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Neuropsychological dysfunction in systemic lupus erythematosus is not associated with changes in cerebral blood flow

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Abstract Cognitive dysfunction is found in a considerable proportion of patients with systemic lupus erythematosus (SLE). SPECT provides an estimate of regional cerebral blood flow (rCBF) which has been claimed to be sensitive to detect brain involvement in SLE. It is, however, uncertain if these perfusion defects are related to cognitive dysfunction. In the present study we investigated whether cerebral dysfunction assessed by neuropsychological measures was associated with changes in rCBF. Fifty-two SLE patients were examined with a battery of neuropsychological tests and MRI of the brain. For each patient ^{99m}TC-HMPAO-SPECT was performed with the visual cortex as reference, and a reduction in rCBF of > 15 % was considered abnormal. Regional CBF was performed with an automated computer program quantitatively estimating blood perfusion in 16 symmetrical sectors of the brain. Several sectors of the brain showed varying areas of reduced rCBF with the temporal lobes most frequently involved. There were generally no associations between cognitive level of functioning and reduced rCBF. MRI demonstrated cerebral infarcts in 9 (17 %) patients. In general rCBF was reduced in all sectors of the brain in patients with infarcts, although statistical significant difference in rCBF between patients with and without infarcts was only seen in the parietal lobe. Several neuropsychological functions were influenced by the presence of cerebral infarcts. There was no significant association between immunological measures and SPECT findings or neuropsychological measures. Neuropsychological dysfunction in SLE was associated with the presence of cerebral infarcts detected by MRI, but not by changes in rCBF. SPECT seems to add little if any information to that obtained by clinical examination, neuropsychological testing, and MRI. Since anticoagulation may prevent cerebral infarcts, such prophylactic intervention may be of importance in preventing cognitive deterioration.

Key words SLE · SPECT · CBF · MRI · Cognitive dysfunction

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory multiorgan disease. It is characterized by a variety of clinical features including abnormalities of the skin, joints, lungs, heart, kidneys, and the central nervous system (CNS). It has a variable course marked by active and inactive disease periods. The aetiology of SLE is unknown, but it is believed to represent a disturb-

ance of the immune system, leading to influence of or damage to various organs.

Involvement of the brain – neuropsychiatric SLE (NPSLE) – is one of the most important manifestations, reportedly ranging from 20% to 75% of cases [1–5]. This can be attributed to differences in patient selection, arbitrary diagnostic criteria for CNS involvement in SLE, and more recently the recognition of milder forms of the disease. The CNS findings vary from global to focal cerebral dysfunction [5–6], and the main features are cerebrovascular disease, seizures, cerebral atrophy, psychosis, headaches, cognitive abnormalities and mood disorder. Unlike many other organ manifestations, the pathophysiology underlying CNS disease is not clear [7]. The observation of both diffuse and focal CNS involvement in SLE has led to the hypothesis that there are several pathogenetic mechanisms in NPSLE such as microvascular damage, small vessel vasculopathy and autoantibody mediated neuronal cell injury [8–10]. It has been proposed that about two-thirds of neurological manifestations in SLE are not related to the disease itself, but result from associated causes, such as drugs, infection, and hypertensive and metabolic complications [11].

Evaluation of NPSLE frequently involves a variety of laboratory and neurodiagnostic methods, but none of these are diagnostic or specific for SLE. Convential EEG rarely shows any correlation with the clinical manifestations [12] and cerebral CT and MRI are only helpful in detecting morphological lesions including infarcts and haemorrhages, but are inconclusive in diagnosing diffuse CNS pathology. MRI is considered more sensitive than CT in showing brain abnormalities such as intracranial haemorrhages or infarcts [13–15].

SPECT provides an estimate of regional cerebral blood flow (rCBF) or global CBF, which, with few exceptions is closely associated with brain metabolism [16]. Such functional brain imaging has been applied in SLE [17], and these techniques are claimed to be highly sensitive in detecting and monitoring CNS involvement [18–20].

Neuropsychological assessment is another method of evaluating brain function [21, 22]. Neuropsychological testing evaluates the functional capacity of the human brain. Assessing cognitive function has been proposed as a sensitive tool for investigating NPSLE [23] and cognitive dysfunction has been reported in a high proportion of SLE patients [23–25].

The aim of this study was to investigate if cerebral dysfunction as evaluated by neuropsychological measures was associated with quantitative rCBF changes assessed by SPECT. Furthermore, we also searched for any possible associations of such findings to medication or disease associated factors.

Patients and methods

Patients

All the medical records of inpatients and outpatients with the diagnosis of SLE seen at the University Hospital of Tromsø from 1979 to 1995, were reviewed. Ninety-four patients who fulfilled the American College of Rheumatology (ACR) 1982 revised criteria for the diagnosis of SLE [26] were identified. At the time of this study, 17 patients had died, 3 had moved to other parts of the country, and 4 patients were excluded from the study because of foreign language (2 patients), Down's syndrome (1 patient), or terminal cancer (1 patient). Of the remaining 70 patients, 57 (81%) gave an informed written consent to be included in the study, which was approved by the Regional Research Ethics Committee. Demographic and clinical data for the SLE patients are presented in Table 1. The most frequent other diseases or complications to SLE were arterial hypertension in 13 patients (23%), coronary heart disease in 6 patients (11%), hypothyroidism in 3 patients (5%), and osteonecrosis and lung fibrosis in 2 patients (4%), respectively. At the time of examination 13 of the 57 patients (23%) were on no medication for SLE. Ten patients (18%) received antimalarials only, ten patients (18%) prednisolone only, while 24 patients (42%) had combination therapy, mostly cytotoxic agents and prednisolone. 35 patients (61%) were on prednisolone. Disease activity was quantitated using the SLE Disease Activity Index (SLEDAI), a standardized index of disease activity for lupus patients [27]. A modified 18-item SLEDAI without measures of CNS manifestations was applied when looking for associations between SLE disease activity and neuropsychological function. The items removed were seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve neuropathy and lupus headache. Most of the patients had a mild and stable disease, as 24 patients (42%) had a SLEDAI score of 0–2. The age and the number of years of education were recorded for each patient. Also other factors known to influence neuropsychological performance including head injuries or other neurological diseases, substance abuse, learning disability or long-lasting toxic chemical exposure were analysed by review of patient records.

Magnetic resonance imaging

MRI of the brain was performed using a 0.5-T magnet (Gyroscan T5 II; Philips, The Netherlands) in 52 patients. A sagittal T1 weighted (WI) sequence (520/20/2 [repetition time/echo time/excitations]) with 6.0/0.6 mm (slice thickness/interspace) followed by an axial T2WI SE (2000/20/90 [repetition time/echo time]) with 5.0/0.5 mm (slice thickness/interspace) were performed through the entire brain.

A circular, transmit-receive head coil with matrix of 256 × 256 and a field of view of 250 mm was used. All images were read by one neuroradiologist (EAJ), blinded to SPECT and neuropsychological test results. An infarct was defined as an area with low T1 or protondensity and high T2 signal intensities, greater than 15 mm.

Tab. 1 Demographic and clinical data of 57 SLE patients

	Mean	SD
Age (years)	47.2	12.8
Education (years)	10.3	3.0
Disease duration (years)	14.5	9.0
SLEDAI	5.7	5.3
Modified 18-item SLEDAI*	5.2	4.5
No. of subjects:		
Female	50 (88%)	
Male	7 (12%)	

* without CNS items

Single photon emission computed tomography

Fifty-six patients were examined. Cerebral blood flow was measured with a brain dedicated imaging system (Siemens Neurofocal SPECT camera). This system has an in plane resolution of 12 mm. Each patient was injected i. v. with 750 MBq Tc–99m-HMPAO (hexamethyl propylamine oxime, Ceretec™) with eyes open during and after the injection. Each patient was positioned in the camera with the orbitomeatal line as reference. The scanning procedure lasted 20 minutes. Twenty-four transaxial images, 3.3 mm thick (1 pixel), and covering the whole brain were reconstructed using filtered back-projection and a linear attenuation correction. In order to perform quantitative estimation of the rCBF distribution we combined slices 9–12 (slice A), slices 13–16 (slice B), and slices 17–20 (slice C). Thirty percent of the measured activity was considered general background which was subtracted from slices A, B and C. The slices had then defined boundaries both laterally and internally versus the ventricles and covered essentially cortical tissue. An automated template with 16 symmetrical sectors was applied to the three slices for computation of regional activity. In slice A, 4 lateral sectors bilaterally were chosen for temporal lobe activity (Temp). In slice B, 4 frontal sectors bilaterally were chosen for the inferior part of the frontal lobes (Fi), 3 sectors bilaterally more posteriorly were chosen for the inferior parietal lobes (PaI) and the most posterior sector bilaterally was chosen for the primary visual cortex. In slice C corresponding sectors were chosen for the superior parts of the frontal (FS) and parietal lobes (PaS) and the primary visual cortex.

During measurement the patients had eyes open. Since the HMPAO method is a measure of relative CBF distribution, the primary visual cortex was used as reference region because it has the highest and most stable CBF. All regional activity was expressed as percent of the activity of the primary visual cortex. Global activity was the sum of all brain regions compared with the primary visual cortex. Reduction in activity of 15 % or more, regionally or globally, compared with visual cortex was defined as abnormal CBF reductions. In an extensive SPECT study in normal man, Waldemar et al. [28] showed that CBF in homologous bilateral brain regions did not differ more than 10 %. We have in the present study used the same method but with a slightly different equipment. Thus, we thought it prudent to be a little more conservative and use 15 % difference to distinguish between normal and abnormal CBF. A side to side CBF reduction in homologous regions of more than 15 % was considered a focal lesion.

Neuropsychological measures

Fifty-seven SLE patients underwent 2.5–3 hours neuropsychological assessment. A battery of standardized tests was applied measuring different areas of cognition, such as memory, attention, language, visuo-spatial processing, psychomotor speed, and executive function. The patients were tested individually by an experienced test technician. The neuropsychological test battery was administrated in two sessions and included Digit Span from the Wechsler Adult Intelligence Scale (WAIS) [29], immediate and 30 minutes delayed recall of two subtests from Wechsler Memory Scale-Revised (WMS-R) [30], namely Verbal Paired Associates and Visual Paired Associates, Seashore Rhythm Test [31], Trail Making Test – part A and B [31], Grooved Pegboard Test [32], Stroop Color and Word Test [33, 34], modified version [35, 36], Controlled Oral Word Association (COWA/FAS) [21, 34], and a computer administrated version of the Wisconsin Card Sorting Test (WCST) [37]. Furthermore, in evaluating intellectual functions Similarities (verbal function) and Block Design (non-verbal function) subtests from WAIS [29] were used. The various neuropsychological tests, grouped according to the respective cognitive domains are summerized in Table 2. Raw scores were used. The description of the tests and cognitive domains is in agreement with the recent work by ACR ad hoc Committee on Neuropsychiatric Lupus Nomenclature [38]. In assessing mood the Beck Depression Inventory (BDI) was used [39]. It was developed to assess current level of depression. This questionnaire of 21 items in multiple-choice format covers a range of depressive symptoms. It is a widely used depression questionnaire with good reliability and validity [40]. No control groups of normal persons or other cerebral diseases were included in the study because the main objective was to evaluate the relationship between continuous variables of neuropsychological function and CBF. The main objective of this study was to evaluate associations continuously over a wide spectrum, which may be lost using a dichotomy of normal and unnormal. This study treated neuropsychological measures as continuous variables and thus used raw scores.

Tab. 2 Neuropsychological domains and tests

	Domains:	Tests:
1.	Simple Attention	Digit Span (WAIS)
2.	Complex Attention	Seashore Rhythm Test
		Trail Making Test – B
3.	Memory: Verbal	WMS-R, Verbal Paired Associates
		Immediate and 1 hour delayed recall
	Visual	WMS-R, Visual Paired Associates
		Immediate and 1 hour delayed recall
4.	Psychomotor function	Trail Making Test – A
	(speed)	Stroop Color-Word Test
		(reading speed)
5.	Executive function	WCST
		Stroop Color-Word Test (interference)
6.	Language	COWA (FAS)
7.	Motor function (speed)	Grooved Pegboard Test
8.	Intellectual functions:	
	Verbal function	Similarities (WAIS)
	(Reasoning/Problem Solving)	
	Non-verbal function	Block Design (WAIS)
	(Visual-Spatial Processing)	
9.	Depression	BDI

Abbrevations.
WAIS = Wechsler Adult Intelligence Scale. WMS-R = Wechsler Memory Scale-Revised. WCST = Wisconsin Card Sorting Test. COWA (FAS) = Controlled Oral Word Association. BDI = Beck Depression Inventory.

Laboratory tests

Routine haematological, biochemical and immunological tests were performed in the hospital's routine laboratory. Anticardiolipin antibodies (aCL) of IgG and IgM isotypes were performed by a commercial ELISA assay according to the manufacturer "Shield". Values above 30 GPL and 30 MPL U/ml were considered positive.

Testing for lupus anticoagulant (LAC) was performed by a commercial lupus anticoagulant-sensitive activated partial thromboplastin time (APTT) reagent (PTT-LA; Diagnostica Stago). In cases with ≥ 6 seconds prolongation of clotting time, confirmation assays were done at the Haematological Laboratory, Ullevål University Hospital, Oslo, as previously described [41].

Statistics

Statistical calculations were performed with Statview 5.0. Results are presented as means for normally distributed data. Relationships between SPECT and cognitive parameters were examined using Pearson's product-moment correlations. Data analysis included unpaired Student's t test or ANOVA for testing differences between two or more groups of quantitative data, and chi square for differences between groups of categorial data. Two-tailed P values are reported through-

out. When appropriate, the Bonferroni method was applied with a significance level of 0.01 to decrease the probability of type I errors. Associations between cognitive measures and rCBF, as well as the possible influence on this by cerebral infarcts as evaluated by MRI, disease duration, age, and education were assessed by simple and multiple regression analyses respectively.

Results

MRI findings

MRI demonstrated cerebral infarctions in 9 SLE patients (17%). Five patients (10%) had a single large infarct, and 4 patients (8%) had multiple small infarcts. Six patients (11%) had cortical infarcts, and 5 of these (83%) had infarcts in the parietal lobes. Four patients (8%) had subcortical infarcts. The parietal, frontal and temporal lobes were most commonly involved in 5, 2 and 2 patients respectively. Of 6 patients with cortical infarcts, 5 had infarcts in the parietal lobes. Just one patient with cerebral infarcts on MRI had abnormal neurological findings indicating a stroke. No significant associations were observed between infarcts and aCL antibodies of IgG and IgM isotypes or LAC.

SPECT findings

The results are presented in Table 3. Thirty-one patients (55%) had abnormal global CBF with different patterns of flow defects. Additionally 17 patients (33%) had 1–10 focal lesions of reduced blood flow. Generalized bilateral CBF reduction, mostly in the temporal or frontal lobes were seen in 50% of the patients. Areas of hypoperfusion were found most frequently in the frontal, temporal and parietal regions. In 31 out of 56 patients (55%) we observed > 15% CBF global reduction, whereas 32 patients (57%) had significantly reduced rCBF in the superior part of the frontal lobe. Seventeen patients (30%) had significant reduction in the frontal inferior lobe, 13 (23%) had rCBF reduction in the parietal superior lobe, 26 (46%) in the parietal inferior lobe, and 43 patients (77%) had significant rCBF in the temporal lobe. Disease activity, disease duration, or type and duration of present medication or no medication at all had no influence on CBF.

Tab. 3 Percent reduction of CBF as measured with 99Tc-HMPAO SPECT in 56 patients with SLE

	FS	FI	PaS	Pal	Temp	Global
% reduction (mean) of CBF:	16.4	12.2	13.4	13.7	21.3	15.4
Range:	8–28	1–22	3–30	2–28	8–31	6.8–25.6
% of patients with > 15% reduction of CBF:	57	30	23	46	77	55

Abbrevations.
FS = Frontal superior lobe; FI = Frontal inferior lobe; PaS = Parietal superior lobe; Pal = Parietal inferior lobe; Temp = Temporal lobe; Global = Global cerebrum

Laboratory tests

Six patients (11%) had aCL IgG antibodies and 2 patients (4%) aCL IgM, while positive LAC was found in 3 (5%) out of 55 patients. No significant associations were observed between infarcts and aCL antibodies of IgG and IgM isotypes or LAC.

SPECT and relationship to cognitive functions

There were significant associations only between reduced rCBF of the superior part of the parietal lobe (PaS) and the Trail Making Test – A, and between rCBF of the superior part of the frontal lobe (FS) and the Perseverative Errors in WCST. No other associations between cognitive scores and global or regional CBF were found. The results are presented as a correlation matrix with significance level chosen as < 0.01 (Table 4).

The significant associations between Trail Making Test – A and reduced rCBF in PaS, as well as between Perseverative Errors and rCBF in FS, were confirmed with simple regression analysis. In the multiple regression equatation with Perseverative Errors as dependent variable and rCBF in FS, cerebral infarcts, disease duration, age, and education as independent variables, the impact on Perseverative Errors was found to be due to age (β= 0.52; p=0.002). Likewise the Trail Making Test – A was significantly influenced by cerebral infarcts (β=12.16; p=0.03).

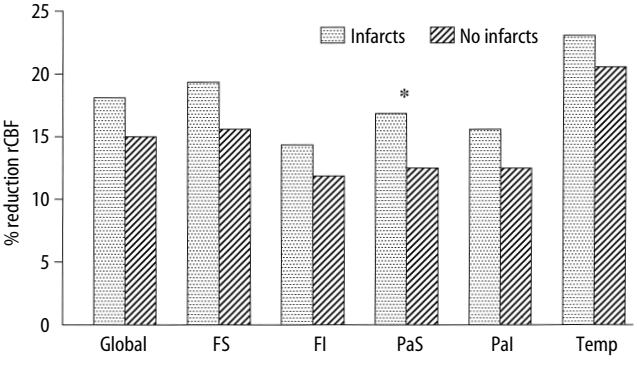

Fig. 1 Percent regional cerebral blood flow reduction as measured with 99Tc-HMPAO SPECT in SLE patients with cerebral infarcts (n=9) on MRI compared with patients without infarcts (n=48).

Abbreviations.
FS = Frontal superior lobe. FI = Frontal inferior lobe. Temp = Temporal lobe. PaS = Parietal superior lobe. Pal = Parietal inferior lobe. Global = Global cerebrum. *p < 0.01

Tab. 4 Relationship (correlation matrix) between CBF and neuropsychological measures

	Global	FS	FI	PaS	PaI	Temp
Digit Span (WAIS)	–0.01	–0.13	–0.09	0.06	0.11	0.01
Trail Making Test – A	0.30	0.31	0.16	0.43*	0.18	0.19
Trail Making Test – B	0.23	0.33	0.17	0.34	0.09	0.10
Seashore Rhythm Test	0.02	–0.003	–0.09	–0.006	0.03	0.12
COWA (FAS), total words	–0.21	–0.24	–0.22	–0.27	–0.10	–0.08
WMS-R, Verbal Paired Associates I	–0.20	–0.21	–0.07	–0.28	–0.04	–0.22
WMS-R, Verbal Paired Associates II	0.01	–0.05	0.10	–0.08	0.08	–0.006
WMS-R, Visual Paired Associates I	0.11	0.08	–0.03	0.11	0.14	0.16
WMS-R, Visual Paired Associates II	–0.18	–0.09	–0.25	–0.08	–0.17	–0.14
Stroop, Color, Time	0.02	0.16	0.04	0.12	–0.15	–0.06
Stroop, Words, Time	–0.03	0.13	0.02	0.11	–0.21	–0.13
Stroop, Color-Word	0.12	0.26	0.08	0.28	–0.03	–0.03
WCST, Total Errors	0.19	0.29	0.13	0.18	0.11	0.10
WCST, Perseverative Responses	0.30	0.40*	0.19	0.36*	0.17	0.18
Grooved Pegboard Test	–0.03	0.15	–0.07	0.04	–0.15	–0.06

* = $p < 0.01$

Abbreviations.
FS = Frontal superior lobe. FI = Frontal inferior lobe. Temp = Temporal lobe. PaS = Parietal superior lobe. PaI = Parietal inferior lobe. Global = Global cerebrum. WAIS= Wechsler Adult Intelligence Scale. COWA (FAS)= Controlled Oral Word Association. WMS-R= Wechsler Memory Scale-Revised. Stroop=Stroop Color-Word Test. WCST= Wisconsin Card Sorting Test.

Significant differences in rCBF between patients with and without infarcts could only be observed in the superior parietal lobe (PaS) (Fig. 1), while several parameters of neuropsychological functions were influenced by the presence of cerebral infarcts (Fig. 2 and 3). This was especially evident for Trail Making Test – A and B, Controlled Oral Word Association, Stroop Color-Word Test, and Wisconsin Card Sorting Test with a significance level of $p < 0.001$, and Seashore Rhythm Test with a level of $p < 0.01$. No significant associations were observed between SPECT findings and depression as measured with BDI scores.

There were no significant associations between cognitive dysfunctions or abnormal CBF and the following parameters: disease duration, modified SLEDAI, type of or duration of present medication or no medication at all, LAC, or aCL. Neither were there any significant associations between SPECT findings or neuropsychological measures and any immunological variables. No significant associations were observed between autoantibodies and BDI scores.

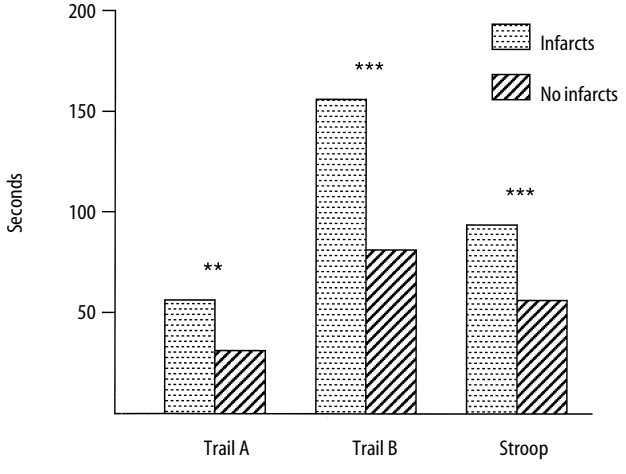

Fig. 2 Neuropsychological test performance for SLE patients with cerebral infarcts (n=9) on MRI as compared to patients without infarcts (n=48).

Abbreviations.
Trail A = Trail Making Test – A. Trail B = Trail Making Test – B. Stroop = Stroop Colour and Word Test. **$p < 0.001$, ***$p < 0.0001$.

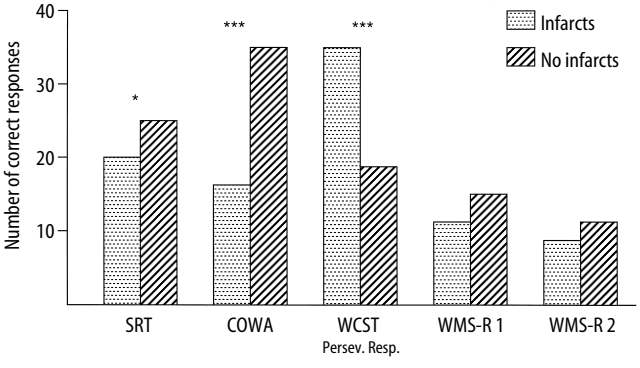

Fig. 3 Neuropsychological tests results for SLE patients with cerebral infarcts on MRI (n=9) as compared to SLE patients without infarcts (n=48). Higher number of responses=better performance, except for Perseverative Responses where there is an inverse relation.

Abbreviations.
SRT = Seashore Rhythm Test. COWA = Controlled Oral Word Association (FAS). WCST = Wisconsin Card Sorting Test, Perseverative Responses. WMS-R 1 = Wechsler Memory Scale-Revised, Verbal Paired Associates. WMS-R = Wechsler Memory Scale-Revised, Visual Paired Associates. *$p < 0.01$, ***$p < 0.0001$

Discussion

A diagnosis of NPSLE remains difficult to establish and is largely based on clinical findings and on the results of imaging methods. Cognitive dysfunction has been reported to occur frequently in SLE [23, 24, 42]. We have previously observed cognitive dysfunction in these SLE patients compared with a control group with chronic illness of nonimmunological nature. There were significant group differences on multiple measures of attentional skills, psychomotor speed, tactile spatial and abstract problem solving (executive function), with lowest test performance for the SLE patient group [42].

The present study investigated whether neuropsychological dysfunction in SLE was associated with signs of metabolic disturbances of brain cells, assessed by SPECT as alterations in CBF. We found significant associations only between slow psychomotor speed and executive dysfunction, and rCBF in the parietal lobe and in the frontal lobe, respectively. Psychomotor speed was influenced by cerebral infarcts and executive function by age. Except for this, there were no associations between dysfunction in any cognitive domain and regional or global CBF changes in any of the brain sectors (Table 4). This indicates that as far as altered brain neuronal metabolism is reflected in changes in CBF detected by SPECT, such a mechanism cannot alone be responsible for cognitive dysfunction in SLE. This view is strenghtened by the SLE studies of Kao et al. [43] and Grünwald et al. [44] who reported that decreased rCBF evaluated by SPECT was not paralleled by PET abnormalities. Also Sailer et al. [45] using PET, showed that brain glucose metabolism of SLE patients did not differ significantly from that of normal controls, nor was glucose hypometabolism associated with cognitive dysfunctions.

Only few studies have focused upon the relationship between CBF (SPECT) or metabolic abnormalities (PET), and cognitive dysfunction in SLE patients. Carbotte et al. [46] reported that neuropsychological test scores was the most sensitive measure of cerebral impairment and correlated well with abnormal metabolic findings using PET scanning of the brain, while two other studies reported no correlation between SPECT and psychometric test results or cerebral function [47, 48]. One PET study investigated whether there were any correlations between overall or regional alterations in cerebral glucose metabolism, cognitive dysfunction and MRI white matter findings [45]. It was concluded that PET added little if any information beyond that obtained by clinical examination, neuropsychological testing, and MRI.

No significant association between SPECT findings and depression was observed as measured with BDI. Our results indicate that depression is not associated with cerebral blood flow in SLE patients.

We found that cerebral infarcts were significantly associated with several cognitive dysfunctions as well as with impaired rCBF in the parietal lobe where the majority of infarcts were located (Fig 1). Another study found that changes in cognitive function in SLE patients paralleled changes on PET [46]. However, two of three patients with fluctuating cognitive abnormalities and corresponding cerebral glucose metabolism defects also suffered from cerebral infarcts in the region concerned, possible responsible for the metabolism abnormalities.

Our study indicates that in an unselected SLE population, cognitive dysfunction is largely due to cerebral infarcts. The size and site of cerebral infarcts may play a crucial role for neurocognitive dysfunction in SLE. In contrast to an investigation of Maeshima et al. [47] who found no relationship between the findings on brain CT and higher cortical dysfunction, our results demonstrate an association between findings in cerebral MRI, and cognitive dysfunction in SLE patients. We have recently reported that cerebral infarcts and cortical atrophy as detected by cerebral CT are the only features of SLE that are significantly associated with cognitive abnormalities [49]. Since anticoagulation may prevent cerebral infarcts, such prophylactic intervention may have a protective effect regarding cognitive deterioration.

Antineuronal antibodies and antiphospholipid antibodies have been claimed to be related to NPSLE such as cognitive dysfunction, but their pathogenic role for cognitive deficits so far remains uncertain. Some studies [47, 50, 51] have proposed a relationship between aCL, LAC and cognitive dysfunction, while another study found no such association [52]. We found no associations between LAC or aCL and cognitive or SPECT abnormalities. We cannot exclude that this may be due to a low prevalence of positive LAC and aCL, but these associations were absent whether LAC or aCL were statistically treated as quantitative or qualitative data. Neither were there any associations between rCBF or cognition and immunological variables, disease activity, duration, or medication for SLE. We found no significant relationship between autoantibodies and BDI scores. In contrast to two other studies [18, 20], we did not find any significant association between disease duration and rCBF.

However, two recently published prospective studies demonstrated an association between persistently elevated aCL titres and cognitive dysfunction [53, 54]. This suggest that aCL may serve as an immunological marker. Both these studies and our study may strengthen the hypothesis that thromboembolic complications might be responsible for a considerable part of cognitive dysfunction in SLE. Several studies have indicated that antiphospholipid antibodies influence cognitive function, but few have taken into consideration that this might be due to cerebral infarcts. Our findings indicate that infarction is a significant contributer of cognitive dysfunction in SLE patients.

PET and SPECT are by some claimed to be the most

useful diagnostic methods for CNS activity in SLE, but our study does not support this. However, one limitation in our study and in most earlier studies using SPECT as a measure of CBF is that one only obtains maps of the relative distribution of the blood flow in the brain. The absolute CBF level can vary considerably in patient groups as well as in normals which means that a certain CBF distribution map may have a different interpretation if it occurs in a situation with high CBF compared with low CBF. Thus, neuropsychological tests remain the most sensitive and valid measures of functional brain condition in SLE. Future studies will need to include control groups of normal persons and patients with other diseases where reduced CBF is known to influence cognitive measures.

In summary, the present study demonstrates that objectively evaluated SPECT findings in SLE patients are in general not associated with cognitive dysfunction or functional brain abnormalities as detected by neuropsychological tests. The cognitive abnormalities present seem mainly to be associated with cerebral infarcts. It appears that SPECT in SLE adds little if any clinical information beyond that obtained by neuropsychological assessment and MRI.

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