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ORIGINAL ARTICLE

Markers of acute neuropsychiatric systemic lupus erythematosus: a multidisciplinary evaluation

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Abstract This study was aimed to assess: (1) the additive diagnostic utility of diffusion-weighted imaging (DWI) and magnetic resonance angiography (MRA) over conventional MRI in detecting brain lesions in patients with acute primary neuropsychiatric systemic lupus erythematosus (NPSLE), and (2) the relevance of their findings to the associated NP manifestations. Included were 34 patients with acute NPSLE with mean age of 33.26 ± 10.14 years and duration of illness of 3.33 ± 1.71 years. Clinical interviewing and psychiatric and cognitive evaluations were performed by applying the criteria of the diagnostic and statistical manual of mental health disorders criteria (DSM–IV), Stanford Binet Subset Testing, Mini-Mental State Examination and Wechsler Memory Scale-Revised. Serologic tests included looking for antinuclear antibodies, anti-double strand DNA, anti-phospholipid antibodies. Radiologic evaluation included conventional MRI, DWI and MRA. One or more NP manifestations were diagnosed in 28 patients, in which cognitive deficits were reported with headache, psychosis and CVS. Anti-phospholipid antibodies were reported in patients with CVS. Twenty patients (71.43 %) with primary NPSLE ($n = 28$) had MRI abnormalities in which hyperintense signals at subcortical and periventricular white matter and at the junction between the gray and white matter represented 75 % ($n = 15$) and with headache ($n = 6$), psychosis ($n = 6$) and acute confusional state ($n = 3$) with and without cognitive deficits, respectively. Moderate-sized infarctions with restricted diffusion in the distribution of middle cerebral arteries were represented in 35 % ($n = 7$) and with CVS, of them, 71.43 % ($n = 5$) had beading and focal narrowing of carotid arteries were consistent with vasculitis. Brain atrophy represented 20 % ($n = 4$) and with psychosis. Compared to those with normal MRI, patients with MRI abnormalities were older ($P < 0.050$) and had longer duration of illness ($P < 0.050$). To conclude, although DWI and MRA are helping in more precise etiopathologic diagnosis compared to conventional MRI, but their relevance to the present NP manifestations is still limited.

Keywords Systemic lupus erythematosus · Neuropsychiatric systemic lupus erythematosus · Magnetic resonance imaging · Diffusion-weighted imaging · Magnetic resonance angiography

Abbreviations

SLE	Systemic lupus erythematosus
NP	Neuropsychiatric
NPSLE	Neuropsychiatric systemic lupus erythematosus
CNS	Central nervous system
CVS	Cerebrovascular stroke
MRI	Magnetic resonance imaging

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T1WI	T1-weighted imaging
FLAIR	Fluid attenuation recovery-weighted images
DWI	Diffusion-weighted imaging
MRA	Magnetic resonance angiography
DSM–IV	Diagnostic and statistical manual of mental health disorders 4th (edition)
SBST, 4th edition	Stanford Binet subsets testing (4th edition)
MMSE	Mini-mental state examination
WMS-R	Wechsler memory scale-revised
SLEDAI	Systemic lupus erythematosus disease activity index
ANA	Antinuclear antibodies
a-dsDNA-a	Antibodies to double-stranded DNA
aPL-a	Anti-phospholipid antibodies

Introduction

Systemic lupus erythematosus (SLE) is a worldwide multisystem autoimmune disease of unknown etiology [1]. It has different prevalence, clinical manifestations and severities, with incidence rates ranging from 1 to 32/100,000 [2] and prevalence rates of 39–51/100,000 [3]. It is usually present in adulthood and affecting ten times as many women as men. Mucocutaneous, articular, renal, serosal, hematologic and immunologic involvements are its main clinical features [4]. Neuropsychiatric SLE (NPSLE) is the 2nd or 3rd most common cause of morbidity and mortality in patients with SLE after renal or infectious complications. Non-SLE diseases (such as infection, hypertension or metabolic derangements such as uremia) or drug side effects represent >60 % of causes of NPSLE (secondary NPSLE), while <40 % are diagnosed by exclusion (primary NPSLE) and may occur at any time during the course of SLE [5, 6]. In 1999, The American College of Rheumatology published the nomenclature and case definitions of primary neuropsychiatric lupus syndromes [6]. They are categorized into: (1) central nervous system (CNS) syndromes (such as aseptic meningitis, cerebrovascular stroke (CVS), seizures, demyelinating syndrome, movement disorder and myelopathy), (2) peripheral nervous system syndromes (such as acute inflammatory demyelinating polyradiculopathy, autonomic disorders, mononeuropathy, myasthenia gravis, cranial neuropathy, plexopathy and polyneuropathy), and (3) diffuse psychiatric/neuropsychological syndromes (such as cognitive deficits, headache, acute confusional state, mood disorders, anxiety and psychosis). The frequency rates of NPSLE are highly variable ranging from 11 to 95 %, which is attributed to the difficulty in diagnosis, differences in the applied diagnostic criteria and poor definitions. Some authors suggest that the number of NPSLE syndromes goes beyond the 19 standardized syndromes and expands from subtle neurologic or psychiatric manifestations (such as neurocognitive dysfunctions and mood changes which are diagnosed by neurophysiological, neuropsychological and neuroimaging testing) to overt manifestations [7, 8]. The course of SLE is highly variable, involving non-organ-threatening symptoms (such as arthritis, arthralgia and rashes) and organ-threatening symptoms such as lupus nephritis and NP disorders [5].

The pathogenesis of primary NPSLE remains poorly understood; however, it has been believed that multiple and complex brain-reactive autoantibodies and cytokine-enhanced autoimmunity and immune complexes are the causes of neuronal cell injury and/or rheological disturbances with vasculopathy, coagulopathy or thrombosis and NP manifestations [9–12]. The reported pathologies include microinfarcts, ischemic demyelination, gross infarcts, hemorrhage, cortical atrophy, (neuronal/axonal loss and atrophy), demyelination and gliosis [13]. Cytotoxic drugs are the main treatment of NPSLE [14].

Early recognition and evaluation of NPSLE is of paramount importance as NPSLE represents 7–13 % of deaths from SLE [5]. Abnormal psychological or behavioral, laboratory (blood and cerebrospinal fluid serology) and radiologic testing were reported in some patients with NPSLE [8–12, 15]. However, no single test with high sensitivity and specificity is available to confirm the diagnostic of NPSLE, and the relevance between NP manifestations, lab results, neuroimaging findings and etiopathologic process(s) is still a challenge.

Conventional magnetic resonance imaging (MRI) is valuable in detecting CNS lesions particularly in acute focal NP manifestations; however, its diagnostic value is limited due to the facts that, in diffuse manifestations (e.g., cognitive dysfunction, acute confusional state, headache, etc.), it is usually unremarkable or shows non-specific abnormalities; and conversely, abnormalities in MRI-brain were detected in some patients without NP manifestations [8]. It has been reported that advanced MRI techniques (e.g., functional and quantitative MRIs) permit easy and clear detection of different macroscopic and microscopic brain lesions, atrophic changes and detection of changes in cerebral blood flow and brain metabolism. The findings of advanced MRI techniques were found to be associated with neurologic, psychiatric and cognitive abnormalities in SLE [8, 15–19].

Aim of the work

This work aimed to assess: (1) the additive diagnostic utility of DWI and MRA over conventional MRI in

detecting brain lesions in patients with acute primary NPSLE, and (2) the relevance of their findings' to the associated NP manifestations.

Materials and methods

Subjects

In this study, included were 34 consecutive patients with confirmed diagnosis of NPSLE (according to ACR classification criteria and definitions [6]). To recruit patients, clinical interviewing and evaluation were performed by specialized rheumatologists and an internist. Patients were recruited over a period of 6 months from the outpatient clinics of the departments of Rheumatology and Rehabilitation and Internal Medicine of Assiut University Hospital (a tertiary referral hospital), Egypt. Excluded were patients with: (1) minor symptoms that are uncontemplated by case definitions (such as poor concentration and mood swings) or when there is difficulty to differentiate the origin of symptoms, (2) non-SLE causes of psychiatric (such as reactive depression or anxiety) or neurologic symptoms (such as bacterial, viral, fungal and parasitic cerebral infections) and primary CNS lymphoma, (3) preexisting cardiovascular (such as angina, myocardial infarction, etc.) and cerebrovascular events (such as transient ischemic attack, ischemic CVS, intracranial hemorrhage, etc.), or other systemic diseases (such as atherosclerosis, liver and endocrinal diseases), (4) other connective tissue diseases such as secondary Sjögren's syndrome [in which dry eyes (xerophthalmia) and keratoconjunctivitis and dry mouth (xerostomia) are its main symptoms and occur after onset of SLE] [20], mixed connective disease [in which there is an overlap between different autoimmune diseases, particularly SLE, scleroderma and polymyositis and also characterized by high quantities of antinuclear antibodies (ANAs); but do not typically have double-stranded DNA antibodies (a-dsDNA-a) that are common in SLE] [21], and (5) cancer discovered within the previous 5 years and drug abuse or alcoholism.

The study protocol was approved by the ethics committee of the Faculties of Medicine of Assiut and Sohag Universities, and informed written consent was obtained from each participant.

Neuropsychiatric assessment

Clinical interviewing, psychiatric and cognitive function evaluations were performed by an experienced neurologist and a psychiatrist using the following: (1) The Diagnostic and Statistical Manual of Mental Health Disorders, 4th edition (DSM–IV) [22], (2) a battery of Arabic translated neuropsychiatric testing for different cognition domains including attention, memory, comprehension, psychomotor speed, visuospatial processing, abstraction, reasoning and problem solving, which include (a) Stanford Binet Subsets Testing (SBST) (4th edition) [23], (b) Mini-Mental State Examination (MMSE) [24] and (c) Wechsler Memory Scale-Revised (WMS-R) [25] as described before [26].

Laboratory evaluation

As the part of the initial evaluation, chest X-ray, electrocardiograms, abdominal ultrasonography, electroencephalography (EEG) and routine laboratory tests were performed. Peripheral blood was collected to assess hematologic, biochemical and serologic variables related to SLE, which included (a) *routine tests*: blood sampling for the examination of complete blood picture (CBC), erythrocytic sedimentation rate (ESR), urea, creatinine, liver functions, glucose, uric acid, lipogram, creatine phosphokinase (CPK), lactic dehydrogenase (LDH) and creatinine clearance and 24 h urine sampling for protein estimation, (b) *special tests*: serologic tests included looking for ANA, a-dsDNA-a and anti-phospholipid (aPL-a) antibodies. ANA were tested using indirect immunofluorescence method using HEp-2 cells as substrate. a-dsDNA-a were tested by indirect immunofluorescence on Crithidia luciliae. aPL-a were tested by direct binding enzyme-linked immunosorbent assay (ELISA). Controls for laboratory and serological comparisons were obtained from healthy blood donors at blood bank of Assiut University Hospital. SLE disease activity was defined according to the Systemic SLE Activity Index (SLEDAI) [27].

Radiologic evaluation

Radiologic evaluation of the extent and localization of brain lesions was performed using conventional MRI and DWI of the brain and MRA of the carotid and vertebrobasilar vessels. Conventional MRI was performed using a 1.5T MR scanner (Philips, Best; Netherlands) with section thickness of 5 mm, field of view (FOV) of 24 × 18, matrix size of 256 × 192 and inter-slice gap of 2 mm. Axial T1WI was performed with TE/TR for 9/520 ms (msec) and scan time of 2.47 min. Axial T2WI was performed with TE/TR for 120/5565 ms and scan time of 38 s. Axial fluid attenuation recovery-weighted images (FLAIR) was performed with TE/TR for 140/8000 ms, inversion time of 2000 ms and scan time of 1.12 min. Axial GRE T2*WI was performed with a GR/20, TR/TE for 500/15 ms. Axial DWI was performed for TE/TR 112/6300 ms, matrix size of 256 × 192, section thickness of 5 mm, FOV of 24 × 24, inter-slice gap of 1 mm and scan time of 1.24 min. With DWI, the freedom of protons to move in their environment (diffusivity) can be assessed. Changes in diffusivity in DWI occur as a result of either: (a) loss of

structural organization of brain tissue due to disappearance of tissue components (myelin sheaths and axons) that limit movement of protons or (b) tissue loss (atrophy) through an increase in free water in the brain, that is, increased cerebral free water could result from an atrophy-induced increase in the size of the perivascular spaces within the brain that are filled with CSF. Axial three-dimensional time-of-flight MRA (3D TOF MRA) was performed with TE/TR for 7.2/35 ms, flip angle of 20°, images interpolated to 1.5-mm slice thickness, matrix size of 200 × 512, FOV of 20 × 20, scan time of 6.18 min and superior saturation band. MRA assesses the structural changes in the wall of the blood vessels, for example, beadings and areas of narrowing due to vasculitis.

Statistical analysis

Calculations were performed using Statistical Package for the Social Sciences (SPSS) for windows, version 10.0 (SPSS Inc, Chicago III). Data were expressed as mean ± SD (standard deviation). Discrete variables were expressed as absolute frequencies and percentages. Comparisons of numerical data between the groups were performed using independent two-sided Student's *t*-test and chi-square or Fisher's exact probability tests for the categorical data. For all tests, $P < 0.05$ was considered significant.

Results

Demographic and clinical characteristics

Included were 34 patients (females = 32; males = 2) with acute NP manifestations for the first time. Patients had mean age of 33.26 ± 10.14 years and duration of SLE of 3.33 ± 1.71 years. Positive ANA, a-dsDNA-a and aPL-a were reported in 27 (79.41 %), 19 (55.88 %) and 10 (29.41 %) of patients with primary NPSLE, respectively. We did not do quantitative analysis for antibodies due to limited financial resources. The majority of patients had ≥ one NP manifestations. NP manifestations were developed within the first 1.6–5 years of onset of active SLE. Each patient was treated differently for at least 1 month according to disease severity, NP manifestations and possible causes, including the followings: (1) non-steroidal anti-inflammatory drugs (NSAIDs), (2) immunosuppressive therapy (such as prednisolone and/or cyclophosphamide, azathioprine and methotrexate), (3) antimalarial drug (such as hydroquinone), (4) antithrombotic/anticoagulants (such as coumarin and acetyl salicylic acid) and (5) symptomatic therapy such as antiepileptic drugs, atypical antipsychotics, antidepressants, anxiolytics and dehydrating measures (when needed) (Table 1). Reactive depression and anxiety were reported in 100 % ($n = 34$) and 15 (44.11 %) of patients, respectively. In secondary NPSLE, the reported neuropsychiatric manifestations were headache and reactive depression. In primary NPSLE, manifestations were (a) cognitive deficits (42.86 %, $n = 12$) were reported in some patients in association with intractable headache ($n = 4$) and CVS ($n = 2$) and with psychosis ($n = 5$). They were in the form of impairment in attention ($n = 4$, 33.33 %), memory ($n = 8$, 66.67 %), problem solving ($n = 6$, 50 %), visual–spatial processing ($n = 12$, 100 %) and psychomotor speed ($n = 8$, 66.67 %), (b) intractable headache (7.14 %, $n = 2$), (c) CVS (17.86 %, $n = 5$), (d) acute confusional state (10.71 %, $n = 3$).

MRI findings

Normal MRI-brain was reported in patients with secondary NPSLE ($n = 6$) and 28.57 % ($n = 8$) of patients with primary NPSLE (Tables 1 and 2). MRI abnormalities were reported in 71.43 % ($n = 20$) of patients with primary NPSLE ($n = 28$) (Table 2). They were in the form of: (1) hyperintense T2WI and FLAIR signals at the subcortical and periventricular white matter regions consistent with ischemic brain lesions and at the junction between the gray and white matter consistent with dots of demyelination (ischemic demyelination) or vasculitis. These lesions represented 75 % of MRI abnormalities and were reported in patients with headache and cognitive deficits ($n = 6$), psychosis and cognitive deficits ($n = 6$) and acute confusional state ($n = 3$), (2) infarctions (moderate- to large-sized) represented 35 % of MRI abnormalities and were reported in patients with CVS; 6 of them were ischemic with restricted diffusion as seen in their DWI, while one had hemorrhagic infarction with normal DWI. These lesions appeared as roughly wedge-shaped areas of abnormal high signals in the distribution of middle cerebral arteries (MCAs) and involving the gray and white matter in T2WI and FLAIR images. In MRA, 4 patients with ischemic infarctions and the patient with hemorrhagic infarction had beadings and areas of narrowing in the MCAs consistent with vasculitis (Fig. 1), and (3) brain atrophy (evidenced by wide ventricle and brain sulci) represented 20 % of MRI abnormalities and was reported in patients with psychosis and cognitive deficits ($n = 4$).

No statistical differences were identified in the demographic, clinical and laboratory data between patients with and without NP manifestations and patients with primary and secondary NPSLE except that patients with MR abnormalities were older (35.48 ± 5.23 vs. 31.55 ± 6.22 years; $P = 0.045$) and had longer duration of illness (3.10 ± 0.74 vs. 2.21 ± 0.89 years; $P = 0.042$) (Table 3).

Table 1 Demographic, clinical and laboratory data of the studied patients with neuropsychiatric systemic lupus erythematosus (NPSLE)

Demographic data, clinical and laboratory data	Total ($n = 34$)	Primary NPSLE ($n = 28$; 82.35 %)	Secondary NPSLE ($n = 6$; 17.65 %)
Female/male	32/2	26/2	6/0
Age; years			
Range	18.00–51.00	18.00–51.00	22.00–49.00
Mean ± SD	33.26 ± 10.14	33.55 ± 8.56	30.48 ± 10.25
Duration of SLE; years			
Range	1.00–7.00	1.00–7.00	2.00–5.00
Mean ± SD	3.33 ± 1.71	3.68 ± 1.04	2.89 ± 0.52
Clinical manifestations of SLE; number (%)			
Malar rash	16 (47.06 %)	14 (41.18 %)	2 (33.33 %)
Discoid rash	1 (2.94 %)	1 (3.57 %)	0
Photosensitivity	27 (79.41 %)	25 (89.29 %)	2 (33.33 %)
Oral ulcers	15 (44.11 %)	14 (41.18 %)	1 (16.67 %)
Arthritis	24 (70.59 %)	24 (85.71 %)	0
Arthralgia	10 (29.41 %)	4 (14.29 %)	6 (100 %)
Pleurisy	9 (26.47 %)	9 (32.14 %)	0
Pericarditis	8 (23.53 %)	8 (28.57 %)	0
Nephritis	10 (29.41 %)	8 (28.57 %)	2 (33.33 %)
SLE disease activity index (SLEDAI) score	19.9 ± 6.9	19.6 ± 5.45	17.8 ± 6.82
Serology; number (%)			
Antinuclear antibodies (ANA)	33 (97.06 %)	27 (96.43 %)	6 (100 %)
Anti-double strand DNA antibodies (a-dsDNA-a)	25 (73.53 %)	19 (67.86 %)	6 (100 %)
Anti-phospholipid antibody (aPL-a)	12 (35.29 %)	10 (35.71 %)	2 (33.33 %)
NPSLE manifestations			
Mixed diffuse manifestations	12 (35.29 %)	12 (42.85 %)	0
Intractable headache and cognitive deficits	4 (11.76 %)	4 (14.29 %)	0
Psychosis and cognitive deficits	6 (17.65 %)	6 (21.43 %)	0
Cerebrovascular stroke and cognitive deficits	2 (5.88 %)	2 (7.14 %)	0
Cerebrovascular stroke	5 (14.71 %)	5 (17.86 %)	0
Intractable headache	2 (5.88 %)	2 (7.14 %)	6 (100 %)
Acute confusional state	3 (8.82 %)	3 (10.71 %)	0
Reactive depression	34 (100 %)	28 (100 %)	0
Reactive anxiety	21 (61.76 %)	15 (53.57 %)	6 (100 %)
MRI-brain abnormalities; number (%)	20 (58.82 %)	20 (71.43 %)	0
Treatments; number (%)			
Non-steroidal anti-inflammatory drugs (NSAIDs)	30 (88.24 %)	24 (85.71 %)	6 (100 %)
Steroids	28 (82.35 %)	22 (78.57 %)	6 (100 %)
Other immunosuppressive drugs (azathioprine, methotrexate and cyclophosphamide)	16 (47.06 %)	14 (50 %)	2 (33.33 %)
Antimalarial drug (hydroquinone)	26 (76.47 %)	26 (92.85 %)	0
Anticoagulants (coumarin)/antiplatelet aggregation (aspirin)	20 (58.83 %)	16 (57.14 %)	4 (66.67 %)
Antiepileptic drugs	2 (5.88 %)	2 (7.14 %)	0
Atypical antipsychotics	9 (26.47 %)	9 (32.14 %)	0
Antidepressants	34 (100 %)	28 (100 %)	6 (100 %)
Anxiolytics	21 (61.76 %)	15 (53.57 %)	6 (100 %)
Dehydrating measures	3 (8.82 %)	3 (10.71 %)	0

Data are expressed as range, mean ± SD, number (%)

Table 2 Brain magnetic resonance imaging (MRI) abnormalities in patients with primary neuropsychiatric systemic lupus erythematosus (NPSLE)

MRI abnormalities ($n = 20$)	MRI-brain abnormalities description	Neuropsychiatric manifestations ($n = 28$)
Ischemic brain lesions and ischemic demyelination) or vasculitis:	*Conventional MRI*:	*Headache and cognitive deficits*:
$n = 15$, 75 %	T2WI and FLAIR images of conventional MRI showed hyperintense foci (multiple/single) mainly at subcortical white matter and periventricular regions (ischemic brain lesions) and at the junction between gray and white matter (ischemic demyelination or vasculitis)	$n = 6$, 21.43 %
	DWI:	*Psychosis and cognitive deficits*:
	Normal	$n = 6$, 21.43 %
	MRA:	*Acute confusional state*:
	Normal	$n = 3$, 10.71 %
Infarctions (moderate-to large-sized):	*Conventional MRI*: (Fig. 1)	*Cerebrovascular stroke*:
$n = 7$, 35 %	T2WI and FLAIR images showed large-sized acute ischemic infarcts in the distribution of the right ($n = 2$ or 5.9 %) and left ($n = 2$ or 10 %) middle cerebral arteries (MCA). Their MRA showed stenosis of the right ($n = 2$ or 10 %) and left ($n = 2$ or 10 %) middle cerebral arteries. Two more patients showed moderate-sized infarcts in the distribution of right middle cerebral artery. Only one patient had hemorrhagic infarction in the distribution of left middle cerebral artery	$n = 7$, 25 %
		With cognitive deficits:
		$n = 2$, 28.57 %
		Without cognitive deficits:
	DWI (Fig. 1):	$n = 5$, 71.43 %
	Areas of restricted diffusion indicative of an acute infarct were seen in addition to abnormalities on T2WI and FLAIR images in the four patients with ischemic infarctions. Such lesions were visualized clearly in DWI b1000 than T2WI and FLAIR images	
	MRA (Fig. 2):	
	Four patients with ischemic infarctions and the patient with the hemorrhagic infarction had beading and narrowing of the MCA consistent with vasculitis	
Diffuse brain atrophy:	*Conventional MRI*:	*Psychosis and cognitive deficits*:
$n = 4$, 20 %	Mild and diffuse parenchymal volume loss was observed in 4 (20 %) patients with psychosis and cognitive deficits	$n = 4$, 14.29 %
	DWI:	
	Normal	
	MRA:	
	Normal	

Discussion

Primary NPSLE is an important cause of acute and chronic morbidity and mortality in patients with SLE [5]. In this study, the majority of patients developed ≥ one NP manifestations (ranged from 1 to 3) which developed within the first 1.6–5 years of onset of SLE particularly during its active phase [as confirmed by high scores of SLEDAI and positive autoantibodies (ANA, a-dsDNA-a and aPL-a)] [9–12, 28–30]. One or more cognitive deficits, CVS, psychosis and acute confusional state were reported in 42.89, 25, 21.43 and 10.71 % of patients with primary NPSLE, respectively. Cognitive deficits were comorbid with other NP manifestations. They involved different aspects of cognitive domains including attention, memory, problem solving, visual–spatial processing and psychomotor speed. Previous studies reported cognitive deficits, CVS, psychosis and acute confusional state (also known as encephalopathy, organic brain syndrome or diffuse cerebritis) in 22.6–81 % [31–33], 2–19 % [34], 0–12 % [35] and 3.7–14 % [29, 30] of patients with primary NPSLE. In this study, headache seems to be non-specific as it was reported in 35.29 % of patients with NPSLE, of them 50 % had secondary NPSLE. Previous studies reported headache in up to 60 % and in NPSLE patients with and without MRI abnormalities [30, 36, 37]. The great variation in the prevalence of NP manifestations is attributed to the difference in sample size, population studied and methodological designs. Although it was observed that focal NPSLE (e.g., CVS) was reported during the first 5 years of SLE and diminishing thereafter [34], on the other hand, diffuse manifestations as cognitive impairment were reported to deteriorate irreversibly over [31].

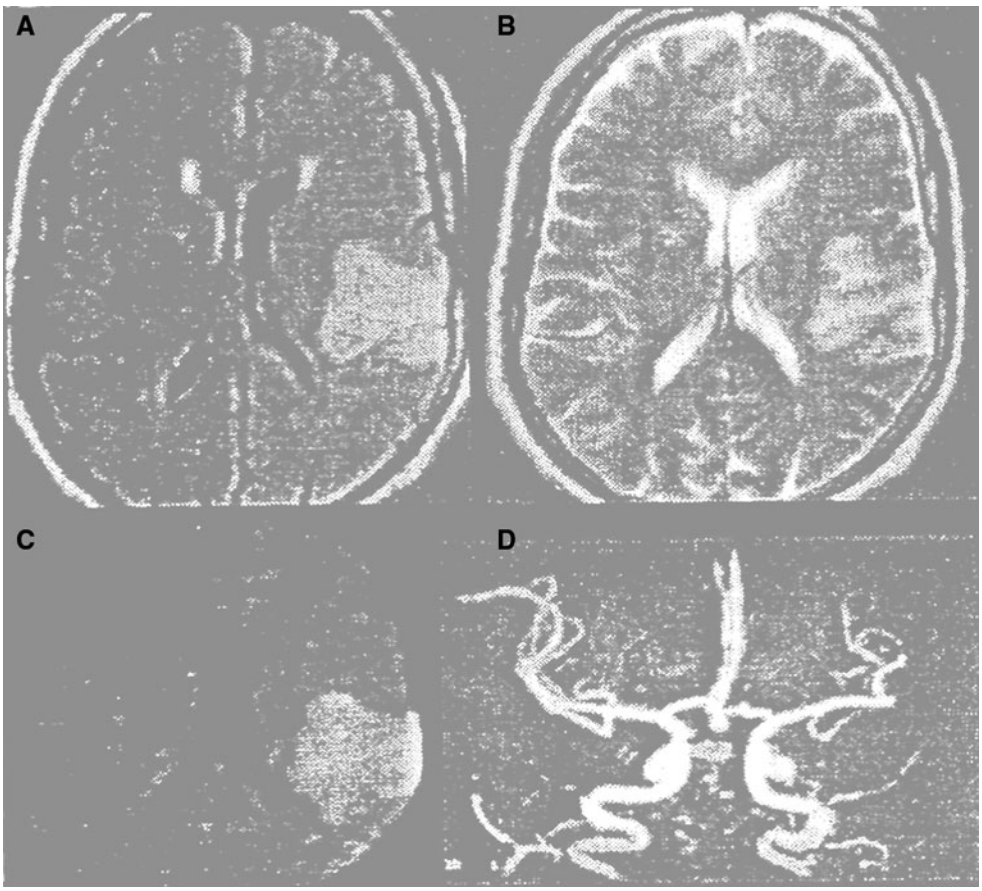

Fig. 1 FLAIR (**a**), T2WI (**b**), DWI (**c**) and MRA (**d**) images of a 36-year-old female with SLE of 2-year duration: She developed acute right-sided hemiplegia (CVS). Her MRI showed left hyperintense cortical and subcortical parietal lesion which was also confirmed as acute infarction by DWI (**c**). Her MRA (**d**) showed narrowing of the left MCA

In this study, MRI-brain abnormalities were identified in 71.43 % of patients with primary NPSLE; of them, the most frequent abnormality was the presence of multiple subcortical white matter at the periventricular regions (consistent with ischemic brain lesions) or at the junction between the gray and white matter (consistent with dots of ischemic demyelination or vasculitis) [37–41]. In accordance, Sibbitt et al. [38] reported small punctate focal lesions in white matter in MRI of all studied patients (100 %) with NPSLE. Jennings et al. [39] reported that 60 % of the studied patients with NPSLE had multifocal small high-signal lesions on T2WI in the frontal and parietal subcortical white matter, while 34 % had normal MRIs. Abreu et al. [40] reported that the most frequent brain imaging findings were focal high-signal intensities in the periventricular white matter in T2WI and FLAIR. Kyu et al. [41] reported periventricular and subcortical multifocal lesions in 13.15 % of MRIs of patients with NPSLE, while 42 % had normal MRIs. It seems that these lesions were non-specific because they were reported in patients with different manifestations of NPSLE [as cognitive deficits, headache, psychosis and acute confusional state], with and without NP manifestations, with abnormal neuropsychological and neurophysiological tests without NP manifestations (subtle or subclinical) [37–41], and with CNS diseases such as meningoencephalitis and other connective tissue diseases (e.g., Behçet's disease) [42, 43]. The second most frequent MRI abnormality was acute cerebral infarctions (35 %) that were reported in patients with CVS [17]; of them, 71.43 % had beadings and areas of stenosis of the MCAs consistent with vasculitis [19] and all were positive for aPL-a. The presence of hemorrhagic infarctions might be attributed to the reperfusion of the ischemic area that carries the risk of edema and hemorrhage [37–41]. The third most frequent MRI abnormality was diffuse brain atrophy (20 %) as evidenced by wide ventricles and brain sulci. This abnormality was reported in patients with psychosis and cognitive deficits. Previous studies reported brain atrophy (gray and white matter) in patients with SLE with variable frequency, but its exact cause remains unclear [15, 16, 18, 35, 37–41]. Sibbitt et al. [38], in their first prospective study to assess MRI and postmortem tissue in NPSLE, reported small punctate focal lesions in white matter (100 %), cortical atrophy (64 %), ventricular

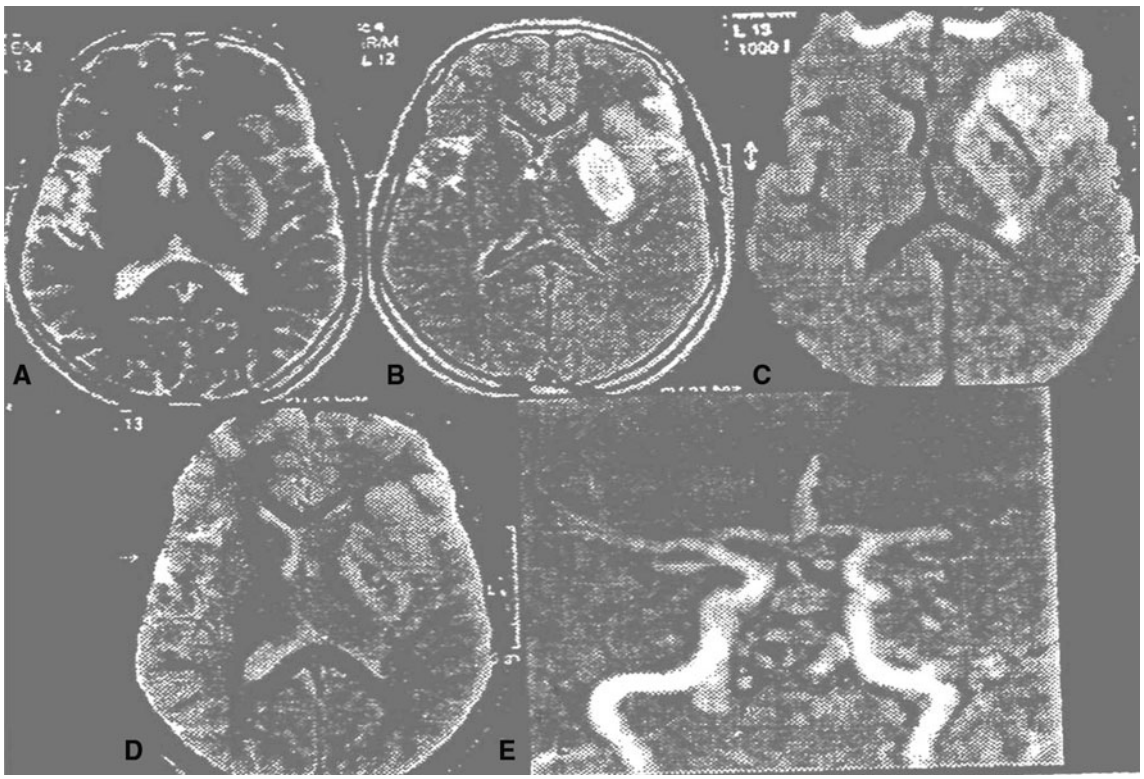

Fig. 2 FLAIR (**a**), T2WI (**b**), DWI (**c**), T2WIGR (**d**) and MRA (**e**) images of a 20-year-old female with SLE of 1-year duration. She developed acute right-sided hemiplegia (CVS). Her MRI (**a**, **b**) showed left hyperintense cortical and subcortical parietal lesion which was also confirmed as acute infarction by DWI (**c**). Her DWI (**c**) and T2WIGR (**d**) showed hyperintense areas suggesting hemorrhagic infarction. Her MRA (**d**) stenotic segment of the left MCA with minute beading of left middle cerebral artery

dilation (57 %), cerebral edema (50 %), diffuse white matter abnormalities (43 %), focal atrophy (36 %), cerebral infarction (29 %), acute leukoencephalopathy (25 %) and intracranial hemorrhage (21 %). In histopathological examination, the authors suggested that white matter lesions may be caused by microinfarcts, ischemic demyelination, multiple-sclerosis-like demyelination bland vasculopathy and hemorrhage due to predominant involvement of arterioles and capillaries [23].

Although the exact mechanisms of the pathogenesis of NPSLE is not well known, however, recent studies suggested that brain endothelium is susceptible to damage in many autoimmune/inflammatory diseases [44, 45]. Systemic lupus erythematosus-related autoantibodies are incriminated as a cause of acute, chronic, focal or diffuse NPSLE of different combinations of manifestations due to induced non-inflammatory coagulopathy and thrombosis, inflammatory focal and/or diffuse vascular injury, alteration of cerebral microcirculation and acute as well as chronic damage [46–50]. This is supported by the findings of this and other studies as follows: (1) The majority of studies reported NPSLE in the active phase of SLE [9–12]; however, and on the other hand, some reported overt and subclinical NP manifestations in the absence of markers for active lupus [8, 31–34, 44], (2) patients with CVS had cerebral infarctions and were positive for aPL-a, (3) in this study, 28.57 % of patients with acute primary diffuse NPSLE had no MRI abnormalities [12, 34] which might be attributed to: (a) physiological brain lesion, (b) unnoticed or subtle structural brain lesions which might be invisible with less sensitive MRI techniques, and (c) the small size of the vessels involved may explain that as few as 5–10 % of patients had abnormal angiography [50], and (4) the lack of differences in the demographic, clinical and laboratory data between patients with and without MRI findings except that patients with MRI findings were older and had longer disease duration. Previous studies reported cognitive deficits in 22.6–81 % of patients with primary NPSLE and was found to deteriorate irreversibly over [46–50].

To summarize, this study indicates that although DWI and MRA helped in more precise etiopathologic diagnosis compared to conventional MRI, but their relevance to the present NP manifestations is still limited. However, we believe that the work performed in this study is an example of the important advances and its findings will further the research in NPSLE despite the following limitations: (a) a relatively small-sized sample, (b) lack of healthy control subjects, and (c) lack of repeated clinical, (other functional

Table 3 Demographic, clinical and laboratory data of patients with primary neuropsychiatric systemic lupus erythematosus (NPSLE) in relation to the presence or absence of MRI-brain abnormalities

Demographic data, clinical and laboratory data of patients with primary NPSLE ($n = 28$)	NPSLE with MRI abnormalities ($n = 20$)	NPSLE without MRI abnormalities ($n = 8$)
Age; years		
Range	18.00–51.00	18.00–51.00
Mean ± SD	35.48 ± 5.23*	31.55 ± 6.22
Duration of SLE; years		
Range	1.00–7.00	1.00–7.00
Mean ± SD	3.10 ± 0.74*	2.21 ± 0.89
Serology; number (%)		
Antinuclear antibodies (ANA)	20 (100 %)	8 (100 %)
Anti-double strand DNA antibodies (a-dsDNA-a)	20 (100 %)	8 (100 %)
Anti-phospholipid antibodies (aPL-a)	8 (40 %)	2 (25 %)
NPSLE manifestations		
Cerebrovascular stroke with and without cognitive deficits	7 (35 %)	0
Psychosis with cognitive deficits	6 (30 %)	0
Intractable headache with and without cognitive deficits	4 (20 %)	3 (37.5 %)
Acute confusional state	3 (15 %)	0
Treatments; number (%)		
Non-steroidal anti-inflammatory drugs (NSAIDs)	16 (80 %)	8 (100 %)
Steroids	20 (100 %)	2 (25 %)
Other immunosuppressive drugs (azathioprine, methotrexate and cyclophosphamide)	12 (60 %)	2 (25 %)
Antimalarial drug (hydroquinone)	20 (100 %)	6 (75 %)
Anticoagulants (coumarin)/antiplatelet aggregation (aspirin)	12 (60 %)	4 (50 %)
Antiepileptic drugs	2 (10 %)	0
Atypical antipsychotics	9 (45 %)	0
Antidepressants	4 (20 %)	0
Anxiolytics	4 (20 %)	0
Dehydrating measures	3 (15 %)	0

* Significance <0.05

and quantitative) neuroimaging techniques and serological follow ups to differentiate the active stage from the chronic stage or the reversibility of manifestations or lesions which will contribute considerably to the treatment decision-making process. This is explained by the lack of local availability and expertise.

Conclusions

Multidisciplinary systematic assessment and prompt diagnosis are still critical parts for valuable therapeutic strategies for patients with SLE because: (a) SLE commonly affects adults, (b) nervous system lesions are part of the pathogenic spectrum of abnormalities of SLE which occur early in the first few years of the disease, and (c) NPSLE is often progressive resulting in high morbidity and mortality rates.

Conflict of interest We declare that this work has no conflict of interests. There is no involvement of sponsor for this work design, data collection, analysis, interpretation, drafting nor the decision to submit this paper for publication. All are authors' responsibility.

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