Imaging modalities in CNS-lupus
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Within the past few years, a clearly defined case definition system for central nervous system systemic lupus erythematosus (CNS-SLE) has been established. This has allowed cross-study comparisons of patients fulfilling the specific case definitions. New imaging techniques used on the subgroup of CNS-SLE patients that did not have any evidence for infarctions suggest that in these patients symptoms are associated with a diffuse process in the brain. Most likely this process leads to axonal damage and demyelination, ultimately leading to cerebral atrophy. With respect to the diagnostic work-up of SLE patients with neuropsychiatric symptoms, it has become clear that cranial magnetic resonance imaging (MRI) is the technique of choice. Preliminary studies using quantitative MRI techniques suggest that patients with neuropsychiatric symptoms caused by active CNS-SLE can be differentiated from patients with the same symptoms caused by residual disease.
Introduction

Neuropsychiatric syndromes in patients with systemic lupus erythematosus (SLE) are far more common than in the general population. The incidence of central nervous system (CNS) manifestations in prospective studies in which consecutive patients were followed for about 10 years is about 25%. Because this frequency is far higher than the frequency of CNS manifestations in the general population, it is assumed that SLE by itself can lead to neuropsychiatric symptoms. From a clinical perspective, the major problem is that the signs and symptoms of neuropsychiatric manifestations in SLE patients do not differ from those in patients with other disorders. Therefore, it is not possible in an individual patient to attribute the symptomatology to either activity of SLE or to the concomitant presence of another disease causing neuropsychiatric symptoms. Thus, in clinical practice, central nervous system systemic lupus erythematosus (CNS-SLE) has always been regarded as a diagnosis per exclusionem.

Another complicated issue is that pathologic studies have almost exclusively been limited to post mortem studies of patients with end-stage disease, thereby limiting insight into the sequelae of events in the pathogenesis of disease in these patients.

Nomenclature and case definition system

In clinical practice, neuropsychiatric symptoms are thought to result from secondary causes (such as infections), infarctions (strongly related to antibodies interfering with the clotting system), or “diffuse CNS-SLE”. Because different investigators have used different approaches to detect secondary causes, it was difficult if not impossible to make cross-study comparisons. Moreover, in many studies, neuropsychiatric symptoms caused by infarctions and those that are not caused by infarctions have been lumped together, creating mixed populations of patients.

Recently, the rather unsatisfactory “diagnosis per exclusionem” for patients with CNS-SLE was changed by the development by the American College of Rheumatology (ACR) of a nomenclature and case definition system for neuropsychiatric lupus syndromes (see http://www.rheumatology.org/ar/1999/aprilappendix.html). The advantage of this classification system is that diagnostic criteria have been formulated, and formally described exclusion criteria are now available. Thus, in patients with, for example, chorea, it is mandated that conditions such as Huntington disease and Wilson disease and medications associated with chorea be excluded. The stringent use of these criteria has led to exclusion of secondary causes and identification of pathologic conditions caused by infarctions. For the pathologic condition caused by infarctions, the ACR nomenclature and case definition system for neuropsychiatric lupus syndromes demands neuroimaging in which, on either a computed tomography (CT) or magnetic resonance imaging (MRI) scan, an abnormality is found that provides a satisfactory explanation for the physical findings and symptoms. Moreover, several examinations such as echocardiography are explicitly required to fulfill the case definitions.

After exclusion of these causes, a group of CNS-SLE patients can be selected that fulfill the case definitions for diffuse manifestations such as aseptic meningitis, demyelinating syndrome, headache, chorea, myelopathy, cranial neuropathy, seizure, confusional state, anxiety disorders,
cognitive dysfunction, mood disorders, and psychosis. This group can be considered as having “diffuse” CNS-SLE. This relatively clear definition of the phenotype allows studies on the pathophysiology of diffuse CNS-SLE and studies to search for diagnostic tools that discriminate between the presence and absence of diffuse CNS-SLE. The knowledge of the pathophysiologic pathways leading to diffuse CNS-SLE symptoms is very limited. Pathologic studies in which a clear description of the clinical phenotype (only diffuse disorders) is given are limited to case reports. The combined knowledge of these case reports and the findings of positron emission tomography or single photon emission computed tomography and other imaging studies are compatible with a hypothesis in which unknown mechanisms lead to hypoperfusion resulting in loss of integrity of the blood-brain barrier, which subsequently allows antineuronal antibodies to pass the blood-brain barrier. This may finally lead to changes in brain composition, most likely loss in myelin. However, this is an interpretation of results obtained by imaging techniques of the brain that have only to a very limited extent been validated by simultaneous pathology studies.

This review focuses on imaging as a diagnostic tool for diffuse CNS-SLE, because progress has been made in techniques that discriminate between patients who are affected and those who are not affected.

Apart from the progress made in clinical classification, application of a variety of MRI techniques has led to a significant advance in the knowledge of CNS-SLE during the last 5 years. Using different MRI techniques, such as magnetization transfer imaging (MTI), diffusion weighted imaging (DWI) and magnetic resonance spectroscopy (MRS), abnormalities have been found in brains of SLE patients with diffuse symptoms. Since these techniques are based on different physical and chemical phenomena, they provide complementary information on the disease processes in the brain. In addition, the availability of quantitative MRI techniques permits assessment of structural brain damage (which is often invisible on conventional MRI scans) in numbers. Information in numbers can be subjected to conventional clinical epidemiologic testing or quantification of the variation between individuals (the 95% confidence interval (CI) of a quantitative MRI value of normal persons, the 95% CI of SLE patients without CNS symptoms, and the 95% CI of SLE patients with specific CNS symptoms). This assessment of variation of the values will provide a solid basis for the interpretation of these diagnostic tests.

**Computed tomography**

CT is insensitive to the diffuse presentations of CNS-SLE and is also insensitive in detecting abnormalities if manifestations of active disease, such as seizures, are present. In 36 randomly collected SLE patients (without information about the proportion who actually suffered from CNS-SLE), no or very weak correlation between neuropsychological function tests and computed tomographic abnormalities such as atrophy were found.
**Conventional magnetic resonance imaging**

MRI is regarded as the diagnostic imaging technique of choice in the evaluation of neuropsychiatric symptoms in SLE patients. MRI is important in excluding other causes of CNS dysfunction such as infarctions and space-occupying lesions. Although MRI abnormalities such as periventricular white matter (WM) hyperintensities, diffuse WM abnormalities, and especially cortical atrophy are more common in patients who have suffered from nonfocal CNS-SLE than in SLE patients without any neuropsychiatric symptoms ever, these abnormalities are indicative but not specific for CNS-SLE. Regrettably, in all the studies on MRI and new quantitative MRI techniques, the number of patients tested is low. Thus, it is currently not known whether the following data are applicable to the general population of CNS-SLE patients.

The use of MRI to study patients with CNS-SLE was studied by Karassa et al. These authors prospectively studied 32 patients with SLE who had been hospitalized with primary neuropsychiatric disease for two years. Initially, five patients had a normal MRI scan and 27 had abnormal findings on MRI. All patients were treated with moderate- to high-dose immunosuppressive therapy (and, if the antiphospholipid syndrome was present, with warfarin therapy). After two years, of the five patients with an initially normal MRI scan, four still had a normal MRI scan and one had a new lesion. Of the 27 patients with an initially abnormal MRI scan, after two years two patients had new lesions, 14 had unchanged lesions on the MRI scan, nine patients had lesions that were partially resolved, and two patients had lesions that were completely resolved. If an MRI lesion was unresolved after two years of therapy, this was significantly associated with an unfavorable clinical response (odds ratio, 4.3; 95% CI, 1.7–65). This prospective study demonstrated that cranial MRI can be used to assess disease progression or reversal. It is tempting to speculate that irreversible MRI lesions are caused by infarctions. Regrettably, this study did not discriminate between the course of MRI lesions in the presence or absence of infarctions.

Galanaud et al. approached the dogma of irreversibility of MRI lesions that are presumably caused by infarctions in patients with CNS-SLE from a different angle. These authors have studied chorea as a manifestation of CNS-SLE that is strongly associated with the presence of antiphospholipid antibodies and that can occur in the primary antiphospholipid antibody syndrome. Thus, it is assumed that infarctions are the underlying pathology of MRI lesions in SLE patients suffering from chorea. These authors found, in seven of the eight patients with chorea, no detectable lesions in the basal ganglia. Since infarcts remain detectable for life, it is questionable whether infarctions are the underlying pathologic condition in these patients. In conclusion, lesions on MRI scans in patients with CNS-SLE may resolve, and prospective studies suggest that resolution of lesions is associated with a good clinical response.

To guide decisions to initiate treatment, it is important to determine whether neuropsychiatric symptoms in CNS-SLE are caused by active disease or by preexisting damage. No solid data exist that conventional MRI techniques can differentiate between active disease and damage caused by past disease. However, it has been suggested that edema, especially of the gray matter (GM), is a more frequent feature in MRI scans performed on patients with active CNS-SLE.
Quantitative magnetic resonance techniques

Relaxation time measurements

Petropoulos et al.\textsuperscript{11}, in an elegant case control study, measured the GM spin-spin ($T_2$) relaxation time and compared it, correcting for volume artifacts such as cerebral atrophy, in the cranial MRI scans of 10 patients with active nonfocal CNS-SLE (generalized seizures, coma, delirium, and psychosis) and in 10 patients with minor CNS-SLE symptomatology such as headaches. The discrimination between these two groups was made because clinicians are willing to prescribe immunosuppressive drugs for major symptoms and not for minor symptoms such as headache. The GM spin-spin relaxation time was indeed about 10% higher in active “major” CNS-SLE (p<0.001), which suggests that this feature may discriminate between patients with active major symptoms and those with mild symptoms.

Magnetization transfer imaging

Another quantitative magnetic resonance technique that allows detection and quantification of structural brain damage is MTI\textsuperscript{12}. This technique is based on the exchange of protons between a pool of protons that is bound to macromolecules and a pool of free water protons that exists in biologic tissues. The exchange of protons can be assessed with MRI by diminishing the magnetization of the bound proton pool using a saturation pulse prior to application of a conventional magnetic resonance sequence. Because a conventional magnetic resonance sequence derives its signal from the protons in free water, and, because following a saturation pulse their magnetization is diminished due to an influx of saturated protons from the bound pool, there is a lowering of the signal intensity of the tissue. This lowering can be quantified by assessing the magnetization transfer ratio (MTR)\textsuperscript{13}. The macromolecules in the brain that mainly contribute to the magnetization transfer effect are the cholesterol component of myelin, cerebrosides, and phospholipids\textsuperscript{14}. It has been demonstrated that in lesions that are associated with loss of myelin or a change in the balance between myelin and free water (such as in edema), abnormal MTR values can be found\textsuperscript{15,16}. MTR values can be calculated in regions of interest to assess tissue composition locally. Using this approach, it has been demonstrated that MTR measurements are able to detect abnormalities in brain tissue that are not apparent on conventional MRI scans.

Another approach is performing MTR analysis in larger tissue volumes: volumetric MTI analysis\textsuperscript{15,17}. Volumetric MTI analysis can be applied to the whole brain. Based on a three-dimensional MTI study of the whole brain, MTR values can be calculated for each brain pixel. The pixel population that represents the brain can then be displayed as an MTR histogram, or the mean MTR value of the whole-brain volume can be calculated. In normal individuals, MTR histograms typically have a single narrow and high peak, which implies that in normal subjects the brain is relatively homogeneous in terms of MTR. It has been demonstrated that in demyelinating disorders such as multiple sclerosis (MS), MTR histograms change considerably\textsuperscript{15,17}. In MS, the histogram peak lowers, owing to an increase in the number of pixels with low MTR values. It has been demonstrated that the peak height reflects the amount of residual normal brain tissue, and that it consequently is a measure for the global lesion load in the brain. In MS, MTR histogram
peak height correlates with clinical and functional measures, indicating that it reflects relevant changes in the brain.\textsuperscript{15,16}

Two different groups found MTR histogram peak height values to be lower in patients with CNS-SLE than in control subjects. Rovaris et al.\textsuperscript{18} compared the MTR histograms of nine patients with CNS-SLE, 15 patients with SLE without any neuropsychiatric dysfunction, five patients with Behçet disease, nine patients with Wegener’s granulomatosis, and six patients with the antiphospholipid antibody syndrome. Ten patients with clinically definite MS and 15 healthy control subjects also underwent the same scanning protocol. Interestingly, only the patients with MS and CNS-SLE had significantly lower peak heights than all other patients.

Bosma et al.\textsuperscript{19} recently demonstrated lower peak heights on MTR histograms in patients with a history of CNS-SLE as compared with non-CNS-SLE patients and healthy control subjects. Also, CNS-SLE patients had a higher mean ratio of cerebrospinal fluid to intracranial volume than both control groups, which is indicative of atrophy. These results point to the capability of volumetric MTI analysis of demonstrating persistent CNS changes in patients with a history of CNS-SLE. Subsequently, the same group showed cerebral changes detectable by volumetric MTI analysis in patients in the active phase of CNS-SLE as compared with patients with CNS-SLE without present CNS activity, non-CNS-SLE patients, MS patients, and healthy control subjects (figure 1). These findings could not be ascribed to atrophy.\textsuperscript{20}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Magnetization transfer ratio (MTR) histograms after correction for intracranial volume (ICV) in five study groups. The scale of the y-axis is arbitrary and reflects the corrected (corr.) number of voxels multiplied by 1000. CNS-SLE, systemic lupus erythematosus with neuropsychiatric symptoms; MS, multiple sclerosis.}
\end{figure}

The fact that two values calculated from the histograms, as shown in figure 1, showed overlap in only three of the 19 patients is encouraging in that volumetric MTI analysis might have diagnostic potential for individual patients, although more studies are necessary to reproduce this finding. It has been suggested that in a group of 20 patients with a history of CNS-SLE, a correlation of structural brain abnormalities measured with volumetric MTR parameters and several measures of cognitive dysfunctioning such as intelligence ($r=-0.7$, $p<0.01$), memory ($r=-0.7$, $p<0.01$), executive function ($r=-0.5$, $p<0.05$), and global dysfunctioning score ($r=-0.6$, $p<0.01$), was demonstrated.
p<0.01) are present. Although these results suggest that MTI might be a valuable diagnostic tool in the evaluation of SLE patients with neuropsychiatric syndromes, the major disadvantage of this method is that it is difficult to standardize between different centers. Thus, the range of normal values of SLE patients without neuropsychiatric symptoms is dependent on the different centers. We expect that as long as this (technical) problem is present, MTI will be used mainly in centers that are referral centers for SLE patients with neuropsychiatric syndromes.

**Magnetic resonance spectroscopy**

MRS permits monitoring of the biochemistry of disorders of the brain. In the most widely used type of MRS, proton MRS, information is obtained from molecules containing protons. Based on the signal stemming from proton-containing molecules, proton MRS permits identification of the type and concentration of these molecules in brain tissue. Molecules that are frequently measured in the brain using proton MRS are N-acetylaspartate (NAA), creatine (Cr), choline (Cho), lactate (Lac), (myo)-inositol (Ins), glutamate (Glu), and glutamine (Gln). The concentrations of these metabolites are often expressed as ratios, such as NAA/Cr, based on the presumption that Cr remains constant in most conditions. Technically more demanding are measurements of absolute concentrations.

In CNS-SLE, a significant reduction of the NAA/Cr ratio has been found in both normal- and abnormal-appearing WM and GM in some patients, as well as reductions in NAA/Cho and increases in Cho/Cr. Sibbitt et al. compared 15 SLE patients with “major” CNS symptoms with 21 patients with “minor” symptoms and healthy subjects. Major CNS-SLE proved to be associated with decreased relative levels of NAA, even if the SLE was not currently active, probably representing some degree of (permanent) brain injury. Axford et al. measured absolute metabolite concentration and concluded that the metabolite markers follow a particular course of changes, ultimately leading to a significant reduction in NAA in nine patients suffering from CNS-SLE (five patients with major symptoms and four with minor symptoms), compared with eight healthy age-matched control subjects. SLE patients with major CNS symptoms had a permanently reduced Ins concentration with near normal Cho concentration in the normal-appearing WM of the brain. Since NAA is a neuronal marker, its reduction may be an indicator of neuronal damage.

The alterations in the other neurometabolite markers (Cho and Ins) are probably caused by neuronal injury, demyelination induced by ischemia, and posts ischemic inflammation. Although these alterations are not specific for CNS-SLE, these studies suggest that changes in the metabolism of brain tissue are present in patients with CNS-SLE. However, no studies on MRS techniques have been published in which patients with and without SLE but with similar neuropsychiatric symptoms are compared. These studies are needed before conclusions can be made about the interpretation of the above-mentioned data with regard to the pathogenesis of CNS-SLE per se instead of the pathogenesis of neuropsychiatric dysfunction per se.
**Diffusion-weighted imaging**

DWI is a magnetic resonance technique that is based on the random, incoherent (brownian) motion of protons on the molecular scale. In free water, proton-containing molecules move unrestricted in all directions, a situation that is referred to as isotropy. In highly structured tissue, such as the corticospinal tract, molecules encounter fewer barriers when moving in a craniocaudal direction than in directions perpendicular to it. This situation gives rise to preferential molecular movement in a certain direction, which is known as anisotropy. Basically, the brain is an anisotropic organ, and pathologic conditions that disturb its highly structured architecture may give rise to changes in diffusional behavior, such as changes in the magnitude of diffusion and loss of anisotropy\textsuperscript{25,26}.

One way to assess the magnitude of diffusion is by calculating the apparent diffusion coefficient (ADC) for individual pixels. ADC values can be assessed locally in regions of interest\textsuperscript{27,28}. Recently, however, a volumetric way to analyze ADC values was proposed\textsuperscript{29}. According to that method, ADC histograms are generated for the whole brain, and these histograms are analyzed in a manner similar to that used to analyze MTR histograms. In MS, it has been suggested that the ADC histogram peak heights are also a measure for the lesion load in the brain. It is important to realize that ADC histogram measures, although generated by similar image processing steps as MTR histogram measures, are based on different chemicophysical processes and probably reflect different aspects of tissue damage\textsuperscript{29}.

In a group of 12 patients with a history of nonfocal CNS-SLE and 10 healthy volunteers, a significant decrease of the peak height and a significant increase in the number of pixels with higher ADC values was shown in the CNS-SLE patients than in the healthy subjects. These abnormal diffusion patterns could be a reflection of decreased uniformity of brain parenchyma, probably due to loss of parenchymal structure\textsuperscript{30}.

It remains to be tested whether abnormal diffusion patterns are different in CNS-SLE patients with active disease in comparison with patients with symptoms due to previous damage. As with the spectroscopy studies, comparative studies of SLE and non-SLE patients with similar symptoms, such as seizures, are lacking, which leads one to question the specificity of the findings by this technique. If this method is as accurate as MTI, however, in detecting differences between normal subjects, SLE patients without CNS symptoms, and CNS-SLE patients with and without active disease, this method seems attractive because of its expected reproducibility between different centers.
Conclusions

The carefully performed longitudinal studies on conventional MRI and the studies with quantitative MRI techniques suggest that nonfocal CNS-SLE is associated with a diffuse process in the brain. Most likely, this process leads to axonal damage and demyelination, ultimately leading to cerebral atrophy. Although the sample size of the patient populations used in the studies is small, several aspects can be highlighted with respect to imaging techniques in nonfocal SLE:

- Currently, conventional MRI is the technique of choice for patients with neuropsychiatric symptoms in SLE.
- Lesions found on conventional MRI scans can be reversible by immunosuppressive therapy.
- Unresolved lesions found on conventional MRI scans are associated with lack of clinical improvement.
- Preliminary studies suggest that active disease can be differentiated from residual disease by quantitative MRI techniques.
- No data are available to tailor treatment decisions with (quantitative) MRI techniques.
References


