Original Article Histopathological characteristics of neuropsychiatric systemic lupus erythematosus in an MRL/Ipr mouse model

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Abstract: Objectives: Patients with neuropsychiatric systemic lupus erythematosus (NPSLE) frequently present with symptoms of central nervous system involvement, such as headaches and cognitive impairment, which significantly impair their quality of life. Due to non-specific clinical manifestations and difficulties in diagnosing NPSLE, research into its pathogenesis and novel treatments has progressed slowly. This study aimed to establish a mouse model of systemic lupus erythematosus (SLE) to investigate the pathological changes and potential mechanisms of NPSLE. Methods: A mouse model of SLE was established, and serum anti-dsDNA antibody concentrations were measured using enzyme-linked immunosorbent assay (ELISA). Pathological changes in brain tissues were observed through hematoxylin-eosin (HE) staining, and further analysis was conducted using immunofluorescence and immunohis-tochemistry techniques. Results: MRL/Ipr model mice exhibited increased activity and signs of encephalopathy, along with elevated serum anti-dsDNA antibody concentrations. Brain lesions (such as hemorrhagic spots) were observed in the cerebral cortex. Co-localization of CD31/CD105 dual fluorescence showed an increased number of microvessels, and immunohistochemistry confirmed CD31 expression in these microvessels. Conclusions: This study provided an important reference for utilizing the MRL/Ipr mouse model in research on the pathogenesis, new therapies, and efficacy assessment of human NPSLE.

Keywords: Systemic lupus erythematosus, neuropsychiatric systemic lupus erythematosus, MRL mouse model, brain tissues, pathological characteristics

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that has an annually increasing prevalence rate, probably due to the low rate of early diagnosis. SLE is characterized, among other things, by multiple immune abnormalities involving the central nervous system (CNS) [1]. CNS involvement in SLE, termed neuropsychiatric SLE (NPSLE), encompasses various neurological and psychiatric manifestations of varying severity, which can be difficult to differentiate from non-SLE-related disorders. NPSLE has a wide spectrum of manifestations, ranging from mild symptoms (such as mood disorders, anxiety, and headaches) to more severe manifestations, which are often underappreciated [2]. Accordingly, the etiology of SLE-related CNS involvement is poorly understood, and evidence-based therapies are lacking. For NPSLE patients, no laboratory or radiological biomarkers are available for diagnosis and therapeutic decision guidance [2]. NPSLE manifestations typically occur early in the course of SLE and are more prevalent in younger women. Recent studies have shown that NPSLE affects up to 45% of SLE patients, representing one of the leading causes of death in these patients. The pathogenesis of NPSLE is multifactorial, involving inflammatory cytokines, antibodies, and immune complexes, which provoke vasculopathy, cytotoxicity, and autoantibodymediated neuronal damage. In recent years, a growing literature has highlighted the importance of microvascular pathology in NPSLE, especially the role of angiogenesis in the progression of the disease.

The underlying pathophysiology of NPSLE can be classified as vasculitis and vasculopathy, antiphospholipid syndrome (APS), demyelination syndrome, or autoimmune antibody-mediated encephalitis according to its immunological, pathological, and imaging features [1]. Nevertheless, the pathogenesis of NPSLE remains obscure. NPSLE has been recently shown to be closely related to vasculitis and vasculopathy. "Angiogenesis" is a physiological or pathological process that generates 'new blood vessels' from pre-existing vessels [3]. Mounting data have confirmed angiogenesis as a part of vasculopathy in SLE. However, the role of angiogenesis in NPSLE has not been well explored, and further investigation is warranted. The pathophysiology of vascular changes is associated with SLE and APS, leading to vascular thrombosis. Some scholars have believed that SLE is a vaso-occlusive disease highly linked to APS, which can contribute to thrombosis and subsequent angiogenesis. Positive anticardiolipin antibodies are tightly associated with the development of lupus retinopathy and chorioretinopathy (Anticardiolipin Antibodies) [4]. Deposition of immune complexes in the vascular endothelium leads to inflammatory responses. Clinically, it has been found that SLE-associated vasculopathy includes vasculitis, angiogenesis, retinal hemorrhage, cottonwool spots, hard exudates, and microaneurysms [5, 6]. A recent report has described the occurrence of pigment epitheliopathy in a rare case of SLE with choroidal angiogenesis as its first manifestation [7]. Angiogenesis occurs in mesodermal-derived angioblasts from the perineural vascular plexus. The establishment and maintenance of an adequate vascular network are crucial for the growth and expansion of normal and tumor tissues in all organs [3, 8]. CD105 (Endoglin) is an angiogenesis-related factor and a co-receptor for members of the transforming growth factor-β (TGF-β) superfamily. During active angiogenesis, endoglin is upregulated in endothelial cells, particularly at the margins of neovasculature [9-11]. CD105 deficiency has been shown to induce defective angiogenesis. For instance, deficient CD105 expression causes hereditary hemorrhagic telangiectasia type 1, which is characterized by vascular malformations [12]. Additionally, in experimental models, deficiency or loss of CD105 results in mildly defective angiogenesis due to altered physiology of vascular endothelial cells [11, 13]. Nonetheless, the effect of CD105 on cerebrovascular pathological changes and angiogenesis in NPSLE has not been intensively studied. CD31 (Platelet-Endothelial Cell Adhesion Molecule-1) is a 130-140 kD type I transmembrane glycoprotein, also known as Platelet-Endothelial Cell Adhesion Molecule-1 (PECAM-1), which is an immunological marker of angiogenesis [14]. CD31 is abundantly expressed on the surface of endothelial cells and located at junctions between adjacent cells, but is minimally expressed in hematopoietic cells [15]. However, little is known about the role of CD31 in early angiogenesis during NPSLE.

In this study, a mouse model of SLE was established, followed by the evaluation of SLE development and the analysis of the histopathological features of NPSLE with wild-type (WT) C57BL/6J mice as the control. This approach provides important references for the future use of mouse models in research on the pathogenesis, new therapies, and efficacy assessment of human NPSLE.

Materials and methods

Mice and ethics statement

This study was conducted at the Laboratory Animal Center of the Youjiang Medical University for Nationalities after approval by the Experimental Animal Ethics Committee of the Youjiang Medical University for Nationalities (Approval No. 2024051001). Twelve female mice (aged 10-12 weeks; weighing 20-30 g), including wild-type (WT) C57BL/6J and MRL/ Ipr lupus-prone mice, were used in this study. Mice were individually housed in cages of different specific pathogen-free grades throughout the study and fed until 17 weeks. Mouse serum was collected. Brain tissues were obtained after the mice were euthanized. Euthanasia of the mice was performed by anesthetizing the mice with isoflurane (2-5% in oxygen), followed by cervical dislocation, which is a standard and approved method for small rodents. This procedure was carried out under the supervision of qualified personnel to ensure the humane treatment of the animals.

Establishment and validation of the MRL/Ipr mouse model of SLE

MRL/MpJ mice were derived from a series of hybridizations of several different strains of LG, AKR, C3H, and C57BL/6 mice to the 12th generation. At the 13th generation, lymphoproliferative positive and negative sublines were selected, which shared 89% of identical genomes. The mutant gene Faslpr, which is located on chromosome 19, can produce strains with clinical manifestations of different autoimmune diseases, such as MRL/MpJ-Faslpr/J, B6.MRL-Faslpr/J. C3.MRL-Faslpr/J. and NOD. MRL-Faslpr/Dvs, when introduced into other strains. The mutant gene Faslpr was introduced into MRL/MpJ mice. Homozygous MRL/ MpJ-Faslpr/J mice spontaneously developed systemic autoimmune diseases, lymph node enlargement, abnormal T cell proliferation, arthritis, and immune-complex glomerulonephritis. Homozygous MRL-lpr/lpr mice showed a significant increase in circulating immune complexes at 3 months of age. MRL/MpJ mice were provided by Huachuang Sino (Jiangsu, China; SCXK [Su] 2020-0009).

Detection of anti-dsDNA antibodies in peripheral blood

The concentration of anti-dsDNA antibodies in the serum of 16-week-old mouse orbits was measured using enzyme-linked immunosorbent assay (ELISA) to validate the successful establishment of the MRL/lpr mouse model of SLE. The procedure was performed as instructed in the manuals of the anti-dsDNA antibody ELISA kit.

Brain tissue fixation and hematoxylin-eosin (HE) staining

Brain tissues were fixed in 10% buffered formaldehyde, dehydrated, embedded, and sectioned. Next, the sections (3 μ m) were subjected to staining on the Thermo Scientific Gemini AS slide stainer and then observed and analyzed under a light microscope. Scanning was conducted with the 3DHistech Pannoramic Midi Scanner, and images were collected with caseviewer software. All chemical reagents used in this study were of analytical grade.

Immunofluorescence

The sections were dewaxed and hydrated, placed in 3% citric acid solutions for 10 min of high-pressure repair (timed from the start of the jet), and slowly cooled to room temperature, followed by 3 phosphate-buffered saline (PBS) washes (5 min each time). After that, the sections were immersed in 3% hydrogen peroxide for 20 min at room temperature, washed in PBS three times (5 min each time), and sealed with bovine serum albumin (BSA) solutions for 20 min at room temperature. Following the removal of the BSA solutions, the sections were incubated with diluted antibodies against CD105 (10862-1-AP; Proteintech, Wuhan, China) and CD31 (GB120005-100: Servicebio, Wuhan, China) at 4°C overnight. On the next day, the sections were taken out, cooled to room temperature, and washed in PBS three times (5 min each time). The sections were incubated with the corresponding fluorescent secondary antibodies (ZSGB-Bio, Beijing, China), including goat anti-rabbit immunoglobulin G (IgG) secondary antibody (ZF-0516) and goat antimouse IgG secondary antibody (ZF-0512), followed by 3 PBS washes (5 min each time) in the dark at 37°C for 20 min. Next, the sections were stained with 4',6-Diamidino-2-Phenylindole solutions at room temperature in the dark for 20 min, washed completely with water, and sealed with water-soluble sealant. To assess the co-localization of CD105 and CD31 in brain tissues, microvessel density (MVD), which is a quantitative indicator of angiogenesis, was determined, and the number of microvessels per unit area was counted. Labeling was performed with two antibodies and observed under a fluorescence microscope (OLYMPUS, Tokyo, Japan), with D105 fluorescence in red, CD31 fluorescence in green, and nuclei fluorescence in blue. The computer image processing system consisted of image acquisition software (UC90; OLYMPUS) and image analysis software (Image-Pro Plus, Media Cybernetics, Silver Spring, Maryland, USA). Positive expression areas were selected based on the images of positive immunoreactivity to determine the number of microvessels with positive immunostaining. The number of microvessels was



Figure 1. Validation of the mouse model of systemic lupus erythematosus (SLE) and co-expression of CD105 and CD31 in brain tissues of SLE mice. A: The serum concentration of anti-dsDNA was tested with enzyme-linked immunosorbent assay (ELISA). P < 0.05, compared with the control group (indicated by "*"). B and C: The expression and co-localization of CD105 and CD31 were detected with immunofluorescence. P < 0.001, compared with the control group (indicated by "***").

the number of vessels with dual fluorescence co-expression.

Immunohistochemistry

Immunohistochemistry was conducted on the sections according to the standard method. Each section was dewaxed, rehydrated with gradient ethanol, autoclaved in 10 mL of citrate buffer (pH 6.0) at 120°C for 2 min to recover antigens, then cooled to 30°C, and washed with PBS (pH 7.3). The sections were subjected to overnight incubation at 4°C with anti-CD31 polyclonal antibodies (GeneTex, Irvine, California, USA) diluted in antibody dilution solutions (Zymed/Invitrogen, Carlsbad, CA, USA) at a ratio of 1:500, and then PBS washing. Afterward, the sections were incubated with secondary antibodies (Dako REAL EnVision Detection System, Dako, UK) for 30 min at room temperature, followed by color development with 3,3'-diaminobenzidine. Cell nuclei were lightly counterstained with hematoxylin.

Evaluation of histopathology, immunofluorescence, and immunohistochemistry

All sections of brain tissues for HE staining, immunofluorescence, and immunohistochem-

istry were interpreted by two pathologists, who performed double-blind observations and analysis under blinding to the relevant data of mice. Any differences in immunohistochemistry scores were resolved by consensus. CD31 was identified as positive when the cytoplasm was stained brown.

Statistical analysis

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). All measurement data were expressed as mean \pm standard deviation. The data were analyzed by comparing the means of multiple samples and through pairwise comparisons. Data were tested for homogeneity of variance using Levene's test. For data with homogeneity of variance, the F-test was used; for data with heterogeneity of variance, the q-test (Newman-Keuls method) was utilized. Differences were considered statistically significant at P < 0.05.

Results

Validation of the mouse model of SLE

The concentration of anti-dsDNA antibodies in the orbital blood of mice was examined with ELISA (**Figure 1A**). The results displayed that



Figure 2. Representative pathological lesions in brain tissues of SLE mice with central nervous system (CNS) involvement. A: Normal capillary in the brain of control mice (magnification: 400×). B: Vasculopathy with vessel wall thickening and inflammatory infiltration (magnification: 400×). C: Micro-thrombosis (magnification: 400×). D: Microinfarction (magnification 200×).

the serum concentration of anti-dsDNA antibodies in the SLE group was significantly higher than that in the control group (P < 0.05), highlighting the successful establishment of the SLE mouse model. In addition, compared to control mice, some SLE mice had significantly increased activity, which constantly ran and climbed inside the cages and were unable to quiet down, accompanied by reduced desire to explore the new environment. After being placed into the new space, instead of actively exploring their surroundings like control mice, these SLE mice showed fearful, retreating, and hypervigilant behaviors.

Co-expression of CD105 and CD31 in brain tissues of SLE mice

Immunofluorescence was utilized to test the expression and co-localization of CD105 and CD31. As observed by the fluorescence microscope, the number of microvessels co-expressing dual fluorescence was substantially higher in the SLE group (65.8 ± 6.55) than in the control group (41.55 ± 7.9) (P < 0.001; Figure 1B, 1C).

Pathological changes in the brain tissues of SLE mice

According to HE staining of brain tissues, 6 control mice showed neurons and glial cells with normal morphology and a small number of capillaries in brain tissues, which mostly consisted of a single layer of vascular endothelial cells (Figure 2A), with no abnormal changes such as intravascular thrombosis or hemorrhage. Among 6 SLE mice, 4 mice presented with multiple types of brain tissue lesions (Figure 2B-D), predominantly including vasculitis, microthrombosis, microinfarcts, and macroinfarcts; scattered hemorrhagic spots, microvascular edema, and neuronal necrosis were also observed in some brain tissues. The other 2 SLE mice developed mild vasculitis in

the encephalopathic tissues, with no other encephalopathic lesions. Immunohistochemistry results revealed that compared with that in the control group (**Figure 3A**, **3B**), the density of CD31-labeled microvessels was higher in the SLE group (**Figure 3C**, **3D**).

Discussion

Although the clinical manifestations of SLE are well documented, there is limited information regarding the pathological characteristics of CNS involvement in SLE. Histopathological changes in the brain are the gold standard for the diagnosis of NPSLE. In the present study, the comprehensive analysis of mouse models of SLE demonstrated a high incidence rate of NPSLE (4/6 mice) and extensive neuropathological damage in SLE mice, with scattered hemorrhagic spots, microvascular edema, neuronal necrosis, diffuse vasculopathy, microinfarcts, vasculitis, and microthrombosis as the most common histopathological changes.

NPSLE is a frequent complication of SLE with a dangerous onset, which is a leading cause of death in SLE patients. A multicenter and large-



Figure 3. High microvascular density in the brain of SLE mice with CNS involvement. (A and B) Lower microvascular density in the brain of control mice according to hematoxylin-eosin (HE) staining (A; magnification: 200×) and CD31 immunohistochemistry (B; magnification: 400×). (C and D) Higher microvascular density in the brain of SLE mice according to HE staining (C; magnification: 200×) and CD31 immunohistochemistry (D; magnification: 400×).

mice, female MRL/lpr mice develop the disease significantly earlier than male MRL/ Ipr mice and produce autoantibodies against dsDNA and Sm [19]. Neurological symptoms in MRL/Ipr mice encompass early depression and pleasure, apathy and solitude, and decreased activity, accompanied by certain spatial learning deficits [20]. Specifically, MRL/lpr mice display marked depression at an early age (8 weeks of age), namely typical features such as lack of curiosity and indifference to novelty [21]. Moreover, they develop cognitive impairment characterized by visuospatial memory deficits by 10 weeks of age [22]. The symptoms of MRL/lpr mice observed in this study are

sample study by Galeazzi et al. [16] has reported that 41.9% of SLE patients encounter neurological changes. In the present study, SLE mice also exhibited mental abnormalities, with markedly increased activity (constant running and climbing in the cages and difficulty in quieting down) and decreased desire to explore the new environment. Clinical manifestations of CNS involvement in SLE are highly variable, ranging from manifestations of psychoemotional disturbances to features of neurological damage [17]. Nevertheless, the disease lacks specific diagnostic methods, and there are currently no clear diagnostic criteria at home or abroad. Among traditional screening methods, the results of cerebrospinal fluid (CSF) examinations are considered an important basis for the diagnosis of NPSLE. Clinically, pressure and leukocytes are elevated and glucose contents are reduced in CSF; however, these results cannot be clearly distinguished from the characteristics of the CSF of bacterial encephalitis and viral encephalitis. Accordingly, these results are of low specificity. As a consequence, the CSF examination cannot be used as the gold standard for the diagnosis of NPSLE.

MRL/lpr mice are generated by hybridization of several mouse strains including Lg/J, C3H/Di, C57BL/6, and ALKR/J [18]. Different from BxSB consistent with the observations of the above studies.

Most NP symptoms in MRL/Ipr mice are provoked by autoimmune diseases. A prior study has unveiled that autoantibodies significantly associated with autoimmunity [including antidsDNA and anti-N-methyl-D-aspartate receptor (NMDAR) antibodies] could be detected in female MRL/lpr mice after 8 weeks and increase with the age of mice [21]. The development of NPSLE in MRL/lpr mice may be attributed not only to autoimmune activation, which affects brain function through chronic inflammatory pain or pro-inflammatory neuropeptides, but also to structural alterations in the CNS, including damage to the mesolimbic dopaminergic pathway, inflammatory responses, and encephalatrophy in the limbic system, or altered neuronal activity in the hippocampus and cortical regions, which ultimately compromise emotion or cognition [21, 23, 24]. In addition, leukocyte infiltration-induced brain growth retardation and brain dysfunction have been validated as the precipitating factors for the development of neurodegeneration in MRL/Ipr mice [25].

CD105 is a co-receptor for ligands of the TGF- β family and is highly expressed in angiogenic endothelial cells. Therefore, CD105-based

imaging has been utilized to visualize lesions in related diseases. Accumulating studies have reported that endoglin deficiency hinders angiogenesis [11, 13, 26]. In contrast, another study has identified that CD105 downregulation is responsible for depressing vascular endothelial cell proliferation and initiating the stabilization process, underscoring that CD105 overexpression impedes angiogenesis [27]. Additionally, CD105 overexpression maintains endothelial cell activation and increases the risk of tumor metastasis, and administration of anti-CD105 antibodies (such as TRC105) can reduce the number of metastatic tumors [28, 29]. Ollauri-Ibáñez et al. [27] have believed that although CD105 upregulation is necessary during the first phase of angiogenesis, downregulation of CD105 to the basal level may alter vessel stability and parietal cell recruitment. Therefore, vascular normalization from antiendoglin therapy may reduce tumor cell intravasation and increase the efficacy of chemotherapy. However, there are currently no reports on CD105 expression in brain tissues during SLE. In the present study, HE staining and immunofluorescence revealed vasculitis, microthrombosis, microinfarcts, and macroinfarcts in the brain tissue sections of SLE mice, accompanied by scattered hemorrhagic spots, microvascular edema, and neuronal necrosis in some brain tissues. Immunofluorescence results disclosed that compared with that in the cerebral cortex of control mice, the number of microvessels co-localized with CD105 and CD31 were markedly elevated in the cerebral cortex of SLE mice, illustrating the occurrence of angiogenesis in the brain tissues of SLE mice. Taken together, it can be concluded that imaging of CD105 and CD31 can be used as markers for visualizing brain tissue lesions in SLE.

This study innovatively explored the role of angiogenesis in NPSLE, particularly by evaluating the expression of CD105 and CD31 as markers for angiogenesis in the brain tissues of SLE mice. In imaging, human NPSLE can manifest as cerebral infarction, cerebral hemorrhage, and cerebral thrombosis-induced cerebral edema. In the present study, diffuse vasculopathy, vasculitis, microthrombosis, scattered hemorrhagic spots, microvascular edema, neuronal necrosis, and microinfarcts were present in the brain tissues of SLE mice. The pathological characteristics of encephalopathy in SLE mice are dominated by vasculopathy, that is, microthrombosis occurs on the basis of vasculitis, further leading to microvascular endothelial cell necrosis and vascular wall disruption and eventually causing microhemorrhage and microinfarcts, which are more clearly defined than the reported imaging findings in humans. This study for the first time uses the MRL/Ipr mouse model to investigate earlystage neurovascular lesions in NPSLE, which could be further explored to detect subclinical stages before obvious morphological changes appear.

In our experimental mouse model, relatively early encephalopathy lesions were also observed. Accordingly, in future studies on the pathogenesis of NPSLE, mouse models can be utilized to investigate earlier lesions or even subclinical stages before morphological changes. These advantages of animal models are not available in human imaging. Our experimental results suggest that the MRL/Ipr mouse model can be used to characterize the mechanisms of CNS involvement in SLE.

Conclusions

Collectively, the mouse models of SLE have similar histopathological characteristics of the brain to clinical imaging and allow for the observation of pathological changes at different stages. In addition, CD105 and CD31 play key roles in angiogenesis as vascular growth-related biomarkers. CD105 and CD31 are abnormally expressed in brain tissues during SLE and are associated with angiogenesis in brain tissues, underlining that CD105 and CD31 may be pivotal indicators for determining angiogenesis in the context of CNS involvement in SLE. Overall, our findings hint that the MRL/lpr mouse model of SLE can be used to explore the pathogenesis and new treatment of human NPSLE and provide new observations that the main neuropathological characteristics of SLE are related to thrombosis-induced ischemic injury and small vessel diseases.

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Disclosure of conflict of interest

None.

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