Magnetic resonance volumetry of pathological brain foci in patients with systemic lupus erythematosus

L. Podrazilová1, V. Peterová2, M. Olejárová1, D. Tegzová1, J. Krásenský2, Z. Seidl3, P. Kozelek4, C. Dostál1

1Institute of Rheumatology, Prague; 2MR Division of the Department of Radiodiagnostics, 3Department of Neurology and 4Department of Psychiatry, First Faculty of Medicine, Charles University in Prague.

Abstract

Objective
The aim of our study was to determine the volume of pathological foci in the brain tissue of patients suffering from systemic lupus erythematosus (SLE) with or without neuropsychiatric manifestations (NP), and also to find out if that volume depends on the study subjects’ data and clinical records. Magnetic resonance (MR) scans of patients with SLE and, in particular, signs of neuropsychiatric involvement, show pathological foci in the cerebral white matter.

Methods
A total of 53 SLE patients, 29 with signs of neuropsychiatric syndromes (NPSLE), 24 without, and 16 healthy controls underwent prospective volumetric magnetic resonance imaging in a flow attenuated inversion recovery (FLAIR) sequence. The disease activity was expressed in terms of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).

Results
All the patients in this study were found to have a larger volume of pathological foci in the brain tissue than the healthy controls. The NPSLE subgroup had a larger volume of pathological foci than the SLE patients without NP (p<0.001). The largest volume of such foci was found in the patients with a history of cerebrovascular disease (p<0.05). These were also noted for a correlation between the duration of the disease and the period of time elapsed from the onset of the first signs of neuropsychiatric lupus (p<0.01). Correlation with SLEDAI-rated disease activity was found statistically significant in all the patients (p<0.05) and in those with NPSLE at a level of p<0.01.

Conclusion
We found that the lesion load was significantly larger in NPSLE than in SLE patients free from NP and controls. Our measurement revealed a positive correlation between the lesion load and SLEDAI in the whole SLE patients group, particularly in the subgroup with NP manifestation. In the future, longitudinal volumetry might conceivably facilitate the therapeutical effect rating.

Key words
Systemic lupus erythematosus, neuropsychiatric lupus, magnetic resonance, volumetry, “lesion load”, FLAIR sequence.

Clinical and Experimental Rheumatology 2008; 26: 604-610.
Introduction

Systemic lupus erythematosus (SLE) is an autoimmune multi-organ disease affecting, in particular, women in child-bearing age. According to various authors, neuropsychiatric symptoms are encountered in 11-95% of SLE patients (1, 2) as one of the main causes of morbidity and mortality in SLE. This wide range of neuropsychiatric lupus (NPSLE) prevalence may be put down to differences in the selection of patients or to the use of different diagnostic criteria for NPSLE. The diversity in the classification of neuropsychiatric manifestations (NP), as used in the past, resulted in the 1999 proposal of new criteria (3) comprising nineteen clinical entities affecting both the neurological central, peripheral and autonomic nervous systems, and psychiatric ones. Any of the clinical signs may appear at any time in the course of the illness and in any combination. However, as the primary manifestation of the lupus disease they may be present in up to 20% of patients (4). To establish the diagnosis and follow-up while the disease is in progress, it is necessary to monitor the autoantibody activity in the serum, and in indicated cases also in the cerebrospinal fluid. Relative to the clinical picture, other auxiliary diagnostic methods may be of use such as electromyography, evoked potentials, electroencephalography and a battery of psychological cognitive tests. Magnetic resonance imaging (MRI) offers the most sensitive method for visualising pathological foci in the brain (5-8). MRI brings out the following three most frequent types of abnormalities, mainly in T2-weighted ed scans and flow attenuated inversion recovery (FLAIR) sequence: wedge-shaped foci of increased intensity in the white matter larger than 6 mm are correlates of brain infarction. Cases of vasculitis/vasculopathy are visualised as tiny multiple foci of hyperintensity (up to 3 mm). The third most frequent type of abnormality is found in T2-weighted images as diffuse foci of hyperintensity larger than 6 mm also localised in the grey matter, indicative of brain edema and often reversible in response to treatment. MRI abnormalities have been reported not only in NPSLE patients from 33 up to 100% but also in non-NPSLE patients at a rate of 16 to 53% (9-11). For the differential diagnosis, all focal affections of the cerebral white matter have to be taken into account, in particular: multiple sclerosis with a different localisation of foci and their temporal and spatial dissemination (12-15), neuroinfections or other systemic diseases including vasculitis (16), as well as simple post-ischaemic and hypertensive changes (17), increasing in number with the patients’ advancing age. Numerous volumetric studies have been published in the past few years, dealing mainly with multiple sclerosis cases (18-20) and exploitable for the detection of early focal changes in the brain as useful tools for diagnosis and for rating the course of treatment. Patients with epilepsy are measured for the volume of the amygdala and hippocampus (21, 22). Volumetric studies are also undertaken in patients with Alzheimer’s or other dementia (23, 24).

Problems of this kind in SLE are currently under scrutiny in a number of studies designed to estimate a whole range of brain lesions by means of volumetric methods. In his works, Bosma (25, 26) makes use of the method of volumetric magnetisation transfer imaging (MTI). In 2005, Ainiala published a similar study of 43 SLE patients with and without NP manifestations comparing the extent of cerebral atrophy and volume of lesions in T1- and T2-weighted images. All the solicited parameters were statistically higher in SLE patients than in healthy controls, mainly in NPSLE (27).

The aim of our study was to determine, in particular, the overall volume of pathological foci in SLE patients, and also to find out if that volume depends on the patients’ age, on the SLEDAI-rated activity of the disease (28), on the time from SLE diagnosis, or on the period of time from the onset of the initial neuropsychiatric manifestations.

Patients and methods

The patients met the 1997 revised criteria for SLE diagnosis (29) and were chosen consecutively from the National SLE patients Clinical Database at the Institute of Rheumatology in Prague...
tending an outpatient or inpatient unit in time 2004-2006. From all the registered SLE patients (380), NP manifestation occurred in 38.4% (146) in the course of the disease. Twenty-nine of the selected patients had a history of some of the neuropsychiatric syndromes (NPSLE 54.7%) meeting the 1999 criteria of the American College of Rheumatology (3), and 24 (45.3%) had no neuropsychiatric complaints whatsoever. The selected patients in both groups had active (SLEDAI >10) or non-active lupus disease with SLEDAI ≤10 and acute (disease duration <0.5 years) or chronic forms at the time of MRI scans.

Sixteen healthy controls matched for sex and age and free from any current or previous neuropsychiatric involvement or systemic disease, and from any circulating specific autoantibodies were examined in the same way. Patients with overlapping syndromes such as rheumatoid arthritis, mixed connective tissue disorders, Sjögren’s syndrome or progressive systemic sclerosis were excluded. The whole project was approved by an ethics committee and an informed consent was obtained from all the study subjects. Their data and clinical records are summarized in tabular form (Table I). The clinical testing of each of the patients was carried out in accordance with the ACR recommendations (3). Detailed physical and neurological examination was performed in all patients. The column graph (Fig. 1.) shows the frequency of each neuropsychiatric manifestation as seen in NPSLE patients.

Sixteen healthy controls matched for sex and age and free from any concurrent or previous neuropsychiatric involvement or systemic disease, and from any circulating specific autoantibodies were examined in the same way. Patients with overlapping syndromes such as rheumatoid arthritis, mixed connective tissue disorders, Sjögren’s syndrome or progressive systemic sclerosis were excluded. The whole project was approved by an ethics committee and an informed consent was obtained from all the study subjects. Their data and clinical records are summarized in tabular form (Table I). The clinical testing of each of the patients was carried out in accordance with the ACR recommendations (3). Detailed physical and neurological examination was performed in all patients. The column graph (Fig. 1.) shows the frequency of each neuropsychiatric manifestation as seen in NPSLE patients.

Each subject had magnetic resonance brain investigation made using a Philips Gyroscan NT 1.5T system of the Department of Radiodiagnostics, First Faculty of Medicine, Charles University in Prague. A standard circular polarising head coil was used for the purpose. The examination protocol comprised sagittal T1- and T2-weighted images, FLAIR sequence 1.5 mm sections in transverse and 3 mm sagittal planes. The results were assessed semi-automatically in the FLAIR sequence with a Scanview computer program operating within a 1-5% range of error and fit for a minimum lesion resolution of 1mm³ (30). The programme makes it possible to transform 1.5 mm sections into 6 mm thick ones, on which the pathological foci are easier to resolve and visualise. The 6 mm sections are only instrumental and the measurement was calculated again in 1.5mm sections.

For evaluation purposes, we first eliminate the signal of fat in the subcutis and marrow of the calva to form brain tissue segments so as to eliminate the signal of calcifications, meninges and cerebrospinal fluid. Thus, the only hyperintense lesions that remain there are pathological foci in the brain tissue or what is called the region of interest (ROI) to be circumscribed with the computer cursor (Fig. 2). Following the application of filters (smooth, Gauss), the average white matter signal has to be very precisely balanced relative to the caudate nucleus. Since the signal is regarded as near constant for a particular value, changes caused by accidental errors are eliminated by the procedure. For such purposes, the term “lesion load” is used in lesion volumetry (30).

We compared antiphospholipid autoantibodies such as anticardiolipin
International Society on Thrombosis and Haemostasis (31). Anticardiolipin (IgG and IgM aCL) and β₂-glycoprotein I autoantibodies (β₂-GPI IgG and IgM) were detected by a commercially available enzyme-linked immunosorbent assay (ELISA, Orgentex, Germany). The diagnosis of antiphospholipid syndrome was made according to the preliminary classification criteria for definite antiphospholipid syndrome of an international consensus workshop held in Saporro, Japan (32). The risk factors for accelerated atherosclerosis were determined in patient groups, for example hypertension, cardiovascular disease, dyslipidemia, diabetes mellitus, smoking, obesity (body mass index-BMI >30).

For the statistical processing of the results we used the analysis of variance (ANOVA) and Kruskal-Wallis non-parametric test to test the quantitative parameters between more than two sets of data. The t-test with Bonferroni correction and Mann-Whitney test were used to test the agreement of the mean values between two independent sets, the Spearman coefficient of correlation, the chi square test, and the Fisher test to test the dependence of qualitative parameters. The $p<0.05$ level was regarded as statistically significant.

Results
Using the above volumetric methods to establish the total volume of pathological foci in the brain, we found a statistically significant difference between those examined in the FLAIR sequence ($p<0.001$). The results are represented in a column graph (Fig. 3). The greatest lesion load was found in NPSLE patients, specifically $\bar{\Omega}19.49\pm27.72\text{cm}^3$ with a major variance of parameters (0.26-94.43 cm$^3$). Quantification in the subgroup with no clinical neuropsychiatric manifestations showed a lesion load of $\bar{\Omega}3.35\pm5.40\text{ cm}^3$ (parameter variance: 0.01-23.90 cm$^3$), unlike the healthy controls where the values were $\bar{\Omega}0.69\pm0.81\text{ cm}^3$ (parameter variance: 0.2-2.86 cm$^3$). The patients group (those with and without NP) showed that the total volume of lesions is correlated with the SLEDAI-rated activity of the disease at the time of imaging ($p<0.05$).
Likewise, a positive correlation was ascertained in NPSLE patients, in whom the lesion load was correlated with SLEDAI ($p<0.01$) (Fig. 4). The duration of the disease also positively correlated with the total length of time of neuropsychiatric complaints ($p<0.01$). As regards the patients’ age, disease duration or the length of time from the appearance of the first neuropsychiatric manifestations, no statistically significant lesion load dependence was found in our study cohort. Patients with a history of cerebrovascular accident (CVA) in the course of the disease, 8/29 (27.6%), had a statistically larger volume of lesions – 36.6 against 7.8 cm$^3$ ($p<0.05$). The exclusion of these CVA patients from the NPSLE group does not alter the fact that lesion load is larger in NPSLE than in non-NPSLE patients and healthy controls ($p=0.001$). Other forms of organ involvement were similar in both subgroups of our patients (Fig. 5). Both subgroups of our patients were homogenous as far the presence of acute/chronic forms as active/ non-active lupus disease is concerned and we found no correlation between the studied parameters in these subgroups. The secondary antiphospholipid syndrome was diagnosed in the course of the disease more frequently ($p=0.05$) in NPSLE patients, 9/29 (31%), than without NP, 2/24 (8.4%). However, the presence of antiphospholipid auto-antibodies at the time of examination was without correlation between lesion load and other studied parameters including CVA manifestation. The presence of risk factors for accelerated atherosclerosis did not differ between NPSLE and SLE patients without NP. The number of risk factors did not affect any studying parameter. Only the patients with dyslipidemia had longer disease duration ($p=0.01$).

**Discussion**

The study is a further contribution to the volumetric assessment of brain lesions in NPSLE, a topic already analysed in some reports previously published by others (25, 33). In our cohort, a total of
53 SLE patients with and without NP syndromes were examined. The rate of occurrence of neuropsychiatric manifestations in our NPSLE subgroup is in agreement with the frequency reported by other authors (33-35). The volume of FLAIR sequence rated pathological foci in our patients was significantly greater in NPSLE than in SLE without clinical NP manifestations or in the healthy controls ($p<0.001$). Each subgroup exhibited a great variance of results. Indeed, even healthy controls showed the presence of minute white matter changes at a rate of 3-4% without neuropsychiatric manifestations or diseases that might account for the finding (17).

It is also worth noticing the presence on MRI of pathological brain foci demonstrable even in SLE patients without as yet expressed clinical signs of NP involvement. Sanna (11) describes the presence of pathological brain foci not only in NPSLE at a rate of 33-100% but also in non-NPSLE patients (16-53%) (11). The moot point remains whether or not this is a latent preclinical NP affection ascertainable thanks to high-sensitivity MRI. Similarly, the connection between pathological foci in the brain and the activity of the underlying disease remains unexplained. Our results, too, stand to support this hypothesis. Our NPSLE patients suffered from the disease for more than 7.2 years (on average), than those without NP manifestations 3.4 years, ($p<0.05$). At the same time, a correlation was found in the NPSLE subgroup between the duration of the disease and the length of time elapsed from the onset of the neuropsychiatric symptomatology. In their communications, Sibbitt (36) and Chinn (37) presumed that SLE patients without as yet expressed neuropsychiatric involvement are threatened with the risk of developing a neuropsychiatric syndrome later in the course of their lupus disease.

SLEDAI, the index which we used for rating lupus activity, has a high rating for each neuropsychiatric symptom: convulsions, psychosis, organic psychosis, visual disorders, cranial neuropathy, headache and cerebrovascular accident (28). For that reason, some of the SLE patients exhibiting considerable clinical activity without NP had a lower SLEDAI rating than almost non-active patients with NPSLE. Therefore we calculated SLEDAI in NPSLE once again without the neuropsychiatric symptoms. Our measurements revealed a positive correlation between the lesion load and SLEDAI both in all SLE patients ($p<0.05$) and in the NPSLE subgroup ($p<0.01$) (Fig. 4). However, SLEDAI without NP revealed no statistic correlation. These results are in agreement with Taccari’s (38). In his study of 21 SLE cases, he found pathological brain foci to be correlated with ECLAM (European Consensus Lupus Activity Measure) and SLEDAI-rated lupus activity, though there was no evidence of a correlation with clinical symptoms or specific autoantibody activity. MRI foci were present not only in patients with NPSLE but also in those without NP at a high activity index (38). In contrast, Ainiala et al. (27) found no correlation between cerebral atrophy or lesion load and ECLAM-rated activity of the disease. The discrepancy in the reported results are due, in part, to the limited numbers of patients in the cohorts under study and, in part, to the choice of different indexes for lupus activity rating. Concurrently with Bosma (26), we found none of the volumetric parameters of brain involvement in SLE patients to depend on the age of the subjects at the time of examination, on the total duration of their lupus disease or, indeed, on the length of time from the onset of the first neuropsychiatric manifestations. The positive correlation which we found between the length of lupus disease duration and the time elapsed from the onset of the first neuropsychiatric symptoms ($p<0.01$) seems to indicate that any of the NP syndromes may become manifest at any time in the course of SLE. This hypothesis is supported also by, as we found, a longer duration of the disease in SLE patients with NP than in those without NP syndromes. So far, though, there are no known predictive circumstances which would warn us of the development of clinical NP signs in threatened patients.

The presence of antiphospholipid autoantibodies is associated independently with CVA, seizures and headache (39-42). This supported the study (43) which demonstrated the presence of antiphospholipid autoantibodies (IgG aCL) in autopsies in which more than 90% died of SLE. The association between the titer of antiphospholipid autoantibodies, clinical manifestation and MR brain imaging has not yet been demonstrated. In our study cohort we diagnosed the secondary antiphospholipid syndrome in the course of the disease more frequently in NPSLE patients than without NP. However, we found no correlation between the presence of antiphospholipid autoantibodies at the time of examination and lesion load or other studied parameters including CVA manifestation. The rather large volume of lesions as found in our patients with a history of CVA (8/29-27.6%) tallies with the outcome of a Finnish volumetric study (27) reporting a larger volume of lesions in a T2 weighted image of patients with stroke as part of NPSLE. The older age of studied patients with a history of CVA, equally as statistical more frequently dyslipidemia in our patients with longer disease duration lend support to the idea of accelerated atherogenesis in patients with SLE (44).

Conclusion

Our comprehensive study is one of a few volumetric works in Europe centered on patients with systemic lupus erythematosus in comparison with a sex- and age-matched reference group. The results of our observations of SLE patients are congruent with existing data from literature. Unlike previous earlier works, we found SLE patients’ lesion load correlated with the SLEDAI-rated activity of the disease. The largest total volume of pathological foci in MRI was found in the subgroup of patients with neuropsychiatric lupus, mainly in those with a history of cerebrovascular accident. The occurrence of NP manifestations in SLE patients correlated positively with the duration of their lupus disease.

References

2. SIBBITT WL JR, BRANDT JR, JOHNSON CR et al.: The incidence and prevalence of neuropsychiatric syndromes in pediatric onset


