Successful Treatment of a Patient with Neuropsychiatric Lupus and Triple Positive Antiphospholipid Syndrome with Chronic Isolated Seizure: A Case Report

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ABSTRACT

Neuropsychiatric SLE (NPSLE) comprises the neurologic and psychiatric syndromes observed in patients with SLE after exclusion of other causes. The diagnosis of NPSLE is challenging due to diverse clinical manifestations and absence of laboratory or radiologic biomarkers.

We present the case of a patient with SLE with a chronic isolated seizure and was successfully managed with anti-epileptic medication and high-dose corticosteroids.

Seizures may occur as an isolated manifestation of an SLE flare. Ischemic and inflammatory causes of seizure may coexist in active lupus and both should be considered in managing patients. A prompt and holistic workup to rule out metabolic, infectious, and structural neural causes and lupus disease activity of seizures is prudent for patients with SLE.

Keywords: neuropsychiatric lupus, antiphospholipid syndrome, SLE, seizure, case report

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a variety of clinical manifestations. Neuropsychiatric SLE (NPSLE) comprises the neurologic and psychiatric syndromes observed in patients with SLE after exclusion of other causes.[1] The diagnosis of NPSLE is challenging due to diverse clinical manifestations and absence of laboratory or radiologic biomarkers.[2]

CASE PRESENTATION

We report the case of a 21-year-old female diagnosed with SLE in 2015, seven years prior to hospitalization. Her initial lupus manifestations were malar rash, polyarthralgia, anemia, and positive serologies (anti-nuclear antibody and anti-double stranded DNA). She was maintained on low-dose prednisone and hydroxychloroquine. In 2019, she had SLE nephritis and was treated with methylprednisolone pulse therapy for three days, monthly cyclophosphamide infusion for six months and 4 quarterly doses. Azathioprine 75 mg daily was added to low-dose prednisone and hydroxychloroquine 200 mg daily. These were taken with good compliance and she remained free of lupus flares. She has no comorbidities. She is a student

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with no history of substance use or psychiatric illness and no family history of autoimmune or seizure disorder.

During her hospitalization on July 2022, she was referred to the rheumatology service because of intermittent seizures of three months duration. Episodes were characterized as blank stares with tonic flexion of the upper extremities lasting for 10-15 seconds, pooling of saliva, and postictal confusion for 10 seconds. The episodes were initially once to twice a month but gradually increased in frequency and duration to almost weekly and lasting for 1 to 2 minutes. She dismissed the early seizure episodes as stress-related due to her studies but grew alarmed when they became more frequent and prolonged. She admitted to being fearful of what the seizures meant for her health, especially since she had previously enjoyed stable disease control. She had no other symptoms of an SLE flare like rash, alopecia, oral ulcers, urinary changes, behavioral changes, musculoskeletal complaints, or menstrual irregularity. She was independent in all activities of daily living in between episodes of seizures.

The physical exam revealed blood pressure of 100/60 mmHg, heart rate of 81 beats per minute, temperature of 36.1°C, and respiratory rate of 19 breaths per minute. She had pink palpebral conjunctivae, no mucocutaneous lesions, clear breath sounds, regular heart rhythm, soft, and non-tender abdomen, strong peripheral pulses, no pedal edema, and no joint swelling and tenderness. Neurologic exam showed an awake, coherent, patient with intact mental status, intact cranial nerves, and 5/5 on manual muscle testing on all extremities. Her laboratory results showed mild normocytic, normochromic anemia (hemoglobin 116 g/L), mild thrombocytopenia (platelet 143 x 10^9/L), and prolonged partial thromboplastin time (PTT, 44.6 seconds, control 30.3 seconds). The electrolytes, glucose, urinalysis, prothrombin time, renal, and transaminases were all normal. Contrast-enhanced cranial CT scan showed no evidence of an infarct, hemorrhage, or focal lesion. The opening pressure was 12 cmH20 and closing spinal pressure of 6 cmH20 were normal. Cerebrospinal fluid (CSF) analysis showed clear, colorless fluid, with zero red blood cell and white blood cell. CSF total protein (15 mg/dL) and glucose (60 mg/dL) were normal. Bactigen latex agglutination assay was negative for bacteria, Cryptococcal latex agglutination system (CALAS) test was negative for Cryptococcus, and aerobic culture was negative after four days of incubation. She was treated with levetiracetam 500 mg every 12 hours intravenously to control the seizures and high-dose glucocorticoids (hydrocortisone then prednisone at 1mg/kg dose), hydroxychloroquine 200 mg daily, and azathioprine 50 mg daily. During the patient's entire hospital stay, there was no recurrence of seizure episodes. She was discharged after seven days with the following medications: prednisone 50 mg daily, hydroxychloroquine 200 mg daily, azathioprine 75 mg daily, and levetiracetam 1 gram daily. She described her hospital stay as a period of mixed emotions, marked by anxiety over her condition but tempered by reassurance from her medical team.

The rest of the laboratory results revealed the following: low serum complement 3, C3 (0.661 g/L, normal value [NV] 0.0-1.5), elevated anti dsDNA (188 IU/mL, NV <25), and triple positive antiphospholipid antibody (DRVVT 2.2 [NV 0.8- 1.2], LAC S 116 seconds [NV 31-44], LAC C 52 seconds [NV 30-38], anti cardiolipin IgG 86 GPL-U/mL [NV <10 GPL-U/mL], anti B2GP1 IgG 171 U/mL [NV <7]. MRI of the brain with gadolinium contrast showed T2W/FLAIR hyperintense foci in the left caudate head along with T2W/FLAIR bright signals in the centrum ovale, corona radiata, and right occipital cortex interpreted as chronic lacunar infarction of the left caudate head and cerebral small vessel disease compatible with vasculitis. Warfarin was started for secondary thromboprophylaxis.

Six months into follow-up, she was seizure-free and had no signs of lupus disease activity on low-dose prednisone (7.5 mg/day) and hydroxychloroquine. She had excellent tolerability of the medications and had reported no side effects.

DISCUSSION

Our patient with SLE for seven years had apparently quiescent disease for three years prior to occurrence of recurrent tonic seizures. Seizures from SLE are most commonly seen as tonic-clonic (60–88%) with secondary generalization, followed by seizure with impaired consciousness, and seizure with retained consciousness.[3,4] The incidence is higher in young females with SLE (22.9–36.5 years old),[5] and within the first year of disease (67%).[6] The median time from diagnosis to first seizure is 51 days.[6] CNS involvement in SLE occurs more frequently among patients with high SLE disease activity. The rarity of chronic isolated seizures as primary manifestation and without other prominent features of a flare makes this case unique. Elevation of the SLEDAI and the SLICC/ACR Damage Index (SDI) are considered risk factors for earlier presentation of the first seizure.[7]

In our patient's case, with longstanding lupus and no apparent symptoms of a flare, other etiologies such as metabolic or infectious causes were therefore first explored but were naught. While waiting for lupus serologic tests, the steroid dose was increased and levetiracetam was started, and these served to control her seizures. The results of low C3, markedly elevated anti-dsDNA, and imaging findings of cerebral small vessel disease served to prove that lupus was in flare. The patient's contrast-enhanced cranial MRI showed T2W/FLAIR bright signals in the centrum ovale, corona radiata, and right occipital cortex suggestive of small vessel vasculitis. MRI is a more sensitive imaging modality for detecting intracranial abnormalities and assessing the chronicity of brain abnormalities. Brain imaging abnormalities are present in 25% of patients with newly diagnosed SLE, including cerebral atrophy, ischemic lesions, and white matter lesions. In the setting of vasculitis and vasculopathy, MRI reveals hyperintense areas (T2W

and FLAIR) and hypointense areas (T1W) in the cerebral white matter, mainly distributed in the subcortical, deep, and periventricular regions similar to our patient.[8] However, more than half of patients diagnosed with NPSLE can also have a normal cranial MRI.[9]

A widely accepted explanation for NPSLE development includes the role of autoantibodies in the CNS. Autoantibodies can induce focal or diffuse CNS damage by induction of ischemic strokes, secondary to blood vessel deposition and occlusion.[4] Other mechanisms related to the non-ischemic pathway include increasing neuronal excitability through the inhibition of the gamma-aminobutyric acid receptor-ion channel complex[10] or permeabilizing and depolarizing brain synaptoneurosomes after binding to phospholipids in the cellular membrane[11].

An incidental finding of chronic lacunar infarct and triple positive antiphospholipid antibody in our patient was consistent with data showing higher prevalence of these aPL antibodies in patients with SLE (10%–44%) compared to the general population (0.1–5.0%).[12] These aPL antibodies activate endothelial cells, platelets, and monocytes, and may result in prothrombotic microparticles. In addition, aPL antibodies accelerate atherosclerosis which is an independent risk factor for cerebrovascular ischemia.[13] This may explain the presence of chronic lacunar infarct in a young patient with no other cardiovascular disease risk factors. Furthermore, Hawro et al. found that patients with anti-β2 glycoprotein antibodies IgG were 11 times more likely to exhibit seizures and 9 times more likely to have tonic-clonic seizures when compared to seronegative patients.[14] These seizures associated with APAS tend to occur with lupus disease activity, severe organ damage, and other NPSLE manifestations[15] which were not present in our patient.

We started the patient with warfarin for secondary thromboprophylaxis in addition to high dose steroid treatment. In most patients, inflammatory and ischemic NPSLE coexist[16], thus addressing both causes may be necessary. We also increased the dose of azathioprine to 100 mg daily to better control the inflammation-driven immune mediated injury and serve as a steroid sparer.

Aside from immunosuppressive treatment, the European League Against Rheumatism (EULAR) recommends that anti-epileptic drug therapy be started in patients with a high risk for seizure recurrences, such as >2 unprovoked seizures occurring in a 24-h interval, which our patient had, or in the presence of symptomatic or imaging-recorded brain lesions or epileptiform discharge on EEG.[17] Our patient has remained seizure-free and still maintaining levetiracetam as of six months after hospitalization.

This case highlights a rare manifestation of neuropsychiatric lupus - isolated seizure activity, without involvement of other organ systems. While seizures occur in approximately 10-25% of patients with systemic lupus erythematosus[3], the specific occurrence of isolated seizures is not commonly discussed in large cohort studies. The six-month follow-up period in this case may not be sufficient to fully evaluate the long-term outcomes of treatment, including the potential recurrence of seizures or lupus flares. A longer follow-up period would be essential to assess the sustained effectiveness of the treatment and to monitor for any late-onset complications related to the disease or its therapy.

CONCLUSION

Seizures may occur as an isolated manifestation of an SLE flare. Ischemic and inflammatory causes of seizure may coexist in active lupus and both should be considered in managing patients. A prompt and holistic workup to rule out metabolic, infectious, structural neural causes, and lupus disease activity of seizures is prudent for patients with SLE.

Ethical Consideration

Informed consent was secured and patient confidentiality was observed.

Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

Both authors declared no conflicts of interest.

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REFERENCES

1. Liang M, Corzillius M, Bae S, Lew R, Fortin P, Gordon C, et al. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum. 1999 Apr;42(4):599-608. doi: 10.1002/1529-0131(199904)42:4<599::AID-ANR2>3.0.CO;2-F. PMID: 10211873.
2. Magro-Checa C, Zirkzee E, Huizinga T, Steup-Beekman G. Management of neuropsychiatric systemic lupus erythematosus: Current approaches and future perspectives. Drugs. 2016 Mar;76(4): 459-83. doi: 10.1007/s40265-015-0534-3. PMID: 26809245; PMCID: PMC4791452
3. González-Duarte A, Cantú-Brito CG, Ruano-Calderón L, García-Ramos G. Clinical description of seizures in patients with systemic lupus erythematosus. Eur Neurol. 2008;59(6):320-3. doi: 10.1159/000121423. Epub 2008 Apr 11. PMID: 18408374.
4. Appenzeller S, Cendes F, Costallat L. Epileptic seizures in systemic lupus erythematosus. Neurology. 2004 Nov 23;63(10):1808-12. doi: 10.1212/01.wnl.0000144178.32208.4f. PMID: 15557494.
5. Andrade R, Alarcón G, González L, Fernández M, Apte M, Vilá LM, et al. Seizures in patients with systemic lupus erythematosus: data from LUMINA, a multiethnic cohort (LUMINA LIV). Ann Rheum Dis. 2008 Jun;67(6):829-34. doi: 10.1136/ard.2007.077594. Epub 2007 Sep 17. PMID: 17875548; PMCID: PMC2735413.
6. Hanly J, Urowitz M, Su L, Gordon C, Bae S, Sanchez-Guerrero J, et al. Seizure disorders in systemic lupus erythematosus results from an international, prospective, inception cohort study. Ann Rheum Dis. 2012 Sep;71(9):1502-9. doi: 10.1136/annrheumdis-2011-201089. Epub 2012 Apr 4. PMID: 22492779; PMCID: PMC4656036.

7. Ramsey-Goldman R, Alarcón G, McGwin G, Petri M, Vilá LM, Edberg J, et al. Profile Study Group. Time to seizure occurrence and damage in PROFILE, a multi-ethnic systemic lupus erythematosus cohort. Lupus. 2008 Mar;17(3):177-84. doi: 10.1177/0961203307086639. PMID: 18372357; PMCID: PMC2787620.
8. Petri M, Naqibuddin M, Carson K, Wallace D, Weisman M, Holliday S, et al. Brain magnetic resonance imaging in newly diagnosed systemic lupus erythematosus. J Rheumatol. 2008 Dec;35(12):2348-54. doi: 10.3899/jrheum.071010. Epub 2008 Sep 15. PMID: 18793003; PMCID: PMC5278777.
9. Toledano P, Sarbu N, Espinosa G, Bargalló N, Cervera R. Neuropsychiatric systemic lupus erythematosus: magnetic resonance imaging findings and correlation with clinical and immunological features. Autoimmun Rev. 2013 Oct;12(12):1166-70. doi: 10.1016/j.autrev.2013.07.004. Epub 2013 Jul 11. PMID: 23851139.
10. Liou H, Wang C, Chou H, Arvanov V, Chen R, Chang Y, et al. Anticardiolipin antisera from lupus patients with seizures reduce a GABA receptor-mediated chloride current in snail neurons. Life Sci. 1994;54(15):1119-25. doi: 10.1016/0024-3205(94)00422-6. PMID: 8152332.
11. Chapman J, Cohen-Armon M, Shoenfeld Y, Korczyn A. Antiphospholipid antibodies permeabilize and depolarize brain synaptoneurosomes. Lupus. 1999;8(2):127-33. doi: 10.1191/096120399678847524. PMID: 10192507.
12. Schreiber K, Sciascia S, de Groot P, Devreese K, Jacobsen S, Ruiz-Irastorza G, et al. Antiphospholipid syndrome. Nat Rev Dis Primers. 2018 Jan 11;4:17103. doi: 10.1038/nrdp.2017.103. Erratum in: Nat Rev Dis Primers. 2018 Jan 25;4:18005. doi: 10.1038/nrdp.2018.5. PMID: 29321641.
13. Cohen D, Rijnink E, Nabuurs R, Steup-Beekman G, Versluis M, Emmer B et al. Brain histopathology in patients with systemic lupus erythematosus: identification of lesions associated with clinical neuropsychiatric lupus syndromes and the role of complement. Rheumatology (Oxford). 2017 Jan;56(1):77-86. doi: 10.1093/rheumatology/kew341. Epub 2016 Oct 25. PMID: 28028157.
14. Hawro T, Bogucki A, Krupińska-Kun M, Maurer M, Woźniacka A. Intractable headaches, ischemic stroke, and seizures are linked to the presence of anti-β2GPI antibodies in patients with systemic lupus erythematosus. PLoS One. 2015 Mar 17;10(3):e0119911. doi: 10.1371/journal.pone.0119911. PMID: 25781014; PMCID: PMC4362944.
15. Natanauan, G. Literature Review on Neuropsychiatric Lupus. IntechOpen. 2023 Sept. doi: 10.5772/intechopen.106955
16. Govoni M, Bortoluzzi A, Padovan M, Silvagni E, Borrelli M, Donelli F, et al. The diagnosis and clinical management of the neuropsychiatric manifestations of lupus. J Autoimmun. 2016 Nov;74:41-72. doi: 10.1016/j.jaut.2016.06.013. Epub 2016 Jul 12. PMID: 27427403.
17. Bertsias G, Ioannidis J, Aringer M, Bollen E, Bombardieri S, Bruce I, et al. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations. Ann Rheum Dis. 2010 Dec;69(12):2074-82. doi: 10.1136/ard.2010.130476. Epub 2010 Aug 19. PMID: 20724309.