HIV infection and seizures

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Summary

New-onset seizures are frequent manifestations of central nervous system disorders in patients infected with human immunodeficiency virus (HIV). Seizures are more common in advanced stages of the disease, although they may occur early in the course of illness. In the majority of patients, seizures are of the generalised type. Status epilepticus is also frequent. Associated metabolic abnormalities increase the risk for status epilepticus. Cerebral mass lesions, cryptococcal meningitis, and HIV-encephalopathy are common causes of seizures. Phenytoin is the most commonly prescribed anticonvulsant in this situation, although several patients may experience hypersensitivity reactions. The prognosis of seizure disorders in HIV-infected patients depends upon the underlying cause.

Keywords: AIDS; human immunodeficiency virus; seizures; epilepsy; toxoplasmosis

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 al*¹ observed an incidence of 11% among 630 HIV-infected patients. In a more recent study, Van Paesschen *et al*² 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.⁴ In the study by Wong *et al*,³ 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.^{3,4} Dore *et al*⁵ in a case-control study observed that 84% of such patients had prior AIDS-defining illness, and mean CD4 T-cell count was 8×10^6 cells/ μ l, while in a control group (patients without seizures) mean CD4 T-cell count was 14×10^6 cells/ μ l, 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.³ 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 activities 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).^{1–7} 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

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

<i>Holtzman et al^a (n=100)</i>	<i>Wong et al^b (n=70)</i>	<i>Van Paesschen et al^c (n=68)</i>	<i>Dore et al^d (n=50)</i>
Mass lesions : 32 toxoplasmosis - 28 lymphoma - 6 HIV-encephalopathy:24 Meningitis : 16 cryptococcal - 13 herpes zoster - 1 aseptic - 1 toxoplasmosis - 1 Others : 8 hyponatraemia - 2 stroke - 3 TTP - 1 PML - 1 renal failure - 1 Non-identifiable : 23	toxoplasmosis - 11 lymphoma - 8 metabolic - 8 cryptococcal meningitis - 7 vascular infarction - 4 non-identifiable (HIV-encephalopathy) - 32	Mass lesions : 25 toxoplasmosis - 8 other cerebral mass lesions - 11 non-identified - 6 Meningoencephalitis: 8 cryptococcal - 3 herpeszoster - 1 neurosyphilis - 1 toxoplasma - 1 tuberculous - 1 unclear - 1 Stroke - 3 Drug abusers - 2 With cerebral atrophy (? HIV-dementia) - 28 Non-identified - 3	toxoplasmosis - 11 cryptococcal meningitis - 4 PML - 3 CMV encephalitis - 3 lymphoma - 1 other causes (pre-HIV) seizures - 7 non-identifiable cause - 21

HIV: human immunodeficiency virus, TTP: thrombotic thrombocytopenic purpura; PML: progressive multifocal leukoencephalopathy; CMV: cytomegalovirus.

three distinct groups: opportunistic infections, neoplasms, and cerebrovascular diseases. Seizures are dominant manifestations of most of these disorders (box 1).⁸

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.^{1–9} 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 treatment 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.^{2–4, 5} 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.⁸ 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 callosum 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 cerebrovascular diseases when accompanied by oedema.¹⁴

Other focal lesions

Other focal lesions without significant mass effect, such as progressive multifocal leukoencephalopathy (PML) may also be responsible for new-onset seizures in several AIDS patients (figure). Moulignier *et al*¹⁵ 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, meningo-encephalitis caused by some opportunistic infections is a frequent source of seizures. The incidence of meningitis and encephalitis in HIV-infected patients with new onset seizures varies from 12% to 16%. Cryptococcal meningitis is the most frequent meningo-encephalitis producing seizures.^{2–6} To confirm the diagnosis, an India ink preparation of CSF should be examined for cryptococcal antigen; fungal culture may increase the diagnostic yield.

Focal CNS lesions associated with seizures in HIV-infected patients

Infections

- toxoplasmosis
- cryptococcal granuloma
- tuberculoma & tuberculous abscess
- cysticercus granuloma
- Herpes zoster
- neurosyphilis
- nocardial abscesses

Neoplasm

- primary CNS lymphoma

Demyelination

- progressive multifocal leukoencephalopathy

Cerebrovascular diseases

- cerebral infarction
- intracerebral haemorrhage

Box 1

Case history

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

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.

Box 2

Infrequent causes include aseptic meningitis, neurosyphilis, Herpes zoster leukoencephalitis, toxoplasma and cytomegalovirus encephalitis.⁵ 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.¹⁶

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*¹⁷ 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*,² 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*,³ 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*,⁴ 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*⁸ observed that 42% of cases had no identifiable cause of seizures, although 18% of patients were receiving foscarnet therapy. They suggested that foscarnet 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

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 channel 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

Box 3

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 (eg, 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

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, foscarnet therapy.²⁰ Solomon *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. Phenobarbitone and valproate are satisfactory alternatives in this situation.^{2 3 19} Patients with mass lesions may experience seizure recurrence despite adequate plasma concentrations of anti-epileptic drug.³ 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.

- 1 Aronow HA, Feraru ER, Lipton RB. New-onset seizures in AIDS patients: etiology, prognosis, and treatment. *Neurology* 1989;**39** (suppl 1):428.
- 2 Holtzman DM, Kaku DA, So YT. New-onset seizures associated with human immunodeficiency virus infection: causation and clinical features in 100 cases. *Am J Med* 1989;**87**:173-7.
- 3 Wong MC, Suite NDA, Labar DR. Seizures in human immunodeficiency virus infection. *Arch Neurol* 1990;**47**:640-2.
- 4 Van Paesschen W, Bodian C, Maker H. Metabolic abnormalities and new-onset seizures in human immunodeficiency virus - seropositive patients. *Epilepsia* 1995;**36**:146-50.
- 5 Dore GJ, Law MG, Brew BJ. Prospective analysis of seizures occurring in human immunodeficiency virus type-1 infection. *J Neuro AIDS* 1996;**1**:59-69.
- 6 Labar DR. Seizures and HIV infection. In: Pedley TA, Meldrum BS, eds. *Recent advances in epilepsy*. Edinburgh: Churchill Livingstone, 1992; pp 119-26.
- 7 Rosenbaum GS, Klein NC, Cunha BA. Early seizures in patients with acquired immunodeficiency syndrome without mass lesion. *Heart Lung* 1989;**18**:526-9.
- 8 Report of the Quality Standards Subcommittee of the American Academy of Neurology. Evaluation and management of intracranial mass lesions in AIDS. *Neurology* 1998;**50**:21-6.
- 9 Wong MC, Suite NDA, Labar DR. Seizures and HIV infection. *Neurology* 1989;**39**(suppl):362.

- 10 Provenzale JM, Jenkins JR. Brain and spine imaging findings in AIDS patients. *Radiol Clin North Am* 1997;**35**:1127-66.
- 11 Farrar DJ, Flanagan TP, Gordon NM, Gold RL, Rich JD. Tuberculous brain abscess in a patient with HIV infection: case report and review. *Am J Med* 1997;**102**:297-301.
- 12 Martinez-Vazquez C, Bordon J, Rodriguez-Gonzalez A, *et al*. Cerebral tuberculoma - a comparative study in patients with or without HIV infection. *Infection* 1995;**23**:49-53.
- 13 Mamelak AN, Obana WG, Flaherty JF, Rosenblum ML. Nocardial brain abscess: treatment strategies and factors influencing the outcome. *Neurosurgery* 1994;**35**:622-31.
- 14 Moriarty DM, Haller JO, Loh JP, Fikrig S. Cerebral infarction in pediatric acquired immunodeficiency syndrome. *Pediatr Radiol* 1994;**24**:611-2.
- 15 Moulignier A, Mikol J, Pialoux G, Fenelon G, Gray F, Thiebaut JB. AIDS-associated progressive multifocal leukoencephalopathy revealed by new-onset seizures. *Am J Med* 1995;**99**:64-8.
- 16 Koppel BS, Poon TP, Khandji A, Pavlakis SG, Pedley TA. Subacute sclerosing panencephalitis and magnetic resonance imaging. *J Neuroimaging* 1996;**6**:22-5.
- 17 Navia B, Jordan B, Price R. The AIDS-dementia complex: I Clinical features. *Ann Neurol* 1986;**19**:517-24.
- 18 Lipton SA. AIDS-related dementia and calcium homeostasis. *Ann NY Acad Sci* 1994;**747**:205-24.

- 19 Delanty N, Vaughan CJ, French JA. Medical causes of seizures. *Lancet* 1998;**352**:383-90.
- 20 Lor E, Liu YQ. Neurological sequelae associated with foscarnet therapy. *Ann Pharmacother* 1994;**28**:1035-7.
- 21 Solomon BA, Haut SR, Carr EM, Shlita AR. Neurotoxic reaction to lindane in an HIV-seropositive patient. An old medication's new problem. *J Fam Pract* 1995;**40**:291-6.
- 22 Barry M, Gibbons S, Back D, Mulcahy F. Protease inhibitors in patients with HIV disease. Clinically important pharmacokinetic considerations. *Clin Pharmacokinet* 1997;**32**:194-209.