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POSSIBLE ROLE OF THE HIPPOCAMPUS IN THE PATHOGENESIS OF COGNITIVE DYSFUNCTION IN NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

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RESEARCH ARTICLE

ABSTRACT. NEUROPSYCHIATRIC DISEASE, manifested in part by cognitive dysfunction, is increasingly recognized as a major cause of morbidity in systemic lupus erythematosus (SLE), a prototypic autoimmune disease. Cognitive deficits in SLE include impaired short-term memory, suggesting potential involvement of the hippocampus and temporal lobe in the development of these aberrations. Similarly, mice that spontaneously manifest lupus-like illnesses exhibit behavioral disturbances which map to the hippocampus. To explore the possibility that cognitive dysfunction in SLE is associated with structural lesions in the hippocampus, five consecutive patients with SLE and subjective complaints of short-term memory impairment underwent neuroimaging of the brain. A qualitative loss of hippocampal volume on high-resolution magnetic resonance imaging was found in all such patients compared with age- and sex-matched controls. The results suggest the hypothesis that the hippocampus is pathogenetically linked to cognitive impairment in SLE.

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1. INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease which may affect multiple organs, including the brain [1]. Central nervous system (CNS) involvement has been reported in 21-74% of patients with lupus and may present with stroke, encephalopathy, seizures, psychosis, myelopathy or neuropathy [2-5]. Increasingly recognized as a component of neuropsychiatric lupus is cognitive dysfunction, which is observed in up to 66% of patients with SLE [6-10]. Cognitive impairment may include deficits of recent and delayed memory, memory retrieval, attention, concentration, verbal information and abstraction, verbal productivity, visuospatial memory and speed; may occur in the apparent absence of systemic disease and lacks consistent serological or radiological correlates [8-12].

Structural and functional imaging of the brain in SLE have shown numerous abnormalities [13-16]. These abnormalities may be focal or diffuse, are extremely dependent on the study technique, and have shown no clear association with specific clinical presentations [17]. The nature of the subjective and objective disturbances in memory seen in patients with SLE suggests possible involvement of the hippocampus and medial temporal lobe [18]. Consistent with this thesis, some patients with SLE have evidence of deficient encoding and initial storage of information in memory based on their poor performance on recognition memory tasks and their failure to demonstrate significant improvement with explicit retrieval clues [19]. Aberrations in hippocampal-dependent learning have also been observed in experimental lupus as evidenced by the impaired capacity of mice which spontaneously develop lupus-like illnesses to navigate the visuospatial version of the water maze [20-22].

In this study we explore the possibility that cognitive dysfunction in lupus is associated with structural aberrations in the hippocampus. The results suggest the hypothesis that the hippocampus is pathogenetically linked to cognitive disturbances in SLE.

2. METHODOLOGY

Five consecutive patients with significant and documented memory disturbances who met American College of Rheumatology criteria for SLE volunteered for the Institutional Review Board-approved research protocol and underwent high resolution MRI. Clinical histories were reviewed and complete physical examinations were performed by the rheumatologist (see TABLE 1). The neuroradiologist and the neurologist were blinded to the history while reviewing the MRI scans. There was complete agreement between the neuroradiologist and neurologist regarding the interpretation of the MRI. MRI scans of the brain were performed utilizing the institutional temporal lobe epilepsy protocol. Scanning was performed on a GE Signa-LX-Echo speed MR unit with 8.3 software. Coronal T2 FSE (fast spin echo) sequences were performed (TE 102, TR 4500, 18 FOV) as well as T1 SE (TE minimum, TR 400, 24 FOV) to optimize visualization of the medial temporal structures along with pre and post gadolinium axial and coronal sequences. Fluid attenuated inversion recovery (FLAIR) sequences were also performed in all patients. Historical controls included five age- and sex-matched patients without any neurologic or rheumatologic disorder. These patients had undergone MRI scanning with an identical imaging protocol and had a neurological evaluation by a neurologist. All controls had a normal neurological evaluation confirmed by a neurologist.

3. RESULTS

All five patients with systemic lupus erythematosus had significant complaints of memory difficulties, including patient number one who had developed psychosis during the period of evaluation.

PATIENT NO. 1

A thirteen-year-old girl, with a 4-month history of SLE manifested by membranous nephropathy, bowel and splenic infarction, presented with aggressive, bizarre and inappropriate behavior. She had evidence of disorganized thought process, flight of ideas, rapid trailing speech and inappropriate responses consistent with a psychotic process.

TABLE 1. CLINICAL FEATURES, DIAGNOSTIC TESTING AND TREATMENT OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Patient	1	2	3	4	5
Age	13	49	16	47	54
Sex	F	F	F	F	F
Clinical manifestation	Membranous nephropathy, splenic infarction, psychosis	Fatigue, arthritis, Raynaud's phenomenon, colitis	Rash, fever, arthritis, seizure	Fever, myalgia, arthritis, headaches	Rash, alopecia, arthritis, myalgia
Duration of disease	4 months	2 years	1 year	8 months	3 years
Serology	ANA 1:16384 Anti-dsDNA 1:80	ANA 1:128 Anti-dsDNA 1:60	ANA 1:128 Anti-dsDNA < 1:10 Low C4	ANA 1:320 Anti-dsDNA 1:80	ANA 1:320 Anti-ds DNA 1:10
MRI results	Right hippocampal atrophy	Left hippocampal atrophy	Left > right hippocampal atrophy	Right hippocampal atrophy	Right hippocampal atrophy
Treatment	Prednisone 30 mg/day	None	Hydroxychloroquine 200 mg twice daily	Prednisone 12.5 mg/day	Prednisone 10-20 mg/day, Hydroxychloroquine 200 mg twice daily

Cognitive testing revealed impaired short-term memory. No clouding of consciousness was noted. Cranial nerve examination was normal; no focal motor or sensory deficits were identified. Serologic testing revealed an ANA titre of 1:16384 (homogenous and speckled). Anti-dsDNA was 1:80 (normal <1:10). Complement levels were normal. The erythrocyte sedimentation rate (ESR) was 75 mm/hr (normal <20).

MRI scan showed evidence of right hippocampal atrophy (FIG. 1 and 2). The initial diagnosis was lupus cerebritis versus steroid-induced psychosis. Reduction of Prednisone dosage and intravenous immunoglobulin therapy resulted in clinical improvement. The memory difficulties persisted notwithstanding decreased steroid dosage.

PATIENT NO. 2

A 49-year-old woman presented with a two-year history of fatigue, arthralgias and Raynaud's phenomenon. She also had a history of facial rash, two miscarriages and colitis. Serologic testing showed an ANA of 1:128 (homogenous and nucleolar) and anti-dsDNA of 1:10. The ESR was 14 mm/hr, lupus anticoagulant was absent and anti-cardiolipin antibody titers were normal. Approximately five months after onset of her clinical symptoms, she experienced memory problems that were documented on clinical testing. MRI scan showed evidence of left hippocampal atrophy.

PATIENT NO. 3

A 16-year-old woman presented with a one-year history of fever, rash, fatigue, arthralgias and Raynaud's phenomenon. Serologic testing revealed positive anti-nuclear and anti-dsDNA antibodies consistent with SLE. She had also been diagnosed earlier with neurocardiogenic syncope. A neurologic evaluation had been undertaken due to a history of memory problems and two episodes of confusion associated with orofacial automatisms that were thought to represent complex partial seizures. Neurological examination, including bedside cognitive testing, performed by a neurologist was normal. EEG was reported as normal. No

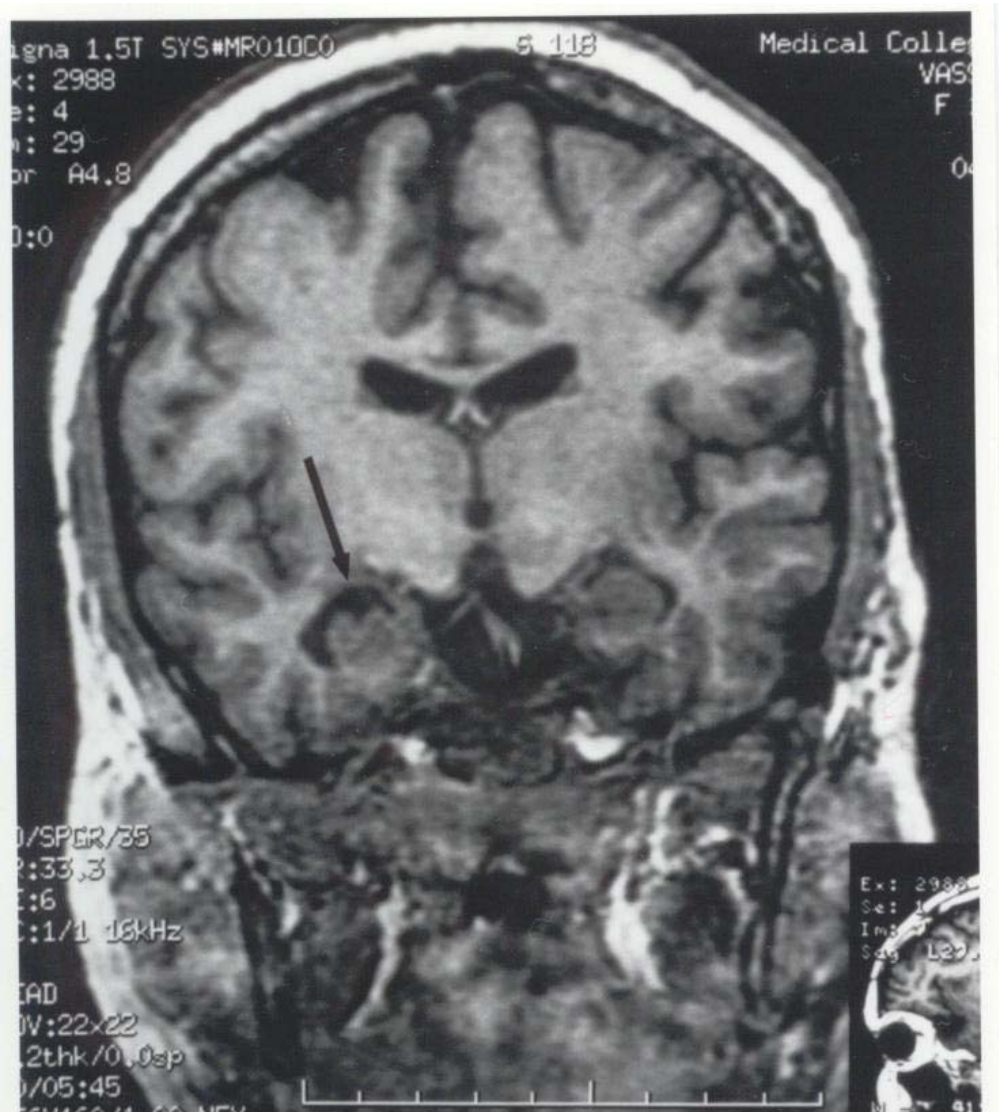

FIGURE 1 T1 WEIGHTED CORONAL SECTION OF PATIENT NO. 1, A 13-YEAR-OLD SHOWING RIGHT HIPPOCAMPAL AND MEDIAL TEMPORAL ATROPHY (ARROW).

antiepileptic treatment was initiated and the patient has not had any further episodes. Memory problems have persisted since the first evaluation 16 months ago. MRI scan showed left greater than right hippocampal atrophy.

PATIENT NO. 4

A 47-year-old woman with an 8-month history of fever, fatigue, myalgias, arthralgias and serology consistent with SLE (ANA 1:320, anti-dsDNA 1:80) complained of significant memory problems as well as emotional difficulties. Vague neurological complaints were noted including headaches, blurred vision and tinnitus. Neurological examination was normal, bedside cognitive testing revealed mild memory disturbance. MRI showed subtle right hippocampal atrophy.

PATIENT NO. 5

A 54-year-old woman presented with a photosensitive rash, alopecia, arthralgias and oral ulcers. She had positive antinuclear (1:256) and

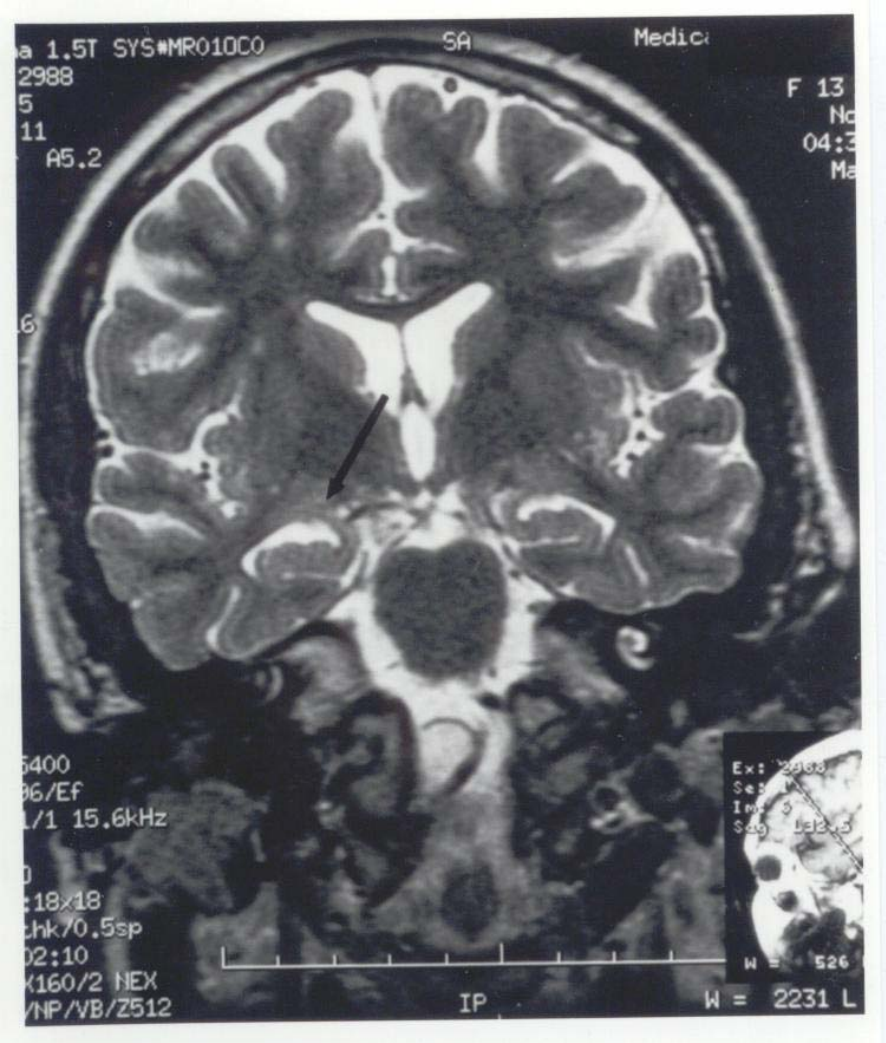

FIGURE 2 T2 WEIGHTED IMAGING OF PATIENT NO. 1, REVEALING ASYMMETRIC HIPPOCAMPAL ATROPHY (ARROW).

anti-dsDNA (1:10) antibodies. Anti-ENA and Sjögren's antibody panel were negative. She developed significant memory problems that were objectively noted on examination. Mild right hippocampal atrophy was noted on the high resolution MRI.

The patients with SLE had no evidence of white matter lesions, infarcts, meningeal enhancement or other structural abnormalities. When compared to controls, there was no significant cortical atrophy noted. None of the controls had evidence of hippocampal atrophy as compared to the SLE patients who had unilateral (patients 1, 2, 4, and 5) or bilateral (patient 3) atrophy.

4. DISCUSSION

This study documents, for the first time, an association between subjective disturbances in memory and hippocampal and medial temporal lobe abnormalities in the setting of SLE. Considerable evidence implicates the hippocampus and the medial temporal lobe in learning and memory [23]. Data derived from the temporal lobe epilepsy literature

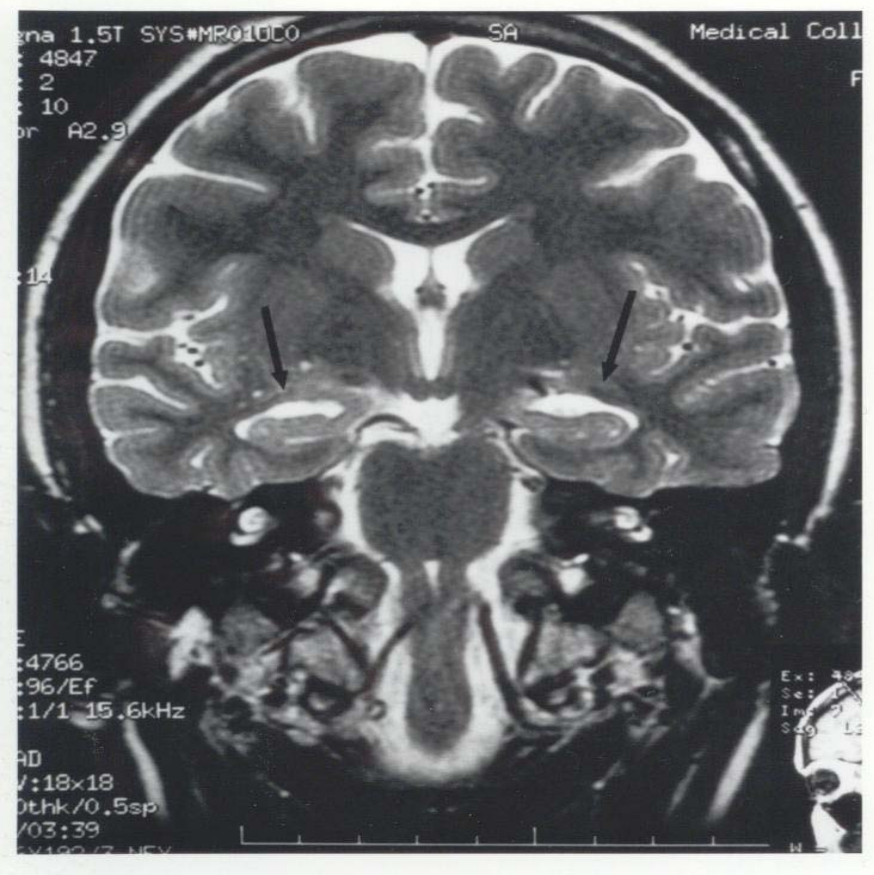

FIGURE 2 T2 WEIGHTED CORONAL SECTION OF PATIENT NO. 3, A 16-YEAR-OLD WITH BILATERAL HIPPOCAMPAL ATROPHY, LEFT GREATER THAN RIGHT (ARROWS).

indicate that damage to one or both hippocampi can result in loss of short-term memory and an inability to learn new tasks [23]. Thus, patients undergoing left anterior temporal lobectomy secondary to an intractable left temporal epileptic focus have impaired recall of verbal material, while patients undergoing right anterior temporal lobectomy with a corresponding epileptic focus have impaired memory involving visuospatial tasks [24]. These observations suggest localization of function within the hippocampus and medial temporal lobe. Functional MRI and PET data also suggest that the medial temporal lobe is important at the time of learning in establishing long-term, declarative memory [25-27]. As stated earlier, studies in mice that spontaneously develop an SLE-like, autoimmune disease also implicate the hippocampus in the pathogenesis of learning deficits. In immunologically normal rodents, hippocampal lesions selectively disrupt performance in the visuospatial platform version of the water maze [28]. Similarly, mice with lupus are markedly impaired in their capacity to learn the spatial relationships required to guide them to the hidden platform of the Morris swim maze [20-22].

Typically, CNS involvement in lupus develops in patients with chronic, progressive or highly aggressive systemic disease, suggesting a link between peripheral immune activation and central innate immune responsiveness [29]. However, numerous studies have documented memory loss in patients with inactive as well as active forms of neuropsychiatric SLE [11,12,19,30] and cognitive problems have been reported in patients with SLE who have never developed overt neuropsychiatric

syndromes [8,12,30], suggesting possible ongoing neuronal injury in lupus. Our findings of subtle structural changes in the absence of well-defined disease activity support the hypothesis that there may be subclinical nervous system injury in SLE.

The mechanism of putative neuronal damage in lupus is not known. The relatively short duration of SLE in our study population, coupled with the lack of chronic steroid use, makes it unlikely that the neuropsychiatric manifestations and structural aberrations which we observed were drug-induced. Potential causes of neuronal damage include, but are not limited to, antineuronal antibody-mediated cytotoxicity, cytokine-induced inflammation and/or programmed cell death, or some hitherto unrecognized neurocytotoxins [31-33]. In this connection, we have recently demonstrated over-expression of genes encoding the cytokines, interleukin (IL)-1 beta, IL-6 and interferon gamma in the hippocampi of MRL-lpr/lpr SLE mice [34]. These Proinflammatory cytokines are known to produce sickness behavior [35], have been suggested to induce neuronal death in neurodegenerative diseases [36], may be instrumental in the pathogenesis of certain inherited disorders of the cerebellum [37], adversely influence the induction and/or maintenance of experimental memory storage and retrieval [38], and drive pathogenetic autoantibody production in SLE [31].

In previous SLE imaging studies, structural abnormalities or lesions were found to correlate poorly with clinical deficits [13]. Four of the five patients reported herein had no significant neuropsychiatric manifestations other than subjective memory problems. All of our patients had evidence of hippocampal volume loss implicating the hippocampus in the development of cognitive dysfunction in SLE. Consistent with our findings, the presence of atrophy and increased apoptosis in the hippocampus of cognitively impaired, autoimmune MRL-lpr/lpr mice has recently been reported [39].

None of our patients had other evidence of active CNS lupus, such as focal high signal intensity lesions on T2 weighted imaging as previously described by Sibbitt et al. [13]. This suggests that CNS involvement in lupus may be localized to specific regions of the brain such as the hippocampus in a subset of patients. The significance of our finding of unilateral atrophy in 4 of 5 patients is unknown and warrants additional studies aimed at investigating the potential relationship between unilateral temporal lobe disease and verbal or visuospatial memory impairment. It is possible that apparent unilateral hippocampal atrophy may be related to asymmetric bilateral involvement that is so subtle as to be missed on purely qualitative imaging studies such as this one. Investigations utilizing quantitative hippocampal volume measurements, performed longitudinally together with neuropsychological testing to correlate the loss of specific neurons with their presumed function, should offer a more productive means of assessing disease activity and may provide new insights into the etiology of nervous system damage in SLE. Notwithstanding its limitations, the results of this study suggest the provocative hypothesis that the hippocampus may be pathogenetically linked to cognitive dysfunction in neuropsychiatric lupus.

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