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ORIGINAL COMMUNICATION

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MRI findings in central nervous system systemic lupus erythematosus are associated with immunoserological parameters and hypertension

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Abstract Involvement of the brain is one of the most important complications of systemic lupus erythematosus (SLE). To investigate the correlation between abnormal cranial MRI findings and age, duration of SLE, neuropsychiatric (NP) manifestations, hypertensive status, and the presence of antiphospholipid antibodies (PA) in patients with SLE we evaluated the MRI results of 81 SLE patients in nine NP clinical subgroups.

Immunoserological status was described by the presence of lupus anticoagulant (LA), and anticardiolipin antibodies (aCL). The MRI findings were categorized as normal [41], cerebral atrophy [15], small subcortical hyperintensity [7], and infarct larger than 10 mm [18]. Mean age differed among the clinical subgroups (ANOVA, $p = 0.002$), whereas there was no age difference among the subgroups based on MRI and immunoserological results. Patients with hypertension (33/81) were a mean of 6 years older at the time of examination ($p = 0.033$) and had stroke more frequently, than normotensive ones ($p = 0.0015$). MRI abnormalities were more frequent in patients with LA positivity ($p < 0.01$) than in those without these antibodies, and in the hypertensive than in the normotensive subgroup ($p = 0.00041$). The presence of PA was associated with abnormal MRI even after controlling for the effect of age and hypertensive status ($p = 0.011$).

In our study the MRI findings in central nervous system SLE were independent of the age of patients and the age at the diagnosis of SLE, and were not influenced by the duration of SLE; however, they were associated with immunoserological parameters and hypertension.

Key words SLE · central nervous system · magnetic resonance imaging · antiphospholipid antibodies · vasculopathy

Introduction

Involvement of the brain is one of the most important complications of systemic lupus erythematosus (SLE). It is a decisive factor in the outcome of the disease, and focal lesions especially indicate poor prognosis and permanent damage [35]. Approximately 30–70 % of SLE patients develop neuropsychiatric (NP-SLE) complications such as cerebrovascular disease, seizures, headaches, cognitive disorders or psychosis [3, 12, 15, 40].

Previous studies have reported that brain magnetic resonance imaging (MRI) is sensitive for detecting central nervous system (CNS) lesions in patients with SLE. A wide range of MRI abnormalities has been described. Subcortical hyperintense lesions, infarcts, and brain atrophy are the most common MRI abnormalities [4, 14, 16, 20, 21, 23, 31]. Haemorrhage and sinus throm-

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bosis can be found in a small percentage of the cases [32, 41].

The lupus anticoagulant (LA) and anticardolipin antibodies (aCL) are closely related autoantibodies belonging to a group of antibodies, which react with proteins associated with phospholipids, therefore they are called antiphospholipid antibodies (PA). These antibodies are present in a clinical syndrome of vascular thrombosis, thrombocytopenia, recurrent fetal loss, and livedo reticularis [30]. The correlation between PA and CNS involvement in SLE was first reported by Harris et al. in 1984 [17], and was confirmed in 1995 [38]. In SLE, PA was reported to be present in approximately 30 percent of the patients [26, 28].

Despite of recent advances of imaging techniques (MRS, SPECT, PET), to reach a definite diagnosis of NP-SLE is extremely difficult. There is a wide variety of neurological events in SLE and they often determine the functional outcome and the prognosis of the disease. In many cases the cause of the neurological event can not be revealed. MRI is the preferred anatomical imaging modality in contemporary practice to detect brain lesions associated with NP-SLE [19, 33].

The aim of the current study was to investigate whether cranial MRI findings correlate with clinical and immunoserological characteristics of the SLE patients. Of the clinical characteristics the age at examination, the age at the time of diagnosis of SLE, the duration of SLE, current or previous neurological symptoms, and hypertensive status were considered, and of the immunoserological parameters the presence of phospholipid antibodies (LA and aCL) was evaluated.

Subjects and methods

Patients

Eighty-one patients were included in this study, who were regularly controlled and followed up at least for 1 year for primary neuropsychiatric syndromes and had MRI investigation as inpatients or outpatients at the Departments of Neurology or Internal Medicine of the University of Debrecen between January 1993 and December 1999. All patients underwent complete history taking and physical examination to assess past and present neurological symptoms and were reviewed for disease duration and manifestations, previous history of hypertension, renal and cardiac disease. Patients were classified according to the presence of neurological abnormalities by physical examination. Neurological deficits included focal motor paresis, sensory disturbances, ataxia, nystagmus. All patients fulfilled four or more of the revised criteria for SLE [36]. Their manifestations were classified according to the American College of Rheumatology (ACR) case definitions for neuropsychiatric (NP) lupus syndromes [1]. Patients with more than one neuropsychiatric syndrome were classified according to the leading clinical disorder (requiring symptomatic treatment or causing the most severe deficit).

Laboratory tests

All patients' sera were tested for the presence of anticardiolipin antibodies (IgG and IgM type aCL) and lupus anticoagulant (LA). The immunoserological status was labelled by the presence or absence of lupus anticoagulant, anticardiolipin IgG, and anticardiolipin IgM. Complete blood cell count, erythrocyte sedimentation rate, urine analysis, serum electrolytes, creatinine, blood urea nitrogen, liver associated enzymes, presence of antinuclear antibodies (ANA), C3 components of complement, autoantibodies to dsDNA, cellular antigens (SS-A/Ro, SS-B/La, RNP, Sm), prothrombin and partial thromboplastin times (PTT) were determined in all patients. Patients with prolonged PTT had the presence of lupus anticoagulant confirmed by platelet neutralization test and/or dilute Russell viper venom test [37, 39]. Anticardiolipin antibodies were measured in serum by enzyme-linked immunosorbent assay, according to a modification of the method of Gharavi et al. [13]. An aCL titre was considered positive (typically based on two measurements at least 6 weeks apart) when its value was > 7 SDs above the mean of 100 healthy subjects.

MRI

Cranial MRI was performed by a Shimadzu SMT-100X 1.0 Tesla scanner, using T1 (TR: 580, 2500 ms, TE: 20 ms) and T2 (TR: 2500 ms, TE: 90 ms) weighted sequences. Axial, coronal and sagittal slices of 4–6 mm were taken and all MRI scans were interpreted by two neuroradiologists and reviewed for abnormalities. The neuroradiologists were blinded to the patients' clinical symptoms and serological profile. The MRI findings were categorized into 4 groups: 1, normal (Fig. 1A), 2, cerebral atrophy based on sulcal and ventricular enlargement (Fig. 1B), 3, < 1 cm lesions with increased signal in T2 in the subcortical white matter or basal ganglia were referred as small subcortical lesions (SSCL) (Fig. 1C), 4, larger than 1 cm white matter lesions or large areas with reduced signal in T1 and an increased signal in T2 involving both the white and the gray matters were referred as infarcts (Fig. 1D, E).

Statistical analysis

Mean ± standard deviations are reported. Normality of the parameters was checked by the Shapiro-Wilk test. Analysis of variance (ANOVA) or Kruskal-Wallis ANOVA was performed to compare continuous variables between subgroups. For categorical data cross-tabulation and the Pearson chi-square test or the Fischer exact test were used. Bonferroni-correction was used in multiple comparisons. A logistic regression model was used to check if abnormality of MRI was associated with the presence of PA after controlling for the effect of age and hypertensive status. Statistical significance was considered when $p < 0.05$. All statistical analyses were carried out using Statistica99 (version 5.5) for Windows (StatSoft, Tulsa, USA).

Results

Patient characteristics

Patient characteristics are given in Table 1. More than 90 % of the patients were women. There was no age dif-

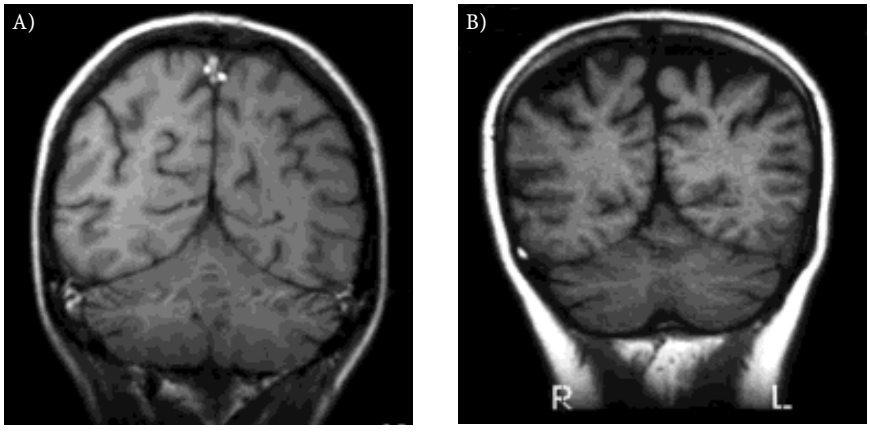

Fig. 1 **A** Normal magnetic resonance imaging (MRI) of the brain of a 24-year-old woman with SLE. **B** Sulcal enlargement of the brain on MRI of a 21-year-old woman with 4 years duration SLE.

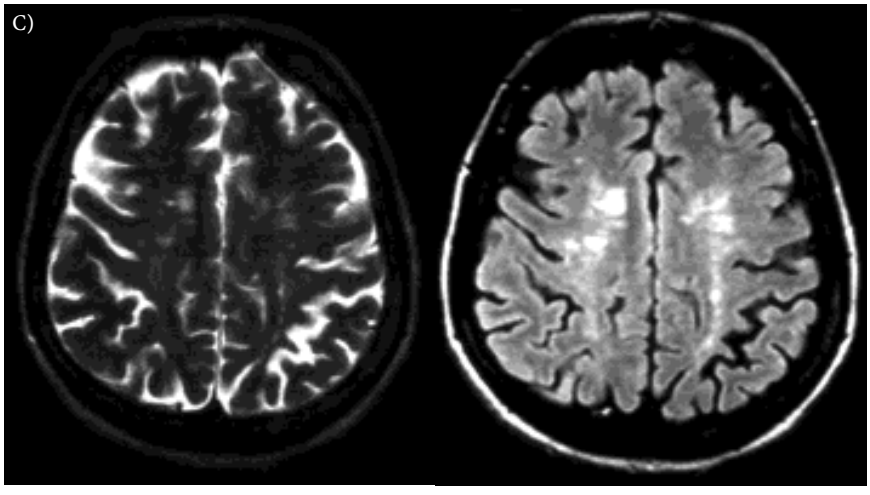

Fig. 1 **C** Several small subcortical lesions (SSCL) – smaller than 1 cm – on T2-weighted and FLAIR MRI of the brain of a 48-year-old woman with 15 years duration of SLE and presence of lupus anticoagulant.

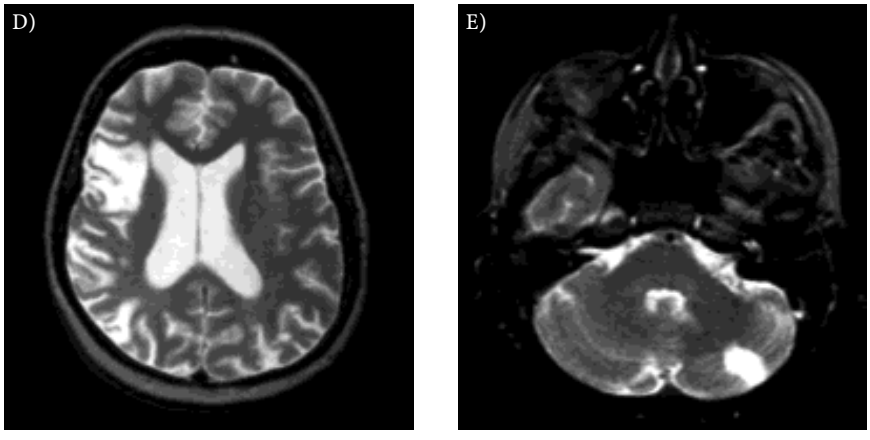

Fig. 1 **D** Infarct in right parietal lobe, sulcal and ventricular enlargement on T2-weighted MRI of the brain of a 39-year-old woman with 6 years duration SLE and anticardiolipin antibodies. **E** 15 mm infarct at the left cerebellar hemisphere on T2-weighted MRI of the brain of a 39-year-old woman with 25 years duration of SLE and anticardiolipin antibodies

ference among the male and female patients at the time of the study (mean age: 40 ± 12.1 versus 42.5 ± 13.2 years), and at the time when SLE was diagnosed (26.1 ± 9.9 versus 34.3 ± 14.3 years). The duration of SLE was longer in male patients than in female patients who entered the study (13.9 ± 6.4 versus 8.2 ± 7.1 years, $p < 0.05$).

There were 8 patients completely free of neurological signs and symptoms. MRI was normal in 7 of them, 1 of them had cortical cerebral atrophy. Neuropsychiatric signs or symptoms were present in 73 of the 81 patients. The number of patients in different clinical subgroups according to the leading clinical disorders is given in Table 1. Twenty six SLE patients had two or more neu-

Table 1 Patient characteristics and different neuropsychiatric manifestations in SLE

Number of patients women/men	74/7
age (years, mean ± SD)	42.3 ± 13.1
age at the time of diagnosis (years)	33.6 ± 14.2
duration of SLE (years)	8.7 ± 7.2
Different neuropsychiatric manifestations	
No neuropsychiatric complaints	8
Headache (tension type headache)	3
Headache (migraine)	16 (3)*
Anxiety disorder	4
Mood disorder (Depression)	1
Seizure disorders	10 (3)*
Mononeuropathy (single, multiplex)	7 (3)*
Aseptic meningitis	2
Cerebrovascular disease (TIA, stroke)	30 (17)*

TIA transient ischaemic attacks
* The numbers in parentheses mean the number of patients with more than one neuropsychiatric manifestation

ropsychiatric disturbances. During the course of the disease only 1 patient had psychotic episode as an associated event, in the subgroup of mononeuropathy. Based on physical examination 49 of the 81 patients showed some neurological deficit. The mean age of patients differed among the various clinical subgroups (ANOVA, $p = 0.002$), patients with a history of epilepsy and major depression were the youngest (about 30 years of age), and patients with a history of stroke were younger than those with peripheral neuropathy (46.2 ± 13 and 55.9 ± 14 years, respectively).

Brain MRI findings

Abnormal MRI results were found in 40 out of 81 patients (mean age: 43.7 ± 12.6, duration of SLE: 9 ± 7.2 years). The 40 cases with abnormal MRI were divided into 15 cases of atrophy and 25 cases of focal parenchymal lesions. In addition to the focal changes in the latter group, 6 patients also had atrophy. By the size of the focal lesions the 25 cases were further divided into 7 patients with multiple lesions < 1 cm located in the subcortical white matter or in the basal ganglia (SSCL) and 18 cases with lesions > 1 cm (infarcts). Fourteen of these 18 patients had multifocal lesions.

The main MRI alterations are shown in Table 2. There was no age difference among those with normal and abnormal (atrophy, SSCL, infarct) MRI. The duration of the disease and the age at the diagnosis of SLE also did not differ among these 4 groups (ANOVA). The distribution of the 4 types of MRI findings (i. e. normal, atrophy, SSCL, > 1 cm infarct) was significantly different among the 9 clinical subgroups ($p = 0.014$).

Thirty-three of the 81 patients had hypertension. Nevertheless, the hypertensive group was 6 years older than the normotensive group ($p = 0.03$) at the time of study, but the duration of SLE did not differ significantly between them. Stroke occurred significantly more frequently in the hypertensive than in the normotensive subgroups (58 % and 23 %, $p = 0.0015$). The distribution of the 4 MRI categories also differed significantly between hypertensive and normotensive patients ($p = 0.00041$, Fig. 2).

Immunoserological findings

Sixty percent (49/81) of SLE patients were PA positive. The mean age of patients with and without PA was not different. Of the patients with antiphospholipid antibodies 32 had aCL, 6 had LA, and 11 had both aCL and LA. In the group of 32 aCL positive patients without LA 10 had IgG isotype alone, 13 had IgM isotype alone, and 9 had both IgG and IgM isotypes. With the presumption of clinical significance the patients were divided into four subgroups by their immunoserological findings: those without PA (n = 32), those with lupus anticoagulants either with or without the presence of anticardiolipin antibodies (n = 17), those with IgG aCL with or without the presence of IgM aCL (n = 19), and those with only IgM aCL (n = 13). The distribution of these 4 immunoserological categories differed significantly among the 9 clinical subgroups ($p = 0.024$).

Table 2 Patient characteristics in MRI categories

Feature (years)	MRI finding				
	normal (n = 41)	atrophy (n = 15)	SSCL (n = 7)	infarcts (n = 18)	All pts (n = 81)
Age	41 ± 13.5	40.6 ± 9.5	43.9 ± 14.3	46.2 ± 14.3	42.3 ± 13.1
Age at diagnosis	32.3 ± 13.8	33.9 ± 13.7	35.7 ± 14.9	35.5 ± 15.9	33.6 ± 14.2
Duration of SLE	8.3 ± 7.2	7.3 ± 6.0	8.1 ± 4.9	10.7 ± 8.7	8.7 ± 7.2

SSCL small subcortical lesions; *infarcts* larger than 10 mm lesions

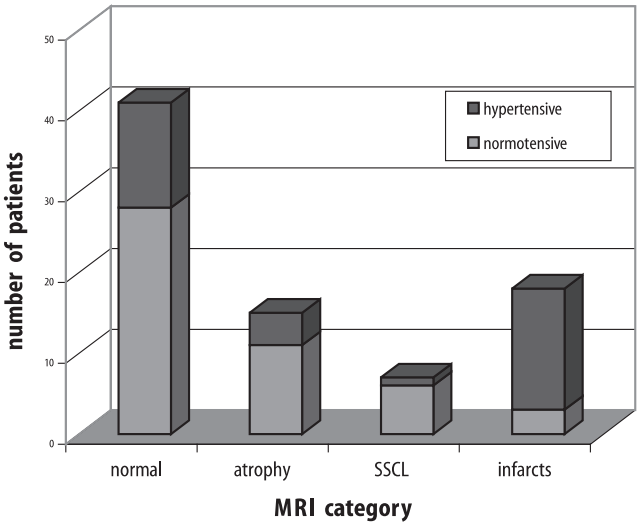

Fig. 2 *Distribution of hypertensive SLE patients according to MRI categories.* The dark part of the columns indicates the hypertensive patients, whereas the shaded one indicates the patients with normal blood pressure

Relationship between immunoserological and MRI findings

The distribution of the four types of immunoserological findings was significantly different among the 4 MRI categories (Table 3, $p = 0.0086$). Pairwise Fisher exact tests were used to see whether the presence of PA differed between those with normal MRI and those with atrophy, ischaemic lesions < 1 cm, and infarcts > 1 cm. The presence of PA differed between the normal and pathological MRI subgroups only for infarcts > 1 cm ($p = 0.018$, after correction for multiple comparisons), where 16 out of the 18 patients had PA. In a further analysis we checked if the rate of pathological MRI differs among the 4 immunoserological subgroups. Compared to those without PA, abnormal MRI was significantly more frequent only in the LA + immunoserological group ($p < 0.01$, after correction for multiple comparisons). The prevalence of hypertension was not significantly different among the 4 immunoserological subgroups ($p = 0.22$). As hypertension and age might be confounding factors, we checked in a multiple logistic regression model if abnormal MRI was associated independently with PA. In the model normality of MRI was the binary dependent variable, the presence of hypertension and the presence of PA were categorical factors and age was used as a continuous predictor. In the model the presence of PA was significantly associated with abnormal MRI ($p = 0.011$) after controlling for the effect of age and the presence of hypertension.

Table 3 Morphological changes associated with phospholipid antibodies (PA)

MRI finding	PA– (n = 32)	LA+ (n = 17)	IgG aCL (n = 19)	IgM aCL (n = 13)
Normal MRI	22	3	7	9
Atrophy	4	4	5	2
SSCL	4	1	2	0
Infarcts	2	9	5	2

The distribution of MRI categories significantly differs among immunoserological subtypes ($p = 0.0086$)

Discussion

Selection of patients

Those SLE patients were included in the study who underwent MRI examination, and had regular neurological follow-up. This could explain the very high prevalence of cerebrovascular disorder – presenting with more severe disease – in our group. These patients had a relatively long duration of SLE so therefore a wide variety of complications could be evaluated. Our study provides additional data on the later stages of the course of the disease: an average 8.7 years of disease duration after the definite diagnosis.

MRI findings

In our study, we did not find a correlation between the MRI findings and the age of patients, the age at the time of diagnosis and the duration of SLE, which supports the notion that CNS involvement can occur any time in the course of SLE. Gonzales [14] reported that central nervous system lesions were associated with patient age and with disease duration, but the patients in their study were younger, the duration of SLE was shorter and the number of patients was smaller than in our current study. With longer disease duration and with older age the effect of confounding factors resulting in more frequent MRI lesions might have more significant influence.

Cerebral atrophy, ischaemic lesions, multiple small high intensity lesions detected by MRI in SLE are more common in patients with neurological deficits than in patients without focal findings and these abnormalities were reported to be associated with the presence of hypertension and lupus nephritis [34]. Others have reported that the number and size of white matter lesions correlated with the presence of neurological deficits [29]. Our MRI findings were associated with the clinical syndrome, as well as with the immunoserological and hypertensive status. Hypertension is a common clinical manifestation in SLE patients. The pathogenic mechanism of renal involvement leading to hypertension beside lupus nephritis, also includes thrombosis in the renal arteries by PA [5]. Our finding that the lupus

anticoagulant antibodies were associated with focal manifestations, predominantly stroke syndromes, is consistent with a previous report [42], but hypertension is also an important additional factor. It is difficult and almost impossible to exclude patients with hypertension to make homogeneous groups of patients suffering from SLE, therefore we used a statistical model to control for the effect of age and hypertension.

A number of different pathogenic mechanisms may be responsible for the variable neuropsychiatric manifestations that can occur in these patients [31]. A great number of autoantibodies are found as the hallmark of SLE, and many have been implicated in immune-mediated pathogenesis [27] involving vasculopathic and autoantibody-mediated neuronal injury [42]. CNS involvement is strongly associated with cutaneous vasculitic lesions and with the antiphospholipid syndrome [24], which increases the risk of adverse outcomes [23]. Transcranial Doppler (TCD) and MRI reveal different aspects of vascular complications [7]. Our previous study suggested an impairment of the cerebral vessels at the early stage of SLE detectable by TCD examination [6]. These changes with the presence of other risk factors (phospholipid antibodies, hypertension) can predict the cerebrovascular complications of SLE.

Pathomechanism of focal MRI changes in SLE

We found stroke as a frequent neurological complication in our group (30 out of 81 patients). The American College of Rheumatology (ACR) for NP-SLE provided case definitions for 19 neuropsychiatric syndromes seen in SLE [1]. Some authors consider that stroke is one of the most important complications of SLE [11, 33]. The most typical lesions in neuropsychiatric lupus include bland vasculopathy, emboli, large and microscopic infarcts and haemorrhage [9], whereas true vasculitis is rare [8, 22]. Our study suggests that multiple cerebral ischaemic lesions or infarcts > 1 cm are strongly associated with LA antibody positivity. Similar correlation was found by another group as well [38].

Subcortical lesions < 1 cm were less frequent (7/81) than larger lesions (18/81) in our patients, and the presence of these lesions did not correlate with either the immunoserological status or neurological deficits of the patients. Case studies of patients with antiphospholipid syndrome and lupus have demonstrated microscopic infarcts of the cortical gray matter and fresh and recanalized thrombi with fibromuscular webs of the leptomeningeal arteries [18]. This type of CNS involvement might remain unrecognized by MRI because of the limited resolution of the examination. Some of our patients with larger infarcts also had small high-intensity subcortical lesions with PA. The small subcortical lesions might be related to vessel wall changes caused by either SLE itself or hypertension whereas the larger infarcts associated with PA of thrombotic origin result in the unique vasculopathy. Several lines of evidence suggest that this unique vasculopathy seen in SLE is highly associated with PA antibodies [2, 10, 25].

In summary, the CNS manifestations detected by MRI are independent of the age of patients and the age at the diagnosis of SLE, and they are not influenced by the duration of SLE. MRI findings highly correlate with positive PA antibodies status, which can be the result of SLE itself and hypertension in patients with cerebrovascular complications.

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