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# Non-Conventional MRI Techniques in Neuropsychiatric Systemic Lupus Erythematosus (NPSLE): Emerging Tools to Elucidate the Pathophysiology and Aid the Diagnosis and Management

Efrosini Z. Papadaki<sup>1</sup> and Dimitrios T. Boumpas<sup>2</sup>

<sup>1</sup>*Department of Radiology*

<sup>2</sup>*Internal Medicine and Rheumatology,*

*University of Crete School of Medicine, Heraklion*

*Greece*

## 1. Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune inflammatory disorder affecting multiple organ systems. 30-40 % of the patients manifest variable neuropsychiatric symptoms leading to significant morbidity and mortality. CNS involvement could be primary if directly related to SLE activity in the CNS or secondary to treatment, infections, metabolic abnormalities or other systemic manifestations such as hypertension (Futrell et al,1992). Primary NPSLE is divided into focal and diffuse disease. Focal NPSLE is characterized by focal neurologic deficits and is strongly associated with the occurrence of thromboembolic events. Diffuse primary NPSLE is a group of neurologic, psychiatric, and cognitive syndromes that vary from overt neurologic and psychiatric symptoms (eg. seizures, psychosis) to more subtle signs such as headache, mood disturbances, anxiety disorders or mild cognitive dysfunction. Neuropsychiatric lupus (NPSLE) manifestations can occur in the absence of either serologic activity or other systemic disease manifestations (Sibbit et al., 1999). Thus, in clinical practice the diagnosis of primary NPSLE is rather presumptive, after the exclusion of alternative causes of the neuropsychiatric symptoms.

There is no single diagnostic test that is sensitive and specific for SLE-related neuropsychiatric manifestations. The assessment of individual patients is based on clinical, neurologic and rheumatologic evaluation, immunoserologic testing, brain imaging, and psychiatric and neuropsychological assessment. These examinations are used to support or refute the clinical diagnostic impression, rule out alternative explanations, and form the basis for prospective monitoring of clinical evolution and response to treatment interventions. The lack of a diagnostic gold standard makes the correct diagnosis of primary NPSLE a challenge. This realization has led us in developing under the auspices of the European League Against Rheumatology (EULAR) evidence and expert based recommendations for the management of NPSLE (Bertsias et al, 2010).

Magnetic resonance imaging (MRI) is the current modality of choice in the imaging assessment of NPSLE patients, due to its high sensitivity in detecting even small alterations in tissue water content (Sibbitt et al., 1999). However, the variable pathologic substrate of the NPSLE lesions result in low MRI specificity. Conventional MRI reveals lesions in about 50-75% of NPSLE patients, depending on the disease activity and the severity and kind of the neurological manifestations (focal or diffuse). In patients with focal symptoms conventional MRI commonly detects small, discrete, frontal-parietal subcortical or periventricular white matter lesions, hyperintense on T2 sequences, that usually represent small acute or chronic infarcts, or even microhemorrhages. Unfortunately, these lesions are not specific for NPSLE and exhibit no clinical correlation. Additional intravenous Gadolinium administration is helpful in differentiating acute from chronic lesions. Mild-to-moderate cerebral atrophy could also be detected by T1 sequences, associated with both generalized and focal brain injury.

In NPSLE patients with diffuse neurological manifestations conventional neuroimaging usually fails to demonstrate abnormalities that explain these symptoms. Additionally, histopathological studies confirm the presence of extensive diffuse parenchymal and cerebrovascular injury that could not be identified by the conventional MRI techniques. On the contrary, brain tissue microscopic structural, hemodynamic or metabolic changes could be assessed by advanced, non-conventional quantitative neuroimaging techniques, such as Diffusion Weighted Imaging (DWI), Diffusion Tensor Imaging (DTI), Perfusion Weighted Imaging (PWI), Magnetization Transfer Imaging (MTI) and Magnetic Resonance Spectroscopy (MRS). Although not available in the current daily practice, these techniques are promising for the better understanding of the NPSLE, and improvement of the diagnostic work-up and treatment.

We critically review the literature on brain imaging in NPSLE, with special emphasis on non-conventional neuroimaging techniques in order to access their contribution to diagnosis, understanding of the pathophysiology and clinical management.

## **2. Histopathological changes in NPSLE**

The underlying pathologic basis of NP-SLE is still under investigation (Bertsias GK, Boumpas DT, 2010). Pathological studies revealed multiple microinfarcts, noninflammatory thickening of small vessels with intimal proliferation, small-vessel occlusion, and intracranial embolism or hemorrhage (Van Dam et al., 1991). True vasculitis, with inflammatory infiltrate and fibrinoid necrosis is relatively rare, occurring in 6-9% of cases (Van Dam et al., 1991). Vasculopathy is most common. SLE vasculopathy affects predominantly arterioles and capillaries, resulting in vessel tortuosity, vascular hyalinization, endothelial proliferation, and perivascular inflammation or gliosis. This vasculopathy could be related to both acute inflammation and ischemia (Hanly et al., 1992; Van Dam et al., 1991).

According to a recent histopathological study (Sibbitt et al., 2010) the basic underlying pathologic process of NPSLE is cerebrovascular injury associated with disease activity and thromboembolism, resulting in focal and diffuse brain ischemia, small and large brain infarcts, focal and diffuse brain edema, brain hemorrhage, and focal and diffuse parenchymal injury. Multiple coexisting pathogenic mechanisms including, thromboembolism by cardiac valvular lesions, hypercoagulability, diffuse endothelial injury, and excitotoxicity could not be excluded (Roldan et al., 2006, 2008).

Four patterns of cerebrovascular disease NPSLE have been suggested: (1) an antiphospholipid antibody cerebrovasculopathy characterized by bland thromboses, thrombotic microangiopathy, and arterial intimal fibrous hyperplasia; (2) a diffuse cerebrovasculopathy characterized by endothelial injury associated with increased SLE disease activity, glomerulonephritis, hypertension, and perhaps neuroexcitotoxic antibodies; (3) thromboembolic NPSLE directly caused by cardiac valvular lesions; and (4) mixed cerebrovascular NPSLE with simultaneous aspects of antiphospholipid-associated thrombosis, increased disease activity, and thromboembolic valvular lesions (Sibbit et al., 2010).

### 3. Conventional MRI

Conventional pre- and postcontrast-enhanced brain MRI appears normal in approximately one-third of both symptomatic and asymptomatic NPSLE patients (Chinn et al., 1997; Jennings et al., 2004). Hyperintense white matter lesions are revealed in up to 70% of SLE patients. In the majority of MRI studies in which white matter lesions were quantified, patient groups with NPSLE (active and inactive) showed a significantly higher number and total volume of white matter hyperintensities compared to non-NPSLE (Appenzeller et al., 2008; Castellino et al., 2008).

According to a recent study (Luyendijk et al, 2011), that reviewed retrospectively the MRI exams of the first episode of active NPSLE in 74 patients, 4 types of findings were observed : 1) focal hyperintensities in white matter (49% of all patients and 84% of patients with abnormalities on MRI) or both white matter and gray matter (5%), suggestive of vasculopathy or vasculitis (Figure 1), 2) more widespread, confluent hyperintensities in the WM, suggestive of chronic hypoperfusion due to the same mechanisms, 3) diffuse cortical GM lesions (12%), compatible with an immune response to neuronal components or post-seizure vasogenic edema, and 4) absence of MRI abnormalities, despite active signs and symptoms (42%). Small punctate focal white matter lesions, the most common imaging finding, are followed in prevalence by cortical atrophy, ventricular dilation and diffuse white matter changes.

The small focal lesions- hyperintense on T2-weighted or FLAIR imaging- typically occur in periventricular and subcortical white matter, especially in the frontoparietal regions. They usually represent small resolved infarcts or focal areas of reduced neuronal density, but in some cases they may be the result of acute infarcts, focal edema, or even acute microhemorrhages (Sibbitt et al., 2010). The corresponding T1-weighted images often appearing normal (Ainiala et al, 2005), while FLAIR images have been shown to be more sensitive for detecting these lesions than T2 images. Periventricular lesions have been particularly associated with the antiphospholipid syndrome (APS) and can be impossible to differentiate on MRI from multiple sclerosis (Peterson et al., 2005).

Although the focal hyperintense white matter lesions are often considered nonspecific- since they are indistinguishable from age-related small vessel disease -they may occur much earlier and in greater numbers in SLE subjects. These findings also seem to be more common in patients with NP-SLE in the presence of antiphospholipid antibodies, although no clinical correlation was observed in most studies (Ainiala et al., 2005). In a large prospective population-based study involving healthy individuals, the presence of focal hyperintense white matter lesions was associated with cognitive impairment (Vermeer et al., 2003). In addition, correlations have been observed between white matter

hyperintensities and both cumulative SLE related injury scores, including neuropsychiatric damage (SLICC/ACRDI), and separate neuropsychiatric component scores of SLE-injury indices (neuro-SLEDAI and neuro-SLICC) (Appenzeller et al., 2008; Ainiala et al., 2005).

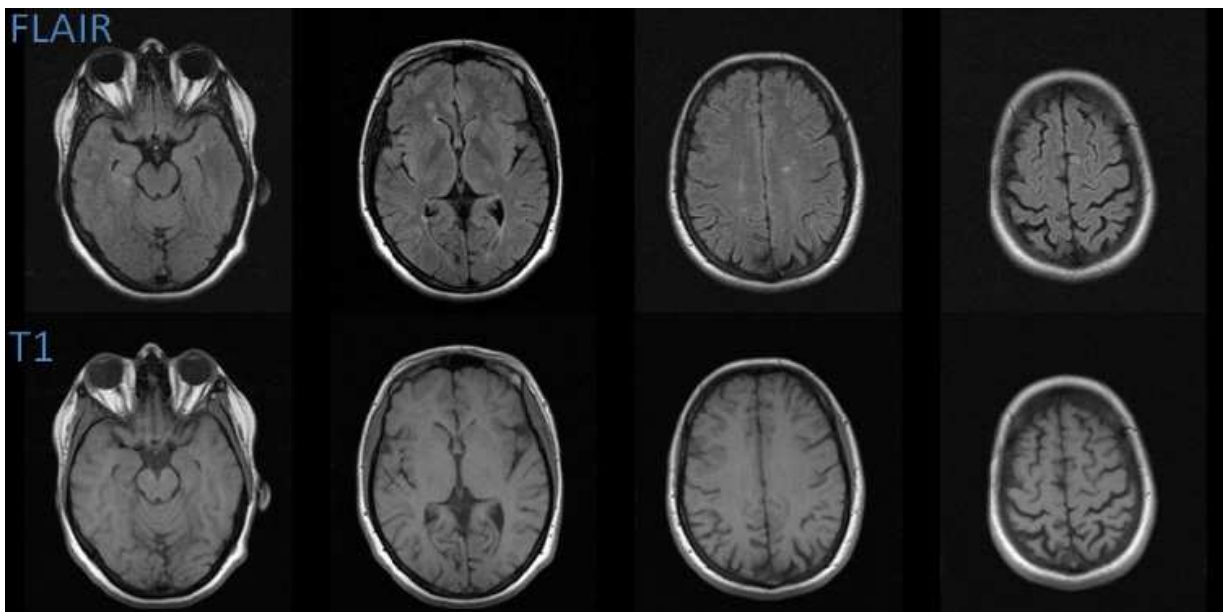


Fig. 1. FLAIR and T1 MR images of a 44 years female with NPSLE reveal multiple focal punctuate lesions-hyperintense on FLAIR and hypointense or isointense on T1- at the periventricular and subcortical white matter, semioval center and the cortex of the left frontal lobe.

Besides aging, white matter hyperintensities are also associated with hypertension, valvular heart disease, and migraine, conditions that commonly occur secondary or concomitantly to NPSLE. Consequently, it is not possible to differentiate NPSLE from other vasculopathies using conventional MRI. The differentiation of acute active disease from old chronic lesions is also difficult. It has been noted that the presence of indiscrete lesion borders, intermediate intensity of T2 lesions and grey matter lesions are all indicative of active disease (Sibbitt et al., 1999). The use of gadolinium has also been shown to be helpful in delineating active inflammatory lesions that usually enhance (Miller et al., 1992). Quantitation of T2 values has also been shown to be helpful in distinguishing active from chronic lesions (Sibbitt et al., 1995). T2 values appear to be increased in the normal appearing frontal grey matter of patients with active diffuse neurological syndromes.

MRI studies may show extensive bilateral, potentially reversible, white matter abnormalities in the cerebral hemispheres, the brainstem, or the cerebellum usually associated with active NPSLE—the so-called “acute posterior leukoencephalopathy,” (Sibbitt et al., 1999). The reversible lesions of acute leukoencephalopathy of NPSLE have been attributed to focal cerebral edema associated with blood vessel injury and microhemorrhages (Sibbitt et al, 2010).

Atrophy was described in 6–12% of SLE patients (Appenzeller et al., 2005,2008) and is associated with multiple factors such as disease duration (Cauli et al., 1994), corticosteroid use (Appenzeller et al., 2005; Ainiala et al, 2005), older age (Appenzeller et al, 2005),

antiphospholipid antibodies (Appenzeller et al., 2008; Provenzale et al., 1996) and the presence of hyperintense white matter lesions (Appenzeller et al., 2005; Chinn et al., 1997). The loss of tissue within the brain is thought to result from a combination of both myelin damage and axonal loss, followed by Wallerian degeneration, and the loss of extracellular space and vascular compartments. The histopathological findings associated with MRI-visible cerebral atrophy were highly variable and included multiple infarcts and reduced neuronal density, suggesting that atrophy in NPSLE may be associated with both generalized and focal brain injury. However, normal histological appearance was also noted in some atrophic brains (Sibbitt et al., 2010).

Cerebral atrophy is usually measured from T1-weighted MRI scans, where good contrast between the cerebral spinal fluid (CSF) and the brain parenchyma is observed (Appenzeller et al., 2008). Because high spatial resolution images allow brain volume measurement with the greatest accuracy and precision, three-dimensional gradient methods are generally preferred. As cerebral atrophy can be measured serially on MRI scans of the brain by linear or volumetric measurements, it has been proposed as a means of monitoring the progression of SLE (Appenzeller et al., 2005, 2008).

Regional atrophy in SLE patients has also been described involving cortical and subcortical regions, with particular clinical significance. Selective involvement of the amygdala in patients with SLE and anti-NMDAR antibodies has been found (Emmer et al., 2006). Cognitive impairment may be present more frequently in both corpus callosum and hippocampal atrophy (Appenzeller et al., 2006, 2008). Mild or clinically insignificant spinal cord pathology has also been described in SLE, which might be secondary to Wallerian degeneration of long tract fibers passing through damaged areas of the brain (Benedetti et al., 2007).

MR Angiography detects medium-to-large vessels involvement. Since a small vessel vasculopathy represents the major histopathological background of brain involvement in NPSLE angiographic techniques are usually negative, although angiographic arterial stenoses or occlusions are rarely reported (Weiner et al., 1991). Multiple mechanisms for angiographic arterial stenosis or occlusion have been considered, including coagulopathy, cardiogenic embolism, atherosclerosis from long-term steroid use and anticoagulant or antiplatelet therapy, vasculitis due to SLE or infection, or a combination of these processes (Devinsky et al., 1998).

Conventional MRI techniques are particularly useful in NPSLE patients with acute focal neurologic deficits, although they cannot always differentiate lesions indicating active acute NPSLE from chronic lesions that represent past NPSLE. The differential diagnosis usually includes thromboembolic events due to vasculopathy, lupus-related CNS vasculitis, antiphospholipid antibodies (APL-Ab)- mediated thrombosis, microangiopathy (including thrombotic thrombocytopenic purpura), Libman-Sacks endocarditis, and accelerated atherosclerosis. The pathogenesis in many patients is probably multifactorial. Accurate assessment is crucial, as treatment for these alternative diagnoses differs. Immunosuppressive agents are typically used for suspected vasculitis, while lifelong anticoagulation is the mainstay of therapy for APL-Ab-mediated thromboembolic events.

In diffuse NPSLE presentation conventional MRI could be unremarkable since it doesn't give information about damage in normal-appearing tissue (Sibbitt et al., 1999). Non-conventional MRI techniques, sensitive to microstructural, hemodynamic and biochemical

characteristics of the tissues have been developed, that could detect gray and white matter abnormalities in NPSLE patients, otherwise occult by conventional imaging.

## 4. Advanced MRI methods

### 4.1 Diffusion-weighted imaging

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. DWI can be used to measure diffusivity in the brain, providing signal proportional to the molecular diffusion of water molecules (Schaefer et al., 2000).

Diffusion Tensor Imaging (DTI) is a DWI technique that permits assessment of the preferential direction of proton diffusivity (Ulug et al., 1999). DTI offers increased resolution compared to conventional MRI regarding white matter microstructure by measurement of water diffusion through cellular compartments in vivo (Pierpaoli et al., 1996). Compared to more isotropic movement of water in gray matter, water diffusion in white matter moves anisotropically, meaning that water diffuses preferentially along the length of the axon compared to perpendicular to the axon. This anisotropic diffusion of water appears to be due to the highly structured axonal membranes and their associated myelin sheaths (Cascio et al., 2007). By tracking the diffusion of water in the brain, the measure fractional anisotropy (FA) and mean diffusivity (MD) can be derived. Higher FA (and lower MD) suggests greater axonal coherence and myelination. Measures of FA are usually considered to be overall measures of axonal integrity, reflecting either increased axonal caliber, increased myelin thickness, increased fiber coherence in a given direction, or some combination of these factors. In contrast, MD, is a measure of the average molecular motion independent of the constraints of tissue boundaries, and is affected by cellular size and degradations in tissue integrity (Pierpaoli et al., 1996). One way to assess the magnitude of diffusion is by calculating the apparent diffusion coefficient (ADC), an index of mean diffusivity, for individual pixels on average apparent diffusion coefficient (ADC) maps. Average diffusion coefficient (ADC) maps provide information on the microstructure of tissue and can be very useful in the detection of disease ADC values that can be assessed locally in regions of interest (ROIs). Another way is the generation of ADC histograms for the whole brain (Nusbaum et al., 2000). Such measures consisted of mean ADC values of the whole brain volume and descriptive parameters of ADC histograms of the whole brain, such as peak height. Relatively few studies have emerged showing water diffusivity changes in NPSLE. DWI was first used by Moritani and co-workers (Moritani et al., 2001) who detected acute or subacute lesions in 9 of 20 patients with SLE (45%). Two main patterns of acute or subacute brain parenchymal lesions were described. The first include hyperintense lesions with decreased ADC indicating acute or subacute infarction due to primary or secondary arterial stenosis or occlusion (Figure 2) and the second isointense or slightly hyperintense lesions on diffusion-weighted images with increased ADC representing vasogenic edema, with or without microinfarcts, due to small-vessel vasculopathy or hypertensive encephalopathy (Figure 3).

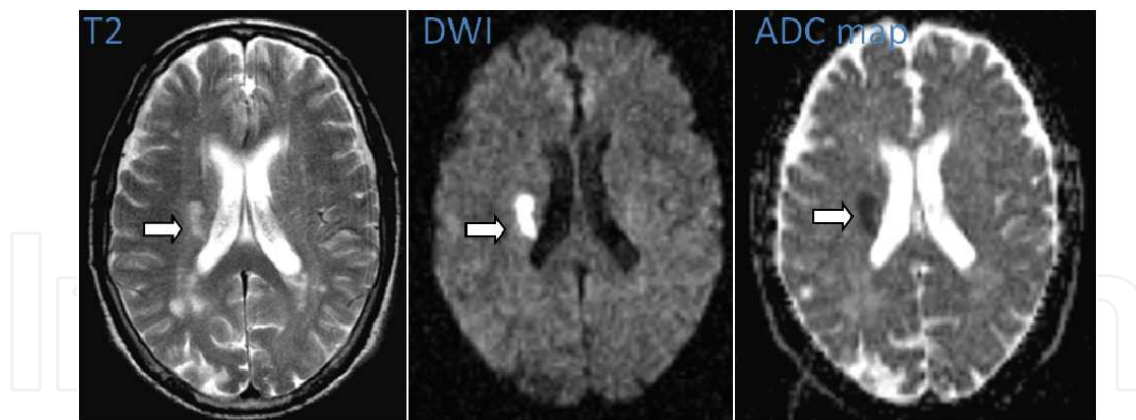


Fig. 2. Hyperintense lesion at the right corona radiata with increased signal intensity on DWI and decreased signal intensity on ADC map due to acute infarction.

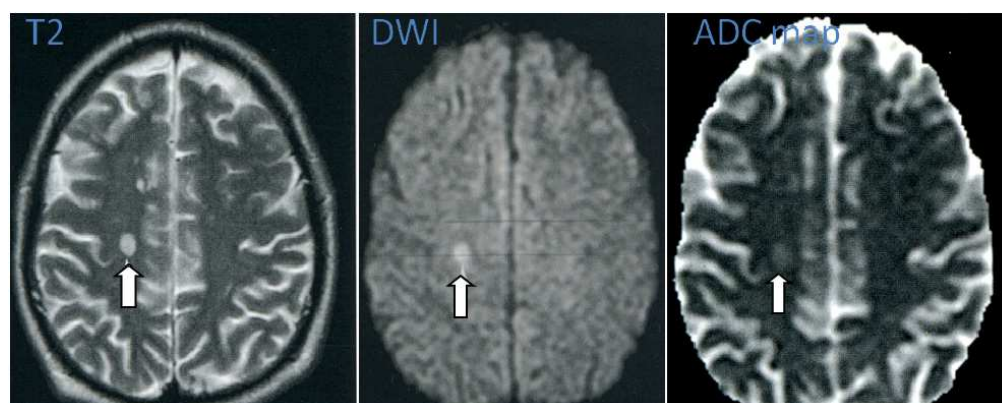


Fig. 3. Hyperintense lesion at the right semioval center with increased signal intensity on DWI and increased signal intensity on ADC map, due to vasogenic edema.

DWI then was used in NPSLE patients to provide quantitative measures of the integrity of the entire brain (Bosma et al., 2003). Using ADC histograms of the whole brain, in a group of 11 patients with a history of non focal NPSLE and 10 healthy volunteers they found changes in NPSLE patients who had no relevant changes on conventional MRI, that correlated with their clinical symptoms. The ADC histograms of the NPSLE group were, on average, significantly lower and broader, with a significant decrease of the peak height and a significant increase in the number of pixels with higher ADC values compared to the healthy subjects. The flatter and broader histograms in the NPSLE group indicate that, in these patients, widespread increased motility of free-water protons occurs. The subtle white matter hyperintensities that were visible on conventional MR images seemed unlikely to be responsible for the significantly different diffusion pattern in NPSLE because their number and sizes were small. These findings suggest that widespread damage exists in the brain parenchyma of NPSLE patients, invisible with conventional MRI. However, the method used in that study did not permit assessment of which parts of the brain were responsible for the observed changes in the ADC histograms of the whole brain.

Welsch and co-workers investigated 21 acute NPSLE patients and 21 healthy volunteers using also ADC histograms (Welsch et al., 2007). Whole-brain histograms, gray matter only



histograms, and white matter only histograms were calculated for each subject. They found increased mean ADC values in acute NPSLE, not only in the whole-brain histograms, but also in the gray matter only and white matter only, indicating that the cerebral alterations is not limited to one tissue compartment.

Zhang and co-workers used a region of interest (ROI) approach for ADC and FA measurements to assess a cohort of 34 patients diagnosed with SLE, and 29 healthy volunteers (Zhang et al., 2007). They found early diffusion changes (higher diffusion values and lower FA values) in the frontal lobe, the genu of the corpus callosum, and the anterior internal capsule in patients with SLE, although routine MRI findings were negative. Another group (Hughes et al., 2007) compared 8 female NPSLE patients, with new onset of symptoms, to 20 healthy controls using diffusion tensor imaging (DTI) and an ROI approach. They found that these patients differed from controls in a wide range of normal appearing gray and white matter regions including the insular cortex, thalamus, parietal and frontal white matter, and corpus callosum. These findings are suggestive of the presence of subtle and widespread damage in the brain parenchyma in NPSLE patients.

Recently Jung and co-workers (Jung et al., 2010) using DTI and the tract-based spatial statistics (TBSS) analysis technique assessed white matter abnormalities in 17 NPSLE patients, 16 SLE patients without NPSLE, and 20 age- and gender-matched controls. According to their findings there were no significant FA or MD differences observed between the SLE patients without NPSLE and the matched controls, although many of the SLE patients had subcortical white matter and periventricular lesions. In contrast, when comparing the acute NPSLE patients to controls, or the acute NPSLE patients to patients with SLE without NPSLE they found decreased FA and increased MD values especially at the corpus callosum and the left anterior corona radiata reflecting diffuse white matter abnormalities. They suggest that either the acute effects of the NPSLE disease, or its treatment, results in white matter changes discernable with conventional MRI techniques. This study provides new evidence that FA and MD may have diagnostic use in NPSLE by demonstrating, for the first time, regional brain specificity, and by distinguishing NPSLE from SLE patients, further indicating the potential diagnostic specificity of this technique for patients in the acute stage of this difficult disease.

Using the same analysis technique Emmer and co-workers (Emmer et al., 2010) investigated 12 patients with SLE (7 with NPSLE) and 28 healthy controls with DTI and found reduction in the FA values of patients with SLE as compared with normal subjects, indicating reduced integrity at particular white matter tracts. The integrity of the subcortical white matter tracts of the occipital, parietal and posterior frontal lobe was relatively preserved, whereas the frontobasal and temporal regions including the inferior fronto-occipital fasciculus, the fasciculus uncinatus, as well as the fornix, the posterior limb of the internal capsule (corticospinal tract), and the anterior limb of the internal capsule (anterior thalamic radiation) seem to be predominantly involved.

The increased ADC values, as well as the decreased FA values, could be explained by reduced structural integrity of the brain parenchyma with permanent loss of neurons and demyelination in patients with NPSLE. This will allow the interstitial water molecules to move freely in a less restricted environment. Normally, the ADC values decrease and the FA values increase by the restriction of motion in a particular direction, for example, due to the boundaries of myelin sheets. Alternatively, loss of structural brain integrity would allow interstitial water molecules to move in a more unrestricted environment, thus resulting in an

increase in ADC and decrease in FA. A breakdown of the myelin sheets, as in demyelination, would result in less restricted movement of the water molecules transverse to the fiber tracts. The observed increase in gray matter ADC can be interpreted as consistent with inflammation and/or vasculitis of the gray matter.

It has been suggested that the abnormal diffusion findings seen in the brain of NPSLE patients are not mainly related to hypoxic/anaerobic events, but, rather, indicate a host response to injury, such as an inflammatory reaction, membrane activation, or demyelination (Sibbitt et al., 1997). Such a theory can be supported by histopathology studies in which gliosis and demyelination has been described in the brain parenchyma of patients with NPSLE (Hanly et al., 1992). Immune-mediated vascular or neuronal injury was postulated and subsequent neuronal and metabolic dysfunction resulting in edematous processes that increase water content in WM regions of the brain.

The white matter damage in NPSLE could be the indirect result of subtle noxious influences in NPSLE, such as repeated episodes of acute inflammation in small vessels. This could cause priming or activation of the wall of these small vessels by complement and/or antiendothelial antibodies. Priming or activation of the vessel wall could subsequently lead to vasculopathy and microinfarcts or subtle hypoperfusion in the small vessels of the brain (Zvaifler et al., 1982). Altered cerebral blood flow was previously demonstrated with PET and SPECT in NPSLE patients (Kuschner et al., 1990; Kao et al., 1999). If hypoperfusion occurs, it might be responsible for the metabolic abnormalities reported in NPSLE patients, as suggested by decreased high energy phosphate levels in phosphorus-31 MR spectroscopic studies and decreased brain oxygen consumption in PET studies. The end stage of this process might be axonal loss and associated demyelination. It is also possible that antibodies aimed directly against myelin, leading to direct white matter damage through a pervasive attack on axonal myelin sheaths or the oligodendrocytes from which they are derived. The involvement of the white matter could be, finally, the reflection of axonal damage through Wallerian degeneration caused by damage to the gray matter (Emmer et al., 2010).

Diffusion differences affecting acute NPSLE patients could also be related to therapy, whereby the introduction of corticosteroids, or other immunosuppression drugs (i.e. cyclophosphamide), and/or disease modifying antirheumatic drugs, can affect water content in the brain parenchyma. Another possible mechanism may be related to platelet or fibrin macro- or microembolism from Libman-Sacks endocarditis or anticardiolipin antibodies causing multiple areas of macroscopic or microscopic ischemia, infarctions, and microhemorrhages with surrounding edema (Roldan et al., 2006).

Undoubtedly, one of the more useful applications of DWI in clinical practice is the assessment of cerebro-vascular accidents; in these conditions DWI allows early detection (within 1 h) of acute ischemic insult showing a reduction of ADC due to cytotoxic edema which occurs rapidly after the onset of ischemia (Figure 2). DWI also permits to discriminate between recent (with restricted diffusivity) and old (with normal diffusivity) hyperintense ischemic lesions which can be otherwise undistinguishable with conventional MRI. Furthermore, for its ability to differentiate between vasogenic and cytotoxic edema, DWI could be also useful in SLE patients to discriminate between inflammatory and ischemic lesions (Iguchi et al., 2007). Increased diffusion occurs although conventional MRI findings are negative in some cases, which suggests that DTI is more sensitive and that quantitative diffusion measurements can be used in detecting early signs of SLE or, furthermore, monitoring disease evaluations. The findings of diffusion-weighted imaging may help guide

the choice of treatment and predict patient outcome in patients with SLE and CNS involvement.

#### 4.2 Perfusion weighted imaging

A variety of imaging techniques have been used to assess cerebral perfusion, beginning with positron emission tomography (PET). PET is a nuclear medicine technique which explores both brain glucose metabolism and cerebral blood flow (CBF). In patients with NPSLE multiple areas of hypometabolism were detected in both MRI normal-appearing white and grey matter regions (Otte et al., 1997). Although PET has high sensitivity (abnormal in 100% of patients with active NPSLE), it lacks specificity and due to its high radiation dose, high cost and limited availability, is rarely applied in the daily clinical practice.

Over the past two decades, two more perfusion imaging techniques, single photon emission computed tomography (SPECT), and perfusion-weighted MRI (PWI), were introduced. These techniques have been used to evaluate a variety of disease states, most commonly acute and chronic ischemia. SPECT is based on the radio-tracer uptake by viable neuronal cells and explores brain perfusion that is the result of both CBF and neuronal integrity. The most commonly observed abnormalities detected by SPECT in patients with NPSLE are diffuse, focal or multifocal areas of decreased uptake corresponding to hypoperfusion, which -according to some authors- correlates with NP disease severity and activity (Colamussi et al., 1995). Other SPECT studies reported CBF abnormalities in NPSLE without correlation to disease activity or serological parameters. There is also no significant associations between perfusion parameters and NP symptoms (Waterloo et al., 2001). A recent voxel-based SPECT study found no difference in perfusion parameters between healthy controls and SLE patients with inactive NP involvement. However the authors found a global hypoperfusion in active NPSLE patients compared to healthy controls, which was mainly located in the cortical gray matter (Appenzeller et al, 2008). Although SPECT has high sensitivity (abnormal in 86-100% of patients with major NPSLE) it lacks specificity (abnormal in 10-50% of SLE patients without NPSLE) and has limited anatomic resolution.

The most commonly used MR perfusion technique is dynamic susceptibility contrast (DSC) imaging. This is a non-invasive dynamic process based on the MR signal changes during the first pass of the intravenously injected contrast agent (a gadolinium chelate) through the vasculature. The change in signal intensity is then measured and perfusion maps are generated, most commonly encountering cerebral blood volume (CBV), cerebral blood flow (CBF), time to peak (TTP), or mean transit time (MTT) values. Nowadays PWI is widely used in the acute stroke, for evaluation of the salvageable tissue and the brain neoplasms to detect neoangiogenesis. This technique could be useful in NPSLE and antiphospholipid syndrome (APS) patients (Figure 4) at risk of cerebro-vascular ischemic events, but reports on the use of PWI in NPSLE are still very few and limited.

The first multimodality approach in patients with SLE was performed by Borelli and co-workers (Borelli et al., 2003) using simultaneously MRI, DWI, PWI and SPECT in 20 SLE patients. They found that SPECT was more sensitive than PWI in detecting brain hypoperfused areas, probably due to the different aspects of brain perfusion explored by these two techniques. PWI is a dynamic process related to the blood supply to the anatomical districts of the brain, while SPECT images reflect the distribution of a flow tracer

whose uptake at the neuronal level may, however, be in part influenced by the metabolic status of the nervous tissue. Therefore the combination of these techniques might yield more information about the underlying pathogenetic mechanism of brain hypoperfusion.

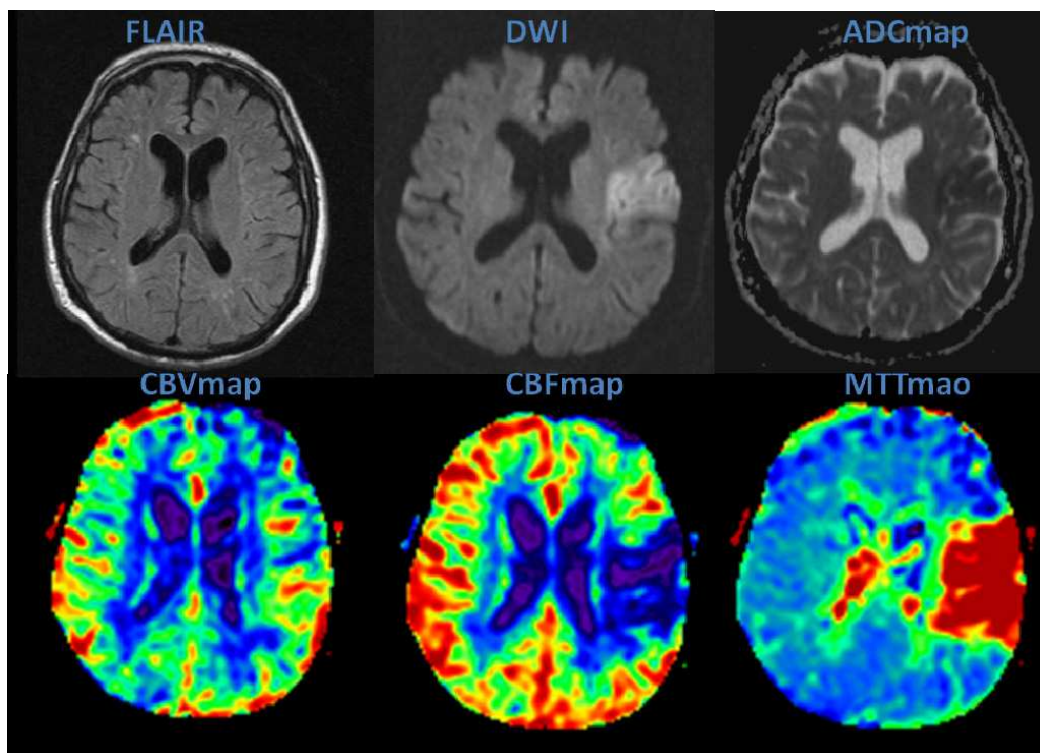


Fig. 4. Imaging of an acute ischemic lesion in a 45 yrs old female with NPSLE and antiphospholipid syndrome (APS), 4 hours after the onset of the symptoms. FLAIR is unremarkable, while the lesion is revealed on DWI and ADC map as hyperintense and hypointense area, respectively, due to cytotoxic edema. Dynamic Susceptibility Contrast (DSC) MR Perfusion technique shows mild increased cerebral blood volume (red on CBV map), decreased cerebral blood flow (dark blue on CBF map) and increased mean transit time (red on MTT map)

Two recent studies with application of dynamic susceptibility contrast perfusion MRI in SLE patients have opposite results. In the first study 15 active NPSLE, 26 inactive NPSLE and 11 control subjects were investigated and no signs of focal or global abnormalities in the perfusion parameters of the patients were found (Emmer et al., 2010). Furthermore, no significant differences were found when comparing patients with a specific SLE criterion (lupus anti-coagulant LAC, anti-cardiolipin antibodies or APS). The main limitation of this study is the fact that the CBF and CBV values have been calibrated to normal white matter, assuming that perfusion in the contralateral white matter is normal. This assumption could be erroneous in SLE patients with diffuse NP symptoms, like cognitive dysfunction or headache.

In the second study (Gasparovic et al., 2010) the DSCMRI technique was performed in 42 SLE patients and 19 healthy controls. They demonstrated higher CBV and CBF throughout cortical and white matter regions in the SLE patients (with or without lesions) relative to the control group. According to the authors the higher global CBF and CBV values may be due

to reactive physiologic or pathogenic factors underlying SLE, such as vasomotor instability, compensatory mechanisms for resolving injury, low-grade excitotoxicity due to antibody impairment of N-methyl D-aspartate (NMDA) receptors, or inflammatory factors. This global hyperperfusion in SEL patients is in contrast with most SPECT studies that reveal patchy hypoperfused areas in SLE patients. More studies should be performed to SLE and NPSLE patients with application of both SPECT and MRI perfusion techniques to further delineate this issue.

#### **4.3 Magnetization Transfer Imaging (MTI)**

MTI is a quantitative MRI technique that is sensitive to macroscopic and microscopic brain tissue changes (Grossman et al., 1994; Wolff et al., 1994) and more sensitive to the presence of disease than conventional MRI. In MRI, the magnetic characteristics of free-water protons determine the contrasts of the images. MTI is based on the magnetization transfer that occurs between the bound pool of macromolecule-related protons in biologic tissues and the pool of free water protons. In MTI, a saturating RF pulse selectively reduces the magnetization of the bound pool. Due to the interactions between the two proton pools, the magnetization of the free-water pool is also reduced, which is called the MT effect. Tissue factors that affect the amount of this magnetization transfer are the concentration of macromolecules and the surface chemistry and biophysical dynamics of the macromolecules (Wolff et al., 1994). Macromolecules that contribute to the MT effect in the brain are the cholesterol component of myelin, cerebroside, and phospholipids (Koenig et al., 2001).

The amount of MT is expressed by the magnetization transfer ratio (MTR) value. MTR values can be easily calculated in regions of interest (ROIs) to assess local tissue composition. In most diseases affecting the brain, MTR values are reduced, presumably due to dilution or destruction of macromolecules (Finelli et al., 1998). Using this approach it has been proved that MTI could detect abnormalities in brain tissue that are not visible in conventional MRI in cases of multiple sclerosis (Rovaris et al., 2000). Whole brain assessment can be also performed using MTR histograms for quantification of the disease burden of the whole brain (van Buchem et al., 1997). According to this volumetric method, the intracranial volume (ICV) is segmented, and the MTR values of the segmented brain are displayed as a histogram. Gray and white matter have different mean MTRs, which is probably mainly due to different concentrations of myelin. Still, the histograms for gray matter and white matter overlap substantially. The summation of these 2 histograms results in a histogram that is characteristic of the whole brain. The shape of this whole-brain histogram reflects conditions that affect the gray and white matter. MTR histograms of normal brains are characterized by the presence of a single, sharp peak, indicating that most normal brain voxels have approximately the same MTR values due to relative homogeneous tissue composition and microstructure. Demyelination, edema, atrophy and gliosis could impair MTR and the MTR histograms shape become flattened with decreased peak height reflecting dyshomogeneity of the brain tissue. In this way MTI allows the evaluation of brain tissue integrity, while simultaneously permits quantification of structural damage.

Studies that compared MS patients with normal controls using MTI revealed that the MTR histogram peak height was the volumetric MTI parameter that differed most significantly (van Buchem et al., 1998). This peak height was found to be decreased in MS patients. It was suggested that the peak height was a measure of the amount of residual normal brain tissue, and therefore inversely reflected the disease burden of the brain (van Buchem et al., 1998). In

several MS studies, this measure was found also to correlate with measures of cognitive and neurologic functioning (van Buchem et al., 1998).

MTI has been applied in NPSLE patients without visible abnormalities on conventional MRI. All these studies used MTR histograms for the quantitative assessment of the whole brain abnormalities. Bosma and co-workers (Bosma et al., 2000) applied the MTI technique to 11 patients with NPSLE, 11 patients with SLE without history of NPSLE (non-NPSLE) and 10 healthy volunteers. In this study, for every patient, an MTR histogram was created after correction for the ICV and another was created after correction for brain volume. In MTR histograms that are adjusted for the ICV, the peak height reflects both the integrity of brain parenchyma and the extent of atrophy. A different distribution of the brain voxels, in terms of changes in MTR values due to disorders of brain parenchyma or a reduction in the total number of brain voxels due to atrophy, can cause a decrease in the peak height. The peak height of the MTR histograms corrected for brain volume is affected only by the aspect of brain parenchyma, and not by the volume of the brain and atrophy (van Buchem et al., 1998). In the group of NPSLE patients, the average peak height of the histograms corrected for intracranial volume and the peak height normalized for brain volume were significantly lower than in either the non-NPSLE patients or the healthy controls at the same position of the peaks. This suggests the presence, in NPSLE, not only of atrophy, but also of an abnormality of the remaining brain parenchyma. The latter disorder in NPSLE is probably primarily present in the normal appearing parenchyma, since the low number and small size of hyperintense lesions observed in these patients cannot solely account for the decreased peak height of the histograms. Since myelin is a major contributing factor to the MT effect in the brain, the decreased peak heights of the MTR histogram corrected for brain volume might have originated from demyelination along with axonal loss. Edema and gliosis are also considered to give rise to abnormal MTRs (Dousset et al., 1992).

In another study (Bosma et al., 2000) MTI was performed to 9 patients with active nonthromboembolic NPSLE, 10 patients with chronic NPSLE, 10 patients with SLE and no history of NPSLE (non-NPSLE), 10 patients with inactive MS, and 10 healthy control subjects, to investigate whether volumetric MTI analysis with MTR histograms can demonstrate abnormalities in patients in the acute stage of diffuse NPSLE and compare these findings with those from chronic SLE, non-SLE and MS. The MTR histograms of both the non-NPSLE group and the healthy controls were similar. There was flattening of the histograms in the active NPSLE group, but with a shift toward higher MTRs. These changes indicate that the uniformity of the brain in patients with active NPSLE is lower than that in SLE patients with no history of NPSLE as well as that in healthy controls, suggesting that patients with active NPSLE can be distinguished from SLE patients with no history of NPSLE by use of MTR histogram analysis. The shift of the MTR histogram peak to the right that was observed in active NPSLE suggest an all-over improvement in the exchange of saturation from the pool of bound protons to that of the free water protons. Increased MTRs were also found in an experimental model of acute inflammation in MS, experimental allergic encephalomyelitis, during the early phase of inflammation in that disease (Dousset et al., 1992). Similar processes may occur during the active phase of NPSLE. In this study, all MTR histogram parameters in chronic NPSLE and MS were identical. Since NPSLE and MS are diseases with a different biologic behavior, it is unlikely that these similarities suggest a

similar pathogenesis. Instead, the similarities indicate that different diseases may give rise to a common final pathway (i.e., gliosis and demyelination) that results in similar changes in the MTR. These results also demonstrate that in the chronic stage of diffuse brain diseases, MTR histograms may not be able to differentiate between different diseases.

The same group (Bosma et al., 2002) further investigated the relationship between quantitative estimates of global brain damage based on magnetization transfer imaging (MTI) and the cerebral functioning, as measured by neurologic, psychiatric, and cognitive assessments, as well as the disease duration in patients with NPSLE. They performed MTI to 24 patients with NPSLE and found significant correlations between the descriptive measures of the MTR histograms and: a) the neurologic functioning quantified by the Kurtzke's Expanded Disability Status Scale (EDSS) b) the cognitive functions with the Wechsler Adult Intelligence Scale Revised (WAIS-R), a standardized psychometric test for assessing intelligence and c) the psychiatric functioning by the Hospital Anxiety and Depression Scale (HADS) questionnaire. Since the EDSS score mainly assesses motor skills, these findings suggest that atrophy and diffuse microscopic damage of the remaining brain parenchyma in NPSLE affect, among other areas, brain regions that are responsible for motor skills. Atrophy and diffuse microscopic cerebral damage also contribute the development of psychiatric symptoms, like anxiety and depression and cognitive impairment. There is no correlation between the quantitative estimates of global brain damage and age, SLE duration, or time elapsed since the first occurrence of neuropsychiatric symptoms suggesting that the accumulation of brain damage over time has a nonlinear aspect.

Dehmeshki and co-workers (Dehmeshki et al., 2002) developed an alternative way of analyzing and globally characterizing MTR histograms by using multivariate discriminant analysis (MDA) and correctly assigned patients with MS to clinical subgroups. The same group proceed to a study in SLE patients in order to explore the diagnostic potential of MDA for assigning patients with SLE to different subgroups of patients with on the basis of MTR histograms (Dehmeshki et al., 2002). MTI was performed to 9 patients with active NPSLE, 10 patients with chronic NPSLE, 10 patients with SLE and no history of NPSLE (non-NPSLE), 10 patients with inactive MS, and 10 healthy control subjects. Three binary comparisons were made: First, comparison of active NPSLE versus past NPSLE groups which is important because in patients with NPSLE, a new episode of neuropsychiatric symptoms could be due to an active intrinsic SLE-related brain process – that is, a recurrent active phase of NPSLE – or to extrinsic processes such as the side effects of drug use. Secondly, comparison of active NPSLE from non-NPSLE which is also important because an acute episode of neuropsychiatric symptoms could be due to active NPSLE or to extrinsic processes in patients with SLE. Finally, comparison of patients with active and/or past NPSLE with those who have MS which important because in patients who present with neuropsychiatric symptoms, the differential diagnosis includes SLE and MS, and these diseases are notoriously difficult to differentiate. In this study, MDA proved to be effective in assigning the majority of individual patients to disease categories in the given binary comparisons. In addition, MDA was shown to be considerably more effective for categorizing patient groups on the basis of MTR histograms than the conventional method of analyzing MTR histograms and might be of help in clinical practice.

Steens and co-workers (Steens et al., 2004) performed MTI in 24 SLE patients with a history of diffuse neuropsychiatric symptoms and 24 healthy controls to assess the distribution of

MTI abnormalities over gray matter (GM) and white matter (WM) in SLE patients without explanatory MRI evidence of focal disease. MTR maps were calculated for GM and WM separately, and GM and WM MTR histograms were generated. Significantly lower peak height and mean MTR of the gray matter were found in NPSLE patients as compared with healthy controls indicative of parenchymal brain damage specifically in the GM in SLE patients with a history of NP symptoms and without explanatory focal abnormalities seen on MRI. This observation supports the model of neuronal damage in diffuse NPSLE, and can be explained by the greater susceptibility of GM to the sequelae of small-vessel disease and hypoperfusion. Small-vessel disease itself may also increase blood-brain barrier permeability, which facilitates the entrance of antineuronal antibodies. In either case, because of the higher concentration of neurons in GM, the GM will be particularly affected. The same group (Steens et al., 2006) examined the correlation between gray and white matter magnetization transfer ratio (MTR) parameters and the presence of IgM and IgG anticardiolipin antibodies (aCLs) and lupus anticoagulant in 18 patients with NPSLE, but without cerebral infarcts on conventional magnetic resonance imaging. Lower gray and white matter mean MTR and peak location were observed in IgM aCL-positive patients than in IgM aCL-negative patients. No significant differences were found in MTR histogram parameters with respect to IgG aCL and lupus anticoagulant status, nor with respect to anti-dsDNA or anti-ENA (extractable nuclear antigen) status.

Various autoantibodies have been implicated in the pathogenesis of NPSLE, including anticardiolipin antibodies (aCLs). Because of their prothrombotic tendency, aCLs may cause cerebral infarctions and as such they are correlated with focal neurological syndromes (Denburg, Denburg, 2003). In a study of Steens and co-workers (Steens et al., 2006) MTI parameters demonstrated brain damage in aCL-positive SLE patients in the absence of cerebral infarcts on conventional MRI. These findings suggest that, apart from giving rise to macroscopic cerebral infarctions, aCLs may play a role in the pathogenesis of diffuse microscopic brain damage in NPSLE. According to the authors there are at least three possible explanations for how aCLs could be involved to diffuse microscopic brain damage in NPSLE. First, the thrombotic tendency of antiphospholipid antibodies, including aCLs, may cause aggregation of thrombocytes and an increase in blood viscosity (Scolding, Joseph 2002; Connor, Hunt 2003). This may affect blood flow in small cerebral blood vessels in particular and cause widespread hypoperfusion, which subsequently causes ischaemic damage to brain tissue. Second, aCLs may activate endothelial cells and cause a diffuse small-vessel vasculopathy - a neuropathological finding that was reported as long ago as 1968 (Connor, Hunt 2003; Scolding, Joseph 2002). The resulting increase in blood-brain barrier permeability permits entrance to the brain parenchyma of substances such as circulating antibodies. Third, it has been shown in vitro that IgG aCLs themselves may interfere with glutamatergic pathways by a mechanism involving over-activation of the N-methyl-d-aspartate receptor (Andreasi et al., 2001).

Emmer and co-workers (Emmer et al., 2006) proved that changes in the clinical status of individual NPSLE patients correspond to changes in the MTR peak height and MTI is a valuable objective measure for following a clinical course in NPSLE. 19 active or inactive NPSLE patients underwent MTI on at least two separate occasions. Their neuropsychiatric status between the first and the second MRI sessions was classified as deteriorated, stable, or improved. In all clinically deteriorated patients the MTR peak height decreased between the first and second scans. In all clinically improved patients the MTR peak height increased



between the first and second scans, indicating that brain involvement in NPSLE patients, as detected by MTR, is at least partly reversible. The nature of the pathophysiological substrate of the reversible MTR changes in NPSLE patients is unclear. According to the authors reversible changes in the integrity of the parenchyma are probably due to edema, since neuronal loss would not show such a degree of reversibility, and neuronal apoptosis is not a common finding in postmortem studies of NPSLE. Inflammation influences the vessel walls and permits extravasation of fluid and inflammatory mediators into the brain tissue that leads to inflammatory brain edema

#### 4.4 Magnetic Resonance Spectroscopy

Proton Magnetic Resonance Spectroscopy (MRS) is an MRI technique that permits study of the metabolites in tissue and provides qualitative and quantitative information about some brain metabolites displayed as spectra. The position of metabolites peaks in the spectrum is determined by its molecular characteristics. Studies in humans have used hydrogen -MRS (H-MRS) and rarely phosphorous-MRS (P-MRS). In normal water-suppressed, localized H-MRS of human brain at echo times (TEs) between 135 msec and 270 msec 3 major neurometabolites are revealed: **1. N-acetylaspartate (NAA)** with peak at 2.0 parts per million, which can be used as a neuronal marker, because is found exclusively in neurons. NAA is reduced in conditions associated with neuronal loss, such as stroke or neuronal degenerative disorders. However, several studies have shown reversible decreases in NAA in a number of conditions have also been recognized, emphasizing that neuronal dysfunction can also lead to a decrease in NAA (Rudkin, Arnold, 1999). **2. Choline (Cho).** Choline peak consists of choline, phosphocholine and glycerocholine. Cho is increased during increased cell -membrane turn over or during active myelin breakdown when these choline-containing membrane phospholipids are released. Increase Cho is detected in demyelination, remyelination, inflammation or gliosis (Rudkin, Arnold, 1999). **3. Creatine and phosphocreatine (Cr).** Total creatine concentration is relatively constant throughout the brain, and is used as an internal reference to normalize NAA and choline. Nevertheless there is loss of creatine in tissue necrosis (Rudkin, Arnold, 1999).

When performing MRS with short TE (30-35 msec) some other metabolites could also be revealed, such as **myo-inositol (mI)**, which is an osmolyte and astrocyte marker and is usually increased in demyelination, inflammation and gliosis. **Lactate** is elevated in anaerobic glycolysis and is not seen in normal brain spectra. The lactate peak is above the baseline when the TE is low (20-35 msec) or high (270-288 msec). At an intermediate TE (135-144 msec), the lactate peak inverts to project below the baseline, a feature that enables its distinction from lipids and some macromolecules seen at a similar location on the spectrum (1.35 parts per million).

Commonly used spectroscopic techniques include the single- voxel spectroscopy which allows evaluation of only small volumes of tissue, and the multivoxel technique that allows examination of different areas of the brain at the same time and also permits the derivation of metabolite maps. The selection of appropriate MRS techniques, including measurement parameters such as repetition time (TR) and TE, depends on the clinical question. Short TE (20-35 msec) evaluations are required when there is a need for detection of metabolites with short relaxation times, such as glutamine, glutamate or mI, whereas studies with long TE (135-270 msec) are sufficient for the detection of the major metabolites such as NAA, Cho, Cr, and lactate/lipids (Rudkin, Arnold, 1999)

Several studies have been performed using MRS in patients with SLE with or without neuropsychiatric manifestations. Most of them used single voxel MRS and proved reduction of the NAA/Cr and NAA/Cho ratios and elevation of Cho/Cr ratio in patients with SLE, not only in lesions, but also in normal-appearing white matter, when compared to controls. Nevertheless no distinction between acute and chronic disease has been demonstrated (Sibbit et al., 1997; Davie et al., 1995; Friedman et al., 1998). The NAA/Cr ratio was negatively correlated to the degree of atrophy in SLE patients, suggesting that cerebral atrophy in SLE is associated with neuronal damage (Sibbit et al., 1994; Chinn et al., 1997).

Decreased NAA/Cr ratio was found in white matter lesions of patients with NPSLE with no correlation with neurologic or psychiatric involvement (Davie et al., 1995). Patients with white matter lesions also had a more pronounced reduction in NAA/Cr ratio, when compared with patients without lesions, suggesting that neuropsychiatric manifestations are associated with a complex multifocal and diffuse neurotoxic process (Brooks et al., 1999). Cerebrovascular abnormalities with small vessel injury, that underlie diffuse cerebral injury in SLE, (small focal lesions), are primarily associated with a decrease NAA/Cr ratio, while medium vessel injury is primarily associated with an increased Cho/Cr ratio (Friedman et al., 1998). It is well known that small focal lesions are also observed in healthy adults, often associated with older age. However, if neurometabolic changes are observed within these lesions, it could be inferred that these white matter lesions represent a serious pathologic process resulting in focal neuronal death or injury (Brooks et al., 1997).

The amount of reduction in NAA/Cr ratio is associated with disease activity and the severity of clinical manifestations (Sibbit et al., 1997). The same group failed to demonstrate lactate even in severely ill patients with major NPSLE, suggesting that extensive anaerobic metabolism is not a fundamental characteristic of NPSLE, although this was contraindicated by others (Sundgren et al., 2005). They also found that increased lipid-macromolecules peaks at 1,2 ppm is an indicator of disease activity representing inflammatory cell infiltration, membrane activation, degradation or demyelination. Appenzeller and co-workers (Appenzeller et al., 2005) also demonstrated that the reduction in NAA/Cr ratio correlated with disease activity, independently of CNS manifestations, and that NAA/Cr ratio in normal-appearing white matter returned to normal range after remission.

Sabet and co-workers (Sabet et al., 1998) proved that NAA/Cr ratio was lower and Cho/Cr was higher in SLE patients with antiphospholipid antibody syndrome (aPLS) compared to those without aPLS. However thrombotic phenomena are most closely associated with the Cho/Cr ratio elevation in patients with SLE. Elevated Cho/Cr ratio was observed in focal lesions and normal-appearing tissues of patients with SLE-aPLS consistent with infarct, activation of cellular membranes, catabolism of myelin, or inflammation. Cho/Cr ratio was increased in normal-appearing tissues, suggesting exaggerated injury to normal-appearing tissue in patients with SLE-aPLS consistent with widespread microinfarction.

Reduction of NAA/Cr ratio and elevation of Cho/Cr ratio seem to reflect the cerebral metabolic disturbance related to the severity of neuropsychiatric symptoms regardless of the presence of abnormal MRI findings (Lim et al., 2000). In that study metabolic changes at the basal ganglia, besides the normal appearing white matter, was also found, indicating small vessel injury. Reduction of NAA/Cr ratio and elevation of Cho/Cr ratio in normal appearing white matter, related to the severity of neuropsychiatric symptoms was also proved by others (Axford et al., 2001; Handa et al., 2003; Castellino et al., 2005). Axford and co-workers also performed quantitative absolute assessment of the metabolites and found

increased absolute concentration of mI in NPSLE patients symptoms, that could be the result of inflammation, with a trend to be reversible in patients with minor. The authors suggest that raised mI, but normal NAA, that characterized SLE minor, may be due to result of vasculitis and inflammatory sequelae, which may be reversible if treated early enough. In contrast with the patients with SLE minor, the patients with SLE major had both increased mI and decreased NAA that may reflect gliosis and irreversible neuronal loss.

Castellino and co-workers (Castellino et al., 2005) assessed metabolites at hypoperfused and normoperfused brain areas according to SPECT finding and found that NAA/Cr ratio was reduced in hypoperfused areas, and Cho/Cr ratio was elevated in normoperfused areas, while new white matter lesions were developed on previous areas of hypoperfusion and NAA/Cr ratio reduction indicating that increased Cho/Cr ratio in normal-appearing white matter may predict the appearance of white matter lesions.

The NAA reduction has been also correlated with cognitive dysfunction and extent of brain damage (Sibbit et al., 1997; Lim et al., 2000). Increased choline was also associated with the presence of cognitive dysfunction in patients with SLE (Kozora et al., 2005) a finding that was further proved by other studies (Lapteva et al., 2006; Filley et al., 2009). Significant correlation was found between cognitive scores and higher Cho/Cr ratio of the dorsolateral prefrontal cortex and white matter (Lapteva et al., 2006) or the left frontal white matter (Filley et al., 2009).

A recent study (Brooks et al., 2010) investigated most-mortem histopathological changes at autopsy in NPSLE patients and matched them voxel-by-voxel with the neurometabolites. They found that neurometabolite abnormalities were closely associated with underlying histopathological changes in the brain. Elevated choline levels were independently associated with gliosis, vasculopathy, and edema, while reduced creatine levels were associated with reduced neuronal-axonal density and gliosis. Reduced NAA levels were associated with reduced neuronal-axonal density and the presence of lactate was associated with necrosis, microhemorrhages, and edema. They suggest that altered neurometabolites in NPSLE patients, as determined by MRS, are a grave prognostic sign, indicating serious underlying histologic brain injury.

Few studies incorporated a multisequence MRI approach in patients with NPSLE to investigate the relationship between the different non-conventional MRI techniques. Emmer and co-workers (Emmer et al., 2008) applied MTI and MRS in SLE and NPSLE patients and healthy controls and found that there was significant association between the MTR histogram peak height of the whole brain parenchyma and the white and gray matter and the NAA/Cr ratio, indicating that demyelination and neuronal/axonal damage often occur together in patients with a history of NPSLE. The Cho/Cr ratio showed no significant association with any MTR parameters. According to another study that investigated the relationship between magnetization transfer imaging (MTI), diffusion weighted imaging (DWI), proton magnetic resonance spectroscopy (H-MRS), and T2 relaxometry findings in patients with primary neuropsychiatric systemic lupus erythematosus (NPSLE) (Bosma et al., 2004), significant correlations were found between the different metrics and cerebral atrophy. The correlations between MTI and DWI parameters indicate that demyelination in NPSLE patients is associated with increased diffusivity, due to either to a breakdown of myelin or a discrete increase of CSF spaces-including perivascular changes-associated with cerebral atrophy. The association between prolonged T2 relaxation time and increased diffusivity could be based not only on atrophy, but also on the presence of gliosis.

## 5. Conclusion

NPSLE is characterized by variable, focal or diffuse, neuropsychiatric symptoms, leading to significant morbidity and mortality. NPSLE manifestations can occur in the absence of either serologic activity or other systemic lupus manifestations and there is no single sensitive and specific diagnostic test. Thus, in clinical practice the diagnosis of primary NPSLE is rather presumptive, after the exclusion of alternative causes of the neuropsychiatric symptoms. In patients with focal symptoms conventional MRI commonly detects small, discrete, hyperintense, frontal-parietal subcortical or periventricular white matter lesions, or even microhemorrhages, which are not specific for NPSLE and exhibit no clinical correlation. In diffuse NPSLE presentation conventional MRI could be totally unremarkable.

Non-conventional MRI techniques, namely diffusion weighted imaging (DWI), diffusion tensor imaging (DTI), perfusion weighted imaging (PWI), Magnetization transfer imaging (MTI) and magnetic resonance spectroscopy (MRS) have been developed. These techniques are sensitive to microstructural (DWI, DTI, MTI), hemodynamic (PWI) and biochemical (MRS) characteristics of the tissues, and could detect gray and white matter abnormalities in NPSLE patients, otherwise occult by conventional imaging. Vasculopathy is the most common pathologic finding in NPSLE, while true vasculitis is rather uncommon. SLE vasculopathy affects predominantly arterioles and capillaries and could be related to both acute inflammation and hypoperfusion resulting in ischemia, demyelination, axonal loss and gliosis. These pathologic findings lead to particular changes of the non-conventional MRI metrics, such as reduced increased diffusivity, decreased fractional anisotropy, decreased MTR values, decreased NAA levels, and elevated choline levels, not only in focal lesions but mostly in normal appearing white and gray matter in patients with NPSLE. These quantitative changes are related to disease activity and severity, cognitive performance, and also the presence of antiphospholipid antibody syndrome and/or anticardiolipin antibodies, while could affect with the prognosis of new lesions and clinical deterioration. Although there are some inconsistencies in the various reports published thus far reflecting heterogeneity in patient selection, sample size and diagnostic criteria used, we believe that there is enough data to support the use in daily clinical practice at tertiary care centers of non-conventional MRI techniques for the diagnostic work up of SLE patients with neuropsychiatric manifestations. For places whereby these modalities are not available the EULAR guidelines recommend at a minimum an MRI protocol (brain and spinal cord) that includes conventional MRI sequences (T1/T2, FLAIR), diffusion-weighted imaging (DWI), and gadolinium-enhanced T1 sequences (Bertsias et al., 2010).

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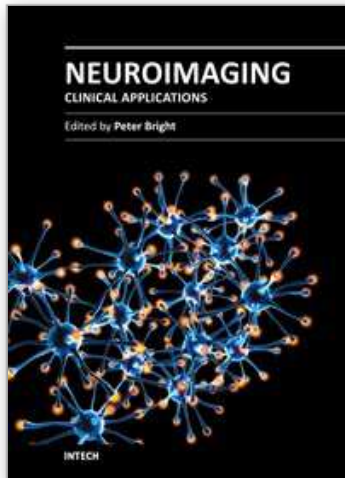
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

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