

ORIGINAL ARTICLE

Reversible basal ganglia lesions in neuropsychiatric lupus: a report of three pediatric cases

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Abstract

Aim: Central nervous system involvement represents a serious and common complication of systemic lupus erythematosus (SLE). We describe the characteristics of patients with neuropsychiatric (NP) SLE complicated with reversible basal ganglia lesions.

Methods: We describe the cases of three NPSLE patients.

Results: They presented with NP manifestations such as headache, cognitive dysfunction, tremors, seizures, and mood disorder. The levels of autoantibodies to NMDA (*N*-methyl-D-aspartate) receptor antibodies and antiribosomal-P antibodies were elevated, indicating the presence of an acute phase. Marked elevation of interleukin-6 in cerebrospinal fluid was noted when these patients showed NP symptoms. Moreover, the patients presented with high-intensity lesions in the basal ganglia on T2-weighted images, fluid-attenuated inversion recovery (FLAIR) images, diffusion-weighted images (DWI) and apparent diffusion coefficient (ADC) maps. Following immunosuppressive treatment, almost complete improvement of the lesions was noted.

Conclusion: The reported cases indicate that reversible vasculopathies represent vasogenic edema localized in basal ganglia lesions and that activation of the autoimmune system and inflammation could lead to NP manifestations in SLE.

Key words: apparent diffusion coefficient, diffusion-weighted images, lupus, neuropsychiatric systemic lupus erythematosus, normal range 2, posterior reversible encephalopathy syndrome.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem disease characterized by pathogenic autoantibodies and immune complex formation. An estimated 15–20% of patients experience the onset of SLE during childhood.¹ The involvement of the central nervous system represents a serious complication of SLE. The American College of Rheumatology (ACR) criteria is used to verify

the clinical manifestations and diagnosis of SLE.² Neuropsychiatric SLE (NPSLE) involves a wide range of focal and diffuse central and peripheral nervous system disorders and affects up to 75% of SLE patients.^{3,4} NPSLE can occur at any time in the course of SLE and is likely to be caused by multiple factors, including autoantibody production, vasculopathy and pro-inflammatory cytokines. Cerebrovascular disease is reported in up to 25% of children with NPSLE.^{5,6} Establishing a diagnosis of NPSLE involves the combined use of immunoserological testing, neuroimaging and neuropsychological assessments, as there is currently no single diagnostic tool specific to NPSLE. Various autoimmune processes are reported to contribute to the

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pathogenesis of NPSLE, including mechanisms involving N-methyl-d-aspartate (NMDA) receptor subunit NR2 antibodies (anti-NR2)^{7,8} antiribosomal-P antibodies (anti-P)⁹ and cytokines/chemokines.¹⁰ Conventional magnetic resonance imaging (MRI) is a powerful tool for the early detection of brain lesions in NPSLE patients,¹¹ and diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) mapping can help detect early ischemic lesions.¹² Cerebrovascular disease (CVD) is one of the focal central nervous system manifestations in NPSLE patients and may be caused by atherosclerosis, embolism, anti-phospholipid antibodies, diffuse vasculopathy, and immune complex deposition.

In the present report, we describe the cases of three NPSLE patients who indicated positive results in tests for anti-NR2 and/or anti-P, showed high levels of interleukin (IL)-6 in the cerebrospinal fluid (CSF), and presented with reversible basal ganglia lesions.

MATERIALS AND METHODS

Patients who fulfilled the 1997 American College of Rheumatology criteria for SLE and presented with neuropsychiatric manifestations were identified. Clinical profiling included age, sex, clinical features, drugs used, laboratory data and MRI details. Written informed consent was obtained from all patients for the publication of this manuscript and any accompanying images.

Immunoglobulin G (IgG) anticardiolipin antibodies (aCL) were measured by standard enzyme-linked immunosorbent assay (ELISA) using a MESACUP-IgG kit (MBL Co., Ltd., Tokyo, Japan), whereas lupus anticoagulant (LA) was measured by the dilute Russell's viper venom time method using a kit from Gradipore Ltd (Sydney, NSW, Australia). Anti- β 2GPI antibodies were measured by ELISA using a kit from Yamasa Co. (Choshi, Japan). IgG anti-NR2 and anti-P were measured by ELISA using recombinant ribosomal P0 protein as an antigen, as previously described.^{8,9}

CASE REPORT

Case 1

A 10-year-old girl who presented with malar rash, arthralgia, photosensitivity, oral ulcers and Raynaud's phenomenon, as well as positive results on anti-nuclear antibodies (ANA) testing (titer, 1 : 80) and anti-DNA antibody testing was diagnosed with SLE. Renal biopsy showed minimal mesangial nephritis. Immunofluorescence study showed mesangial localization of IgG, IgM, C1q and C4. Initial treatment included oral steroids.

When the steroid doses were tapered, she again exhibited fever and headache. The patient was admitted to the hospital at the age of 11 years with fever, headache, arthralgia, tremors and mood disorder. Physical examination on admission revealed facial erythema, blood pressure of 102/74 mmHg, and pulse rate of 90 beats/min. Neurological examination revealed that she was conscious, without any evidence of neglect, aphasia or apraxia. Peripheral blood analysis yielded the following results: white blood cell count, 4800 cells/mL; hemoglobin, 14.5 g/dL; and platelets, 193 000 cells/mL. The erythrocyte sedimentation rate (ESR) was 38 mm/h and the serum creatinine level was 0.42 mg/dL. The levels of anti-double-stranded DNA (anti-dsDNA) antibodies and complements C3 and C4 were normal. The patient showed positive results for tests for ANAs (titer, 1 : 80), but negative results for anti- β 2GPI antibodies, aCL, and LA. A brain MRI examination showed increased signal intensity in the anterior basal ganglia on both sides of the T2-weighted images, fluid-attenuated inversion recovery (FLAIR), DWI and ADC maps (Fig. 1 a-d). The anti-NR2 titers in the serum and CSF were > 55 (normal range [NR], < 14.7 U/mL) and > 100 U/mL (NR, < 9.88 U/mL), respectively. The level of anti-P was 15.2 U/mL (NR, < 3.68 U/mL) and the level of IL-6 in the CSF was 43.1 pg/mL. Based on the above findings, a diagnosis of NPSLE was made.

Following diagnosis, we administered high-dose pulsed intravenous (i.v.) steroids (methylprednisolone); however, the clinical symptoms persisted and the patient also experienced seizures. Additional treatment with i.v. immunoglobulin (IVIG), plasma exchange, and i.v. cyclophosphamide (CYC) was administered. Ten days after these treatments, her fever gradually subsided and the ESR gradually reduced. Her CSF IL-6 level was 1.3 pg/mL. The anti-NR2 titers in the serum and CSF were 12.5 and 9.3 U/mL, respectively. Her malar rash, headache and fever ameliorated. Monthly i.v. CYC infusions were continued. A brain MRI (Fig. 1e,f) performed 5 months later showed improvement.

Case 2

A 13-year-old girl who presented with fever, polyarthritides, headache, oral ulcers, purpura, pancytopenia, hypocomplementemia, false positive serologic test for syphilis, and positive result for ANA testing (titer, 1 : 2560) was diagnosed with SLE. Initial treatment included steroids. When the steroid doses were tapered, she again exhibited fever and headache. The patient was admitted at the age of 14 years, with fever, headache, tremors and memory dysfunction. At the time of

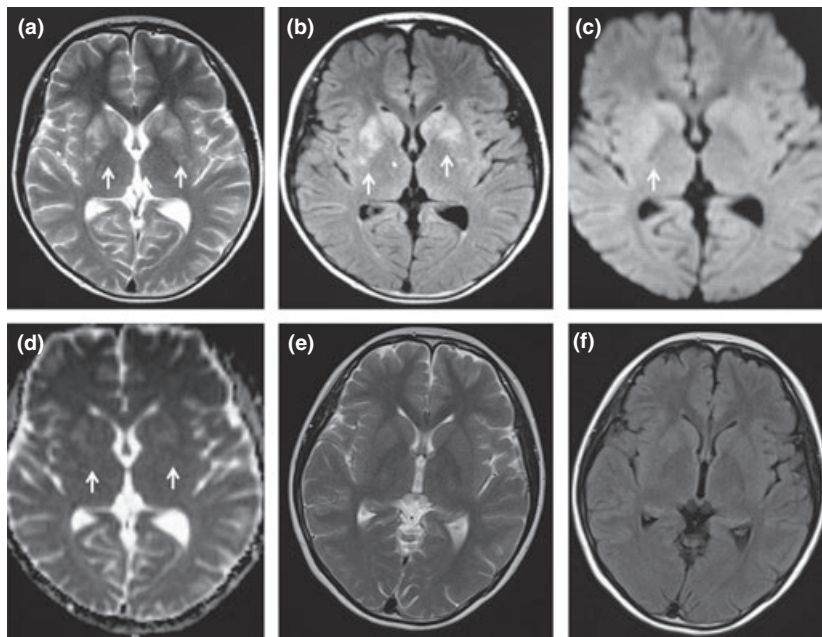


Figure 1 Axial brain magnetic resonance imaging (MRI) on admission and after treatment in Case 1. (a) T2-weighted image. (b) Fluid-attenuated inversion recovery (FLAIR) image. (c) Diffusion weighted imaging (DWI) scan. (d) Apparent diffusion coefficient (ADC) map. (e,f) Follow-up T2-weighted and FLAIR show normal findings.

admission, she was not completely conscious (Glasgow coma scale score, 14). Both eyes were in the midline position and ocular movements were found to be normal in all directions. The pupils were equal (in size and shape) and reactive to light. Her blood pressure and heart rate were 103/70 mmHg, 85 beats/min, respectively. Brain MRI evaluation showed increased signal intensity in the right caudate nuclei and paraventricular ventricle (Fig. 2a–d). Psychological evaluation with the Wechsler Intelligence Test for Children (3rd edn) (WISC-III) test indicated that her non-verbal intelligence quotient (IQ) was 57, (within the range of mild mental retardation) and her verbal IQ was 79 (borderline mental retardation). Her global IQ was 65, which indicates mild cognitive dysfunction. Peripheral blood analysis yielded the following results: white blood cell count, 2300 cells/mL; hemoglobin, 11.1 g/dL; and platelets, 48 000 cells/mL. The C-reactive protein (CRP) level was 4.0 mg/dL and the ESR was 54 mm/h. The serum creatinine level was 0.59 mg/dL. The levels of anti-dsDNA antibodies, anti- β 2GPI antibodies, and complements C3 and C4 were normal. The patient indicated positive results for ANAs (titer, 1 : 160), anti-SS-A/Ro antibodies (level, 99.4 U/mL; NR, < 10 U/mL), aCL (level, 11 U/mL; NR, < 10 U/mL), and LA (level, 1.43; NR, < 1.3). A bone marrow puncture biopsy was performed. Activated macrophages with hemophagocytosis were found, which together with the clinical and laboratory data (bicytopenia with hypofibrinogenemia (level, 153 mg/dL; NR, 200–400), and

afterwards a ferritin of 7479 ng/mL (NR, < 138), Lactate dehydrogenase (LDH) of 730 U/L (NR, 106–211) and triglycerides of 293 mg/dL (NR, 38–150). D-dimer and soluble IL-2 receptor levels were 55.75 μ g/mL (NR, < 0.8) and 1830 U/mL (NR, 220~530). The anti-NR2 titers in the serum and CSF were 24.0 and 8.6 U/mL, respectively, and the level of IL-6 in the CSF was 558 pg/mL. Based on the above findings, a diagnosis of NPSLE and hemophagocytic syndrome was made.

Following diagnosis, we administered high-dose pulsed i.v. steroids, cyclosporin A; however, the patients continued to exhibit fever. Additional treatment with IVIG and i.v. CYC was administered. After the second course of intravenous pulse methylprednisolone and IVIG treatments, improvement of leukocytopenia and thrombocytopenia was noted. Subsequently, her headache and tremors ameliorated. Her CSF IL-6 level was 1.3 pg/mL. The anti-NR2 titers in the serum and CSF were 10 and 3.22 U/mL, respectively. She continued to receive monthly i.v. CYC infusions. Her cognitive impairment gradually decreased. Brain MRI (Fig. 2e,f) performed 6 months later showed improvement.

Case 3

A 14-year-old girl who presented with prolonged fever, oral ulcers and malar rash was diagnosed with SLE. She indicated positive results in tests for ANAs (titer, > 1 : 1280), anti-dsDNA, anti-Sm, anti-RNP and LA. Renal biopsy showed minimal mesangial nephritis.

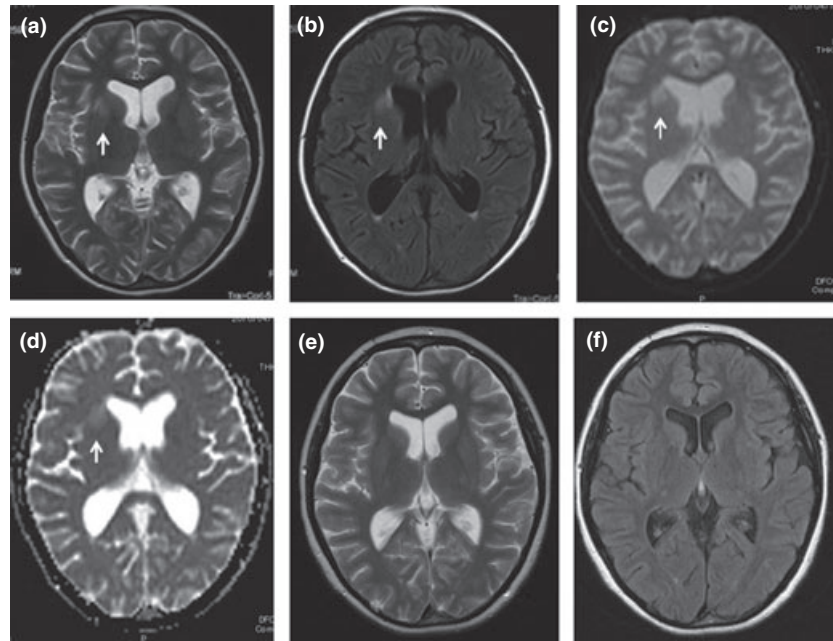


Figure 2 Axial brain magnetic resonance imaging (MRI) on admission and after treatment in Case 2. (a) T2-weighted image. (b) Fluid-attenuated inversion recovery (FLAIR) image. (c) Diffusion weighted imaging (DWI) scan. (d) Apparent diffusion coefficient (ADC) map. (e,f) Follow-up T2-weighted and FLAIR show normal findings.

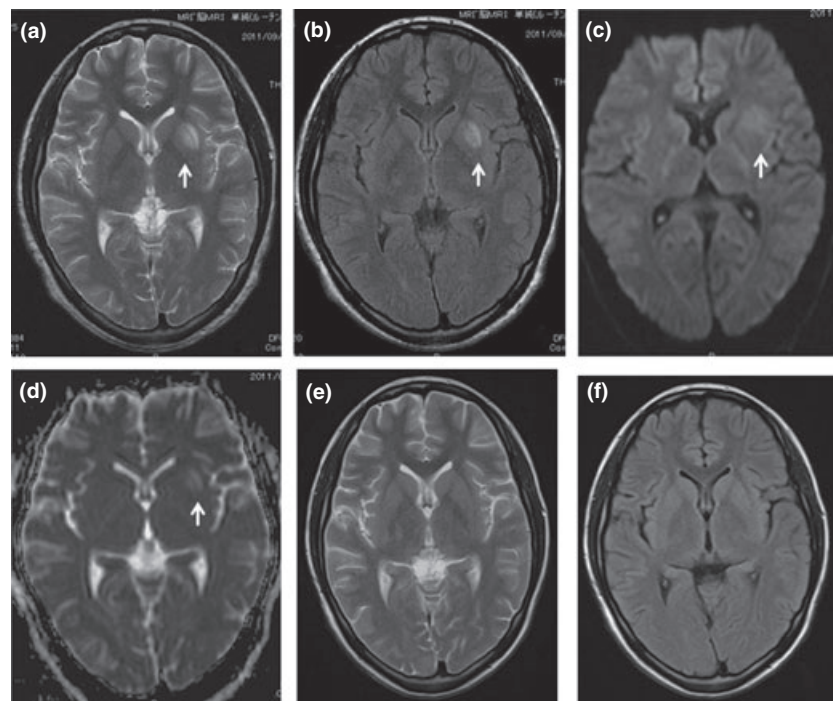


Figure 3 Axial brain magnetic resonance imaging (MRI) on admission and after treatment in Case 3. (a) T2-weighted image. (b) Fluid-attenuated inversion recovery (FLAIR) image. (c) Diffusion weighted imaging (DWI) scan. (d) Apparent diffusion coefficient (ADC) map. (e,f) Follow-up T2-weighted and FLAIR show normal findings.

Initial treatment included steroids. When the steroid doses were tapered, she again exhibited fever and headache.

The patient was admitted at the age of 15 years with fever, headache and rash. Her blood pressure was

100/53 mmHg and pulse rate was 100 beats/min. A physical examination revealed oral ulcers and malar rash. Sensory disturbance was not observed. Moreover, pathological reflexes, including Babinski's reflex, were not noted. Peripheral blood analysis yielded the

following results: white blood cell count, 2700 cells/mL; hemoglobin, 12.8 g/dL; and platelets, 117 000 cells/mL. ESR was 32 mm/h and serum creatinine level was 0.72 mg/dL. The levels of complements C3 and C4 were 60 and 10 mg/dL, respectively. The patient indicated positive results in tests for ANAs (titer, 1 : 320), anti-dsDNA and anti-Sm antibodies. The levels of anti- β 2GPI antibodies, aCL and LA were normal. A brain MRI showed increased signal intensity in the anterior lentiform nuclei on the left side (Fig. 3a–d). The CSF IL-6 level was 795 pg/mL. The anti-NR2 titers in the serum and CSF were 9.0 and 20 U/mL, respectively. The level of anti-P was 20 U/mL. Based on the above findings, a diagnosis of NPSLE was made.

After diagnosis, we administered high-dose pulsed i.v. steroids. Additional treatment with mycophenolate mofetil was administered. After the first course of i.v. pulse methylprednisolone, her headache and fever ameliorated. Six days after this treatment, she exhibited improvement of oral ulcers and malar rash. The CSF IL-6 level was 12.5 pg/mL. The anti-NR2 titers in the serum and CSF were 7.4 and 11.2 U/mL, respectively. A brain MRI (Fig. 3e,f) performed 3 weeks later showed that the high-intensity lesions had disappeared.

DISCUSSION

In the present report, we describe the cases of three SLE patients who presented with high-intensity lesions in the basal ganglia on T2-weighted images, FLAIR images, DWI scans and ADC maps. These lesions almost completely disappeared after immunosuppressive therapy. Reversible involvement of the basal ganglia has rarely been reported in pediatric cases of SLE. Kimura *et al.*¹³ reported on reversible focal neurological manifestations, including CVD manifestations, in SLE. Furthermore, posterior reversible encephalopathy syndrome (PRES) has been described in many conditions, including hypertension, eclampsia, renal failure, immunosuppressant drugs and autoimmune diseases, particularly SLE.^{14,15} In the patients in the present study, DWI showed high signal intensity in the basal ganglia, and high ADC values were observed at these lesions, indicating vasogenic edema. Vasogenic edema has been observed in several conditions, including PRES.¹⁶ However, none of our patients showed hypertension and distribution of lesions in basal ganglia without typical posterior hemisphere involvement. All patients responded well to immunosuppressive therapy, which resulted in the disappearance of lesions, as observed on MRI scans. Moreover, the signal intensities

on the DWI scans changed from high to normal, which was consistent with the recovery of neurological deficits. This result might reflect an improvement in vasogenic edema rather than that in the acute ischemic lesions and infarction. A high ADC value indicates vasogenic edema and vascular changes occurring directly due to the vasculitic process. In this regard, these manifestations may be classified under CVD according to the 1999 ACR nomenclature. However, these manifestations are different from CVD in several aspects. Ischemic stroke and/or transient ischemic attack comprise over 80% of CVD cases, whereas CNS vasculitis is rare. Moreover, strong risk factors of CVD include persistently positive moderate-to-high titers of anti-phospholipid antibodies.¹⁷ However, all patients in the present report showed negative or low titers for CL or lupus anticoagulant (LAC).

The pathogenesis of NPSLE is not well understood. Vasculopathy in lupus as a result of infarction has been associated with antibodies that bind CL or phospholipids. NPSLE has been linked to anti-NR2 and anti-P. The NMDA receptor subunit NR2 has been shown to be a target of autoantibodies in SLE, thus supporting the antigenic target hypothesis as a mechanism of NP manifestation. Anti-NR2 might activate the NF- κ B pathway as a result of the up-regulated expression of IL-6 and IL-8¹⁸. In addition, anti-P might modify a variety of inflammatory responses by up-regulating the expressions of pro-inflammatory cytokines tumor necrosis factor- α (TNF- α) and IL-6.¹⁹ In some reports, the level of cytokines such as IL-6, IL-1, IL-8, TNF- α , interferon-gamma, monocytes chemoattractant protein (MCP-1), and interferon gamma-induced protein 10 were shown to be elevated, allowing these cytokines to be used as diagnostic tool.²⁰

In summary, we report three cases of reversible basal ganglia lesions in pediatric NPSLE. In these cases, the clinical course, including immunosuppressive therapy and MRI findings, was distinct from that of CVD. Based on our findings, a diagnosis of NPSLE was made. The MRI data, as well as ADC values and the pathological tests, point to an immune-mediated pathogenesis. However, further research is required to determine the significance and prognosis of the findings obtained via DWI and ADC value studies, and a careful clinical correlation for neurological abnormalities is important.

CONFLICT OF INTEREST

None.

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