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Can conventional brain MRI support the attribution process in neuropsychiatric SLE? A multicentre retrospective study

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ABSTRACT

Objectives We aimed to investigate which elementary lesions, identified through conventional brain MRI, correlated with the attribution of neuropsychiatric (NP) manifestations of SLE as determined by clinical judgement (CJ) and a validated attribution algorithm (AA).

Methods We conducted a multicentre, retrospective cohort study of patients with SLE (1999–2018) from four tertiary SLE centres. Patients were assessed using American College of Rheumatology nomenclature and underwent MRI at their first NP event. NP manifestations were attributed to SLE using CJ and the AA. Elementary lesions were classified as follows: large infarcts, parenchymal haemorrhages, subarachnoid haemorrhages, inflammatory-type lesions, myelopathy, T2/fluid-attenuating inversion recovery (FLAIR) hyperintense lesions, lacunes, cerebral atrophy and microbleeds. Statistical analyses were performed using χ^2 and Fisher's exact tests. Univariable and multivariable logistic regression models were performed. A sensitivity analysis was performed using a revised AA, which excluded the item 'presence of abnormal MRI' from the list of favouring factors.

Results Among 154 patients, 88 (57%) had NP events attributed to SLE by CJ and 85 (55%) by AA. MRI was normal in 57/154 (37%) cases, while T2/FLAIR hyperintense lesions were the most frequent findings (71/154, 46%). A normal MRI was more common in non-attributed NP events per CJ and AA (OR 0.42, 95% CI 0.21 to 0.82 and 0.27, 95% CI 0.13 to 0.52, respectively). Cerebral atrophy was more frequent in non-attributed events per CJ (adjusted OR 0.06, 95% CI 0.01 to 0.35), while inflammatory-type lesions were more prevalent in SLE-attributed events according to AA (OR 3.91, 95% CI 1.15 to 18.1), with no significant change in sensitivity analyses.

Conclusions Our study elucidates the role of conventional MRI findings in the attribution process in NPSLE. The presence of selected elementary lesions or, instead, their absence could have a relevant weight in assessing NP events. These findings may assist clinicians in achieving a more accurate attribution of NP manifestations.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies have described a variety of MRI-detected lesions in patients with neuropsychiatric SLE (NPSLE), yet the specific contribution of individual or combined lesions on the attribution of NP manifestations to SLE remains poorly defined.

WHAT THIS STUDY ADDS

⇒ Although MRI findings are non-specific, a normal MRI points towards non-attributed NP manifestations, while inflammatory lesions are more strongly associated with NP events attributed to SLE.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides a comprehensive characterisation of elementary individual and combined MRI lesions in SLE, refining their diagnostic significance; this contributes to harmonisation of neuroimaging studies and accuracy of NPSLE attribution, until novel biomarkers become available.

INTRODUCTION

Neuropsychiatric (NP) involvement in SLE is a clinical challenge, and its diagnosis requires a comprehensive and multidisciplinary approach to rule out mimicking conditions.[1 2] To discriminate among the protean forms of NP involvement, clinicians should deal with clinical, laboratory, neurophysiologic and neuroimaging diagnostic procedures. The ultimate goal is to accurately attribute the NP event and tailor the pharmacological treatment in agreement with the suspected underlying pathogenic mechanism (eg, inflammatory vs thrombotic/ischaemic),[3–6] given the absence of validated and unequivocal diagnostic biomarkers. As confirmed by the recently released European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of SLE, a careful attribution process should always be performed when addressing neuropsychiatric SLE (NPSLE),[7] and the use of validated attribution models can provide valuable support. Among others, the validated attribution

algorithm (AA) proposed by the NPSLE study group of the Italian Society for Rheumatology (SIR) has demonstrated adequate sensitivity and specificity,[8 9] and it has been progressively implemented in both clinical evaluations and research settings.[1 10]

With reference to neuroimaging, conventional brain MRI is still considered the method of choice for evaluating patients with NP manifestations, although it may present non-specific lesions and can be negative in up to 40% of NPSLE cases.[3 11] Several elementary lesions have been described and associated with NPSLE, with white matter (WM) T2/fluid-attenuating inversion recovery (FLAIR) hyperintense lesions being the most common, yet least specific.[12 13] The presence of large infarcts or parenchymal haemorrhages has been linked to cerebrovascular events, while myelopathic lesions are characteristic of myelitis.[3] However, a full classification of brain MRI lesions has not been endorsed in NPSLE, and it is still unclear whether different types of lesions are associated with the proper diagnosis and attribution of NP manifestations to SLE according to validated algorithms. Advanced quantitative MRI techniques might aid to this end,[14] but they are still burdened by limited clinical applicability, which currently restricts their use to research purposes.[15–17] Recently, international groups have addressed the links between MRI lesions and attribution adopting volumetric analyses. Researchers highlighted that patients with NPSLE had higher T2/FLAIR hyperintense lesions volume than patients with NP events not attributed to SLE, in particular for 'inflammatory' phenotypes, and with a more complex shape of the lesions.[18–22] Concerning the distribution of the MRI lesions, applying a self-supervised contrastive learning method on T1-weighted images, the abnormalities located next to the lateral ventricles and periventricular WM, as well as the third ventricle and basal cisterns, were more common in NPSLE versus patients with non-SLE attributed NP events.[23] In parallel, the adoption of a fully automated method to identify predominant patterns of T2/FLAIR hyperintensities demonstrated that lesions involving the forceps major, forceps minor, the left and right anterior thalamic radiation and the right inferior fronto-occipital fasciculus were most suggestive of NP events attributed to SLE.[22]

Here, using a large multicentre cohort of patients with SLE assessed at the time of their first NP event, we aimed to assess the associations between MRI elementary lesions and: (1) attribution of NP events, evaluated through clinical judgement (CJ) or AA; (2) presence of a single NP manifestation or clusters; (3) choice of the pharmacological treatment.

MATERIALS AND METHODS

Study design and participants

This analysis was carried out adopting a retrospective multicentre cohort study.[10] Patients were eligible if they satisfied the 1997 revised American College of Rheumatology (ACR) classification criteria for SLE,[24] had their first-ever NP event, as defined in the ACR case definitions of NP syndromes,[25] and had available conventional MRI data at the time of the NP event. Patients pertaining to two centres from Italy (Ferrara, Cagliari), and one centre each from Greece (Heraklion) and Brazil (Campinas) were selected for the analysis.

Variables collected

Data were retrospectively collected for all patients by reviewing their clinical charts from 1999 to 2015. Access to medical records, particularly from earlier time periods, was primarily in physical format. Demographic variables registered for each patient included sex, ethnicity, serology, systemic manifestations, age at diagnosis of SLE, disease duration, SLE Disease Activity Index—2000 and Systemic Lupus International Collaborating Clinics/ACR Damage Index at the time of the first NP event.[26 27] Exposure to different therapeutic approaches is described in online supplemental materials.

Clustering of events

NP manifestations were clustered into three subgroups: focal central nervous system (CNS), diffuse CNS and peripheral nervous system (PNS) manifestations categorised per ACR recommendations.[25] Focal central events were cerebrovascular disease, movement disorder, myelopathy and seizure disorders; diffuse central events were aseptic meningitis, demyelinating syndrome, headache, acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder and psychosis; peripheral events were Guillain-Barré syndrome, autonomic neuropathy, mononeuropathy, myasthenia gravis, cranial neuropathy, plexopathy and polyneuropathy.

Conventional MRI data

MRI data were collected for clinical purposes at the time of the first NP event in all patients. The acquisition was performed adopting T1/T2-weighted, FLAIR, diffusion-weighted imaging and gadolinium-enhanced T1-weighted sequences, in compliance with the EULAR recommendations.[11] The details of the MRI scanner models and the corresponding magnet field strengths at each centre are described in the online supplemental materials. MRI images were reviewed by experienced neuroradiologists at each centre, blinded to clinical attribution, and detected lesions were classified, per protocol, as follows: large infarcts, parenchymal haemorrhages, subarachnoid haemorrhages, inflammatory-type lesions, T2/FLAIR hyperintensities (WM and grey matter (GM)), lacunes, cerebral atrophy and microbleeds[3 12] (online supplemental figure S1). Inflammatory-type lesions were defined according to the available literature, as T2/FLAIR hyperintense lesions involving GM or WM, generally medium-large, ill-defined, without vascular territory distribution, with possible mass effect or gadolinium enhancement.[3 28] Spinal cord MRI (when available) was performed to evaluate myelopathy in suspected cases.[3 29]

The same radiologist assessed all the MRI examinations at each centre.

Attribution of NP event

Attribution of NP events to SLE was established by CJ and AA.[8 9] In each centre, a careful assessment of clinical and laboratory findings was performed, by discussing attribution in the presence of lead experts in the field and, when necessary, adopting multidisciplinary team assessments.[10 30] The same team of clinicians assessed all the NP events at each centre. The AA proposed by the Study Group of the SIR is a validated instrument which includes four items: (1) the timing of onset of the NP event (ie, before, >6 months; concurrent, within 6 months or after SLE diagnosis); (2) the type of NP event (major vs minor/common, according to Ainiala *et al*[31]); (3) the presence of confounding non-SLE factors (ie, 'associations' suggested in the glossary for the 1999 ACR case definitions); and (4) the presence of 'favouring factors' (ie, supporting attribution).

Statistical analysis

Descriptive analyses were used to summarise all data with mean and SD or median and IQR, when appropriate. Comparison of continuous data with a normal distribution was performed using the t-test; continuous data with a non-parametric distribution were analysed using the Wilcoxon's rank-sum test.

For primary analyses, a comparison of categorical data was performed using the χ^2 test or Fisher's exact test (if appropriate) between events attributed or not according to (1) CJ or (2) AA. Sensitivity and specificity were calculated for the most frequent lesions. An univariable logistic regression model was performed to estimate the association between single MRI lesions and attribution according to CJ and AA. Then, a multivariable analysis was performed including each lesion and considering a normal MRI pattern as reference. Results were expressed as OR and 95% CI.

For secondary analyses, the distribution of each elementary lesion detected at MRI was compared (1) in each event type (according to ACR nomenclature)[25] and cluster (focal central, diffuse central, peripheral events), (2) according to the type of treatment adopted (antiplatelets, anticoagulant, antimalarials, immunosuppressants, steroids), by using the Fisher's exact test.

Since the AA recognises MRI alterations as factors supporting attribution, we performed sensitivity analyses assessing the validity of the AA in the absence of favouring factors related to neuroimaging (specifically the item for 'abnormal neuroimaging'),[8] resulting in a revised algorithm without MRI data. A further sensitivity analysis was performed by removing the PNS events in the entire cohort to assess the accuracy of the association between MRI lesions and CNS manifestations. We evaluated the distribution of elementary MRI lesions based on age at NP events (<50/≥50 years) and disease duration categories (<5/≥5 years). Finally, we assessed the frequency of the most relevant MRI lesions according to attribution (CJ) across the centres. All the analyses were performed with RStudio.[32]

RESULTS

Demographic and clinical data

Out of 154 NP events collected, 88 (57%) had events attributed to SLE according to CJ and 85 (55%) according to the AA. According to the type of NP events collected, the most frequent manifestation overall was headache, followed by cerebrovascular disorders (online supplemental table S1). Diffuse central events were the most common ones (84/154, 55%), prevalently not attributed according to CJ and AA (p=0.005 and <0.001, respectively). The characteristics of the included patients with NP events are presented in table 1 and online supplemental table S2. No significant difference emerged in demographic characteristics between attributed and non-attributed events. Similarly, the frequency of the other SLE manifestations (non-NP) and the presence of antiphospholipid antibodies syndrome did not differ between patients with attributed and non-attributed events (table 1 and online supplemental table S2). Most non-attributed events occurred after the diagnosis of SLE (47/154, 71% for CJ, 53/154, 77% according to AA, p=0.005).

Type and combination of elementary lesions detected with MRI

57/154 (37%) cases had normal MRI results. Hyperintense lesions in T2/FLAIR sequences were the most prevalent (71/154, 46%) findings, followed by large infarcts (17, 11%). Microbleeds and subarachnoid haemorrhages were not detected in the present cohort (table 2). Evaluating heatmaps of MRI lesions combinations (figure 1), we observed that myelopathy and large infarcts frequently appeared as isolated lesions. Hyperintense T2/FLAIR lesions were present either as a single type of lesion or in combination with inflammatory-type lesions and, less frequently, with atrophy.

Frequency of MRI elementary lesions according to the attribution to SLE

Normal MRI findings were more common in non-attributed events according to both CJ and the AA (32/25 for CJ, p=0.011; 37/20 according to AA, p<0.001) (table 2). A higher incidence of cerebral atrophy was observed in patients with NP events non-attributed to SLE according to CJ (8 (12%) vs 2 (2.3%), p=0.020), while inflammatory-type lesions (13 (15%) vs 3 (4.3%), p=0.027) and myelopathies (8 (9.4%) vs 1 (1.4%), p=0.043) were more frequent in those attributed according to AA. The frequency of T2/FLAIR hyperintensities, large infarcts and lacunes did not differ between the groups, either in the CJ or the AA cohorts (table 2), even when the analysis was restricted to central manifestations (figure 2). The presence of inflammatory-type lesions and myelopathies had good specificity for attribution using AA (95.65% and

Table 1 Demographic and clinical characteristics of patients with SLE included

Characteristics	Total, n=154	Attribution according to CJ (1=yes, 0=no)			Attribution according to AA (1=yes, 0=no)		
		1, n=88	0, n=66	P value*	1, n=85	0, n=69	P value*
Male sex, n (%)	16 (10)	11 (12)	5 (7.6)	0.3	12 (14)	4 (5.8)	0.092
Age at diagnosis, mean (SD)	37 (13)	37 (14)	36 (12)	0.9	37 (13)	37 (12)	>0.9
Disease duration, mean (SD)	46 (68)	35 (51)	60 (84)	**0.02**	45 (63)	47 (74)	0.3
Age at NP event, mean (SD)	40 (13)	40 (14)	41 (12)	0.5	40 (14)	41 (12)	>0.9
Timing of NP event, n (%)							
After	102 (66)	55 (62)	47 (71)		49 (58)	53 (77)	
Before	12 (7.8)	3 (3.4)	9 (14)		1 (1.2)	11 (16)	
Concurrent	40 (26)	30 (34)	10 (15)		35 (41)	5 (7.2)	
Antiphospholipid syndrome, n (%)	17 (11)	12 (14)	5 (7.6)	0.2	11 (13)	6 (8.7)	0.4
aPL positivity, n (%)	59 (39)	38 (44)	21 (33)	0.2	34 (40)	25 (37)	0.7
Therapy at the time of NP event, n (%)							
Antiplatelets	27 (18)	16 (18)	11 (17)	0.8	6 (7.1)	21 (30)	***<0.001***
Anticoagulant	8 (5.2)	6 (6.8)	2 (3.0)	0.5	5 (5.9)	3 (4.3)	0.7
HCQ	86 (56)	42 (48)	44 (67)	**0.019**	38 (45)	48 (70)	**0.002**
Immunosuppressants	24 (16)	10 (11)	14 (21)	0.10	12 (14)	12 (17)	0.6
Steroids	55 (36)	27 (31)	28 (42)	0.13	19 (22)	36 (52)	**<0.001**
SLEDAI-2K, mean (SD)	10 (9)	13 (10)	7 (5)	**<0.001**	13 (11)	7 (5)	**<0.001**
SDI, mean (SD)	0.54 (0.91)	0.58 (1.02)	0.48 (0.75)	>0.9	0.51 (0.96)	0.57 (0.86)	0.4
Event type, n (%)				**0.005**			**<0.001**
Diffuse central	84 (55)	38 (43)	46 (70)		30 (35)	54 (78)	
Focal central	52 (34)	37 (42)	15 (23)		42 (49)	10 (14)	
Peripheral	18 (12)	13 (15)	5 (7.6)		13 (15)	5 (7.2)	

p values in bold refer to p<0.05.
*Pearson's χ^2 test; Fisher's exact test.
AA, attribution algorithm; aPL, antiphospholipid antibodies; CJ, clinical judgement; HCQ, hydroxychloroquine; NP, neuropsychiatric; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

98.55%, respectively), with low sensitivity (online supplemental table S3).

Association of MRI elementary lesions and attribution to SLE

In univariable analyses, a normal MRI pattern associated with non-attribution according to both CJ and AA (OR 0.42, 95% CI 0.21 to 0.82, and 0.27, 95% CI 0.13 to 0.52, respectively) (table 2). Considering CJ, the presence of brain atrophy associated with lack of attribution in both univariable and multivariable models (OR 0.17, 95% CI 0.02 to 0.70 and 0.06, 95% CI 0.01 to 0.35, respectively). Moreover, myelopathies and T2/FLAIR hyperintensities were associated with CJ attribution in multivariable models, with a normal MRI as reference. With respect to AA, inflammatory-type lesions were associated with attribution in both univariable and multivariable models (OR 3.97, 95% CI 1.22 to 17.9 and 3.91, 95% CI 1.15 to 18.1, respectively), while myelopathies were only in the multivariable model (table 2).

Sensitivity analyses

Since abnormal neuroimaging was listed as a contributing factor in the original validated AA, we conducted a sensitivity analysis by removing the MRI item from the original AA. The revised algorithm reclassified only seven NP events (online supplemental figure S2). The primary results did not change (online supplemental table S4 and S5 and online supplemental figure S3). Similarly, after removing the 18 PNS events, no significant variation from primary results emerged (online supplemental table S6).

Based on sensitivity analyses stratified by age (<50/≥50 years) and disease duration (<5/≥5 years), we found a higher frequency of inflammatory lesions in the case of early disease (9 (19%) vs 7 (6.5%), p=0041) (online supplemental table S7). We observed that normal MRI was significantly more prevalent in non-attributed events (according to AA and CJ), among patients under 50 years of age and with a disease duration longer than 5 years.

Table 2 Frequency and associations of MRI elementary lesions according to attribution of the NP event (CJ and AA)

	Attribution according to CJ (1=yes, 0=no)				Univariable model			Multivariable model		
Lesions	**Tot, n=154***	**1, n=88***	**0, n=66***	**P value†**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Normal MRI	57 (37)	25 (28)	32 (48)	**0.011**	0.42	0.21 to 0.82	**0.011**	Ref.		
Large infarcts	17 (11)	10 (11)	7 (11)	0.9	1.08	0.39 to 3.13	0.9	2.55	0.77 to 10.0	0.14
Parenchymal haemorrhages	1 (0.6)	1 (1.1)	0 (0)	>0.9	–			–		
Subarachnoid haemorrhages	0 (0)	0 (0)	0 (0)		–			–		
Inflammatory-type lesions	16 (10)	10 (11)	6 (9.1)	0.6	1.28	0.45 to 3.95	0.6	1.19	0.38 to 4.04	0.8
Myelopathy	9 (5.8)	8 (9.1)	1 (1.5)	0.079	6.50	1.15 to 122	0.081	9.21	1.55 to 176	**0.042**
T2/FLAIR hyperintensities	71 (46)	44 (50)	27 (41)	0.3	1.44	0.76 to 2.77	0.3	2.32	1.14 to 4.83	**0.023**
Lacunes	6 (3.9)	4 (4.5)	2 (3.0)	0.7	1.52	0.29 to 11.2	0.6	2.48	0.38 to 26.0	0.4
Cerebral atrophy	10 (6.5)	2 (2.3)	8 (12)	**0.020**	0.17	0.02 to 0.70	**0.028**	0.06	0.01 to 0.35	**0.005**
Microbleeds	0 (0)	0 (0)	0 (0)		–			–		
Unknown	1	1	0							
	Attribution according to AA (1=yes, 0=no)				**Univariable model**			**Multivariable model**		
Lesions	**Total, n=154***	**1, n=85***	**0, n=69***	**P value†**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Normal MRI	57 (37)	20 (24)	37 (54)	**<0.001**	0.27	0.13 to 0.52	**<0.001**	Ref.		
Large infarcts	17 (11)	12 (14)	5 (7.2)	0.2	2.10	0.74 to 6.91	0.2	3.26	1.04 to 11.8	0.053
Parenchymal haemorrhages	1 (0.6)	1 (1.2)	0 (0)	>0.9	–			–		
Subarachnoid haemorrhages	0 (0)	0 (0)	0 (0)		–			–		
Inflammatory-type lesions	16 (10)	13 (15)	3 (4.3)	**0.027**	3.97	1.22 to 17.9	**0.037**	3.91	1.15 to 18.1	**0.045**
Myelopathy	9 (5.8)	8 (9.4)	1 (1.4)	**0.043**	7.06	1.25 to 133	0.069	9.78	1.61 to 188	**0.038**
T2/FLAIR hyperintensities	71 (46)	43 (51)	28 (41)	0.2	1.50	0.79 to 2.86	0.2	1.93	0.95 to 3.95	0.070
Lacunes	6 (3.9)	3 (3.5)	3 (4.3)	>0.9	0.80	0.14 to 4.47	0.8	0.66	0.10 to 4.02	0.6
Cerebral atrophy	10 (6.5)	6 (7.1)	4 (5.8)	>0.9	1.23	0.34 to 5.00	0.8	0.67	0.14 to 3.22	0.6
Microbleeds	0 (0)	0 (0)	0 (0)		–			–		
Unknown	1	1	0		–			–		

The multivariable model estimates the association between single MRI lesions and attribution according to CJ and AA, considering a normal MRI pattern as reference.
p values in bold refer to p<0.05.
*n (%); mean (SD).
†Pearson's χ^2 test; Fisher's exact test.
AA, attribution algorithm; CJ, clinical judgement; FLAIR, fluid attenuated inversion recovery; NP, neuropsychiatric.

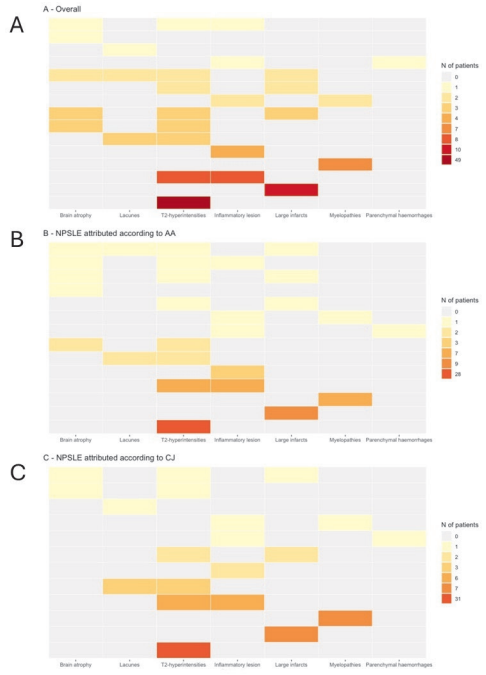

Figure 1 Heatmap of combinations of MRI elementary lesions in patients with NPSLE. Columns identify the individual lesions, rows represent a combination of the different MRI lesions observed, while the colours highlight the frequency of each combination (ie, in (A), T2/fluid-attenuating inversion recovery hyperintensities were observed more frequently isolated (49) or in combination with inflammatory lesions (8)). (A) All patients. (B) Patients with attribution according to AA. (C) Patients with attribution according to CJ. AA, attribution algorithm; CJ, clinical judgement; NPSLE, neuropsychiatric SLE.

In cases with abnormal MRI findings, inflammatory-type lesions were more common in patients with a disease duration of less than 5 years (9 (19%) vs 7 (6.5%), p=0.041) and in events attributed according to AA, especially in patients younger than 50 years (p=0.041). Brain atrophy was more frequently observed in non-attributed events according to CJ, particularly in patients with a disease duration exceeding 5 years (p=0.031), although this association was not statistically significant when assessed according to age at NP event. The frequency of the most relevant MRI features according to attribution per CJ did not significantly differ across the centres that assessed the majority of the patients (online supplemental table S8).

Frequency of MRI elementary lesions according to clusters of NP manifestations and treatment choice

A normal MRI was more common in cases of central diffuse events (eg, headache, mood disorders, aseptic meningitis) (44 cases, 52%, p<0.001). Large infarcts, lacunes and myelopathies were observed almost exclusively in central focal events (table 3, online supplemental table S9 and S10). Online supplemental table S2 shows the distribution of each NP manifestation according to the type of single NP events. No significant association was found between event clusters and T2/FLAIR hyperintense or inflammatory-type lesions. No distinct treatment pattern emerged across specific lesion types relative to NP event clusters; however, corticosteroid use was more prevalent in inflammatory-type lesions in the case of focal central events (online supplemental table S11).

DISCUSSION

Brain MRI remains the elective imaging method for assessing NP manifestations of SLE; however, the role of different elementary lesions observed in cases of SLE with NP manifestations still needs to be addressed.[3 33] To the best of our knowledge, this study is the first to demonstrate, through a large multicentre cohort of patients with NPSLE observed at the time of their first-ever NP event, the significance of the elementary lesions detected by brain MRI in relation to the attribution process according to CJ and a validated AA.[9] We demonstrated an influence of single elementary lesions, for example, inflammatory lesions, myelopathy, atrophy, in the attribution process, while the presence of normal neuroimaging associates with non-attributed events according to both CJ and the AA.

Even if brain MRI is the neuroimaging method of choice in the assessment of NPSLE, as suggested by the EULAR recommendations,[11] a validated classification of brain MRI elementary lesions in the context of NPSLE is missing. Our group previously proposed a clinical distinction based on the hypothetical acute or chronic appearance,[3] and here we focused only on the most common MRI findings. The absence of a fully accepted classification of the individual types of lesions justifies the large heterogeneity present in the literature.[34 35] Again, in recent years, the research in the field prevalently focused on advanced quantitative MRI, and the assessment of elementary lesions, although with relevant clinical implications, was performed prevalently in case series or in single centre case–control studies.[12 33 36–38] Advanced MRI techniques remain primarily a peculiarity for research; in fact, even if these techniques can be useful at single-patient level, the majority of published studies focused on group differences in single centre analyses, and the challenges in standardising multicentre protocols should be overcome with concerted efforts before being tested in prospective studies.[16 39 40] Moreover, one of the main barriers to the generalisability of the literature on MRI lesions and NPSLE is the lack of a standardised attribution process for NP events in the published works. Since the expert opinion remains the gold standard to define NPSLE, the use of validated AAs is an exception in MRI studies conducted in NPSLE.[22 41] Recently, Ramirez *et al* adopted the SIR AA to define NPSLE in a cross-sectional study with volumetric MRI analyses.[19] Here, the authors evaluated patients with and without NP involvement, and the AA was coupled to clinical impression in the assessment of the NP event. In other studies, a multidisciplinary team consensus was employed to refine the attribution, as in the Leiden NPSLE cohort.[18 21]

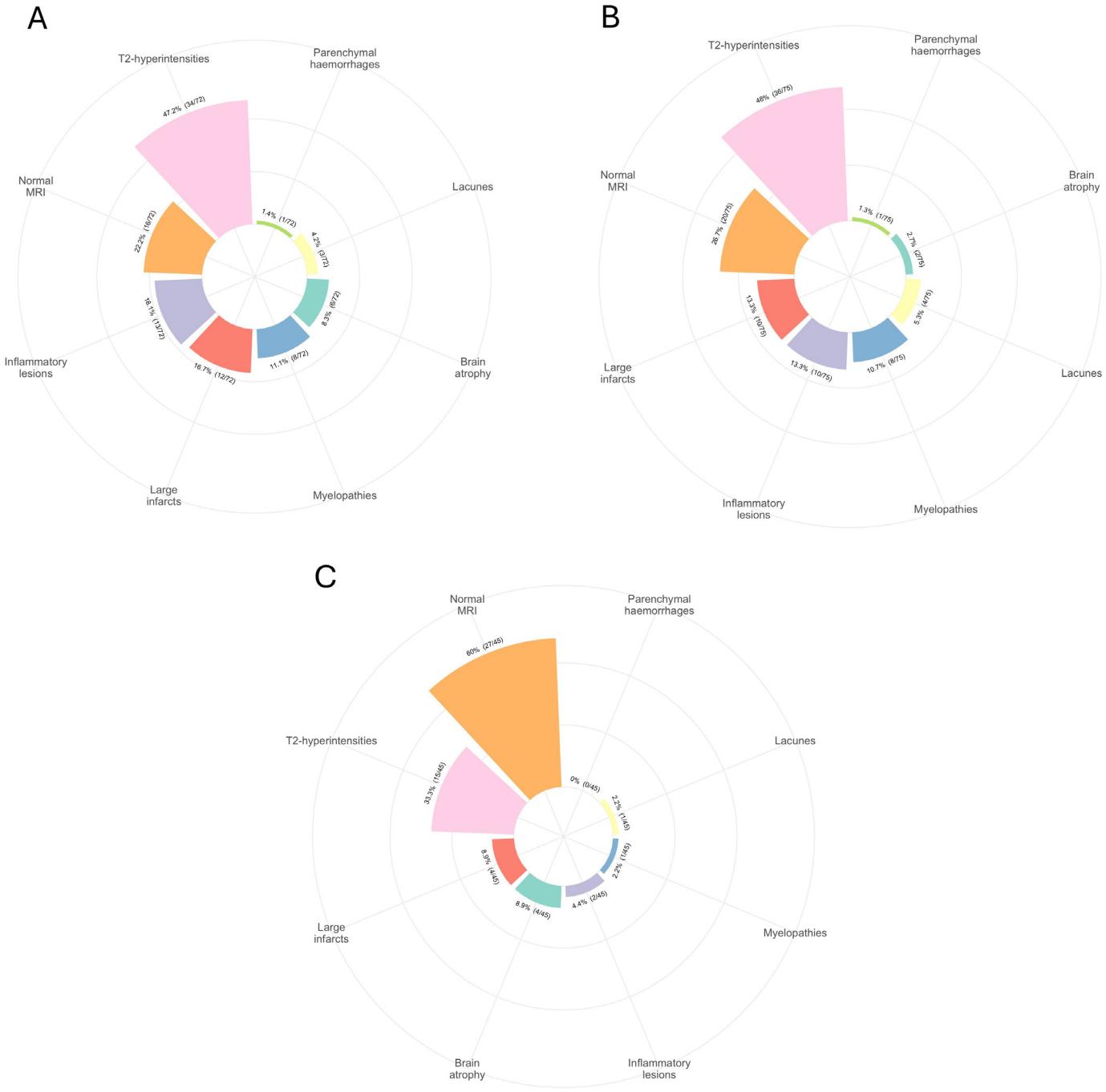

Figure 2 Schematic representation of the frequency of MRI lesions in CNS events (diffuse or focal central events) attributed according to AA (A), CJ (B), not attributed according to any of the rules (C). Each trapezoid area identifies a selected lesion, proportional to the frequency of the lesion among all the CNS events. AA, attribution algorithm; CJ, clinical judgement; CNS, central nervous system.

In line with the literature,[6 12] we found that normal brain MRI was present in nearly 40% of cases. In our cohort, normal MRI was predominantly associated with non-attributed events according to both CJ and AA, confirmed by logistic regression models. This may have significant implications in supporting expert clinicians in the interpretation and contextualisation of individual NP manifestations. In addition, the AA corroborated expert opinion, as the absence of any lesions detected by MRI, despite being non-specific, could be considered an aspect supporting the lack of attribution. On the contrary, we found a significant association between cerebral atrophy and the absence of attribution according to CJ (but not AA), as well as an (expected) association between specific MRI lesions, such as inflammatory-type lesions and—to a lesser extent—myelopathies and attributed events according to AA; interestingly, this association was not confirmed in the case of CJ. We should underline that several other studies have analysed the presence of elementary lesions in brain MRI of NPSLE.[36 42–44] In one of

Table 3 Frequency of MRI elementary lesions according to clusters of NP events

Lesions	Overall, n=154	Diffuse central, n=84	Focal central, n=52	Peripheral, n=18	P value*
Normal MRI, n (%)	57 (37%)	44 (52%)	6 (12%)	7 (39%)	**<0.001**
Large infarcts, n (%)	17 (11%)	0 (0%)	17 (33%)	0 (0%)	**<0.001**
Parenchymal haemorrhages, n (%)	1 (0.6%)	0 (0%)	1 (1.9%)	0 (0%)	0.5
Subarachnoid haemorrhages, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Inflammatory lesion, n (%)	16 (10%)	8 (9.5%)	7 (13%)	1 (5.6%)	0.7
Myelopathies, n (%)	9 (5.8%)	1 (1.2%)	8 (15%)	0 (0%)	**0.002**
T2/FLAIR hyperintensities, n (%)	71 (46%)	34 (40%)	26 (50%)	11 (61%)	0.2
Lacunes, n (%)	6 (3.9%)	1 (1.2%)	5 (9.6%)	0 (0%)	**0.041**
Brain atrophy, n (%)	10 (6.5%)	5 (6.0%)	5 (9.6%)	0 (0%)	0.4
Cerebral microbleeds, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

p values in bold refer to p<0.05.
*Fisher's exact test.
FLAIR, fluid attenuated inversion recovery; MRI, Magnetic Resonance Imaging; NP, neuropsychiatric.

the most important studies, Luyendijk *et al* assessed individual MRI lesions (hyperintensities, parenchymal defects and atrophy) in patients with NPSLE, as defined by expert opinion, during their first active episode of NP manifestations.[12] A normal brain MRI was detected in 31/74 (42%) patients, while T2/FLAIR hyperintensities were confirmed as the most frequent finding, present in almost half of the patients. However, no formal comparison was performed between attributed and non-attributed events, similarly to other reports.[28] The role of MRI elementary lesions in the attribution of NP manifestations to SLE has been investigated recently, mostly focusing on T2/FLAIR hyperintensities and adopting volumetric analyses. A single-centre study identified a higher T2/FLAIR hyperintensities volume in AA-attributed NPSLE with respect to controls and non-NP SLE patients, suggesting that implementing volumetric analyses might aid in attribution.[19] In our study, we found a higher association of T2/FLAIR hyperintensities with attributed NP events according to CJ in multivariable analyses, but volumetric analyses were not available. Moreover, in the cited study, patients with attributed NPSLE were mostly compared with patients without NP symptoms.[19] Recently, adopting multidisciplinary team consensus to establish attribution, higher T2/FLAIR hyperintensities volumes, higher numbers of deep lesions and a more complex shape were highlighted in NPSLE, prevalently in inflammatory patterns.[18 20 22] Although these works are innovative for the type of techniques adopted and rigorous for the patients' evaluation methods applied, they lack the assessment of other elementary lesions different from T2/FLAIR hyperintensities. With respect to atrophy, several works suggest a higher prevalence in NPSLE with respect to non-NP SLE patients,[41] but the comparison between attributed and non-attributed events has been less extensively performed. We also assessed how the individual types of lesion combined with each other, highlighting that T2 hyperintensities, inflammatory lesions and large infarcts were found frequently alone, but we also confirmed a combination of T2 hyperintensities and other types of lesions (eg, atrophy), as described in similar papers.[12 28] We should underline that the presence of abnormal MRI imaging is enlisted among the factors favouring the attribution of NP events in the AA purposed by the SIR.[8] Therefore, we performed sensitivity analyses considering a revised AA, excluding the item related to neuroimaging abnormalities. Our main result remained consistent, suggesting that neuroimaging assessment had a minimal impact on the overall results of the AA in this cohort, but even that a more reasoned assessment of neuroimaging can have a relevant role in the attribution process, allowing for potential refinements of the AA with neuroimaging data, as suggested by other authors.[19] Besides, we should underline that the refinement of the AA might generate a variation in the threshold necessary for attribution, and these aspects should be tested in future prospective studies. Moreover, we did not demonstrate significant differences in the frequency of elementary lesions according to age and disease duration, apart from a slightly higher frequency of inflammatory lesions in the case of shorter (<5 years) disease duration. In the literature, a higher number of T2/FLAIR hyperintensities correlated with age,[43] while higher T2/FLAIR hyperintensities volumes correlated with longer disease duration[18 19] but, again, the assessment of attribution was not uniformly performed. The absence of volumetric analyses in our dataset precludes the comparison with other works on cerebral atrophy, which reported lower WM and GM volumes in case of longer disease duration, as well as with higher corticosteroid dosages.[45–47] Here, a normal MRI was more common in non-attributed events according to AA and CJ in younger patients and longer diseases, suggesting that the absence of lesions in these contexts could be helpful for attribution assessment. In

parallel, brain atrophy confirmed its association with non-attributed events according to CJ only for disease duration categories longer than 5 years, while inflammatory-type lesions were more frequent in attributed events according to AA in patients<50 years old.

Our results align with the necessity to improve the clinical value of conventional MRI interpretation in practice.[11] In the literature, however, more advanced quantitative MRI techniques were adopted to this end. For instance, the WM magnetisation transfer ratio histogram peak heights were significantly different in inflammatory versus ischaemic NPSLE, or SLE without NP symptoms, and changed consistently with modifications in disease status during follow-up.[33 48] Perfusion parameters, and specifically the cerebral blood flow in the left semioval centre, displayed good sensitivity and specificity in discriminating primary NPSLE,[14] and resting-state functional MRI analysis has shown promising results, as well.[49] The potential to further homogenise advanced MRI protocols and MRI data analyses across different centres is fascinating, and combining data from conventional MRI studies might help target a multifactorial stratification of attributed events and clusters, in line with emerging approaches in the context of SLE-related cognitive impairment.[50]

The secondary objective of this study was to assess the relationship between MRI lesions and the patterns of events. We demonstrated that a normal MRI pattern was more common in the case of central diffuse events, while large infarcts, lacunes and myelopathies occurred in the case of central focal events. A similar analysis was performed by Sarbu *et al*,[28] but a formal comparison remains difficult as no distinction was made between focal and central clusters of events. Moreover, we assessed the association between elementary lesions and selected treatment choices, according to the cluster of NP event. The trajectories of treatments adopted for individual types of lesions reflected mostly the cluster of NP events. However, we documented a higher prevalence of corticosteroid use in case of inflammatory-type lesions for focal central events. Even if the exiguity of data for certain lesions precludes a more robust reasoning, these considerations reinforce the idea that conventional brain MRI is not only a tool to rule out other (secondary) diagnoses, but remains a useful method for a comprehensive clinical and prognostic assessment of the patient with NP symptoms.

Our work has several limitations that we should mention. First, the retrospective design of the study prevented us from collecting specific information not included in the original dataset which could have influenced MRI data, for example, the comorbidities,[10] the cumulative dosage of corticosteroids[43 45 46] or follow-up data[33]; second, we did not enrol patients with rarer clinical manifestations, such as mononeuropathy, myasthenia gravis, autonomic neuropathy and plexopathy. With reference to the type of lesions, we focused on selected MRI alterations,[3] and we considered T2/FLAIR hyperintensities globally, without information on the shape, the volume and the location.[20 51 52] Since GM T2 hyperintense lesions were found in only two cases of this cohort, these were evaluated along with WM T2 hyperintense lesions.[12] In parallel, we acknowledge the lack of advanced quantitative MRI techniques or relevant biomarker assessment as a limitation; however, the focus of the work was on conventional MRI, and this increases its overall clinical applicability. The absence of a central blinded evaluation of MRI images may have induced a variability in reporting the presence of specific lesions, but this increases the generalisability to real-life clinical practice, as well, given the overall homogeneity in the assessment of patients with NPSLE in the centres. Although a formal inter-rater agreement analysis among the clinical teams and radiologists from the four referral centres was not performed, we conducted sensitivity analyses to account for the contribution of each centre in assessing the most relevant MRI features. Finally, it should be noted that the MRI assessments required for the purposes of this analysis might have introduced a selection bias with the inclusion of more severe NP events. Notwithstanding these limitations, the strengths of this work refer to the assessment of a large multicentre cohort with a standardised approach to NPSLE, evaluated at their first ever NP event attributed adopting a validated AA.

CONCLUSIONS

Conventional brain MRI supports the attribution process in NPSLE, and the presence of selected elementary lesions or, instead, their absence could have a relevant weight in the assessment of NP events, at least at the time of their initial evaluation. Clinicians should perform brain MRI not only to exclude secondary causes but also to refine their critical approach to NP symptoms, until more specific (neuroimaging) biomarkers could modify the actual diagnostic paradigm in NPSLE.

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