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Unusual Headaches Revealing Neurolupus In Lome: Case Report And Review Of Literature

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic idiopathic autoimmune disease that affects various organs, including the central nervous system (CNS) and peripheral nervous system (PNS). Neurological and psychiatric manifestations of systemic lupus erythematosus or neurolupus (NPSLE) may present as a headache. We report a case of neurolupus characterized by diagnostic wandering. The patient, a 38-year-old woman, was admitted because of persistent headaches refractory to analgesics in the context of chronic headaches that had developed since adolescence diagnosed as migraine. Her personal medical history was marked by pyrosis, polyarthralgias, dermatosis. She was admitted to the hospital with right hemicorporeal paresthesias and worsening headaches, and the clinical examination found hyperreflexia, a malar rash, multiple hypochromic sequelae lesions of dermatosis in all 4 limbs. Brain MRI showed a non-systematised left parieto-occipital lesion on T1 isosignal, T2 and FLAIR hypersignal, not enhanced by gadolinium. The cerebrospinal fluid showed a relative hyperproteinorrhea, the presence of red blood cells (05/mm³), and leukocytes (46/mm³). Blood biology found an inflammatory syndrome with moderate anaemia, an accelerated sedimentation rate of 100 mm at the first hour, a C-Reactive Protein (CRP) at 22.8 g/l (normal less than 5 g/l), positive rheumatoid factors, positive antinuclear antibodies in the indirect immunofluorescence assay (on Hep 10-20 slides), at a titer of 1/320, negative deoxyribonucleic acid antibodies and positive anti-Smith antibodies. The diagnosis of SLE was confirmed based on the American College of Rheumatology (ACR) criteria with a score of 23. Excluding primary and secondary headaches, the patient's headaches satisfied the criteria for NPSLE. She was treated with corticosteroids and then methotrexate. After 3 months of treatment, a regression of headaches and cerebral signal abnormalities was noted.

Key words: Headaches, Neurolupus, Togo, Systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic idiopathic autoimmune disease that affects various organs, including the central nervous system (CNS) and peripheral

nervous system (PNS) (1). Neurological and psychiatric manifestations of SLE or neuro-lupus (NPSLE) can present with various symptoms: cognitive dysfunction, organic brain syndromes, delusional syndrome, and seizures (1). The term "lupus headache" is defined as a severe persistent headache, which can be migraine-prone and does not respond to narcotics (2).

The worldwide prevalence of SLE is 4-178 per 100,000 population, and incidence is 0.3-23.7 per 100,000 population per year (3). The majority of NPSLE symptoms manifest at the time of SLE diagnosis or subsequently, typically within the first year after diagnosis (4). Overall, NPSLE affects 56.3% of SLE patients, predominantly the CNS (93.1%) rather than the PNS (6.9%) (4), (5). A diagnosis of NPSLE is reached through the utilisation of a range of clinical, serological, immunological, electro-physiological, and neuroimaging studies (5). Given the absence of a singular diagnostic test for NPSLE, the initial step is to rule out secondary causes of neurological conditions, including infections, metabolic or endocrine disorders, adverse drug reactions, and malignancy (4).

Few data on NPSLEs are available in sub-Saharan Africa (6), (7). In Togo, cases of neurolupus have been reported in hospitals, but no cases of neurolupus have been published (8). It seemed appropriate to us to report a case of neurolupus that was initially misdiagnosed.

OBSERVATION

The patient was a 38-year-old female farmer who was admitted to the hospital at the end of March 2024 due to persistent headaches that were refractory to conventional analgesics. Her medical history included chronic headaches since adolescence diagnosed as migraines, gastro-oesophageal reflux disease associated with pyrosis for 5 years, and a suspected dermatosis for 3 years, with no further details (erythematous rash in the chest and lower limbs). There is no surgical history. She is single, primiparous, and has no history of miscarriage. There is no known family defect. She does not report alcohol and tobacco intoxication.

In December 2023, the patient presented with an unusual headache in the context of chronic cephalalgia. The intensity of the headaches was rated on the Visual Analogue Scale (VAS) as 7-8/10. She consulted a health centre where a brain CT scan was performed and returned normal. Biological analysis revealed lymphopenia at 1200/mm³ and a C-reactive protein (CRP) level of 22.8 g/l (normal range: less than 5 g/l). She was diagnosed with migraine-like headaches and was treated with ergotamine 1 mg + caffeine 100 mg + belladonna 0.1 mg + paracetamol 400 mg: 2 tablets x2/day, tramadol 50 mg x2/day, aceclofenac 100 mg x2/day, amitriptyline drops 10 mg to be taken in the evening at bedtime with a transient improvement in symptoms with a residual VAS score between 4 and 5. In January 2024, she presented with inflammatory polyarthralgias and right hemicorporeal paresthesias, described as a tingling sensation. Despite ongoing treatment with tramadol and amitriptyline, the patient's headaches worsened, necessitating hospital admission in March 2024. These headaches were helmet-style, tight-type, with VAS at 8/10. There was no sonophobia or photophobia. Nausea, vomiting, or blurred vision were also not reported, and no precipitating factors were identified.

The entrance examination revealed a fever at 38°C, good haemodynamic status, and a weight of 67 kg for a height of 155 cm (BMI at 27.9). The neurological examination revealed no impairment of higher functions, no sensory-motor deficit, sharp osteotendinous reflexes in all 4 limbs, no cerebellar syndrome, and no sign of meningeal irritation. Dermatological examination noted a malar rash and multiple hypochromic sequelae lesions of dermatosis in all 4 limbs. Systemic, infectious, vascular, metabolic, toxic, or tumour conditions were the initial diagnostic hypotheses.

A non-systematised lesion was identified in the left parieto-occipital white matter-gray matter junction on a brain MRI. This lesion exhibited T1 isosignal, T2 hypersignal, FLAIR, and no enhancement by gadolinium (Figures 1 and 2). Biology (Table 1) found anaemia, an accelerated sedimentation rate of 100 mm at the first hour, a positive protein

reactive C, serum protein electrophoresis showed an inflammatory profile; rheumatoid factors were positive.

An examination of the cerebrospinal fluid (CSF) revealed a clear fluid. The cytology showed the presence of red blood cells (05/mm³), leukocytes (46/mm³), polynuclear cells (56%), lymphocytes (44%), glycorachia (0.59 g/l), and hyperproteinarachia relative to 0.51 g/l. Additionally, a negative culture was observed, and the Genexpert test with *Mycobacterium tuberculosis* returned a negative result. Isoelectrofocusing of the CSF was not conducted.

The antinuclear antibodies performed in France returned a positive result (indirect immunofluorescence on Hep 20-10 slides) at a titer of 1/320, with a speckled appearance. The anti-Deoxyribonucleic Acid antibodies were negative, while the anti-Smith positive antibodies were present (Table 1). The results of the antiphospholipid antibody test were negative. Antinuclear antibodies are immunoglobulins directed against autologous components of the nucleus and cytoplasm. The technique employed is recommended by the American College of Rheumatology (ACR), namely an indirect immunofluorescence (IFI) technique on HEp2 cells (a human epithelial cell line obtained from a laryngeal carcinoma). In practice, HEp2 cells (at different stages of the cell cycle) are fixed on a microscope slide and exposed to the patient's serum, which may be more or less diluted. The determination of the specificity of antinuclear antibodies (native anti-DNA, soluble anti-antigen) was carried out by the technique ELISA (enzyme-linked immunosorbent assay). For the soluble anti-antigen antibodies of the nucleus (ENA: Extractable Nuclear Antigen), the ELISA screening technique was employed, whereby a well is covered by different soluble antigens of the nucleus: Sm, SSA/Ro, SSB/La, U1-RNP, Jo1, and Scl70. In the event of a positive screening result, the target antigen of the autoantibody is identified via ELISA identification.

Based on the results of the additional analyses, the infectious pathologies mentioned were acute bacterial encephalitis or tuberculosis encephalitis. These hypotheses were dismissed due to the aspect of cerebrospinal fluid, negative culture, there was no context of antibiotic intake that could make a beheaded meningoencephalitis suspect, there was no precarity, no tuberculosis infection, Genexpert was negative for *Mycobacterium tuberculosis*. Routine biochemistry tests have ruled out uremic and hepatic encephalopathies, and no toxic substances were detected.

The diagnosis was made possible by brain MRI. The symptoms' progressive nature, the absence of hypersignal at the diffusion sequence, and the non-systematized aspect of the lesion in the FLAIR sequence (not respecting the arterial territory) ruled out the possibility of a stroke. Similarly, cerebral cysticercosis at the vesicular phase was eliminated due to the absence of pork meat consumption or residence in a pig breeding area, as well as radiological arguments. In the T1 MRI, the cystic lesion manifested as a fluid cavity with an intensity comparable to that of cerebrospinal fluid. The scolex is usually practically isointense to white substance. In T2, the cystic lesion appears hyperintense. In FLAIR, the scolex is better highlighted. Finally, the cerebral MRI has temporarily eliminated a low-grade glioma, subject to a control cerebral MRI at 3 months, because usually, the glioma appears in hyposignal T1, hypersignal T2 or FLAIR, with an absence of contrast.

Following the elimination of the majority of differential diagnoses and subsequent application of the American College of Rheumatology (ACR) criteria with a score of 23, the diagnosis of systemic lupus was retained. Disease activity was assessed by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, which returned to a score of 13 points. The headaches met the criteria for the definition of neurolupus, and thus neurolupus was concluded to have occurred. At the therapeutic level, she performed an IV bolus of methylprednisolone at 1 g for 3 days combined with pantoprazole IV at 40 mg/day. The evolution was favourable with a regression of headaches (VAS at 2/10) allowing the patient to return home on D+10 of hospitalization. Corticosteroid treatment with prednisone at 60 mg/day was continued

for 1 month and then stopped at 1 month after a degressive regression. At 2 months, the headaches were completely amended and methotrexate at 7.5 mg/week was introduced. The brain MRI at 2 months noted the complete resolution of signal abnormalities.

Table 1: Key Laboratory Results.

BLOOD TESTS	RESULTS	STANDARDS
Urea	0.26 g/l	N [0.15-0.45 g/l]
Creatinine	6.4 mg/l	N [07-14mg/l]
Serum sodium	Na^+ 135 mmol/l	N [133-143 mmol/l]
Serum potassium	K^+ 3.6 mmol/l	N [3.5-5 mmol/l]
Serum Chloride	Cl^- 100 mmol/l	N [95-105 mmol/l]
Creatinine clearance (CPK-EPI)	131.19 ml/mn	N : 95+/-20 ml/mn
Blood sugar	0.90 g/l	N [0.7-1.1 g/l]
Thyroid-stimulating hormone	0.52 µIU/ml	N [0.3-4.2 µIU/mL]
Alanine aminotransferase	10 IU/l	N [0-30 IU/l]
Aspartate aminotransferase	30 IU/l	N [0-40 IU/l]
Alkaline phosphatase	75 IU/l	N [35-104 IU/l]
Gamma-glutamyltransferase	25 IU/l	N [5-42 UIL/l]
Prothrombin level	86,5%	N [70-100%]
Creatine phosphokinase	36 IU/L	N [24-170 IU/l]
HIV, hepatitis B, hepatitis C serology	Negative	
Complete Blood Count		
Haemoglobin	**Hb 9.80**	N [12-16]
Mean Corpuscular Volume	MCV=88.10	N [80-100]
Mean Corpuscular Hemoglobin Content	MCHC=28.50	N [27-34]
Leukocytes	6900 /mm3	N 4000-10,000/mm3]
Platelets	357,000/mm3	N [150,000-400,000/m
Erythrocyte Sedimentation Rate	**100 mm**	N<20mm
C-reactive protein	**73.1 mg/l**	N <5 mg/l
D-Dimer	**2117 ng/ml**	N<500 ng/ml
Serum protein electrophoresis	**Albumin:31.8 g/l** **Alpha 1:5,4 g/1** **Beta 2: 7,0 g/l** **Gamma: 30.8**	N[40.2-47.6] N[2.1-3.5] N[2.3-4.7] N[8.0-13.5]
Rheumatoid factors	**15**	N [0-14 IU/l]
Antinuclear antibodies (IFI - *Indirect immunofluorescence on Hep 20-10 slides*)	**Title at 1/320** **Speckled appearance**	N <1/160
Anti-native DNA antibodies	< 10 IU/ml	N <10 IU/ml
Soluble nuclear antigen autoantibodies (ENA screening)	**3**	N<1,1
SSA/Ro 60 kD(*Soluble nuclear ribonucleoprotein A*)	<2 IU/ml	N <7 IU/ml
SSA/Ro 52 kD	<2 IU/ml	N <7 IU/ml
SSB/LA (*Sjögren syndrome B*)	<2 IU/ml	N <7 IU/ml
SmD1 (*Smith*)	**12 IU/ml**	N <7 IU/ml
U1RNP (*Uracil 1 ribonuclear protein*)	<2 IU/ml	N <5 IU/ml
Jo1 (*anti-aminoacyl-t-RNA-synthetases*)	<2 IU/ml	N <7 IU/ml
Scl 70 (*anti-topoisomerase I*)	<2 IU/ml	N <7 IU/ml

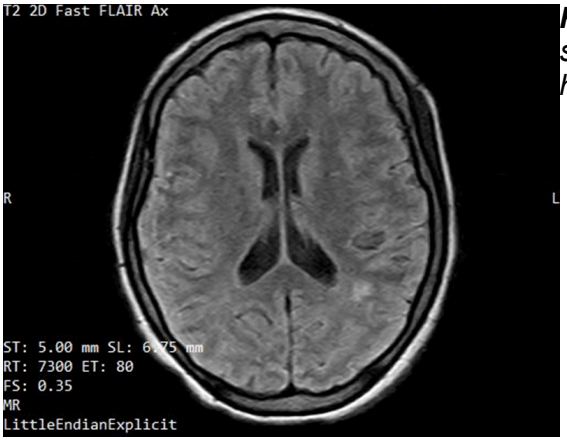

Figure 1: *Brain MRI axial section FLAIR sequence showing a left parieto-occipital hypersignal*

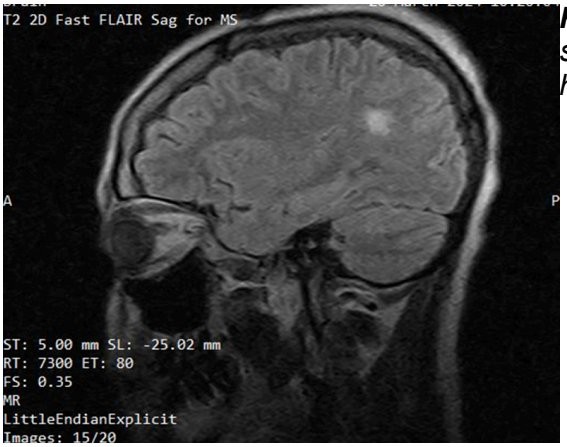

Figure 2: *Brain MRI sagittal section FLAIR sequence showing a left parieto-occipital hypersignal*

DISCUSSION

In 1999, the American College of Rheumatology (ACR) published a list of the neuropsychological manifestations of SLE in its nomenclature, which included 19 distinct categories, seven of which were associated with PNS involvement (9). It is estimated that NPSLE affects 56.3% of individuals with SLE, with headache representing the most common neurological manifestation, occurring in 28.3% of cases (5). Similar NPSLE data can be found in Africa. Adelewo et al. (6) in Nigeria reported a frequency of 51.6%, while Mapouré et al. in Cameroon (7) reported a frequency of 55.5%. There is a higher incidence of NPSLE in individuals of African and Asian descent compared to Caucasian subjects; however, the severity of NPSLE is greater in the Caucasian population (10). The development of NPSLE in an individual depends on genetic, environmental, and hormonal factors (11). Several pathogenic pathways have been identified: antibody-mediated neurotoxicity, vasculopathy due to anti-phospholipid antibodies (aPL), cytokine-induced neurotoxicity, and loss of neuroplasticity and other mechanisms (11). NPSLE may precede the onset of lupus or occur at any time during its course (12).

The patient presented with chronic headaches, which were initially diagnosed as migraines or migraine-like migraines. Over the past few months, she also reported tingling-like paresthesias in the right hemibody, which led to the persistence of the diagnosis of migraine with aura. It is challenging to determine the precise onset of the autoimmune disease in the patient, as she has a long history of cephalalgia, dating back approximately twenty years. Cutaneous and joint manifestations first manifested 5 years ago. It is unclear whether the autoimmune disease in question commenced with the onset of

headaches during adolescence, 20 years ago, or 5 years ago. In the series by Mapouré et al., NPSLE was present at the initial diagnosis of SLE in 37% of patients and occurred in 18.5% of cases during the first year (7). At the onset of NPSLE, the central nervous system was predominantly affected, with demyelinating syndrome occurring in 27.8% of cases and headache in 21.3% (7).

Primary headaches, particularly migraines and tension headaches, are generally recognised as neurological manifestations of SLE (13). However, it is important to exclude some secondary headaches, such as cerebral vasculitis, cerebral venous thrombosis, reversible posterior encephalopathy syndrome, subarachnoid haemorrhage, and meningitis. In this patient, who was unaware of her lupus diagnosis, it was the presence of signal abnormalities on brain MRI that led to the identification of lupus. In sub-Saharan Africa, where the causes of meningoencephalitis are predominantly infectious (14), tuberculosis encephalitis was initially suggested. Aseptic meningoencephalitis and drug-induced meningitis were also discussed at the outset. These 2 entities are mentioned in the SLE: aseptic meningoencephalitis in the presence of neuropsychiatric signs (depression, psychosis, convulsions), extra neurological signs (joint, renal, and skin involvement), and pleocytosis with a weak CSF (< 50 elements/mm^3), but always lymphocytic (15). Drug-induced meningitis is described in lupus patients using drugs (non-steroidal anti-inflammatory drugs, antibiotics, IV immunoglobulins, anti-CD3 monoclonal antibodies, or antiepileptics) (15). In this meningitis, the CSF is predominantly polynuclear neutrophils (60—80%); there is a high cellularity (median 300 elements/mm^3, normal glycorachia, proteinorachia <2 g/L). The patient was not taking any of these medications.

A pathological CSF analysis is often observed in patients with neurolupus, revealing non-specific findings that primarily serve to exclude other potential aetiologies (16). CSF can be inflammatory with high total protein, high IgG, pleocytosis, and slightly low blood sugar. Elevated protein can be seen in 20-30% of patients with NPSLE with levels ranging from 1 g/L to more than 2 g/L.

In Cameroon, the factors associated with the occurrence of NPSLE were the presence of cutaneous and articular signs, high lupus activity, and anti-nuclear factors (7).

MRI signal abnormalities are common in lupus. In a study of brain MRI of lupus patients, the authors reported a 69% percentage of brain MRI abnormalities regardless of whether the patients had neuropsychiatric signs (73.3%) or not (64.3%) (17). These abnormalities include posterior demyelination periods associated with a widening of the perivascular spaces.

This observation is characterised by an under-diagnosed disease in sub-Saharan Africa (6), (7). The diagnosis of neurolupus is based on the prior diagnosis of lupus, underdiagnosed contributing factor. Indeed, the process of diagnosing NPSLE can be likened to that of assembling a puzzle: first, the clinician must diagnose SLE and then exclude non-SLE intercurrent illnesses, medication side effects, and psychosocial or functional-related conditions (11). It is also important to note that the manifestations of NPSLE may overlap with the neuropsychiatric manifestations of Sjögren's syndrome and aPL syndrome, as well as other autoimmune diseases (11). In sub-Saharan Africa, SLE was previously considered a rare condition until the late 20th century (18). This notion was further solidified by data from a literature review which outlined infrequent cases of SLE in West and Central Africa.

The clinical technicalities and complexity of diagnosing SLE may have contributed to assertions that the disease is rare in Africa (19). However, emerging reports indicate that the prevalence of SLE in sub-Saharan Africa was 1.7%.

The current treatments for NPSLE are based on observational studies and refer to the experience of treating other subtypes of SLE, such as lupus nephritis and similar neuropsychiatric disorders (14). In the case of our patient, whose manifestation of neurolupus was a headache, a standard

treatment plan involving corticosteroids and then oral immunosuppressive therapy proved sufficient. A Chinese study published in 2023 demonstrated that intrathecal dexamethasone plus methotrexate treatment was associated with a more favourable prognosis for NPSLE (16). This treatment may serve as a valuable adjunctive therapy for NPSLE patients, particularly those with elevated protein levels in the cerebrospinal fluid.

It must be acknowledged that this observation is not without its limitations. The absence of long-term follow-up data precludes the reporting of the evolution or potential generalisation of lupus disease. A further study was conducted in China, in which 101 patients were observed for NPSLE (21). The overall survival rates were found to be 89%, 85%, and 84%, respectively, at 1, 3, and 5 years. The most prevalent cause of mortality was NPSLE-related conditions (7/15, 47%), comprising intracranial hypertension syndrome, cerebrovascular disease, and motor neuron disease.

CONCLUSION

A persistent headache that is resistant to analgesics may be indicative of neurolupus. In the event of an unusual headache, a biological inflammatory syndrome, and a signal anomaly on brain MRI, with infectious and tumor causes ruled out, it will be necessary to consider systemic autoinflammatory pathologies. As SLE is the autoimmune pathology with the most neuropsychiatric manifestations, it must be mentioned first. A screening of antinuclear antibodies by indirect immunofluorescence should be carried out, which will be completed by determining the specificity of antinuclear antibodies (native anti-DNA, soluble anti-antigen).

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