Special Populations: The Management of Seizures in HIV-positive Patients

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An increasing percentage of patients with new-onset seizures are HIV positive. The evaluation and management is distinctly different from managing the non–HIV-infected patient. Clinicians must be familiar with comorbid infectious etiologies and the relative value of electroencephalogram, imaging, and serum and cerebrospinal fluid laboratory tests. Traditional antiepileptic drug (AED) therapies are contraindicated and may lead to increased HIV viral replication through either directed cellular mechanisms or interference with antiretroviral therapies. Newer AEDs have pharmacokinetic properties that make them reasonable choices, although none have been specifically studied for efficacy or safety in HIV. Lastly, optimal choice of an AED should reflect commonly encountered neurologic and psychiatric comorbidities.

Introduction

As the global incidence of AIDS continues to rise and life expectancy increases for patients receiving antiretroviral therapy, more HIV infected patients are presenting with a first seizure. Although an exact measure of incidence is unknown, seizures appear to occur two to three times more often than in non–HIV-infected patients. Many things distinguish the diagnosis and management. In addition to defining the seizure syndrome, the evaluation includes a search for treatable central nervous system (CNS) infections. The high rate of seizure recurrence warrants early initiation of antiepileptic drugs (AEDs), but the most commonly prescribed medications are contraindicated due to either direct effects on HIV viral replication or drug interactions that lead to antiretroviral failure. Clinicians must be familiar with newly released anticonvulsants and be willing to prescribe "off label," as most do not have an indication from the US Food and Drug Administration (FDA) for initial monotherapy. Many new AEDs have significant behavioral effects; thus when choosing an anticonvulsant, a clinician must also be aware of the patient's cognitive and psychiatric state. Lastly, a carefully chosen AED can potentially treat both seizures and painful HIV-associated neuropathy, which is the most common comorbid neurologic complication of HIV infection.

Consider HIV in the Diagnosis

Traditionally, the evaluation of a first seizure begins with a detailed history, physical examination, and screening laboratories to detect metabolic or infectious etiologies that may have resulted in the seizure. Today, the evaluation is not complete unless the clinician considers HIV infection in the differential diagnosis. A prospective study of 98 consecutive patients who presented to an emergency department with a first seizure found that eight were infected with HIV. This represented an alarming 8.2% of all the patients and 20% of the 15- to 45-year-old patients [1]. The study, which took place 11 years ago, concluded HIV-infected subjects represent a significant percentage of patients presenting with seizures. Although in the past it was considered appropriate to discuss HIV testing only in select high-risk populations, today it is reasonable to inquire about HIV risks and offer testing to any patient with new-onset seizures, particularly adolescent and young adults.

No single seizure type is associated with HIV infection. In fact, the literature contains reports of almost all electroclinical seizure syndromes in HIV-positive patients, including absence seizures, generalized seizures, myoclonic seizures, partial seizures with and without secondary generalization, convulsive and nonconvulsive status epilepticus, and epilepsia partialis continua treated with high-dose corticosteroids and anti–HIV-1 therapy [2–6].

Etiologies of Seizures

The majority of seizure patients with HIV infection have a brain lesion or AIDS-defining illness. Most commonly identified are cerebral toxoplasmosis, cryptococcal meningitis, tuberculoma, the AIDS dementia complex, syphilitic meningovasculitis, and primary CNS lymphoma.

Although epileptic seizures are traditionally associated with disease processes affecting the cerebral cortex (gray matter), progressive multifocal leukoencephalitis is a disease that predominantly involves the white matter and is frequently complicated by seizures. In a 5-year retrospective study of 49

HIV-infected patients with progressive multifocal leukoencephalopathy (PML) who did not meet criteria of the AIDS dementia complex and who did not have a concomitant opportunistic infection, 20% had presented with new-onset seizures [7]. Lastly, seizures may be the only clinical manifestation of CNS HIV infection, as no other causes can be identified in as many as 30% of patients [2,3].

Evaluation of Patients

Electroencephalogram

For any HIV-positive patient with seizures, an electroencephalogram (EEG) with activation procedures is indicated. A normal EEG does not rule out seizures, as a lack of epileptiform abnormalities is more the rule than the exception. The first EEG in HIV-positive patients with seizures demonstrates epileptiform findings in 19% of the patients, which is well below the expected yield of 55% for the first EEG in non–HIV-infected patients with seizures [2,8]. Even so, an EEG should be performed, as the nature of abnormalities detected will influence the choice of therapy. Given the low yield of routine outpatient EEG, inpatient EEG video-telemetry monitoring can be extremely valuable for when there is a need to differentiate seizures from other nonepileptic events.

Imaging

As reviewed recently, neuroimaging is crucial for early identifications of lesions and guiding the infectious evaluation, as well as monitoring the efficacy of treatments [9••]. A computed tomography (CT) scan is often the first study performed due to its availability in the emergency setting; however a magnetic resonance imaging (MRI) scan with contrast is the study of choice. The fluid-attenuated inversion recovery sequence is sensitive to many of the brain lesions found in HIV-infected patients [10]. Advanced imaging techniques, including diffusion-weighted imaging, perfusion-weighted imaging, and magnetic resonance spectroscopy, can also be used and add a greater degree of sensitivity to neoplasia, infections, cerebrovascular disease, and hemorrhage [11]. When a lesion is found, functional imaging studies such as single photon emission computed tomography and positron emission tomography scanning may be used to further narrow the differential diagnosis [12]. A systematic approach to ordering neuroimaging studies is shown in Table 1.

Cerebrospinal Fluid and Serum Studies

The test for screening patients with HIV risk factors is the serum HIV enzyme immunoassay (EIA) antibody, which has a 99.7% sensitivity and a 99.9% specificity [13,14]. If the antibody test is positive or equivocal, protocol in most laboratories requires automatic Western blot confirmation. In the setting of acute HIV-1 infection (acute retroviral syndrome), the HIV-EIA is often negative, thus testing should include serum quantitative HIV-RNA measurement and CD4 lymphocyte counts. The HIV-RNA will be remarkably high and the CD4 count is transiently low.

In patients with seizures who are known to be HIV positive or meet clinical criteria for AIDS, serum and cerebrospinal fluid (CSF) analysis must be performed to rule out underlying opportunistic infections. Specific studies ordered can be guided by radiographic findings. New-onset seizures with no radiographic CNS lesions should prompt an evaluation for infections known to cause diffuse encephalitities, including herpes simplex virus 1 and 2 [15,16], direct HIV-1 encephalopathy [17,18], cryptococcal meningitis, the encephalitic form of toxoplasmosis, tuberculosis meningitis, early stage PML, leptomeningeal lymphoma, cytomegalovirus, and varicella zoster virus (VZV).

In patients with new-onset seizures and radiographic findings, CSF studies ordered should reflect the location and distinct characteristics of the lesions. Seizure-associated infections with characteristic neuroimaging findings include AIDS dementia complex, toxoplasmosis, cryptococcoma, tuberculoma, neurocysticercosis, lymphoma, nocardia, and PML, as well as cerebral infarction associated with varicella zoster vasculitis [19] or meningovascular syphilis. CSF studies may include cryptococcal antigen, tuberculosis polymerase chain reaction (PCR) and CSF acid-fast bacillus (AFB) culture; cysticercosis CSF serology (especially in Latino, Indian, and Middle Eastern patients), cytology, and PCR to Epstein-Barr virus (EBV) DNA if primary CNS lymphoma is suspected; and JC virus PCR for PML, VZV PCR, and a modified AFB stain for nocardia. If the diagnosis of AIDS dementia complex is suspected, there appears to be a moderate correlation with a CSF β-2 microglobulin level greater than 3 mg/L. Positive serum toxoplasma immunoglobulin G serology will suffice when characteristic lesions are present, as CSF toxoplasmosis antibody analysis does not increase sensitivity for toxoplasmosis. PCR for toxoplasma antigen is at this time an experimental CSF test.

When no cause for the seizures is determined other than HIV infection, it may be worthwhile to measure quantitative CSF HIV RNA levels, which are a measure of CSF viral load. As HIV infection establishes itself in the human host, the CNS becomes an independent reservoir for HIV-1 replication [20]. Patients on highly active antiretroviral therapy may have undetectable serum levels but significant CSF HIV-1 RNA levels. Furthermore, HIV mutations may confer discordant HIV resistance between the serum and CSF [21]. The blood-brain barrier also makes the CNS a distinct pharmacologic compartment, and some antiretroviral medications have very poor penetration. Although the use of these measures is an area of growing interest and the clinical utility needs to be validated, checking CSF RNA levels, CSF HIV-resistance testing, and CSF antiretroviral levels may be beneficial to optimize antiretroviral therapy for not only seizures, but other CNS complications of HIV.

Table 1. Neuroimaging of patients with HIV/AIDS and seizures

Imaging technique	Protocol	Utility
Initial study: MRI of head using all of the following		More sensitive/specific than CT
T1-weighted axial, pre- and post-contrast	CSE, 5 mm	Gadolinium contrast adds sensitivity and specificity
T2-weighted axial	FSE, 5 mm	Sensitive to posterior fossa and sinus disease
Fast FLAIR axial	5 mm	Sensitive to supratentorial parenchymal and CSF disease
T1-weighted sagittal	CSE, 4 mm	Visualizes midline structures
Diffusion-weighted axial	EPI/ADC, 5 mm	Sensitive to ischemia/infarction
If mass lesion and need to differentiate further, choose one of the following		
SPECT	Perfusion or cellular tracer	Differentiate infection from lymphoma; more available and less costly than PET
PET	Perfusion or cellular tracer	Higher resolution than SPECT
MRS	Single voxel or multi-voxel	May have role in differentiating infection from lymphoma

ADC–apparent diffusion coefficient mapping; CSE—conventional spin-echo; CSF—cerebrospinal fluid; CT–computed tomography; EPI—echoplanar imaging; FLAIR—fluid-attenuated inversion recovery; FSE—fast spin-echo; MRI—magnetic resonance imaging; MRS—magnetic resonance spectroscopy; PET—positron emission tomography; SPECT—single photon emission computed tomography.

Early Initiation of Anticonvulsants

The seizure recurrence rate for non–HIV-infected patients with idiopathic unprovoked seizures is less than 50%, thus most practitioners wait until a second seizure occurs before initiating anticonvulsants. In patients who are HIV positive, the rate of reoccurrence is much higher and approaches 70%; thus it is reasonable to begin treatment after a first seizure [3].

The choice of an appropriate anticonvulsant can be challenging. Phenytoin, carbamazepine, and valproic acid, the three most commonly prescribed AEDs in the United States, are relatively contraindicated. Both phenytoin and carbamazepine are strong inducers of the hepatic cytochrome P450 system. HIV-protease inhibitors are substrates for and inhibitors of this system, particularly CYP3A. Not only is an interaction between these medications expected, but the literature contains numerous reports where the addition of anticonvulsant led to failure of antiretroviral therapy [22,23].

When absolutely necessary, phenytoin may be initiated. However antiretroviral medications need to be increased to compensate for the liver-inducing effects, and the plasma levels of both AED and antiretroviral drugs must be measured and monitored [24].

Valproic acid (VPA) has been studied in cell culture and actually stimulates replication of HIV via a dose-dependent increase in reverse trancsriptase activity. This has been observed in both acute and chronically HIV-infected cell lines. The exact molecular mechanism is not determined, but it is postulated that a VPA-induced decrease in intracellular glutathione allows for increased viral transcription and expression [25,26]. Additionally, valproate has been associated with hepatic and multiorgan system failure when used with antiretroviral drugs [27]. Thus, VPA should not be recommended for the treatment of seizures or other illnesses in HIV-positive patients.

There have been eight new AEDs released since 1992. None have been studied specifically for the treatment of seizures in HIV-positive patients; however, some have pharmacokinetic properties, routes of metabolism, and a lack of drug-drug interactions that make them potentially good choices. Most do not have an FDA-approved indication for initial use as monotherapy, even though this is the standard of care in HIV patients. For medical-legal purposes, it is often beneficial to document and discuss with the patient the rationale for using the medication off-label.

Although the choice of medication must consider efficacy against a seizure type or syndrome, it is equally important to address comorbid neurologic and psychiatric illnesses. HIV-associated peripheral neuropathies have become the most frequent neurologic disorder associated with infection [28]. Most common are the HIV-associated distal sensory polyneuropathy and antiretroviral toxic neuropathies. Both are marked by subacute or chronic sensory symptoms, including spontaneous and evoked pain. Many AEDs have good analgesic properties and they have become first line for symptomatic pain management. When necessary, it is often possible to choose an AED that will treat both the seizures and neuropathic pain.

There is a very high rate of comorbid psychiatric illness. Recent epidemiologic studies report one third of HIV-infected patients are on a psychotropic medication, the most common being antidepressants and anxiolytics, followed by neuroleptics [29]. In addition to the complications of drug-drug interactions, many of the new anticonvulsant medications have profound behavioral and psychiatric side effects. Optimal prescribing must consider whether the AED will alleviate or aggravate psychiatric symptoms.

Commonly Used Medications

Gabapentin

Gabapentin, a structural analog of the neuroinhibitor gamma-aminobutyric acid, is approved for adjunctive therapy in partial-onset seizures. This AED lacks protein binding, is eliminated by renal secretion unchanged, and has essentially no interactions with other AEDs. It has a favorable psychiatric profile and is anxiolytic. It is frequently prescribed for HIV-associated neuropathies, and the literature contains a single unblinded study of 19 HIV-positive patients where gabapentin resulted in a substantial and clinically meaningful reduction of pain [30]. It does not have a monotherapy indication; however, there is evidence of efficacy in new-onset seizures when used at doses of 1800 to 3600 mg/d or higher [31]. Overall, gabapentin has an extremely good profile for the management of seizures in HIV-infected patients, but it has relatively decreased potency when compared with other AEDs. This problem may be solved when pregabalin is released, which is a new molecule similar to gabapentin, but with approximately six times the potency.

Topiramate

Topiramate, a neurosaccharide, has multiple mechanisms of anticonvulsant activity [32] and thus is efficacious against a very wide variety of seizure types, including partial-onset and generalized seizures. It is one of the most potent of the new anticonvulsants with a pending approval for monotherapy, which makes this a very good choice for patients with frequent or difficult-to-control seizures. It has very low protein binding (9% to 17%) and a route of elimination that is 80% renal excretion and 20% hepatic processing. Of seven cytochrome P450 isoenzymes studied, only the CYP2C19 was inhibited [33]. Based on studies of topiramate and oral contraceptives, it is not likely to not induce hepatic enzymes if prescribed at doses of 200 mg/d or lower [34]. Some patients experience cognitive impairment, especially word-finding difficulties; thus it may not be a good AED for patients with AIDS-related dementia. It may be associated with weight loss, which is a consideration for patients with anorexia or generalized wasting. Topiramate has a mixed psychiatric profile and in rare instances has been associated with psychosis and aggravated depression. At the same time, it has been demonstrated efficacious for mood stabilization and is a possible alternative to valproate for the management of mania [35]. Lastly, although not yet studied in HIV-associated neuropathy, it has been shown efficacious in other syndromes of neuropathic pain, including diabetic neuropathy [36].

Lamotrigine

Lamotrigine is another chemically novel compound that has broad-spectrum activity against a wide variety of seizure types, both partial and generalized. Although hepatically metabolized, this AED is glucoronidated and has no effect on the hepatic cytochrome P system. In addition to good potency, it has a very favorable cognitive and behavioral profile and has recently received an indication for long-term maintenance therapy of bipolar I disorder through all mood spectrums. Although it does not have an FDA indication for initiation as monotherapy, this has become common practice among epileptologists, and there have been many efficacy studies to support this. Lastly, it is the only anticonvulsant that has been studied in a double-blinded clinical trial for treating HIV-associated painful neuropathy, and it was found to be highly effective [37]. This drug must be initiated slowly to avoid rash, which may occur at a higher frequency in HIV-positive patients.

Oxycarbamazapine

Oxycarbamazapine is a chemically related analog of carbamazepine, but with a different metabolic profile. It undergoes rapid metabolism to its monohydroxy derivative via nonoxidative, noninducible reduction. Processing of the metabolite occurs principally through renal excretion and glucoronidation, and only a marginal amount undergoes a hydrozylation reaction that depends on microsomal CYP450 enzymes [38]. Although there have been single cases of pancytopenia and thrombocytopenia, oxycarbamazapine does not suppress the leukocyte count, a clear advantage over carbamazepine that is particularly important in an immune-suppressed population. It has an FDA approval for use as monotherapy, a positive behavioral profile with minimal or no effects on cognition, and a favorable response when given to patients with affective disorders [39]. It has been shown efficacious when used in syndromes of neuropathic pain; however, it has not been studied specifically in HIV neuropathies.

Levetiracetam

Levetiracetam is one of the most recently released AEDs that is often used in HIV positive patients. It has low protein binding and renal excretion, with no known induction of either hepatic CYP or UDP enzyme systems. Clinically, it has broad-spectrum activity against a wide variety of seizure types and an FDA indication for monotherapy. Unfortunately a high percentage of patients experience adverse behavioral side effects. In the placebo-controlled clinical trials, nonpsychotic behavioral symptoms such as nervousness, emotional liability, and hostility occurred in 13% of patients [40]. After its release, a significant number of patients have had to discontinue levetiracetam due to more severe symptoms such as severely depressed mood and psychosis. Given the very high percentage of comorbid psychiatric illness in HIV-positive patients, patients should be cautioned and observed for negative psychiatric side effects when starting this medication.

Iatrogenic Seizures

In general, antiretroviral therapies are not known to reduce the seizure threshold. Isoniazid, which is frequently used

Table 2. Protein binding and metabolic pathways of new anticonvulsants and retrovirus inhibitors

Drug	Protein binding, %	Metabolism	Mechanism of metabolism
Gabapentin	40	Renal	Eliminated unchanged
Topiramate	10	Renal (80%), hepatic (20%)	Majority of drug excreted unchanged; trace metabolites detected, specific metabolic enzymes responsible unidentified
Lamotrigine	55	Hepatic	Glucoronidation via UDP-glucoronosyltransferase; mild (14%) autoinduction; no cytochrome P
Oxcarbazepine	60	Hepatic	Nonoxidative, noninducible reduction; CYP isoenzymes minimally involved in processing of the major metabolite MHD
Levetiracetam	None	Renal	66% eliminated unchanged; 27% inactive metabolites; metabolic pathways undetermined; no CYP- or UGT-mediated reaction
NRTI class			
HIV antivirals			
Abacavir	50	Hepatic	P450: Alcohol dehydrogenase and gluuronyl transferase; 82% renal elimination
Didanosine	< 5	Hepatic	50% renal excretion
Emtricitabine	< 4	Hepatic (only 13% metabolized)	Oxidation and conjugation; renal excretion
Lamivudine	< 36	Hepatic (5%–6% metabolized)	Trans-sulfoxide metabolism; renal excretion
Stavudine	Negligible	Unknown	40% renal excretion
Tenofovir	< 7.2	Unknown (not hepatic)	80% renal excretion unchanged
Zalcitabine	NA	None	70% renal excretion
Zidovudine	< 38	Hepatic	88%
NNRTI class			
HIV antivirals			
Delavirdine	98	Hepatic	P450 3A (CYP3A inducer, CYP2D6) by N-desalkylation and purine hydroxylation; renal and fecal elimination
Efavirenz	99	Hepatic	P450 (CYP3A4 mixed inducer and inhibitor, CYP2B6) by hydroxylation, glucuronidation; renal and fecal excretion
Neverapine	60	Hepatic	P450 (CYP3A inducer) by oxidation and glucuronidation; 80% renal excretion, 10% feces
Protease inhibitor class			
Amprenavir	90	Hepatic	P450 (CYP3A4 inhibitor) by oxidation and glucuronidation; urine and fecal excretion
Atazanavir	86	Hepatic	P450 (CYP3A) by monooxidation and dioxidation; fecal and renal excretion
Indinavir	60	Hepatic	P450 (CYP3A4 inhibitor) by oxidation and glucuronidation; renal excretion
Lopinavir/ritonavir	98–99	Hepatic	P450 (CYP3A4 inhibitor) by oxidation; urine and fecal excretion
Nelfinavir	98	Hepatic (only 18% metabolized)	P450 (CYP3A4 inhibitor, CYP2C19) by oxidation; 87% fecal excretion
Ritonavir	-	Hepatic	P450 (CYP3A4 inhibitor, CYP2D6); 86% fecal excretion, 34% renal
Saquinavir	97	Hepatic	P450 (CYP3A4 inhibitor) by hydroxylation; 81% fecal excretion, 3% urine
Fusion inhibitor class			
Enfuvirtide	92	Peptide catabolism	Elimination routes unknown

NRTI—nucleoside reverse transcriptase inhibitor; NNRTI—non-nucleoside reverse transcriptase inhibitor.

to treat mycobacterium tuberculosis and *Mycobacterium kansafsii* infections, blocks production of pyridoxal phosphate and is associated with seizures [41]. Concomitant administration of pyridoxine (vitamin B_6) at a dose of 50 to 100 mg/d should be prescribed and may prevent seizures. At this time, there is no consensus on how to manage patients who require isoniazid and also have seizures. In tuberculosis regimens, isoniazid and pyrizinamide have the highest CNS penetrance of all the mycobacterial antibiotics, and isoniazid is considered a key component of therapy for any patient with tuberculosis meningitis. In patients with documented tubercular meningitis, it may be necessary to treat with antiseizure medications and continue the isoniazid.

Conclusions

The diagnosis and management of seizures in HIV-positive patients differs greatly from noninfected patients. Many aspects remain unknown and need to be formally studied, including overall incidence of seizures, incidence as related to specific opportunistic infection, seizure recurrence rate, the predictive value of EEG and its role both for initiation and discontinuation of medication, as well as the safety of the new AEDs for these patients. A basic understanding of the pharmacokinetic properties, potential for drug interactions, and cognitive/psychiatric side-effect profile can serve as a guide when an anticonvulsant must be initiated. Until more is known, it is reasonable to check both viral titers as well as retroviral inhibitor levels when initiating antiseizure medications and then recheck at regular intervals. Both diagnosis and management can be most effective if neurologic care is coordinated with the multiple physicians involved in patient care, including infectious disease specialists, internists, psychiatrists, and neurologists.

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