Brain glucose utilization in systemic lupus erythematosus with neuropsychiatric symptoms: a controlled positron emission tomography study

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Abstract. In contrast to morphological imaging [such as magnetic resonance imaging (MRI) or computed tomography], functional imaging may be of advantage in the detection of brain abnormalities in cases of neuropsychiatric systemic lupus erythematosus (SLE). Therefore, we studied 13 patients (aged 40±14 years, 11 female, 2 male) with neuropsychiatric SLE who met four of the American Rheumatism Association criteria for the classification of SLE. Ten clinically and neurologically healthy volunteers served as controls (aged 40±12 years, 5 female, 5 male). Both groups were investigated using fluorine-18-labelled fluorodeoxyglucose brain positron emission tomography (PET) and cranial MRI. The normal controls and 11 of the 13 patients showed normal MRI scans. However, PET scan was abnormal in all 13 SLE patients. Significant group-to-group differences in the glucose metabolic index (GMI=region of interest uptake/global uptake at the level of the basal ganglia and thalamus) were found in the parieto-occipital region on both sides: the GMI of the parieto-occipital region on the right side was 0.922±0.045 in patients and 1.066±0.081 in controls (P<0.0001, Mann Whitney U test), while on the left side it was 0.892±0.060 in patients and 1.034±0.051 in controls (P=0.0002). Parieto-occipital hypometabolism is a conspicuous finding in mainly MRI-negative neuropsychiatric SLE. As the parieto-occipital region is located at the boundary of blood supply of all three major arteries, it could be the most vulnerable zone of the cerebrum and may be affected at an early stage of the cerebrovascular disease.

Key words: Neuropsychiatric systemic lupus erythematosus – Positron emission tomography – Fluorine-18 fluorodeoxyglucose – Parieto-occipital brain hypometabolism

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Introduction

Studies with positron emission tomography (PET) and single-photon emission tomography (SPET) have shown that in certain brain disorders functional imaging is more sensitive than morphological imaging such as magnetic resonance imaging (MRI) and X-ray computed tomography. This applies to traumatic brain injury [1–8], whiplash injury [9, 10], migraine [11], or Alzheimer's disease [12, 13], and also neuropsychiatric systemic lupus erythematosus (SLE) [14–16]. Neuropsychiatric SLE has in most cases been studied in late stages of the disease; little is known of early neuropsychiatric SLE. There are conflicting reports regarding the regions involved in neuropsychiatric SLE: using azetazolamide-enhanced SPET in an SLE patient with preclinical central nervous system (CNS) involvement, Grünwald et al. [14] showed a marked reduction in the cortical perfusion reserve, particularly in both frontal lobes, whereas Kovacs et al. [17] showed various other abnormal regions such as the occipital cortex or the basal ganglia in cases of active neuropsychiatric SLE. Szer et al. [18] reported on a girl with a concurrent ischaemic event involving both parietal lobes. Therefore, we wondered whether there is a typical pattern of metabolism in neuropsychiatric SLE, reflecting the vulnerability of the different zones in the cerebrum.

Materials and methods

Each study participant signed an informed consent form, explaining the investigative nature of the study, its risks, and its merits.

Study population. Ten normal controls (mean age 40±12 years, 5 female, 5 male) and 13 patients (mean age 40±14 years, 11 fe-

male, 2 male) were studied. All patients met four of the American Rheumatism Association criteria for the classification of SLE [19]. All study participants were interviewed with regard to headache, vertigo, visual symptoms (blurred vision, scintillating scotoma, oscillopsia), impaired memory and/or concentration, depression, sleep disturbances, anxiety and instability [20].

None of the study participants exhibited anamnestic hints of neurovascular or neurodegenerative diseases. Secondary causes such as infection, uraemia, hypertension, drugs and metabolic abnormalities were excluded. Eleven of the 13 neuropsychiatric SLE patients received corticosteroid treatment and three received immunosuppression with cyclophosphamide or azathioprine. As regards the control group, only participants with normal clinical and neurological findings were included in the study. For the patient group, only those patients were included who showed clinical and neurological findings indicating CNS involvement by the disease. Neuropsychiatric manifestation due to SLE was defined as an abnormality of neurological function identified by current history and physical examination and noted as a change from a prior state, if this abnormality could not be attributed to any cause other than the disease process itself. The CNS manifestations were classified into "major" (seizures, focal motor or sensory deficits, generalized disturbances, psychosis, organic brain syndrome) and "minor" signs (paraesthesia or clumsiness without objective findings, headache, cognitive disorders) according to the classification of How et al. [21]. Nine patients with "initial" CNS SLE had shown neuropsychiatric signs for no longer than 1 year, whereas four patients with "manifest" CNS disease had been symptomatic for more than 1 year. All patients diagnosed as having manifest CNS SLE ($n=4$) had one or more major signs, and two of them showed pathological findings on MRI. Patients in the initial CNS SLE group had one major sign ($n=5$) or one to three minor signs ($n=4$).

MRI of the brain was also undertaken in all patients and controls.

The following neuropsychiatric symptoms were observed in the SLE patients:

– Impairment of memory and of intelligent function: $n=6$ patients
– Psychosis: $n=4$
– Seizure: $n=1$
– Focal motor deficits: $n=2$
– Persistent headache: $n=4$
– Paraesthesia: $n=2$
– Vertigo: $n=3$
– Impairment of orientation and perception: $n=1$
– Visual symptoms: $n=4$
– Recurrent apoplexy: $n=1$

The following concomitant clinical and serological parameters were observed in the SLE patients:
– Positive antinuclear antibodies: $n=13$ patients
– Positive anti-ds DNA: $n=7$
– Positive antibodies against extractable nuclear antigen: $n=10$
– Phospholipid antibodies: $n=6$
– Cutaneous lesions: $n=7$
– Lupus nephritis: $n=8$
– Arthralgia: $n=6$
– Myalgia: $n=4$
– Sicca complex: $n=4$
– Cytopenia: $n=4$

Radiopharmaceuticals. All participants were injected with 370 MBq fluorine-18 fluorodeoxyglucose (FDG) into a peripheral vein. FDG was synthesized and prepared as reported previously [22].

PET study protocol. Before the start of the PET procedure, each study participant had to fast for at least 12 h before the study and to empty the bladder. Then, during the 10-min waiting period prior to injection, patients and controls were placed on a bed in the preparation area in a quiet room with dim lights, remaining awake, but with closed eyes. After injection, patients and controls remained on the bed for another 30 min. The head of each subject was then positioned parallel to the orbitomeatal line with the aid of a laser beam, after which it was placed in a moulded thermoplastic head support to minimize head movements during the scanning procedure. All subjects were studied at rest. The acquisition started about 35 min p.i. PET imaging was performed on a Siemens CTI ECAT EXACT tomograph. This device records 31 planes simultaneously, which encompass a 10.8-cm field of view. The spatial resolution is 6.0 mm full-width at half-maximum. Photon attenuation was automatically calculated using Siemens-CTI standard software [23]. A total of six frames, each of 5 min duration, were acquired. Images were reconstructed using filtered back-projection (Shepp-Logan filter, cut-off 0.3 cycles/pixel). For data analysis, summed images were used (summing the dynamically acquired frames 1–6 into one image).

Data analysis. Standardized cortical and subcortical elliptical regions of interest (ROIs) were assigned to three adjacent transaxial slices of the following regions by consensus of two independent investigators:

1. Frontal
2. Parietal
3. Occipito-frontal
4. Temporo-lateral
5. Temporo-mesial
6. Parieto-occipital (P-O)
7. Thalamus
8. Putamen
9. Caudate nucleus
10. Cerebellar (mean of lateral and dorsal cerebellum)
11. Brain stem
12. Global at the level of the thalamus and basal ganglia

The shape and size of ROIs were the same in all patients and controls, since the ROI templates were copied onto the corresponding planes of each study. The shape and size of global ROIs were fitted to actual head form by manipulation. The position of all ROIs was adjusted to the corresponding anatomical localization. In each ROI the average uptake per pixel per time was determined.

ROI analysis was performed using a SUN sparc station and SUNVIEW software. To allow inter-individual comparisons, regional cerebral metabolism was normalized by global glucose metabolism (glucose metabolic index, GMI; GMI=ROI uptake/global uptake) determined from the global brain ROI at the level of the thalamus and basal ganglia.

Statistical analysis. All data are expressed as mean ±1 SD. Group-to-group differences were tested using the Mann Whitney U test (M.W.) and the software StatView 4.10.

Results

MRI of the brain showed no pathological findings in any of the controls or in 11 of the 13 patients. The two patients with pathological MRI findings had had organic neuropsychiatric symptoms for more than 1 year. In con-
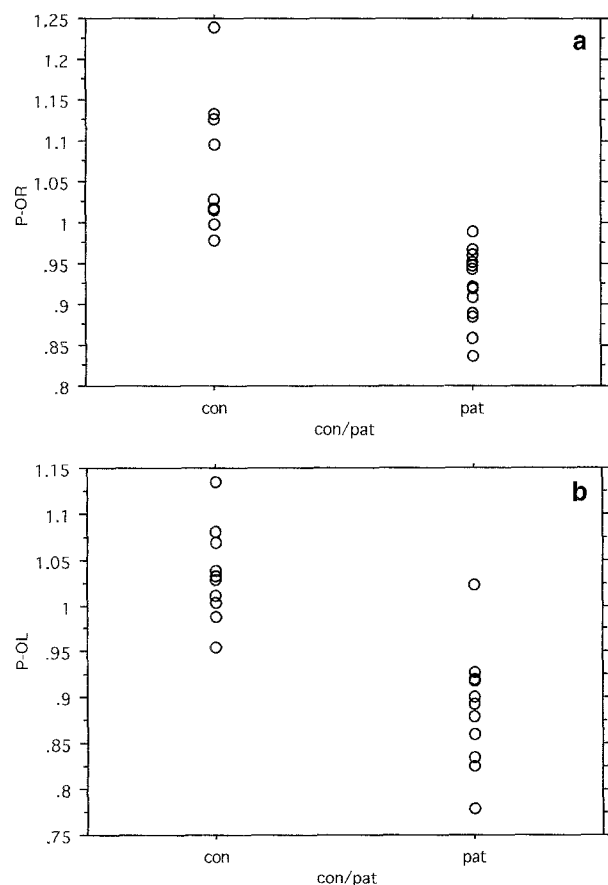

Fig. 1. Scattergrams of GMI values of P-O on the right (**a**) and left (**b**) sides, in the control group (*con*, *n*=10) and the patient group (*pat*, *n*=13)

trast, the patient group revealed a significant hypometabolism in the P-O regions [on the right (R) and left (L) side] as compared to the control group (Fig. 1):

- GMI P-O R: controls 1.066±0.081, patients 0.922±0.045; $P<0.0001$
- GMI P-O L: controls 1.034±0.051, patients 0.892±0.060; $P=0.0002$

Group-to-group differences in regions other than the P-O were not statistically significant. However, careful evaluation of the individual metabolic pattern did additionally reveal, in six of the 13 patients (46%), GMI values which were more than one or two standard deviations below normal control values in regions other than the P-O. In one patient (no. 5), P-O hypometabolism was combined with a patchy uptake pattern over the whole brain, while in another (no. 1) it was combined with a relative hypermetabolism in the basal ganglia and thalami (Table 1).

Furthermore, when the SLE patient group was divided into patients who showed CNS involvement for the first time at admission (group 1, *n*=9) and patients with organic neuropsychiatric symptoms for more than 1 year (group 2, *n*=4), no significant difference was found between groups 1 and 2 with regard to glucose utilization in any of the analysed brain regions.

Discussion

Our study indicates that neuropsychiatric SLE – irrespective of the stage of CNS involvement (i.e. initial or non-initial) – has a typical pattern of hypometabolism in the P-O region, although non-P-O regions may also be affected. Since the P-O region is located at the boundary of supply of all three major arteries, it is thought to be the most vulnerable zone of the cerebrum [24]. There-

Table 1. Brain PET findings in patients

Pat.	P-o,R	P-o,L	P,R	P,L	F,R	F,L	O-F,R	O-F,L	CN,B	PUT,B	TH,B	P-P
1	-	- -	Ø	Ø	Ø	Ø	Ø	Ø	++	++	++	No
2	-	- -	- -	- -	- -	- -	- -	Ø	Ø	Ø	Ø	No
3	-	- -	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	No
4	- -	- -	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	No
5	- -	- -	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Yes
6	-	- -	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	No
7	-	-	-	-	Ø	Ø	Ø	Ø	Ø	Ø	Ø	No
8	-	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	No
9	- -	- -	- -	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	No
10	- -	- -	- -	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	No
11	- -	-	-	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	No
12	- -	- -	Ø	Ø	Ø	Ø	-	-	+	Ø	Ø	No
13	-	- -	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	Ø	No

P-O, Parieto-occipital; P, parietal; F, frontal; O-F, occipito-frontal; CN, caudate nucleus; PUT, putamen; TH, thalamus; P-P, patchy uptake pattern; R, right brain side; L, left brain side; B, both sides. -, GMI>1 SD *below* normal controls; - -, >2 SD; +, GMI>1 SD *above* normal controls; ++, >2 SD; Ø, GMI within normal limits.

fore, we think that this region is frequently affected at an early stage of SLE with suspected CNS involvement. MRI findings are inconspicuous in early neuropsychiatric SLE, in contrast to the well-known MRI findings in manifest and chronic CNS SLE [25–27]; against this background the information provided by our PET data might have important diagnostic and therapeutic implications at an early stage of the disease. However, the question of whether vasculitis or infarctions and haemorrhages in this P-O zone are the consequence or a cause of the SLE process remains open.

Abnormalities in the P-O region are not pathognomonic for neuropsychiatric SLE: they can also be found, for example, in the late whiplash syndrome [9, 10, 28], in dementia of the Alzheimer type [12], in the elderly [13], in sleep apnea syndrome [13] and following cerebral hypoxia [13]. However, after careful clinical and serological classification of our neuropsychiatric SLE patients, these differential diagnoses could be excluded.

In studies on the pathology of cerebral lupus, vasculopathy, infarctions and haemorrhages are often observed, whereas vasculitis is rare [29]. Furthermore, the concept of hypercoagulability in SLE patients has diverted the direction of therapy from immunosuppression [30] (as in the majority of our patients) towards anticoagulation [31]. Randomized trials have commenced in order to determine the optimal mode of therapy for SLE patients under strict inclusion criteria, based on well-defined patient categories. Functional imaging like PET, or SPET, could be a powerful tool for such an enterprise.

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