75

A 25-Year-Old Woman from Zambia With a New-Onset Seizure

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Clinical Presentation

History

A 23-year-old HIV-positive Zambian woman is referred from a health centre to a local teaching hospital in Lusaka after suffering her first ever seizure. The seizure occurred out of sleep. Her son walked into her bedroom after hearing a noise and found his mother on the floor unresponsive and shaking all four limbs. This continued for 5 to 10 minutes.

The patient had been diagnosed with HIV infection 1 month earlier. She is not yet on antiretroviral therapy (ART) but has been taking co-trimoxazole prophylaxis for 7 days. She was successfully treated for pulmonary tuberculosis 4 years ago.

The patient is unmarried with three children. She works in the hospital cafeteria. She does not drink alcohol or use any recreational drugs.

Clinical Findings

On examination she looks well, her GCS score is 15/15, her vital signs are normal and she is afebrile. There is no meningism. The chest is clear. The neurological examination is unremarkable.

Laboratory Results

The malaria rapid diagnostic test is negative. Additional blood results are shown in Table 75.1.

A lumbar puncture is done. The opening pressure is normal. The cerebrospinal fluid (CSF) is clear. CSF results are shown in Table 75.2.

Imaging and EEG Results

Electroencephalography (EEG) demonstrates focal slowing in the right hemisphere (Fig. 75.1). A CT scan of her brain shows frontal and parietal hypodense lesions in the white matter of the right hemisphere (Fig. 75.2). No contrast enhancement is present.

TABLE 75.1 Blood Results on Admission

Parameter	Patient	Reference Range
WBC ($\times 10^9$/L)	5.8	4–10
Haemoglobin (g/dL)	11.0	12–14
Platelets ($\times 10^9$/L)	215	150–350
CD4 count (cells/μL)	153	500–1200
Serum sodium (mmol/L)	135	130–145
Serum glucose (mmol/L)	4.5	3.9–5.5

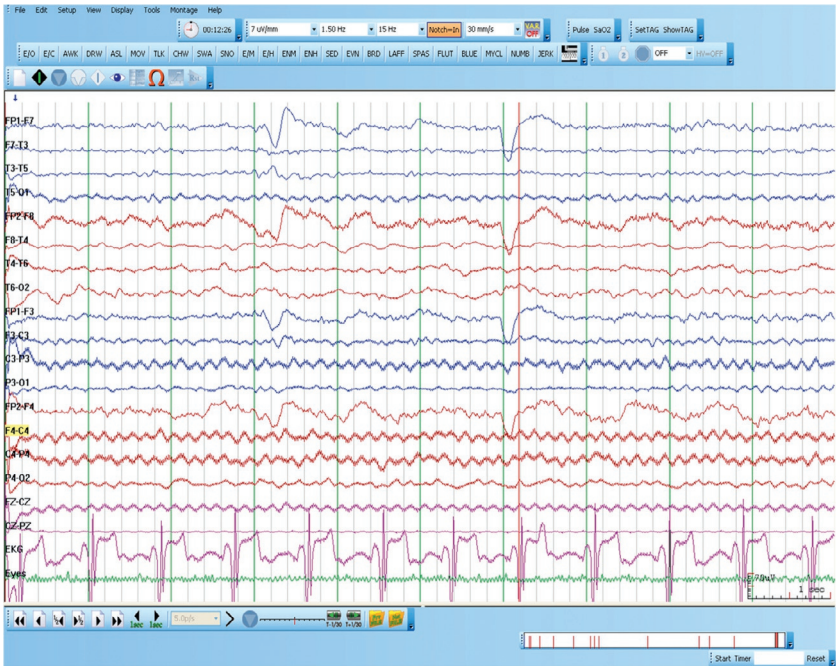
TABLE 75.2 CSF Results on Admission

Parameter	Patient	Reference Range
Leukocytes (cells/μL)	5	0–5
CSF protein (g/L)	0.78	0.25–0.55
CSF glucose (mmol/L)	2.9	2.25–2.97*
Cryptococcal antigen (CrAG)	Negative	Negative
India Ink stain	Negative	Negative
Gram stain	Negative	Negative
Ziehl–Neelsen stain	Negative	Negative

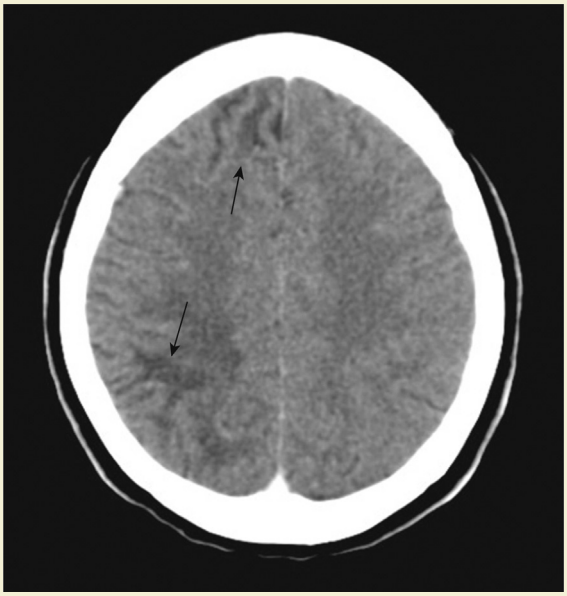
*½ to ⅔ of paired serum glucose sample.

Questions

1. How would you manage this patient?
2. What is your general approach to a patient presenting with new-onset seizures in sub-Saharan Africa?



• **Fig. 75.1** EEG demonstrating a slow background with superimposed delta frequency slowing of the right hemisphere.



• **Fig. 75.2** CT scan showing right frontal and parietal hypodensities in the subcortical white matter.

Discussion

A young Zambian woman presents with a new-onset seizure. There are no focal neurological deficits on examination. The CSF examination is normal, apart from a slightly raised protein level. Neuroimaging reveals hypodense lesions without contrast enhancement restricted to the subcortical white matter. Electroencephalography demonstrates focal slowing in the right hemisphere. The patient is HIV-positive, and her CD4 count is low. She is not yet on antiretroviral treatment.

Answer to Question 1

How Would You Manage This Patient?

The patient presents with a symptomatic seizure; there are obvious lesions in her brain and she is HIV-positive with advanced immunosuppression.

Treatment should aim at both preventing further seizures (antiepileptic treatment) and managing the underlying condition (causative treatment). The patient and her guardians should be counselled about the nature of her epileptic disorder, respecting their beliefs and attitudes. The choice for an antiepileptic drug should take into account the local availability and costs for the patient. Phenobarbitone is the most widely available and most affordable drug in sub-Saharan Africa, followed by carbamazepine. Newer drugs with fewer interactions and a better side effect profile, such as levetiracetam, are not yet routinely available. Phenytoin and valproic acid are also used but their delivery might be unreliable. Reliability of supply is an important factor to consider, because the discontinuation of the antiepileptic medication might put the patient at risk of withdrawal seizures. When starting a patient on phenobarbitone or carbamazepine, the effects of hepatic enzyme induction on antiretroviral therapy and hormonal contraception must be considered.

Syndromically, focal brain lesion is the underlying pathology in our patient. Differential diagnosis for focal brain lesions in an HIV patient with a new-onset seizure includes tuberculoma, progressive multifocal leukoencephalopathy (PML), cerebral toxoplasmosis, cryptococcoma, brain abscess and primary CNS lymphoma. Neurocysticercosis, which can occur unrelated to HIV infection, also needs to be considered.

Lesions that selectively affect the white matter without contrast enhancement and without perifocal oedema are strongly suggestive of PML. There is no causative treatment available for PML. Commencing antiretrovirals is currently the only therapeutic option.

Answer to Question 2

What is Your General Approach to a Patient Presenting With New-Onset Seizures in Sub-Saharan Africa?

The approach is influenced by (1) the high prevalence of HIV and subsequent immunosuppression; (2) the high burden of infection, including tuberculosis, bacterial meningitis and tropical diseases, e.g. cerebral malaria; and (3) the lack of resources, in particular, low availability of imaging studies and antiepileptic drugs (AEDs).

CNS infections are a prominent cause of epileptic seizures in sub-Saharan Africa. They can cause seizures during the acute illness (acute symptomatic seizures), as well as weeks or months after the acute episode, if the infection leaves an epileptogenic 'scar' in the brain (remote symptomatic seizures).

Three questions should be addressed when managing a patient with possible epileptic disorder:

1. Is it actually an epileptic seizure/epilepsy?
2. Is there an underlying cause for the seizure disorder which can be identified and treated?
3. Does the patient require antiepileptic drug treatment and for how long should it be given?

The available diagnostic and therapeutic means dictate the clinical procedure. Mimics of epileptic seizures such as syncope and psychogenic non-epileptic attacks (so-called pseudoseizures) must be considered. Here, the history taken from the patient as well as from witnesses and guardians is decisive. Feelings of lightheadedness before the loss of consciousness, pallor and brief reorientation after the fall are typical for syncope. Psychogenic non-epileptic attacks are characterized by eye closure, long duration and bizarre motor manifestations. They often occur when the patients are subjected to emotional stress, such as during spiritual rituals and church masses.

In all patients with unknown HIV status, HIV testing should be performed. In all febrile patients, a CNS infection including cerebral malaria should be ruled out. Opportunistic CNS infections should be considered in immunosuppressed patients. In areas with high prevalence of *T. solium,* neurocysticercosis should be taken into consideration. In view of the limited resources, the diagnosis will be based on clinical and epidemiological evidence; hence, the knowledge of local distribution and prevalence of possible causes is helpful.

When initiating antiepileptic treatment, the issues of availability, including reliability of supply, affordability and interactions between AEDs and the patient's medications, must be taken into consideration (particularly, antiretrovirals, antituberculous drugs and contraceptives).

Treatment of women of child-bearing age might pose some additional challenges. In all women of child-bearing age, folic acid (5 mg/day) should be added to the regimen. AEDs recommended for women of child-bearing age in resource-rich settings with low HIV prevalence, such as lamotrigine, are not available in sub-Saharan Africa and might have adverse interactions with ARVs, especially protease inhibitors. In those cases where several AEDs are available, the specific drug chosen for epilepsy treatment of a woman of child-bearing age will be a trade-off between the health of the fetus and that of the mother. Here, one should consider that leaving out a drug because of its possible fetal toxicity, such as valproic acid, and using an enzyme-inducing drug with a better record regarding foetal malformations instead, might lead to a virological failure that would jeopardize both the mother and the child.

Counselling the patients and their guardians is of paramount importance. An epileptic seizure is a dramatic event. In some African communities, epileptic disorder is still attributed to supernatural causes. Patients who have experienced epileptic seizures might become socially stigmatized. Patient-tailored, non-judgemental counselling, taking into account the patient's perception of the disease, might assist in securing the patient's cooperation. Involving local health workers from the community might help overcome misconceptions and reduce stigma.

The Case Continued…

The patient was started on carbamazepine 200 mg bid. Valproic acid was initially requested but the patient could not afford it.

JC-virus DNA was later detected in the CSF as part of a research study, further confirming the suspected diagnosis of PML. She was commenced on ART and remained on carbamazepine. After 6 months, she remained seizure-free and carbamazepine was stopped. After 1 year of ART, the patient's CD4 count reached 535 cells/μL and she had returned to work.

SUMMARY BOX

Seizure Management in HIV

HIV patients are at risk for developing seizures related to HIV-associated neurological diseases and metabolic disturbances. The decision to initiate AEDs in an HIV patient with seizures depends on their aetiology and the duration for which the patient remains at risk for seizure activity. If the cause is readily reversible, such as hypoglycemia, there is no need to initiate antiepileptic treatment. If the patient has a seizure related to a reversible process of medium duration such as an opportunistic infection (OI), it is reasonable to initiate an AED and continue it for 3 to 6 months after treatment for the OI has been completed. If a patient develops persistent seizure activity without a reversible cause, then a diagnosis of epilepsy should be given and long-term AED will be required.

Ideally, one should select an AED that avoids hepatic metabolism because of drug–drug interactions with antiretroviral therapy. However, this may not be possible in a resource-limited setting where the only available drugs are hepatically

metabolized agents such as carbamazepine, phenobarbital and valproic acid. In this case valproic acid is the recommended agent, because it is a cytochrome P450 enzyme inhibitor as opposed to carbamazepine and phenobarbitone, which are cytochrome P450 enzyme inducers. When long-term treatment with carbamazepine or phenobarbital is the only option, the patient needs to be monitored closely for virological failure.

Further Reading

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3. Radhakrishnan K. Challenges in the management of epilepsy in resource-poor countries. Nat Rev Neurol 2009;5(6):323–30.
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5. Bonello M, Michael BD, Solomon T. Infective causes of epilepsy. Semin Neurol 2015;35(3):235–44.