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Case Report

Focal onset Seizures as the First Manifestation of Anti-Ds-DNA Negative Systemic Lupus Erythematosus: A Case Report and Review of Literature

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Abstract

Systemic lupus erythematosus (SLE) is a quintessential autoimmune disease once thought to be rare in Africans. It may affect any organ or tissue, synchronously or asynchronously. 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 female with new-onset focal seizures preceding overt clinico-laboratory diagnosis of anti-dsDNA negative SLE. It may be important to recognize SLE as a potential cause of adult-onset seizures in female subjects to allow early recognition and improved care. Baseline ANA may be a viable screening tool as part of the work up for Adult onset seizure disorders especially in females, in the absence of offending drugs, known metabolic or structural disease.

Key Words: seizures; neuropsychiatric SLE; NPSLE; connective tissue disease; auto-immune disease

Introduction

Systemic lupus erythematosus (SLE) is a quintessential autoimmune disease [1] once thought to be rare in Africans [2]. It may affect every organ and tissue, synchronously or asynchronously. Genetic predisposition, environmental triggers, and hormonal factors, interplay in the pathophysiology of the disease development as well as in disease activity. Clinical manifestations and the pattern of organ involvement are protean, thus reflecting the complex mosaic of pathophysiologic pathways converging into the SLE clinical phenotype [1].

Among the systemic autoimmune disorders, neurological manifestations have been most recognized and well-studied in SLE and less prevalent in other systemic inflammatory and autoimmune disorders [3]. The American College of Rheumatology (ACR) Nomenclature for Neuropsychiatric SLE (NPSLE) provides case definitions for 19 neuropsychiatric syndromes seen in SLE, with reporting standards and recommendations for laboratory and imaging tests [4].

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[10, 11,12,15]. It is important to note that in most of these reviews and case reports, the diagnosis of NPSLE rarely preceded that of SLE. We present a case report of a 19-year-old female with new-onset focal seizures preceding overt clinico-laboratory diagnosis of anti-dsDNA negative SLE.

Case Presentation

A 19-year-old lady seen at the neurology out-patient on account of new-onset seizures, described as focal onset with bilateral tonic-clonic involvement of the limbs. Each episode was associated with facial twitching, upward eye rolling and teeth clenching; lasting 2 minutes with associated postictal sleep. She had a total of four episodes prior to the initial review and had no headaches or premonitory aura. Seizures had started during a febrile illness that was treated with parenteral antimalarials. There were no reports of seizures in the past, head trauma, vascular risks. There was no photosensitivity, joint pain, weight loss or drenching night sweat. She had no history to suggest renal or hepatic decompensation. She neither took alcohol nor use tobacco in any form. She had no previously diagnosed medical comorbidities. She had no known family history of epilepsy. Pregnancy, birth, and attainment of developmental milestones were unremarkable. Clinical examination as well the neurological, cardiovascular, chest and abdominal findings were otherwise unremarkable.

Investigations

Serum calcium, uric acid, electrolytes, creatinine, and liver enzymes were normal, but serum albumin level was 2.8 g/dl. Urinalysis showed sediments,

leucocytes+++, squamous epithelial cells++, bacteria ++ and sterile urine culture study.

Diagnosis

An assessment of acute symptomatic seizures was considered and she was commenced on tab carbamazepine 400mg BD.

Outcome and Follow Up

She presented at the clinic two weeks later (second visit) after having had another two episodes of seizures since the last review despite being regular on prescribed medications. Further neurological exam revealed a conscious and oriented lady with subtle dysdiadochokinesia and past pointing - attributable to the carbamazepine, otherwise essentially normal findings. The erythrocyte sedimentation rate (ESR) as assessed by the Westergreen method was 50mm in the first hour. Her chest radiograph was normal and Brain MRI showed multiple T2/FLAIR sub-centimeter white matter hyperintensities. The Electroencephalogram was otherwise normal.

Approximately three months after the first review (the third clinic visit), she reported exertional fatigue, breathlessness, worsening malaise, anorexia, and abdominal swelling. She was reported to have had episodic irrational behavior and aimless wandering few weeks prior. Clinical examination showed periorbital swelling, generalized maculopapular non-itchy skin rash on the trunk and proximal extremities, a suggestion of a facial rash sparing the nasolabial fold as well as patchy alopecia **(figure 1)**. There was marked epigastric tenderness, abdominal swelling, and ascites.

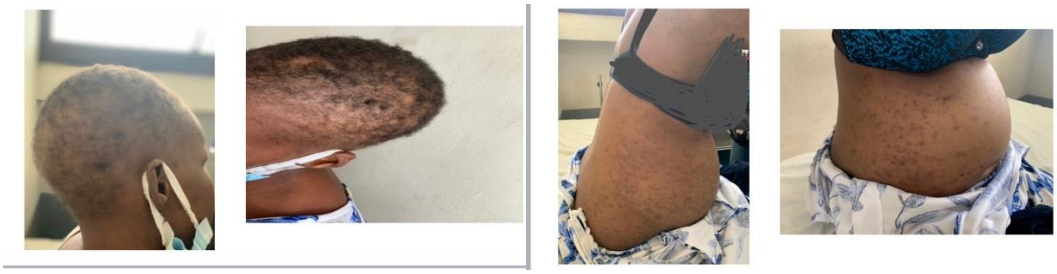

Figure 1: (three months after initial review)

A repeat ESR was 150mm in the first hour, serum anti-nuclear antibodies was 1:640 with low complement (C3, C4) levels. The anti-dsDNA assay returned negative. The ultrasonography of the abdomen and pelvic showed right kidney size at 109x54mm, left kidney size at 127mmx65mm with loss of corticomedullary differentiation, ascites, bilateral pleural effusion suggestive of pan-serositis (figure 3). Repeat urinalysis showed blood 3+, protein 3+. She was admitted and received pulse doses of steroids and was transitioned to oral prednisolone, mycophenolate mofetil (MMF) as well as hydroxychloroquine. She developed angioedema to MMF and this was switched to azathioprine. Due to the persistently low albumin levels and worsening ascites, she was planned for intravenous albumin infusion; paracentesis was attempted but unsuccessful. She is currently receiving multidisciplinary care from the rheumatologist, nephrologist, and neurologist as well as the gastroenterologist

Discussion

The 2019 EULAR-ACR new classification criteria, used in this case, was developed using rigorous methodology with multidisciplinary and international input and has excellent sensitivity and specificity for the diagnosis of SLE. Use of ANA entry criterion, hierarchically clustered and weighted criteria accurately reflect current thinking about SLE and provide an improved foundation for SLE research and diagnosis [9]. According to this criterion [9], our patient had the entry criteria of ANA: >1:80 (1:640) while meeting criteria across the clinical and immunologic domains. The constitutional symptoms of fever/malaise, neuropsychiatric features, mucocutaneous manifestation (scarring alopecia = 2), serositis (ascites and pleural effusion; score of 5), renal manifestations with 3+ proteinuria, and immunologic domains with low C3 and C4 gives a total score of 10.

The learning point of this case is the initial presentation of SLE with focal onset seizures which had hitherto been unreported in sub-Saharan Africa and may pose a diagnostic challenge in resource limited settings. This may be due to under-recognition or under-diagnosis. The patient presented with neurological symptoms and only began to manifest features of an autoimmune illness three months later, prompting an autoimmune screen using ANA. A retrospective review from a foremost rheumatology clinic in Nigeria noted that a high index of suspicion is needed to diagnose SLE [2] while highlighting that concomitant presentation of neuropsychiatric manifestations and SLE may be rare. Baseline ANA may be part of the work up for Adult-onset seizure disorders especially in female subjects. The negative anti-dsDNA is a major highlight of this case and the early urinalysis findings raised concerns for lupus cystitis.

In a retrospective review by Adelowo et al, out of a total of 1,250 rheumatology cases seen over a period of 6 years, 5.25% accounted for SLE with a 95.5% female preponderance and a mean of 33 years at presentation [2]. The mean duration of symptoms was 2.6 years with polyarthralgia, fever and hair loss being the most common presentation. Neuropsychiatric presentations were reportedly common, however this did not precede the diagnosis of SLE, as was documented in this case.

In a follow up review by the same author, out of a total of 64 subjects diagnosed with SLE, thirty-three subjects (51.6%) had features of NPSLE. Headache was the commonest presentation (66.6%) while other common presentations were seizures (42.4), psychosis (30.3%) [10]. Our patient had focal-onset seizures and psychosis months before overt clinical features of SLE. In another prospective of 146 pediatric subjects with SLE from Iran, 41 (28%) had NPSLE with the most common neuropsychiatric symptoms being headache (13%), seizure (9.5%) and chorea (3.4%), others were migraine, depression. From the 41 patients with NPSLE, 18 (43.9%) presented with symptoms at the time of diagnosis; 10 (24.4%) showed NPSLE within one year of SLE diagnosis; while thirteen (31.7%) patients, developed neurological symptoms more than 1 year after the diagnosis of SLE [11].

A recent case report from Nigeria also highlighted a diagnosis of NPSLE concomitantly diagnosed in a Nigerian teenager [12]. The patient had persistent headache, anxiety, confusion and generalized tonic clonic seizures. It is important to note that in this reviews and case report, the diagnosis of NPSLE did not precede that of SLE. In turkey, a case report of a 7-year-old girl who had no initial history of seizure presenting with Status epilepticus, without clinico-laboratory findings of SLE (except for anemia) has also been documented [15].

However, in a recent study of a cohort of 519 consecutive patients with SLE, followed up for 4 - 7.8 years, sixty (11.6%) patients with epileptic seizures were identified and epileptic seizures occurred at the onset of SLE symptoms in 19 (31.6%) and after the onset of SLE in 41 of 60 (68.3%) patients. Fifty-three of 60 (88.3%) patients had acute symptomatic epileptic seizures, and 7

of 60 (11.7%) had recurrent epileptic seizures [13]. In a review of factors associated with time-to-seizure occurrence occurring at or after diagnosis (TD) of systemic lupus erythematosus, younger age and disease activity were independent predictors of a shorter time-to-seizure occurrence; antimalarials appear to have a protective role in seizure occurrence [14]. Our patient was young and appeared to have high disease activity evidenced by the low complement levels. She also received antimalarials at onset of illness, the effect of antimalarials on seizure occurrence however is yet unclear.

Neuropsychiatric SLE and association with specific autoantibodies have also been described. One of such is antiphospholipid antibodies associated with acute epileptic seizures at SLE onset [13]. This is important as our patient has anti-dsDNA negative antibodies. In a study from western India, Anti-Rib-P antibodies as well as anti-neuronal antibodies did not show statistically significant correlation with neuropsychiatric manifestations in NPSLE patients[16]. In another study, anti-dsDNA status influences the clinical and immunological features of SLE patients. Nonetheless, it does not appear to affect disease activity [17].

The low serum albumin finding of 2.8 g/dl in our patient is a negative acute phase reactant in light of the underlying inflammatory process. This was also supported by the urinalysis finding showing sterile pyuria with prominent gastrointestinal symptoms raising concerns for a possible lupus cystitis which has also been widely reported in literature [18,19]. Lupus cystitis can precede SLE diagnosis and may present with very unspecific urinary and digestive tract symptoms [20] or no symptoms at all. The exact mechanism of bladder inflammation in lupus is not fully understood; however, histopathological studies suggest a possible role of immune complex-mediated small vessel vasculitis [18]. Immune-complex mediated small vessel vasculitis in SLE has helped to explain the myriad of systemic inflammatory manifestations involving the skin, joints, renal, hematologic as well as the neurologic system, which was manifest in our patient.

Conclusion

The hallmark of this case is the initial presentation of SLE with focal onset seizures which had hitherto been unreported in sub-Saharan Africa and may pose a diagnostic challenge. It may be important to recognize SLE as a potential cause of new adult-onset seizures in female subjects to allow early recognition and improved care. Baseline ANA may be a viable screening tool as part of the work up for Adult-onset seizure disorders especially in females, in the absence of offending drugs, known metabolic or structural disease.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Disclosure

The authors have no multiplicity of interests to disclose.

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