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Case Report

Not Always an Infection: A Case Series of Immune-Mediated Encephalitis, Including the First Report of Hashimoto's encephalopathy From Sub-Saharan Africa

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Abstract:

Encephalitis is a global health problem particularly frequent in Sub-Saharan Africa (SSA), where aetiologies are most often thought to be infectious despite the low microbiological yield. Some evidence suggests that autoimmune encephalitis (AE) could, however, be more prevalent than reported.

We report four (4) cases of immune-mediated systemic and non-systemic encephalitis, spanning across the large spectrum of this entity, presenting with a wide clinical and etiological heterogeneity. The first case is that of a 67-year-old lady with a three-month history of memory loss and abnormal behaviour. She was diagnosed with Hashimoto's encephalopathy with a very good response on steroids. Case 2 is that of a 52-year-old man with an acute confusional syndrome with fever. He was diagnosed with encephalitis due to an undifferentiated connective tissue disorder responsive to immune therapy. The third case is that of a 14-year-old girl with a recurring history of motor deficits admitted for a rhomboencephalomyelitis due to neuromyelitis optica. Evolution was unfavourable in this case. The last case reports a 51-year-old male with an acute onset of behavioural abnormalities. MRI confirmed limbic encephalitis. Improvement was noted on steroids. The patient was lost to follow-up.

We discuss the context-specific challenges of identifying AE, mainly due to diagnostic technologies' financial and geographical inaccessibility (cerebral imaging, serological tests, antibody panels). The goal of this case series is to raise awareness among clinicians managing patients with encephalitis in SSA to look beyond infectious causes and consider AE

especially in the presence of subacute cognitive impairment, inflammatory cerebrospinal fluid (CSF), and limbic involvement on brain imaging.

Key words: autoimmune encephalitis; hashimoto's encephalopathy; limbic encephalitis; neuromyelitis optica; subacute cognitive impairment

Introduction

Encephalitis is a frequent diagnosis in Sub-Saharan Africa (SSA) in neurology, internal medicine, emergency and intensive care departments. A recently published review evaluating the global magnitude of encephalitis burden concluded that low-middle-income countries, including most countries of SSA, had the highest incidence worldwide (31.63/100,000 compared to 6.17 per 100,000 in high-income countries) [1]. Several studies have emphasized the challenges of etiological diagnosis of encephalitis in SSA [2,3]. In a multicentric series including patients from Rwanda, Uganda and Malawi presenting with an acute non-traumatic coma, a definite etiology was identified only in 37% of cases using conventional diagnostic techniques [4]. Historically, autoimmune diseases were considered to be rare in tropical Africa. This is evident in that a medline search with the keywords "Encephalitis" AND "Africa" yields data mainly on infectious causes. A scoping review of etiologies of encephalitis in 16 western African countries identified 21 pathogens. The authors argued that infectious causes are probably more common than non-infectious etiologies in tropical countries [5]. A more recent review series on Neuroimmunology in Africa equally underlined the scarcity of reported non-infectious causes of encephalitis [6,7]. However, a few studies suggest that auto-immune encephalitis could be as frequent as infectious cases and could etiologically account for a sub-group of "cryptogenic" encephalitis [8,9]. Data on inflammatory causes in sub-Saharan Africa are limited to a few case reports of autoimmune encephalitis from Kenya, Togo, South Africa and Soudan [10-13]. In these studies, only patients with antiNMDA and LGI1 were reported. As such, our setting might significantly underdiagnose the full spectrum of inflammatory encephalitis. This case series of four patients adds to recent data on immune-mediated encephalitis in sub-Saharan Africa, insisting on the diagnostic difficulties related to its wide clinical and etiological diversity and context-specific challenges to both diagnosis and management.

Case presentations

Case 1:

a 67-year-old right-handed lady and retired accountant, was referred by her attending endocrinologist to the outpatient neurology clinic for behavioural disorders. She was accompanied by her daughter, who reported a progressive onset of incoherent speech during conversations (without any logorrhoea) and psychomotor agitation with anterograde episodic memory loss over a period of two months before consultation. She had recently become verbally and physically aggressive, could not recognise familiar faces, and was disoriented in time and space to the point of becoming dependent on her children for most of her daily activities. Her daughter denied any hallucinations, insomnia, convulsions and fever. She had initially consulted a physician who diagnosed hyperthyroidism based on a very low ultrasensitive Thyroid Stimulating Hormone (TSHus) at 0.0012mUI/L (normal 0.4-4mUI/L and elevated total T4 and T3 hormones at 204.9 and 4.75 respectively (normal 4-12.5mcg/dl; 1.2-3.0nmol/l respectively. A contrast-enhanced cerebral CT scan revealed mild cortical atrophy but was otherwise normal. Despite the concern that the behavioural symptoms were not typical of hyperthyroidism, the endocrinologist initiated Carbimazole at 20mg twice daily (TID) and Propanolol at 40mg TID with rather worsening symptoms after a month. She was then referred to the psychiatric ward where Alzheimer's dementia was diagnosed and started on Paroxetine and Mexazolam. Her persisting symptoms prompted the family to seek for a second opinion from our endocrinology clinic.

Her past medical history prior to the current illness was unremarkable. She denied consumption of alcohol or tobacco. There was no family history of psychiatric or neurologic diseases.

Her physical exam revealed an altered general state (WHO grade II) and normal vital signs (blood pressure: 123/69 mmHg, heart rate: 83 beats per minute, respiratory rate at 20 cycles per minute, temperature: 37.2°C). An evaluation of her higher mental functions revealed predominantly anterograde but also retrograde episodic memory loss, which was not improved by hinting. She equally presented apraxia, acalculia and was disoriented in time and space. Her mini-mental status examination score was 15/30. She had no cranial nerve palsies, no focal motor deficit, neither static nor kinetic cerebellar dysfunction. Her thyroid gland was not enlarged, and her physical exam was unremarkable. Hashimoto's encephalopathy or paraneoplastic encephalitis was suspected, given the subacute cognitive impairment in the context of a biologically proven hyperthyroidism with persisting symptoms despite one month of treatment with antithyroid medications. Infectious, limbic encephalitis and Creutzfeldt Jacob disease were considered as differential diagnoses. A brain MRI was requested but could not be performed because of financial constraints. The CSF analysis was normal (proteins, 0.23g/l with no leucocytes, no germs on direct microscopy and sterile cultures). HIV, hepatitis B, C and syphilis serologies were all negative. Erythrocyte sedimentation rate was 28mm in the first hour (normal values <20mm), C-reactive protein was < 6mg/l (normal values < 6mg/l) and serum protein electrophoresis indicated a polyclonal hyperglobulinemia. Full blood count was equally normal. Antithyroperoxidase antibodies were very high at 600IU/ml (Normal value < 34), as well as her TSH receptor antibodies at 6,60IU/ml (normal value < 1.75). Antithyroglubulin antibodies were normal at 15IU1/ml). A thyroid ultrasound indicated bilateral nodules graded TIRADS 3. The left lobe showed two oval-shaped, moderately hyperechogenic nodules of mixed liquid and tissular content, 18 and 20mm in diameter, respectively. There were two similar nodules on the right lobe but of small size (12 and 5mm respectively). The total thyroid volume was normal at 11ml. Serum onconeuronal antibodies, and an EEG were equally requested but could not be performed due to financial limitations. Hashimoto's encephalopathy was retained as the diagnosis and high dose steroids were started. She received 1g of Methylprednisone daily for five days intravenously with adjunct therapy. Her clinical state remained unchanged at the acute phase [6]. The induction therapy was followed by an oral relay at 1mg/kg/day of prednisone (60mg daily). Carbimazole was decreased to 40mg once daily [6]. After one month, her daughter on a phone call visit (the patient was out of town) reported improvement of her symptoms. She was less aggressive and more coherent and could recognize familiar faces. Two months post-hospitalization, she was brought in for an office control visit. Her general state and cognition were markedly improved. Her Mini Mental Status Examination (MMSE) score was normal at 27/30 (losing points only on immediate and delayed recall). The normalization of her overall condition (WHO grade 0) was highly in favour of Hashimoto's encephalopathy following treatment with steroids. At this visit, her Free T4 (FT4) was mildly decreased at 7.4ng/l (N 8-19) with a slightly elevated TSHus at 6.438 mUI/L. Prednisone was slowly taken and stopped over the next three months without any worsening of her neurological condition. She is currently followed up at the endocrinology outpatient clinic with a normal thyroid function and no neurological abnormalities.

Case 2

a 52-year-old was admitted at the emergency department following a 24-hour history of abnormal behaviour, incoherent speech and psychomotor agitation with intense fatigue but no fever initially. At the emergency department he presented a tonic-clonic generalized seizure which lasted five minutes. His past medical history revealed he was a sickle cell disease trait carrier (Hb AS) with no acute crises. He had previously suffered gout crises but was not on treatment at the time of his admission. He was diagnosed with acute infectious encephalitis and started on Ceftriaxone 2 grams every 12 hours intravenously (IV), diazepam 10 mg stat IV and phenobarbital 200 mg every 24 hours intramuscularly (IM). A neurological consultation was requested to evaluate the persistence of his clinical condition three days after his admission. He had an altered general state (grade III of the World Health Organization classification) and a high-grade fever at 39.7°C with stage 2 hypertension at 169/100 mmHg. His neurological examination revealed a confusional syndrome with a Glasgow coma score of 14/15 (Eye opening: 4/4, verbal response: 4/5 and motor response: 6/6). There were no meningeal irritation signs. His pupils were normal and reactive to light, and there were no cranial nerve palsies or focal motor deficits. He equally had markedly symmetrically swollen and painful joints involving the proximal interphalangeal joints, the elbows, knees and ankles. Inflammatory encephalitis rather than infectious was suspected, especially considering the pattern of the concomitant joint involvement, which was atypical for a gout crisis. A brain CT scan and subsequent MRI scans were strictly normal. A post-ictal EEG showed non-specific diffuse delta slowing (see figure 1). CSF analysis showed mildly raised proteins at 0.62g/l (normal values 0.2-0.45g/l) and no cells. The C-reactive protein (CRP) was elevated at 48mg/l (normal <6mg/l), the erythrocyte sedimentation rate (ESR) was 29mm at the first hour (normal <20mm). The full blood count was normal. There was an acute kidney injury indicated by serum creatinine levels of 14.56mg/l (normal values 7-13mg/l), which subsequently normalized after 72 hours of IV rehydration. Serum electrolytes indicated a mild hypokalemia at 3.1mmol/l. There were signs of liver failure with a low prothrombin time at 56.7%, low serum albumin levels at 23.08g/l (normal values 34-54g/l), elevated liver enzymes (SGOT 63.50IU/l [<50UI/l] and SGPT 134.46IU/l [<50UI/l]) and elevated total and direct bilirubin levels (145.35mg/l [normal value 12mg/l] and 84.38mg/l [normal value 2mg/l] respectively). Ferritin levels were equally raised at 1838.28ng/ml (18-270ng/ml). Normal blood and urine culture as well as a normal chest X-ray ruled out a sepsis. Though CSF Herpes simplex virus (HSV1 and 2) PCR could not be carried out, Herpes simplex encephalitis was ruled out with the normal brain MRI, the non-specific EEG pattern and the absence of cells in the CSF.

After consultation with an internist, inflammatory encephalitis due to an adult-onset Still's disease was considered the most probable diagnosis as the patient fulfilled 2 major and 2 minor criteria of Yamaguchi diagnostic criteria [14]. A connective tissue disorder was considered as a differential diagnosis.

The patient was started on high-dose IV steroids (500mg of Methylprednisone daily for three days) with marked improvement in his overall clinical condition [6]. There was a complete regression of the confusional syndrome at day 9 of admission. Fever and joints inflammation signs equally regressed. The prothrombin time improved from 56 to 65%. The patient was discharged on day 12 with the provisional diagnosis of adult onset Still's disease (while awaiting the results of the blood autoantibodies), on oral prednisone at 1mg/kg (80mg) with the usual adjunct therapy (calcium at 1000mg OD and vitamin D 800IU OD supplementation as well as a pantoprazole 40mg OD) At the one-month follow-up visit, the patient presented a deep venous thrombosis of the right popliteal vein for which rivaroxaban was administered initially at 15mg BID for 21 days, followed by 20mg daily. His antinuclear antibodies received at this visit were very high at 1/640 with negative anti ENA antibodies, native anti DNA antibodies as well as anticardiolipin, anti-beta 2 glycoproteins and antiprothrombin antibodies. A final diagnosis of an undifferentiated connective tissue disorder was deemed more probable than Still's disease. The absence of symptoms and signs of dry eyes and mouth and oral and urogenital ulcers argued against Sjogren's syndrome and Behcet's disease respectively. Oral methotrexate at 7.5mg daily was added to his treatment. At the three-month follow-up visit, the patient was well, with no signs of a neurological or systemic relapse.

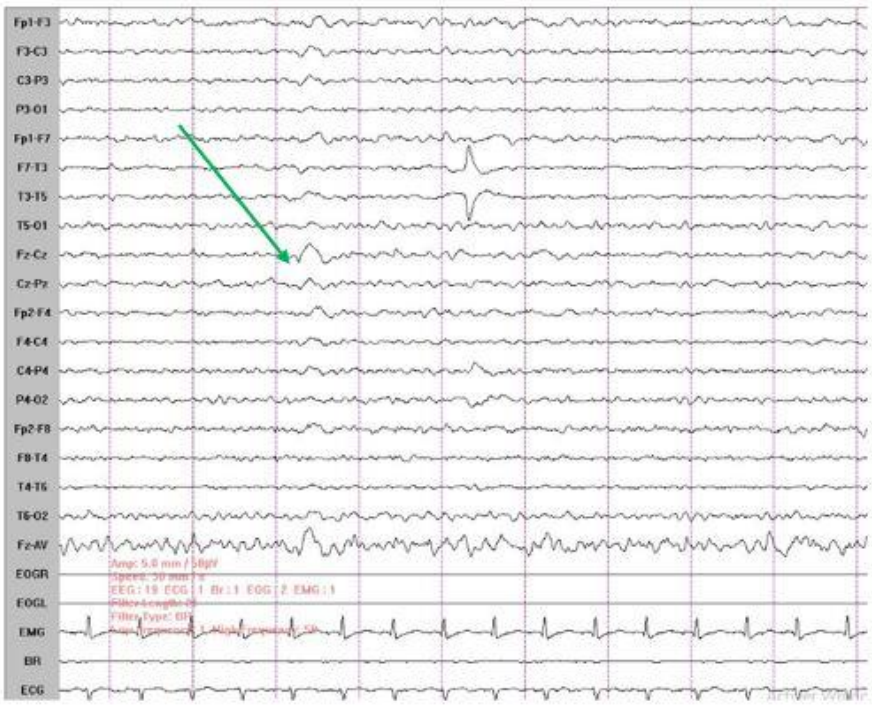

Figure 1: A 10 second EEG epoch showing diffuse generalised theta slowing at 5-6Hz with a one second burst of delta slowing at the 4th second (green arrow) indicative of a non-specific encephalopathy of mild to moderate severity.

Case 3:

a 14-year-old consulted at the neurology clinic for a rapidly progressive motor weakness of the left upper and lower limbs over a few days in an afebrile context. She had no headaches nor other signs of raised intracranial pressure. Her history indicated a similar weakness of the right hemi body for which she was admitted at another centre three months earlier. Her family history was unremarkable. A brain MRI performed at the time revealed supratentorial juxta cortical and periventricular white matter lesions and pontine, medullary and upper cervical lesions limited to C1 and C2 spine. None of these were contrast-enhancing. Her CSF was inflammatory with raised proteins (0.73g/l) and three leucocytes/mm3. No bacteria were identified on microscopic examination or after CSF cultures. Antinuclear antibodies, anti ENA antibodies were negative. She was treated with high dose steroids (1g of Methylprednisone for five days with a partial improvement of the right motor deficit which allowed her to be autonomous for most activities of her daily life. She was then discharged and was lost to follow-up.

Physical examination at the author's clinic revealed tachycardia at 100bpm, hyperpnea at 23cpm with a normal temperature and blood pressure at 37.3°C and 93/57mmHg. She was conscious, with a tetrapyramidal syndrome. On the right she had a proportional 4/5 motor deficit with brisk myotatic reflexes. On the left she equally presented a 3/5 proportional motor deficit. There were no sensory deficits. Cranial nerves exam revealed a left convergent strabismus and a right horizontal nystagmus The provisional diagnosis at this stage was a relapse of an inflammatory disease of the central nervous system. Another five-day course of high dose Methylprednisone (1g per day) [6] was initiated with potassium supplementation at 600mg BID, Omeprazol 20mg OD and Mebendazole 500mg stat. Her etiologic workup was completed with the search for oligoclonal bands in her CSF, anti-aquaporin 4 and antiMOG antibodies. Upon discharge (pending the aforementioned results), there was a significant functional improvement. Her muscle strength was 4/5 on the left upper and lower limbs, the right lower limb, and 5/5 on the right upper limb. At her one-week follow-up visit she presented her complementary CSF analysis which was negative for oligoclonal bands. Six weeks later, the patient presented with a one-week history of dysarthria and motor weakness of the left upper and lower limbs was well as the right upper limb. Another relapse was suspected. A control brain and spinal cord MRI revealed a 120mm long T2 and Stir hypersignal extending from the medulla oblongata to the C7 vertebra (see figure 2) with a marked increase of the antero-posterior cervical diameter (10-11mm). The brain MRI was normal. The patient was admitted for another high dose steroid course. Despite of first bolus (1g) of Methylprednisone her level of consciousness rapidly dropped to a GCS score of 6/15 (eye opening: 4, verbal and motor responses: 1). Her antiaquaporine 4 antibodies at this time were positive and anti-Myelin Oligodendrocyte Glycoprotein (MOG) negative. We concluded on a severe rhomboencephalomyelitis due to neuromyelitis optica (NMO). The absence of fever, and the relapsing nature of her symptoms argued against infectious causes such as tuberculosis and listeriosis. The patient was transferred to an intensive care unit for invasive respiratory support. High dose steroids were maintained at 1g/daily for a total of seven days and a first course of rituximab (1g) equally administered [15]. Her evolution was initially favourable with an improvement of her GCS to 15/15 on day 4 of admission. She subsequently developed a high-grade fever which was treated as a nosocomial infection. Despite being conscious, the patient could not be weaned off ventilatory support. She died on day 13 of admission at the ICU.

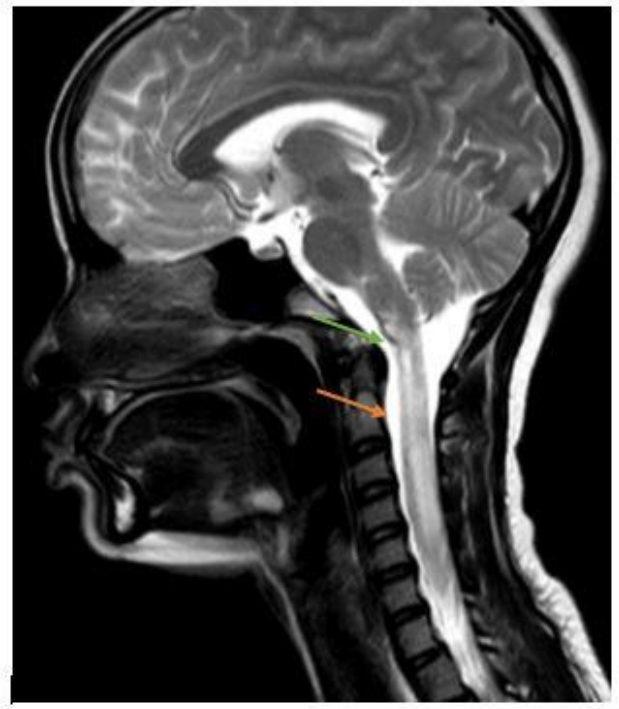

Figure 2: T2 sagittal brain and cervical spinal cord MRI showing a 5-segment-long (C1-C5) spinal hypersignal (red arrow) extending upwards to the medullary oblongata (green arrow)

Case 4:

A 51-year-old male was admitted at the emergency department for a rapid onset of diffuse intense headaches which began 24 hours prior to consultation. He was accompanied by his wife who reported having noticed on the same day, that her husband had some memory loss. The patient was logorrheic with incoherent speech and psychomotor agitation.

He had visual and tactile hallucinations as he insisted on seeing and feeling an electric discharge entering his body from the head. There was no nausea, vomiting nor fever. He had a three-month history of newly

diagnosed type 2 diabetes already associated with length-dependent sensory polyneuropathy. He was non-compliant to Metformin which his endocrinologist had prescribed. His wife equally reported a history of chronic alcohol consumption. His physical examination revealed an altered general state (grade III WHO), a grade II hypertension at 166/97mmHg, a random blood sugar at 2.7g/l, a heart rate of 64 bpm and a temperature of 37°C. The patient was confused with a GCS of 14/15 (eye opening 4, verbal response 4, motor response 4). He had no meningeal signs, cranial nerve palsies or a motor or sensory deficit. Considering the recent onset of headaches, a subarachnoid haemorrhage or cerebral venous thrombosis were considered as differential diagnoses, coupled with an alcohol withdrawal syndrome. A contrast enhanced brain CT scan was normal but the brain MRI showed bilateral and symmetrical hippocampal T2 Flair hyperintensities with no gadolinium enhancement (figure 3). CSF was clear with a protein level of 0.49g/l, no cells nor bacteria identified. The patient's full blood count, kidney function tests, liver enzymes, and serum electrolytes where within normal values. The CRP and D-dimer levels were mildly elevated at 12mg/l and 722ng/ml respectively. Limbic encephalitis was diagnosed considering the characteristic MRI pattern and the patient was started on high dose steroids (1g per day of Methyl prednisone) with adjunct therapy [6]. On the third day of treatment the patient was calm but still had incoherent speech. On day 5, the aforementioned hallucinations persisted and the steroid treatment was continued to day 7. The patient was discharged on oral prednisone at 1mg/kg (80mg) with calcium, vitamin D and pantoprazole. Antineuronal antibodies (antiLGI1, Caspr2, anti GAD, anti NMDA) and onconeuronal antibodies (anti Hu, Ri, Yo, Ma2 and antiamphyphysin antibodies) as well as thoraco-abdomino-pelvic scan were requested to investigate an autoimmune or paraneoplastic origin of the limbic encephalitis. The patient was however lost to follow-up.

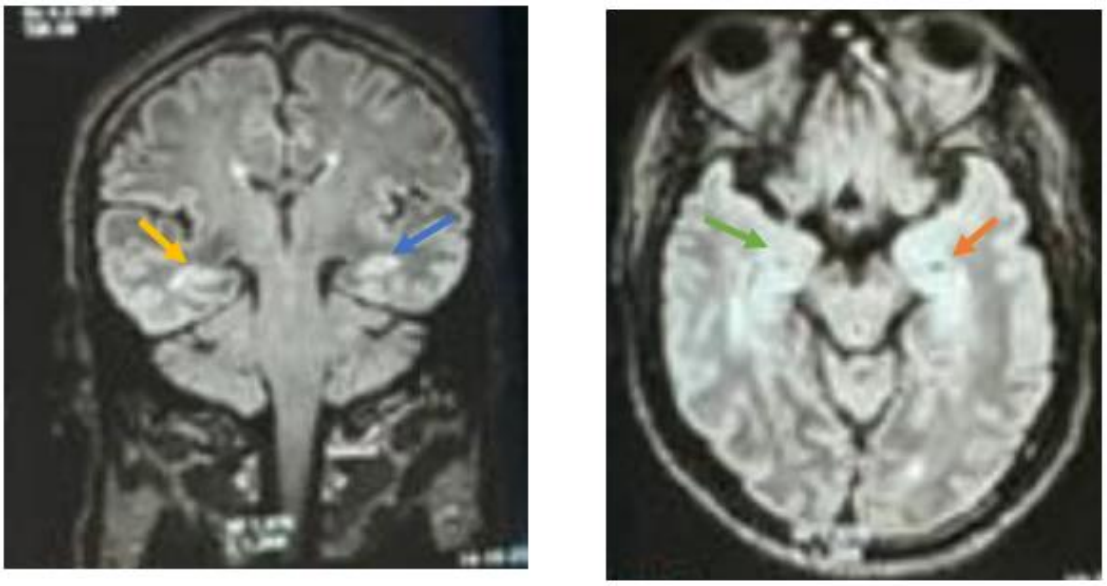

Figure 3: 1.5 Tesla Brain MRI scans (case 4) A) Coronal and Axial B) T2 Flair sequences showing bilateral hypersignal in the medial temporal lobe structures.

Discussion

This series presents multiple interests as it adds to the scanty literature on inflammatory encephalitis in SSA. Data on the subject is mainly limited to case reports and case series. Three cases of anti NMDA receptor encephalitis were reported from Kenya in 2019 by two teams [10,16]. A similar case each was described from Sudan and Togo in 2021 and 2022 respectively [11,13]. Izanne et al. also described a case of antiNMDA receptor encephalitis coupled with one case of LGI1 antibodies from South Africa [12]. Ndondo et al. reviewed several cases of Acute Disseminated Encephalomyelitis and COVID 19 acute necrotizing encephalopathy [17]. To our knowledge this is the first report from Cameroon and the central African sub-region. This increasing data should prompt health care professionals in SSA to consider non-infectious aetiologies of encephalitis in their clinical practice. There is mounting evidence that AE could be as frequent as infectious causes [7]. This is again plausible considering the low yield of microbiological CSF analysis of patients with meningitis or encephalitis even in developed countries with optimal resources [18]. Abboud et al. suggests diagnosing and treating autoimmune encephalitis after the exclusion of infectious aetiologies as well as metabolic and toxic causes, particularly in the setting of inflammatory CSF [8].

The originality of this paper is the presentation of almost the entire spectrum of inflammatory encephalitis, particularly in a context where the causes are empirically thought to be infectious. In its broad form, inflammatory encephalitis refers to all the conditions in which symptoms are related to immune-mediated inflammatory responses. Patel et al. proposed classifying systemic, non-systemic and post-infectious immune-mediated encephalitis [19]. Systemic autoimmune encephalitis comprises connective tissue disorders, Hashimoto's encephalopathy and neurosarcoidosis. Non-systemic conditions include idiopathic or paraneoplastic autoimmune encephalitis including neuromyelitis optic spectrum disorders (NMOSD) with target surface antigens against aquaporine 4 or antiMOG [8]. Our series therefore demonstrates the wide range of the full spectrum of immune-mediated both systemic and non-systemic encephalitis with which the clinician could be confronted. The neurologist should consider these different clinical scenarios when approaching patients with encephalitis.

Despite this clinical and etiological heterogeneity, the diagnosis of inflammatory encephalitis should follow a common algorithm as given by the diagnostic criteria for AE (Table 2) [20]. These include mostly acute or subacute evolution of symptoms frequently cognitive or neuropsychiatric (as with cases 1 and 3), supportive paraclinical examinations with brain imaging (MRI), EEG and CSF analysis. Other causes, particularly infectious should be ruled out with appropriate serological and polymerase chain reactions (PCR) exams and autoantibodies searched for in serum and CSF. This approach immediately underscores the challenges of diagnosing AE in many SSA countries. Firstly, the scarcity and high cost of MRI scans in the context where the cost of health care is endured mainly by the patient and his family. Ogbole et al. identified 84 MRI units for a combined population

of 372,551,411 in West Africa (0.22 per million population) Most of these were low field strength systems [21]. Comparatively, Japan reported 51.67 MRI units per million population in the same study. Secondly, extensive serological and PCR tests for ruling out infectious causes are generally unavailable in several African countries. This is the same for autoantibody panels which are not only costly but often performed in specialised laboratories out of the country thus delaying the diagnosis as was particularly the case for the third patient of our series. In the Togolese study mentioned above, there was a three-week (23 days) delay between the request for CSF and serum NMDAr antibodies and the availability of the result [11]. Cases 1 and 4 in our series could not carry out all prescribed exams mostly because of financial limitations. In Cameroon for example, an AE antibody panel comprising anti Hu, Ri, Yo, Ma2, CV2, amphyphysin, NMDAR, AMPAR, mGluR1, mGluR5, glycine R, LGI1, Caspr2, DPPX and GABAB just in the serum costs altogether 2,000,000 FCFA (3210 US dollars). This largely surpasses the minimum wage of an average Cameroonian which was 36,270 FCFA (58.0USD) in 2024 [22]. As in similar situations, the neurologist and physician practicing in SSA must rely on a detailed clinical evaluation and a good clinical judgement to diagnose correctly [23]. In case 1 for example though HSV PCR examinations could not be done, Herpes simplex encephalitis was ruled out considering the normal brain MRI, non-specific EEG pattern and the presence of systemic signs (symmetric polyarthritis) which was the main clue for the diagnosis. Therefore, the SSA clinician should maintain a high level of clinical suspicion for AE particularly when faced with a subacute onset of psychiatric and behavioural disturbances [24], cognitive dysfunction [25], involuntary movements [26], intractable seizures [27], sleep disturbances [28], autonomic instability, and decreased level of consciousness [19]. Once infectious, metabolic and toxic causes have been ruled out, autoimmune encephalitis should be considered especially in the presence of CSF pleocytosis and despite the unavailability of serum and CSF autoantibodies. The 2016 AE clinical criteria emphasize the importance of early empirical immunotherapy once AE is highly suspected and infectious etiologies are excluded even in the absence of autoantibodies. The authors feel that this recommendation is especially relevant for good patient care in resource-limited settings such as ours [20]. That notwithstanding, improving the diagnoses of AE in SSA will require sensitisation not only of healthcare professionals but equally of policy makers, to improve economic access to care. In this regard, Cohen et al. had already underlined the high cost of diagnosing and managing patients with AE encephalitis with median hospital charges per admission ranging from 50 000 US dollars in non-ICU patients to 173 000USD in those admitted to the ICU [29].

	Case 1	**Case 2**	**Case 3**	**Case 4**
Age (years)	67	52	14	51
Gender	Female	Male	Female	Male
Presenting complaint	Behavioral disorders Memory loss	Behavioral disorders	Four limb weakness Altered mental state	Behavioral disorders Headaches
Duration of symptoms	Two months	24 hours	1 week	24 hours
Fever	No	Yes	No	No
Systemic signs	Yes	Yes	No	No
Disease course	Monophasic	Monophasic	Relapsing	Monophasic
CSF proteins g/l	0.23 (normal)	0.62 (slightly raised)	0.73 (slightly raised)	0.41 (normal)
CSF cells/mm^3	00	00	03	00
CSF oligoclonal bands	Not done	Note done	Absent	Note done
CRP levels mg/l	< 6 (normal)	48 (raised)	< 6 (normal)	12 (slightly raised)
ESR (first hour) mm^3	< 20 (normal)	29 (raised)	7 (normal)	Not done
Brain CT scan or MRI results	Normal	Both normal	MRI Flair hypersignals brainstem and cervical cord	MRI bihippocampal Flair hypersignals
EEG	Not done	Generalised intermittent slowing	Note done	Not done

Table 1: Summary of clinical and paraclinical findings

1. Subacute onset (within the last 3 months) of short-term memory loss, altered mental status (personality change, lethargy or altered level of consciousness) or psychiatric symptoms
2. At least one of:
a. **new focal neurological deficits**
b. **new onset seizures**
c. **CSF pleocytosis (white cell count of more than 5 cells/mm^3)**
d. **MRI features suggestive of encephalitis**
3. Reasonable exclusion of alternative causes

Table 2 Diagnostic criteria for possible autoimmune encephalitis (all three of the following criteria were met in our patients) [30].

The individual cases equally present specific interests. To the best of our knowledge, case 1 represents the first report of Hashimoto's encephalopathy (HE) from sub-Saharan Africa. Although rare and somewhat controversial, HE should be considered as diagnosis in the presence of encephalopathy with no obvious aetiology or rapid onset cognitive decline even in the absence of clinical and biological signs of an abnormal thyroid function. In this series, neurological symptoms were attributed to Hashimoto's encephalopathy rather than direct effect of hyperthyroidism mainly because of the persistence of symptoms despite one month of antithyroid medication and a favourable response on steroid medication in the context of high titres of antiTPO antibodies. Xu Huang et al. used a similar paradigm of diagnosing HE in a patient unresponsive after two weeks of antithyroid medication [31]. Misdiagnosis of HE for Alzheimer's dementia as in case 1 of our series or for a viral encephalitis have equally been described in previous reports [32, 33]. Clinicians should keep this diagnosis in mind as it is highly treatable and steroid responsive. Neuromyelitis Optica is an inflammatory disease of the CNS that generally affects the optic nerve and the spinal cord. Brainstem involvement in NMO as was the case for the third patient in this series has recently been described in NMOSD and is seemingly more frequent in non-Caucasian populations [34]. The most frequent signs and symptoms were uncontrolled vomiting, intractable hiccups, cranial nerve palsies and pruritis. A recent systematic review in African series reported a prevalence of brainstem syndromes between 11-25% [35]. Overt encephalopathy with frank comatose state as was the case in our series is seemingly rare in literature. Case 4 emphasis the role of brain imaging in diagnosing inflammatory encephalitis. Though the clinical diagnosis was not specific, the MRI lesions were characteristic. According to the 2016 AE clinical criteria by Graus et al., the presence of bilateral limbic encephalitis is the only MRI finding sufficient to diagnose definite AE in the correct clinical setting (for example, negative CSF viral studies) even in absence of neuronal antibodies [20]. Unfortunately, the patient was lost to follow-up and a specific aetiology could not be identified.

The present case series has many limitations. Indeed, in most cases, all appropriate investigations according to international standards could not be carried out because of financial constraints or technical limitations. A brain MRI, EEG, thyroid scintigraphy would have improved diagnostic accuracy in case one. CSF viral PCR evaluations would have equally been necessary to rule out viral encephalitis in cases one to three formally.

Conclusion

This case series intends to raise awareness of clinicians on immune-mediated causes of encephalitis even in the tropical countries where most aetiologies are thought to be infectious. It underlines the clinical and etiological heterogeneity of this syndrome. Moreover, our report underscores the challenges, both financial and technical, faced by health professionals specifically practising in SSA in the diagnosis and management of inflammatory encephalitis. In most cases however, the prognosis could be favourable with immunomodulatory drugs thus the need to maintain a high index of suspicion in the face of acute/subacute cognitive or behavioural disorders for a timely and accurate diagnosis.

Declarations

Consent for publication

The patients gave their consent agreeing to publication of the manuscript

Competing interest

The authors have no competing interests.

Authors' contributions

ESC, GL, GA, RN received the patient and did the initial management under the supervision of AKN. ESC and GA wrote the first draft of the manuscript. GL, LN, KD, FD, EM, NLN, YF, GT, HMA and AKN critically reviewed the first draft and validated the final manuscript. AKN took the decision to submit.

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