Single photon emission computed tomography and magnetic resonance imaging evaluation in SLE patients with and without neuropsychiatric involvement

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Objective. To assess the relationship between clinical picture and neuroimaging in patients affected by SLE with and without neuropsychiatric (NP) involvement.

Methods. One hundred and seven SLE patients including 66 with NP involvement (NPSLE) with focal or diffuse presentation and 41 without underwent single photon emission computed tomography (SPECT) and MRI.

Results. After stratification for diffuse or focal NP involvement, in the 52 patients with diffuse presentation, abnormalities detected with MRI or SPECT did not differ from patients without NP; however, after combining the two techniques, a normal result was more frequently observed in patients without NP involvement ($P = 0.010$). In the 14 patients with focal presentation, MRI alone and concordant abnormal MRI plus SPECT were more frequently detected in the NPSLE group; again normal findings by both techniques simultaneously applied were more frequently found in SLE patients without NP involvement. While matter hyperintense T2-weighted lesions were the most frequent MRI abnormal findings in both groups, but the presence of multiple lesions (>5) involving both the hemispheres at subtentorial level was limited to NPSLE patients. Multifocal hypoperfused SPECT areas were more frequently observed in frontal and parietal lobes of NPSLE.

Conclusions. Combining SPECT and MRI appears more useful than the two techniques alone and may help the clinician in the assessment of patients with NP involvement since normal findings contemporarily detected by these two techniques have been rarely observed in patients with NP involvement especially in those with focal manifestations where MRI and SPECT were never simultaneously normal.

Key words: Systemic lupus erythematosus, Central nervous system, Magnetic resonance imaging, Single photon emission computed tomography.

Introduction

Neuropsychiatric (NP) symptoms in SLE are common, affecting 15–75% of patients depending on differences in test batteries and criteria for defining impairment [1].

According to ACR case definition, a wide variety of abnormalities ranging from global cerebral dysfunction to focal deficits has been attributed to NP lupus [2]. Along with clinical examination, neuroimaging techniques, both morphological and functional, are available and have become important tools both in diagnosing and assessing SLE patients with NP involvement (NPSLE). However, none of them allows distinction between SLE patients with and without NP involvement, particularly in those with diffuse NP presentation. It has been suggested that, in these cases, coupling morphological with functional imaging can help in the diagnosis [3].

Because of the high quality of anatomic details due to the excellent soft tissue contrast and the ability to acquire multiplanar images, MRI is preferred for the morphological assessment of the brain in patients with NPSLE [4–7]. About functional imaging, single photon emission computed tomography (SPECT) has been found to be useful for the early identification of perfusion abnormalities in NPSLE. However, SPECT, although very sensitive, has poor specificity for NPSLE and the interpretation of functional abnormalities in patients with normal MRI findings is still a debated issue [8–10].

In this study, we have investigated the relationship between clinical symptoms (diffuse or focal) and morphological and/or functional cerebral changes detected respectively by MRI and SPECT in 107 SLE patients in order to clarify (i) whether combined MRI and SPECT, when simultaneously applied, may allow a better differentiation—among patients with SLE—between those with and without NP involvement and (ii) whether there were distinctive MRI and/or SPECT pathological patterns in patients with NP manifestations stratified as focal or diffuse.

Patients and methods

Patients

The Department of Clinical and Experimental Medicine of the University of Ferrara is located inside the Sant’ Anna Teaching Hospital and our rheumatology unit is a tertiary referral centre for SLE with particular interest in the field of NP complications in systemic autoimmune diseases. The health care district in which it is located has a mean population of about 346 000 individuals (2002 census estimates) almost entirely composed of white Caucasian people.

Sixty-six consecutive SLE patients with NP involvement and 41 patients without history of NP symptoms, matched for sex and mean disease duration, were enrolled in this study. All patients fulfilled the 1997 revised American College of Rheumatology criteria for the classification of the disease [11]. A patient was identified as having NP involvement if there were significant and unequivocal changes in neurological or psychiatric function in the history or physical examination as judged by a rheumatologist and a neurologist or a psychiatrist (when necessary). In particular, a clinical NP finding was considered SLE-related on the basis of its severity, time of onset (concomitant or subsequent to SLE diagnosis) and response to treatment with corticosteroid or immunosuppressive drugs. Secondary causes known to induce neurological manifestations such as uraemia (blood urea nitrogen >35.5 mmol/l), infections, drugs, severe electrolyte imbalance,
neoplasms or diseases other than SLE were ruled out after extensive evaluation. Patients with uncontrolled hypertension (diastolic blood pressure >120 mmHg) were excluded. In patients with CNS involvement, only the first NP event and the corresponding neuroimaging evaluation were considered for analysis.

The clinical pictures of the 66 patients with NP symptoms were classified and assessed according to the ACR nomenclature and case definition statements and guidelines. These patients were also subdivided into those with diffuse presentation (n = 52) (i.e. cognitive dysfunctions, severe depression, acute confusional state, aseptic meningitis, generalized seizures, headache and psychosis) and those with focal presentation (n = 14) (cerebrovascular accident, partial seizures, chorea). For cognitive dysfunctions a neuropsychological evaluation was performed and the diagnosis was established if significant deficits in any or all of the following cognitive functions were observed in the patients: attention, reasoning, executive skills, language, visual–spatial processing and psychomotor speed. Patient written informed consent was obtained according to the Declaration of Helsinki and the design of the work has been approved by local ethical committees.

All SLE patients who underwent SPECT and MRI in the period lasting from 1995 to 2001 were included in the study, since after 2001 SPECT machinery has been substituted; the two imaging techniques were performed 2–4 weeks apart, one from each other, and—in those with NP involvement—close to the NP event (within 1–28 days for focal presentation and within 3 months for diffuse presentation). In the patients without NP events, MRI and SPECT evaluation have been carried out during the course of SLE. The mean disease duration of these SLE patients at the moment of imaging acquired was comparable with that of patients with NP involvement at the time of the occurrence of their first NP event.

All SLE patients with and without NP involvement, at the time of the imaging, were on low-dose steroids (prednisolone <10 mg/day). Eighty-two patients (42 with NPSLE and 40 without NPSLE) were on hydroxychloroquine (6 mg/kg/day) and 10 patients (all with NPSLE) were on azathioprine. Three patients with diffuse involvement took steroids (3 boluses) and cyclophosphamide (6 boluses) between the event and the time of imaging. Any therapy change was performed in NPSLE patients with focal presentation in the interval between the NP event and the imaging acquired.

For each patient, SPECT and MRI findings were analysed double-blinded by both two experienced neuroradiologists and two experienced nuclear physicians. Since the aim of our study was not to assess sensitivity and specificity of SPECT and MRI in SLE patients compared with other diseases, but to evaluate whether a combined MRI and SPECT approach might be of some utility in differentiating SLE patients with and without NP involvement and whether there were recognizable distinctive MRI and/or SPECT pathological patterns in NPSLE patients, a control healthy group has not been included in the study.

SPECT
Ten minutes after the intravenous injection of 925 MBq (25 mCi) of 99mTc-HMPAO, brain SPECT was carried out with a rotating single head gamma camera system (Orbiter 7500; Siemens, Erlangen, Germany), equipped with a high-resolution collimator. 99mTc-HMPAO was purchased from Amersham International (Amersham, UK), prepared according to the manufacturer’s instructions and used within 5 min of labelling. Data were acquired in a 64 × 64 matrix over a 360° rotation at 6° intervals. The average radius of rotation was 20 cm. The spatial resolution of the system, expressed as FWHM (full-width half-maximum) at the centre of the field of view and at a depth of 20 cm from the camera crystal, was 17 mm. Approximately eight million counts were acquired. Data storage and reconstruction of transverse images were carried out using a computer system (micro Delta-Max Delta; Siemens) coupled with the gamma camera on a 64 × 64 matrix. Neither scatter nor attenuation correction was made. SPECT reconstruction was processed using a Butterworth filter (order 4.0; cut-off frequency 0.30 cycles/pixel). Transaxial slices 2 pixels thick (pixel size = 6.2 mm) were reconstructed. The transaxial slices were normalized to the maximum pixel count and displayed on a colour scale with a lower threshold of 0%.

According to Chang et al. [12] visual interpretation of SPECT images obtained in each patient was carried out twice in random order, evaluating agreement between two independent and experienced observers blind to the clinical picture. In case of divergences between the two observers, a consensus was reached after discussion. SPECT was considered abnormal if any of the following findings were observed: heterogeneous regional cerebral blood flow (rCBF) with regions of hypoperfusion or evident asymmetry on at least two consecutive slices unanonymously detected by the two observers. Hypoperfused areas and asymmetry were assessed comparing the amount and homogeneity of tracer uptake with adjacent and/or controlateral corresponding areas of the brain. Focal perfusion defects corresponded to well-defined areas of low tracer concentration. Conversely normal findings included homogeneous rCBF in the grey matter of the cortex and basal ganglia without regions of hypoperfusion or visible asymmetry. This type of subjective evaluation has proved to be accurate for the evaluation of both cerebral lupus and other diseases [13, 14].

MRI
MRI was performed using a conventional 1.5 tesla whole-body MT imaging Magnetom SP 4000 (Siemens), using a standard circular polarized head coil. T1 (500 ms TR, 14 ms TE) and T2 (2002 ms TR, 90 ms TE) sequences—weighted images and fluid attenuated inversion recovery (FLAIR) sequences (8002 ms TR, 104 ms TE, 2000 ms T1, 6.0 mm thickness, 1.0 mm gap, 256 × 192 matrix) were acquired.

MRI was considered abnormal if any or more of the following findings were observed: white matter T2-hyperintense small (<10 mm) punctate lesions (WMHL) located in the subcortical and/or in the periventricular regions, T2-hyperintense small (<10 mm) punctate lesions (GMHL) located in the grey matter of the cortex or basal ganglia, cortical atrophy, major infarcts (>10 mm).

Statistical analysis
Statistical analysis has been performed using Fisher’s exact test. The Statistical Package for the Social Sciences (SPSS; Information Technology Services) was used to analyse the data. In all tests, P-values <0.05 were considered as statistically significant.

Results
Baseline characteristics of the patients with and without NP involvement are listed in Table 1. The sex ratio and mean disease duration at the moment of instrumental evaluation were comparable between the two groups. In spite of a similar disease duration at the time of imaging evaluation, patients with NPSLE showed a delayed disease onset compared with those without NP.

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics in NPSLE and controls</th>
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<tr>
<td>SLE (n = 41)</td>
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<tr>
<td>Women/men</td>
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<tr>
<td>Mean age at disease onset, ± S.D. (yrs)</td>
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<td>Mean age at the moment of instrumental evaluation, ± S.D. (yrs)</td>
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<td>Mean disease duration at the moment of instrumental evaluation, ± S.D. (yrs)</td>
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NS, not significant.
manifestations. In both groups, mean age at the moment of instrumental evaluation was <45 yrs.

Table 2 summarizes CNS events in the NPSLE patients. Headache was the most common clinical finding followed by mood disturbances, cerebrovascular disease and seizures. For 17 patients (25.7%), the NP event was the heralding symptom of SLE. The intraobserver and interobserver variation in the lecture of both SPECT and MRI were, respectively, 0.87 and 0.82.

On comparing NPSLE, as a whole, with SLE patients without NP involvement, MRI abnormalities were detected in 41 out of 66 (62.1%) NPSLE and in 15 out of 41 (36.6%) SLE controls; the difference did prove statistically significant (P = 0.018). Although SPECT abnormalities were also more frequently detected in NPSLE group (68%) than in SLE patients without NP involvement (50%), differences did not reach statistical significance. When combining MRI and SPECT, concordant abnormalities detected by these two techniques were more frequently observed in the NPSLE patients than in SLE patients without NP involvement. However, the difference did not reach statistical significance (P = 0.153); on the contrary, non-concordant findings were significantly more frequently detected in patients without NPSLE (41.4%) than in patients with NPSLE (12.1%), (P = 0.001) (Table 3).

After stratification of NPSLE patients into two categories according to the type of CNS involvement (i.e. diffuse or focal), among the 52 patients with diffuse NPSLE, the frequency of MRI (55.8%) or SPECT (65.4%) alterations and concordant abnormal MRI and SPECT (36.5%), although higher among NPSLE patients, did not differ statistically from those observed in SLE patients (abnormal MRI = 36.6%; abnormal SPECT = 48.8%; combined abnormal MRI and SPECT = 26.8%). Conversely, concordant normal findings carried out by the two combined techniques were significantly more frequently observed in SLE patients without NP involvement (41.4% vs 15.4%; P = 0.010) (Table 3).

In patients with focal NP symptoms, compared with SLE controls, MRI and SPECT abnormalities were detected in a larger percentage (MRI = 85% vs 36.6% and SPECT = 78.6% vs 48.8%, respectively), but only for abnormal MRI (when considered alone) and abnormal MRI coupled with abnormal SPECT the difference reached the statistical significance (P = 0.004 and 0.028, respectively). No patients with focal involvement had simultaneously both normal SPECT and MRI (Table 3).

The occurrence of discordant findings by coupling MRI and SPECT (i.e. normal MRI/abnormal SPECT or abnormal MRI/ normal SPECT) was similar between the two groups despite focal or diffuse stratification (data not shown).

T2-weighted WMHL localized at subcortical supratentorial regions and/or in periventricular areas were the most frequently observed abnormal MRI findings in both groups (Tables 4 and 5). These kinds of lesions were observed at subtentorial level only in NPSLE patients (7 patients, 10% vs none) and never occurred isolated but always in association with concomitant supratentorial lesions. The most frequently affected areas in all subjects were frontal and parietal lobes. Involvement of both the hemispheres was more frequently observed in NPSLE patients (69% vs 50%) while monohemispheric involvement was more common among patients without NP involvement (50% vs 23%). A roughly semiquantitative evaluation of the lesion load revealed that SLE patients without NP involvement had more frequently one single lesion (43% vs 15%) while multiple lesions (>5) were
Concerning neuroimaging investigations, similar to previous reports, our study showed that MRI is a sensitive tool for the assessment of NPSLE especially for patients with focal presentation [5, 16–18]. According to these findings, we found abnormal MRI in 62.2% of NPSLE, 55.8% with diffuse and 85.7% with focal presentation; interestingly, but not surprisingly, only in this latter group this finding reached statistical significance in comparison with what was observed in SLE patients without NP involvement. Unfortunately, similar to the data previously reported by others [19], a high percentage of SLE patients without NP involvement showed abnormal MRI findings (36.6%), thus lowering the specificity of MRI. Interpretation of MRI abnormalities in this setting is still uncertain although one hypothesis suggests that these alterations could predict the later appearance of defined NPSLE [20].

SPECT scanning has been used in the assessment of CNS involvement in SLE and proved more sensitive than MRI in detecting abnormalities in up to 90% of patients with overt NP involvement [21]. However, SPECT has very low specificity and comparable abnormalities have been described in patients with other neurological conditions along with SLE patients without CNS involvement [3]. In the present study, abnormalities were observed in more than two-thirds of the NPSLE patients (both with diffuse or focal presentation) but also in a high percentage of SLE patients without NP involvement (almost 50%). These results are in agreement with those of other authors who reported a lack of association between NP dysfunction and SPECT findings [19, 22]. As aforementioned, a purpose of our study was to evaluate the utility of the two imaging techniques when used in combination. Combining SPECT and MRI in all the 107 patients and comparing the frequency of abnormal results with those obtained with each technique alone, we found both MRI and SPECT abnormalities in a lower percentage of patients, both in NPSLE (42.4%) and SLE patients without CNS involvement (26.8%). These results were confirmed when the analysis was stratified for diffuse and focal NP involvement; it is worth noting that only patients with focal NP presentation showed a significantly higher frequency of combined abnormalities compared with patients without NP involvement (64.3% vs 26.8%; \( P = 0.028 \)). However, a major finding emerging from our study seems to be the value of the combined normality of MRI and SPECT rather than their combined pathological results. In fact, either considering NPSLE patients as a whole or after stratification for diffuse and focal NP involvement, the simultaneous concordant normality of both MRI and SPECT has been found very rarely in patients with NP manifestations. This was especially true in focal NPSLE where a combined normal MRI and SPECT has never been observed.

Thus, a first preliminary conclusion of the present study is that, at present, coupling a morphological with a functional diagnostic tool may be more helpful in excluding NP involvement than in confirming it. This reinforces the notion that the diagnosis of NPSLE cannot be based only upon neuroimaging but needs a deep clinical assessment and a careful match between clinical and instrumental findings. From a practical point of view, conventional MRI remains the technique of choice in the evaluation of patients with NP involvement, especially in patients with focal manifestations. The addition of SPECT seems to be of some utility in patients with diffuse NP presentation and normal MRI, which represents a frequently occurring situation. In focal NPSLE, the combination of SPECT and MRI may be, in general, useful since it slightly improves the performance of MRI alone (64.3% of abnormal results vs 62.1%) in differentiating NPSLE from SLE patients without NP involvement.

Another aim of the study was to concurrently evaluate SPECT and MRI in SLE patients in order to define some pathological patterns useful to diagnose a cerebral involvement in the presence of NP symptoms whose assignment to the underlying connective

### Table 6. Topographic distribution of T2-weighted hyperintense lesions in the brain

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<tr>
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<th>NPSLE 39 patients*</th>
<th>SLE 14 patients*</th>
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<tbody>
<tr>
<td></td>
<td>D</td>
<td>F</td>
</tr>
<tr>
<td>Frontal</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Parietal</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Temporal</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Occipital</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Monohemispheric</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Bihemispheric</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Single lesion</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Multiple lesions (&gt;5)</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Large lesions (&gt;10mm)</td>
<td>0</td>
<td>2</td>
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</tbody>
</table>

*Numbers indicate the number of patients with T2-weighted hyperintense small lesions localized in the corresponding brain lobes; patients may have multiple lesions. NS, not significant; D, diffuse; F, focal.

more commonly observed in NPSLE patients (28% vs 14%) (Table 6).

Similar to MRI results, patients evaluated by SPECT had hypoperfused areas (HA) more frequently localized in frontal and parietal lobes in both groups but multifocal HA were more common in NPSLE patients (50% vs 26%).

### Discussion

Diagnosis of NPSLE is still controversial due to the incomplete knowledge of the underlying multiple pathogenetic mechanisms and the lack of standardized tests. Neuroimaging has greatly improved the understanding of NPSLE both for diagnostic purposes and for clinical follow-up. Without a ‘gold standard’ technique, it is very difficult to identify an ideal and specific diagnostic approach and to assess the sensitivity and specificity of any available imaging technique. When dealing with NPSLE, given the great heterogeneity of NP manifestations that may complicate the course of the disease, it seems more reasonable to combine different diagnostic tools (both anatomic and functional) to encompass the different physiopathological pathways underlying the different NP pictures, since each modality may have special uses in the proper clinical and research situation and may give different and complementary information.

The aim of our study was to evaluate the relationship between clinical symptoms and morphological and/or functional cerebral changes detected by MRI and SPECT in a SLE population with and without NP involvement and to assess whether a combined MRI and SPECT approach might allow for a better differentiation between patients with and without NP involvement.

Distinctive features of this study are the relatively large number of patients evaluated by two commonly available neuroimaging techniques, the young age of the SLE population (overall mean age was <45 yrs), short disease duration (~5 yrs) and the timing of the two imaging techniques, very close to the first NP event. The importance of these features, with particular reference to the timing of imaging, rarely focused upon in previous studies, is strengthened by some reports showing how both MRI and SPECT findings may change over time and can be influenced by ageing and disease duration [15].

The clinical-demographic analysis of the data acquired demonstrated that while the mean disease duration (calculated at the moment of the first NP event for NPSLE) was similar between SLE patients with and without NP involvement, in NPSLE the mean age at the disease onset was higher (almost 10 yrs). This finding suggests that an older SLE onset could look like a risk factor for the future appearance of NP complications. However, this suggestion needs confirmation from prospective studies.
tissue disease is questionable as in the case of headache and/or mood disturbances.

Although the most prevalent MRI brain lesions in both groups were WMHL in the periventricular white matter of frontal and parietal lobes, in NPSLE patients the number of these lesions was significantly higher. These findings are in accordance with those by McCune et al. [22]. Even more, while supratentorial lesions were detected in similar proportions of patients in both groups, only patients with CNS involvement had subtentorial localization. At bedside, this finding—although not frequently observed—could reinforce the clinical suspicions that a particular neurological picture could be related to the underlying SLE. Bihemispheric and multiple lesions were more suggestive of the presence of NPSLE even if, due to the small number of patients, we could not prove a statistical difference. The meaning of the isolated little hyperintense lesions frequently observed in SLE patients without overt NP is still a matter of discussion and probably their clinical relevance is poor. However, considering the young age of the studied population these lesions deserve attention and a close follow-up monitoring.

In conclusion, in the present study, we have evaluated a large number of SLE patients by two neuroimaging techniques (MRI and SPECT) used alone and in combination; MRI findings clearly correlated with CNS manifestations in patients with NPSLE, particularly in those with focal presentation. SPECT was more frequently abnormal than MRI in diffuse NPSLE where MRI does not yield significant information about metabolism or perfusion defects, detected by SPECT. In the near future, a multimodal approach—including other functional and quantitative techniques—may further improve the performance of neuroimaging in the assessment of NP lupus.

**Disclosure statement:** The authors have declared no conflicts of interest.

**References**