)	0.201	23 (52.27)
Baseline WMHIs score: 1, *N* (%)	3 (13.64)	1 (4.55)		4 (9.09)
Baseline WMHIs score: 2, *N* (%)	5 (22.73)	13 (13.64)		8 (18.18)
Baseline WMHIs score: 3, *N* (%)	6 (27.27)	3 (13.64)		9 (20.45)
Baseline mean WMHIs score, mean (SD)	1.41 (1.26)	0.73 (1.16)	0.0690	1.07 (0.19)
Baseline abnormal MRI,[a] *N* (%)	14 (63.64)	7 (31.82)	*0.0350*	21 (47.73)
FU atrophy score: 0, *N* (%)	15 (68.18)	18 (81.82)	0.3040	33 (75.00)
FU atrophy score: 1, *N* (%)	5 (22.73)	4 (18.18)		9 (20.45)
FU atrophy score: 2, *N* (%)	2 (9.09)	0 (0.00)		2 (4.55)
FU atrophy score: 3, *N* (%)	0 (0.00)	0 (0.00)		0 (0.00)
FU mean atrophy score, mean (SD)	0.41 (0.67)	0.18 (0.39)	0.2499	0.30 (0.55)
FU WMHIs score: 0, *N* (%)	8 (36.36)	12 (54.55)	0.4800	20 (45.45)
FU WMHIs score: 1, *N* (%)	3 (13.64)	2 (9.09)		5 (11.36)
FU WMHIs score: 2, *N* (%)	3 (13.64)	4 (18.18)		7 (15.91)
FU WMHIs score: 3, *N* (%)	8 (36.36)	4 (18.18)		12 (27.27)
FU mean WMHIs score, mean (SD)	1.5 (1.34)	1.0 (1.23)	0.2044	1.25 (1.30)
FU abnormal MRI,[a] *N* (%)	15 (68.18)	11 (50.00)	0.220	26 (59.09)
Worsened atrophy score, *N* (%)	3 (13.64)	2 (9.09)	0.6350	5 (11.36)
Worsened WMHIs score, *N* (%)	5 (22.73)	4 (18.18)	0.7090	9 (20.45)
Worsened MRI, *N* (%)	7 (31.82)	5 (22.73)	0.4980	12 (27.27)

[a]abnormal MRI: presence of atrophy or WMHIs.
List of abbreviations: MRI: magnetic resonance imaging; NPSLE: neuropsychiatric systemic lupus erythematosus (patients with NP events attributed to SLE); SD: standard deviation; WMHIs: white-matter hyperintensities; FU: follow-up.

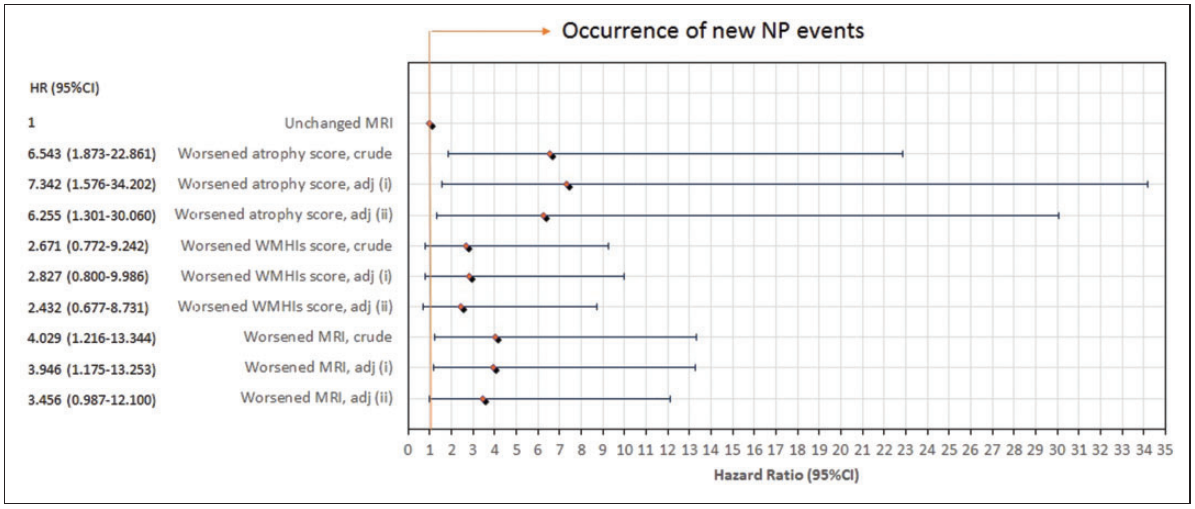

Figure 1 Relationship between MRI worsening and occurrence of NP manifestations during follow-up.
(i): adjustment for age, sex, NPSLE; (ii): adjustment for age, sex, NPSLE, aPL positivity.
MRI: magnetic resonance imaging; NP: neuropsychiatric; HR: hazard ratio; 95%CI: 95% confidence interval; NPSLE: neuropsychiatric systemic lupus erythematosus (patients with NP events attributed to SLE); aPL: anti-phospholipid antibodies; WMHIs: white matter hyperintensities.

diagnosis of SLE (47.7% of the patients meeting the eligibility criteria), in particular in NPSLE patients, but even in a substantial percentage of patients without NP events (31.8% of non-NPSLE; 20.0% of patients without any NP symptoms). Our data partially confirmed previous results,[7] which highlighted the prevalence of MRI abnormalities in 25% of cases, atrophy in 18% and WMHIs in 8% of early SLE subjects. Compared with our data, in that study fluid-attenuated inversion recovery images were not available for all patients, which could have reduced the global impact of WMHI recognition. Furthermore, the recruitment window of patients in this study was narrower than ours, limited to within 9 months from SLE diagnosis; this aspect could have reduced the prevalence of cerebral abnormalities with respect to our study group, in which inclusion was permitted up to 24 months from SLE diagnosis. However, in our dataset, the mean time interval between baseline scan and SLE diagnosis was less than 1 year, thus highlighting the early recognition of abnormalities in the course of SLE, with a trend towards higher prevalence of MRI abnormalities in patients with NP symptoms, either attributed to SLE or not. A higher prevalence of MRI abnormalities in NPSLE is widely recognized, even if data are heterogeneous, with different modalities of reporting MRI alterations, and with no abnormality considered specific to NPSLE. This occasionally generates a tangible clinical–radiological paradox in the presence of patients with NPSLE events displaying a completely normal MRI.[2] However, when multiple, occurring in the absence of cardiovascular risk factors and associated with elevated disease activity, T2-hyperintense lesions could be considered one of the hallmarks of NPSLE.[5] A better characterization of the morphology and properties of WMHIs is expected in the near future to profile the features of these lesions, to increase sensitivity and specificity to NPSLE, and to depict their association with small vessel disease and accelerated atherosclerosis in SLE patients.[11]

As the vast majority of brain MRI studies are performed in patients with established SLE, our findings could be of importance in depicting a population at risk of developing NP symptoms, in particular because of the recognized high occurrence of NP symptoms in the early phases of the disease.[2,6] Longitudinal evaluation of MRI is challenging in clinical settings, and how to manage worsening MRI findings in the absence of worsening clinical NP status has been debated. In our analysis, we demonstrated a worsening in the semiquantitative score in 12/44 cases; patients with LAC positivity were more likely to display such deterioration. Antiplatelet/anticoagulant therapies did not seem to play a protective role. aPL antibodies are intimately connected to the subclinical accrual of white-matter damage. In recent work from the Leiden NPSLE clinic,[12] patients with aPL positivity displayed more lacunar infarcts (odds ratio (OR) 1.37 (95%CI 1.02–1.99)) and gliosis (OR 2.15 (95%CI 1.37–3.37)) than aPL-negative patients, though aPL is not associated either with WMHIs or inflammatory-type lesions. The importance of sequential MRI evaluation in patients with SLE facing new NP symptoms is not surprising. In research by Piga et al.,[13] 23/30 patients had MRI worsening across a 20-year FU period, and patients with new NP events showed significantly higher cumulative MRI damage (OR 1.9 (95% CI 1.2–3.0)). Previously, other authors have demonstrated an increased rate of longitudinal MRI worsening in patients with previous CNS manifestations.[14,15] Our results suggest, similarly, that patients facing new NP symptoms are prone to progressive accrual of MRI abnormalities, and baseline MRI examination is of significant importance even in absence of overt NP symptoms.

Our study has some limitations: firstly, its retrospective design, incorporating data that were collected for nonresearch purposes. Moreover, as we selected only patients with available FU MRI scans, an MRI-driven selection bias cannot be excluded. However, MRI scans, for the purposes of this study, were selected irrespective of the occurrence of NP symptoms, thus reducing the weight of this possible bias; for this reason, it was not possible to infer a predictive role for worsened MRI in the occurrence of new NP events. We did not have a matched-control group to define normality in MRI assessment, and we adopted the semiquantitative scoring system derived from Petri et al.,[7] instead of other scales, for example, Fazekas' or Pasquier's scales (for WMHIs and atrophy definition, respectively).[12] None of the multiple quantitative and semiquantitative MRI scales have been validated for SLE.[2] We believe that young and recently diagnosed SLE subjects have less cerebral damage than elderly patients suffering from small vessel disease, and our approach, in line with previous studies,[7,13] could be more reliable in capturing early changes in the disease course.

The main clinical strength of this study is that it has underlined the importance of depicting a clinical–radiological picture in all patients with SLE at the time of diagnosis, in order to compare this initial portrait with subsequent ones, in particular when patients are facing new NP events, in an aim to provide improvements in recognition, attribution and, possibly, treatment.

Conclusions

Despite the limitations intrinsic in its retrospective nature, this study highlights the role of conventional brain MRI evaluation in patients with newly diagnosed SLE, even in the absence of overt NP symptoms, specifically, to compare this basal examination with further analysis performed during FU. Occurrence of new nonspecific MRI abnormalities could relate to the onset of NP manifestations in the patient's clinical history. This seminal evidence needs to be confirmed in prospective studies, combining conventional MRI with quantitative techniques, in order to profile those patients that need to be strictly monitored for occurrence of NP events, and to understand the pathogenic significance of brain MRI abnormalities in the context of SLE, which are far from understood at present.

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All the authors made substantial contributions to the concept or design of the work, or to the acquisition, analysis or interpretation of data; all authors drafted or critically revised the article for intellectual content, and approved the final version submitted for publication.

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Supplemental material

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