# Studies on Neuropsychiatric SLE

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# CHAPTER 9

## Neuropsychiatric SLE: lessons learned from MRI

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## Abstract

### Objective
The clinical manifestations of nervous system involvement in systemic lupus erythematosus (neuropsychiatric SLE [NPSLE]) are highly diverse and their etiology is incompletely understood. The aim of this study was to provide an inventory of abnormalities on conventional brain magnetic resonance imaging (MRI) in NPSLE and to interpret the findings in relation to possible underlying pathogenetic mechanisms.

### Methods
MR images of the first episode of active NPSLE of 74 patients were retrospectively reviewed. All patients fulfilled the American College of Rheumatology (ACR) 1982 revised criteria for the classification of SLE and were classified according to the 1999 ACR case definitions for NPSLE syndromes. We excluded patients with a history of brain disease, and patients in whom other mechanisms unrelated to SLE caused the neuropsychiatric symptoms.

### Results
The principal findings were: 1) focal hyperintensities in white matter (WM) (49% of all patients) or both WM and gray matter (GM) (5% of all patients) suggestive of vasculopathy or vasculitis, 2) more widespread, confluent hyperintensities in the WM, suggestive of chronic hypoperfusion due to the same mechanisms, 3) diffuse cortical GM lesions (12% of all patients), compatible with an immune response to neuronal components or post-seizure changes, and 4) absence of MRI abnormalities, despite signs and symptoms of active disease (42% of all patients).

### Conclusion
Several distinct brain MRI patterns were observed in patients with active NPSLE, suggestive of different pathogenetic mechanisms. To advance our understanding of the various processes leading to NPSLE, the radiological manifestations may be a good starting point and useful for categorization of patients in further research.

## Introduction

In the course of their disease many patients with systemic lupus erythematosus (SLE) develop neurological or psychiatric symptoms. After exclusion of other causes such as concomitant illnesses, infection, or drug side effects, these neuropsychiatric manifestations are attributed to involvement of the nervous system in SLE, which is referred to as neuropsychiatric SLE (NPSLE).[1] Correct attribution of neuropsychiatric events to NPSLE or to an alternative etiology is a challenge given the absence of a diagnostic gold standard for NPSLE. In clinical practice, NPSLE is a diagnosis per exclusionem, achieved case-by-case using clinical, laboratory and imaging data.[1,2] Consequently, the diagnosis is inevitably presumptive. Magnetic resonance imaging (MRI) is the imaging technique of choice in the diagnosis of NPSLE.[2,3] It is widely available and permits identification of lesions associated with NPSLE and many differential disorders.

Neuropsychiatric SLE comprises a wide range of clinical conditions affecting the central, peripheral or autonomic nervous system, such as cognitive dysfunction, psychosis, depression and acute confusional state, but also more focal syndromes, such as stroke, seizures, chorea or transverse myelitis.[4] The severity of the symptoms is also highly variable. The etiology of NPSLE is still incompletely understood. In 1999 the American College of Rheumatology (ACR) established a nomenclature and detailed case definitions for 19 NPSLE syndromes, which provide a clear description of the multiple clinical faces of the disorder.[4] In diseases of the central nervous system (CNS) however, MRI often provides a better clue to the underlying cause of symptoms than the symptoms themselves. Therefore, a thorough inventory and interpretation of the manifestations of NPSLE on conventional MRI of the brain, may help in understanding the etiologic processes and may be useful for categorization of patients in further research.

A wide variety of conventional MRI findings has been described in NPSLE previously.[5-14] However, many studies antedate the 1999 ACR case definitions for NPSLE syndromes, and MRI findings have been reported on heterogeneous patient groups consisting of different combinations of SLE patients with active NPSLE symptoms, those with a history of NPSLE events (past NPSLE), or those without any CNS involvement ever (non-neuropsychiatric SLE). It is also not always clear whether patients with other previous CNS disease, potentially resulting in MRI abnormalities, were excluded. Analysis of MRI findings during the first active episode of NPSLE in patients without previous brain disorders will provide data without these possible confounders. Furthermore, large case series are rare, radiological descriptions have been limited, and studies aimed at interpreting the MRI-defined manifestations of NPSLE in terms of possible underlying pathomechanisms are even scarcer.

The objective of this study was to provide a systematic inventory and description of cerebral abnormalities seen on conventional MRI in a large group of patients during their first episode of active NPSLE manifestations classified according to the 1999 ACR nomenclature and case definitions for NPSLE syndromes. The second objective was to interpret the observed patterns in terms of possible underlying pathogenetic mechanisms.

## Materials and Methods

### Subjects

We screened a total of 312 cases of patients with neuropsychiatric symptoms who underwent MR imaging at our institution between 1989 and 2008 because of suspected NPSLE. Our institution is a national tertiary referral center for patients with SLE and suspected neuropsychological involvement. Manifestations of NPSLE were retrospectively assessed and classified by two rheumatologists (GMS-B and TWJH) experienced in the clinical and research field of NPSLE. A total of 74 patients with NPSLE were selected, each of whom fulfilled at least 4 of the 11 revised 1982 ACR criteria for SLE[15,16] as well as ≥1 of the 1999 ACR case definitions for NPSLE syndromes[4], and in whom MR imaging had been performed during the first episode of active NPSLE. For each patient only the first MRI examination performed in our hospital was reviewed.

Patients with neuropsychiatric symptoms that could be attributed to causes other than SLE were excluded.[1] Among those were SLE patients with previous existing epilepsy, migraine and psychiatric disorders, infection, traumatic brain injury and medication side effects. Also excluded were patients with other diseases such as multiple sclerosis, (which retrospectively could be adequately excluded) or progressive multifocal leucoencephalopathy as well as patients with hypertensive encephalopathy, including lupus patients with posterior reversible encephalopathy syndrome. None of the included patients, except 1, had a history of neurological or psychiatric symptoms prompting medical examination or cerebral MRI. The exception was a patient in whom Lambert-Eaton myasthenic syndrome was diagnosed 5 years prior to SLE (Fig 1A+B). No malignancies were found and the patient had only symptoms of the peripheral nervous system consistent with Lambert-Eaton myasthenic syndrome before the onset of NPSLE and obtaining the examined MR images.

Patients were included if the MRI protocol at least included T1- and T2-weighted images and either proton density-weighted or fluid-attenuated inversion recovery (FLAIR) images. When available, additional sequences such as T1 weighted images following intravenous gadolinium (Gd) administration, diffusion-weighted images (DWI) and apparent diffusion coefficient maps were also reviewed. The mean ± SD age of the patients at the time of imaging was 37.9 ± 13.7 years (range 14.7-68.7 years) (Table 1). Of 74 patients only 9 were older than age 55 years; among these 9 patients, 4 were older than age 59 years. Two patients had previously used methotrexate (MTX) but showed no clinical or imaging signs of MTX leucoencephalopathy. Thirteen patients had elevated blood pressure at the time of admission, which in itself was not believed to account for their symptoms. Eleven of those patients had SLE-related renal disorder and received antihypertensives. Six patients had definite antiphospholipid syndrome (APS) at time of imaging, according to proposed updates to the Sapporo criteria.[17] Nineteen patients with multiple distinct neuropsychiatric symptoms were classified as having >1 NPSLE syndrome according to the 1999 ACR nomenclature and case definitions.

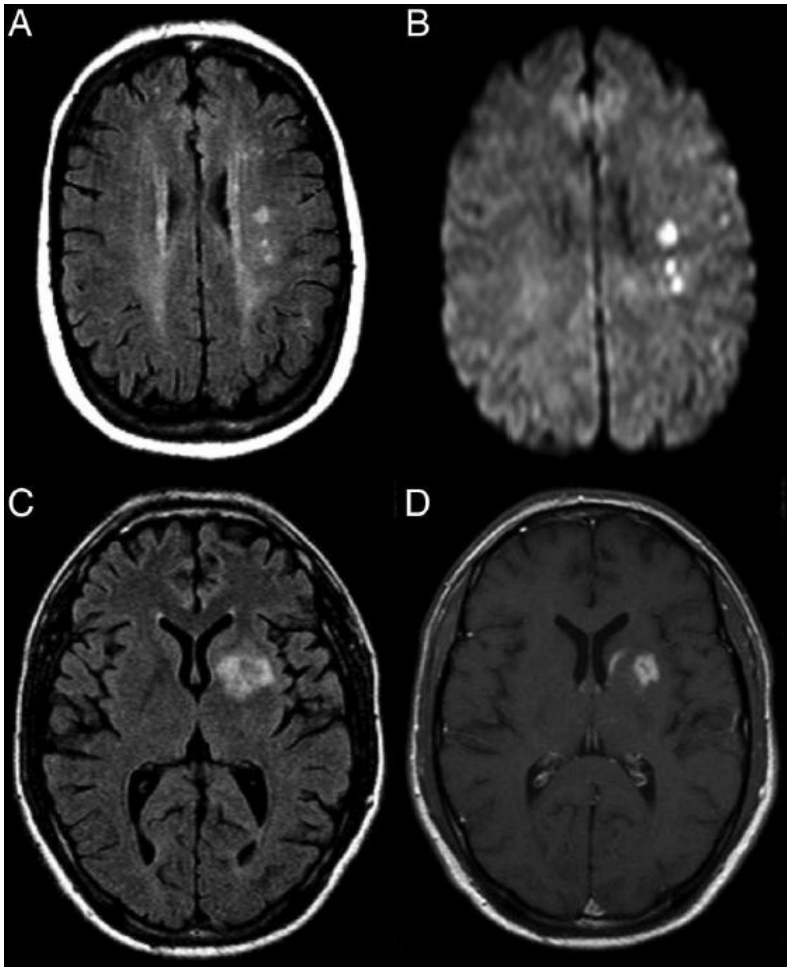


**Figure 1.** Additional magnetic resonance imaging characteristics of T2-weighted/fluid attenuated inversion recovery (FLAIR) hyperintense lesions in patients with active neuropsychiatric systemic lupus erythematosus (NPSLE).
A and B, FLAIR images of the brain of a 64 year old woman, showing multiple focal white matter (WM) hyperintensities
**(A)** with high signal on diffusion-weighted imaging **(B)** and low signal on the apparent diffusion coefficient map (not shown), indicating cytotoxic edema. The patient (patient 3 in Table 3) had more similar lesions in the WM and gray matter. She had a history of polyarthritis and Lambert Eaton myasthenic syndrome and was admitted with sudden aphasia, right-sided facial paralysis and spatial disorientation. Computed tomography angiography and ultrasound showed no abnormalities of the carotid and larger cerebral arteries or cardiac embolic sources. The patient was diagnosed as having NPSLE vasculitis (SLE with polyarthritis, antinuclear antibody [ANA] and anti-double stranded DNA [anti-dsDNA] positivity, photosensitivity and butterfly exanthema); she was negative for antiphospholipid antibodies.
**C** and **D**, Hyperintense lesion on a FLAIR image of the brain of a 34 year old man
**(C)** showing ring-shaped enhancement on the T1-weighted gadolinium sequence **(D)** indicative of blood-brain barrier disruption. The patient was admitted for recurrent episodes of headache, decreased emotional affect, arthralgia, chestpain, fever and weight loss. He was diagnosed as having NPSLE de novo (SLE based on pleuritis, positivity for ANAs, anti-dsDNA and IgM anticardiolipin antibodies, and class IV SLE nephritis). Ultrasonography revealed no cardiac embolic sources.

**Table 1:** Demographic and clinical features of the 74 studied NPSLE patients.*

| | |
|---|---|
| Female/male | 66/8 |
| Age, mean ± SD (range) years | 37.9 ± 13.7 (14.7-68.7) |
| ACR SLE criteria† | |
| 1. Malar rash | 25 |
| 2. Discoid rash | 28 |
| 3. Photosensitivity | 18 |
| 4. Oral ulcers | 18 |
| 5. Nonerosive arthritis | 56 |
| 6. Pleuritis or pericarditis | 30 |
| 7. Renal disorder | 34 |
| 8. Neurologic disorder | 18 |
| 9. Hematologic disorder | 46 |
| 10. Immunologic disorder | 62 |
| Anti-dsDNA positive | 47 |
| Anti-dsDNA negative | 14 |
| Anti-dsDNA unknown | 13 |
| 11. ANA positive | 70 |
| Cumulative ACR SLE criteria, mean ± SD (range)† | 5.3 ± 1.1 (4-8) |
| SLE duration, mean ± SD/median (range) months‡ | 60.6 ± 72.0/30,0 (0.3-302) |
| Antiphospholipid antibody status | |
| Anticardiolipin IgG or IgM antibody positive or LAC positive § | 26 |
| Antiphospholipid antibody status | |
| Anticardiolipin IgG or IgM antibody positive¥ | 7 |
| Antiphospholipid syndrome | 6 |
| Ethnicity | |
| Caucasian | 57 |
| Other | 17 |
| Medication received# | |
| Corticosteroids | 59 |
| Immunosupressant agents | 29 |
| Antimalarial agents | 32 |
| Anticoagulants | 15 |
| Antihypertensives | 20 |
| Cyclophosphamide | 4 |
| Methotrexate | 2 |

* Except where indicated otherwise, values are the number of patients. Unless specified otherwise, features were measured at the time of the examined magnetic resonance (MR) image. NPSLE, neuropsychiatric systemic lupus erythematosus; ACR, American College of Rheumatology; ANA, antinuclear antibody; LAC, lupus anticoagulant; anti-dsDNA, antibodies against double stranded DNA.

† Present at the time of scanning or any time before.

‡ Five patients with SLE de novo were not included.

§ Forty-one patients were tested for all antiphospholipid antibodies.

¥ Eighteen patients were tested only for anticardiolipin antibodies.

# Includes agents used at any time before onset of the first episode of NPSLE for which the examined MR image was performed.

## MRI acquisition

MRI examinations included in this study were obtained over a 19-year period (1989-2008) and were consequently performed using different scanners with different field strengths and sequence parameters. All scans (0.5T, 1.5T or 3T) were acquired in the axial plane on Philips MR systems located in the same hospital.

## Assessment of MRI abnormalities

For the 74 patients included in this study, 74 T1-weighted images, 74 T2-weighted images and 68 proton density-weighted scans, 46 FLAIR images, 35 T1-weighted images following intravenous Gd administration, 40 diffusion-weighted images, and 10 apparent diffusion coefficient maps were reviewed. An experienced neuroradiologist (MAvB) who was blinded to the clinical status of the patients examined all images for the presence of any abnormality. Based on previous clinical experience, lesions were categorized as hyperintensities (i.e. showing high signal intensity on T2-weighted images, proton density-weighted images, and/or FLAIR images), parenchymal defects, or areas of focal atrophy. Parenchymal defects were areas of missing brain tissue, with signal intensity identical to that of cerebrospinal fluid (CSF) on all pulse sequences; they could be surrounded by brain tissue (lacunar lesions) or they could be continuous with the subarachnoid CSF space. To distinguish lacunar lesions from Virchow-Robin spaces, we included only parenchymal defects in the cerebrum and brainstem with a diameter of the shortest axis of ≥3 mm, that were surrounded by a rim of high signal intensity on FLAIR or proton density-weighted images.[18] Since Virchow-Robin spaces are usually not observed in the cerebellar hemispheres, and since infarcts in the cerebellar foliae are typically small and generally not surrounded by gliosis, all defects in the cerebellar hemispheres were included, irrespective of size and signal of surrounding parenchyma.[19]

Focal atrophy was defined as a focal area of brain parenchyma characterized by volume loss. Diffuse brain atrophy was not included in the analysis, since it is impossible to detect on visual assessment of MR images in a reproducible way. MRI findings were attributed to the single radiological category that best corresponded with their characteristics. For each lesion, the size, shape, location, signal characteristics and behavior following Gd administration were registered. Depending on the location of their epicenter, lesions were scored as cortical gray matter (GM), supratentorial white matter (WM), basal ganglia (BG), brainstem (BS) or cerebellar WM and GM lesions. Smooth ventricular caps at the frontal and occipital horns of the lateral ventricles and smooth ventricular rims with hyperintense signal on T2-weighted, proton density-weighted and/or FLAIR images were not included in the results. Periventricular circumscribed lesions or diffuse areas with hyperintensity touching the ventricles, but not following their curvature, were included.

## Results

### No abnormalities

In 31 of 74 patients (42%) no cerebral abnormalities were found on the available MR images. Normal MR images were observed in all 15 ACR-defined NPSLE manifestation categories in this study except for chorea (Table 2).

### WM hyperintensities (WMHIs)

The most frequent radiographic finding in our patients was the presence of WMHIs. One or more WMHIs were observed in 36 of 43 NPSLE patients with MRI abnormalities (49% of all 74 patients), occurring in various numbers and sizes. Of all 74 patients, 22 (30%) had 1-5 WMHIs, 5 (7%) had 6-9 WMHIs, 4 (5%) had 13-16 WMHIs, and 5 (7%) had ≥23 WMHIs.

The WMHIs ranged from 3 mm to 35 mm. Small WMH of ≤5 mm were mostly punctiform and were found in almost all (32 of 43) NPSLE patients with MRI abnormalities (Figure 2A). In 12 patients only such small punctate WMHIs were observed, whereas 20 patients also had larger focal WMHIs (Figure 1A). Most lesions were isolated, but in patients with multiple WMHIs confluence of lesions could be observed (Figure 2B). WMHIs occurred in all regions of the supratentorial WM, the brainstem and in the medullary WM of the cerebellum. In patients with multiple, bilateral WMHIs, the lesions were distributed asymmetrically. The larger WMHIs especially tended to occur in the deep WM of the corona radiata and centrum semiovale.

On T1-weighted sequences, the WMHIs showed decreased or normal signal intensity. Diffusion-weighted images were available in 23 of the 36 patients with WMHIs. In two of those 23 patients, ≥1 of the WMHIs corresponded to areas of high signal intensity on diffusion-weighted images (Figure 1B) and to areas of low intensity on apparent diffusion coefficient maps (not shown), indicating restricted diffusion). Enhancement of a WM lesion occurred in only 1 of 19 patients with WMHIs and available T1-weighted images following intravenous Gd administration. This patient had a 35 mm-deep WM lesion in the occipital lobe, showing a remarkable ring-shaped pattern of enhancement.

White matter lesions were present in patients with almost all types of ACR-defined NPSLE syndromes in this study (Table 2). They were seen with a wide variety of neuropsychiatric symptoms, with different severity.

### GM Hyperintensities (GMHIs)

In 18 of 74 NPSLE patients GMHIs were observed, affecting the cortex in 13 patients (18%) and the basal ganglia in 5 patients (7%).

Table 2. Patients with MRI findings corresponding to ACR-defined NPSLE syndromes.*

| NPSLE syndrome | Patients with syndrome† | Patients with no abnormalities‡ | Hyperintensity T2-weighted/ FLAIR images | | | | | Parenchymal defect§ | | | Atrophy | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Supratentorial WM | BS | Cortical GM | BG | CB | Supratentorial WM | BG | CB | Supratentorial WM | Cortical GM |
| Acute confusional state | 5 | 1 | 3 | 1 | 1 | - | 1 | - | 1 | 1 | - | - |
| AIDP | 2 | 1 | 1 | - | - | - | - | - | - | - | - | - |
| Aseptic meningitis | 2 | 2 | - | - | - | - | - | - | - | - | - | - |
| Chorea | 1 | - | 1 | - | - | - | - | - | - | - | - | - |
| Cognitive dysfunction | 14 | 2 | 11 | 1 | 4 | 1 | 1 | 2 | 1 | 2 | - | 1 |
| Cranial neuropathy | 2 | 1 | 1 | - | - | - | - | - | - | - | - | - |
| Cerebrovascular disease | 26 | 4 | 18 | 1 | 11 | 3 | 1 | 1 | 1 | 4 | - | 4 |
| Headache | 17 | 10 | 6 | 2 | 5 | - | 1 | 1 | 1 | 2 | - | 2 |
| Mononeuropathy | 1 | 1 | - | - | - | - | - | - | - | - | - | - |
| Mood disorder | 2 | 1 | 1 | - | - | - | - | - | - | - | - | - |
| Myelopathy | 3 | 2 | 1 | 1 | - | - | - | - | - | - | - | - |
| Plexopathy | 2 | 1 | 1 | - | - | - | - | - | - | - | - | - |
| Polyneuropathy | 3 | 1 | 1 | - | - | - | - | - | - | 1 | 1 | - |
| Psychosis | 8 | 5 | 3 | - | - | 1 | - | - | - | - | - | - |
| Seizures | 12 | 7 | 5 | - | 3 | 1 | 1 | - | - | 2 | - | - |

* Values are numbers of patients (total n = 74).

MRI, magnetic resonance imaging; ACR, American College of Rheumatology; NPSLE, neuropsychiatric systemic lupus erythematosus; No abn, no abnormalities; FLAIR, fluid attenuated inversion recovery; WM, white matter; BS, brainstem; GM, gray matter; BG, basal ganglia; CB, cerebellum; AIDP, acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome) (see Table 1 for other definitions).

† Total number of patients with the corresponding NPSLE syndrome according to the 1999 ACR nomenclature and case definitions for NPSLE syndromes (multiple syndromes could in one patient).

‡ No abnormalities on conventional magnetic resonance imaging (MRI) of whole brain.

§ Parenchymal defects are due to lacunar infarctions.

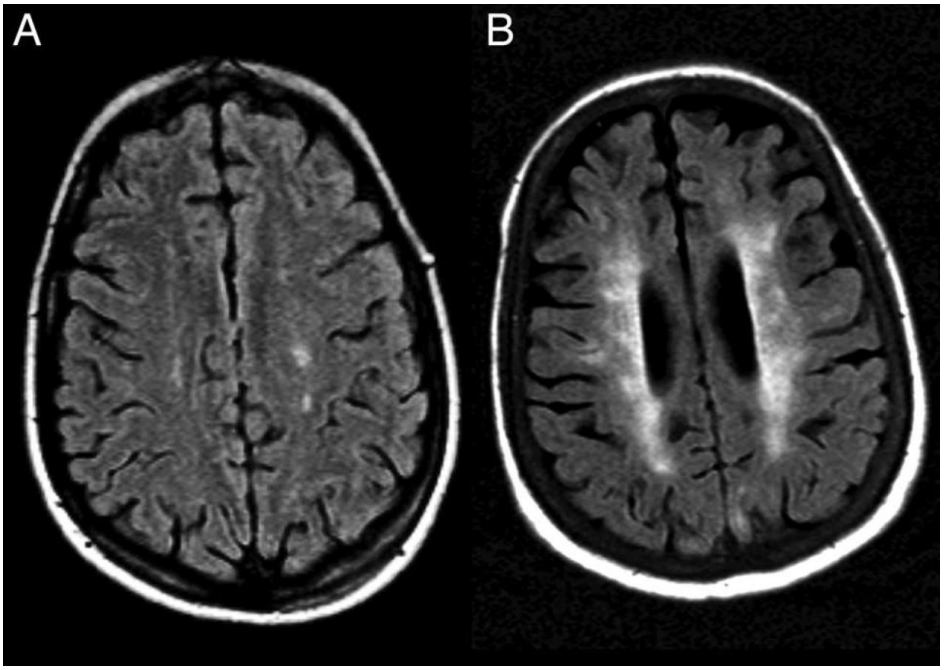


**Figure 2.** White matter hyperintensities (WMHIs) in patients with active NPSLE.
**(A)** Small focal WMHIs on a FLAIR image of the brain of a 29-year-old woman, admitted for left-sided hemichorea, mood disorder, regressive behavior and cognitive dysfunction, following a period of arthralgia, Raynaud's phenomenon, weight loss and fatigue. She was diagnosed as having NPSLE de novo (SLE based on arthritis, positivity for ANAs and anticardiolipin antibodies, anemia and leucopenia). No other abnormalities were observed on magnetic resonance imaging.
**(B)** FLAIR image of the brain of a 55-year-old woman showing extensive symmetric periventricular WMHIs in the corona radiata, capsula interna, and centrum semiovale. Other findings were single hyperintensities in the pons and cerebellum and old small lacunar infarctions in the basal ganglia and cerebellum. The patient, diagnosed as having NPSLE, presented with lethargy and progressive migrainous headache. During admission she became increasingly confused and developed expressive aphasia and diminished consciousness. Tests revealed positivity for ANAs and IgM anticardiolipin antibodies. Her medical history included diagnosis of SLE at the age of 50 (based on serositis, Coombs-positive autoimmune hemolytic anemia, thrombocytopenia, and positivity for ANAs and anti-dsDNA antibodies), steroid induced diabetes mellitus, thrombotic microangiopathy in the digits, emphysema with secondary pulmonary hypertension and decompensated heart failure, and renal insufficiency with microscopic hematuria and proteinuria. See Figure 1 for other definitions.

In 4 patients (5%) small focal lesions 3-11 mm in size were found within the cortex (Table 3 and Figure 3A and B). All 4 patients with small focal GMHIs also showed multiple, similar-appearing, focal WM lesions (Table 3).

In 9 patients (12%) larger diffuse hyperintensities were observed (13-60 mm), the epicenters of which were located within the cortical GM (Table 3 and Figure 3C). These lesions diffusely affected the cortex, covering ≥1 gyri and extending through the full width of the cortex. Nearly all diffuse cortical GMHIs showed some involvement of the adjacent WM, varying from minimal

**Table 3.** Cortical GMHIs on T2-weighted/FLAIR MR images in 13 patients with active neuropsychiatric SLE.*

| Patient | Cortical lesions (n) | Shape | Size, mm | Location | Other characteristics | Other MRI abnormalities |
|---|---|---|---|---|---|---|
| 1 | 2 | Focal | 3-5 | LF, RF | - | 14 WMHIs (3-7 mm), 1 WMHI pons (20 mm), 2 CB infarcts |
| 2 | 1 | Focal | 8 | RP | - | 9 WMH (2-8 mm), 1 CB infarct |
| 3 | 1 | Focal | 11 | Left insula | Restricted diffusion | 16 WMHIs (4-19 mm, 12 with restricted diffusion), 1 CB infarct |
| 4 | 2 | Focal | 10 -12 | LP, RP | 1 lesion focal atrophy | 13 WMHIs (3-15 mm) |
| 5 | 2 | Diffuse | 13 -25 | LP, LO | - | 3 WMHIs (3 mm) |
| 6 | 9 | Diffuse | 20-30 | LF, LP, LT, RF, RP, RT | - | 1 WMHI (15 mm) |
| 7 | 1 | Diffuse | 20 | Left insula | - | 6 WMHIs (3-5 mm), 1 CB infarct |
| 8 | 1 | Diffuse | 40 | RF | - | None |
| 9 | 1 | Diffuse | 60 | RP-T-O | Restricted diffusion | None |
| 10 | 2 | Diffuse | 15-30 | Left insula RT | 1 lesion restricted diffusion, 1 lesion laminar necrosis | 1 WMHI (20 mm, restricted diffusion), 1 WMH (20 mm + extension into GM + focal atrophy),1 parenchymal defect right thalamus |
| 11 | 1 | Diffuse | 22 | RO | Diffuse cortical enhancement | 2 WMH (5-10 mm) |
| 12 | 2 | Diffuse | 35-50 | RP/RT overlap, LO | Both lesions focal atrophy | 1 WMH (1x7 mm), 1 parenchymal defect WM (8 mm) |
| 13 | 2 | Diffuse | 30-32 | LF, RF | Both lesions focal atrophy | None |

* GMHIs, gray matter hyperintensities; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; LF, left frontal lobe; RF, right frontal lobe; WMHIs, white matter hyperintensities; CB, cerebellum; RP, right parietal lobe; LP, left parietal lobe; LO, left occipital lobe; RO, right occipital lobe; LT, left temporal lobe; RT, right temporal lobe; RO, right occipital lobe.

extension to a considerable overlap. The number of diffuse cortical lesions per patient differed from 1 to 9, and they occurred in all cerebral lobes. Most NPSLE patients with diffuse GMHIs also showed some WMHIs in various number and sizes (Table 3). However, in 3 patients isolated GM lesions were the only MRI abnormalities observed.

In 3 out of 5 patients with GMHIs and available diffusion-weighted images, the diffuse GM lesions showed restricted diffusion (Figure 3D). Two of these patients also showed areas of abnormal diffusion in the WM (Table 3). In 5 of the 13 patients with cortical GMHIs, T1-weighted contrast-enhanced imaging was performed, and in 1 patient a single cortical lesion with diffuse contrast enhancement was observed.

In 1 patient (Patient 10 in Table 3) a GMHI in the left insular cortex showed a pattern of increased signal intensity on the native T1-weighted sequence, which was compatible with cortical laminar necrosis. Cortical GMHIs occurred mainly in patients with focal neurological defi-

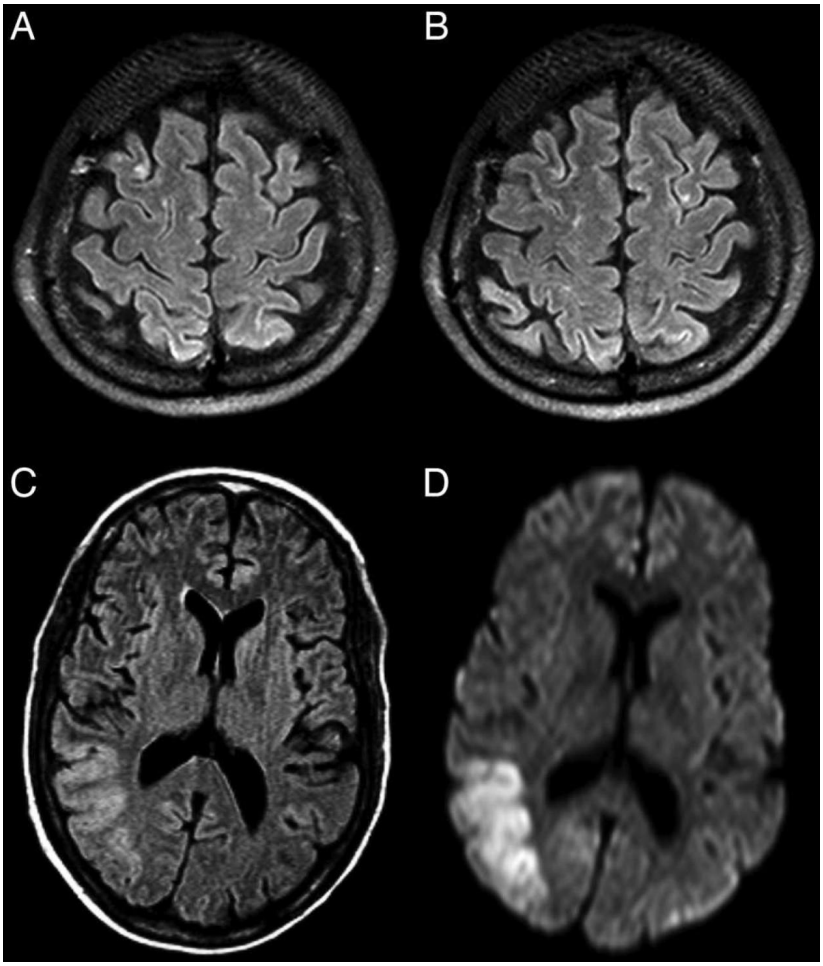


**Figure 3.** Gray matter hyperintensities (GMHIs) in patients with active NPSLE.
**A** and **B**, Punctiform cortical GMHIs on 2 slices of the FLAIR image of the brain of a 53-year-old woman with active NPSLE (patient 1 in Table 3). The patient was admitted for recent progressive memory loss. Her medical history included emphysema with pulmonary hypertension and decompensated heart failure, pleuritis and pericarditis. At age 50 years she was diagnosed as having SLE (based on serositis, positivity for ANAs and anti-dsDNA and anticardiolipin antibodies, and leucopenia). Neuropsychological testing revealed moderate-to-severe global cognitive deterioration.
C and D, FLAIR image of the brain of a 48-year-old woman (patient 9 in Table 3) diagnosed as having NPSLE, showing diffuse hyperintense signal in the cortical GM
**(C)** with high signal on the diffusion-weighted imaging sequence **(D)** and low signal on the apparent diffusion coefficient map (not shown), indicating cytotoxic edema. The patient was admitted for progressive headache, confusion and aphasia followed by a generalized seizure 3 days later, and progressive decrease of consciousness despite normalization of epileptic activity on EEG, resulting in a state of coma. The patient was positive for IgG and IgM anticardiolipin antibodies, and negative for lupus anticoagulant. No cardiac source of embolism was found. Six months earlier she was diagnosed as having SLE (based on polyarthritis, Raynaud's phenomenon, ANA positivity, Coombs-positive anemia, and leucopenia) which worsened one month before admittance. See Figure 1 for other definitions.

cits or sudden cognitive disorders, but diffuse headache and seizures could also be presenting symptoms (Table 2).

Foci with high signal on T2-weighted images were observed in the basal ganglia in 5 patients. Four of those patients showed 1, 2 or 3 small focal hyperintense lesions (<8 mm), located within one or both thalami or putamina. None of these patients showed cortical lesions, but they all had WMHIs, and in 1 patient cerebellar lesions. In the fifth patient 2 areas of ring shaped enhancement were observed in the nucleus lentiformis and the head of the caudate nucleus (Figure 1D). These areas were surrounded by an extensive area of hyperintensity on T2-weighted and FLAIR images, which partly showed restricted diffusion. In 1 patient, a diffuse T2-weigted hyperintensity was found selectively affecting the cerebellar cortex.

### Parenchymal defects and focal atrophy

One or more small parenchymal defects, surrounded by brain tissue and with a diameter of <10 mm, were found in a total of 12 patients (16%). They were observed in the supratentorial WM (centrum semiovale) in 2 patients and in the basal ganglia in 2 other patients. A striking finding was the high frequency of small parenchymal defects in the cerebellum, 16 of which were found in nine patients (12%). In 6 patients 1 cerebellar defect was found and 3 patient, respectively, showed 2, 3 and 5 defects. Both the supratentorial and cerebellar defects were found concomitant to all sorts of WMHIs and GMHIs. Local atrophy of the cortex, consisting of gyral atrophy and widening of sulci, was seen at the site of hyperintense lesions in 4 patients.

## Discussion

In this observational study an inventory was made of cerebral abnormalities on conventional MR images in 74 patients during their first episode of active primary NPSLE manifestations, classified according to the 1999 ACR case definitions for NPSLE syndromes. The most frequent radiographic finding was the presence of multiple focal WMHIs, affecting up to 75% of patients.[3,6-8,20-22] Although WMHIs are common, their role in the etiology of NPSLE is unclear. Similar WMHIs are found in patients with active NPSLE, in patients with past NPSLE, and in SLE patients without a history of neuropsychiatric events (non-neuropsychiatric SLE).[3,7,8,20,21,23,24] Furthermore, WMHIs are associated with hypertension[25], APS[26], valvular hart disease[27], and migraine[19], conditions that commonly occur secondary or concomitant with (NP)SLE. Moreover, similar focal WMHIs are frequently observed in the general population, associated with old age and other factors such as diabetes mellitus, and also in healthy individuals of mid-adult life.[28] Given their non-specificity, part of the WMHIs observed in patients with active NPSLE might not be related to SLE. The observation of WMHIs in cases of peripheral NPSLE (plexopathy, polyneuropathy, cranial neuropathy and Guillain-Barré syndrome) illustrate WMHIs observed in NPSLE that are not responsible for the experienced symptoms. Also, since WMHIs are observed

much more frequently in SLE patients (without neuropsychiatric symptoms) than in the healthy population, it is likely that some are a subclinical manifestation of SLE in the brain.

In contrast, there is evidence that WMHIs can be a manifestation of SLE disease activity in the brain giving rise to neuropsychiatric signs and symptoms. In the majority of MRI studies in which WM lesions were quantified, patient groups with NPSLE (active and past) showed a significantly higher number and total volume of WMHIs compared to non- neuropsychiatric SLE.[7,8,20-23] In addition, correlations have been observed both between WMHIs and cumulative SLE-related injury scores, including those for neuropsychiatric damage (Systemic Lupus International Collaborating Clinics/ACR Damage Index [SDI][29]), and between WMHIs and separate neuropsychiatric component scores of SLE-injury indices (SLE Disease Activity Index[30] and SDI).[7,20,23,24] Furthermore, on repeated MRI, occurrence of new lesions has been observed during onset of new neuropsychiatric symptoms, and resolution of WMHIs has been found to coincide with clinical improvement.[3,6,9,11,12] In our study, some WMHIs showed restricted diffusion, representing cytotoxic edema, and contrast enhancement (indicating blood-brain barrier disruption), suggesting active ongoing pathological processes, during active neuropsychiatric symptoms.

The pathophysiology of NPSLE-related focal WMH is unclear. Focal WMHIs have been attributed to multiple non-specific histological changes, such as gliosis, necrosis, focal reduced neuronal density, focal edema, inflammatory infiltrates, demyelination, and dilated perivascular spaces.[6,10-12,24,31] The observation of concomitant restricted diffusion is indicative of underlying cytotoxic edema, suggesting a role for acute ischemia. Furthermore, the bilateral, confluent WMHIs in some of our patients could be a sign of chronic hypoperfusion. Pathomechanisms that could result in acute ischemia, hypoperfusion and focal edema in SLE are non-inflammatory small vessel vasculopathy and vasculitis –both found in pathohistologic studies of NPSLE-, anti-phospholipid-, and other autoantibody mediated activation of endothelium and the coagulation system–, and premature atherosclerosis, all of which, in isolation or in concert, could contribute to narrowing of cerebral vessels and thromboembolic events.[5,12,20,31-35]

A striking finding of this study was the high prevalence of cortical GMHIs, which were observed in 18% of all patients and 30% of patients with MRI abnormalities. In 4 patients (5%) cortical GMHIs were small focal lesions that coexisted with similar-appearing focal WMHIs. This suggests that these lesions share the same pathogenetic mechanism. Underrecognized and only briefly described so far are the larger diffuse cortical GMHIs on T2-weighted and FLAIR images that we observed in 9 of our patients (12%).[3,6,9,11-14,24] Additionally observed characteristics included swelling, restricted diffusion, contrast enhancement, laminar necrosis, and focal cortical atrophy. The radiographic aspect of these diffuse cortical GMHIs suggests a pathophysiological process different from those underlying focal WMHIs and GMHIs.

First, the observed confinement of these GMHIs to large cortical areas with no or only little extension in the underlying WM is difficult to reconcile with large thromboembolic vascular occlusion or vasculopathy, in which lesions with such extensive cortical coverage typically also affect a major part of the underlying WM. These diffuse GMHIs also do not follow vascular

territories in the way it typically occurs in infarctions following occlusion of major cerebral blood vessels.

Second, the radiographic appearance of a widespread cortical area of diffuse hyperintensity with continuous extension over several neighboring gyri, and the absence of other notable abnormalities in cases with 1 or more isolated GM lesions, makes microembolisms in microvessels of the GM an improbable pathomechanism. This is also not expected in cerebral vasculitis, in which multiple dispersed focal and noncontinuous lesions are typically observed, predominantly in the WM. In neuropathologic studies of NPSLE patients, generalized bland (thrombotic) microvasculopathy has been detected in the brain, including the GM, but this has never been directly related to localized GMHIs on MR images similar to those in the present study. However, diffuse endothelial injury and activation are believed to play a pivotal role in the etiology of the clinicoradiographic posterior reversible encephalopathy syndrome, which is seen with SLE, other autoimmune diseases and, among others, (pre-)eclampsia, acute hypertensive encephalopathy, and thrombotic microangiopathies. The diffuse GMHIs that we observed in the present study, however, lacked the subcortical WM extension and occipital location that are characteristic for posterior reversible encephalopathy syndrome.

GMHIs in NPSLE are similar to the GMHIs that can be observed following seizures. Therefore, it is conceivable that seizure-induced vasogenic edema is responsible for the occurrence of lesions in those NPSLE patients experiencing seizures. However, this cannot account for all GMHIs in our series, since GMHIs were also observed in patients without seizures. Another potential pathomechanism of diffuse cortical GMHIs is an inflammatory immune response mediated by autoantibodies directed against antigens on neurons or other CNS components.[33,35-37] Antineuronal antibodies have been detected in the serum and/or CSF of patients with SLE, and their presence has been associated with predominantly diffuse clinical neuropsychiatric manifestations, such as cognitive dysfunction and psychosis.[32,36,37]

In recent years attention has been focused on antibodies against the *N*-methyl-D-aspartate (NMDA) receptor subunits NR2a and NR2b, the pathogenetic potential of which has been demonstrated in animal and in vitro studies.[38] Recent studies in humans showed an association between neuropsychiatric symptoms and the presence and increased levels of anti-NMDA receptor antibodies within the CSF of SLE patients.[39,40] Furthermore, Emmer *et al.* measured selective restricted diffusion in the amygdala of SLE patients and NPSLE patients compared with healthy controls and in the amygdala of anti-NMDA receptor antibody-positive patients compared with anti-NMDA receptor antibody-negative patients.[41]

So far no conventional MRI characteristics have been associated with antineuronal antibody-mediated immune processes in NPSLE. However, in paraneoplastic encephalitis, diffuse GMHIs are found that are considered to be caused by an autoantibody- and cytotoxic T cell-mediated immune response directed against antigens expressed both by the underlying tumor and by neuronal brain cells. In limbic encephalitis, FLAIR and T2-weighted images typically show areas of diffuse signal hyperintensity in the cortex of the medial part of one or both temporal lobes, which on follow up may resolve or give rise to focal, cortical atrophy.[42,43] The discovery of

different antineuronal antibodies has led to identification of several variants of paraneoplastic and nonparaneoplastic autoimmune encephalitis, in which diffuse GM signal hyperintensities have been observed in frontoparietal and temporal regions of the cortex, with and without subcortical involvement, that bear a striking resemblance to those observed in the present study.[42-46]

Small parenchymal defects were observed in 16% of our patients. These lesions were all interpreted as irreversible remnants of old subclinical lacunar infarcts, which can be caused by the same pathomechanisms of ischemia as the focal WMHIs. The high frequency of cerebellar defects we found in this study was striking (12%). Such defects have been associated with migraine in 2 recent population-based studies.[19,45] Since the prevalence of migraine in SLE patients is increased, it is not unlikely that these infarcts are migraine related. Unlike previous reports of infarctions due to thromboembolic occlusion of a large brain vessel, we did not observe this type of lesions in our patient group. This might be explained by referral bias and the fact that only scans of patients' first NPSLE episodes were included. Focal atrophy, seen in the cortical GM and occasionally with extension into the underlying WM, was invariably observed in conjunction with large diffuse surrounding GMHIs and WMHIs hyperintensities and is presumably the result of their underlying pathologic processes.

In the present study, no MRI abnormalities were observed in as much as 42% of clinically active NPSLE patients, with a wide variety of 1999 ACR-defined NPSLE syndromes, with mild to severe symptoms. These results corroborate the findings of previous studies.[7,8,20,21] Using quantitative MRI techniques, abnormalities have been detected in the normal appearing GM and WM of symptomatic NPSLE patients without explanatory findings on conventional MRI.[48-51] Interestingly, magnetization transfer imaging abnormalities were found particularly in the GM in patients with past diffuse NPSLE.[52] Results of quantitative MRI studies are not indicative of a specific pathogenetic pathway, but they do demonstrate that the GM is probably affected diffusely or multifocally, which is in line with our current observation of frequent and widespread diffuse conventional MRI lesions in the GM. This correspondence suggests that antineuronal autoantibody-mediated immune processes may also cause the invisible changes in the gray matter. However, the nature and cause of invisible changes detected by quantitative MRI techniques remain to be elucidated.

A limitation of this study is the variation in MRI scanners and consequently inconsistency in the applied pulse sequences. Such variation is hard to prevent in a retrospective clinical study of such a long as that of our study. However, this variation did not seriously hamper our study, since we used a qualitative approach, visually screening for abnormalities that could be detected and characterized on conventional MRI sequences (such as T1-weighted [with and without contrast agents], T2-weighted and FLAIR images) that have been more or less constant over the years; however, further characterization of the lesions with more recent techniques such as diffusion-weighted imaging were performed in only a limited number of patients. Further, due to its retrospective nature, this study did not allow us to assess the relationship

between clinical and radiolographic parameters. Further studies are needed to address these questions.

In summary, in this study we made an inventory of abnormalities on conventional MRI in patients with active NPSLE, and we tried to interpret these abnormalities in terms of possible underlying pathophysiology. We observed several distinct radiological patterns that are suggestive of different NPSLE pathogenetic mechanisms: 1) punctiform or focal hyperintensities in WM or both WM and GM, suggestive of vascular inflammation (vasculitis) or multifactorial autoimmune-mediated mechanisms of vascular occlusion or narrowing (vasculopathy with ischemia), 2) more widespread, confluent hyperintensities in the WM, suggestive of chronic hypoperfusion due to the same mechanisms, 3) diffuse cortical GM lesions, compatible with an (autoantibody mediated) immune response to neuronal or other CNS components, or post-seizure changes, and 4) no conventional MRI abnormalities at all, despite signs and symptoms of active disease. To advance our understanding of the various processes leading to NPSLE, the radiographic manifestations may be a good starting point.

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