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SHORT REVIEW

Cognitive Dysfunction and White Matter Abnormalities in Systemic Lupus Erythematosus

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Abstract

Brain abnormalities have been documented by neuropsychological assessment as well as a variety of neuroimaging techniques in patients with systemic lupus erythematosus (SLE). Conventional neuroimaging in patients with neuropsychiatric disease (NPSLE) typically discloses periventricular white matter (WM) hyperintensities, infarcts, hemorrhages, and cerebral atrophy. In SLE patients with none of these findings, sophisticated neuroimaging techniques have recently supported associations between microstructural WM abnormalities and abnormal attention, executive function, and processing speed. This mild cognitive dysfunction in SLE (MCD-SLE), which may result from early myelinopathy, precedes the more severe cognitive dysfunction of NPSLE, related to more obvious WM and neuronal damage. (*JINS*, 2011, *17*, 385–392)

Keywords: Lupus, Neuropsychology, Magnetic resonance imaging, Magnetic resonance spectroscopy, Mechanisms, Methodology

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease in which circulating auto-antibodies target a variety of body tissues including the brain. Neuropsychiatric (NP) manifestations in SLE are diverse and may include major syndromes, such as stroke and seizures, or other problems including headaches, mood disorders, and cognitive changes. Estimations of NP manifestations in SLE range from 37 to 95%, a variability that largely reflects differences in classification, subject selection, and attribution of cause (Hanly, Kuznetsova, & Fisk, 2007). In many studies, SLE patients have been classified as having overt neurological or psychiatric disorders (NPSLE). NPSLE has been further classified as active or inactive (Denburg, Carbotte, & Denburg, 1987) and from severe to mild. Those without NP syndromes or histories of central nervous system involvement have typically been classified as nonNPSLE or SLE-only. In the most recent nomenclature for NP disorders in SLE ("The American College of Rheumatology Nomenclature and Case Definitions for Neuropsychiatric Lupus Syndromes," 1999), 19 syndromes were identified, including cognitive dysfunction. However, the distinction between nonNPSLE and NPSLE can be confusing because patients with nonNPSLE can still manifest cognitive dysfunction. While the ACR categories will be used in this review, the concept of mild cognitive dysfunction in SLE (MCD-SLE) will also be introduced to describe SLE patients who have cognitive impairment less severe than those with the cognitive dysfunction of NPSLE. The presence of MCD has clearly been established in nonNPSLE (Kozora, 2008), indicating that subtle brain pathology likely affects many SLE patients early in the disease. The course and prognosis of cognitive decline in SLE are largely unknown, and mechanisms underlying this problem have remained elusive, but the hypothesis that MCD-SLE is a precursor to the moderate to severe cognitive dysfunction suggested by NPSLE may help clarify these issues.

WM is essential for information transfer, enabling rapid axonal conduction and the synchronous, highly integrated activity of distributed neural networks. The cognitive dysfunction of SLE suggests that WM injury may be centrally involved in pathogenesis, as impaired attention, executive

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function, and information processing speed are commonly observed. These deficits, combined with the relative preservation of language, are more reminiscent of the frontal—subcortical dementias and closely resemble the cognitive profile of patients with multiple sclerosis (MS). Over 100 WM disorders are recognized, and all have been associated with some form of neurobehavioral disturbance (Filley, 2001). Damage to WM tracts may thus be relevant to cognitive dysfunction in SLE. This review will offer a summary of neuropsychological and neuroimaging studies in SLE that support the association between neurobehavioral changes and cerebral WM damage. The hypothesis will also be presented that early myelinopathy may underlie MCD-SLE, in contrast to the more extensive white and gray matter pathology associated with NPSLE.

NEUROPSYCHOLOGICAL AND NEUROIMAGING FINDINGS IN SLE

Neuropsychological Studies

Studies using standard neuropsychological tests have reported cognitive impairment in 14–79% of SLE patients, and a comprehensive review of this literature has been published (Kozora, 2008). Inconsistencies across studies are largely methodological, including differences in the characteristics of the sample and the selection of tests used to classify impairment. Deficits in attention, verbal and nonverbal learning and recall, verbal and nonverbal fluency, complex psychomotor functions, visuospatial skills, and motor dexterity are identified when SLE patients are compared to healthy control subjects. The prevalence of cognitive dysfunction in SLE patients is higher in NPSLE (~50%) compared to non-NPSLE (~25%). Attention and processing speed are the most commonly impaired areas in these patients, with NPSLE patients demonstrating greater severity. The duration of disease, disease activity, use of prednisone, and depression have not been consistent mediators of cognitive dysfunction in SLE. In contrast, antiphospholipid antibodies (aPL) have been associated with cognitive dysfunction, and although rarely studied, measures of inflammation and pro-inflammatory cytokine activation have been similarly implicated (Kozora, 2008; Shucard, Gaines, Ambrus, & Shucard, 2007). Investigations of immune activity have primarily used peripheral measures in the serum, and continued analyses with cerebrospinal fluid (CSF) measures are likely to yield stronger correlations.

Neuroimaging Studies

Several neuroimaging techniques are available to investigate brain abnormalities in patients with SLE. The data generally support a substantial burden of both macrostrucutral and microstuctural WM disease in these patients.

Magnetic resonance imaging (MRI) analysis using conventional instruments reveals diffuse WM hyperintensities (WMHI), infarcts, hemorrhage, and cerebral atrophy in SLE. WMHI occur throughout the cerebral hemispheres, most often in the periventricular regions, in up to 70% of SLE patients (Appenzeller, Pike, & Clarke, 2008). In several well designed studies with clearly defined characterizations of NP activity in adult SLE patients, the number of WMHI has been significantly higher in NPSLE patients compared to those with nonNPSLE (Ainiala et al., 2005; Appenzeller, Vasconcelos Faria, Li, Costallat, & Cendes, 2008; Handa et al., 2003). With the use of both 1.5 and 2.0 T scanners, WMHI were documented in up to 35–50% of well-defined adult nonNPSLE patients, but data on control subjects in these studes were not presented (Abreu et al., 2005; Appenzeller, Vasconcelos Faria, et al., 2008). In a recent study using a 3.0 T scanner, no differences were noted in WM volume or number and volume of WM lesions in well-defined adult nonNPSLE patients compared to controls (Filley et al., 2009).

Magnetic resonance spectroscopy (MRS) is the only neuroimaging technique that identifies and quantifies chemicals in living tissue. MRS data are typically displayed as spectra of nuclear resonances from active compounds in a selected area, and are thought to demonstrate abnormalities in tissue metabolism. The peaks of MRS spectra reflect the chemical structure and concentration of individual metabolites. Creatine (Cr) is a storage form of high-energy phosphates and is used as a reference marker. N-acetylaspartic acid (NAA) is produced by neurons and is a marker of neuronal health; levels decrease markedly with brain insult and nonspecific neuronal loss. Choline (Ch) is a precursor to acetylcholine, an essential chemical for neuronal membrane integrity and synaptic transmission. Elevated Ch/Cr is associated with increased cell production (as occurs with brain tumors), and with increased membrane turnover related to inflammation, demyelination, ischemia, and gliosis. Most SLE studies have focused on NAA/Cr and Ch/Cr in an effort to assess neuronal and myelin integrity.

For this review, MRS studies were selected if they included only SLE patients who met ACR criteria, measurements of NAA/Cr and Ch/Cr in cerebral WM, and similar age controls; 16 such studies were found (Table 1, A–P). These studies generally reported decreased NAA and increased Ch/Cr in both the normal-appearing (NAWM) and abnormal-appearing WM (AAWM). The studies differed in their methods, however, including variation in subject selection, sample size, and neuroimaging techniques. Specific details regarding SLE disease activity, such as duration of disease, level of disease, and prednisone use were missing in many early studies (Table 1, A–D,G–I,N), and, when available, included confounders such as SLE samples with high disease activity (Table 1, B,D,J,M,O) or mean daily doses of prednisone over 15 mg (Table 1, B,C,F,M,O). Duration of disease varied significantly from 1 month to over 30 years, and was rarely studied in relation to MRS findings in studies with small sample sizes. Study groups were primarily women, and only two studies reported ethnicity (Table 1, K and P). Although mean age was between 30 and 40 years in all studies, several

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Table 1. Review of 16 MRS studies investigating (Ch/Cr) and NAA/Cr in SLE compared to controls

Author	Groups	Areas studied	Ch/Cr	NAA/Cr
A. (Davie et al., 1995)	13 NPSLE	**AAWM-**frontal	NS	SLE AAWM < SLE NAWM and controls
	10 controls	**NAWM**-frontal		
B. (Sibbitt et al., 1997)	15 NPSLE-major	**NAWM**-parietal	NS	Major NPSLE < minor NPSLE and controls
	21 NPSLE-minor			
	8 controls			
C. (Chinn et al., 1997)	47 SLE	**NAWM**-frontal and parieto-occipital	SLE > controls	SLE < controls in parieto-occipital and frontal WM
	25 Controls			
D. (Brooks et al., 1997)	14nonNPSLE (6 with and 8 without lesions)	**NAWM**-periventricular and occipital	NS (SLE to controls); nonNPSLE with lesions > nonNPSLE without lesions in all areas of NAWM, AAWM, and GM	NonNPLE with lesions < controls in all areas
	13 controls	**AAWM**-periventricular and occipital		
		GM- occipital		
E. (Friedman, Stidley, Brooks, Hart, & Sibbitt, 1998)	49 SLE and	**NAWM**-parieto-occipital	NS	NS
	23 controls			
F. (Sabet et al., 1998)	12 SLE-aPL	**NAWM-**parieto-occipital	SLE-aPLs > SLE only and controls	SLE-aPLs < SLE < controls
	37 SLE-only (non-aPLs)			
	23 controls			
G. (Lim et al., 2000)	17 NPSLE	**WM**-L peritrigonal	NPSLE > nonNPSLE, and controls in L peritrigonal WM	NPSLE < nonNPSLE and controls in basal ganglia
	9 nonNPSLE	**GM** - basal ganglia		
	8 controls			
H. (Axford, Howe, Heron, & Griffiths, 2001)	9 NPSLE	**NAWM**-parietal	NPSLE > controls	NPSLE < controls
	8 controls			
I. (Handa et al., 2003)	10 NPSLE	**NAWM** frontal and parieto-occipital	NPSLE > nonNPSLE and controls	SLE combined < controls; NPSLE < nonNPSLE
	10 nonNPSLE	**AAWM**-frontal and parieto-occipital		
	9 controls			
J. (Mortilla, Ermini, Nistri, Dal Pozzo, & Falcini, 2003)	24 SLE	**WM**-supraventricular	NS	NS
	20 controls			
K. (Kozora, Ellison, & West, 2004)	7 nonNPSLE	**NAWM-**frontal and periventricular	NS	NS
	7 controls			
L. (Castellino et al., 2005)	8 inactive SLE	**NAWM-**frontal	SLE > controls	NS

(Continued)

Table 1. Continued

Author	Groups	Areas studied	Ch/Cr	NAA/Cr
M. (Appenzeller, Li, Costallat, & Cendes, 2005)	20 controls 29 active NPSLE, 28 active nonNPSLE 14 inactive past NPSLE 19 inactive nonNPSLE 23 controls	**NAWM**- L superior-posterior CC	NS	Active NPSLE, inactive NPSLE and active nonNPSLE < controls
N. (Sundgren et al., 2005)	8 NPSLE 7 controls	**WM**-periventricular **GM**- basal ganglia	NPLSE > controls in WM and GM	NS
O. (Appenzeller et al., 2007)	30 SLE (NP and nonNP) 23 controls	**WM**-left superior-posterior CC	SLE combined > controls	NS
P. (Filley et al., 2009)	60 nonNPSLE 24 controls	**NAWM**-L and R frontal and periventricular	nonNPSLE > controls	NS

Note. NAA = n-acetylaspartate; Ch/Cr = choline/creatine; NAWM = normal-appearing white matter; AAWM = abnormal-appearing white matter; GM = gray matter; CC = corpus callosum; R = right; L = left; aPLs = antiphospholipid antibodies present.

included subjects less than 18 (ages, 6–15; Table 1, D–G, H, J, L), and some included subjects over 50 (Table 1, A, B, N) and over 60 (Table 1, C, E, H). Classification of nonNPSLE and NPSLE varied as studies used different criteria to characterize NP activity. Some early studies (B, D, G) used previous NP classification (Denburg et al., 1987), and most included active psychiatric and neurological conditions while not screening for or categorizing others such as head injury and substance abuse. Five later studies used the ACR NP classifications, four of which carefully screened out other problems such as head injury and substance abuse (Table 1, K, M, O, and P). A majority of the MRS studies were performed on 1.5 T scanners, with only K, M, O, and P using a more sensitive 2.0 T or 3.0 T magnet, potentially influencing and limiting MRS findings in earlier studies. As shown in Table 1, the areas studied also varied considerably, another factor that could influence results. In summary, WM abnormalities were often found in SLE, suggesting both microstructural and macrostructural WM damage, but methodological differences should be considered in data interpretation.

Whereas decreased NAA and elevated Ch/Cr are both found in SLE, the earliest change may be higher Ch/Cr, which is more likely due to inflammatory myelinopathy than ischemia or gliosis at this disease stage (Filley et al., 2009). Studies with carefully characterized nonNPSLE patients suggest that increased Ch/Cr can occur without, and perhaps before lowered NAA/Cr (Appenzeller, Li, Costallat, & Cendes, 2007; Filley et al., 2009; Sundgren et al., 2005). MRS studies have also documented NAA/Cr and Ch/Cr abnormalities before MRI shows WMHI (Appenzeller et al., 2007; Castellino et al., 2005). Castellino and colleagues (2005) found that non-NPSLE patients with high Ch/Cr at baseline had more MRI WM abnormalities at follow-up. Appenzeller and colleagues (2007) reported that SLE patients (both NPSLE and non-NPSLE) whose disease activity increased over the course of the study had a concomitant decline in NAA/Cr, that Ch/Cr increased in SLE patients compared to controls, and that patients with elevated Ch/Cr and normal MRI at baseline developed WMHI approximately 1 year later.

Few studies have evaluated autoantibody activity in relation to MRS findings in SLE. SLE patients with antibodies against phospholipids (aPL) had higher levels of Ch/Cr than those without aPL (Sabet, Sibbitt, Stidley, Danska, & Brooks, 1998), and a significant association between increased Ch/Cr and aPL was reported by Appenzeller and colleagues (2007). APL were also associated with increased number and volume of WMHI in SLE (Appenzeller, Vasconcelos Faria, et al., 2008).

Diffusion tensor imaging (DTI) provides an index of the structural integrity of WM by using quantitative directional diffusion properties of water molecules for each voxel. The technique is based on the principle of anisotropy, a term referring to the propensity for water in the normal state to diffuse along the direction of WM tracts. Damaged WM, in contrast, is characterized by isotropic diffusion, which is correspondingly less directional and more random. Key DTI measures include the apparent diffusion coefficient (ADC), mean diffusivity (MD), and fractional anisotropy (FA).

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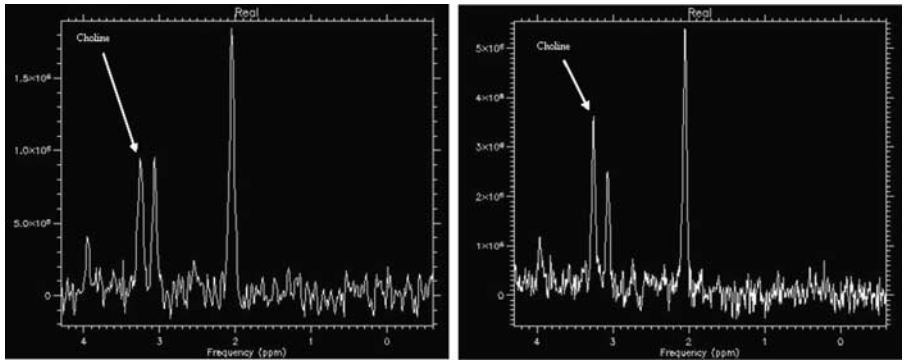

Fig. 1. Magnetic resonance spectroscopy spectra from right frontal lobe white matter showing normal choline (Ch) in a control subject (left) and elevated choline (Ch) in an SLE subject (right)

DTI is particularly sensitive to microstructural changes in WM, including both myelin and axonal damage, and is an ideal tool for the study of WM because it can assess the structural integrity of specific tracts in relation to cognitive functions.

DTI studies suggest WM damage in well-defined NPSLE patients (Bosma et al., 2004; Hughes et al., 2007; Jung et al., 2010) and in relation to controls (Hughes et al., 2007; Jung et al., 2010; Zhang et al., 2007) using 1.5 T scanners. A study of 34 NPSLE patients compared to controls reported increased MD in the frontal lobe and the internal capsule, and decreased FA in the corpus callosum (CC) (Zhang et al., 2007). Abnormal findings were seen in patients with normal MRI scans, supporting the sensitivity of DTI to early WM changes. FA values were also decreased in frontobasal and temporal WM tracts of 12 SLE patients (NPSLE and nonNPSLE) (Emmer et al., 2010) using a 3.0 T scanner. In a recent study, increased ADC was reported in the frontal lobe as well as the CC splenium and genu in 15 well-characterized nonNPSLE patients compared to controls (Ulug et al., 2010) using a 3.0 T scanner. DTI thus shows promise as another method by which cerebral WM changes may be correlated with cognition in SLE (Filley, 2009).

COGNITION AND WHITE MATTER ASSOCIATIONS IN SLE

Studies supporting an association between abnormal WM neuroimaging and cognitive deficits in SLE are beginning to accumulate. Early MRI investigations demonstrated that the number of WMHI was associated with cognition, particularly attention, in 20 nonNPSLE patients, while no relationship was found between cognitive change and cerebral atrophy (Kozora et al., 1998). Volumetric WM analyses were then conducted, and the CC was studied as a readily identifiable WM tract. In 20 nonNPSLE patients compared to controls, decreased CC volume was noted and associated with decline in measures of visuomotor reasoning and speed (Johnson, Pinkston, Bigler, & Blatter, 1996). Appenzeller, Rondina, Li, Costallat, and Cendes (2005) reported that CC volumes were significantly smaller in 115 SLE patients compared to controls, with approximately 25% also demonstrating cerebral atrophy. The NPSLE patients in this study had greater CC volume loss than those with nonNPSLE, but did not show significantly more cerebral atrophy. SLE patients with cognitive impairment had reduced CC sizes; however, only a third of the patients were cognitively tested and no data were available for review.

MRS was then used as a method to study WM that does not show abnormality on conventional MRI (NAWM), and correlations with cognition were made. Elevated Ch/Cr was reported in frontal WM of eight nonNPSLE patients compared to eight demographically similar controls, and patients with greater cognitive impairment had significantly increased Ch/Cr (Kozora et al., 2005). In a later study from our group, there was no evidence of cerebral atrophy (based on volumetric analysis) or neuronal damage (based on NAA/Cr measurements) in 60 nonNPSLE patients compared to 24 demographically similar controls (Filley et al., 2009). However, higher Ch/Cr was found in the right frontal WM ($p = .03$) and left frontal WM ($p = .05$) in the nonNPSLE patients compared to controls. Figure 1 demonstrates higher Ch/Cr in an SLE patient compared to a control subject. A WM Cognitive Score (WMCS) was developed using a stepwise backward regression model to predict Ch/Cr from nine measures of attention and executive function derived from the nonNPSLE subjects. The total WMCS was found to correlate positively with total WM volume and negatively with left frontal WM Ch/Cr (Filley et al., 2009). In another disease affecting WM, human immunodeficiency virus (HIV) infection, elevated Ch/Cr in frontal WM was related to executive dysfunction (Chang et al., 2002), providing supportive evidence that elevated Ch/Cr may have a similar implication in this disease.

The available MRS data in SLE indicate that early changes in WM, particularly in myelin, may play an important role in cognitive impairment. Strong correlations between elevated frontal WM Ch/Cr and cognitive dysfunction in nonNPSLE patients have been evident in our studies thus far. Elevated frontal WM Ch/Cr may underlie MCD-SLE, which appears to be a precursor of more obvious brain pathology, advancing cognitive dysfunction, and clinical deterioration.

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The development of a WMCS that correlates with Ch/Cr may allow testing for the strength of this hypothesized brain-behavior relationship. One potential confound in this effort may be the stability of Ch/Cr in nonNPSLE patients, as some SLE studies suggest variability in neurometabolite levels over time (Sibbitt, Haseler, Griffey, Friedman, & Brooks, 1997; Sundgren et al., 2005).

No studies have evaluated DTI parameters in relation to cognition in SLE patients. However, studies of MS, a disease sharing much in common with SLE, reported correlations between various DTI measures and indices of attention and executive function (Rovaris et al., 2008). These findings, particularly in the NAWM, highlight the potential for DTI to shed light on the pathogenesis of cognitive dysfunction in SLE.

Although this review is not intended to discuss details of pathogenesis, it is possible that MCD-SLE results from immune-mediated myelinopathy whereas cognitive dysfunction in NPSLE tends to involve a combination of immune-mediated and vascular injury affecting both WM and gray matter. An autopsy and MRS study of patients who died with NPSLE found widespread vascular injury in the brain, and lowered NAA/Cr was associated with reduced neuronal density while higher Ch/Cr was related to gliosis (Brooks et al., 2010). Whereas these MRS changes are consistent with those observed in less affected SLE patients, the neuropathology of those dying with NPSLE is of course more extensive and severe than would be expected in nonNPSLE, and evidence exists to support early myelinopathy accounting for MCD-SLE before any other brain pathology develops (Filley et al., 2009).

CONCLUSIONS

Recent observations may compel a major shift in the conceptualization of cognitive dysfunction in autoimmune diseases such as SLE, bringing into focus pathology in the myelin and axons of cerebral WM. As one conclusion among many, damage to the myelin within frontal WM may lead to impaired attention, executive dysfunction, and slowed processing speed before more pervasive cognitive dysfunction develops.

A key implication of our review is the hypothesis that microstructural WM abnormalities produce cognitive dysfunction by affecting the operations of frontal systems in SLE. Correspondingly, these effects may account for deficits in attention, executive function, and speed of processing. Another less studied but intriguing possibility is that memory retrieval may be specifically affected, as has been observed in a wide range of WM disorders (Filley, 2001). Advanced neuroimaging can help address all these issues. MRS has proven highly productive thus far in the study of WM and cognition in SLE (Filley et al., 2009; Kozora et al., 2005). DTI is also sensitive to microstructural WM changes (Zhang et al., 2007), and recent evidence of frontal WM damage in patients with nonNPSLE (Ulug et al., 2010) suggests that impaired cognition may be related to WM abnormalities as detected by this technique. The pathogenesis of WM injury putatively underlying MCD-SLE is uncertain, but an autoimmune process is suspected, and CSF studies may permit identification of inflammatory mediators that may contribute to microstructural WM damage. Ultimately, a combination of neuropsychological, neuroimaging, and immunological techniques appears likely to advance our understanding of the role of WM in the cognitive dysfunction of SLE at all stages of the disease.

Many other implications arise from this work. Evidence of WM damage (Emmer et al., 2010) and deficits in attention and executive function (Kozora, 2008) are emerging in patients with rheumatoid arthritis and Sjogren's syndrome, suggesting that our studies of WM damage in SLE may also have implications for the mechanisms and treatment of cognitive dysfunction in other autoimmune diseases. In a broader sense, the study of WM in relation to cognitive dysfunction and dementia holds great promise for improving our knowledge of a wide variety of poorly understood neurologic and psychiatric disorders that cause significant human suffering (Filley, 2001). In SLE, the concept of MCD-SLE offers a useful clinical model that may facilitate a deeper understanding of cognition in this disease, distinguishing these patients both from cognitively unaffected SLE patients, and those with the more severe cognitive dysfunction of NPSLE. Future studies in this area would benefit from selection of demographically diverse and well characterized NP activity in patient samples, use of reliable and valid cognitive tests, sophisticated neuroimaging (volumetric MRI, MRS, and DTI) across a variety of white and gray matter areas with scanners at field strength of 3.0 T or above, and investigations of CSF inflammatory activity. Finally, longitudinal studies are necessary, particularly with early, nonNPSLE patients, to understand the complex relationships between biological and neurobehavioral processes in SLE and to confirm that MCD-SLE is a precursor to more significant cognitive problems associated with NPSLE.

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REFERENCES

Abreu, M.R., Jakosky, A., Folgerini, M., Brenol, J.C., Xavier, R.M., & Kapczinsky, F. (2005). Neuropsychiatric systemic lupus erythematosus: Correlation of brain MR imaging, CT, and SPECT. *Clinical Imaging*, *29*(3), 215–221. doi:10.1016/j.clinimag.2004.07.007

Ainiala, H., Dastidar, P., Loukkola, J., Lehtimaki, T., Korpela, M., Peltola, J., & Hietaharju, A. (2005). Cerebral MRI abnormalities and their association with neuropsychiatric manifestations in SLE: A population-based study. *Scandinavian Journal of Rheumatology*, *34*(5), 376–382. doi:10.1080/03009740510026643

https://doi.org/10.1017/S1355617711000191 Published online by Cambridge University Press

The American College of Rheumatology Nomenclature and Case Definitions for Neuropsychiatric Lupus Syndromes. (1999). *Arthritis and Rheumatism, 42*(4), 599–608. PMID: 10211873. doi:10.1002/1529-0131(199904)42:4<599::AID-ANR2>3.0.C0;2-F

Appenzeller, S., Li, L.M., Costallat, L.T., & Cendes, F. (2005). Evidence of reversible axonal dysfunction in systemic lupus erythematosus: A proton MRS study. *Brain*, *128*(Pt 12), 2933–2940. doi:10.1093/brain/awh646

Appenzeller, S., Li, L.M., Costallat, L.T., & Cendes, F. (2007). Neurometabolic changes in normal white matter may predict appearance of hyperintense lesions in systemic lupus erythematosus. *Lupus*, *16*(12), 963–971. doi:10.1177/0961203307084723

Appenzeller, S., Pike, G.B., & Clarke, A.E. (2008). Magnetic resonance imaging in the evaluation of central nervous system manifestations in systemic lupus erythematosus. *Clinical Reviews in Allergy and Immunology*, *34*(3), 361–366. doi:10.1007/s12016-007-8060-z

Appenzeller, S., Rondina, J.M., Li, L.M., Costallat, L.T.L., & Cendes, F. (2005). Cerebral and corpus callosum atrophy in systemic lupus erythematosus. *Arthritis and Rheumatism*, *52*(9), 2783–2789. doi:10.1002/art.21271

Appenzeller, S., Vasconcelos Faria, A., Li, L.M., Costallat, L.T., & Cendes, F. (2008). Quantitative magnetic resonance imaging analyses and clinical significance of hyperintense white matter lesions in systemic lupus erythematosus patients. *Annals of Neurology*, *64*(6), 635–643. doi:10.1002/ana.21483

Axford, J.S., Howe, F.A., Heron, C., & Griffiths, J.R. (2001). Sensitivity of quantitative (1)H magnetic resonance spectroscopy of the brain in detecting early neuronal damage in systemic lupus erythematosus. *Annals of the Rheumatic Diseases*, *60*(2), 106–111. doi:10.1136/ard.60.2.106

Bosma, G.P., Steens, S.C., Petropoulos, H., Admiraal-Behloul, F., van den Haak, A., Doornbos, J., … van Buchem, M.A. (2004). Multisequence magnetic resonance imaging study of neuropsychiatric systemic lupus erythematosus. *Arthritis and Rheumatism*, *50*(10), 3195–3202. doi:10.1002/art.20512

Brooks, W.M., Sabet, A., Sibbitt, W.L. Jr., Barker, P.B., van Zijl, P.C., Duyn, J.H., & Moonen, C.T. (1997). Neurochemistry of brain lesions determined by spectroscopic imaging in systemic lupus erythematosus. *Jouranl of Rheumatology*, *24*(12), 2323–2329.

Brooks, W.M., Sibbitt, W.L. Jr., Kornfeld, M., Jung, R.E., Bankhurst, A.D., & Roldan, C.A. (2010). The histopathologic associates of neurometabolite abnormalities in fatal neuropsychiatric systemic lupus erythematosus. *Arthritis and Rheumatism*, *62*(7), 2055–2063. doi:10.1002/art.27458

Castellino, G., Govoni, M., Padovan, M., Colamussi, P., Borrelli, M., & Trotta, F. (2005). Proton magnetic resonance spectroscopy may predict future brain lesions in SLE patients: A functional multi-imaging approach and follow up. *Annals of the Rheumatic Diseases*, *64*(7), 1022–1027. doi:10.1136/ard.2004.026773

Chang, L., Ernst, T., Witt, M.D., Ames, N., Gaiefsky, M., & Miller, E. (2002). Relationships among brain metabolites, cognitive function, and viral loads in antiretroviral-naive HIV patients. *Neuroimage*, *17*(3), 1638–1648. doi:10.1006/nimg.2002.1254

Chinn, R.J., Wilkinson, I.D., Hall-Craggs, M.A., Paley, M.N., Shortall, E., Carter, S., … Harrison, M.J. (1997). Magnetic resonance imaging of the brain and cerebral proton spectroscopy in patients with systemic lupus erythematosus. *Arthritis and Rheumatism*, *40*(1), 36–46. doi:10.1002/art.1780400107

Davie, C.A., Feinstein, A., Kartsounis, L.D., Barker, G.J., McHugh, N.J., Walport, M.J., … Miller, D.H. (1995). Proton magnetic resonance spectroscopy of systemic lupus erythematosus involving the central nervous system. *Journal of Neurology*, *242*(8), 522–528. doi:10.1007/BF00867424

Denburg, S.D., Carbotte, R.M., & Denburg, J.A. (1987). Cognitive impairment in systemic lupus erythematosus: A neuropsychological study of individual and group deficits. *Journal of Clinical and Experimental Neuropsychology*, *9*(4), 323–339. doi:10.1080/01688638708405054

Emmer, B.J., Veer, I.M., Steup-Beekman, G.M., Huizinga, T.W., van der Grond, J., & van Buchem, M.A. (2010). Tract-based spatial statistics on diffusion tensor imaging in systemic lupus erythematosus reveals localized involvement of white matter tracts. *Arthritis and Rheumatism*, *62*(12), 3716–3721. doi:10.1002/art.27717

Filley, C.M. (2001). *The behavioral neurology of white matter*. New York: Oxford University Press.

Filley, C.M. (2009). Exploring white matter microstructure: New insights from diffusion tensor imaging. *Neurology*, *73*(21), 1718–1719. doi:WNL.0b013e3181c2936b [pii] 10.1212/WNL.0b013e3181c2936b

Filley, C.M., Kozora, E., Brown, M.S., Miller, D.E., West, S.G., Arciniegas, D.B., … Zhang, L. (2009). White matter microstructure and cognition in non-neuropsychiatric systemic lupus erytematosus. *Cognitive and Behavioral Neurology*, *22*(1), 38–44. doi:10.1097/WNN.0b013e31818190d174

Friedman, S.D., Stidley, C.A., Brooks, W.M., Hart, B.L., & Sibbitt, W.L. Jr. (1998). Brain injury and neurometabolic abnormalities in systemic lupus erythematosus. *Radiology*, *209*(1), 79–84.

Handa, R., Sahota, P., Kumar, M., Jagannathan, N.R., Bal, C.S., Gulati, M., … Wali, J.P. (2003). In vivo proton magnetic resonance spectroscopy (MRS) and single photon emission computerized tomography (SPECT) in systemic lupus erythematosus (SLE). *Magnetic Resonance Imaging*, *21*(9), 1033–1037. doi:10.1016/50730-725x(03)00200-5

Hanly, J.G., Kuznetsova, A., & Fisk, J.D. (2007). Psychopathology of lupus and neuroimaging. In D.J. Wallace, & B.H. HaHn (Eds.), *Dubois' Lupus Erythematosus* (7th ed.). Philadelphia: Lippincott, Williams & Wilkins.

Hughes, M., Sundgren, P.C., Fan, X., Foerster, B., Nan, B., Welsh, R.C., … Gebarski, S. (2007). Diffusion tensor imaging in patients with acute onset of neuropsychiatric systemic lupus erythematosus: A prospective study of apparent diffusion coefficient, fractional anisotropy values, and eigenvalues in different regions of the brain. *Acta Radiologica*, *48*(2), 213–222. doi:772612189 [pii] 10.1080/02841850601105825

Johnson, S.C., Pinkston, J.B., Bigler, E.D., & Blatter, D.D. (1996). Corpus callosum morphology in normal controls and traumatic brain injury: Sex differences, mechanisms of injury, and neuropsychological correlates. *Neuropsychology*, *10*(3), 408–415.

Jung, R.E., Caprihan, A., Chavez, R.S., Flores, R.A., Sharrar, J., Qualls, C.R., … Roldan, C.A. (2010). Diffusion tensor imaging in neuropsychiatric systemic lupus erythematosus. *BMC Neurology*, *10*, 65. doi:1471-2377-10-65 [pii] 10.1186/1471-2377-10-65

Kozora, E. (2008). Neuropsychological functioning in systemic lupus erythematosus. In J.E. Morgan & J.H. Ricker (Eds.), *Textbook of clinical neuropsychology* (pp. 636–649). New York: Taylor and Francis.

Kozora, E., Arciniegas, D.B., Filley, C.M., Ellison, M.C., West, S.G., Brown, M.S., & Simon, J.H. (2005). Cognition, MRS neurometabolites, and MRI volumetrics in non-neuropsychiatric systemic lupus erythematosus: preliminary data. *Cognitive and Behavioral Neurology*, *18*(3), 159–162.

Kozora, E., Ellison, M.C., & West, S. (2004). Reliability and validity of the proposed American College of Rheumatology neuropsychological battery for systemic lupus erythematosus. *Arthritis and Rheumatism*, *51*(5), 810–818. doi:10.1002/art.20692

https://doi.org/10.1017/S1355617711000191 Published online by Cambridge University Press

Kozora, E., West, S.G., Kotzin, B.L., Julian, L., Porter, S., & Bigler, E. (1998). Magnetic resonance imaging abnormalities and cognitive deficits in systemic lupus erythematosus patients without overt central nervous system disease. *Arthritis and Rheumatism*, *41*(1), 41–47. doi:10.1002/1529-0131(199801)41:1<41::AID-ART6>3.0.C0;2-7

Lim, M.K., Suh, C.H., Kim, H.J., Cho, Y.K., Choi, S.H., Kang, J.H., … Lee, J.H. (2000). Systemic lupus erythematosus: Brain MR imaging and single-voxel hydrogen 1 MR spectroscopy. *Radiology*, *217*(1), 43–49.

Mortilla, M., Ermini, M., Nistri, M., Dal Pozzo, G., & Falcini, F. (2003). Brain study using magnetic resonance imaging and proton MR spectroscopy in pediatric onset systemic lupus erythematosus. *Clinincal and Experimental Rheumatology*, *21*(1), 129–135.

Rovaris, M., Riccitelli, G., Judica, E., Possa, F., Caputo, D., Ghezzi, A., … Filippi, M. (2008). Cognitive impairment and structural brain damage in benign multiple sclerosis. *Neurology*, *71*(19), 1521–1526. doi:01.wnl.0000319694.14251.95 [pii] 10.1212/01.wnl.0000319694.14251.95

Sabet, A., Sibbitt, W.L., Stidley, C.A., Danska, J., & Brooks, W.M. (1998). Neurometabolite markers of cerebral injury in the antiphospholipid antibody syndrome of systemic lupus erythematosus. *Stroke*, *29*, 2254–2260.

Shucard, J.L., Gaines, J.J., Ambrus, J. Jr., & Shucard, D.W. (2007). C-reactive protein and cognitive deficits in systemic lupus erythematosus. *Cognitive and Behavioral Neurology*, *20*(1), 31–37. doi:10.1097/WNN.0b013e31802e3b9a

Sibbitt, W.L. Jr., Haseler, L.J., Griffey, R.R., Friedman, S.D., & Brooks, W.M. (1997). Neurometabolism of active neuropsychiatric lupus determined with proton MR spectroscopy. *American Journal of Neuroradiology*, *18*(7), 1271–1277.

Sundgren, P.C., Jennings, J., Attwood, J.T., Nan, B., Gebarski, S., McCune, W.J., … Maly, P. (2005). MRI and 2D-CSI MR spectroscopy of the brain in the evaluation of patients with acute onset of neuropsychiatric systemic lupus erythematosus. *Neuroradiology*, *47*(8), 576–585. doi:10.1007/s00234-005-1371-y

Ulug, A.M., Vo, A., Kozora, E., Ramos, G.G., Vega, J., Zimmerman, M., … Lockshin, M.D. (2010). fMRI in systemic lupus erythematosus and antiphospholipid syndrome. *Proceedings of the International Society for Magnetic Resonance in Medicine*, *18*, 4466A.

Zhang, L., Harrison, M., Heier, L.A., Zimmerman, R.D., Ravdin, L., Lockshin, M., & Ulug, A.M. (2007). Diffusion changes in patients with systemic lupus erythematosus. *Magnetic Resonance Imaging*, *25*(3), 399–405. doi:10.1016/j.mri.2006.09.037

https://doi.org/10.1017/S1355617711000191 Published online by Cambridge University Press