Send Orders for Reprints to reprints@benthamscience.net

178 *Current Cardiology Reviews,* **2020**, *16,* **178-186**

REVIEW ARTICLE

Combined Brain/Heart Magnetic Resonance Imaging in Systemic Lupus Erythematosus

Sophie Mavrogeni[1,*], Loukia Koutsogeorgopoulou[2], Theodoros Dimitroulas[3], George Markousis-Mavrogenis[1], Kyriaki Boki[4], Gikas Katsifis[5], Vasiliki Vartela[1], Cees G. Kallenberg[6], Genovefa Kolovou[1] and George Kitas[7]

[1]Onassis Cardiac Surgery Center, Athens, Greece; [2]Department of Pathophysiology, Laikon Hospital, Athens, Greece; [3]4th Department of Internal Medicine, School of Medicine, Hippokration Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece; [4]Sismanoglion Hospital, Athens, Greece; [5]Naval Hospital, Athens, Greece; [6]Department of Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [7]Arthritis Research UK Epidemiology Unit, Manchester University, Manchester, M13 9PL, UK

Abstract: Cardiovascular Disease (CVD) in Systemic Lupus Erythematosus (SLE) and Neuropsychiatric SLE (NPSLE) has an estimated prevalence of 50% and 40%, respectively and both constitute major causes of death among SLE patients. In this review, we proposea combined brain/heart Magnetic Resonance Imaging (MRI) for SLE risk stratification has been proposed.

The pathophysiologic background of NPSLE includes microangiopathy, macroscopic infarcts and accelerated atherosclerosis. Classic brain MRI findings demonstrate lesions suggestive of NPSLE in 50% of the NPSLE cases, while advanced MRI indices can detect pre-clinical lesions in the majority of them, but their clinical impact still remains unknown. Cardiac involvement in SLE includes myo-pericarditis, valvular disease/endocarditis, Heart Failure (HF), coronary macro-microvascular disease, vasculitis and pulmonary hypertension. Classic and advanced Cardiovascular Magnetic Resonance (CMR) indices allow function and tissue characterization for early diagnosis and treatment follow-up of CVD in SLE.

Although currently, there are no clinical data supporting the combined use of brain/heart MRI in asymptomatic SLE, it may have a place in cases with clinical suspicion of brain/heart involvement, especially in patients at high risk for CVD/stroke such as SLE with antiphospholipid syndrome (SLE/APS), in whom concurrent cardiac and brain lesions have been identified. Furthermore, it may be of value in SLE with multi-organ involvement, NPSLE with concurrent cardiac involvement, and recent onset of arrhythmia and/or heart failure.

ARTICLE HISTORY

Received: April 01, 2019
Revised: July 08, 2019
Accepted: July 19, 2019

DOI:
10.2174/1573403X15666190801122105

Keywords: Magnetic resonance imaging, systemic lupus erythematosus, brain lesions, cardiovascular disease, neuropsychiatric symptoms, cognitive dysfunction.

1. INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic, multisystem autoimmune disorder, causing inflammation, tissue injury and organ dysfunction. Fatigue, fever, and weight loss are typically present during the course of the disease, occurring in 50 to 100% and joint symptoms in >90% of the SLE patients at some time during the disease course. The skin and/or mucous membranes are involved in >80% of the SLE patients, ranging from the classic butterfly rash to fixed lesions that may be associated with scarring and atrophy. Self-reported skin color changes consistent with Raynaud phenomenon occur in 16 to 40% of the SLE patients. Lupus Nephritis (LN) may develop in up to 75% of the SLE patients and is higher in blacks (34-51%), Hispanics (31-43%), and Asians (33-55%) than in whites (14-23%). The gastrointestinal tract is often involved, mainly due to the side effects of medication. SLE vasculitis can lead to pancreatitis, peritonitis, colitis and esophageal irritation. Liver abnormalities and a positive ANA test are more consistent with chronic active hepatitis, as part of polyautoimmunity (*i.e.*, "lupoid hepatitis"). Pleurisy, pleural effusion, pneumonitis, interstitial lung disease, pulmonary hypertension and alveolar hemorrhage can all occur in SLE. Furthermore, SLE patients frequently develop abnormalities in one or more of the blood cell lines and also leukopenia [1]. Finally, SLE is also associated with Metabolic Syndrome (MetS). SLE patients with MetS have higher Health Assessment Questionnaire (HAQ)

*Address correspondence to this author at the Onassis Cardiac Surgery Center, FESC, 50 Esperou Street, 175-61 P. Faliro, Athens, Greece; Tel/Fax: +30-210-98.82.797; E-mail: soma13@otenet.gr

1573-403X/20 $65.00+.00

scores, major organ involvement, age and disease duration [1].

Our aim in this review was to describe the pathophysiologic background of brain/heart involvement in SLE, present the diagnostic power of Magnetic Resonance Imaging (MRI) and emphasize the potential role of a combined brain/heart MRI evaluation in risk stratification of SLE patients.

At the moment, there are no universally accepted methods for diagnosing neuropsychiatric SLE (NPSLE) and clinical assessment represents the cornerstone for the diagnosis of these patients [2, 3]. Therefore, NPSLE remains a major diagnostic challenge, after ruling out other possible causes such as trauma, infection, drug effects, epilepsy, migraine, psychiatric disorders, multiple sclerosis, posterior reversible encephalopathy and previous nervous system disorders [4-6]. According to the 1999 American College of Rheumatology (ACR) Case Definitions for NPSLE, 19 neuropsychiatric syndromes were defined, divided into 12 central and 7 peripheral [7]. The central manifestations are divided into neurologic (aseptic meningitis, cerebrovascular disease, migraine, demyelinating syndrome, benign intracranial hypertension, movement disorders, myelopathy, epilepsy), and psychiatric (acute confusional states, anxiety disorder, cognitive dysfunction, affective disorder), while the peripheral syndromes include acute inflammatory demyelinating polyradiculopathy (Guillain-Barre syndrome), autonomic disorder, mononeuropathy (single/multiplex), myasthenia gravis, cranial neuropathy, plexopathy and polyneuropathy. It is also divided into primary, due to SLE specific mechanisms, and secondary, which is the result of infections, drugs or metabolic abnormalities [3]. The pathophysiologic background of NPSLE includes:

a) Microangiopathy (the most frequent neuropathological finding, typically multifocal, due to intimal hyperplasia, erythrocyte extravasation and fibrin thrombi) [8],

b) Macroscopic infarcts (potentially due to secondary coagulopathy, as in antiphospholipid syndrome or embolic lesions, as in Libman-Sacks endocarditis) [8],

c) Accelerated atherosclerosis (either due to steroid treatment, or vasculitis and microhemorrhages), direct immune mediated alterations, demyelination and microembolisms [9-12].

Anti-ribosomal P antibodies have been associated with lupus psychosis and depression by some authors [13], but other authors have not confirmed this association. Some data suggest that cognitive defects may be associated with the presence of elevated levels of antineuronal antibodies, antiphospholipid antibodies, or antibodies to N-methyl-D-aspartate (NMDA) receptors [14].

Cardiovascular Disease (CVD) is also an important contributor to increased mortality in SLE [15, 20], as it has been documented by the high incidence of myocardial infarction in young women with SLE [16]. CVD in SLE occurs as a result of a complex interaction between traditional CVD risk factors, disease activity and immune dysregulation. A systemic review and meta-analysis of 17,187 SLE patients after a follow-up period of 8 years showed that CVD events occurred in 25.4%. In addition, male gender, hyperlipidaemia, family history of CVD and hypertension, as well as SLE-related factors such as the presence of autoantibodies and neurological disorders, predicted myocardial infarction and stroke occurrence. A low correlation was shown between the severity of organ damage and SLE activity, as well as the age at diagnosis [17]. Furthermore, myocardial infarction leading to Heart Failure (HF) occurs 3 times more frequently in SLE patients than in age- and sex-matched controls [18]. Traditional CVD risk factors are common in SLE patients [19]; however, they cannot explain the increased frequency of CVD, found in SLE [20, 21]. Longer disease duration, elevated C-Reactive Protein (CRP) levels and antiphospholipid antibody (aPL) positivity have been proved as significant factors, associated with high incidence of CVD in SLE in the LUMINA study - a multiethnic SLE cohort study [22]. Finally, adequate disease control is required to reduce CVD morbidity/mortality in SLE [23]. Cardiac involvement in SLE presents with various clinical phenotypes including myo-peri-carditis, valvular disease, aseptic endocarditis (known as Libman-Sacks endocarditis), Heart Failure (HF), coronary macro- micro-vascular disease, vasculitis and pulmonary hypertension. All these entities may contribute to increased CVD morbidity and mortality in SLE patients [15-17].

The probability of surviving 5 years after the diagnosis of SLE increased from <50% in the 1950s to 95% in most recent studies [2]. Nonetheless, Standardized Mortality Ratios (SMRs) for SLE patients remain 2-4-fold higher as compared to the general population. In the Hopkins Lupus Cohort, survival probabilities were 95%, 91%, 85%, and 78% at 5, 10, 15, and 20 years after diagnosis, respectively [2]. After the introduction of corticosteroids and immunosuppressive drugs turned SLE from a rapidly-fatal into a chronic disease, the distribution of the major causes of death began to change. In the late 1970s, it was reported that deaths occurring within 2 years of diagnosis were due to active disease, while those occurring after disease duration ≥ 5 years were attributable to vascular diseases. Infections remained a major cause of death throughout the course of the disease. Such a bimodal distribution of the causes of death has been reported in several large series from the USA, Canada, Denmark, and other European countries, but also from Mexico and Martinique [24-28].

The outcome of SLE patients has improved significantly during the last decades. However, both cardiac and neuropshychiatric involvement are included in the 4 most important causes of morbidity-mortality [1]. Although the real prevalence of Neuropsychiatric SLE (NPSLE) and Cardiovascular Disease (CVD) in SLE remains unknown, with significant heterogeneity between studies depending on the inclusion criteria, a percentage of 40% and 50%, respectively, is widely accepted [1].

The judgment of whether a patient with SLE is better or worse is a crucial question in patient management. For this purpose, various indices such as British Isles Lupus Assessment Group (BILAG) index and BILAG-2004, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Systemic Lupus Activity Measure (SLAM) index have been successfully used. There was a good agreement between

these indices in distinguishing flares and their absence. However, there is much less consistency in distinguishing mild to moderate flares. After the failure of various clinical trials of biologic therapy in SLE, the management of SLE in our days remains an art rather than science. Pitfalls in SLE disease activity measurements have a significant impact on the interpretation of studies about treatment efficacy. This emphasizes the need for improving the current indices by adding more objective measurements that should be simple, reliable and valid [29].

Magnetic resonance imaging is a noninvasive modality without radiation that can give objective, reproducible and operator-independent information about disease activity in vital organs such as the brain and the heart that are considered as major contributors for the increased mortality in SLE. Our aim in this review was to describe the pathophysiologic background of the SLE lesions in brain/heart, present the diagnostic power of MRI in their assessment and emphasize the potential role of a combined brain/heart MRI evaluation in risk stratification of SLE patients.

2. COMBINED BRAIN AND HEART INVOLVEMENT IN SLE

Although both CVD and NPSLE have been mentioned as major causes of death in SLE, there are only a few reports presenting simultaneous involvement of heart/brain in SLE, specifically in cases with Libman-Sacks endocarditis [30]. A combined brain/heart evaluation has been proposed by our team in cases with clinical suspicion of brain/heart involvement, especially in those at high risk for CVD/stroke such as SLE/APS [31]. However, this combined assessment of brain/heart is not a part of the routine diagnostic algorithm for SLE.

3. MAGNETIC RESONANCE IMAGING OF THE BRAIN

Magnetic Resonance Imaging (MRI) is the gold standard for brain evaluation. The role of Computer Tomography (CT) is currently restricted to rule out acute complications such as hemorrhage or large infarcts [32, 33]. However, the large spectrum of neurologic findings in NPSLE made the neuroradiologic findings nonspecific [34]. The most frequent findings of conventional MRI in NPSLE were multiple small white-matter lesions (30-75%) and cortical atrophy (15-20%), but the large majority of SLE patients (25-60%) has a normal MRI scan [35, 36]. Advanced MRI techniques including diffusion-tensor, magnetization-transfer and volumetric studies offer micro-structural and functional information that could reveal subtle brain changes and allow a better understanding of the NPSLE mechanisms. The conventional MRI is normal in 50% of the NPSLE patients, mainly in diffuse syndromes such as headache, mood disorder, and psychiatric disease [3]. In the other half of the patients, the most common findings can be classified as vascular and inflammatory lesions.

Vascular lesions, although nonspecific, are the main findings of NPSLE [3]. They are defined as hyperintense areas on T2 (Fig. **1**), and moderately hypointense or isointense areas on T1 images. Large vessel disease presents as large infarcts, roughly wedge-shaped, occurring in a vascular territory distribution, involving both grey and white matter. Diffusion-Weighted Imaging (DWI) can potentially determine if they are in the acute, subacute or chronic phase. Large vessel infarcts are found in 10-15% of patients and at a mean age of 35-40 years [35, 37, 38]. When infarcts occur in NPSLE, there is a tendency to a high recurrence of ischemic events [3]. The middle cerebral artery is mainly involved, as in the general population [3]. A stroke recurrence of around 50% was reported in SLE patients with positive antiphospholipid antibodies [35, 37, 39].

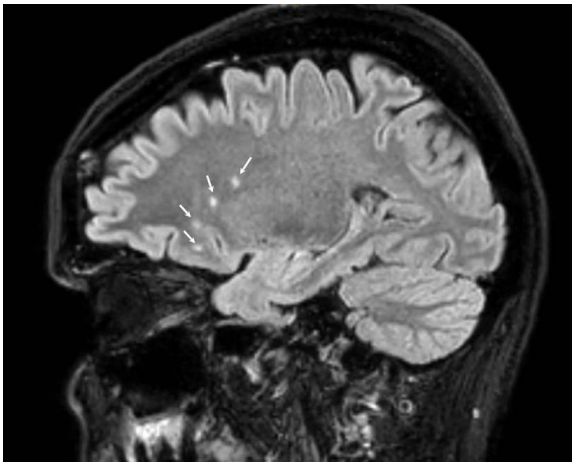

Fig. (1). Flair T2 image showing silent brain lesions in an SLE patient. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Small vessel disease is characterized by lesions <1 cm following the distribution of the white matter (periventricular, deep, subcortical). The MRI findings include white-matter hyperintense areas, recent small subcortical infarcts, lacunes, microbleeds and brain atrophy [40]. They are characterized as small hyperintense areas on T2 and FLAIR sequences, without cavitation [40, 41]. The differential diagnosis of white matter hyperintensities (WMH) includes many conditions including ageing, dyslipidemia, diabetes, hypertension, heart diseases and migraine [40]. However, many reports have already proved an increased frequency of WMH in SLE and NPSLE [42-49]. They involve preferentially the frontal and parietal lobes, re consistent with an anterior to a posterior gradient, similar to other causes of WMH, but different from inflammatory demyelinating diseases such as multiple sclerosis [3, 50]. In a quantitative brain MRI assessment, Appenzeller *et al*. [47] showed that age, duration of neuropsychiatric symptoms and cumulative corticosteroid dosage were independent predictors for WMH in SLE. In a recent study in newly diagnosed SLE, WMH were found in 8% of them [51]. Nevertheless, these lesions were observed more frequently in NPSLE as compared to non NPSLE, ranging from 40-60% [3, 49, 51, 52]. WMH were associated with cerebrovascular disease, cognitive dysfunction, seizures, antiphospholipid antibodies, low complement, age, disease duration, and cumulative corticosteroid dose [8, 46]. Previous reports demonstrated a significant association of both NPSLE activity (Neuro-SLEDAI) and injury (Neuro-SLICC) scores with WMH number [47, 49, 51, 53]. Furthermore, new lesions were found at the onset of NPSLE and

showed resolution after clinical improvement [54, 55]. Quantitative methods are increasingly proposed for the assessment and follow-up of the WMH in NPSLE, as they can be used as an independent predictor for NPSLE activity and treatment response [47, 51].

Recent small subcortical infarcts, known as lacunar infarcts are usually observed in the territory of perforating arterioles of less than 20 mm in maximum diameter with imaging or clinical signs indicative of a recent lesion [40]. They may present an evolution into lacunes, WMH without cavitation, or disappear. Lacunes in NPSLE were found with a prevalence of 11.5-16%, higher than in the general population [3]. Cerebral microbleeds are small (usually 2-5 mm) round or oval areas of the signal void with associated blooming on paramagnetic-sensitive sequences such as T2*-weighted Gradient Recalled Echo (GRE) or Susceptibility-Weighted Images (SWI). In NPSLE, microbleeds were found in 14.5% of the patients on GRE/SWI sequences, and were correlated with antiphospholipid antibodies [3].

Cortical atrophy is a generalized enlargement of peripheral cerebrospinal fluid spaces and is best evaluated on volumetric 3D-T1 or FLAIR images. Brain atrophy occurs more frequently in the presence of small vessel disease, such as WMH, high lesion burden, lacunes and microbleeds [3]. Brain atrophy was also correlated with lupus anticoagulant, low complement, longer disease duration, cognitive dysfunction and cerebrovascular disease [35, 49]. The atrophy might be the result of prednisone use [49], or due to other mechanisms [43, 51, 52].

Less frequently, some NPSLE patients show inflammatory-type lesions, described as the hyperintense area on T2 and FLAIR, involving the grey and white matter, generally medium or large-sized, some of them with contrast enhancement or diffusion restriction, without vascular territory distribution. They are reported in 5-10% of the SLE patients, correlated with low complement levels and resolved after aggressive corticosteroid treatment [53].

Myelitis, an inflammatory disease of the central nervous system, is one of the most debilitating complications of NPSLE and occurs in 1-5% of the SLE patients. It develops early in the course of the disease and associates with a worse outcome. In 39% of the SLE patients, myelopathy constitutes the presenting symptom of SLE, and in another 42%, it occurs during the first 5 years of post diagnosis. The commonest MRI pattern in SLE myelitis is transverse myelitis: commonly affecting more than 2-3 vertebral bodies in length [53].

4. ADVANCED MRI TECHNIQUES

Up to 40-50% of the NPSLE patients have no brain abnormalities on conventional MRI [3]. However, advanced MRI sequences in NPSLE demonstrated underlying abnormalities in normal-appearing white and grey matter, proving the limitations of conventional sequences. Recent studies used advanced MRI in NPSLE, as voxel-based morphometric techniques [50, 53], diffusion-tensor imaging [53], magnetization transfer imaging [54], magnetic resonance spectroscopy and perfusion MRI [54].

Voxel-based Morphometry (VBM) allows the detection of focal differences and brain atrophy and can assess differences between brain areas and hemispheres. Morphometric studies showed that decreased whole brain volume with increased lateral ventricle volume and both global gray and white matter atrophy are present in SLE patients, but not in healthy controls [55]. The macroscopic lesions of the cortical gray matter might be more important to identify NPSLE patients than the micro- or macrostructural damage in the white matter [54], although an association of NPSLE with both cortical and central atrophy was also observed [53-55].

Diffusion-Tensor Imaging (DTI) is based on the measurement of water diffusion through cellular compartments and provides better resolution than conventional sequences regarding white matter microstructure [56, 57]. Compared to the more isotropic movement of water in gray matter, the diffusion in white matter presents higher anisotropy, with preferential diffusion along the length of the axon, which is due to the well-structured axonal membranes and their myelin sheaths. The diffusion can be quantified by the following parameters: Apparent Diffusion Coefficient (ADC), Fractional Anisotropy (FA), Mean Diffusivity (MD), Radial Diffusivity (RD) and Axial Diffusivity (AD). FA is a measure of myelination and axonal integrity, and MD, a measure of molecular motion. High FA and low MD suggest greater myelination and axonal integrity. Previous studies found changes in various DTI indices in SLE and NPSLE patients, in relation to important microscopic injury of the white matter [58]. In SLE patients, white matter injury in frontal lobes, corpus callosum, and thalamus has been found [59-61]. FA values were reported to be lower and MD values to be higher in the brain of NPSLE patients than in healthy controls. Increased AD of white matter was also correlated with NPSLE, as compared to healthy populations. Very recent publications underline the role of DTI as an imaging biomarker of NPSLE [62].

Magnetization Transfer Imaging (MTI) is based on the interaction between free water protons and bound protons. The differences in the proton mobility in various macromolecules are used to generate differences in image signal capable to quantify cerebral lesions in different diseases, mainly in multiple sclerosis. Bosma *et al*. [63] compared MTI parameters among 5 groups of patients: active NPSLE, chronic NPSLE, SLE without NPSLE, multiple sclerosis and healthy controls. The magnetization transfer ratio histograms in SLE without NPSLE and healthy controls were similar, whereas those in chronic NPSLE and multiple sclerosis groups were flattened. The active NPSLE patients also showed flattening of the histograms, but with a higher magnetization transfer ratio. This suggests that MTI could be used to differentiate active NPSLE from inactive NPSLE and monitor treatment trials in NPSLE. A report combining MTI with Magnetic Resonance Spectroscopy (MRS) found a correlation between brain atrophy and MRS markers of axonal and myelin damage [54]. Studies combining MTI with DWI, MRS and T2 relaxometry suggest common pathogenesis of NPSLE in spite of differences in the neuropsychiatric clinical presentation [53].

MRS allows the analysis of brain metabolites. Different proton groups resonate at different frequencies of the mag-

netic field, which can be demonstrated by MRS as peaks corresponding to different metabolites. N-acetylaspartate (NAA), one of the main MRS markers, is higher in neurons and is considered as a marker of neuronal viability. Glutamate, a non-essential amino acid, is the most important excitatory neurotransmitter and prolonged neuron excitation by glutamate can be toxic to neurons. NAA and glutamine-glutamate changes were demonstrated in the normal-appearing brain in SLE patients before neuro-imaging manifestations became apparent. It seems that these markers predict early cerebral involvement of SLE [64]. Lower NAA was also reported in both SLE and NPSLE, and increased myo-inositol, a marker of gliosis, was considered as a marker of poor prognosis in NPSLE [65].

There are 3 types of perfusion MRI, based on the administration of gadolinium (dynamic susceptibility contrast imaging and dynamic contrast enhanced imaging) or without contrast administration (arterial spin labeled imaging). The main parameters derived are Mean Transit Time (MTT), Time To Peak (TTP), Cerebral Blood Flow (CBF) and Cerebral Blood Volume (CBV). The pathologic patterns include hypoperfusion (high MTT/TTP, low CBF/CBV) and hyperperfusion (low TTP/MTT, high CBV/CBF) [66]. Some studies documented that perfusion in SLE patients was not different from controls [67], while others reported a pattern of hypoperfusion in both SLE and NPSLE [68], or even hyperperfusion in active disease [69].

To conclude, the advanced MRI techniques are able to detect early microstructural brain damage that is not visible on conventional sequences and is expected to facilitate a better understanding of the underlying pathophysiology of cerebral lesions in NPSLE. However, despite MRI being the imaging modality of choice, there are neither diagnostic nor specific radiologic findings for NPSLE. This means that MRI can neither confirm nor exclude the diagnosis of NPSLE. Future longitudinal studies are needed to determine if early changes in NPSLE patients may lead to a higher degree of brain atrophy and to what extent it would be possible to monitor disease progression and treatment response.

5. CARDIOVASCULAR MAGNETIC RESONANCE IMAGING FOR EVALUATION OF CARDIOVASCULAR DISEASE IN SLE

Cardiovascular Magnetic Resonance imaging (CMR) has been already applied in the evaluation of CVD because of its excellent reproducibility and the capability to perform functions and tissue characterisation. Specifically, in SLE, where CVD can be oligo-asymptomatic, CMR is of great value for early diagnosis and treatment follow- up [70]. The main pathophysiologic phenomena occurring in SLE include myocardial inflammation, macro-micro-coronary artery disease, valvular disease, vasculitis and pulmonary hypertension [70].

The CMR sequences that are necessary to clarify the above-mentioned pathophysiologic phenomena include: [71].

a) Steady-State Free Precession Imaging (SSFP) for the evaluation of RV-LV volumes, wall motion and ejection fraction. Although echocardiography is the routinely used modality, CMR represents the gold standard for ventricular function evaluation and is more accurate and preferable compared to all other imaging modalities, specifically in patients with heart failure [72].

b) T2-W imaging (oedema imaging) using STIRT2 to assess recent myocardial involvement and also active myocardial disease, even if the underlying systemic disease is quiescent (Fig. **2**).

c) Early (EGE) and late (LGE) gadolinium-enhanced T1-W imaging is used for the detection of myocardial inflammation and fibrosis, respectively. These indices have been already used for the diagnosis of both autoimmune myocarditis in SLE and also infective myocarditis in non-SLE patients [73, 74]. However, while LGE (Fig. **3**) is the gold standard to detect replacement fibrosis, it is unable to detect diffuse fibrosis, commonly found in SLE [75].

d) T2, T1 mapping and ECV for the quantification of myocardial oedema and diffuse fibrosis, respectively. Native T1 and T2 mapping support the recognition of SLE myocarditis and reflect the response to anti-inflammatory treatment in SLE myocarditis [76]. Furthermore, these techniques can assess the presence of low-grade myocardial inflammation in patients within active disease [77]. Finally, T1 and ECV can detect diffuse myocardial fibrosis, missed by LGE [75].

e) Adenosine stress perfusion CMR for the detection of macro- micro-vascular ischemia (perfusion defects) using first-pass T1 imaging. Myocardial perfusion rate index (MPRI), a stress CMR index of myocardial perfusion, can be reduced in asymptomatic or mildly symptomatic SLE patients [78, 79].

6. WHEN IS THERE A PLACE FOR A COMBINED BRAIN/HEART MRI IN SLE?

MRI is a non-invasive, highly reproducible, non-radiating modality, and therefore it is ideal for the evaluation

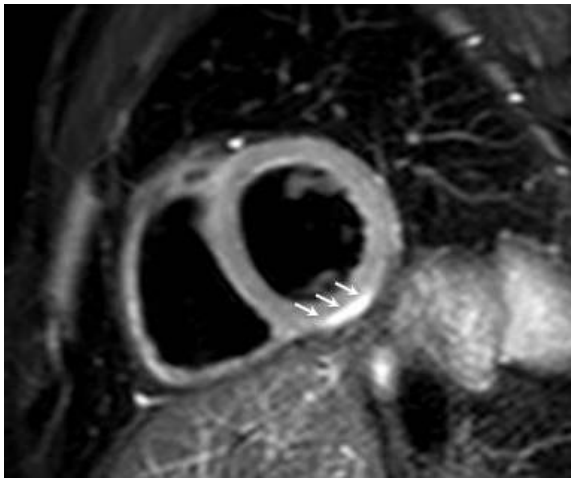

Fig. (2). T2 STIR image showing silent myocardial oedema of the inferior wall of LV (BRIGHT AREA) in the same SLE patient. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

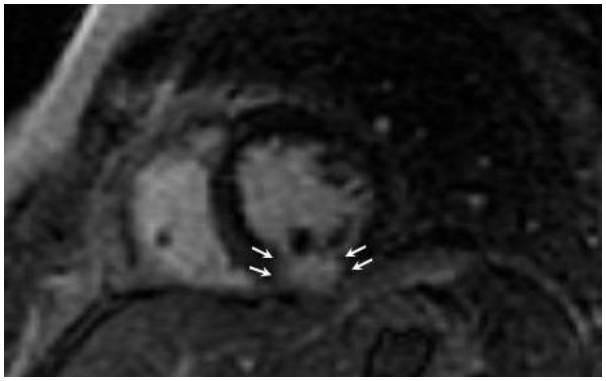

Fig. (3). LGE image presents a transmural myocardial infarction in the inferior wall of LV. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

of systemic diseases with a high prevalence of brain/heart involvement as SLE. Furthermore, there is a correlation between radiographic findings and percentage of apoptotic blood cells in SLE that will potentially introduce apoptotic biomarkers as molecular probes for clinical molecular imaging to early diagnose organ involvement in SLE [80].

Unfortunately, high cost, lack of availability/expertise and awareness among the clinicians about its contribution to SLE risk stratification still do not allow its routine application. On the other hand, rheumatologists are very familiar with the currently used clinical disease indices (SLEDAI, *etc*.) and therefore ask for sophisticated, expensive imaging modalities, such as MRI, only in diagnostic dilemmas. However, considering the limitations of clinical disease indices and the increased cost of hospital admittance for cardiac and neurologic complications, the cost of a combined brain/heart MRI in SLE seems rather reasonable.

To our knowledge, there are no data about the potential therapeutic benefit of an MRI approach in SLE patients, except for one paper by our group supporting the role of CMR in both rheumatic and cardiac medication modification in these patients (30). However, until more clinical data will be available, a combined brain/heart MRI can be potentially proposed if there is a clinical suspicion of either brain and/or heart involvement in SLE patients. In more details, the proposed clinical indications include:

a) Patients at high risk for CVD and stroke such as SLE patients with APS.

b) SLE patients with cardiac involvement, specifically Libmann-Sacks endocarditis. According to our experience (unpublished data), the majority of SLE patients with abnormal CMR findings have also concurrent brain lesions.

c) SLE patients with clinical suspicion of NPSLE.

d) SLE patients with new onset of arrhythmia and/or HF (potential of embolic brain disease, due to coexistence of atrial fibrillation).

e) SLE with aggressive presentation and multiple organ involvement.

A flow chart of a combined brain/heart MRI in SLE is presented in Fig. (**4**).

CONCLUSION

Brain/heart involvement are the major causes of increased morbidity/mortality in SLE. Although at the moment, there are no data supporting the use of a combined brain/heart MRI in asymptomatic SLE patients, this diagnostic approach may be considered, if there is a clinical indica-

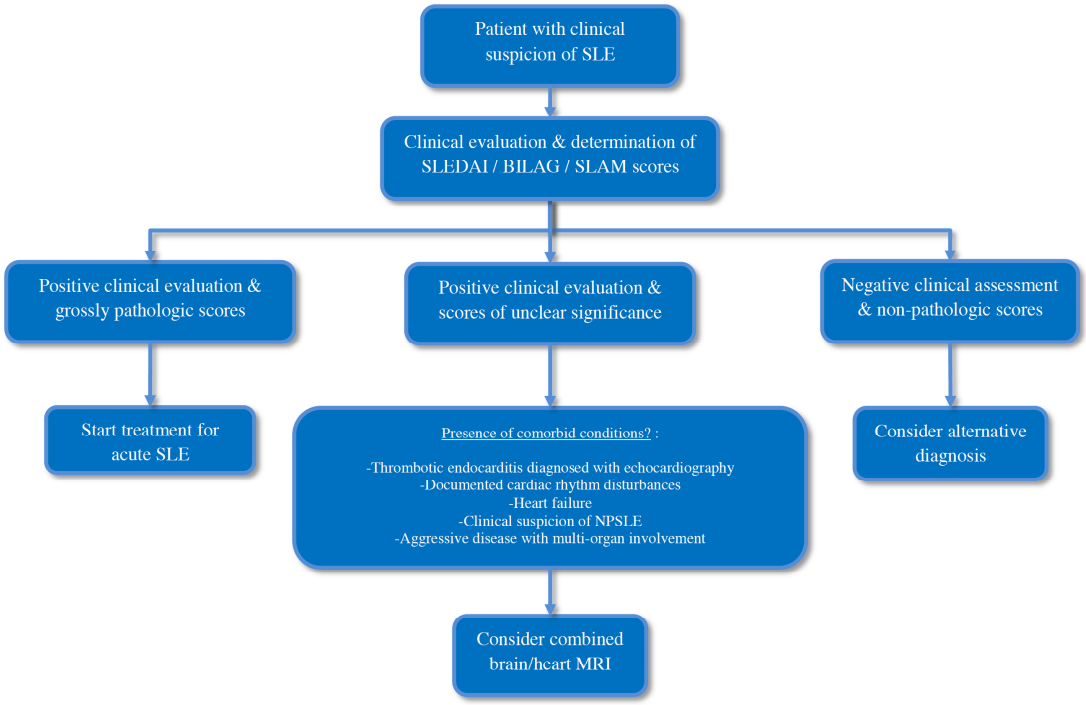

Fig. (4). Flow chart of a combined brain/heart MRI in SLE. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

tion of brain/heart involvement, specifically in those at high risk for CVD/stroke such as SLE with APS. Furthermore, it can be recommended in SLE patients with multiple organ involvement, NPSLE and new onset of heart disease presenting arrhythmia and/or HF.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Doria A, Iaccarino L, Ghirardello A, *et al.* Long-term prognosis and causes of death in systemic lupus erythematosus. Am J Med 2006; 119(8): 700-6. http://dx.doi.org/10.1016/j.amjmed.2005.11.034 PMID: 16887417

[2] Cervera R, Abarca-Costalago M, Abramovicz D, *et al.* Systemic lupus erythematosus in Europe at the change of the millennium: lessons from the "Euro-Lupus Project". Autoimmun Rev 2006; 5(3): 180-6. http://dx.doi.org/10.1016/j.autrev.2005.06.004 PMID: 16483917

[3] Bertsias GK, Ioannidis JP, Aringer M, *et al.* EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: Report of a task force of the EULAR standing committee for clinical affairs. Ann Rheum Dis 2010; 69(12): 2074-82. http://dx.doi.org/10.1136/ard.2010.130476 PMID: 20724309

[4] Luyendijk, J, Steens SC, Ouwendijk WJ. Neuroimaging evidence of white matter inflammation in newly diagnosed systemic lupus erythematosus. Arthritis Rheum 63(3): 722-32.2011;

[5] Ramage AE, Fox PT, Brey RL. Neuroimaging evidence of white matter inflammation in newly diagnosed systemic lupus erythematosus. Arthritis Rheum 63(10): 3048-57.2011; 2011.

[6] Bortoluzzi A, Scire C, Bombardieri S. Development and validation of a new algorithm for attribution of neuropsychiatric events in systemic lupus erythematosus. Arthritis Rheum 2015; 54(5): 891-8.

[7] The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999; 42(4): 599-608. http://dx.doi.org/10.1002/1529-0131(199904)42:4<599::AID-ANR2>3.0.CO;2-F PMID: 10211873

[8] Netto TM, Zimmermann N, Rueda-Lopes F. Neuropsychiatric lupus: Classification criteria in neuroimaging studies. Can J Neurol Sci 2013; 40(3): 284-91.

[9] Ellis SG, Verity MA. Central nervous system involvement in systemic lupus erythematosus: A review of neuropathologic findings in 57 cases, 1955--1977. Semin Arthritis Rheum 1979; 8(3): 212-21. http://dx.doi.org/10.1016/S0049-0172(79)80009-8 PMID: 424765

[10] Sibbitt WL Jr, Brooks WM, Kornfeld M, Hart BL, Bankhurst AD, Roldan CA. Magnetic resonance imaging and brain histopathology in neuropsychiatric systemic lupus erythematosus. Semin Arthritis Rheum 2010; 40(1): 32-52. http://dx.doi.org/10.1016/j.semarthrit.2009.08.005 PMID: 19880162

[11] Sarbu MI, Salman-Monte TC, Rubio Muñoz P, Lisbona MP, Almirall Bernabé M, Carbonell J. Differences between clinical and laboratory findings in patients with recent diagnosis of SLE according to the positivity of anti-dsDNA by the Crithidia luciliae method. Lupus 2015; 24(11): 1198-203. http://dx.doi.org/10.1177/0961203315573852 PMID: 25716418

[12] Fanouriakis A, Boumpas DT, Bertsias GK. Pathogenesis and treatment of CNS lupus. Curr Opin Rheumatol 2013; 25(5): 577-83. http://dx.doi.org/10.1097/BOR.0b013e328363eaf1 PMID: 23836074

[13] Conti F, Alessandri C, Bompane D, *et al.* Autoantibody profile in systemic lupus erythematosus with psychiatric manifestations: A role for anti-endothelial-cell antibodies. Arthritis Res Ther 2004; 6(4): R366-72. http://dx.doi.org/10.1186/ar1198 PMID: 15225372

[14] Omdal R, Brokstad K, Waterloo K, Koldingsnes W, Jonsson R, Mellgren SI. Neuropsychiatric disturbances in SLE are associated with antibodies against NMDA receptors. Eur J Neurol 2005; 12(5): 392-8. http://dx.doi.org/10.1111/j.1468-1331.2004.00976.x PMID: 15804272

[15] Ballocca F, D'Ascenzo F, Moretti C, *et al.* Predictors of cardiovascular events in patients with systemic lupus erythematosus (SLE): A systematic review and meta-analysis. Eur J Prev Cardiol 2014. PMID: 25139772

[16] Bernatsky S, Boivin JF, Joseph L, *et al.* Mortality in systemic lupus erythematosus. Arthritis Rheum 2006; 54(8): 2550-7. http://dx.doi.org/10.1002/art.21955 PMID: 16868977

[17] Gustafsson J, Gunnarsson I, Börjesson O, *et al.* Predictors of the first cardiovascular event in patients with systemic lupus erythematosus - a prospective cohort study. Arthritis Res Ther 2009; 11(6): R186. http://dx.doi.org/10.1186/ar2878 PMID: 20003285

[18] Rosner S, Ginzler EM, Diamond HS, *et al.* A multicenter study of outcome in systemic lupus erythematosus. II. Causes of death. Arthritis Rheum 1982; 25(6): 612-7. http://dx.doi.org/10.1002/art.1780250602 PMID: 7046757

[19] Petri M, Spence D, Bone LR, Hochberg MC. Coronary artery disease risk factors in the Johns Hopkins Lupus Cohort: Prevalence, recognition by patients, and preventive practices. Medicine (Baltimore) 1992; 71(5): 291-302. http://dx.doi.org/10.1097/00005792-199209000-00004 PMID: 1522805

[20] Esdaile JM, Abrahamowicz M, Grodzicky T, *et al.* Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Rheum 2001; 44(10): 2331-7. http://dx.doi.org/10.1002/1529-0131(200110)44:10<2331::AID-ART395>3.0.CO;2-I PMID: 11665973

[21] Rahman P, Urowitz MB, Gladman DD, Bruce IN, Genest J Jr. Contribution of traditional risk factors to coronary artery disease in patients with systemic lupus erythematosus. J Rheumatol 1999; 26(11): 2363-8. PMID: 10555892

[22] Toloza SMA, Uribe AG, McGwin G Jr, *et al.* Systemic lupus erythematosus in a multiethnic US cohort (LUMINA). XXIII. Baseline predictors of vascular events. Arthritis Rheum 2004; 50(12): 3947-57. http://dx.doi.org/10.1002/art.20622 PMID: 15593203

[23] Pons-Estel GJ, González LA, Zhang J, *et al.* Predictors of cardiovascular damage in patients with systemic lupus erythematosus: Data from LUMINA (LXVIII), a multiethnic US cohort. Rheumatology (Oxford) 2009; 48(7): 817-22. http://dx.doi.org/10.1093/rheumatology/kep102 PMID: 19454606

[24] Borchers AT, Keen CL, Shoenfeld Y, Gershwin ME. Surviving the butterfly and the wolf: Mortality trends in systemic lupus erythematosus. Autoimmun Rev 2004; 3(6): 423-53. http://dx.doi.org/10.1016/j.autrev.2004.04.002 PMID: 15351310

[25] Kasitanon N, Magder LS, Petri M. Predictors of survival in systemic lupus erythematosus. Medicine (Baltimore) 2006; 85(3): 147-56. http://dx.doi.org/10.1097/01.md.0000224709.70133.f7 PMID: 16721257

[26] Urowitz MB, Gladman DD, Tom BD, Ibañez D, Farewell VT. Changing patterns in mortality and disease outcomes for patients with systemic lupus erythematosus. J Rheumatol 2008; 35(11): 2152-8. http://dx.doi.org/10.3899/jrheum.080214 PMID: 18793004

[27] Ocampo-Piraquive V, Nieto-Aristizábal I, Cañas CA, Tobón GJ. Mortality in systemic lupus erythematosus: Causes, predictors and interventions. Expert Rev Clin Immunol 2018; 14(12): 1043-53. http://dx.doi.org/10.1080/1744666X.2018.1538789 PMID: 30338717

[28] Anderson E, Nietert PJ, Kamen DL, Gilkeson GS. Ethnic disparities among patients with systemic lupus erythematosus in South Carolina. J Rheumatol 2008; 35(5): 819-25. PMID: 18381790

[29] Mikdashi J, Nived O. Measuring disease activity in adults with systemic lupus erythematosus: The challenges of administrative burden and responsiveness to patient concerns in clinical research. Arthritis Res Ther 2015; 17(1): 183. http://dx.doi.org/10.1186/s13075-015-0702-6 PMID: 26189728

[30] Roldan CA, Gelgand EA, Qualls CR, Sibbitt WL Jr. Valvular heart disease is associated with nonfocal neuropsychiatric systemic lupus erythematosus. J Clin Rheumatol 2006; 12(1): 3-10. http://dx.doi.org/10.1097/01.rhu.0000200378.42836.7f PMID: 16484873

[31] Mavrogeni S, Kitas GD, Lamb HJ, *et al.* Combined brain and heart magnetic resonance imaging in systemic vasculitides: Fiction or real need? Clin Exp Rheumatol 36(2): 152-9.2018;

[32] Sibbitt WL Jr, Sibbitt RR, Griffey RH, Eckel C, Bankhurst AD. Magnetic resonance and computed tomographic imaging in the evaluation of acute neuropsychiatric disease in systemic lupus erythematosus. Ann Rheum Dis 1989; 48(12): 1014-22. http://dx.doi.org/10.1136/ard.48.12.1014 PMID: 2619353

[33] Zardi EM, Taccone A, Marigliano B, Margiotta DP, Afeltra A. Neuropsychiatric systemic lupus erythematosus: Tools for the diagnosis. Autoimmun Rev 2014; 13(8): 831-9. http://dx.doi.org/10.1016/j.autrev.2014.04.002 PMID: 24704869

[34] Castellino G, Govoni M, Giacuzzo S, Trotta F. Optimizing clinical monitoring of central nervous system involvement in SLE. Autoimmun Rev 2008; 7(4): 297-304. http://dx.doi.org/10.1016/j.autrev.2007.11.022 PMID: 18295733

[35] Csépány T, Bereczki D, Kollár J, Sikula J, Kiss E, Csiba L. MRI findings in central nervous system systemic lupus erythematosus are associated with immunoserological parameters and hypertension. J Neurol 2003; 250(11): 1348-54. http://dx.doi.org/10.1007/s00415-003-0223-0 PMID: 14648152

[36] Toledano P, Sarbu N, Espinosa G, Bargalló N, Cervera R. Neuropsychiatric systemic lupus erythematosus: Magnetic resonance imaging findings and correlation with clinical and immunological features. Autoimmun Rev 2013; 12(12): 1166-70. http://dx.doi.org/10.1016/j.autrev.2013.07.004 PMID: 23851139

[37] Mikdashi J, Handwerger B. Predictors of neuropsychiatric damage in systemic lupus erythematosus: Data from the Maryland lupus cohort. Rheumatology (Oxford) 2004; 43(12): 1555-60. http://dx.doi.org/10.1093/rheumatology/keh384 PMID: 15342927

[38] Wardlaw JM, Smith EE, Biessels GJ, *et al.* Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013; 12(8): 822-38. http://dx.doi.org/10.1016/S1474-4422(13)70124-8 PMID: 23867200

[39] Wahlund LO, Barkhof F, Fazekas F, *et al.* A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001; 32(6): 1318-22. http://dx.doi.org/10.1161/01.STR.32.6.1318 PMID: 11387493

[40] Rovaris M, Inglese M, Viti B, *et al.* The contribution of fast-FLAIR MRI for lesion detection in the brain of patients with systemic autoimmune diseases. J Neurol 2000; 247(1): 29-33. http://dx.doi.org/10.1007/s004150050006 PMID: 10701894

[41] Sanna G, Piga M, Terryberry JW, *et al.* Central nervous system involvement in systemic lupus erythematosus: Cerebral imaging and serological profile in patients with and without overt neuropsychiatric manifestations. Lupus 2000; 9(8): 573-83. http://dx.doi.org/10.1191/096120300678828695 PMID: 11035431

[42] Jennings JE, Sundgren PC, Attwood J, McCune J, Maly P. Value of MRI of the brain in patients with systemic lupus erythematosus and neurologic disturbance. Neuroradiology 2004; 46(1): 15-21. http://dx.doi.org/10.1007/s00234-003-1049-2 PMID: 14648006

[43] Appenzeller S, Pike GB, Clarke AE. Magnetic resonance imaging in the evaluation of central nervous system manifestations in systemic lupus erythematosus. Clin Rev Allergy Immunol 2008; 34(3): 361-6. http://dx.doi.org/10.1007/s12016-007-8060-z PMID: 18084729

[44] Katsumata Y, Harigai M, Kawaguchi Y, *et al.* Diagnostic reliability of magnetic resonance imaging for central nervous system syndromes in systemic lupus erythematosus: A prospective cohort study. BMC Musculoskelet Disord 2010; 11: 13. http://dx.doi.org/10.1186/1471-2474-11-13 PMID: 20096132

[45] Appenzeller S, Vasconcelos Faria A, Li LM, Costallat LT, Cendes F. Quantitative magnetic resonance imaging analyses and clinical significance of hyperintense white matter lesions in systemic lupus erythematosus patients. Ann Neurol 2008; 64(6): 635-43. http://dx.doi.org/10.1002/ana.21483 PMID: 19107986

[46] Castellino G, Padovan M, Bortoluzzi A, *et al.* Single photon emission computed tomography and magnetic resonance imaging evaluation in SLE patients with and without neuropsychiatric involvement. Rheumatology (Oxford) 2008; 47(3): 319-23. http://dx.doi.org/10.1093/rheumatology/kem354 PMID: 18218648

[47] Ainiala H, Dastidar P, Loukkola J, *et al.* Cerebral MRI abnormalities and their association with neuropsychiatric manifestations in SLE: A population-based study. Scand J Rheumatol 2005; 34(5): 376-82. http://dx.doi.org/10.1080/03009740510026643 PMID: 16234185

[48] Benedict RH, Shucard JL, Zivadinov R, Shucard DW. Neuropsychological impairment in systemic lupus erythematosus: A comparison with multiple sclerosis. Neuropsychol Rev 2008; 18(2): 149-66. http://dx.doi.org/10.1007/s11065-008-9061-2 PMID: 18521755

[49] Petri M, Naqibuddin M, Carson KA, *et al.* Brain magnetic resonance imaging in newly diagnosed systemic lupus erythematosus. J Rheumatol 2008; 35(12): 2348-54. http://dx.doi.org/10.3899/jrheum.071010 PMID: 18793003

[50] Doubal FN, Dennis MS, Wardlaw JM. Characteristics of patients with minor ischaemic strokes and negative MRI: A cross-sectional study. J Neurol Neurosurg Psychiatry 2011; 82(5): 540-2. http://dx.doi.org/10.1136/jnnp.2009.190298 PMID: 20584742

[51] Sarbu N, Bargalló N, Cervera R. Advanced and conventional magnetic resonance imaging in neuropsychiatric lupus. F1000Res 2015; 4: 162.

[52] Karassa FB, Ioannidis JP, Boki KA, *et al.* Predictors of clinical outcome and radiologic progression in patients with neuropsychiatric manifestations of systemic lupus erythematosus. Am J Med 2000; 109(8): 628-34. http://dx.doi.org/10.1016/S0002-9343(00)00603-3 PMID: 11099682

[53] Xu J, Cheng Y, Chai P, *et al.* White-matter volume reduction and the protective effect of immunosuppressive therapy in systemic lupus erythematosus patients with normal appearance by conventional magnetic resonance imaging. J Rheumatol 2010; 37(5): 974-86. http://dx.doi.org/10.3899/jrheum.090967 PMID: 20231206

[54] Zivadinov R, Havrdová E, Bergsland N, *et al.* Thalamic atrophy is associated with development of clinically definite multiple sclerosis. Radiology 2013; 268(3): 831-41. http://dx.doi.org/10.1148/radiol.13122424 PMID: 23613615

[55] Appenzeller S, Carnevalle AD, Li LM, Costallat LT, Cendes F. Hippocampal atrophy in systemic lupus erythematosus. Ann Rheum Dis 2006; 65(12): 1585-9. http://dx.doi.org/10.1136/ard.2005.049486 PMID: 16439436

[56] Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G. Diffusion tensor MR imaging of the human brain. Radiology 1996; 201(3): 637-48. http://dx.doi.org/10.1148/radiology.201.3.8939209 PMID: 8939209

[57] Le Bihan D. Looking into the functional architecture of the brain with diffusion MRI. Nat Rev Neurosci 2003; 4(6): 469-80. http://dx.doi.org/10.1038/nrn1119 PMID: 12778119

[58] Schmidt-Wilcke T, Cagnoli P, Wang P, *et al.* Diminished white matter integrity in patients with systemic lupus erythematosus. Neuroimage Clin 2014; 5: 291-7. http://dx.doi.org/10.1016/j.nicl.2014.07.001 PMID: 25161895

[59] Kozora E, Filley CM. Cognitive dysfunction and white matter abnormalities in systemic lupus erythematosus. J Int Neuropsychol Soc 2011; 17(3): 385-92. http://dx.doi.org/10.1017/S1355617711000191 PMID: 21338548

[60] Zhang L, Harrison M, Heier LA, *et al.* Diffusion changes in patients with systemic lupus erythematosus. Magn Reson Imaging 2007; 25(3): 399-405. http://dx.doi.org/10.1016/j.mri.2006.09.037 PMID: 17371731

[61] Lee SP, Wu CS, Hsieh LC, Cheung WK, Chou MC. Efficacy of magnetic resonance diffusion tensor imaging and three-dimensional fiber tractography in the detection of clinical manifestations of central nervous system lupus. Magn Reson Imaging 2014; 32(5): 598-603.
http://dx.doi.org/10.1016/j.mri.2014.02.005 PMID: 24629511

[62] Jones JT, DiFrancesco M, Zaal AI, *et al.* Childhood-onset lupus with clinical neurocognitive dysfunction shows lower streamline density and pairwise connectivity on diffusion tensor imaging. Lupus 2015; 24(10): 1081-6.
http://dx.doi.org/10.1177/0961203315572718 PMID: 25701565

[63] Bosma GP, Rood MJ, Huizinga TW, de Jong BA, Bollen EL, van Buchem MA. Detection of cerebral involvement in patients with active neuropsychiatric systemic lupus erythematosus by the use of volumetric magnetization transfer imaging. Arthritis Rheum 2000; 43(11): 2428-36.
http://dx.doi.org/10.1002/1529-0131(200011)43:11<2428::AID-ANR9>3.0.CO;2-H PMID: 11083265

[64] Cagnoli P, Harris RE, Frechtling D, *et al.* Reduced Insular Glutamine and N-acetylaspartate in systemic lupus erythematosus: A single-voxel (1)H-MR spectroscopy study. Acad Radiol 2013; 20(10): 1286-96.
http://dx.doi.org/10.1016/j.acra.2013.07.011 PMID: 24029061

[65] Guillen-Del Castillo A, Alonso J, Martínez-Valle F, *et al.* Increased myo-inositol in parietal white and gray matter as a biomarker of poor prognosis in neuropsychiatric lupus: A case report. Lupus 2014; 23(10): 1073-8.
http://dx.doi.org/10.1177/0961203314534303 PMID: 25118052

[66] Sarbu N, López-Rueda A, Chirife O, Capurro S. CT-perfusion time-maps likely disclose the earliest imaging signs of posterior reversible encephalopathy syndrome (PRES). J Neuroradiol 2014; 41(2): 147-9.
http://dx.doi.org/10.1016/j.neurad.2013.08.003 PMID: 24075649

[67] Emmer BJ, van Osch MJ, Wu O, *et al.* Perfusion MRI in neuropsychiatric systemic lupus erthemathosus. J Magn Reson Imaging 2010; 32(2): 283-8.
http://dx.doi.org/10.1002/jmri.22251 PMID: 20677252

[68] Zimny A, Szmyrka-Kaczmarek M, Szewczyk P, *et al. In vivo* evaluation of brain damage in the course of systemic lupus erythematosus using magnetic resonance spectroscopy, perfusion-weighted and diffusion-tensor imaging. Lupus 2014; 23(1): 10-9.
http://dx.doi.org/10.1177/0961203313511556 PMID: 24192079

[69] Wang PI, Cagnoli PC, McCune WJ, *et al.* Perfusion-weighted MR imaging in cerebral lupus erythematosus. Acad Radiol 2012; 19(8): 965-70.
http://dx.doi.org/10.1016/j.acra.2012.03.023 PMID: 22608862

[70] Mavrogeni S, Koutsogeorgopoulou L, Markousis-Mavrogenis G, *et al.* Cardiovascular magnetic resonance detects silent heart disease missed by echocardiography in systemic lupus erythematosus. Lupus 2018; 27(4): 564-71.
http://dx.doi.org/10.1177/0961203317731533 PMID: 28927316

[71] Mavrogeni SI, Kitas GD, Dimitroulas T, *et al.* Cardiovascular magnetic resonance in rheumatology: Current status and recommendations for use. Int J Cardiol 2016; 217: 135-48.
http://dx.doi.org/10.1016/j.ijcard.2016.04.158 PMID: 27179903

[72] Bellenger NG, Burgess MI, Ray SG, *et al.* Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? Eur Heart J 2000; 21(16): 1387-96.
http://dx.doi.org/10.1053/euhj.2000.2011 PMID: 10952828

[73] Zhang Y, Corona-Villalobos CP, Kiani AN, *et al.* Myocardial T2 mapping by cardiovascular magnetic resonance reveals subclinical myocardial inflammation in patients with systemic lupus erythematosus. Int J Cardiovasc Imaging 2015; 31(2): 389-97.
http://dx.doi.org/10.1007/s10554-014-0560-3 PMID: 25352245

[74] Mavrogeni S, Bratis K, Markussis V, *et al.* The diagnostic role of cardiac magnetic resonance imaging in detecting myocardial inflammation in systemic lupus erythematosus. Differentiation from viral myocarditis. Lupus 2013; 22(1): 34-43.
http://dx.doi.org/10.1177/0961203312462265 PMID: 23035042

[75] Mavrogeni SI, Sfikakis PP, Markousis-Mavrogenis G, *et al.* Cardiovascular magnetic resonance imaging pattern in patients with autoimmune rheumatic diseases and ventricular tachycardia with preserved ejection fraction. Int J Cardiol 2019; 284: 105-09.

[76] Hinojar R, Foote L, Sangle S, *et al.* Native T1 and T2 mapping by CMR in lupus myocarditis: Disease recognition and response to treatment. Int J Cardiol 2016; 222: 717-26.
http://dx.doi.org/10.1016/j.ijcard.2016.07.182 PMID: 27521546

[77] Lagan J, Schmitt M, Miller CA. Clinical applications of multiparametric CMR in myocarditis and systemic inflammatory diseases. Int J Cardiovasc Imaging 2018; 34(1): 35-54.
http://dx.doi.org/10.1007/s10554-017-1063-9 PMID: 28130644

[78] Mavrogeni S, Bratis K, Koutsogeorgopoulou L, *et al.* Myocardial perfusion in peripheral Raynaud's phenomenon. Evaluation using stress cardiovascular magnetic resonance. Int J Cardiol 2017; 228(228): 444-8.
http://dx.doi.org/10.1016/j.ijcard.2016.11.242 PMID: 27870974

[79] Ishimori ML, Martin R, Berman DS, *et al.* Myocardial ischemia in the absence of obstructive coronary artery disease in systemic lupus erythematosus. JACC Cardiovasc Imaging 2011; 4(1): 27-33.
http://dx.doi.org/10.1016/j.jcmg.2010.09.019 PMID: 21232700

[80] Böhm I. Novel approach to improve molecular imaging research: Correlation between macroscopic and molecular pathological findings in patients. Eur J Radiol 2011; 79(3): 365-8.
http://dx.doi.org/10.1016/j.ejrad.2010.08.030 PMID: 20863640]