HIV medicine

HIV infection and seizures

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Disorders of the central nervous system (CNS) in patients with human immunodeficiency virus (HIV) type-1 infection is often associated with severe morbidity and mortality. Seizures are relatively common manifestations of HIV infection itself and of its several complications involving the brain.1-6

Incidence

Available data on the incidence of new-onset seizures in HIV-infected persons are derived from hospital-based studies. Wong et al3 observed an incidence of 11% among 630 HIV-infected patients. In a more recent study, Van Paesschen et al4 observed that 4% of AIDS patients had new-onset seizures. In their study, the incidence of seizures was much lower than in the former study, presumably because strict inclusion criteria were applied. All patients were admitted, or were already in-patients, on the day of first seizure. Out of 68 selected patients, 62 had acquired immunodeficiency syndrome (AIDS), only six (9%) patients had AIDS-related complex or were asymptomatic HIV-seropositive.5 In the study by Wong et al,6 28% of the patients had AIDS-related complex or were asymptomatic HIV-seropositive.

Associated seizure disorders

In most AIDS patients, seizures are seen in advanced stages of the disease.1-4 Dore et al5 in a case-control study observed that 84% of such patients had prior AIDS-defining illness, and mean CD4 T-cell count was $8 \times 10^6$ cells/μl, while in a control group (patients without seizures) mean CD4 T-cell count was $14 \times 10^6$ cells/μl, and AIDS-defining illness was present in 80% of the patients.

Seizures may be the presenting clinical symptom of HIV disease. In a few patients seizures can occur early in the course of HIV-infection. The majority of patients have generalised seizures; partial seizures are less frequently observed and do not necessarily imply the presence of focal mass lesions.1-6 Both simple and complex partial seizures are seen in patients with diffuse brain disease, such as HIV encephalopathy and meningitis.7 The incidence of convulsive status epilepticus has been reported as between 8% and 18% in different studies,2-4 and is often associated with poor prognosis. The frequent occurrence of generalised seizures and status epilepticus suggests that the HIV-infected brain has a low cortical excitability and impaired mechanisms for terminating seizure activity. Electroencephalographic (EEG) findings are usually non-specific, diffuse slowing being the most common abnormality. Focal slowing and epileptiform activity are infrequently seen.2-3

Aetiology

Work-up for HIV-infected patients presenting with new-onset seizures includes neuroimaging studies (computed tomography (CT), magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) analysis), as well as blood chemistry and, in some patients, neuropathological studies of biopsied brain tissue. In a few patients, diagnosis may not be clear until post-mortem neuropathological evaluation. Approximately 50–60% of patients have an apparent secondary disease process to which the seizures can be attributed; at rest, no demonstrable cause is seen (table).4-7 Various electrolyte and metabolic disturbances, such as hyponatraemia, hypomagnesaemia and renal failure, are associated with an increased risk of seizure recurrence and increased occurrence of convulsive status epilepticus.2-4

Mass lesions

Intracranial mass lesions account for nearly half the neurological disorders in AIDS patients. The nature of these mass lesions can be broadly divided into
three distinct groups: opportunistic infections, neoplasms, and cerebrovascular
diseases. Seizures are dominant manifestations of most of these disorders
(box 1).

Toxoplasmosis is the most common cause of intracranial mass lesions in AIDS
and occurs in 3–10% of patients in the USA and in up to 50% of patients in
Europe and Africa.8 Seizures have been reported as an early manifestation in
15–40% of patients with cerebral toxoplasmosis.19 The diagnosis is usually made
by demonstrating the presence of ring-enhancing lesions on CT scan, positive
toxoplasma antibody titre, and clinical improvement with antitoxoplasma treat-
ment which is confirmed by repeat CT brain scan.10 Various studies have
described different incidences (12–28%) of toxoplasmosis in patients with new-
onset seizures among HIV infected persons.245 Identification of cerebral
toxoplasmosis is important because timely treatment with sulfadiazine and
pyrimethamine is most likely to result in rapid clinical improvement.

Primary CNS lymphoma, the second most common cause of AIDS-related
intracranial mass lesions, occurs in up to 2% of patients with AIDS.5 It is also the
second most common mass lesion producing seizures in HIV-infected persons.
A number of imaging features are helpful in distinguishing this condition from
cerebral toxoplasmosis. Involvement of, and extension across, the corpus callo-
sum is frequent in primary CNS lymphoma. Exclusive involvements of white
matter, periventricular location and sub-ependymal spread (seen as contrast
enhancement along the ventricular surface) are also common in lymphoma.10

Other causes of intracranial mass lesions which are likely to produce seizures
in AIDS patients include tuberculous abscesses11 and tuberculomas,12
cryptococcal abscesses,10 nocardial abscesses,13 syphilitic gummas and cerebro-
vascular diseases when accompanied by oedema.14

Other focal lesions

Other focal lesions without significant mass effect, such as progressive multifoc-
alfocal leukoencephalopathy (PML) may also be responsible for new-onset seizures in
several AIDS patients (figure). Moulignier et al15 reported on 10 HIV-infected
patients with PML in whom partial or generalised seizures were the presenting
neurological manifestations. They suggested that demyelinated lesions adjacent
to the cerebral cortex acting as irritative foci, axonal conduction abnormalities,
or disturbance of the neuron–glia balance are the possible reasons for a pure
white matter disease producing seizures. Confirmation of the diagnosis of PML
requires neuropathological studies of biopsied brain tissue from the lesion (box 2).

Meningitis and encephalitis

In patients without mass lesions, meningitis and encephalitis caused by some
opportunist infections is a frequent source of seizures. The incidence of men-
ingitis and encephalitis in HIV-infected patients with new onset seizures varies
from 12% to 16%. Cryptococcal meningitis is the most frequent meningi-
encephalitis producing seizures.24 To confirm the diagnosis, an India ink prepa-
ration of CSF should be examined for cryptococcal antigen; fungal culture may
increase the diagnostic yield.

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Table Causes of seizures in HIV infected patients: a summary of observations of 4 studies

<table>
<thead>
<tr>
<th>Holtzman et al10 (n=100)</th>
<th>Wong et al19 (n=70)</th>
<th>Van Pauwels et al10 (n=68)</th>
<th>Dore et al15 (n=50)</th>
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HIV: human immunodeficiency virus, TTP: thrombotic thrombocytopenic purpura; PML: progressive multifocal leukoencephalopathy; CMV: cytomegalovirus.
HIV infection and seizures

**Pathogenesis of HIV-encephalopathy and seizures in AIDS patients**

- HIV- or immune-related toxins indirectly produce neuronal death
- Interactions between macrophages (microglia), astrocytes, and neurons produce neurotoxic substances
- Known neurotoxic substances include eicosanoids, platelet-activating factor, quinolinate, cysteine, cytokines, and free radicals
- Macrophages activated by HIV-1 envelope protein gp120 release similar toxins
- The final common pathway is through increased glutamate activity, activation of voltage-dependent calcium channels and NMDA receptor-operated channels
- Influx of calcium into the cells ultimately leads to neuronal death
- The resultant relative imbalance of excitatory and inhibitory neurotransmitters and neurotoxicity of other substances in brain may predispose to seizures

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**Case history**

A 38-year-old man presented 3 days after two episodes (48 h apart) of right partial seizures with secondary generalisation. His neurological examination was normal. He was treated with carbamazepine (200 mg, 8 hourly) and had remained seizure-free for 10 days, when he was brought to the emergency department in convulsive status epilepticus. He was unconscious (Glasgow coma scale score 8). At this time his right plantar was extensor. His serum biochemistry was normal. Serum carbamazepine level was within the therapeutic range. He was immediately treated with intramuscular paraldehyde (5 ml in each buttock) and, in addition to carbamazepine, clobazam (10 mg, 8 hourly). His seizures stopped and he regained consciousness. A CT scan showed multiple hypolucencies in the cortical white matter, consistent with a diagnosis of progressive multifocal leukoencephalopathy (figure). He was subjected to ELISA test for HIV-infection which was positive on two occasions; HIV infection was later confirmed by Western-blot. On enquiry, the patient admitted having a high-risk heterosexual contact 4 years earlier. He was discharged after 4 seizure-free days and was lost to follow-up.

**Figure** Cranial CT scan showing multiple white matter hypolucencies suggestive of progressive multifocal leukoencephalopathy

**Box 2**

Infrequent causes include aseptic meningitis, neurosyphilis, Herpes zoster leukoencephalitis, toxoplasma and cytomegalovirus encephalitis. In the developed countries, subacute sclerosing panencephalitis has re-emerged in children infected with HIV and can present with seizures and encephalopathy. The diagnosis is confirmed with characteristic periodic electroencephalographic changes and high measles antibody titre in CSF.

**HIV infection**

Approximately half of HIV-infected patients with seizures have no definite identifiable disease of the brain, and cerebral HIV infection seems to be the most likely cause of the seizures. 1-7 Navia et al 2 reported nine patients with AIDS-dementia complex who had new-onset seizures and in whom autopsies did not reveal any secondary infections or neoplastic processes. The authors considered direct HIV infection of brain to be the cause of the seizures. In the study by Holtzman et al, HIV encephalopathy was responsible for seizures in 24% of the patients. The diagnosis was established with the help of characteristic clinical features and histopathology of brain tissues. Later, in a series by Wong et al, 17 patients within an unidentified group underwent post-mortem neuropathological examination of brain; six of them had microglial nodules or multinucleated cells or both, suggesting the diagnosis of HIV infection as a primary cause of seizures. In a series by Van Paesschen et al, 5 41% of patients had cerebral atrophy on CT scan without meningitis or other demonstrable CT lesions. Autopsies of two patients from the latter group who died after seizure onset revealed subacute HIV-associated encephalitis in one patient, and cytomegalovirus encephalitis in the other. In a more recent study, Dore et al, 6 observed that 42% of cases had no identifiable cause of seizures, although 18% of patients were receiving foscarin therapy. They suggested that foscarin therapy and subclinical HIV-1 involvement of the brain may be factors responsible for seizure activity. Thus, available data strongly suggest an epileptogenic role of HIV infection of the brain.

Among the various pathologies reported in the brain of patients of AIDS is neuronal injury and loss, however, neurons themselves are not infected by HIV. There is strong evidence for the existence of HIV- or immune-related toxins that produce injury or death of neurons via a potentially complex interaction between macrophages, microglia, or monocytes, especially after interacting with astrocytes. These neurotoxic substances can lead to increased glutamate release...
or decreased glutamate re-uptake. This mechanism involves the activation of voltage-dependent calcium channels and N-methyl-D-aspartate (NMDA) receptor-operated channels and influx of calcium inside the neurons and other cells. The same mechanisms which have been proposed for the pathogenesis of the AIDS–dementia complex are considered responsible for early and late occurrences of seizures in these patients (box 3). 18 19

Drugs

HIV-related seizures may also be provoked by concurrently administered drugs, for example, foscarinet therapy. 20 Soloman et al 21 reported one HIV-infected patient who developed new-onset generalised seizures following a single topical application of lindane for scabies.

Treatment

Seizure recurrences are frequent among these patients. Long-term anti-epileptic therapy needs to be considered, even after a single seizure. Phenytoin has been the most widely prescribed anti-epileptic drug for these patients, but a significant number of patients are likely to experience undesirable side-effects, including skin rashes, leucopenia, thrombocytopenia and hepatic dysfunction. Phenobarbital and valproate are satisfactory alternatives in this situation. 3 5 12 Patients with mass lesions may experience seizure recurrence despite adequate plasma concentrations of anti-epileptic drug. 1 As patients with HIV disease are likely to take long-term anti-epileptic medication, this may lead to drug interactions as a result of hepatic enzyme induction. Anti-epileptic drugs may also reduce the plasma concentrations of the protease inhibitors and so reduce their antiviral efficacy. 22

Conclusion

Seizures are frequently associated with neurological manifestations of HIV infection. Correct diagnosis of underlying causes and their treatment along with anticonvulsant therapy is required for proper management. Proper control of seizures will help to improve the quality of life in these patients who are already suffering from a dreaded disease.

Summary points

- Seizures are common manifestations of CNS involvement in HIV-infected patients.
- Generalised seizures are the most common type of seizures encountered.
- Convulsive status epilepticus is also common because of frequent serum electrolyte abnormalities.
- Lumbar puncture, CT, and MRI, if available, along with assessment of serum biochemical parameters are needed for evaluation.
- Cerebral mass lesions (e.g., toxoplasmosis), HIV-encephalopathy, and cryptococcal meningitis, are the commonest causes of seizures in these patients.
- Phenytoin is the most widely prescribed anti-epileptic drug; hypersensitivity reactions are common.
- Prognosis depends upon the underlying cause.

Box 4