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Lupus Cerebritis Presenting as a Seizure in a Patient with Systemic Lupus Erythematosus

Saad Atawneh[1], Moath Atiani[2*], Lana Hasasna[2], Hlayel Nasasreh[2], Mayar Al-atawneh[2], Halima Malash[2]

[1]Faculty of Medicine, Al Quds University, Jerusalem, Palestine.

[2]Faculty of Medicine, Hebron University, Hebron, Palestine.

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Corresponding Author: Moath Atiani, Faculty of Medicine, Hebron University, Hebron, Palestine, ORCID ID: **https://orcid.org/0000-0002-3396-9462**

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Abstract

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disorder diagnosed based on multiple clinical and serological criteria. According to the Systemic Lupus International Collaborating Clinics (SLICC), patients with SLE may have neuropsychiatric manifestations (NPSLE) that may indicate a severe form of the disease. These manifestations are often associated with high morbidity and mortality, with a widely variable prevalence according to different series.

In this paper, we present a rare and severe form of SLE in an adolescent female.

She presented with neurological symptoms in the form of seizures and had good outcomes after being treated according to the guidelines.

Keywords: Systemic lupus erythematosus, lupus cerebritis, seizure.

Introduction

Systemic lupus erythematosus (SLE) is a multi-systemic disease of autoimmune underlying pathogenesis characterized by a wide variety of manifestations from mild mucocutaneous involvement to severe multi-organ affection, including renal, cardiac, musculoskeletal, and CNS disease **[22]**.

Despite the fact that it affects any system in the body, not all systems are affected in every patient since it occurs in different percentages. Constitutional symptoms are seen in more than 90% of patients with SLE, more than 80% for mucocutaneous and musculoskeletal involvement, 50% of patients have a hematologic manifestation in the form of anemia of chronic disease, and the most common neuropsychiatric demonstration is headache reported in the more than 50% of cases, rather than seizures which are associated with disease activity and multiple other central and peripheral CNS manifestations **[12]**.

Multiple immune pathogenic pathways are involved in SLE development in both innate and adaptive immunity. Furthermore, there is an important role played by mitochondria and the production of multiple types of interferons with various pathogenic antibodies such as anti-nuclear antibodies (ANA) and anti-double-stranded DNA (anti-dsDNA) antibodies **[1]**. Despite the advancement of recent technology, the exact mechanism of SLE is still not fully understood, making its diagnosis challenging.

Several diagnostic criteria have been established to ensure a consistent definition of SLE for research and surveillance targets. However, their implementation in clinical settings is still a subject of discussion **[2, 22]**.

Lupus cerebritis is one of the most critical neuropsychiatric SLE (NPSLE) complications that may present as seizure, cognitive impairment, or psychosis. Approximately 40% of adult NPSLE symptoms appear either prior to or during the same time of an SLE diagnosis, while 60% emerge within the first year following the diagnosis, and it can be presented in the presence or absence of the active disease **[24]**.

We report a case of a 22-year-old female patient who presented with the unusual manifestation of SLE as a tonic-clonic seizure, Imaging findings were suggestive of lupus cerebritis with positive ANA and Anti-DsDNA antibodies. She was diagnosed with lupus cerebritis and started on corticosteroids, cyclophosphamide, and hydroxychloroquine.

Case Presentation

A 22-year-old female with a known history of SLE was diagnosed 7 years ago. Based on clinical and serological criteria, following the Systemic Lupus International Collaborating Clinics (SLICC), presented with three episodes of generalized tonic-clonic seizures, each episode lasted 3-5 mins and was associated with loss of consciousness, frothing of saliva, and post-ictal confusion lasting 10-15 mins.

A month ago, the patient reported progressive lower limb and periorbital edema, bilateral symmetrical polyarthralgia involving the knees and wrists, increasing fatigue, mood swings, confusion, and sleepiness. Painful oral ulcers were also noted during this period. In addition to her medical history of SLE, the patient had an appendectomy 6 years ago and had an insignificant family history. She did not smoke or use illicit drugs.

She was on hydroxychloroquine and low-dose corticosteroids for disease control; however, she was not adherent to her medications. During the examination, her vitals were as follows: blood pressure 154/95mmHg, pulse 76 beats per minute, temperature 36.8 C°, respiratory rate 16 breaths per minute. Once the seizure had ceased, the patient appeared reasonable, conscious, and oriented. There was a focal neurological deficit of power in 4 out of 5 all limbs, with no sensory or cerebellar deficits and negative

meningeal signs. She had two oral ulcers, malar rash, and mild tenderness with no swelling or limitation of movements of the affected joints. Cardiovascular and respiratory examinations were normal.

According to the investigation, a complete blood count revealed normochromic normocytic anemia with hemoglobin of 11.73 g/dl, a low platelet count of 128.4, and a normal total leukocyte count. Elevated D-dimer: 4090, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRB) were normal. Serum albumin was low: 2.3 g/dl, urinalysis showed +1 protein, 52 WBCs, and erythrocytes 70, with an elevated creatinine level of 1.54, and liver function test was normal. Serologies for cytomegalovirus (CMV) and Epstein-Barr virus (EBV) were negative. Blood and urine cultures were negative. The patient and her family did not consent to lumbar puncture, so cerebrospinal fluid analysis could not be done. An autoimmune profile was done, which showed positive ANA and positive Anti-DsDNA antibodies but negative Anti-Phospholipid antibodies with low complement, measuring C3 of 54 and C4 of 5.5. MRI of the brain revealed multiple bilateral T2WI/FLAIR hyperintense signals involving the cortical and subcortical regions of the frontoparietal lobes and the occipital lobe that represent multiple acute and subacute lacunar infarcts, correlating with lupus CNS vasculitis, as shown in**c**.

Figure 1 and **Figure 2**. MRA and MRV of the brain were unremarkable. Echocardiography was done on the second day of admission and showed dilated cardiomyopathy with an ejection fraction of 30% and severe diffuse hypokinesia. Abdominal ultrasound (US), the liver is enlarged, measuring approximately 17 cm in the midclavicular line (MCL), but otherwise, the US is unremarkable. Electroencephalography (EEG) showed active generalized epileptiform waves with slow, sharp waves.

After the seizures were aborted with diazepam, she was admitted to the hospital to complete her course of management and was initially started on prednisolone, hydroxychloroquine, and mycophenolate.

After discussing the side effects with her family, the patient was given the first dose of cyclophosphamide, which improved her clinical status and laboratory findings, with a recommended second dose after 2 weeks. She was also given anti-failure treatment of sacubitril/valsartan, Aldactone, bisoprolol, and furosemide after she complained of chest pain and shortness of breath with an echocardiography finding of heart failure. With levetiracetam for seizure control. After eight days of admission, she showed a significant improvement and was discharged in accordance with the same plan of treatment and follow-up in the outpatient clinic.

Figure 1. T2WI/FLAIR Hyperintense Signals Involving the Cortical and Subcortical Regions of The Frontoparietal Lobes.

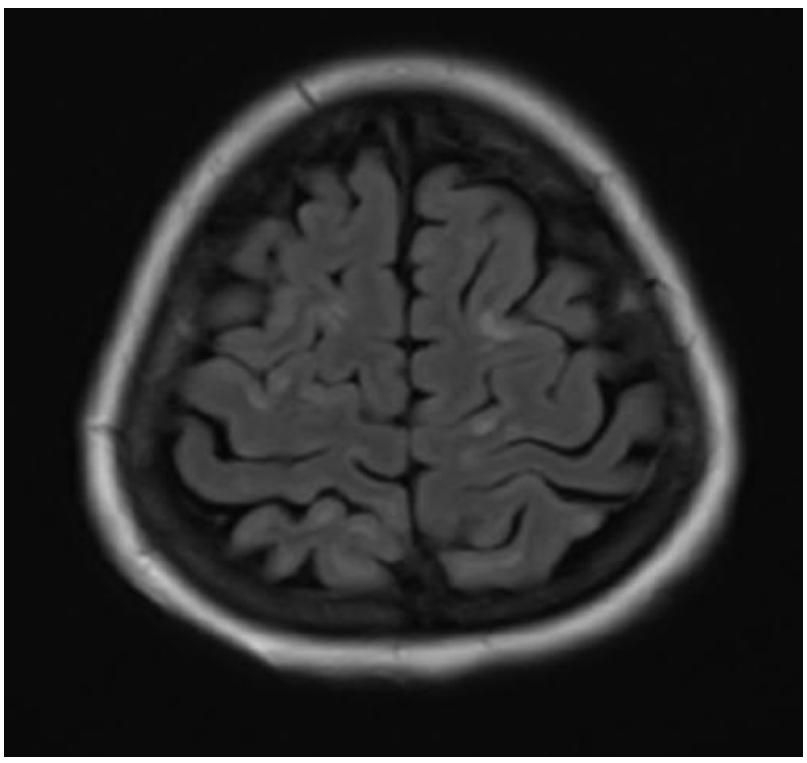
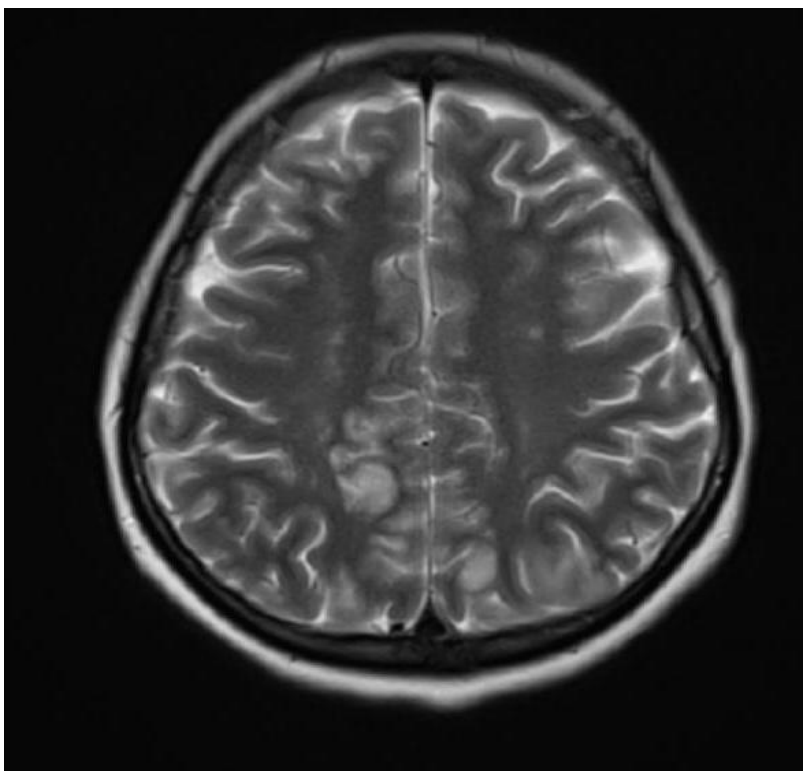


Figure 2. T2WI/FLAIR Hyperintense Signals Involving the Cortical and Subcortical Regions of The Occipital Lobe.



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Discussion

Systemic lupus erythematosus is a multi-organ system autoimmune disease with clinical and serological heterogeneity. According to the Systemic Lupus International Collaborating Clinics (SLICC), it indicates that SLE is diagnosed based on fulfilling at least four of the clinical (constitutional, hematological, neuropsychiatric, serosal, musculoskeletal, renal, and mucocutaneous) and immunological (antiphospholipid antibodies, complement proteins, and SLE-specific antibodies) criteria or having lupus nephritis **[18]**. Since SLE is a multi-systemic disease, it can cause a wide range of symptoms related to any affected body system, one of which is the nervous system, which is referred to as Neuropsychiatric SLE (NPSLE). It consists of either central or peripheral neurological and psychiatric manifestations. Those may occur in the early stages of SLE and represent 39%-50% of SLE patients. Any of those manifestations may present either as an initial presentation of the disease or as a flare-up **[29]**. With the ongoing research, the awareness of medical practitioners about SLE and its multiple presentations has risen, which has helped in its early detection. Given proper management that reflects on improving the mortality and morbidity of SLE from the 1950s to the 2000s, their overall survival rates witnessed a notable rise, improving from 74.8% to 94.8% for 5-year survival and from 63.2% to 91.4% for 10-year survival **[14]**. Meta-regression analysis showed that neuropsychiatric and renal damage adversely influenced overall 5-year survival, with neuropsychiatric damage continuing to have a negative impact on 10-year survival over the past 50 years. Additionally, the prevalence of neuropsychiatric damage has risen significantly over the last five decades **[19]**.

Clinical presentation of lupus cerebritis is variable based on the site of the areas affected and the extent of involvement, as it may include headache, cognitive dysfunction, ataxia, anxiety, psychosis, depression, focal or diffuse seizures, mood changes, altered consciousness, or hemiplegia ("The American College of Rheumatology Nomenclature and Case Definitions for Neuropsychiatric Lupus Syndromes," 1999). However, based on the American College of Rheumatology (ACR), status epilepticus (SE) and transverse myelitis (TM) remain two of the most widely discussed neuropsychiatric manifestations of SLE. SE and TM had a prevalence of 1-2%. Other less common manifestations may include movement disorders, psychiatric manifestations (mood disorder, psychosis, anxiety disorder, or other rare neurological manifestations such as peripheral neuropathy and autonomic dysfunction, ocular involvement, and posterior reversible encephalopathy syndrome (PRES) **[4]**.

As it has previously been reported, a case of a patient who had a history of mixed connective tissue disease(MCTD) with SLE features that presented with status epilepticus and acute respiratory failure and needed respiratory support **[16]**, a case was reported from Pakistan for a patient who presented with generalized tonic-clonic fits with a history of previous other SLE symptoms such as headaches, recurrent painless oral ulcers, arthralgia of small joints of the hand, and intermittent fever **[3]**.

In our case, which presented as a tonic-clonic seizure, that is attributed to lupus cerebritis as a final diagnosis, since she had a systemic lupus erythematosus disease activity index (SLEDAI) score of 40, which is consistent with a severe disease activity after the recommended medical workup was done **[9, 26]**; "The American College of Rheumatology Nomenclature and Case Definitions for Neuropsychiatric Lupus Syndromes," 1999).

The diagnostic work-up of these patients should consider all investigations that should be carried out in non-SLE patients presenting with the same manifestations **[22]**. Hence, to confirm the diagnosis of our patient, she tested positive for ANA and anti-dsDNA antibodies, indicating an underlying mechanism consistent with the established pathogenesis of SLE **[23]**. Additionally, the patient's low serum complement levels (C3 and C4) further support the immunological basis of SLE. These complement levels, typically assessed during the initial workup and for disease monitoring, can markedly decrease secondary to consumption and granular deposition **[13]**. The principal findings in MRI of (NPSLE) patients include focal hyperintensities in white matter in 49% or both white matter and gray matter in 5% of all patients, suggestive of vasculopathy or vasculitis as the findings of our patient MRI, more widespread, confluent hyperintensities in the white matter, suggestive of chronic hypoperfusion due to the same mechanisms, with 12% of patients showed diffuse cortical grey matter lesions which compatible with an immune response to neuronal components or post-seizure changes, and absence of MRI abnormalities, despite signs and symptoms of active disease in 42% of all patients **[17]**. Moreover, the MRI excluded infection and malignancy. EEG findings also supported the diagnosis by indicating a generalized epileptiform activity, which was reported in 30.8% of patients with lupus cerebritis presenting with seizures **[20]**.

Clinically apparent cardiomyopathy or myocarditis associated with SLE is uncommon; most studies have noted a prevalence of about 10% **[7,10,11]**. A study of echocardiographic findings in systemic lupus erythematosus found that patients with the clinical findings of congestive heart failure were corroborated by reduced echocardiographic systolic function in the form of reduced left ventricular contractility in one-half of the patients was associated with previous myocardial infarction, the other cases of global hypokinesis were likely to happen due to a cardiomyopathic process attributable to SLE, possibly myocarditis since these patients did not have other evidence of ischemic heart disease or myocardial infarction **[7]**. Our patient's echocardiography showed dilated cardiomyopathy, severe hypokinesia, and suspected perimyocarditis.

Given the fact that there is a variety in clinical practice of SLE management that depends on disease severity and organ system involvement, it is considered an actual medical challenge. Treatment in SLE should aim at remission or low disease activity and prevention of flares in all organs, maintained with the lowest possible dose of glucocorticoids. Flares of SLE can be treated according to the severity of organ involvement by adjusting ongoing therapies (glucocorticoids, immunomodulating agents) to higher doses and switching or adding new therapies **[5,8]**. Since then, the treatment of neuropsychiatric lupus has mainly been achieved by glucocorticoids/immunosuppressive agents for manifestations considered to reflect an inflammatory process and antiplatelet/anticoagulants for atherothrombotic/antiphospholipid-related manifestations; our patient started on prednisolone and a first dose of cyclophosphamide without a need of anticoagulation since she had negative anti-phospholipid antibodies, in addition to mycophenolate for her renal involvement **[8]**. However, the side effects of cyclophosphamide, depending on the cumulative dose, range from

gastrointestinal upset (nausea, vomiting, anorexia) to infertility, bone marrow suppression, increased infection risk, and even the risk of malignancies, all of them discussed with the patient before the first dose **[6]**. Our patient was not adherent to her previously prescribed medications mainly hydroxychloroquine, which is the recommended drug of maintenance for all patients with SLE because it prevents flares and is useful in treating fatigue and mucocutaneous and musculoskeletal manifestations while improving long-term survival by protecting against irreversible organ damage, thrombosis, and bone mass loss, that increase the suspicious from the start of the presentation that it could be an SLE flare in the form of cerebritis **[25]**. In the absence of risk factors for retinal toxicity, ophthalmological screening (by visual fields examination and/or spectral domain-optical coherence tomography) should be performed at baseline, after 5 years, and yearly thereafter **[15,21]**.

Conclusion

We report a rare case of lupus cerebritis presented as a tonic-clonic seizure, which highlights the importance of understanding that autoimmune diseases, such as SLE, can present with nonspecific symptoms, ranging from mild to severe presentations. Seizures are one of the most serious neurological manifestations in SLE patients; they can be a symptom of SLE or a sign of some other complications linked to the disease. In general, those patients require regular follow-ups and close monitoring to control the progression of underlying fatal complications.

Consent: Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.

Conflict of Interest: The authors have declared that there are no conflicts of interest.

Ethical Approval: Ethical approval for this publication by the IRB at Hebron University, Faculty of Medicine, is available upon request.

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