ORIGINAL RESEARCH

Application Study of Brain Structure and Functional Magnetic Resonance Imaging in Patients with Systemic Lupus Erythematosus and Cognitive Dysfunction

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ABSTRACT

Objective • This study was aimed to investigate the application value of brain magnetic resonance imaging (MRI) technique, including arterial spin labeling (ASL) and diffusion tensor imaging (DTI) in patients with systemic lupus erythematosus (SLE) and cognitive dysfunction (CDF).

Methods • A total of 50 patients with SLE admitted to the hospital from September 2020 to December 2022 were selected and divided into the group with CDF (n = 21) and the group without CDF (n = 29) according to the score of Montreal Cognitive Assessment Scale (MoCA). Additionally, 10 healthy individuals who underwent physical examinations during the same period were recruited as controls. After the conventional MRI, DTI and ASL data of all subjects were collected, statistical parametric mapping software combined with voxel morphology is applied for gray matter volume, white matter and gray matter cerebral blood flow (CBF) analysis among different groups.

Results • There is a statistically significant difference in conventional MRI findings between the SLE group and the control group ($P < .05$). However, There was no significant difference in white matter fractional anisotropy (FA) values between the two groups ($P > .05$). The apparent diffusion coefficients (ADC) of the right precuneus and the right Brodmann's area 21 and 6 in SLE patients with CDF were significantly higher than SLE patients without CDF ($P < .05$). In comparison to the non-CDF group, the CDF group exhibited reduced gray matter volume, primarily in the anterior cingulate gyrus, left frontal lobe, and right insula ($P < .05$). Meanwhile, the white matter and gray matter cerebral blood flow (CBF) of SLE patients with CDF were significantly lower than those without CDF. ($P < .05$). Correlation analysis showed that the MoCA score was positively associated with the volume of gray matter in the right insula, bilateral frontal lobe, left temporal lobe, and cingulate gyrus ($P < .05$). Additionally, MoCA score was also found to be positively associated with the CBF of white matter and gray matter ($P < .05$).

Conclusions • Alterations in gray matter volume and CBF in SLE patients are closely associated with combined CDF and can be observed by DTI and ASL techniques. (*Altern Ther Health Med.* 2023;29(8):60-65)

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a prevalent chronic autoimmune disease that typically affects females of childbearing age. SLE can involve multiple organs, such as the brain, spinal cord, and peripheral nerves. It manifests diverse central and peripheral neurologic symptoms, among which cognitive dysfunction (CDF) is the most common.[1] According to incomplete statistics, approximately 21% to 95% of SLE patients have CDF, and in severe cases,[2] it may lead to epilepsy and cerebrovascular disease, posing a serious threat to the patient's overall well-being. Therefore, early diagnosis and intervention are significant to SLE patients' prognoses. The Montreal Cognitive Assessment Scale (MoCA) is often used in clinical assessment of cognitive impairment. However, different operators' choice of cognitive function assessment scale and proficiency in the scale will affect the diagnostic accuracy of cognitive impairment. The Montreal Cognitive Assessment (MoCA) is a commonly used clinical method for screening for CDF. At present, magnetic resonance imaging (MRI) has been widely used in assessing central nervous system injury. Still, the lack of specificity of conventional MRI findings in the evaluation of brain structural changes in SLE patients often produces

atypical test results.[3] Therefore, more accurate MRI techniques are needed to evaluate the brain structure and cerebral blood flow perfusion of SLE patients.

In recent years, multiple studies have confirmed the effectiveness of magnetic resonance diffusion tensor imaging (DTI) in evaluating the structure and function of the human brain.[4,5] In recent years, multiple studies have confirmed the effectiveness of magnetic resonance diffusion tensor imaging (DTI) in evaluating the structure and function of the human brain. In addition, arterial spin labeling (ASL) based on MRI can directly measure cerebral blood flow without using a contrast agent, which has a significant advantage in diagnosing cerebrovascular diseases.[6] This study aims to observe changes in gray matter blood flow in SLE patients using ASL and analyze the characteristics of damaged white matter fiber bundles using DTI. The goal is to assess the diagnostic value of DTI and ASL in SLE cases with CDF and to offer insights for clinical diagnosis and treatment.

PATIENTS AND METHODS

Study Subjects

There were 50 SLE patients and 10 healthy individuals in the study. 50 SLE patients admitted to our hospital (Affiliated Hospital of Hangzhou Normal University) from September 2020 to December 2022 were selected as the study subjects, including four males and 46 females. All participants aged from 18 to 52 years (mean, 29.57 ± 7.28 years) with inclusion criteria: (1) all patients were in line with the American College of Rheumatology (ACR) 2009 diagnostic classification criteria for SLE,[7] (2) right-handedness, (3) received DTI and ASL examination, (4) patients were able to cooperate to complete the cognitive function scale assessment, (5) patients with complete clinical data, (6) patients agreed to participate and signed the informed consent.

The exclusion criteria were as follows: (1) rheumatoid arthritis, Sjogren's syndrome and other autoimmune diseases, (2) neurological diseases such as epilepsy, central nervous system infection, and diffuse cerebral hemorrhage, (3) patients with a family history of mental illness or long-term alcoholism or taking psychotropic drugs, (4) pregnant or lactating women, (5) contraindication to MRI scan. Moreover, 10 healthy people who underwent physical examination in our hospital during the same period were recruited as the control group (2 males and 8 females, age range: 27–50 years, mean age: 30.35 ± 8.12 years). All of them were right-handed, able to complete cognitive function and conventional MRI examination with MoCA score ≥26, excluding the family history of cognitive dysfunction (CDF) and other neurological diseases. All subjects signed the study informed consent, and the Medical Ethics Committee of the hospital approved this study.

Grouping Method

The cognitive function of all subjects was evaluated using MoCA.[8] The Montreal Cognitive Assessment (MoCA), a widely used tool for evaluating cognitive function, is frequently employed for clinical assessment of cognitive impairment. This assessment process is frequently employed for clinical evaluation of cognitive impairment. However, variations in operators' choice of cognitive function assessment scale and proficiency can affect the diagnostic accuracy of cognitive dysfunction (CDF). The scale includes 11 items, such as language, attention and concentration, memory, and executive ability, with a total score of 30 points. For subjects with education years ≤ 12 years, an additional score is required to correct for cultural level bias. A MoCA score of<26 indicates CDF, while a score of ≥ 26 indicates normal cognitive function. According to MoCA score, 50 patients with SLE were divided into CDF group (n = 21) and non-CDF group (n = 29).

Data Collection

Electronic medical records were used to collect clinical data, including age, gender, years of education, disease duration, results of autoantibody, and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). SLEDAI was evaluated using a score scale of 9, which included 21 items such as psychiatric symptoms, joint lesions, organic encephalopathy, etc. The scale was divided according to the standards[10] formulated by Gladman: ≥15 was classified as severe activity, 10-14 as moderate activity, 5-9 as mild activity, and 0-4 as basically inactive.

MRI Examination

All MRI images were acquired using a 3.0 T Siemens MRI system (GE Healthcare, USA) with an 8-channel head-phased array coil. After the subject's head was fixed, the axial and positioning MRI images were collected. Then conventional T1WI, T2WI, and T2 fluid-attenuated inversion recovery sequences were obtained, and functional data were collected after excluding intracranial organic lesions.

Diffusion-weighted imaging (DWI) was acquired using an echo-planar sequence in a planar scan parallel to the anterior-posterior commissure line (repetition time (TR)/echo time (TE) = 8000/87.6 ms, slice thickness = 5 mm, field of view (FOV) = 240 mm × 240 mm, matrix =128×128, slice number = 27). Image data were processed by Aws 4.3-MR workstation to obtain the fraction of anisotropy (FA) and apparent diffusion coefficient (ADC). The cerebral blood flow data was measured by pseudo-continuous arterial spin labeling sequence (TR/TE = 4000/12 ms, FOV = 230 mm × 230 mm, flip angle = 90°, matrix = 80×80, slice thickness = 5 mm, post labeling delay = 1800 ms, 90 frames). Weighted three-dimensional magnetization prepared rapid acquisition gradient echo sequence (MPRAGE) was used to acquire whole brain structure images (TR/TE = 2300/298 ms, FOV = 256 mm × 256 mm, flip angle = 90°, NEX=1, matrix = 256×256, slice thickness = 1 mm, consecutive, 176 layers sagittal section).

Image processing method: The data of DTI and ASL were processed by statistical parametric mapping (SPM8) software. The total radiographic scoring criteria of MRI refer to the cerebral microvascular imaging total load score, which includes: (1) brain atrophy, (2) Fazekas score: deep white

matter hypersignal score ≥ 2 and/or paraventricular white matter hypersignal score = 3, (3) moderate and severe persistent vegetative state in basal ganglia (grade 2-4), and (4) more than one deep and infratentorial cerebral microhemorrhage. Each of the four items scored 1 point and the total score was 4 points.

Observation Indicators

(1) Conventional MRI findings of the SLE group and control group were compared. (2) The values of white matter FA and ADC in patients with and without CDF were compared; (3) The volume difference of gray matter in patients with and without CDF was compared. (4) Compare the white matter and gray matter cerebral blood flow (CBF) in SLE patients with and without CDF before treatment. (5) The relationship between gray matter volume, white matter, and gray matter CBF and MoCA score was analyzed. The total radiographic scoring criteria combined with cerebral microvascular imaging techniques allow for a comprehensive evaluation of structural and functional brain changes in SLE patients. This assessment can aid in early detection, monitoring disease progression, and understanding the underlying mechanisms of cognitive dysfunction in SLE.

Statistical Analysis

Statistical analysis was processed by Statistic Package for Social Science (SPSS) software (version 23.0, Armonk, NY, USA). Measurement data subject to normal distribution are expressed as mean ± standard deviation, and $P \leq .05$ indicates a statistically significant difference. The independent t-test was applied for comparison of the measurement data between the two groups, while F -the test for multiple-group comparisons. The F-test for multiple-group comparisons, also known as the analysis of variance (ANOVA), is a statistical test used to determine if there are significant differences between the means of two or more groups. It is an extension of the independent *t* test, which is used for comparing means between two groups only. The F-test assesses whether the variability between group means is significantly greater than the variability within each group. By calculating the ratio of the mean square between groups to the mean square within groups, the F-test generates an F-statistic. This F-statistic is then compared to a critical value to determine if there is a statistically significant difference among the group means. The counting data were expressed in case or ratio (%), and the chi-square test was adopted for comparison. An analysis of correlation was performed using Pearson correlation.

RESULTS

Comparison of Clinical Data

The clinical data differences of the three groups were not statistically significant ($P > .05$), as mentioned in Table 1. The mean age in the SLE with CDF group was 30.48 ± 7.25, in the SLE without CDF group was 29.13 ± 7.58, and in the control group was 30.35 ± 8.12. The p-value for the comparison was 0.799, indicating no significant difference. In the SLE with CDF group, there was 1 male and 20 females. In the SLE without CDF group, there were 3 males and 26 females. In the control group, there were 2 males and 8 females. The p-value for the comparison was 0.416, suggesting no significant difference. The mean years of education in the SLE with CDF group was 8.15 ± 1.23, in the SLE without CDF group was 8.91 ± 1.57, and in the control group was 9.05 ± 1.64. The p-value for the comparison was 0.141, indicating no significant difference. The disease duration was available for the SLE with CDF group (21.67 ± 6.23) and the SLE without CDF group (17.29 ± 8.85), but it was not reported for the control group. The p-value for the comparison was 0.058, suggesting a borderline significant difference. The SLEDAI score was available for the SLE with CDF group (8.38 ± 1.28) and the SLE without CDF group (7.02 ± 2.94), but it was not reported for the control group. The p-value for the comparison was 0.054, indicating a borderline significant difference.

Table 1. Comparison of clinical data among the three groups

Items	SLE with CDF group (n = 21)	SLE without CDF group (n = 29)	Control group (n = 10)	test value	*P* value
Age(years)	30.48 ± 7.25	29.13 ± 7.58	30.35 ± 8.12	0.266	.799
Gender				1.755	.416
male	1	3	2		
female	20	26	8		
Years of education(years)	8.15 ± 1.23	8.91 ± 1.57	9.05 ± 1.64	2.029	.141
Disease duration(months)	21.67 ± 6.23	17.29 ± 8.85	-	1.944	.058
SLEDAI(points)	8.38 ± 1.28	7.02 ± 2.94	-	1.984	.054

Note: Data are present as Mean ± SD.

Table 2. Comparison of MRI findings between SLE group and control group (number)

Group	n	Normal Microbleeding	Abnormal				
			High white matter signal	Subneocortical infarct	Old infarcts	lacunar	Encephalatrophy
SLE group	50	22	3	23	1	2	0
Control group	10	10	0	0	0	0	0
χ^2		10.501	0.632	7.459	0.204	0.414	-
P value		.001	.427	.006	.652	.520	-

Comparison of MRI Findings

There was a statistically significant difference between SLE group and control group in conventional MRI findings ($P < .05$). The number of patients with high white matter signal in SLE group was significantly lower than that in the control group ($P < .05$). See Table 2. "High white matter signal" refers to a finding observed on conventional MRI scans where there is an increased signal intensity in the white matter of the brain. This can be seen as areas of bright signal on T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences. The significance of the difference in high white matter signal between the SLE group and the control group suggests that there are distinct abnormalities present in the white matter of patients with Systemic Lupus Erythematosus (SLE). It indicates that there might be changes in the structure or integrity of the white matter, which could be indicative of underlying disease-related damage or inflammation. White matter is composed of nerve fibers that

Table 3. Comparison of ADC values of white matter between the CDF group and the non-CDF group

Area	MNI (mm)			*t*	*P* value
	X	Y	Z		
Right precuneus	-10	-74	62	5.632	<.05
Right Brodmann's area 21	-60	-2	-24	5.238	<.05
Right Brodmann's area 6	-42	4	62	5.451	<.05

Table 4. Comparison of gray matter volume between the CDF group and the non-CDF group

Area	MNI(mm)			*t*	Voxel values	*P* value
	X	Y	Z			
Anterior cingutate gyrus	0	47	18	8.247	657	<.05
Left superior frontal gyrus	-22	60	3	7.445	995	<.05
Right superior frontal gyrus	28	62	3	6.528	1156	<.05
Left medial frontal gyrus	-27	57	6	8.772	1359	<.05
Right medial frontal gyrus	30	54	17	8.294	950	<.05
Left medial frontal gyrus	-3	50	18	7.107	2405	<.05
Right medial frontal gyrus	3	65	12	7.009	1296	<.05
Left inferior frontal gyrus	-36	24	-3	6.824	1218	<.05
Left superior temporal gyrus	-42	6	-15	7.252	626	<.05
Left medial temporal gyrus	-57	-32	-3	7.926	861	<.05
Right insula	41	22	-5	8.660	305	<.05

Table 5. Comparison of white matter and gray matter CBF between the CDF and non-CDF groups (ml·100g^{-1}·min^{-1})

Group	n	White matter CBF	Gray matter CBF
CDF group	21	20.89 ± 3.24	35.26 ± 3.18
non-CDF group	29	25.77 ± 3.68	41.27 ± 3.52
t		4.861	6.201
P value		<.001	<.001

Note: Data are present as Mean ± SD.

facilitate communication between different parts of the brain. Abnormalities in the white matter can disrupt these connections and lead to various neurological symptoms. In the context of SLE, high white matter signal may reflect processes such as demyelination, inflammation, or small vessel disease. The findings reported in Table 2 show that in the SLE group, 23 out of 50 patients had high white matter signal, whereas none of the individuals in the control group exhibited this abnormality. This statistically significant difference suggests that high white matter signal could serve as a potential marker for identifying brain involvement in SLE patients and distinguishing them from healthy individuals.

Comparison of FA and ADC Values

There was no significant difference FA value of white matter between the CDF group and the non-CDF group ($P > .05$). ADC values in the right precuneus and the right Brodmann's area 21 and 6 were significantly higher in SLE patients with CDF than those without CDF ($P < .05$). See Table 3. ADC values reflect water diffusion in tissues. Higher ADC in the right precuneus and Brodmann's areas 21 and 6 of SLE patients with cognitive dysfunction may indicate microstructural alterations, inflammation, vascular abnormalities, and potential biomarkers for cognitive dysfunction. Further research is needed to understand these implications and establish a stronger association between ADC values and cognitive dysfunction in SLE patients.

Comparison of Gray Matter Volume

Compared with the non-CDF group, SLE patients with CDF showed decreased gray matter volume, mainly in the anterior cingulate gyrus, left frontal lobe, and right insula ($P < .05$). See Table 4. The decreased gray matter volume in specific brain regions (e.g., anterior cingulate gyrus, left frontal lobe, and right insula) in SLE patients with cognitive dysfunction (CDF) may have clinical significance. It may contribute to cognitive impairment, emotional dysregulation, altered pain perception, and be a consequence of inflammation and neurodegeneration in SLE. Understanding these volumes can help manage cognitive symptoms in SLE, but further research is needed to establish the underlying mechanisms and causative relationships.

Comparison of CBF

Compared with the non-CDF group, the CBF in the white matter and gray matter of the SLE patients with CDF was significantly decreased ($P < .05$). See Table 5. The significantly decreased cerebral blood flow (CBF) in both white matter and gray matter of SLE patients with cerebral cognitive dysfunction (CDF) may impact cognition, neuronal function, inflammatory processes, and disease progression. Reduced CBF can lead to cognitive impairment by depriving brain tissue of oxygen and nutrients. It can also affect neuronal activity, disrupt neural signaling, and impair cognitive processes. Inflammatory processes in SLE may contribute to decreased CBF. Diminished CBF may be a marker of disease severity and could potentially increase the risk of developing more severe cognitive deficits over time. Further research is needed to establish causality and underlying mechanisms.

Correlation Analysis

The correlation analysis results revealed that the MoCA score was positively correlated with the gray matter volume of the right insula ($r = 0.711$), bilateral frontal lobes ($r = 0.754$), left temporal lobe ($r = 0.748$), and cingulate gyrus ($r = 0.735$) ($P < .05$). Meanwhile, the MoCA score was positively correlated with white matter CBF ($r = 0.822$) and gray matter CBF ($r = 0.851$) ($P < .05$). The positive correlations between MoCA scores and specific brain regions (right insula, bilateral frontal lobes, left temporal lobe, cingulate gyrus) provide insights into their relationship with cognitive function. Higher MoCA scores are associated with increased gray matter volume in these regions, indicating a potential link between larger volumes and better cognitive performance. The right insula regulates cognition and emotions, frontal lobes handle executive functions, the left temporal lobe is involved in memory and language, and the cingulate gyrus supports attention and emotion control. Positive correlations with white and gray matter cerebral blood flow suggest that better cognitive function is associated with improved blood flow, supporting brain metabolism and communication for optimal function.

DISCUSSION

As an autoimmune disease involving multiple organs and systems of the whole body, SLE may clinically manifest as damage to hematologic, nervous, psychiatric and another system. Due to the in-depth clinical research of SLE and the development of medical technology, the prognosis of SLE has been greatly improved. However, nervous and psychiatric injury are still the main contributing factors of death in patients with SLE, among which the incidence of CDF is the highest.[11] Epidemiological survey reported that,[12] the incidence of CDF in SLE with neurological involvement is as high as 63.2%, seriously affecting patients' quality of life. Traditional methods like the MoCA scale for cognitive function assessment face challenges such as limited scope, subjective ratings, lack of sensitivity, cultural and educational influences, and being time and resource-intensive. They may not capture the full complexity of cognitive function, rely on subjective interpretation, have limited sensitivity, be culturally biased, and require significant time and resources..[13] Overcoming these challenges is important to develop comprehensive, culturally sensitive, and efficient assessment methods that accurately measure cognitive abilities across diverse populations. Therefore, accurate techniques are needed to evaluate the occurrence of CDF in SLE patients.

Although MRI technology has been widely used in the assessment of central nervous system injury, conventional MRI results still cannot accurately reflect the changes of brain structure and function in SLE patients. The atypical examination results may easily lead to some SLE patients with CDF not being diagnosed with nervous system injury, resulting in delayed treatment and irreversible damage to the cognitive function of patients.[14] As a new medical imaging technique, DTI is developed on the basis of diffusion tensor imaging, which has a good effect on evaluating the structure and function of the human brain.[15,16] It can outline the number, direction, and integrity of the main nerve fiber bundles in the white matter, and quantitatively and noninvasively evaluate the injury degree of demyelinating plaques in the brain to show the microscopic anatomical structure of white matter. We can accurately observe the tissue changes of spatial three-dimensional structure, the transport of water and pathological tissue in the intracellular and extracellular microenvironment, and the information of the three-dimensional structure of water diffusion in human tissue. In addition, ASL is a method to obtain CBF value by labeling water magnetically as a freely diffusible endogenous tracer, which has the advantages of no contrast agent, no trauma and simple, and has been applied maturely in other fields. Previous studies on cerebrovascular diseases,17,18 confirmed that ASL technology is comparable to nuclear medicine technology. Rubbert et al.[19] pointed out that about 90% of SLE patients with central nervous system involvement have abnormal CBF perfusion, and 73% of SLE patients with mild symptoms, such as headache and memory impairment, also have abnormal CBF perfusion, indicating that the decrease of CBF in SLE patients is related to the cognitive decline of patients.

In the results of this study, SLE patients with concomitant CDF showed a significant increase in ADC values in the right precuneus and the right Brodmann's area 21 and 6. The increase in ADC values and decrease in gray matter volume observed in specific brain regions of SLE patients indicate potential neuronal damage, loss of cellular integrity, and structural atrophy. These findings align with existing knowledge of cognitive decline in SLE, suggesting that neuroinflammation, immune dysfunction, and vascular abnormalities contribute to brain abnormalities. These changes are associated with cognitive impairments seen in SLE, such as memory deficits and attention problems. Understanding these neuroimaging findings helps identify the underlying mechanisms of cognitive decline in SLE and can guide interventions and monitoring strategies for managing cognitive dysfunction in these patients. Additionally, there was a significant decrease in gray matter volume, mainly in the anterior cingulate gyrus, left frontal lobe, and right insula, and CBF in white matter and gray matter, suggesting that there was a close relationship between gray matter volume, CBF and CDF in patients with SLE. Furthermore, correlation analysis demonstrated that the MoCA score was positively correlated with the gray matter volume of the right insular lobe, bilateral frontal lobe, left temporal lobe and cingulate gyrus, as well as with white matter and gray matter CBF, indicating that the changes of cerebral gray matter volume and CBF play an important role in the occurrence and development of CDF in patients with SLE. The positive correlations between MoCA scores and gray matter volume in specific brain regions, as well as white and gray matter CBF, suggest that changes in cerebral gray matter volume and blood flow contribute to cognitive dysfunction in SLE. Larger gray matter volume and higher CBF are associated with better cognitive performance. Monitoring these neuroimaging markers can help identify individuals at risk for cognitive decline and guide interventions aimed at preserving gray matter integrity and optimizing blood flow. Understanding these correlations has clinical implications, allowing for early detection and targeted strategies to improve cognitive outcomes in SLE patients.

In conclusion, our results provide evidence that the changes in gray matter volume and CBF in SLE patients can be observed through DTI and ASL techniques, and there is a close correlation between gray matter volume and CBF changes in SLE patients with combined CDF. These observations may provide a reference for further investigation of the pathological and physiological mechanisms of central nervous system involvement in SLE. However, as a cross-sectional study, we cannot establish causality. Longitudinal research is needed to validate these findings and determine the precise relationship. Despite this limitation, our findings provide valuable insights into the potential mechanisms underlying SLE-related cognitive impairments. Further investigation will enhance our understanding and enable the development of targeted interventions to improve cognitive outcomes in SLE patients.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

LW and YC designed the study and performed the experiments, GZ and XJ collected the data, GZ, XJ and XZ analyzed the data, LW and YC prepared the manuscript. All authors read and approved the final manuscript.

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