

Reversible Bilateral Basal Ganglia and Brainstem Lesions in Neuropsychiatric Systemic Lupus Erythematosus: A Case Report

Rocksy Fransisca V Situmeang^{1,2}, Reza Stevano², Ekawaty Yasinta Yohana Larope^{2,3}, Ratna Sutanto^{2,4}

¹ Department of Neurology, Siloam Hospitals Lippo Village

² Faculty of Medicine, Pelita Harapan University

³ Department of Pediatrics, Siloam Hospitals Lippo Village

⁴ Department of Radiology, Siloam Hospitals Lippo Village

Abstract

Citation : Situmeang Rocksy Fransisca V, Stevano Reza, Larope Ekawaty Yasinta Yohana, Sutanto Ratna.

Reversible Bilateral Basal Ganglia and Brainstem Lesions in Neuropsychiatric Systemic Lupus Erythematosus: A Case Report. *Medicinus*. 2021 October; 9(3): 118-123

Keywords: Systemic lupus erythematosus; Neuropsychiatric lupus; Immunoglobulin therapy; Case report

***Correspondance:** Rocksy Fransisca V Situmeang. Department of Neurology, Siloam Hospitals Lippo Village, Faculty of Medicine, Pelita Harapan University

E-mail : rocksy.situmeang@lecturer.uph.edu

Online First : Desember 2021

The pathophysiology behind neuropsychiatric SLE (NPSLE) remains poorly understood and its clinical and radiological manifestations are highly varied. In this report, we present a complex case of an adolescent female patient with a three-week history of systemic symptoms (fever, nausea, vomiting, weight-loss, polyarticular joint pain), progressive motor weakness, tremor, and altered mental status. Physical examination was significant for oromandibular and cervical dystonia rigidity, and general weakness with imposed right-sided hemiparesis. A head MRI demonstrated bilateral hyperintense lesions of the basal ganglia and brainstem, SSwithout restricted diffusion. The patient was diagnosed with NPSLE, lupus nephritis, electrolyte imbalance, severe hypoalbuminemia, lupus cardiomyopathy, autoimmune hemolytic anemia, pulmonary tuberculosis, and sepsis. The patient was given treatment in the ICU with pulse dose corticosteroids, intravenous antibiotics, intravenous immunoglobulins (IVIg), and supportive treatment with correction of hematologic and electrolyte abnormalities. Her condition improved rapidly. Full alertness was regained, and symptoms of oromandibular dystonia, tremor, and weakness diminished significantly. A follow-up MRI three weeks later revealed complete disappearance of lesions, which we attribute to resolution of the inflammatory process in the brain.

Introduction

Nervous system involvement in systemic lupus erythematosus (SLE), or neuropsychiatric SLE (NPSLE), constitutes a serious complication affecting up to 40% of all SLE patients.¹ According to nomenclature set by the American College of Rheumatology (ACR), NPSLE can be categorized into 19 distinct manifestations, 12 involving the central nervous system (CNS) and 7 involving the peripheral.² The clinical and radiological manifestations of NPSLE are widely varied, from mild cognitive dysfunction to potentially fatal

cerebrovascular accidents, with serious implications to both prognosis and quality of life.³ Multiple diagnostic modalities, such as serology and neuroimaging, are often required to support the diagnosis and exclude the presence of other conditions. Previous studies have shown that approximately 50% of NPSLE patients present with abnormal MRI features, in which vascular lesions were the most common finding, accounting for nearly 70% of MRI abnormalities, while inflammatory lesions compose just 6.5% of abnormalities.^{4,5} We present an adolescent NPSLE patient with an atypical feature of bilateral near-

symmetrical basal ganglia and brainstem lesions, suspected of inflammatory origin, that disappeared completely following the administration of immunoglobulin therapy.

Case

A 16-year-old Melanesian female was referred from Sorong, West Papua, with a three-week history of remittent fever, nausea, vomiting, abdominal pain, poor intake, palpitations, headaches, progressively worsening general weakness with pronounced right-sided involvement, tremor, and polyarticular joint pain. The patient reports a history of weight loss within the past three months, and experienced difficulties in moving her neck and mouth, producing difficulties in communication. She has a history of pulmonary tuberculosis diagnosed one month before and was started on anti-tubercular drug therapy. Two days before admission, she fell unconscious. Previous medical, family, and social history was found to be non-significant. Examinations in the previous hospital reveal the presence of anemia, leukopenia, thrombocytopenia, severe hyponatremia, and an elevated ESR. Tests for the presence of malaria, dengue, and ASTO were found to be negative. Urinalysis was significant for marked albuminuria and hematuria. An ANA profile was ordered, and the patient was found to be positive for anti-SM, anti-dsDNA, anti-NUC, anti-HI, anti-RIB, anti-M2, and anti-DFS70. Findings were suggestive of SLE with lupus nephritis and pulse dose corticosteroids were given and hyponatremia corrected, after which her condition improved in following days. She was then referred to our hospital.

Upon physical examination, she was somnolent, tachycardic, tachypneic, hypotensive and febrile. General examination found conjunctival pallor,

bilateral rhonchi, epigastric tenderness, and bilateral lower extremity pitting edema. On neurological examination, severe oromandibular and cervical dystonia were found that resulted in speech difficulties and the inability to open her mouth and move her neck, while still able to understand and obey commands. General weakness with imposed right-sided hemiparesis was also present. Physiological reflexes were decreased, and no pathological reflexes nor clonus were found, as well as sensoric abnormalities.

Laboratory tests reveal the presence of a normocytic normochromic anemia with features suggestive of autoimmune hemolysis (elevated LDH, and positive coombs' test), thrombocytopenia, hyponatremia, hypocalcemia, as well as elevated D-dimer, procalcitonin, transaminases, direct bilirubin and ureum levels. Complement levels (C3, C4), lupus anticoagulants (LA1, LA2), and anti- β 2GPI IgG and IgM, were also found to be low. An echocardiogram revealed a regional wall motion abnormality with reduced left-ventricular systolic function, mild-moderate mitral and tricuspid regurgitation, and mild pericardial effusion, suggestive of lupus cardiomyopathy. A lumbar puncture was planned, but could not be performed due to hemodynamic compromise. Diagnoses considered include tuberculous meningitis, osmotic degradation syndrome (ODS), and acute disseminated encephalomyelitis (ADEM). A head MRI with contrast was done, and revealed bilateral hyperintense lesions of the basal ganglia, with greater involvement of the left hemisphere, and the posterior aspect of the midbrain-pons, on T2, FLAIR, and DWI sequences, without restricted diffusion or contrast-enhancement. Due to the presence of these lesions, frank signs of systemic SLE, absence of

leptomeningeal enhancement typical of meningitis, and white matter lesions as in ADEM, a final diagnosis of NPSLE was made, along with lupus nephritis, electrolyte imbalance, severe hypoalbuminemia, lupus cardiomyopathy, autoimmune hemolytic anemia, pulmonary tuberculosis, and sepsis.

During hospitalization, the patient was transferred to the ICU for four days due to cardiorespiratory failure and was intubated and ventilated mechanically. She received methylprednisolone, calcium gluconate, digoxin, bisoprolol, lisinopril, furosemide, vitamin D supplementation, albumin, ceftriaxone, meropenem, micafungin, and multiple packed red cell transfusions. Anti-tubercular drugs were temporarily halted due to suspected hepatotoxicity. Considering the lack of neurological improvement and presence of contraindications in administering immunosuppressants, we decided to give 10% IVIg (2 grams per kilogram of body weight over a period of five days) beginning on day-eight of care. She improved markedly, with complete resolution of oromandibular and cervical dystonia, tremor, and significant motor improvement following physical therapy. Antitubercular drugs were reintroduced in stages, starting with isoniazid and ethambutol, and the full regimen was successfully reintroduced with good tolerance. At a follow-up MRI performed three weeks later, both bilateral basal ganglia and pontine lesions disappeared completely.

Discussion

The pathomechanism behind NPSLE remains poorly understood and could be a result of multiple factors. There are two primary theories regarding the process involved in NPSLE: the non-

inflammatory and inflammatory mechanisms. Non-inflammatory mechanisms of NPSLE are attributable to thromboses of both large and small intracranial blood vessels, possibly mediated by autoantibodies, immune complex formation, complement deposition, leukoagglutination, and accelerated atherosclerosis. The inflammatory mechanism involves autoantibody and inflammatory mediator-mediated dysfunction, and may be accompanied by blood-brain-barrier dysfunction and intrathecal immune complex formation.^{6,7}

The clinical and radiological features of NPSLE vary immensely, complicating efforts in establishing the diagnosis, which often requires a combination of multiple modalities such as immuno-serology tests, neuroimaging, and neuropsychiatric evaluation. Previous studies demonstrated that abnormal appearances on MRI are found in approximately 50% of NPSLE patients, in which vascular lesions (composed of a range of small vessel manifestations and large vessel disease) are the most common finding, accounting for nearly 70% of abnormalities.^{4,5} In a different study evaluating MRI features in diffuse NPSLE, abnormalities were observed in 47.2% of patients, among which multiple white matter hyperintensities, seen on T2-weighted or FLAIR, were the most common finding (88% of abnormal results). Grey matter hyperintensities, located in the basal ganglia, cerebellum and brainstem, followed with 28% (86% of which existed concurrently with white matter lesions).⁸ Another study corroborated these results, in which 46% of NPSLE patients were found to have white matter hyperintensities on MRI.⁹

In our case, the lesions were of gray-matter origin, and distributed near-symmetrically in the basal ganglia and

midbrain-pons. The lesions exhibited high intensity signaling on T2, FLAIR, and DWI sequences, without restricted diffusion or contrast enhancement. The symmetrical distribution of lesions, as well as its selectiveness for gray-matter areas, effectively excludes vascular, specifically large vessel disease, as the cause for the patient's condition. Furthermore, the pattern of increased signaling on T2, FLAIR, and DWI, without restricted diffusion, may be suggestive of vasogenic edema or inflammation, while the lack of contrast enhancement denotes a relatively intact blood-brain barrier.¹⁰ Taken together, the constellation of these findings suggests an inflammatory, perhaps vasculitic, process involving the basal ganglia and midbrain-pons. The physical findings observed in the patient, such as tremor, oromandibular and cervical dystonia, and right-sided hemiparesis, are consistent with abnormalities found on imaging. Both tremor and oromandibular dystonia may appear secondary to lesions of the basal ganglia.¹¹ Additionally, the significant improvement in symptoms experienced by the patient following IVIg administration serves as further evidence that an immune-mediated process underlies the patient's condition. A limitation to our case report is that we could not perform a lumbar puncture and CSF analysis due to risks of hemodynamic compromise, hence we could not objectively confirm nor exclude the presence of intracranial inflammation.

Based on imaging, a number of disease entities may be suspected as the cause for the patient's condition, including ADEM, posterior reversible encephalopathy syndrome (PRES), and progressive multifocal leukoencephalopathy (PML). ADEM, PRES, and PML are inflammatory disorders of the CNS, and consistent with

what can be observed in the patient, may appear as hyperintense on T2 and FLAIR, with variable restricted diffusion and contrast enhancement patterns. While most commonly appearing in subcortical white-matter areas, cases of gray-matter lesions, including basal ganglia and brainstem involvement, have been reported.⁽¹²⁻¹⁴⁾ Additionally, all three diseases have been associated with SLE, either as a direct result of an immune process, secondarily as complications of immunosuppressive treatment, or both. Additionally ODS, which could potentially manifest bilateral basal ganglia lesions as a result of extrapontine involvement, has also been considered in the patient, considering her history of severe hyponatremia and correction. However, ODS is unlikely as pontine lesions in ODS tend to be centrally placed with a characteristic "trident-shaped" lesion, while the midbrain-pons lesion found in the patient is located posteriorly.¹⁵

Although rare, similar cases have been reported.¹⁶⁻²⁰ Of note, while MRI imaging profiles of the lesions were always nearly identical, the same cannot be said for clinical manifestations experienced by patients, or the attributable cause, in which proposed mechanisms include aseptic meningitis¹⁶, immune-mediated lupus vasculopathy¹⁷, and ADEM.¹⁸ Common to these cases are the presence of unilateral or bilateral basal ganglia hyperintensities on T2W, FLAIR, and DWI, while additional hyperintensities could be found in periventricular areas¹⁷, thalamus, midbrain, pons, and cerebellum.¹⁸ Also common are their improvement and reversibility following therapy with corticosteroids and immunosuppressants, which are consistent with current approaches in the treatment of NPSLE.²¹ Compared to these reports however, our case is unique in that immunosuppressant

medication cannot be given due to contraindications, and IVIg therapy was administered instead. In our patient IVIg also had the added benefit as an adjunctive treatment to sepsis in addition to NPSLE, as previous studies have shown that IVIg is effective in reducing mortality in septic patients.²²

Conclusion

The underlying pathophysiology of NPSLE has not yet been completely elucidated, and as NPSLE consists of an umbrella term reflecting 19 distinct

entities, the clinical and radiological features found in NPSLE remain equivocal and non-specific. We report a unique case of an adolescent NPSLE patient with hyperintense lesions of the basal ganglia and midbrain-pons suggestive of vasogenic edema, with complete resolution of both symptoms and imaging following immunoglobulin therapy. We suspect the lesions may be due to an immune-mediated inflammatory process. However, research is needed to further understand the clinical and prognostic significance of these findings.

References

1. de Amorim JC, Frittoli RB, Pereira D, Postal M, Dertkigil SSJ, Reis F, et al. Epidemiology, characterization, and diagnosis of neuropsychiatric events in systemic lupus erythematosus. *Expert Rev Clin Immunol* [Internet]. 2019;15(4):407-16. <https://doi.org/10.1080/1744666X.2019.1564040>
2. Vivaldo JF, de Amorim JC, Julio PR, de Oliveira RJ, Appenzeller S. Definition of NPSLE: Does the ACR nomenclature still hold? *Front Med*. 2018;5(MAY):1-6. <https://doi.org/10.3389/fmed.2018.00138>
3. Monahan RC, Beart-Van De Voorde LJJ, Steup-Beekman GM, Magro-Checa C, Huizinga TWJ, Hoekman J, et al. Neuropsychiatric symptoms in systemic lupus erythematosus: *Impact on quality of life*. *Lupus*. 2017;26(12):1252-9. <https://doi.org/10.1177/0961203317694262>
4. Sarbu N, Bargalló N, Cervera R. Magnetic Resonance Imaging in Neuropsychiatric Lupus. *F1000Research*. 2015;4(0):162. <https://doi.org/10.12688/f1000research.6522.1>
5. Sarbu N, Alobeidi F, Toledano P, Espinosa G, Giles I, Rahman A, et al. Brain abnormalities in newly diagnosed neuropsychiatric lupus: Systematic MRI approach and correlation with clinical and laboratory data in a large multicenter cohort [Internet]. *Vol. 14, Autoimmunity Reviews*. Elsevier B.V.; 2015. 153-159 p. <https://doi.org/10.1016/j.autrev.2014.11.001>
6. Hanly JG. Diagnosis and management of neuropsychiatric SLE. *Nat Rev Rheumatol* [Internet]. 2014;10(6):338-47. <https://doi.org/10.1038/nrrheum.2014.15>
7. Jeltsch-David H, Muller S. Neuropsychiatric systemic lupus erythematosus: Pathogenesis and biomarkers. *Nat Rev Neurol* [Internet]. 2014;10(10):579-96. <https://doi.org/10.1038/nrneuro.2014.148>
8. Arinuma Y, Kikuchi H, Wada T, Nagai T, Tanaka S, Oba H, et al. Brain MRI in patients with diffuse psychiatric/neuropsychological syndromes in systemic lupus erythematosus.

- Lupus Sci Med.* 2014;1(1):1-7. <https://doi.org/10.1136/lupus-2014-000050>
9. Zaky MR, Shaat RM, El-Bassiony SR, Abdel Razek AA, Farag SEM. Magnetic resonance imaging (MRI) brain abnormalities of neuropsychiatric systemic lupus erythematosus patients in Mansoura city: Relation to disease activity MRI brain abnormalities of neuropsychiatric systemic lupus erythematosus patients. *Egypt Rheumatol.* 2015;37(4):S7-11. <https://doi.org/10.1016/j.ejr.2015.09.004>
 10. Schaefer PW, Buonanno FS, Gonzalez RG, Schwamm LH. Diffusion-weighted imaging discriminates between cytotoxic and vasogenic edema in a patient with eclampsia. *Stroke.* 1997;28(5):1082-5. <https://doi.org/10.1161/01.STR.28.5.1082>
 11. Hallett M, Pisani A. Neurophysiology of Dystonia: The Role of Inhibition Mark. *Neurobiol Dis*[Internet]. 2011;42(2):177-84. <https://doi.org/10.1016/j.nbd.2010.08.025>