Migraine During Systemic Lupus Erythematosus: Findings from Brain Single Photon Emission Computed Tomography

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ABSTRACT. ***Objective.*** Headache in systemic lupus erythematosus (SLE) is controversial, as is evidence of brain impairment in patients with SLE and headache. Perfusion single photon emission computed tomography (SPECT) was performed to investigate brain impairment in SLE patients with migraine-like headache either from the period of diagnosis or later in the course of disease.

Methods. Eighteen patients with SLE (mean age 40.8 ± 13.6 yrs) matching these characteristics underwent brain SPECT with ^{99m}Tc-HMPAO in the interictal period. Electroencephalography (EEG) and magnetic resonance imaging (MRI) were performed in 12 and 10 patients, respectively. SPECT was analyzed through visual and asymmetry combined analysis as well as by voxel-based statistical analysis compared to a control group of matched healthy subjects (statistical threshold: $p = 0.01$).

Results. Focal hypoperfusion was evidenced in 15 (83%) patients, often matching the main side of pain location, whereas EEG and MRI each gave a positive result in 50% of cases. Using voxel-based analysis, significant hypoperfusion was found in 8 (44%) patients, either lateralized to one side or localized to the anterior cingulate cortex, independent of pain location.

Conclusion. Brain perfusion SPECT is a sensitive tool for identifying brain impairment in SLE-related migraine, although the mechanisms of brain damage remain to be elucidated. Besides confirming focal hypoperfusion in some patients, in 4 patients statistical analysis revealed interictal hypofunction of the anterior cingulate cortex, a key structure for cortical elaboration of pain in the midline network. (J Rheumatol 2006;33:2184–91)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS HEADACHE MIGRAINE BRAIN PERFUSION SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY MAGNETIC RESONANCE IMAGING ELECTROENCEPHALOGRAPHY

The issue of headache in patients with systemic lupus erythematosus (SLE) is complex. An ad-hoc committee of the American College of Rheumatology (ACR) has classified several syndromes within SLE headache, including migraine, headache due to pseudotumor cerebri, and nonspecific intractable headache[1]. A number of confounding variables, including the high prevalence of headaches in the female population and the high prevalence of mood disorders, often complicate interpretation of headache in young women with SLE.

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Systematic reviews on the prevalence and characteristics of the several headache types in SLE have led to conflicting results for the causal association between SLE and headache[2-7], and a specific link between headache and SLE has recently been questioned[8,9]. Thus SLE headache subtypes and their possible connection with the underlying disease represent a matter of debate and investigation.

When a relationship between headache and SLE is suspected, the specific headache types must be carefully identified according to the classification criteria of the International Headache Society (IHS)[10] due to the different clinical meanings they can have during SLE. A common protocol that may clarify the underlying pathophysiological correlates includes magnetic resonance imaging (MRI) and regional cerebral blood flow assessment[11], which show brain changes in some patients with SLE and headache. Although both the ^{133}xenon planar method and single photon emission computed tomography (SPECT) have been applied to the study of neuropsychiatric SLE (NP-SLE), the reports of their application to SLE headache remain mostly anecdotal. The largest group was studied with SPECT by Rubbert, *et al*[12], who found focal or multifocal hypoperfusion in the majority of 10 patients,

including 4 cases with migraine and 6 cases with tension-type headache. Fewer cases were investigated in other SPECT studies[13,14] using positron emission tomography (PET)[15] or the ^{133}xenon method[16-18]. What is missing in the majority of these studies is the definition of headache type (tension-type, migraine-type, or other) according to the IHS criteria and the temporal relationship between the onset of headache and the onset of SLE. Indeed, it is common to observe adult women with SLE who have also experienced primary migraine since adolescence. Despite this limited experimental evidence, brain SPECT is often used in patients with SLE headache to investigate brain impairment[11].

Our objective was to verify the presence of cerebral hypoperfusion in patients with SLE migraine. This was achieved by systematic analysis of brain perfusion SPECT in a consecutive series of SLE patients with migraine-like headache, according to the definition of the IHS[10], that had started around the time of SLE diagnosis or later during the course of the disease. SPECT data were analyzed both semiquantitatively and statistically, compared to a healthy control group, by voxel-based analysis, with no *a priori* topographic hypothesis.

MATERIALS AND METHODS

Patients. In a 2 year period, all outpatients with SLE coming to one of the SLE units of our hospital, who presented with migraine-like headache with onset dated to the same period as SLE diagnosis or later during the disease course, were considered eligible for study. Diagnosis of SLE followed the ACR classification criteria[19]. The SLE Disease Activity Index (SLEDAI)[20] was computed at the time of SPECT examination. Definition of migraine-like headache followed the IHS criteria[10]. Both newly diagnosed patients and patients already followed by the SLE unit were enrolled.

A possible relationship between SLE and migraine could only be established when the onset of migraine occurred no earlier than 1 year before the formal diagnosis of SLE, independent of the patient's age. Careful anamnestic evaluation excluded all patients with migraine episodes during their childhood or adolescence. Moreover, patients with migraine but with other signs and/or symptoms of brain involvement, such as epilepsy, trauma, cerebrovascular episodes, and major psychiatric syndromes, were excluded. In cases where a cognitive disturbance was neither reported by the patient nor observed during neurological and psychiatric evaluations, a formal neuropsychological examination was not performed; thus, we can reasonably rule out relevant cognitive deficits, although we cannot exclude subtle ones.

Other exclusion criteria were the evidence of uncontrolled arterial hypertension, adverse drug effects, and major depressive episodes. A mild depressive trait was not an exclusion criterion and indeed 3 patients (Patients 1, 7, 14) were undergoing treatment with an oral antidepressant agent (citalopram, 20 mg/day). In these 3 patients, the psychiatric consultant detected a mild reactive depression, confirmed by good response to citalopram therapy; thus this mild depressive reaction was not considered within the spectrum of NP-SLE.

Following these criteria, 8 out of 26 patients with migraine and SLE were excluded from further analysis. Thus, the patient group consisted of 18 patients (17 women, 1 man, aged 21 to 64 yrs, mean age 40.8 ± 13.6 yrs) who suffered migraine episodes either with (4 patients) or without (14 patients) aura. Severity of migraine was based on both frequency and severity of attacks and arbitrarily graded using a 4-point scale: grade 1 (very mild): one or fewer episodes per month with moderate pain; grade 2 (mild): one or fewer episodes per month with severe pain, or 2–4 episodes per month with moderate pain; grade 3 (moderately severe): 2–4 episodes per month with severe pain or more than 4 episodes per month with moderate pain; and grade 4 (severe): more than 4 episodes per month with severe pain. Administration of common analgesics was ineffective in all patients. Therefore, patients with grades 1 or 2 were managed with a single dose of corticosteroids during the migraine attack, whereas in patients with grade 3 or 4 an increased dosage of the main maintenance drug was followed by moderate to marked improvement in frequency and severity of migraine attacks.

Patients were taking regular treatment with a maintenance dosage of corticosteroids, ranging from 5 to 30 mg/day of prednisone equivalent (Table 1; Patients 2, 4, 5–8, 10–13, 18), hydroxychloroquine (Patients 9, 12, 14, 15, 16–18), azathioprine (Patients 5, 7, 10, 12, 13), mycophenolate mofetil (Patients 2 and 8), aspirin (Patients 1, 3, 10, 11, 12), and nonsteroidal antiinflammatory drugs (Patients 14 and 15). Other drugs, such as antihypertensives and proton pump inhibitors, were used according to clinical need.

Patients underwent general medical, neurological, and psychiatric evaluation and complementary MRI and/or EEG to clarify the pathophysiology of headache, according to the clinical judgment of the treating physician. All patients underwent brain SPECT in the interictal period of their migraine-like headache. Clinical information on patients is reported in Table 1.

The study was approved by the local ethics committee. All patients gave their written informed consent.

Controls. The control group consisted of 15 healthy subjects chosen from the laboratory database, matched to patients for age and sex (15 women aged 19–47 yrs, mean 35.7 ± 8.4; p = not significant in comparison with patients, unpaired t test). The controls were all volunteers who consented to undergo SPECT as part of controlled studies; all gave informed consent. The healthy condition of controls was checked at the time of SPECT examination by general medical and neurological interviews; no control subject was taking medication with neuropsychoactive drugs or drugs known to interfere with brain perfusion, such as antihypertensive or other cardiovascular drugs. Written informed consent was obtained at the time of SPECT examination, according to the Declaration of Helsinki.

Brain SPECT. Brain SPECT was performed using a 2-head gamma-camera (Millennium VG; General Electric, Milwaukee, WI, USA) equipped with low-energy, high-resolution collimators. All SPECT acquisitions started between 45 and 120 min after intravenous injection of about 1000 MBq of ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO) (Ceretec; Amersham, GE Healthcare, USA), according to the guidelines of the European Association of Nuclear Medicine[21]. A step-and-shoot acquisition protocol acquired images by 120 projections. Technical parameters for image acquisition were radius of rotation ≤ 15 cm; acquisition matrix 128 × 128; zoom, 1.8; pixel size 2.33 mm; total counts between 7 and 9 millions. SPECT images were 3-dimensionally reconstructed by the ordered-subset expectation-maximization algorithm with 10 subsets and 8 iterations, followed by Gaussian post-filtering (full width – half maximum = 8 mm). Compensation for attenuation was performed at the reconstruction stage by the iterative algorithm itself. The attenuation contour was automatically given by the skull contour and the related anatomical shapes were carefully taken into account.

Reconstructed SPECT images underwent visual analysis by 2 expert readers who were blinded to the clinical condition of patients. The 2 readers independently identified areas of possible reduced uptake, and only the areas agreed upon by both readers were considered. Interobserver agreement was 92%. A transaxial section was then prepared by summing 3 adjacent slices in which reduced uptake was identified, and an irregular region of interest (ROI) was hand-drawn around it. The ROI was then mirrored on the contralateral hemisphere; mean count per pixel in each ROI was computed.

Finally, an asymmetry index was computed by subtracting the uptake between the 2 ROI and dividing that by the mean value of the 2 ROI. Only asymmetries > 10% were considered of clinical interest, according to the procedure used in previous studies[22,23].

Statistical analysis. Comparison between individual SPECT data of SLE patients and controls was performed using voxel-based analysis (VBA) by statistical parametric mapping[24], 1999 version (SPM99), following the procedure first proposed by Signorini, *et al*[25] and used in patients with other pathological conditions such as transient global amnesia[26] and Alzheimer's disease[27].

Table 1. Main laboratory and clinical features of 18 SLE patients with migraine-like headache (all female except Patient 12).

Patient	Age, yrs	Age at Diagnosis, yrs	ANA Titer	Pattern	ENA	C3, mg/dl	C4, mg/dl	IgG, aPL IU	IgM, aPL IU	ds-DNA	Previous or Present Non-neurological Impairment	SLEDAI Score
1	40	39	1:160	Nucl	Neg	120	29	350	50	Neg	Hughes:axillary vein thrombosis, erythema	8
2	38	18	1:80	Hom	SSA	112	23	< 12*	< 12*	Neg	Hughes:relapsing thrombo-phlebitis; thrombocytopenia; pulmonary embolism; arthritis; Raynaud	28
3	36	23	> 1:160	Hom	Neg	69	20	< 12	< 12	Neg	Fever, arthritis	14
4	22	21	1:160	Hom	Neg	96	15	< 12	< 12	Neg	Stage II GN	19
5	52	42	> 1:160	Hom	Neg	71	13	21	< 12	Pos	Arthritis, Raynaud	29
6	49	36	1:160	Speck	Neg	110	16	120	98	Neg	Arthritis, vasculitis, Raynaud	20
7	34	21	1:80	Nucl	SSA	85	21	< 12	< 12	Neg	Stage III GN, vasculitis, Raynaud, arthritis	31
8	51	33	> 1:160	Hom	Neg	89	5	85	< 12	Pos	Stage III GN; pericarditis	19
9	21	15	Neg*	—	RNP	119	28	< 12	63	Neg	Arthritis	13
10	32	29	1:80	Speck	SSA	60	9	60	90	Neg	Stage IV GN	21
11	64	57	1:80	Speck	RNP	104	22	< 12	< 12	Neg	Fever, arthritis	12
12	29	19	1:160	Hom & Nucl	Neg	89	25	20	< 12	Pos	Arthritis	19
13	51	41	1:80	Speck	SSA	110	33	< 12	< 12	Pos	Myopathy	8
14	30	23	> 1:160	Hom	Neg	86	24	< 12	< 12	Neg	Stage III GN, fever, arthritis	21
15	59	58	> 1:160	Speck	SSB	117	33	< 12	< 12	Neg	Arthralgia	9
16	39	38	1:80	Speck	Sm, RNP	117	39	< 12	< 12	Neg	Fever, arthritis, mucosal ulcers	22
17	64	55	> 1:160	Hom	Sm	117	34	< 12	< 12	Neg	Stage IV GN, pericarditis	23
18	35	34	> 1:160	Speck	Neg	86	11	< 12	< 12	Neg	Arthritis	13
Mean	41.4	33.4										18.3
SD	13.3	13.6										7.0

* Positive before immunosuppressive therapy. ANA: antinuclear antibodies; ENA: antibodies to extractable nuclear antigen; Hom: homogeneous; Speck: speckled; Nucl: nucleolar; aPL: antiphospholipid antibodies; ds-DNA: anti-double-stranded DNA antibodies; GN: glomerulonephritis; Hughes: Hughes syndrome; SLEDAI: SLE Disease Activity Index.

Default SPM99 procedures were followed for image spatial normalization, grey-matter threshold, normalization of global cerebral blood flow, as described[28]. The resulting statistical parametric maps, SPM{t}, were then transformed to the unit of normal distribution (SPM{z}) and reached a threshold at $p = 0.01$, which is an accepted procedure in a clinical setting even in pathologies with severe hypoperfusion[26,27]. Because of the lack of any topographic hypothesis, the significance of identified regions was assessed using p values corrected for multiple comparisons ($p = 0.05$ was the first significance to be accepted at the cluster level). Only clusters containing more than 200 voxels were considered significant.

Comparison analysis was applied to SPECT examinations by means of the "compare populations: ANCOVA" option, where one population was the control group and the other the patient under investigation. Age was used as a covariate to rule out a possible effect of age on perfusion comparisons[29]. Both the SPM contrasts "1 –1" and "–1 1" were defined in each comparison to search for reduced or increased uptake, respectively.

RESULTS

Controls. Visual analysis was performed by the same expert SPECT readers who examined the patients' scans. They found neither focal perfusion defects nor asymmetries, with 100% interobserver agreement. This procedure was performed *a priori* on a larger series of subjects intended to form the control group, before the selection of the final 15.

Patients. Table 2 summarizes patients' clinical features of migraine and EEG, MRI, and SPECT data.

Briefly, pain was lateralized on the left side in 4 patients and on the right side in 6, and it was bilateral or diffuse in the remaining 8 patients. The degree of pain was very mild in 2 patients, mild in 7, moderate in 7, and severe in the remaining 2 patients. EEG was available for 12 patients and showed mild to moderate changes in 6 of them (50%). EEG changes consisted of theta waves, with or without sharp waves, which were either bilateral (4 patients) or localized over the left frontal-temporal region (2 patients). MRI were available for 10 patients, and showed abnormalities in 5 (50%), i.e., multiple bilateral hyperintensity white-matter lesions were found in 3 patients, a small right cerebellar ischemia in 1 patient, and mild atrophy of the left temporal cortex in 1 patient.

Asymmetry SPECT analysis was positive in 15 patients (83%), showing one or more areas of reduced tracer uptake in one hemisphere in 14 patients (3 examples are shown in Figure 1) or in both hemispheres in one of them (Patient 9).

VBA showed significantly reduced tracer uptake in 8 (44%) patients, 2 of whom presented a normal result by asym-

Table 2. Main neurological features of 18 SLE patients with migraine-like headache (all female except Patient 12).

Patient	Main Pain Localization	Severity of Migraine Syndrome	EEG	MRI	SPECT Reduced Uptake (asymmetry analysis)	SPECT SPM Analysis
1	L side	3	Normal	Normal	L–F	NS
2	R side	1	Mild bilateral T	NA	R–F	NS
3	Bilateral F*	2	Normal	NA	L–FP	NS
4	Diffuse	3	Moderate diffuse	Normal	Normal	NS
5	R side	2	NA	Bilateral, multiple white-matter hypertensities (especially R side)	R–F	NS
6	Bilateral O*	1	Normal	Small right cerebellar ischemia	Normal	R anterior cingulate gyrus. BA 24
7	Bilateral F	2	Normal	Normal	L–F	NS
8	Diffuse	2	NA	NA	L rolandic	L precentral gyrus. BA 4. R cerebellum
9	Bilateral F	2	Normal	Normal	R–O, L–F	NS
10	RF	4	NA	NA	L–F	Cerebellar vermis. L superior F gyrus. BA 8. R insula BA 13
11	Diffuse	2	Moderate bilateral FT	Bilateral, multiple white-matter hyperintensities	L–P	L posterior cingulate. BA 29
12	R side*	2	NA	NA	R–F	NS
13	L side*	3	NA	Normal	Normal	R anterior cingulate. BA 24
14	Diffuse	3	Mild L–FT	NA	L–O	NS
15	R side	4	Mild bilateral FT	NA	L–F	R anterior cingulate. BA 24
16	R side	3	Normal	mild atrophy of left amygdala and T mesial cortex	R–O	NS
17	L side	3	NA	Bilateral F, multiple white-matter hyperintensities	L–F	R anterior cingulate. BA 24. L middle F gyrus. BA 11
18	L frontal	3	Moderate L–T	NA	L–F	L middle F gyrus. BA 8

* Visual aura. EEG: electroencephalography; MRI: magnetic resonance imaging; SPECT: single photon emission computed tomography; SPM: statistical parametric mapping. F: frontal; T: temporal; P: parietal; O: occipital. NA: not available; NS: not significant; BA: Brodmann's area. Severity of migraine syndrome: grade 1 (very mild), grade 2 (mild), grade 3 (moderately severe), grade 4 (severe).

metry analysis. Figure 1 shows 2 examples of the location and extent of areas of reduced uptake in Patient 11 (panel E) and Patient 17 (panel H). It should be noted that reduced tracer uptake was found in the anterior cingulate gyrus in 4 patients (Patients 6, 13, 15, 17) and in the right insula and cerebellar vermis in Patient 10, independent of pain location and SPECT asymmetry results. In no instance did VBA reveal areas of increased tracer uptake. Thus, by combining asymmetry and statistical SPECT analysis, a positive result was obtained in all patients except one, Patient 4.

In the 2 patients with severe pain (Patients 10 and 15), both visual and SPM-SPECT analyses were positive, but no further correlation between degree of pain and SPECT was observed. Finally, no unusual SPECT finding was found in the 4 patients (Patients 2, 5, 6, 7) who had Raynaud's syndrome.

DISCUSSION

This is the first study specifically designed to investigate brain perfusion changes in patients with SLE during the interictal period of migraine-like episodes that had onset in the same period as SLE diagnosis or later during the disease course.

SPECT data analysis was consistent with the hypothesis of brain functional impairment in these patients. The rate of impairment was high according to qualitative and asymmetry analyses (83%), but a reduced uptake was found in a substantial portion (44.4%) of the patients even with a rather restrictive statistical approach, which produced lower sensitivity but greater robustness of results. It should be noted that SPECT was positive not only in patients with signs of brain impairment previously identified by MRI or EEG, but also in 3 patients who had had inconclusive results from these 2 methods.

Few cases of SLE migraine studied by SPECT appear in the literature. A normal ^{133}xenon SPECT was reported in 2 cases of headache and SLE[17]. In the report by Rubbert, *et al*[12], 4 patients with migraine exhibited focal or multifocal brain hypoperfusion by visual SPECT analysis (EEG and MRI were unavailable), although their age at the onset of migraine was not specified. Only one of 3 SLE patients with headache studied by Kovacs, *et al*[13] showed focal hypoperfusion, which was attributed to an old cerebral infarction, but the headache type of these 3 patients was not specified. No useful comparison can be made with the patients reported by Lin, *et al*[30], exhibiting an 84.6% rate of abnormal SPECT, as the patients with headache (neither type nor period of onset was specified) were grouped together with patients with dizziness or recent memory impairment in a group with "minor neuropsychiatric SLE." The only patient with migraine and no other brain

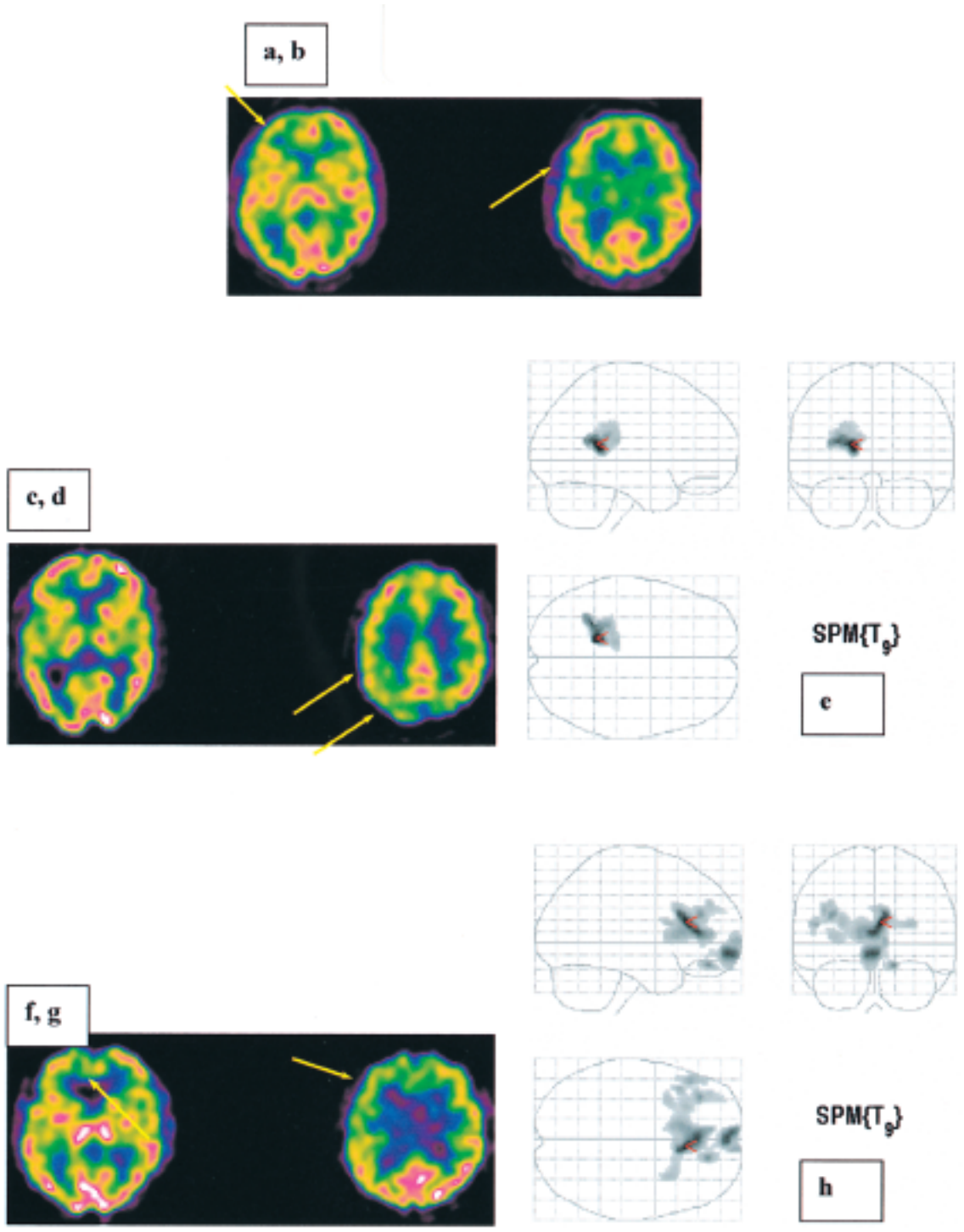

Figure 1. Panel A, B. Two transaxial sections of brain perfusion SPECT (neurological rule: left hemisphere on left side), showing asymmetric perfusion (asymmetry index value > 10%). Each section represents the sum of 3 adjacent slices. Perfusion values are shown according to a pseudo-color scale: white and red represent highest values, green and yellow intermediate values, blue and black lowest values. This example from Patient 1 shows hypoperfusion in the left frontal lobe (arrows), in both lateral and polar portions, which did not reach the statistical threshold fixed by VBA. Panel C, D. SPECT in Patient 11 shows hypoperfusion in the left parietal lobe (arrows). Panel E. Patient 11: VBA area of significance extended to the posterior cingulate gyrus. Panel F, G. SPECT in Patient 17 shows hypoperfusion in the left frontal lobe (arrows). Panel H. Patient 17: VBA confirmed this area and also disclosed hypoperfusion in the anterior cingulate gyrus not revealed by visual analysis.

symptom reported by Nossent, *et al*[31] had a normal SPECT, but quality of SPECT scanning was rather poor at that time. In a study of ^{99m}Tc-HMPAO SPECT compared with ^{18}FDG-PET, 2 of 6 patients with unspecified headache showed SPECT hypoperfusion[32]; whereas in another study all 5 patients with headache (2 with migraine-like episodes and 3 with diffuse, persistent headache) scanned with the planar ^{133}Xe method had abnormal quantitative regional cerebral blood flow measurements[18].

Our results support the hypothesis of a possible pathogenic link between the 2 entities. Indeed, focal brain hypoperfusion was observed in patients with migraine that started together with the disease or later, and thus we believe we have minimized the possibility that a migraine syndrome independent of SLE may have occurred. By contrast, migraine in the general population usually starts in childhood, adolescence, or early adult life, with onset in adulthood being uncommon. Since more than half of our patients were at least in their forties when SLE was diagnosed, the chance that a non-SLE-related migraine might ensue so late seems unlikely.

Since EEG and MRI were available in 67% and 56% of patients, respectively, a systematic analysis could not be done. However, it may be noted that SPECT revealed focal perfusion cortical defects (asymmetry analysis) in all 3 patients with bilateral white-matter hyperintensities, whereas statistical parametric mapping analysis disclosed abnormal results in 2. Since the white matter contains the long axons connecting the cortex with the deep brain and cord structures in both directions, this phenomenon may be the result of disconnection of the cortex from deeper structures (e.g., deafferentation or diaschisis). In one instance, SPECT was normal despite the presence of a small cerebellar ischemic lesion, but it should be noted that the small dimension of the lesion was below the spatial resolution limits of SPECT (about 8 mm). On the other hand, SPECT revealed hypoperfusion in 4 patients with normal MRI findings. This suggests that mechanisms other than disconnection may play a role in the pathogenesis of hypoperfusion.

In all patients but one, SPECT was positive when EEG was abnormal, but the reverse was not true, pointing to SPECT as a more sensitive tool, in keeping with a study comparing the ^{133}Xe planar method and quantitative EEG[18]. In another study, quantitative EEG was shown to yield higher sensitivity[33].

Although it had lower sensitivity, brain hypoperfusion was confirmed by a statistical voxel-based analysis comparing an individual patient to a control group. In studies of Alzheimer's disease, the use of VBA in an individual patient led to reduced sensitivity but increased specificity compared to a healthy control group or elderly depressed patients[27]. Indeed, the statistical correction procedure for multiple comparisons is rather restrictive, and the increase in specificity means less sensitivity, as also happened in our study. This means that hypoperfusion found with asymmetry analysis, but not with VBA, is probably moderate and not severe enough to be detected by this rather restrictive approach. Nevertheless, moderate hypoperfusion even in the hemisphere contralateral to the main site of pain may indicate a more diffuse brain involvement in patients who experience migraine attacks on either side.

In some patients (Patients 8, 10, 17, 18), VBA confirmed the hypoperfused areas found by asymmetry analysis, but in others it revealed areas of hypoperfusion along the medial brain structures, such as the anterior (Patients 6, 13, 15, 17) and posterior (Patient 11) cingulate and the cerebellar vermis (Patient 10), that had not been revealed by asymmetry analysis. These data seem to be of particular relevance for 2 reasons. First, visual-guided asymmetry analysis failed to show hypoperfusion in brain structures of the median line, probably because even trained SPECT readers are accustomed to considering mainly asymmetries distant from the sagittal line structures. This supports the use of VBA on an individual basis, and indeed, VBA is increasingly applied in centers carrying out brain SPECT[34]. Second, the frequent finding of hypoperfusion in the anterior cingulate cortex (ACC) is somewhat unexpected, and more than one interpretation is possible. The 4 patients with ACC hypoperfusion tended to be older than the others, but comparisons were co-varied for age to rule out the possible confounding effect of age. Although this interpretation should be considered cautiously, because only 22% of our patients showed ACC hypoperfusion, an hypothesis could be based on possible involvement of the ACC as one of the key structures of the midline circuitry of pain elaboration. In this network, the ACC is closely related to pain discomfort and may subserve the integration of general affect, cognition, and response selection[35]. Anatomic and electrophysiologic data show that these cortical regions receive direct nociceptive thalamic input, and there is growing evidence that they are activated during elaboration of pain experience, including headache. ACC activation has been reported during cluster headache induction[36], in patients with chronic migraine during pain perception due to the switching off of implanted bilateral suboccipital stimulators[37], and in the acute phase of pain in patients with migraine with or without aura[38]. In the interictal phase, deactivation may result in hypofunction, as described in patients with borderline personality disorder and severe headache or migraine[39]. However, until a similar VBA is performed in other NP-SLE groups, the association between ACC hypoperfusion and SLE migraine remains speculative.

The main limitation of our study is that another group of patients with primary migraine (i.e., without SLE) to compare with the control group would have allowed more precise estimation of the relative influence of SLE migraine on brain perfusion changes. Some patients with primary migraine may show focal hypoperfusion in the interictal phase. Thus, such a comparison can only be made with literature data. A finding of 43% focal hypoperfusion was reported by visual SPECT

analysis[40], and a similar rate has been confirmed by another study[41]. These figures are far from the 83% of abnormalities with a comparable analysis in our series of patients with SLE migraine. Therefore, although we cannot qualify our results as specific for patients with SLE migraine, the rate of SPECT abnormalities we found is almost double that in patients with primary migraine, suggesting that the SPECT changes could be related to SLE in some of the patients. In this regard, no study reporting SPECT changes in patients with SLE migraine or in other NP-SLE syndromes considered a control group of patients with primary migraine. A direct comparison within a single study between the rate and severity of SPECT abnormalities in patients with a primary brain disease and those in SLE patients with a similar clinical presentation will improve our knowledge of specificity of NP-SLE.

It might also be argued that a group of neurologically asymptomatic SLE patients was not included in this study, as regional cerebral blood flow abnormalities may be found in these patients as well. However, evidence of SPECT changes concerns just a few of these patients, usually around 10% to 20%, suggesting a subclinical cerebral involvement[18,42-47]. Only a multicenter study found a rate as high as 71%, very close to the rate achieved in symptomatic patients, but that study had methodological limitations, such as visual analysis only and lack of information on raters (how many, whether blinded or not, whether interobserver agreement was reached)[48].

We showed that brain SPECT was sensitive enough to detect hypoperfusion in 83% of patients with SLE-related migraine, with a good correlation with the clinical presentation. Hypoperfusion was found in 44% of patients even with a more robust, although less sensitive, voxel-based statistical approach. These results represent a starting point to elucidate the issue of regional cerebral blood flow abnormalities in SLE patients with migraine-like headache; further investigation including patients with primary SLE and SLE migraine within the same study is needed.

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