Central Nervous System Involvement in Systemic Lupus Erythematosus: An Imaging Challenge

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ABSTRACT: Systemic lupus erythematosus (SLE) is a complex autoimmune disorder involving multiple organs. One of the main sites of SLE morbidity is the central nervous system (CNS), specifically the brain. In this article we review several imaging modalities used for CNS examination in SLE patients. These modalities are categorized as morphological and functional. Special attention is given to magnetic resonance imaging (MRI) and its specific sequences such as diffusion-weighted imaging (DWI), diffuse tensor imaging (DTI) and magnetic resonance spectroscopy (MRS). These modalities allow us to better understand CNS involvement in SLE patients, its pathophysiology and consequences.

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KEY WORDS: systemic lupus erythematosus (SLE), neuropsychiatric systemic lupus erythematosus (NPSLE), magnetic resonance imaging (MRI), diffusion-weighted imaging (DWI), diffuse tensor imaging (DTI), computed tomography (CT)

Central nervous system involvement is a common and dangerous manifestation of systemic lupus erythematosus. Various studies have shown a variable prevalence of radiological CNS involvement in patients with SLE, ranging from 15% to 90%. A further differentiation of CNS involvement in the course of SLE is the clinical entity neuropsychiatric systemic lupus erythematosus. In 1999 a multidisciplinary committee appointed by the American College of Rheumatology assembled 19 case definitions of central, peripheral and autonomic manifestations of the nervous system in patients with SLE that excluded other causes. Among the latter are seizures, mood disorders, headache, aseptic meningitis and others [1].

It is estimated that up to 90% of patients with SLE will suffer eventually from NPSLE [2]. The most common manifestations are headache (24%), cerebrovascular disease (17.6%) and mood disorders (16.7%) [3,4]. While a clinical examination of the nervous system combined with psychological assessment are still the cornerstones of NPSLE diagnosis, laboratory tests, cerebrospinal fluid tests, electroencephalography and imaging are also used to support the diagnosis [5]. Different imaging modalities, both morphological and functional, can be used for evaluating NPSLE and have become an important tool in its diagnosis [6-10].

This review article is intended to provide clinicians who treat SLE patients with a broad view of current imaging modalities and techniques, as well as the most prevalent pathological findings encountered. Also, the most recent data on each modality are reviewed. Among the morphological modalities used are multi-detector computed tomography, magnetic resonance imaging, diffuse tensor imaging, and magnetic resonance spectroscopy. Functional modalities include positron-emission tomography, single positron-emission computed tomography, and functional MRI. The focus of this review is MRI since it is the gold standard for CNS evaluation in SLE patients today [Table 1]. Nonetheless, the other modalities are presented as well, describing both the method and the pathological findings of CNS involvement in SLE patients [Table 2].

FUNCTIONAL MODALITIES

SPECT

Single positron-emission computed tomography provides a tomographic reconstruction for the imaging of single photons emitted by radiolabeled tracers. Following intravenous administration of these tracers, regional blood flow and neuronal integrity are measured, making it possible to diagnosis areas with normal flow and hypoperfusion [9]. In several studies, abnormal SPECT scans, mainly at the parietal, frontal and temporal lobes, were correlated with overall disease activity and damage [5,11]. It has also been correlated in patients with antiphospholipid syndrome [12]. The most commonly observed abnormalities detected by SPECT are diffuse,

> Current imaging modalities and techniques enable not only morphological imaging of the patient's brain but a functional view as well

CNS = central nervous system
SLE = systemic lupus erythematosus
NPSLE = neuropsychiatric systemic lupus erythematosus

SPECT = single-positron emission computed tomography

focal or multifocal areas of decreased uptake corresponding to hypoperfusion [13].

PET

The PET exam measures the brain glucose uptake and oxygen consumption by using 2-18G-fluoro-2-deoxyglucose. In NPSLE, the most common areas affected are the parieto-occipital and parietal regions, demonstrating hypometabolism. It has been reported that successful treatment of NPSLE eliminated functional abnormalities seen before treatment in several cases [14].

FMRI

Functional MRI is based on the blood-oxygen-level dependence (BOLD) as an MRI contrast of blood deoxyhemoglobin. Changes in BOLD signal are well correlated with changes in blood flow and are therefore able to demonstrate functionally active areas in the brain. Several studies have shown abnormal increased regional brain activity in NPSLE patients compared to controls [15] during memory tasks and was correlated to disease duration, supporting the hypothesis that the pathological effect of SLE on the brain is cumulative [16].

MORPHOLOGICAL MODALITIES

MDCT

Multiple-detector computed tomography provides cross-sectional images by means of variable absorption of X-ray radiation by different tissues. MDCT is used mainly in emergency settings to exclude acute infarct, hemorrhage, abscess, edema, or meningitis. In addition, MDCT has low specificity and sensitivity to NPSLE. Among the chronic findings relevant to NPSLE are cerebral atrophy and calcifications.

MRI

Magnetic resonance imaging is considered the gold standard for NPSLE imaging today. It uses the magnetic characteristics of hydrogen nuclei to obtain images of tissues based on their different proton compositions. There are several sequences that help to delineate different pathologies. These include T1, T2, FLAIR, DWI and PWI (perfusion weighted images) [Figure 1, Table 1]. T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging enable visualization of pathologies such as fluid and edema as a bright signal, as they are sensitive to fluid content [17-19]. T1-weighted imaging, which is a fat-sensitive sequence, is usually normal in patients with NPSLE. The most common MRI abnormalities are small subcortical hyperintense lesions, infarcts and brain atrophy [5,20-23] and are more common in patients with NPSLE than in those without.

PET = positron-emission tomography
BOLD = blood-oxygen-level dependence
MDCT = multi-detector computed tomography
MRI = magnetic resonance imaging

Figure 1. MRI scan, axial plane, in a 24 year old woman with NPSLE. **[A]** T1-weighted image: arrow indicates hypointense lesion. **[B,C]** T2-weighted and FLAIR images: arrow indicates subcortical hyperintense lesion. **[D,E]** DWI image and ADC map: arrow indicates restricted diffusion in the lesion. **[F]** T1 + gadolinium images: the lesion enhanced after gadolinium administration
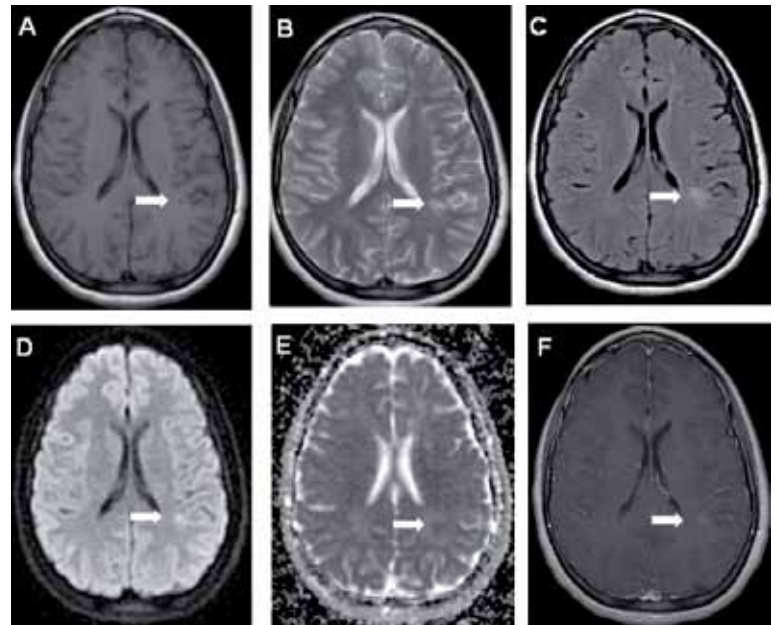

Table 1. MRI sequences used in CNS imaging

Sequence	Description	Common findings	Refs
T1	Fat-sensitive sequence	Brain atrophy	
T2	Fluid-sensitive sequence	Subcortical hyperintense lesions, infarcts, atrophy	[16-18]
FLAIR	Fluid-sensitive sequence	Subcortical hyperintense lesions, infarcts, atrophy	[16-18]
DWI	Shows inflammatory changes Differentiates from ischemic lesions	Decreased intensity on inflammatory changes Differentiates cytotoxic (high) and vasogenic (low) edema	[30-32]
ADC	Same as DWI Removes T2 shine-through artifacts	Increased intensity on inflammatory changes Differentiates cytotoxic (low) and vasogenic (high) edema	[30-32]
DTI	Measures axonal integrity, which is disrupted in NPSLE patients	Pathological signal from white matter of corpus callosum, left arm of forceps major and left anterior corona radiata	[33-35]
MRS	Measures disease activity	Reduced NAA levels (not a specific finding) Elevated choline levels	[3,7,12, 31,36-39]

FLAIR = fluid-attenuated inversion recovery, DWI = diffusion-weighted imaging, ADC = apparent coefficient of diffusion, DTI = diffuse tensor imaging, MRS = magnetic resonance spectroscopy

Morphological changes, as shown by MRI, can be caused by the disease itself (primary NPSLE) or is due to disease complications or to treatment [9]. It is now an accepted notion that a morphological imaging modality (such as MRI) cannot differentiate between acute or chronic lesions [9]. However, recent work by Katsumata et al. [10] has shown in a prospective study

Table 2. Neuro-imaging modalities in SLE

Modality	Pros	Cons	Indications	Common findings	Refs
SPECT	Measures tissue function	Very low resolution Radiation exposure	Disease activity Tissue damage	Area of hypoperfusion	[7,9 10, 11,12]
PET	Measures metabolic activity	Low resolution Radiation exposure	Functional/ metabolic changes	Hypometabolic areas	[13]
fMRI	See MRI	Special skills needed	Functional changes	Abnormally increased regional brain activity	[14,15]
MDCT	High availability Provides information on other brain pathologies	Low sensitivity and specificity	Rules out acute infarct, hemorrhage, abscess, edema	Cerebral atrophy, calcifications	
MRI	No radiation High resolution images	Cannot differentiate between acute and chronic lesions	Numerous tests Parenchymal damage	Small subcortical hyperintense lesions, infarcts, brain atrophy	[3,4,7,8, 10,12, 16-40]

SPECT = single-positron emission tomography, PET = positron-emission tomography, MRI = magnetic resonance imaging, fMRI = functional MRI, MDCT = multi-detector computed tomography

that large pathological signals (≥ 10 mm) occur only in NPSLE patients, while lesions smaller than 10 mm occur in both NPSLE and non-NPSLE patients. Moreover, chronological changes in the large pathological areas showed correlation with the clinical conditions and even partial reversibility in NPSLE patients, while smaller areas did not [6,10,19,24-26]. The exact pathophysiological mechanism reflected by the large pathological signals has not yet been determined. Among the differential diagnoses are gray matter lesions, edema, and new infarcts.

Autoantibodies theoretically contribute to neuronal dysfunction by various mechanisms such as reaction with endothelial, glial or neuronal cells. These antibodies reach the brain tissue because of an altered blood-brain barrier caused by autoantibodies or immune complexes [5].

The small (< 10 mm) subcortical hyperintense lesions were also shown not to correlate with the immunoserological status of patients, especially regarding lupus anticoagulant and anticardiolipin antibodies. However, anti-lupus anticoagulant antibodies were shown to correlate with multiple cerebral ischemic lesions or infarcts > 10 mm [27-29]. Other antibodies such as anti-TUB, anti-PSYC (lactosylsphingosine) and anti-SULF did not show any correlation with abnormal imaging studies [30].

Differentiation of acute from chronic NPSLE in modalities such as DTI and MRS and fMRI is becoming increasingly accurate

In the future a complete morphological and functional imaging profile will be combined with clinical data to create better treatment and an improved prognosis for SLE patients

DWI

Diffusion-weighted imaging measures the diffusion of water molecules in the brain. In normal brain tissue, water molecules flow along white matter tracts. Inflammatory changes, which cause disruption of white matter tracts, will result in an elevation of water diffusion, measured by apparent coefficient of diffusion, which will be higher. However, an acute ischemic insult will result in an initial reduction of diffusion, which will show a higher DWI signal. A few studies have shown an increased diffusion (higher ADC signal, lower DWI signal) in patients with NPSLE [31,32]. This finding indicates a loss of tissue integrity in NPSLE patients in both gray and white matter [33]. Moreover, because of its ability to discriminate between cytotoxic (high DWI) and vasogenic (low DWI) edema, it can discriminate between inflammatory and ischemic lesions in SLE patients.

• DTI

Diffusion tensor imaging quantifies the exchange of protons between those bound in macromolecules, such as myelin composites, and free water. Compared with a more isotropic movement of water in gray matter, water diffusion in white matter moves anisotropically. DTI enables tracking of the diffusion of water in the brain by measuring fractional anisotropy and mean diffusivity. FA measures overall axonal integrity, while MD measures the average molecular motion, independent of tissue boundaries. A previous study by Jung et al. [34] showed that while MD and FA were not significantly different between patients with SLE without NPSLE and healthy controls, in acute NPSLE patients numerous FA and MD changes were found, reflecting diffuse white matter abnormalities as compared to both healthy controls and SLE patients without NPSLE. Among the explanations given for the changes are immune-mediated vascular or neuronal injury, therapy-induced CNS changes, macro-micro embolisms causing infarcts, or small hemorrhages and edema. Interestingly, the DTI pathological areas did not correlate with common pathological areas shown by other sequences. These studies showed that a specific pathological signal from the white matter of corpus callosum, left arm of the forceps major and left anterior corona radiata correlates with acute NPSLE, as shown earlier [35,36].

DWI = diffusion-weighted imaging
ADC = apparent coefficient of diffusion
DTI = diffusion tensor imaging
FA = fractional anisotropy
MD = mean diffusivity

• MRS

Also known as nuclear magnetic resonance spectroscopy, this technique allows a quantitative assessment of several metabolites in the brain tissue. Most of the studies are conducted by using ¹H (proton) MRS. Some studies used phosphorus magnetic resonance, usually for measurements of high energy molecule content in muscles. Different molecules can be distinguished by their frequency, and a quantitative assessment is achieved at each frequency. The most common molecules measured in the brain tissue are *N*-acetyl aspartate, a neuronal marker found exclusively in neurons; choline, a marker of cell membrane metabolism that can reflect inflammation or demyelination; creatine, which is involved in phosphate transport system and found abundantly in glial and neuronal cells and is usually used as a reference; and myoinositol, which is found in glial tissue [3,9]. All these metabolites have been studied in SLE patients [37,38]. MRS profiles have been shown to be changed in NPSLE patients, although they are not specific for NPSLE patients [13]. It has been shown that not only is NAA reduced in CNS lesions of SLE patients, it is reduced in normal-looking brain tissue as well [9]. NAA changes are more profound in NPSLE patients than in SLE patients without neuropsychiatric manifestations. This change can be permanent, which implies neuronal death or transitory damage to the cells that may correlate with overall disease activity [9,39]. A decrease in NAA was noted in NPSLE patients with seizures, psychosis, confusional state and cognitive dysfunction [3,37,40]. However, it is important to recognize that a reduction in NAA levels can occur in other brain pathologies as well, such as Alzheimer's disease, multiple sclerosis and even sleep apnea [3].

Choline levels were shown to be elevated in NPSLE patients, and its levels correlated with disease activity and cognitive state [32]. To date, MRS is not considered a diagnostic tool in NPSLE diagnosis but should be part of disease management and follow-up as it can quantify organic brain injury and help characterize the type of injury. It is possible that in the future, automated metabolic profiling could differentiate between acute and chronic NPSLE.

SUMMARY

Imaging modalities and techniques have advanced tremendously in the last decade. They enable not only a morphological imaging of the patient's brain, but a functional view as well. The most dramatic change occurred in the MRI field, with modalities such as DWI, DTI, fMRI and MRS, which allow us to better understand CNS involvement in SLE patients, its pathophysiology and consequences. There is initial information regarding differentiation of acute from chronic NPSLE in modalities such as DTI and MRS fMRI. Moreover, some

of these modalities may have a huge impact on the patient's treatment, since differentiating between the direct effects of the disease or the treatment effect on the brain is critical. One can assume that in the future a complete morphological and functional imaging profile will be combined with the clinical data to create better treatment and an improved prognosis for SLE patients.

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MRS = magnetic resonance spectroscopy
NAA = *N*-acetyl aspartate

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Capsule

Negligible impact of rare autoimmune-locus coding-region variants on missing heritability

Genome-wide association studies (GWAS) have identified common variants of modest-effect size at hundreds of loci for common autoimmune diseases; however, a substantial fraction of heritability remains unexplained, to which rare variants may contribute. To discover rare variants and test them for association with a phenotype, most studies re-sequence a small initial sample size and then genotype the discovered variants in a larger sample set. This approach fails to analyze a large fraction of the rare variants present in the entire sample set. Hunt et al. performed simultaneous amplicon-sequencing-based variant discovery and genotyping for coding exons of 25 GWAS risk genes in 41,911 UK residents of white European origin, comprising 24,892 subjects with six autoimmune disease phenotypes and 17,019 controls. They showed that rare coding-region variants at known loci have a negligible role in common autoimmune disease susceptibility. These results do not support the rare-variant synthetic genome-wide association hypothesis (in which unobserved rare causal variants lead to association detected at common tag variants). Many known autoimmune disease risk loci contain multiple, independently associated, common and low-frequency variants, and so genes at these loci are a priori stronger candidates for harboring rare coding-region variants than other genes. These data indicate that the missing heritability for common autoimmune diseases may not be attributable to the rare coding-region variant portion of the allelic spectrum, but perhaps, as others have proposed, may be a result of many common-variant loci of weak effect.

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Eitan Israeli

"We should take care not to make the intellect our god; it has, of course, powerful muscles, but no personality"

Albert Einstein (1879–1955), German-born theoretical physicist who developed the general theory of relativity, one of the two pillars of modern physics alongside quantum mechanics