Clinical and radiological features of neuropsychiatric systemic lupus erythematosus: case series from East Africa

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Abstract

Neurological and psychiatric manifestations of Systemic Lupus Erythematosus (NPSLE) are clinically diverse, may occur early in the disease, and can be the first manifesting symptom. A high index of suspicion is thus required in such cases to allow timely diagnosis and appropriate treatment in order to avoid irreversible damage of the brain. Magnetic Resonance Imaging (MRI) may offer a diagnostic clue, and several patterns have been described in the literature. We present here a series of cases of NPSLE with index neurological symptoms and uncommon MRI brain findings: diffuse white matter changes, optic tract signal change, slow dural venous sinus flow, and large non-dominant hemisphere stroke. The diagnosis of NPSLE was missed in the initial presentations, but was only made when the clinical picture, these MRI features and laboratory findings were put together for each case. Our case series highlight the broad spectrum of neurological manifestations and MRI brain scan findings in NPSLE.

Key words: Neuropsychiatric systemic lupus erythematosus, Magnetic resonance imaging, Stroke

Introduction

Systemic Lupus Erythematosus (SLE) is a classic multi-system autoimmune disease, more common in women and those of African origin[1]. Neuro-psychiatric presentations (NPSLE) occur in up to 75% of cases[2], and there are 13 recognised patterns of neurological syndromes encompassing both the central (CNS) and peripheral nervous system[3]. The commonest CNS symptoms are impaired cognition, seizures, headaches, and stroke[4], in addition to other diverse neurological symptoms[5], which pose a diagnostic challenge compounded by other mimicking insults such as SLE medications or concurrent infections[6]. NPSLE symptoms occur relatively early in the disease, correlate with disease activity levels, and are associated with higher SLE-related mortality and morbidity[7].

The pathophysiology leading to CNS damage in NPSLE is thought to be a combination of vascular insults, direct neuronal injury, precocious atherosclerosis and embolisms[8]. Magnetic Resonance Imaging (MRI) of the brain is the modality of choice for investigating CNS involvement in NPSLE, and MRI abnormalities correlate with clinical and immunological features[9], including on post-mortem examination[10]. Interestingly, up to 40% of NPSLE cases have normal MRI brain scans[11]. Abnormal brain MRI findings in NPSLE are largely classified into[12]:

(i) *Vascular:* Which includes small vessel disease, resulting in White Matter Hyperintensities (WMH) and cortical atrophy (both of which are the commonest abnormal findings on MRI in NPSLE[11] at 30-75% and 15-20% respectively), and large vessel disease causing strokes which are probably the most debilitating but occur less frequently at 10-15%[13].

(ii) *Inflammatory/demyelinating*: Characterised by ill-defined hyperintensities involving either grey or white matter and not conforming to vascular territories on T2 or Fluid-Attenuated Inversion Recovery (FLAIR) sequences, sometimes with contrast enhancement. These neuroradiological features are less frequent at around 7% of NPSLE cases[11], and demyelination is one of the rarer CNS manifestations of NPSLE[5].

NPSLE in Africa has been reported from the northern[14-16], western[17] and southern[18] regions of the continent; the study from South Africa focused on the neuroradiological correlates of the disease and interestingly MRI abnormalities were more common than other studies at 81.9% of NPSLE cases[18].

Materials and methods

We report here four cases of newly diagnosed NPSLE patients from East Africa who fulfil the international diagnostic criteria[3,19] managed at our regional tertiary referral centre, whose

MRI brain scans were conspicuously heterogeneous and not well described in the literature but were vital towards the eventual diagnosis and management in each case.

Case reports

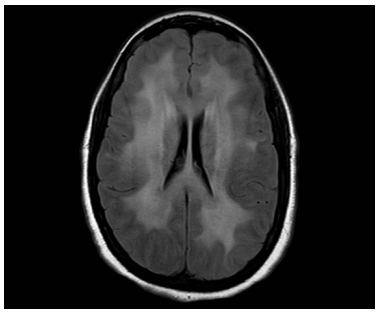
Case 1

A 41-year old female self-referred to our facility from Tanzania, having been evaluated in the interim in The Netherlands with no clear diagnosis. She presented with a six-month history of new-onset continuous migraine-sounding headaches with dizziness, unresponsive to standard therapies. Latterly, she experienced gait imbalance resulting in falls, and then intermittent painful swelling of her ankle, wrist and knee joints. Positive findings on physical examination were neck stiffness, nystagmus with broken pursuit of eye movements, brisk reflexes in the limbs, and inability to tandem walk; her joints had non-specific swelling. Laboratory investigations showed a normocytic anaemia with haemoglobin 8.4 g/dL (normal range, NR, 11.5 – 16.5), but otherwise normal kidney, thyroid, liver, and inflammatory marker profiles, with negative serum Angiotensin Converting Enzyme (ACE) levels and HIV serology testing. MRI brain scan [Figure 1(a) through (c)] revealed confluent bilateral symmetrical T2 and FLAIR white matter hyper-intensities extending to the brainstem, superior and inferior cerebellar peduncles, with patchy pachymeningeal and basal leptomeningeal but no parenchymal enhancement. Cerebrospinal Fluid (CSF) analysis revealed normal constituents including white cell count and protein, and was negative for Gram and Zeel-Neilsen (ZN) stains, Gene Xpert, adenosine deaminase levels, and viral PCR for Herpes Simplex, Epstein Barr and cytomegalovirus (HSV, EBV, and CMV). CT scan of the abdomen and chest revealed bilateral axillary and pelvic lymphadenopathy, and an ultrasound-guided biopsy of the axillary node showed non-specific inflammation. She was reviewed by a rheumatologist (author FOO), and a subsequent autoimmune panel revealed positive speckled Anti-Nuclear Antibodies (ANA), with a high titre at 1:640 (NR: negative), Low C3 complement at 0.85 g/L (NR 0.9 – 1.8) and positive Anti-smith antibody (NR: negative), as well as a strongly positive Anti-Phospholipid Antibody (APLA), all of which confirmed the diagnosis of SLE.

She was pulsed with methylprednisolone 1 gram daily for 3 days, followed by rituximab infusion and was thereafter discharged on mycophenolate mofetil, hydroxychloroquine, gabapentin and tapering doses of prednisone. She reported marked improvement over subsequent months, and her headaches resolved after 6 weeks. Follow up MRI brain scan done at six months and a year later [Figure 1(d) and (e)] revealed significant interval decrease in the extent of abnormal white matter T2/FLAIR hyperintense signals in the supra-tentorial and infra-tentorial brain, and no new abnormalities.

Figure 1: Magnetic Resonance Imaging (MRI) Fluid-Attenuated Inversion Recovery (FLAIR) sequences of the brain of Case 1. There is extensive confluent white matter hyperintensities on axial [images (a) and (d)], coronal [images (c) and (e)], and sagittal [image (b)] views, with improvement in respective images after >6 months of NPSLE treatment [images (d) and (e) when compared to (a) through (c)]

(a)



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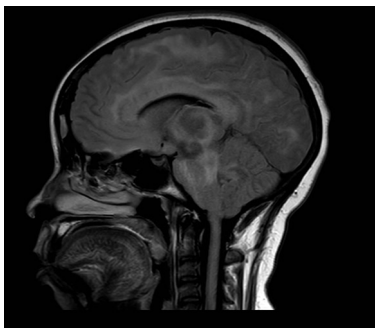

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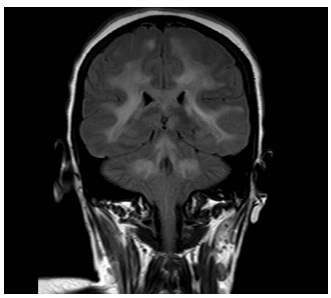
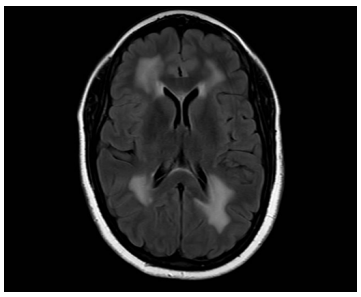
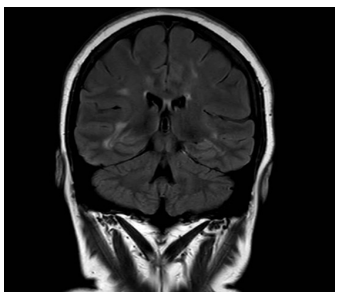


(d)



(e)



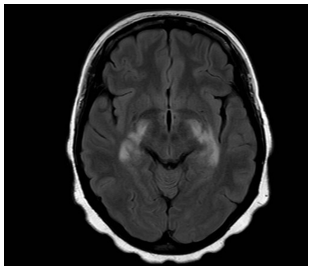
Case 2

A 47-year-old female presented to our rheumatology clinic with one month history of polyarthralgia, proximal upper limb myalgia and periorbital swelling, but no skin or mouth ulcers. Her examination revealed restricted shoulder movements, tenderness in the arm muscles, but no other stigmata of connective tissue disease. She was however noted to have a smooth, non-pulsatile goitre. She was due for further clinical work-up but got lost to follow up until she attended the endocrinology clinic with ongoing joint pains, worsening neck swelling and now additional visual obscuration, not accompanied with headaches. On examination by the ophthalmologist, she was found to have epiphora, mild periorbital oedema with conjunctival chemosis but no proptosis, and lid retraction with no impairment in extraocular muscle motility, and no abnormalities in the posterior segment. Blood tests revealed Thyroid Stimulating Hormone (TSH) 10.84 μIU/mL (NR 0.27 – 4.2); free T4 0.58 ng/dL (NR 0.89 – 1.52) and high titres of antibodies to thyroid-specific peroxidase at > 1000 IU/ml (NR 0 – 8); thyroid ultrasound showed heterogeneous enlarged thyroid gland so she was initiated on thyroxine replacement.

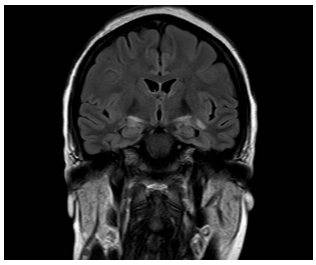
Her visual symptoms did not improve and an MRI scan of the orbits done at an external facility reported features of idiopathic orbital inflammatory disease rather than thyroid ophthalmopathy, so she was referred to a neurologist (author DSS) for further evaluation. MRI brain scan (Figure 2a) revealed non-enhancing, non-restricting bilateral symmetrical T2/FLAIR hyperintense signals within the optic chiasm and retro-chiasmatic optic tracts up to the level of the occipital lobes, with extension into the adjacent temporal lobes, posterior limbs of the internal capsule and peri-trigonal white matter. An auto-immune panel revealed positive speckled ANA (titre 1:320), positive Extracted Nuclear Antibodies (ENA) for SM/RNP and SSA/Ro, but negative anti-double-stranded DNA (dsDNA). These results confirmed NPSLE so after consultation with the rheumatologist she was started on mycophenolate mofetil, hydroxychloroquine and prednisone. She reported resolution of her joint pains two months later, and repeat MRI brain scan showed complete resolution of the abnormalities (Figure 2a).

Figure 2: MRI FLAIR sequences of the brain of Case 2 showing white matter hyperintensities along the optic chiasm to optic tracts on axial [images (a) and (d)], coronal [images (b) and (e)], and sagittal [image (c)] views, with improvement in respective images after 2 months of immunosuppression [images (d) and (e) when compared to (a) through (c)]

(a)



(b)



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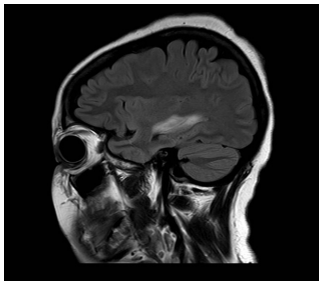
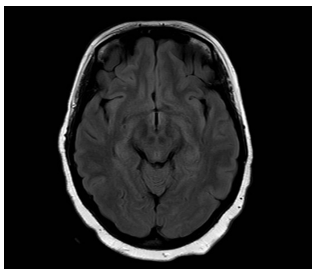


(d)



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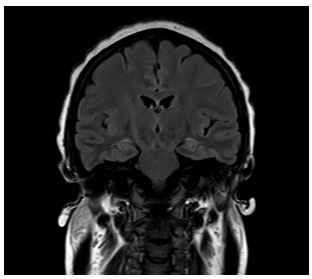


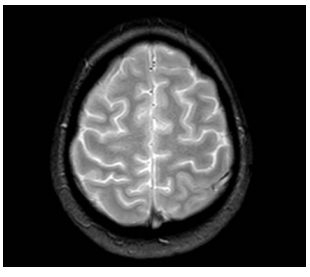
Case 3

A 16-year-old female was seen in the rheumatology clinic with unexplained chest pains, a facial rash and finger swelling for one month, and on clinical suspicion of a connective tissue disorder was treated with mycophenolate mofetil, hydroxychloroquine and prednisone. However, one month later she was admitted to our critical care unit because of new headaches, confusion, fevers and generalized weakness. MRI brain scan was normal except for high T2 and FLAIR signal in the left vein of Trolard with absence of blooming on gradient echo sequences, likely representing sluggish flow rather than thrombosis (Figure 3a). CSF studies were negative, and her laboratory tests from her rheumatology clinic were reviewed as she was found to have a positive ANA (positive speckled 1:640 titre), dsDNA and ENA (for Sm, Sm/RNP, SSA and SSB antibodies).

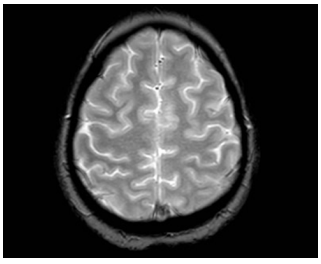
We therefore diagnosed NPSLE and she was pulsed with 1 gram intravenous methylprednisolone daily for five days with some improvement in her headaches, then three days later started having hallucinations, refusing oral medications and food, and catatonic posturing with hypersalivation. She received psychotropic medication but continued to have labile mood, abnormal mannerisms and episodes of confusion so we initiated intravenous cyclophosphamide and her symptoms gradually improved. She was discharged from the hospital one month later after the admission date, and continued outpatient cyclophosphamide for six doses and was thereafter continued on hydroxychloroquine, mycophenolate mofetil and a tapering dose of prednisone. She was able to resume school four months later and repeat scans showed resolution of the anomaly (Figure 3b), and to date she has had no flare up of her SLE.

Figure 3: Axial gradient echo (T2*) MRI sequences of Case 3 showing the blooming along the left vein of Trolard [image (a)] which resolved after 3 months of immunotherapy [image (b)]

(a)



(b)



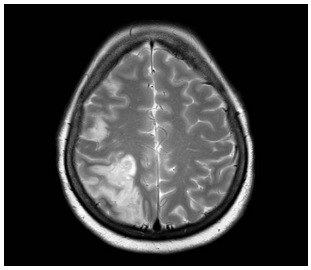
Case 4

A 31-year-old female initially presented with chest pain and progressive breathlessness found to be due to an unprovoked segmental Pulmonary Embolus (PE) with no known risk factors, and a thrombophilia screen was negative. She was managed by the haematology team and treated with rivaroxaban for 6 months, towards the end of which she began to suffer initially episodic then constant right-sided migraine-sounding headaches. Her husband then noted she was bumping into furniture on her left hand side and she was struggling to drive so she was admitted under our neurology service. On neurological examination she had a left homonymous hemianopia but no other neurological deficit. Neuro-imaging confirmed large sub-acute right hemisphere ischaemic strokes [Figure 4(a) and (b)], with normal venography and angiography.

As per our in-hospital stroke pathway, we requested a 'young-onset stroke' investigation panel including cardiac evaluation (24-hour holter monitor and trans-oesophageal echocardiogram) and laboratory tests which were all normal except for elevated Erythrocyte Sedimentation Rate (ESR) of 113 mm/hour (NR <30), and a positive connective tissue screen which was positive for anti-SSA and anti-RO52 antibodies, positive for ANA (anti-centromere titre 1:320) but negative for anti-dsDNA. She was switched to warfarin and commenced on prednisolone, mycophenolate mofetil and hydroxychloroquine. When reviewed in the neurology clinic one month later her visual fields were improving on clinical examination although she still had a significant homonymous hemianopia on Humphrey's Visual Field assessment [Figure 4(c)]. She had no further neurological complications, but later developed micro-albuminuria thought to be SLE-related, so her treatment regimen was appropriately modified.

Figure 4: Axial T2-weighted [image (a)] and diffusion-weighted [image (b)] MRI sequences revealing large right hemisphere acute ischaemic infarction, with corresponding left homonymous hemianopia on Humphrey's visual fields [image (c)]

(a)



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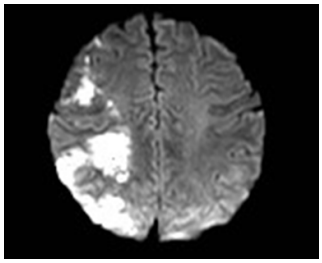


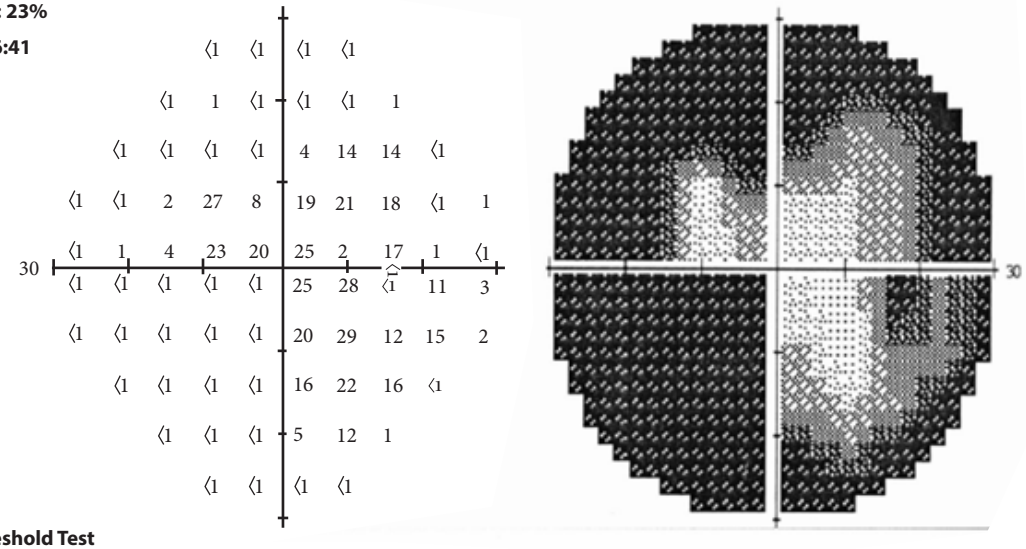
(c)

Single Field Analysis **Eye: Right**

Name:	**DOB:**
ID:	

Central 30-2 Threshold Test

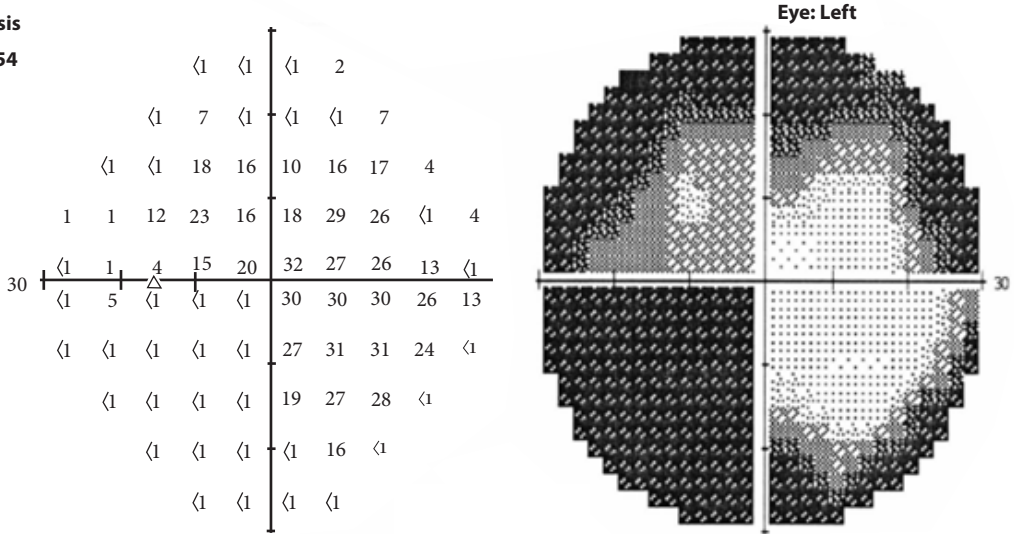
Fixation Monitor: Gaze/Blind Spot	**Stimulus: III White**	**Pupil Diameter**	**Date:**
Fixation Target: Central	**Background: 31.5 ASB**	**Visual Acuity**	**Time:**
Fixation Losses: 0/17	**Strategy: SITA-Standard**	**RX: +1.00 DS DC X**	**Age:**
False POS Errors: 0%			
False NEG Errors: 23%			
Test Duration: 06:41			
Fovea: OFF			



Central 30-2 Threshold Test

Fixation Monitor: Gaze/Blind Spot	**Stimulus: III White**	**Pupil Diameter**	**Date:**
Fixation Target: Central	**Background: 31.5 ASB**	**Visual Acuity**	**Time:**
Fixation Losses: 0/17	**Strategy: SITA-Standard**	**RX: +1.00 DS DC X**	**Age:**
False POS Errors: 0%			
Single Field Analysis			
Test Duration: 06:54			
Fovea: OFF			

Eye: Left



Discussion

All our patients were black African females, in whom SLE is known to be more prevalent[1], with the average age of our cohort being 34 years (range 16-47) which is also in keeping with other studies of NPSLE from Africa[17]. All patients fulfilled the 1982 criteria (with 1997 modification) international diagnostic criteria for SLE[19], but the average delay from initial presentation to diagnosis was 6.5 months (range 1-9), with Case 3 being diagnosed within 1 month as they presented acutely with neuropsychiatric features which tend to be more clinically urgent and more prevalent in younger patients with SLE[18]. This delay to diagnosis is significantly longer when compared to e.g. 2.9 months in European cohorts[20], but much less when compared to other parts of the developing world e.g. 23 months in a study from Israel[21]. A recent survey of physicians and specialists across Africa found that delays to diagnosis of SLE is due to a combination of lack of access to healthcare, low disease awareness in the population and in the primary health systems, inadequate specialist staffing, and lack of availability of diagnostic tools[22]. There is relatively easy availability of diagnostic services at our centre given it is a regional specialist referral hospital which may explain why we did not experience as much delay.

All our cases were treated with the appropriate immunosuppressive therapy[19] which may explain why they had good outcomes (except for Case 4 who then also developed lupus nephropathy), whereas NPSLE is usually associated with poorer outcomes[7].

Three of our cases presented with headaches, with one progressing to more florid neuropsychiatric features, which is in keeping with other studies from the continent where headache was the most common presenting feature in NPSLE[15,17]. However, interestingly none of our cases had seizures, which is similar to the NPSLE cohort reported from Egypt[15] (and in Tunisia only 6% presented with seizures[15]), but contrasts with Nigeria[17] and South Africa[18] where seizures were reported in 42.4% and 45.8% of NPSLE presentations respectively. The newer SLE classification place more weightage on seizures in the neuropsychiatric domain, more than delirium or psychosis[23]; other specific neurological syndromes as per the 1999 criteria do not appear. From our experience institutionally we have had NPSLE with more common MRI findings experiencing seizures as part of their presentation but have not reported them here.

The neuro-imaging of Case 1 illustrates the extreme end of the rarer demyelinating and inflammatory changes that can be seen in NPSLE, but have not been reported to be so extensive[11,12], which is probably why the diagnosis was not made initially. The patient also had positive APA which are known to be associated with more diffuse WMH on MRI in NPSLE[24]. This case would be the first with NPSLE coming from Tanzania, with only one previous published SLE report from Tanzania who presented with lupus nephritis[25].

The demyelinating/inflammatory changes seen in the imaging for Case 2 are quite unique. In the absence of uveitis and papillary involvement, the differential diagnosis included neoplastic causes such as optic nerve and tract glioma – which is more commonly described in children with neurofibromatosis type 1[26] – or inflammatory causes such a connective tissue disease. In comparison to the well described ocular SLE manifestations of uveitis and retinopathy, optic nerve and tract involvement are rarer entities in SLE[27], and to our knowledge such striking imaging findings such as in our case, which melted away on SLE treatment, have not been published in the literature. It is unlikely that her MRI findings were related to the thyroid disease, given they persisted despite thyroxine treatment for several months before she presented with visual disturbance, and the MRI of the orbits excluded thyroid ophthalmopathy.

Case 3 and 4 show MRI changes consistent with vascular pathology. Slow flow in the cerebrovasculature has been reported in NPSLE[28], physiology of which is not clear but is probably related to vasculopathy from SLE[8,9]. Complete venous sinus occlusion in the form of Cerebral Venous Sinus Thrombosis (CVST) is more frequently described in the literature reported, although SLE is deemed a very rare cause of CVST, approximately 1.3% of all predisposing conditions according to some studies[29].

Case 4 had an unprovoked PE heralded by pleuritic symptoms, but was not fully investigated for the underlying cause; SLE doubles the risk of PE compared to the general population, more so in females and the African-American race[30]. This explains why she then suffered a large-vessel stroke syndrome, though she was largely asymptomatic apart from headaches and the hemianopia as the non-dominant hemisphere was affected. In a large Swedish population-based study, individuals with SLE had over double the incidence of ischaemic stroke when compared with the general population, with the highest hazard ratios being in females and younger cases[31]. Acute ischaemic stroke can be the first manifestation of SLE, and tends to occur in younger females and in the posterior circulation[32]. The mechanism of stroke in SLE can be due to the presence of APA, Libman-Sacks endocarditis, Sneddon syndrome or CNS vasculitis[5], although our patient had none of these, which suggests a different mechanism that may also be attributed to her developing lupus nephritis later on. Large-vessel strokes affected 9.6% of the South African NPSLE cohort[18], and the global average is somewhere between 10-15%[13]. Case 4's stroke syndrome would have gone unnoticed had it not been for timely neuro-imaging; some propose routine MRI neuro-imaging, and even cardiac MRI, as pre-symptomatic biomarkers for all SLE cases[33,34].

Conclusions

NPSLE can be the presenting feature of the systemic disease, but the protean manifestations present a diagnostic challenge. Neuroradiological features, especially on MRI brain scans, can aid the diagnostic process. The few studies from sub-Saharan Africa on NPSLE describe some features that are unique to the continent. Our case series, the second such report on NPSLE brain imaging from Africa, highlight the diversity of MRI brain findings in NPSLE which fall into the two main pathophysiological categories: vascular, including small- and large-vessel disease as in Cases 3 and 4 respectively; and demyelinating, as in Cases 1 and 2. There was a delay to diagnosis of several months in most of our cases, as has been previously reported in NPSLE. Appreciation of the MRI features we have described can lead to earlier diagnosis and therefore timely initiation of appropriate treatment to reduce morbidity.

Data availability

The clinical history and imaging data used to support the findings of this study are included within the article.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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This case series did not receive any specific funding. The cases have been compiled as part of authors' current employment under the Aga Khan University Medical College of East Africa, Faculty of Health Sciences.

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Ethical Considerations

Our work has been conducted in accordance with the Declaration of Helsinki (1964). We have documented consent from all patients to use their images for publication. Case 1 and 2 have arisen as clinic mimics from a larger project that is collecting case of multiple sclerosis at our institution [approved by our Institutional Ethics and Research Committee (IERC) reference REC/2018-99]. Case 3 and 4 arise from a larger project on strokes presenting to our institution (IERC reference 2019-62). In line with our IERC guidelines, these case reports are exempted from full IERC review.

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