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Positron emission tomography and magnetic resonance imaging for cerebral involvement in patients with systemic lupus erythematosus

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Abstract Central nervous system (CNS) involvement in systemic lupus erythematosus (SLE) remains difficult to diagnose, particularly since structural abnormalities may not be revealed by magnetic resonance imaging (MRI). Glucose utilisation was measured by positron emission tomography (PET) in 35 SLE patients to detect signs of CNS involvement. The patients were examined by a standardised neurological examination, a battery of tests to evaluate neuropsychological performance and MRI. Antineuronal antibodies were determined to investigate their putative role in CNS involvement in SLE. Twenty patients had distinct neurological (17) and/or psychiatric (3) symptoms. Ten patients had pronounced cognitive impairment. Neurological and cognitive deficits were thus found to be unrelated disorders in SLE. Global glucose utilisation of SLE patients did not differ significantly from that of normal controls, nor were differences found between SLE patients with or without neurological or cognitive abnormalities. On MRI of the brain, the number and size of white matter lesions correlated with the presence of neurological deficits but were unrelated to the severity of cognitive impairment. Within the normal range, lower global glucose utilisation tended towards lower values with increasing number and size of white matter lesions. Patients with lesions larger than 8 mm also showed distinctly increased IgG anticardiolipin antibody titres, whereas measuring antineuronal antibodies did not reveal any relation to the variables investigated. We conclude that the demonstration of CNS lesions by MRI can contribute confirmatory evidence for CNS involvement in SLE, but PET or the presence of antineuronal antibodies adds little if any information beyond that obtained by clinical examination, neuropsychological testing, and MRI.

Key words Systemic lupus erythematosus · Central nervous system · Cognitive deficits · Antineuronal antibodies · Magnetic resonance imaging · Positron emission tomography

Introduction

Central nervous system (CNS) involvement has been described in 20–74% of patients with systemic lupus erythematosus (SLE) [11, 18, 40], its prevalence depending on patient selection, diagnostic criteria employed, and study design [45]. In addition to focal or diffuse neurological manifestations and psychiatric symptoms, more recent investigations have revealed the existence of cognitive deficits with a considerable incidence compared with other connective tissue diseases [5, 23]. In SLE reduced

attention and concentration, memory disturbances, and deficits in concept finding have been detected [5, 9, 10, 23]. No correlations have been found between systemic disease activity, the presence of other organ manifestations, focal or diffuse neurological symptoms [21, 23], and the presence or the extent of cognitive disorders [17, 19, 21].

The diagnosis of SLE involving the CNS has been based on clinical presentation as well as, more recently, on the findings of imaging methods, i.e. of magnetic resonance imaging (MRI), single photon emission tomography (SPECT), and positron emission tomography (PET) [2, 13, 27, 34, 41, 42, 47]. Cerebrospinal fluid (CSF) analysis has been reported to provide little additional evidence but to be helpful in excluding secondary CNS involvement such as infections. In a few patients evidence of intrathecal synthesis of autoantibodies or oligoclonal immunoglobulins identified on isoelectric focusing (IEF) of CSF and serum samples has recently been published, indicating an autonomous immune reaction within the CNS [24]. Of the many autoantibodies found in SLE patients, antineuronal antibodies [8], antiribosomal P protein antibodies [44], antisynaptosomal 50 kDa protein antibodies [22] and antiphospholipid antibodies have all been claimed to be related to CNS SLE, but their pathogenic role has so far remained uncertain [31].

In an earlier investigation on a selected group of 13 SLE patients with cerebral lesions and neurological symptoms, regional disturbances of cerebral glucose utilisation were demonstrated by PET [42]. In three other patients who were investigated longitudinally by PET and neuropsychological testing, fluctuating neuropsychological deficits could be observed [6]; the latter investigators reported that cognitive deficits went along with decreased regional glucose utilisation, indicating a possible relationship to the corresponding test results [6]. Since at present PET and magnetic resonance spectroscopy (MRS) are the two non-invasive methods rendering direct information on brain metabolism [7, 38], the combination of either method with MRI offers a means to obtain both information on metabolic changes and possibly related structural CNS lesions at a given time. The first aim of our study was to investigate brain glucose metabolism in SLE patients with CNS involvement and to assess the diagnostic value of PET. Secondly we wished to determine if correlations existed between overall or regional changes in glucose utilisation as documented by PET, neuropsychiatric or neuropsychological findings, CNS white matter lesions detected by MRI, and the presence of antineuronal or anticardiolipin antibodies.

Patients and methods

We present a cross-sectional study on 35 patients with longstanding SLE not preselected for certain or suspected CNS involvement. Two other patients with structural brain damage following territorial cerebral infarctions and haemorrhage detectable by MRI were excluded because of expected localised alteration of glucose metabolism. The patients' average age was 43 years (SD = 14.4), their mean age at onset of the disease was 36 years (SD = 12.6). The average disease duration was 9 years (SD = 6.1) amounting to a total of 321 patient years. On average the patients had completed 10.8 (SD = 4.9) years of formal education.

Standardised clinical and neurological examinations were performed at the beginning of the study. The clinical findings were entered into a computerised data base along with all other findings. All patients included fulfilled four or more American Rheumatism Association diagnostic criteria for SLE [43]. Overall disease activity was expressed by the Systemic Lupus Activity Index (SLAM) [30]. Based upon current or previously documented neurological and psychiatric findings, patients were classified as SLE with (NP^+, $n = 20$) or without (NP^- $n = 15$) CNS involvement. Patients gave their informed consent according to institutional guidelines. All clinical examinations and laboratory investigations were performed within 1 week prior to or after the PET and MRI studies. ^{18}F-fluoro-2-deoxy-D-glucose (FDG) PET scans and MRI were performed on the same day in 28 patients, and within 48 h in 7 others. Neuropsychological testing was completed 1 week prior to the imaging examinations.

Neuropsychological tests

A test battery to be completed within 90 min was carried out prior to the imaging examinations and clinical workup. General intellectual ability, and assessment of the verbal and non-verbal IQ was performed by the Wechsler Adult Intelligence Scale (shortened version, WIP) using the following subtests: Information, Similarities, Picture Completion and Block Design. Selective attention was tested by using the Stroop Color Word Interference Test. The Kimura Recurring Figures test was employed for examining immediate memory. Concept finding and problem solving was assessed by the Kramer Two Group Card Test. The FPI-K personality questionnaire was used for judging depression and emotional status. For statistical computation each test score was converted to a standard *Z* score [29]. Normal control values for mean and standard deviation of the test scores were obtained from a group of 42 healthy blood donors. There were no significant differences between the SLE and control groups with respect to averages of the following variables: age, sex, and educational status. Using a mean *Z* score derived from all neuropsychological tests applied, a group of SLE patients (10/35) with profound cognitive deficits (COG^+) could be defined comprising those with a mean *Z* score below –1.5.

Positron emission tomography

^{18}F-FDG PET of the brain was performed with a Siemens ECAT 951/31 positron emission tomograph (31 slices, reconstructed resolution 8 mm FWHM). After positioning the patient's head parallel to the OM line the attenuation correction was achieved by acquiring a 10-min transmission scan. The emission scan was initiated with a slow injection of 370 MBq [^{18}-F]-fluorodeoxyglucose. Sixteen time frames of varying length were recorded over 50 min. The input function was derived from pseudoarterial blood samples at midframe time. Serum glucose concentration was determined at 35 and 45 min after injection. Quantification of the glucose study was performed according to a two-compartment model under the assumption of k4 = 0 for times less than 50 min. The algorithm is a modification of the Patlak/Gjedde plot [36], which allows the generation of quantitative parametric images of regional glucose consumption. Region-of-interest analysis is based on these parametric images. The normal range of global glucose utilisation amounted to 0.320, SD 0.060 μmol/cm^3 per min as determined in 12 age-matched, healthy control persons.

Magnetic resonance imaging

MRI was performed with a Magnetom 1 T (Siemens). Standard, flow-compensated spin-echo sequences were used to obtain T1- and T2-weighted images usually in transverse sections. Slice thickness was 6 mm with 30–50% intersection gap. Sequence parameters for T2-weighted images were TR/TE 2500/90 and 600/20 for T1-weighted images. Hyperintense signals surrounding the poles of lateral ventricles (hyperintense caps) were carefully excluded from counting [14, 15]. Patients were categorised according to the number of white matter lesions and were separated into three groups: group 1 (0–3 lesions, $n = 15$), group 2 (4–10 lesions, $n = 12$), and group 3 (> 10 lesions, $n = 8$). Another parameter used was the size of the lesions, where we classified patients according to the largest lesion detected on T2-weighted images: group A (no lesions, $n = 8$), group B (lesion diameter up to 8 mm, $n = 20$), and group C (lesion diameter > 8 mm, $n = 7$). Thus, a patient with six lesions, the largest of which measured 8 mm in diameter, belonged to group 2 with respect to number and to group B with respect to the size of the lesions.

Laboratory investigations

Antineuronal antibodies were investigated by an indirect immunofluorescence assay employing cultured neuroblastoma cell lines SK-H-MC and NMB-7 as substrates [25]. All sera were tested at a dilution of 1:20. A rim stain was considered as a positive immunofluorescence pattern for antineuronal antibodies. Positive sera were serially diluted to obtain their final titre. IgG and IgM anticardiolipin antibodies were assayed using commercially available ELISA kits (ELIAS, Freiburg, Germany), the results being expressed in phospholipid U/ml. Laboratory investigations included blood counts, serum total protein and creatinine determinations, and urine analysis. Antinuclear antibodies were detected and titrated by standard indirect immunofluorescence techniques with Hep-2 cells as the substrate. Antibodies to double stranded DNA were measured using a commercial radioimmunoassay kit (Amersham, Braunschweig, Germany). Total complement activity was assessed by determining 50% haemolytic units/ml fresh serum (CH_{50}/ml) [32].

Statistics

Both parametric and non-parametric statistics were used depending on whether the data distribution was considered to be normal or not. Comparison between two independent samples was undertaken with two-sample *t*-tests and Mann-Whitney *U* tests. One-way analysis of variance (ANOVA) and Kruskal-Wallis ANOVA were used in analysing differences between more than two subgroups. In the case of non-parametric analysis, the median is quoted. Two-tailed *P* values are reported throughout. Correlations between variables were assessed with Pearson's rank correlation coefficients. Measures of association for nominal variables (Table 4) was performed based on chi-square statistics calculating the Phi coefficient. Statistical analysis was performed using SPSS/PC programs.

Results

Clinical results

Definite neurological or psychiatric CNS involvement (NP^+) was recognised by a standardised neurological examination in 20 of 35 (57%) patients, revealing the following neurological deficits. Hemiparesis was observed in 5 (25%) patients; 4 (20%) patients had a hemisyndrome consisting of at least two of the three following findings: extensor plantar response, increased muscle tone or brisk reflexes on the side of the previous finding(s); 4 patients had movement disorders (20%), 2 patients had seizures (10%), and 2 (10%) developed a psychosis and one an episode of an acute confusional state (5%) without any findings of secondary CNS involvement. One patient each presented with myelitis (5%) and optic neuritis (5%).

At the time of the investigation, a moderate disease activity was observed in 19 patients with SLAM scores ranging between 6 and 14, whereas 13 patients exhibited scores varying from 0 to 5, reflecting a low systemic disease activity. Only 3 patients had a score of 15, 16 and 18 on the SLAM rating scale. The mean SLAM score for all 35 SLE patients was 7.5. The disease activity did not correlate with neurological and/or psychiatric (NP^+) CNS involvement. None of the patients suffered from severe kidney, heart or lung involvement or pronounced arterial hypertension (diastolic blood pressure > 95 mmHg). Clinical, serological, or CSF evidence indicating secondary CNS involvement was not obtained in any patient. We observed a significantly shorter duration of the disease in

Table 1 The relationship between systemic lupus erythematosus (SLE) patient subgroups (NP+, NP–, COG+ and COG–): age, disease activity, disease duration, antineuronal antibodies and global glucose utilisation. Two-sample *t*-tests were applied to test significant differences between groups; values represent the mean and (standard deviation) of the groups

	n	Age (years)	Disease activity (SLAM)	Disease duration (years)	Corticosteroid therapy (mg/day)	Anineuronal antibodies (reciprocal titre)	Global glucose utilisation (μmol/cm³/min)
All patients	35	44.5 (14.3)	7.5 (4.1)	8.2 (6.1)	20.6 (30.4)	65 (167.5)	0.322 (0.065)
NP	+ 20	45 (15.9)	7.2 (4.2)	6.4 (5.3)	26.7 (38.3)	45 (75.0)	0.310 (0.074)
	– 15	44 (12.6)	7.6 (3.9)	11.2* (6.1)	11.8 (11.2)	92.6 (240.3)	0.340 (0.048)
COG	+ 10	38.6 (17.6)	8.9 (5.1)	8.9 (6.6)	16.7 (19.0)	68 (190.7)	0.321 (0.094)
	– 25	47.8 (12.2)	6.7 (3.5)	8.8 (6.0)	21.0 (34.2)	59 (96.0)	0.321 (0.052)

* $P < 0.05$

Table 2 Neuropsychological test results for all SLE patients and COG+, COG–, NP+ and NP– subgroups expressed as median *Z* scores. Values represent the median of the groups; (*Z* score of the control group = 0)

n	Control 42		All SLE patients 35	COG+ 10	COG– 25	NP+ 20	NP– 15		
	d								
		a		b			c		
IQ (HAWIE)	*	NS	–0.63	–2.34	*	–0.09	–0.52	NS	–1.05
Kimura	*	*	–0.88	–1.79	*	–0.58	–1.03	NS	–0.88
Kramer	*	*	–1.0	–1.87	*	–1.0	–1.0	NS	–1.00
Stroop I	*	*	–0.91	–1.12	NS	–0.91	–0.70	NS	–0.91
Stroop II	*	*	–1.03	–2.41	*	–0.69	–0.86	NS	–1.03
Stroop III	*	*	–1.56	–2.21	*	–1.11	–1.63	NS	–1.41

[a] Normal controls vs all SLE patients, Mann-Whitney *U* test
[b] COG+ vs COG– SLE patients, Mann-Whitney *U* test
[c] NP+ vs NP– SLE patients, Mann-Whitney *U* test
[d] Normal controls vs COG+ and vs COG– SLE patients, Kruskal-Wallis test
* $P < 0.05$, *NS* no significant difference between groups

Table 3 Number and size of white matter lesions on T2-weighted MRI of the brain, global glucose utilisation, cardiolipin and antineuronal antibodies (Ab) in SLE. ANOVA was applied to test significant differences between groups; values represent the mean of the groups and (standard deviation)

	n 35	Global glucose utilisation (µmol/cm³/min)		IgG cardiolipin Ab (pIU/ml)		Antineuronal Ab (reciprocal titre)	
		Mean	SD	Mean	SD	Mean	SD
Number of lesions		*		NS		NS	
Group 1 (0–3)	15	0.342	(0.065)	25.4	(30.2)	80	(255)
Group 2 (4–10)	12	0.308	(0.033)	89.9	(200.4)	40	(76)
Group 3 (> 10)	8	0.277	(0.046)	109.0	(231.1)	40	(50)
Size of lesions		*		*		NS	
Group A (none)	8	0.338	(0.046)	17.4	(22.1)	160	(300)
Group B (< 8 mm)	20	0.326	(0.061)	33.3	(47.6)	40	(56)
Group C (< 8 mm)	7	0.260	(0.074)	227.2	(205.4)	40	(50)

* $P < 0.05$, *NS* not significant

SLE patients with neurological CNS involvement (NP^+, mean = 6.4 years) compared with those without neurological deficits ($NP^–$, mean = 11.2 years, $P < 0.02$; two-sample *t*-test, Table 1). No difference in antineuronal or IgG anticardiolipin antibodies titres was noted between NP^+ and $NP^–$ groups.

Neuropsychological test results

No significant differences were noted when comparing the verbal and non-verbal IQ between our control group and SLE patients. However, neuropsychological testing revealed significant differences ($P < 0.001$, Mann-Whitney *U*) in the performance of distinct cognitive abilities between control and SLE patients (Table 2). Depression did not account for cognitive deficits as indicated by the FPI-K personality questionnaire used for judging emotional status (data not shown). Significant differences emerged when measuring attention, cognitive flexibility (Stroop Color and Word Test, Kramer Two Group Test) and immediate and recall memory (Kimura Recurring Figures), all of which were significantly impaired in the SLE group (Table 2). Using a mean *Z* score derived from all neuropsychological tests applied, 10 of 35 patients (29%) comprising the COG^+ group (those with profound cognitive deficits) showed a *Z* score below –1.5. This group differed significantly from both the $COG^–$ (those without cognitive cognitive deficits) and the control groups in all tests applied (Table 2). In the COG^+ group, 8 patients were diagnosed as NP^+ and 2 were $NP^–$, whereas the $COG^–$ group consisted of 12 NP^+ and 13 $NP^–$ SLE patients. A difference in cognitive performance was, however, independent of the presence of neurological or psychiatric symptoms (Table 2). Significant differences between the COG^+ and $COG^–$ groups regarding disease activity, age, disease duration, or the presence of antineuronal and anticardiolipin antibodies was not found (Table 1).

PET results

Regarding global glucose utilisation a marginal but insignificant difference ($P = 0.076$, two-sample *t*-test) was

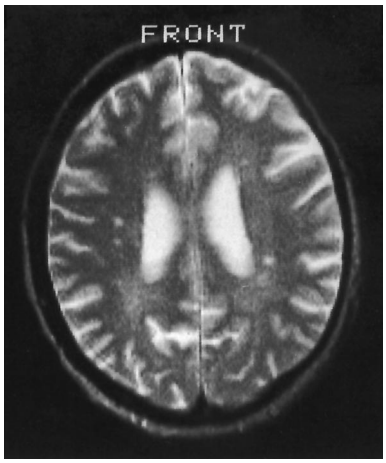

Fig. 1 T2 weighted MRI of the brain with small disseminated white matter lesions. Patient belonging to group 2 with respect to number and to group B with respect to size of the lesions

detected between all SLE patients and the control group (n = 12). No regional differences in glucose utilisation were measured (data not shown). When comparing the NP^+(20/35) with the NP^- group (15/35) or the NP^+ patients with controls we could not detect significant differences in brain glucose utilisation. An alteration in brain glucose metabolism was not observed with respect to severity and type of cognitive dysfunctions; no significant difference was measured between COG^+ and COG^- SLE patient groups (P = 0.4, two-sample t-test, Table 1). Eight patients who suffered from both neurological and cognitive deficits did not differ significantly from other SLE patients in their glucose utilisation. In 13 SLE patients without any CNS involvement (NP^- and COG^-) a non-significant trend was measured towards a higher glucose utilisation compared with the remaining group of patients (P = 0.064, two-sample t-test). A significantly decreased global glucose utilisation was noted in the two groups (group 3 and group C) characterised by a high lesion load on MRI (Table 3). In particular, significant correlations were found between both number (r = 0.4, P < 0.03), and size (r = 0.41, P < 0.01) of white matter lesions, and a decrease in brain glucose metabolism. Other characteristics such as disease activity, duration of the disease, and presence of antineuronal serum antibodies showed no relation to global or regional brain glucose metabolism.

MRI findings

We observed pathological changes on T2-weighted MRI in 20 patients (57%) patients. The predominant findings were disseminated white matter lesions that were equally distributed in subcortical and, to a lesser degree, in periventricular regions (Fig. 1). Eight patients (23%) displayed more than ten lesions on their T2-weighted images, 7 patients had at least one lesion larger than 8 mm in diameter (Table 4, Fig. 2). We found significant associations between both number and size of disseminated lesions and neurological CNS involvement (NP^+), whereas no association was observed between number or size of such lesions and neuropsychological performance (Table 4). Another significant correlation was found between the size of MRI lesions and the level of IgG anticardiolipin antibody titres (r = 0.48, P < 0.005). In particular, significantly (P < 0.018, ANOVA) higher mean IgG anticardiolipin antibody titres (227 plU/ml) were detected in group C (n = 7) compared with group B (n = 20) with smaller lesions (33 plU/ml) and group A including patients (n = 8) with normal brain scans (17 plU/ml) (Table 3). Disease duration, age, titre of antineuronal antibodies or activity of the disease had no significant influence on the number or size of the lesions determined on T2-weighted MRI.

Table 4 The relationship between number and size of white matter lesions on T2-weighted MRI of the brain and patients with neurological and neuropsychological CNS involvement in SLE

n = 35	NP		COG	
	+ n = 20	– n = 15	+ n = 10	– n = 25
Number of lesions	**		NS	
Group 1 (0–3)	5	10	4	11
Group 2 (4–10)	7	5	5	7
Group 3 (> 10)	8	0	1	7
Size of lesions	*		NS	
Group A (none)	1	7	1	7
Group B (< 8 mm)	13	7	7	13
Group C (> 8 mm)	6	1	2	5

** Phi coefficient = 0.52; P < 0.01; * Phi coefficient = 0.51; P < 0.01; *NS* not significant

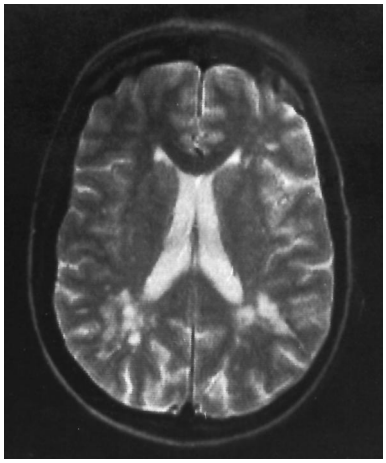

Fig. 2 T2 weighted MRI of the brain with periventricular and to a lesser degree subcortical distribution of white matter lesions. Patient belonging to groups 3 and C

The subgroup of patients (8/35) that suffered from both neurological and cognitive deficits did not significantly differ from the others in the number or size of white matter lesions. On the other hand, the group of 13 patients without any evidence of CNS involvement (NP^- and COG^-) revealed a significantly lower number ($P < 0.001$, two-sample *t*-test) and smaller size ($P < 0.002$, two-sample *t*-test) of lesions on T2-weighted images compared with the remaining SLE patients. The two subgroups did not differ significantly regarding the other variables investigated, including the titres of antineuronal and anticardiolipin antibodies.

Discussion

Although there is little doubt that CNS involvement in SLE occurs with considerable frequency, the diagnosis remains somewhat difficult [1, 35]. This difficulty arises from the lack of clear-cut, generally accepted diagnostic criteria, the possibility of secondary CNS involvement due to infections, hypertension or side effects of drugs such as corticosteroids, as well as from the absence of specific signs distinguishing CNS lupus from other systemic diseases involving the CNS. There is also no agreement regarding the diagnostic and/or pathogenic role of several autoantibodies supposed to be related to CNS SLE, since findings of different investigators have not been confirmed by others [1, 3, 8, 22, 31, 35, 44]. The majority of reports, however, agree on the existence of two types of CNS involvement, one characterised by neurological and/or psychiatric symptoms that can presumably be traced back to focal events, and another one predominantly of cognitive disorders thought to be related to a more diffuse process. The majority of reports have dealt with CNS involvement during the acute stage of SLE [3, 16, 31, 35, 39], or shorter duration of the disease [28], whereas less attention has been paid to the chronic phase of this disorder. We have focused our attention on the characterisation of CNS involvement in the chronic phase, i.e. that phase which constitutes by far the longest part of an SLE patient's history, acute exacerbations occurring only every 7 years on average [33].

By standardised neurological examination including a detailed history, and by using a battery of tests compiled to detect cognitive disorders, we have been able to separate two types of CNS involvement from each other. Twenty of them (57%) had clinically manifest neurological ($n = 17$) and psychiatric ($n = 3$) CNS involvement, whereas 10 (29%) showed pronounced cognitive disorders. Neurological and cognitive deficits were found to be unrelated disorders in SLE. These findings confirm earlier reports on the existence of cognitive deficits independent of other organ manifestation including neurological ones, and without obvious relation to the overall disease activity [17, 21].

Apart from the clinical diagnostic procedures, we have employed two imaging methods to examine the brain: MRI and ^{18}F-FDG PET. We excluded patients with known cerebral infarcts from the current study, for an altered glucose utilisation pattern was to be expected from such lesions and the surrounding brain area, regardless of whether such damage might have resulted from SLE vascular disease [12, 48] or from other events unrelated to SLE.

By PET, neither global nor regional glucose utilisation deviated significantly from the normal range in any of the patient groups. There was, however, a significant tendency towards lower utilisation values with increasing number and size of white matter lesions within the normal range (Table 3). Disease activity, duration, and antineuronal serum antibodies had no influence on glucose brain metabolism. Thus PET failed to provide additional evidence of CNS SLE beyond that obtained by clinical neurological examination, testing and MRI. This result is apparently at variance with an earlier report [42] based on a small number of selected SLE patients, including several with brain infarcts; indeed 2 of the 3 patients with fluctuating cognitive abnormalities and corresponding cerebral glucose utilisation abnormalities presented by Carbotte et al. [6] also suffered from cerebral infarcts in the region concerned, these being responsible for an altered glucose utilisation pattern rather than a functional impairment of the brain tissue with a hampered glucose utilisation.

The overall prevalence of lesions in our study is notably high (57% patients with > 3 lesions) when the mean age of 43 years and the absence of severe risk factors such as severe kidney involvement with hypertension or arteriosclerosis is considered [15, 26, 46]. The prevalence of white matter lesions differed significantly in the NP^+ (75%) and NP^- (33%) groups, indicating a possible aetiological relationship between presumably vascular local pathological events including focal lesions, which in turn may cause neurological symptoms, and which may become visible as lesions on MRI once a critical size is reached. The presence of clinically silent lesions, also reported by Stimmler et al. [41], who found 41% pathological MR images in SLE patients without overt CNS involvement, and NP symptoms without an increased number of lesions (Table 4), however, demonstrate the limited value of MRI as a diagnostic tool searching for, or excluding, CNS involvement in SLE. This diagnostic uncertainty may be limited to patients with a low lesion load, since > 10 lesions were always present with clinical evidence of NP symptoms. We cannot, on the other hand, confirm the results of Jarek et al. [28], who did not find an increased prevalence of lesions in their SLE patients without neuropsychiatric abnormalities (Table 4).

Regarding cognitive deficits, we did not find any differences between COG^+ and COG^- SLE patients with respect to number and size of lesions. This lack of correlation has led us to the conclusion that the process responsi-

ble for the development of cognitive deficits probably differs from the one causing neurological symptoms, and may indeed not be related to focal events such as those discussed above. Another possibility to explain this observation might be a lower total lesion load in SLE compared with, for example, patients suffering from multiple sclerosis. Rao et al. [37] reported a lower probability of cognitive deficits with a low total lesion load, which could account for a missing significant interdependence between the number of lesions and cognitive deficits, but studies comparing these two disorders are lacking. Still, a low lesion load may not exclude possible cognitive deficits, as demonstrated by Callanan et al. [4] in multiple sclerosis patients presenting with clinically isolated syndromes and only a few MRI abnormalities. The pathological nature and the site of MRI abnormalities may play a crucial role in the development of distinct neuropsychological dysfunctions in SLE. It has previously been suggested that there are two different types of CNS SLE, one related to focal events and the other of a "diffuse" nature [17, 19, 21, 23], mostly based on observations in acute-phase patients [3, 16, 31, 35, 39]. Our findings in patients in remission, based on objective clinical signs and neuropsychological test results, and supported by MRI and PET of the brain, corroborate such a distinction, although the pathogenetic events leading to the NP or COG deficits still remain hypothetical at present. Longitudinal observations, frequent MRI studies, and more sensitive magnetisation parameters will be necessary to clarify the importance of silent white matter lesions in SLE. These may be early signs of CNS involvement not yet detectable by clinical means. Studies of the underlying pathology of lesions using MRI techniques such as MRS and magnetisation transfer will be of great value in distinguishing oedema, inflammation, infarctions and gliosis, all of which may appear with increased signal in T2-weighted scans. At present, MRI provides only ancillary evidence for CNS involvement in SLE.

Whether the significantly shorter disease duration of the NP^+ group deserves more than transient interest, perhaps as one indicator for CNS SLE being an independent entity within the "family" of disorders collectively called SLE at present, remains to be seen. A similar reservation pertains to the relationship between significantly increased IgG anticardiolipin antibody titres and increasing lesion size; particularly elevated titres were found in 7 patients of group C (Table 3). To date, a pathogenic role of phospholipid antibodies remains unproved [31] and the alternative hypothesis of such autoantibodies as transporters of catabolic products is by no means refuted [20].

Taken together, clinical judgement supported by neuropsychological testing continues to form the basis for diagnosing CNS involvement in SLE. MRI offers additional evidence; here, the importance of clinically silent lesions and their underlying pathology remains to be established by prospective MRI studies. FDG PET, at least in its basic form of measuring global or regional brain glucose utilisation, provides little if any supportive information. We also conclude that because of the many unresolved questions regarding causes, diagnosis, and clinical course of different manifestations of CNS SLE, a rational basis for treatment is obviously lacking, at least for CNS symptoms encountered during the chronic or remission phase of SLE with low or intermediate disease activity. Prospective studies are needed to unravel the many unresolved questions in CNS SLE.

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