Adult-Onset Seizures as the First Manifestation of Anti-dsDNA Negative Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a quintessential autoimmune disease once thought to be rare among Africans. Neuropsychiatric manifestations of SLE (NPSLE) range from headaches, mood/behavioral disorders to seizures. There are documented reports of seizures accompanying the diagnosis of SLE, with varying prevalence according to specific regions. However, seizures rarely precede the diagnosis of SLE. We present a case report of a 19-year-old African woman with adult-onset seizures preceding an overt diagnosis of negative anti-dsDNA SLE. A preceding short course of anti-malarial and carbamazepine prompted early consideration of drug-induced lupus erythematosus (DILE). However, the clinical features of SLE progressed and persisted despite their discontinuation. Among high-risk groups, it is important to recognize SLE as a potential cause of adult-onset seizures. In the absence of clear offending agents, metabolic or structural disease, baseline anti-nuclear antibody (ANA) may be imperative in the diagnostic work up of such patients.

Keywords: Systemic Lupus Erythematosus; Neuropsychiatry; Autoimmune Disease; Nigeria

Introduction

Systemic Lupus Erythematosus (SLE) is a quintessential autoimmune syndrome once thought to be rare in Africans.[1,2] It affects every organ and tissue, synchronously or asynchronously. The complex mosaic of pathophysiologic pathways converging into SLE phenotype is influenced by diverse factors including the patient's genetic predisposition, environmental triggers, and hormones, resulting diverse clinical manifestations and ways of organ involvement.[3–6]

Literature is replete with reports of seizures accompanying the diagnosis of SLE, with prevalence ranging from 9.5% in Iran to 42.4% in Nigeria.[7–10] In most of these reviews and case reports, the diagnosis of NPSLE rarely preceded that of SLE. In such cases, the possibility of drug-induced lupus like syndrome should be investigated and ruled out before considering treatment with antiseizures.[11] We present a case of a 19-year-old woman with adult-onset seizures which preceded the overt clinico-laboratory features of anti-dsDNA-negative SLE.

Case Report

A 19-year-old woman was seen at the neurology out-patient clinic on account of new-onset seizures, described as focal to bilateral tonic-clonic involvement of the limbs. The seizures started with right-sided facial twitches

and jerky movements of the right hand. This was followed by abnormal breathing and phonation, eventually culminating in generalized tonic-clonic convulsion lasting 2–3 minutes. There was ensuing post-ictal sleep lasting approximately 15 minutes. There was also upward rolling of the eyes, teeth clenching, but no tongue biting, excessive salivation, or sphincteric disturbance. She had four episodes prior to the initial review and had no headaches or premonitory aura. Prior to onset of the current symptoms, she had a brief non-specific febrile illness that was treated empirically with parenteral artemether though the blood film was negative for malaria parasite. There was no accompanying neck stiffness, light or sound hypersensitivity.

There was no personal or family history of epilepsy, childhood febrile seizures, head trauma, intercurrent central nervous system (CNS) infections or previous stroke. There were no motor and sensory deficits, visual disturbances, behavioral changes, or cognitive or gait impairment. There was no photosensitive skin rash, joint pain, weight loss, or drenching night sweat. The patient had no history to suggest renal or hepatic decompensation. She did not consume alcohol, psychoactive substances, or tobacco. Examination of the skin and integuments showed no unusual skin growths, ash-leaf spots, Shagreen patches, or facial port-wine staining. The neurologic examination results were not remarkable.

The blood report showed leukocyte count of 5530/uL (neutrophils 48.3%; lymphocytes 39.4%; platelets 378,000/uL). Repeat test for malaria parasite was negative and the urinalysis was normal. Serum calcium, uric acid, electrolytes, urea, creatinine, and liver enzymes were normal, but serum albumin level was low (2.8 g/dL). Urinalysis showed sediments, leucocytes+++, squamous epithelial cells++, and bacteria++, while urine culture was sterile.

For seizures, the patient was prescribed oral carbamazepine 400 mg twice daily (BD). However, two weeks later, she presented again and reported two new seizure episodes, despite her medication compliance. An assessment of breakthrough seizures was made. Carbamazepine was stopped and switched to levetiracetam 500 mg twice daily. Magnetic resonance imaging (MRI) of the brain showed a few T2/FLAIR sub-centimeter white matter hyperintensities [Figure 1]. The erythrocyte sedimentation rate (ESR) was 50 mm in the first hour.

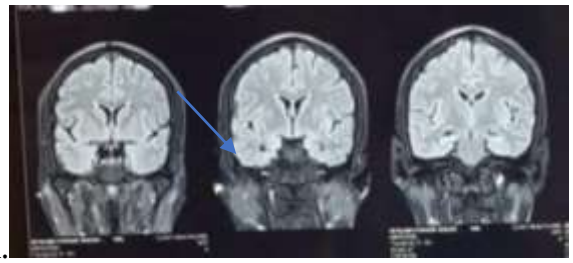
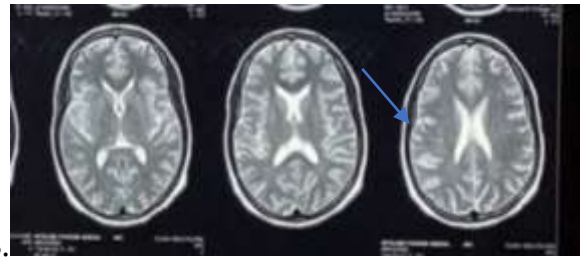
A.  B. 

Figure 1 a-b: Magnetic resonance images (MRI) of the brain show (A) normal mesial temporal lobe (arrow) in the fluid attenuated inversion recovery (FLAIR) corona image, and (B) white matter hypo-intensities (arrow) in the T2-weighted sequence.

Breakthrough seizures did not recur thereafter. Three months later, the patient presented again with complaints of exertional fatigue, breathlessness, worsening malaise, anorexia, and abdominal swelling. She also reported having a brief spell of irrational behavior and aimless wandering. Neurologic examination yielded normal findings except for mild asterixis. Physical examination revealed periorbital swelling, multiple well-circumscribed oval-to-round hyperpigmented maculopapular non-itchy skin rashes on the trunk and proximal extremities [Figure 2]. There was malar (butterfly) rash sparing the nasolabial fold, in addition to scarring alopecia [Figure 2]. Also noted were epigastric tenderness, abdominal swelling, and ascites. Urinalysis showed sediments and elevated levels of urea and creatinine. A repeat ESR yielded 150 mm in the first hour. Serum anti-nuclear antibodies were 1:640 with low complement (C3, C4) levels. The anti-dsDNA as well as anti-histone antibody assays returned negative. Cerebrospinal fluid (CSF) was normal.

The patient was diagnosed as having SLE with worsening renal function (uremia) secondary to lupus nephritis, and was managed conservatively.

Over the subsequent months, she manifested further target-organ involvement indicating disease progression. Ultrasonography of the abdomen and pelvis showed right kidney size of 109 × 54 mm and left kidney size of 127 × 65 mm, loss of corticomedullary differentiation, ascites, and bilateral pleural effusion, suggestive of pan-serositis. Urinalysis showed blood 3+ and protein 3+. The patient was admitted and initially given pulse doses of methylprednisolone, and subsequently oral prednisolone, mycophenolate mofetil (MMF), and hydroxychloroquine. She developed angioedema to MMF, which was switched to azathioprine.

Months later, the patient developed worsening ascites and respiratory difficulty (due to splinting of the diaphragm) with persistently low albumin levels. She is currently on disease-modifying anti-SLE medications and remains seizure-free.

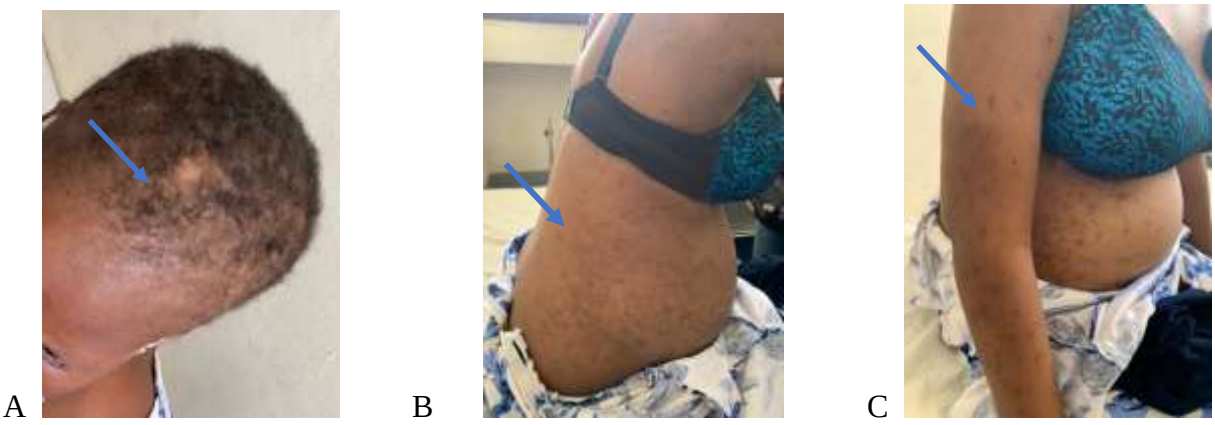


Figure 2: Cutaneous manifestations, three months after initial review. A: The scalp shows scarring alopecia. B & C: Multiple well-circumscribed oval-round hyperpigmented macules and patches on the trunk and abdomen and proximal extremities.

Discussion

This case was diagnosed using the 2019 criteria of European League Against Rheumatism / American College of Rheumatology (EULAR-ACR) for SLE.[12] Our patient satisfied the entry criterion of ANA: >1:80 (1:640) as well as the clinical and immunologic criteria. The constitutional symptoms of fever/malaise, neuropsychiatric features, mucocutaneous manifestation (scarring alopecia; score 2), serositis (ascites and pleural effusion; score 5), renal manifestations with 3+ proteinuria, and immunologic domains with low C3 and C4, together gave a total score of 10.

The negative anti-dsDNA finding was a highlight of this case and raised early concerns for drug-induced lupus erythematosus (DILE).[13] While some antimalarials such as quinine are known to cause DILE, carbamazepine is rarely implicated.[14–16] Our patient had a three-day course of artemether, which is not known to cause DILE, and she did not receive quinine. She received carbamazepine only two weeks before the switch to levetiracetam, but the switch did not improve her symptoms, thereby substantially weakening the case for carbamazepine induced SLE. In addition, pan-serositis, renal compromise, and hematologic findings are rare in drug-induced lupus erythematosus (DILE).[17]

Furthermore, DILE is rarely found in young black Africans, who are instead at risk for idiopathic SLE. In addition, carbamazepine is not a well-recognized cause of DILE. Also, our attempt to use Naranjo algorithm to estimate possible causal relationship between carbamazepine and SLE yielded 'doubtful' results.[18] Lastly, DILE is not typically associated with severe SLE.[11]

A systematic review of 1,250 rheumatology cases in Nigeria found 5.25% prevalence of SLE with a 95.5% female preponderance, with a mean presentation age of 33 years.[2] Though neuropsychiatric presentations were common, they did not precede the diagnosis of SLE, as also found in this case. In a follow up review by the same authors, 51.6% of Nigerian SLE patients had features of NPSLE. Headache was the most common presentation (66.6%) followed by seizures (42.4%) and psychosis (30.3%).[7] Our patient had behavioral symptoms described as brief moments of irrational behavior and aimless wandering. This was attributed to uremic encephalopathy as she had clinical asterixis and deranged renal biochemical parameters.

Our patient had adult-onset seizures months before the overt clinical features of SLE. In an Iranian study on 146 children with SLE, 28% had NPSLE of whom 43.9% presented with neuropsychiatric symptoms at the time of SLE diagnosis, 24.4% developed these symptoms within a year, and 31.7% after a year.[8] It is important to note that in these reviews, neuropsychiatric symptoms did not precede those of SLE.

Seizures constituted a prominent neurological symptom in our patient. In a long-term followup study on SLE patients with epileptic seizures, 13.6% had seizures at the onset of SLE symptoms, while the remaining 68.3% started having seizures after the onset of SLE.[19] In a review of factors associated with time-to-seizure occurrence occurring at or after diagnosis of SLE, younger age and disease activity were independent predictors of a shorter time-to-seizure occurrence; antimalarials appeared to play a protective role against seizures.[20] Our patient was young and had received antimalarials. She also had high disease activity evidenced by the low complement levels.

Neuropsychiatric SLE has been found to be associated with specific autoantibodies,[19] which is important, as our patient had anti-dsDNA negative antibodies. In a large single-center study, serositis was seen more frequently in anti-dsDNA negative SLE patients (82.3%) than in their anti-dsDNA positive counterparts.[21] A similar finding was demonstrated in our patient who developed refractory ascites and pleural effusion that required drainage.

The low serum albumin in our patient was indicative of the underlying inflammatory process. Immune-complex mediated small vessel vasculitis in SLE helped explain her myriad systemic inflammatory manifestations involving the skin, joints, renal, hematologic, and neurologic systems.

Conclusion

Among indigenous Africans, idiopathic SLE should be excluded as potential cause of adult-onset seizures. In the absence of clear offending agents, metabolic or structural disease, screening with ANA is helpful in the diagnostic evaluation of such patients as anti-dsDNA may be negative.

Disclosure

The authors declare no conflicts of interest. Written informed consent was obtained from the patient for publication of this report along with images.

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