Prospective Study of New-Onset Seizures in Patients With Human Immunodeficiency Virus Infection

Etiologic and Clinical Aspects

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Objective: To determine the frequency and etiologic and clinical aspects of new-onset seizures in patients with human immunodeficiency virus (HIV) infection.


Setting: Outpatients and inpatients in a university hospital in Barcelona, Spain.

Patients: Five hundred fifty HIV-infected patients recruited over 1 year.

Main Outcome Measure: Analysis of new-onset seizures, with detailed medical history and appropriate workup.

Results: Seventeen HIV-infected patients (3%) had a new-onset seizure during the study period. Fourteen (82%) of 17 patients had acquired immunodeficiency syndrome diagnosed according to the 1993 CDC Expanded AIDS Definition. Mean latency (±SD) between diagnosis of HIV infection and the first seizure was 60.7 ± 37.6 months. Seizure cause was drug toxicity in 8 patients (47%) and intracranial lesion in 6 patients (35.3%). Two patients had seizures related to metabolic derangements. No cause was found in 1 case. The first seizure was generalized in 12 patients (70.6%), simple partial motor seizure in 2 (11.8%), and simple partial seizure evolving to generalized seizure in 3 (17.6%). We found partial seizures in 66.6% of patients who had intracranial lesions. Most patients were treated with phenytoin, which was well tolerated and effective in controlling seizures.

Conclusions: New-onset seizures are infrequent in patients with HIV. In most cases a definite or probable cause is identified, which is usually related to toxic and/or metabolic factors. Most seizures are generalized, and partial seizures suggest a focal cerebral lesion.

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Nervous system clinical involvement, both central and peripheral, is found in about 40% to 65% of patients infected with human immunodeficiency virus (HIV) sometime during the disease course. Postmortem studies show 70% to 80% of cases have nervous system involvement. Retrospective studies estimate that 11% to 17% of HIV-infected patients will have seizures sometime during their course. We prospectively studied the clinical and etiologic spectrum of seizures in HIV-infected patients.

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RESULTS

PATIENTS

Of 550 patients, 17 (3%) had a new-onset seizure during the study (Table). Eleven (64.7%) were men and 6 (35.3%) were women, with a mean age (± SD) of 32.8 ± 5.7 years (age range, 22-45 years). Human immunodeficiency virus risk factors were intravenous drug use (IVDU) in 10 patients (5 men), homosexual activity in 4 (all men), and heterosexual transmission in 3 (1 woman). At the time of first seizure, 14 (82.3%) had an AIDS-defining condition (13 stage C3, 1 stage C2); mean latency between HIV diagnosis and the first seizure was 60.7 ± 37.6 months (range, 1-120 months). Mean CD4+ cell count was 0.115 ± 0.016 × 10⁹/L (115 ± 16/mm³) (range, 0.002-0.56 × 10⁹/L [2-560 mm³]). Eight patients (47%) died, with a mean survival period from first seizure of 3 months. All deaths were in patients who were in an advanced HIV infection stage (mean CD4+ cell count of 0.018 ± 0.016 × 10⁹/L [115 ± 16/mm³]) at the time of first seizure. Mean follow-up was 5.0 ± 2.9 months for all patients (range, 1-10 months), and 6.8 ± 3.2 months for survivors (range, 1-10 months).
PATIENTS AND METHODS

We studied 350 HIV-infected patients older than 18 years whose disease was diagnosed with standard methods and staged according to the Centers for Disease Control and Prevention’s Revised Classification System for HIV Infection. Over a 1-year period, patients infected with HIV were consecutively seen in the AIDS Unit of the Department of Internal Medicine of the Hospital de Sant Pau, Barcelona, Spain. The Hospital de Sant Pau is one of 4 reference hospitals in Barcelona and has an active acquired immunodeficiency syndrome (AIDS) unit. Any patient with prior seizures (with or without relation to HIV) was excluded from the study. Any patient with a first seizure during this 1-year period was examined by physicians from the Department of Neurology and followed up quarterly until death or study end.

Clinical data recorded for each patient were age, sex, HIV risk factors, first seizure date, toxic drug use, latency between diagnosis of HIV infection and first seizure, stage of disease, prior anti-HIV treatments, neurologic complications related to HIV, nonneurologic complications, and seizure characteristics (duration, interval between seizures, precipitating drugs, frequency, and clinical seizure type based on the International Classification of Epileptic Seizures of 1981). Examination included testing glucose and serum electrolyte levels, liver and renal function, blood cell count, serologic tests for *Toxoplasma gondii* and cytomegalovirus, computed tomographic or magnetic resonance imaging brain scans, and, if required, toxicologic screens, electroencephalographic and cerebrospinal fluid studies (biochemical tests, serologic tests for syphilis and *T. gondii*, Gram stain, cultures for *Cryptococcus neoformans* and *Mycobacterium*, stains for acid-fast *Bacillus*, and polymerase chain reaction for herpes simplex virus).

CAUSE

Seizures were attributed to drug toxicity in 8 patients (47%): infusions of intravenous (IV) foscarne sodium (n = 2) ceftazidime (n = 1), oral sulfonamides and zidovudine (n = 1), infusions of IV imipenem (n = 1), IV cocaine (n = 1), IV heroin (n = 1), and medazepam hydrochloride withdrawal (n = 1). Drug toxicity was considered a definite or probable cause when the time was close between use of the drug and the seizure. Six patients (35.3%) had intracranial lesions: 5 had cerebral toxoplasmosis (TXP) and 1 had progressive multifocal leukoencephalopathy (PML). Metabolic derangements (hypoglycemia and hypomagnesemia) were observed in 2 patients (11.1%). Toxic-metabolic factors were thus the cause of the seizure in 10 patients (38.8%). No cause was found in 1 patient, despite a thorough examination.

CLINICAL SEIZURE TYPE

First seizure was generalized in 12 patients (70.6%), simple partial seizure without generalization (both motor type) in 2 (11.8%), and simple partial seizure evolving to generalized seizure in 3 (17.6%). During follow-up, the 2 patients with initial simple partial seizure evolved to generalized seizure. All 17 patients had a generalized seizure at some time. All generalized seizures were tonic-clonic, except for 1 patient who had myoclonic seizures. No complex partial seizures were observed. Three patients (17.6%) had status epilepticus: 2 with simple partial motor status (1 with cerebral TXP and 1 with an unknown cause) and 1 with myoclonic status (IV infusion of diacetylmorphine hydrochloride). Four patients (23.5%) had a single seizure (3 with generalized tonic-clonic [GTC] seizure and 1 with simple partial seizure with secondarily generalized seizure). Focal seizures were most frequently seen in patients with cerebral mass lesions (4/6 [66%]). Seizures were refractory to therapy in 3 patients (17.6%): 1 with PML, 1 with relapsing cerebral TXP, and 1 with myoclonic status due to IV infusion of diacetylmorphine.

THERAPY

Seven patients (41.1%) were not treated as having a single first seizure and/or the seizure was related to a toxic-metabolic cause. Two untreated patients had cerebral TXP: 1 died within a few hours of cerebral edema and 1 responded to anti-TXP therapy, without recurrence of seizures.

Phenytoin was initially prescribed for 8 patients (47%) and carbamazepine for 2 (11.8%). Carbamazepine therapy was discontinued in both patients because of adverse effects (severe skin reaction and ataxia) and was changed to phenytoin. No serious adverse effects were observed in patients who received phenytoin, except in 1 patient with ataxia and nystagmus because the dosage was too high. Seizures were well controlled with treatment.

COMMENT

New-onset seizures were relatively infrequent in our HIV-infected patients (3%). A cause was identified in most of our patients (94.1%), with toxic-metabolic factors the main cause (nearly 60%). Fourteen patients (82.3%) had AIDS at the time of the first seizure, confirming, as in previous reports, that seizures usually occur in patients with severe immunodepression. Generalized tonic-clonic seizures were the most common, and a focal seizure suggested a structural cerebral lesion. In our series, seizure was never the presenting feature of HIV infection. Patients who had seizures responded well to therapy.

In the literature, HIV represents 8% of the cause in adults who have a first epileptic seizure. In the 15- to 45-year age group, this number increases to 20%. Frequency of first seizure in HIV-infected patients ranges from 11% to 17% in retrospective studies. We found a frequency of 3%. Van Paesschen et al report 4% in hospitalized patients. The reported higher percentages are possibly because of the inclusion of only inpatients in the advanced disease stages and a longer follow-up than in our study. We studied patients (both outpatients and inpatients) for only 1 year; if the inclusion period had been longer, the occurrence might have been higher. Since the number of HIV-infected patients with first seizure in our study is relatively low, seizure characterization is limited.
The HIV-infected population treated at our hospital has characteristics similar to other HIV-infected populations in Spain. In our series the main HIV risk factor was IVDU (58.8%), reflecting the nature of our population.12 Van Paeschen et al also report IVDU as the most common risk factor (46%). In other reports, sexual transmission was the most common risk factor.3,9 Mode of exposure to HIV seemed to influence the cause of seizures in our study: 3 (30%) of 10 patients had seizures that were related to IVDU.

Prior to their first seizure, 14 patients (82.3%) had already been diagnosed as having AIDS. Previous studies have ranged from 55.7% to 91.0%.3,8-10 In our series, we did not observe such a high prevalence of prior diagnosis.

In the literature, seizures have been reported as a presenting manifestation of HIV-related disease in 3.8% to 18% of patients.3,9,10 In our series, we did not observe a seizure as the initial manifestation of HIV infection. We were able to identify the cause of seizure in 94.1% of cases. Previous studies have been unable to establish cause of seizure in 23% to 46% of patients, and the seizure was attributed to the HIV infection. The HIV stage was less advanced in those with no identifiable cause than in those with an identifiable cause. In our series, we were unable to identify a presumed cause in only 1 patient in whom the HIV infection alone was the presumed cause.

Opportunistic infections may affect up to 20% of HIV-infected patients and cause 40% of neurologic manifestations.3,9,10 Six (35.3%) of our patients had a central nervous system infection as the underlying seizure cause, although most seizures were partial. Only 1 patient with cerebral TXP had refractory seizures. It has been estimated that 18% to 25% of patients with cerebral TXP will have epileptic seizures.4,16

One patient had simple partial seizures with PML. This disease was first described as a cause of seizures in 1983.18 Since then other cases9,10,13,19-21 have been reported. Wong et al found no PML in 70 patients who had seizures, but 2 studies21,22 have reported seizure as an initial manifestation of HIV infection in 20% of patients with PML.

A variety of other causes have been associated with HIV-infected patients who have seizures (infection, neoplasm, and stroke).3,6,10,13,23-26 but we did not see these causes in our patients.

Unlike previous studies5,10 according to our study, toxic-metabolic factors accounted for more than half (58.8%) the seizures patients experienced. Surprisingly, in series with larger groups of patients,9,11 no seizures caused by toxic-metabolic factors were observed.

The cause of seizures in 2 patients was hypoglycemia and hypomagnesemia. Hypomagnesemia can induce epileptic seizures,27,28 and Van Paesschen et al emphasized metabolic causes as important in HIV-infected patients. Van Paeschen et al found hyponatremia to be a common disorder (46%) in their patients and reported an association between hypomagnesemia, renal failure, and status epilepticus. None of the patients with status epilepticus had these disorders. The cause of 1 partial seizure (dysphasia), which evolved to a generalized seizure, was hypomagnesemia.

Neurotoxicity due to use of zidovudine has been long recognized as a cause of epileptic seizures.29-33 One of our patients attempted suicide with an overdose of sulfonamides and zidovudine, both of which may have contributed to the GTC seizure. In 1 patient, imipenem produced a GTC seizure, a well-known adverse effect.30 Two
of our patients had seizures with an IV infusion of foscarinet, and in both cases, seizures reappeared with further foscarinet treatment. Calcium and magnesium levels in 1 patient were normal. Seizure frequency related to the use of foscarinet is about 3% to 15%.

Seizures directly related to substance use, abuse, and withdrawal are increasingly common. Diacetylmorphine is a known epileptogenic drug, and we observed to the use of foscarnet is about 3% to 15%. In both cases, seizures reappeared with further IV infusions of diacetylmorphine or cocaine. A third patient had a GTC seizure related to medazepam hydrochloride treatment withdrawal.

Most seizures in our series were generalized and, in agreement with previous reports (65%–80%), occurred during advanced disease stages. Similar to other reports, we observed status epilepticus in 3 patients (17.6%), although some authors report a lower frequency. We could not correlate status to cause or HIV risk factor, although we had only a limited number of cases. Van Paesschen et al. report a higher occurrence of status epilepticus in patients with IVDU than in other risk factor groups. A single seizure occurred in 4 patients (23.5%) in our study. In 3 patients (17.6%), the seizures were recurrent and refractory to standard antiepileptic therapy. Medically refractory seizures have been reported in 12% to 54% of HIV-infected patients.

Although others have reported adverse effects of 14% to 26% from phenytoin therapy, none of our 10 patients had serious adverse effects. While seizures tended to be well controlled with the use of phenytoin, the duration of follow-up is insufficient to estimate effectiveness. Eight patients (47%) died during follow-up, almost all within 4 months of the first seizure, suggesting that seizures are a marker of poor outcome, as previously reported. However, 2 of the 3 patients who had status epilepticus did not die. Thus, in contrast to other authors, we did not find a relationship between status epilepticus and poor outcome.

Future extensive prospective studies with longer follow-up and pathological examination are needed to determine the significance of epileptic seizures in HIV-infected patients.

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