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New-onset seizures among HIV infected drug naïve patients from south India

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Abstract

Objective: The purpose of the study is to analyze the frequency, etiology and clinical aspects of seizures occurring among HIV infected patients presenting with neurological disorders from south India where HIV infection is due to clade C subtype. All were drug naïve without antiretroviral therapy. *Methods:* Among the 500 HIV seropositive patients with neurological manifestations evaluated at a tertiary referral center and university teaching hospital (NIMHANS) at Bangalore (1989-2001), 99 patients who had new onset seizures were analyzed. *Results:* The mean age at presentation was 32.1 ± 7.5 years, male to female ratio was 11.4 : 1. The types of seizures were primary generalized in 62 patients (62.6%) and partial with/without generalization in 37 patients (37.4%) including 8 patients with status epilepticus. The mean duration of symptoms of underlying neurological illness was 23.7±52.1 days. Seizures, as the first symptom was noted in 20 patients. Seizure was difficult to control in 6.1% cases. Granulocytopenia (<4000/ cu. mm) was seen in 6 patients, 3 each of the phenytoin and phenobarbital treated patients. Ninety three patients (93.9%) had opportunistic infections, monomicrobial in 77.7% and polymicrobial in 16.2%. The underlying neurological illnesses were tuberculosis (44.4%), cryptococcosis (41.4%), toxoplasmosis (23.2%), HIV encephalitis (3.1%), and others (10.1%). Twenty five patients (25.3%) with seizures died compared to 95/401 patients (23.7%) without seizures.
Conclusion: Approximately, one fifth of HIV infected drug naïve patients with neurological disorders have new onset acute symptomatic seizures, mainly secondary to opportunistic neuroinfections. A fifth of these had seizures as their initial symptom. One fourth died because of underlying illness and presence of seizures did not alter the mortality rate.

INTRODUCTION

Seizures occur among 2% to 20% of all human immunodeficiency virus (HIV) infected individuals and with the increasing incidence of HIV infection, this may be an important cause for acute symptomatic seizures in future.[1] Seizure may often be the presenting symptom. The commonly associated conditions with this disorder are underlying opportunistic infections, systemic illness, drug or alcohol abuse, antiretroviral drug usage, and AIDS encephalopathy.[1] The treatment of these seizures includes administration of antiepileptic drugs (AEDs), specific treatment of the underlying conditions and antiretroviral drugs. The ideal AED used should not affect the cytochrome P450 system of the body, viral replication and should be less protein binding. Risk for AED induced skin rashes and allergic manifestations are also more frequent when used among the seropositive individuals.[2,3] There are few reports from Indian subcontinent on this important topic.[4] We analyzed the frequency, etiology and clinical aspects of new onset seizures in a large cohort of HIV infected individuals presenting with neurological disorders in a tertiary referral institution in south India.

METHODS

A large cohort of HIV seropositive individuals with neurological involvement are being evaluated and regularly followed up at the department of neurology, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, a university teaching hospital and a major referral center in south India. Case records of all the 500 HIV seropositive patients attending the neurological services from 1989 to 2000 were reviewed. The diagnosis of underlying neurological illness supposedly related to HIV seropositive status was confirmed after detailed

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clinical evaluation assisted by appropriate investigations such as neuroimaging, serum and cerebrospinal fluid (CSF) serological and immunological studies for diagnosis of various opportunistic infections, microbiological culture and pathological study of brain tissue when available either by biopsy or autopsy. Serum enzyme-linked immunosorbent assays (ELISA) of 3 different antigens were used as test for detecting HIV-1 and HIV-2 as per national AIDS control programme (NACO) criteria. Granulocytopenia was defined as total white blood cell count of less than 4000/cu mm.

Data related to clinical history about the nature of seizures, its duration, underlying aetiology, the results of various available investigative procedures, treatment received, response to treatment and mortality were obtained from the hospital database. None of the patients were on anti-retroviral therapy in this series.

RESULTS

The demographic data of HIV patients with (n=99) and without (n=401) seizures are shown in Table 1. The majority of them were young males in their most productive period of life. Most of the patients acquired infection by heterosexual contact. They had a short duration of illness, a mean of 23.7 days. A total of 25/99 patients (25.3%) with seizures expired, mainly because of underlying illnesses during the course of illness. There was no statistical difference in the demography and mortality between the groups with and without seizures.

Of the 99 (19.8%) HIV infected patients with new onset acute symptomatic seizures, 20 patients (4.0%) presented with seizure as the initial symptom. This was 20.2% (20/99) of HIV infected patients with new onset seizures. The types of seizures are shown in Table 2. Generalized seizures were the most frequent (62.6%). Status epilepticus was noted in 8 patients (8.1%). The patient with epilepsia partialis continua had HIV infection without opportunistic central nervous system complications.

The diagnosis of underlying illness was determined by the clinical manifestations and laboratory investigations including CSF examinations (n=75), CT brain scan (n=99) and/or MR imaging (n=10) and pathological study of the brain at autopsy (n=12). Opportunistic infections were detected in 93 patients (93.3%); monomicrobial in 77 patients (77.7%) and polymicrobial in 16 patients (16.1%). Non-infective neurological illness of the brain was present in 3 patients (Table 3). A total of 25/99 patients (25.3%) with seizures expired while 95/401 patients (23.7%) without seizures died; mainly because of underlying illnesses later during the course of illness. Thirty two patients (32.3%) were followed for a mean period of 12.3$\pm$3.2 months.

The patients with seizures were evaluated and managed in the emergency services. The commonest AED used were phenytoin (50.5%), phenobarbital (27.3%), a combination of 2 AEDs (14.8%), and 3 AEDs (1.9%) including sodium valproate or carbamazepine. Seizures were poorly controlled in 6 cases. A low white blood cell count of less than 4000/cu. mm was incidentally detected in 6 patients during follow up, 3 each were on phenytoin and phenobarbital.

DISCUSSION

Twenty percent of our cohort of HIV seropositives patients with neurological disorders had new onset acute symptomatic seizures. Dal Pan *et al* reported 15/268 (5.6%) patients of AIDS dementia complex to have seizures.[1] Pascual-sedano *et al* found 17/553 (3%) patients of HIV to have seizures.[5] Chadha *et al* from India reported seizures in their 23/455 (5%) HIV patients.[4] Higher frequency of seizure in the present study could be because all patients in this cohort had neurological illness, predominantly neuro-AIDS with underlying brain lesions, unlike other studies which included HIV seropositive patients with either neurological or non-neurological illnesses. Udgirkar *et al* reported a higher incidence of seizures (75%) in 8 children with HIV encephalopathy.[6] As there is an upsurge in the number of HIV infected cases in India, seizures among HIV infected patients might become an important and common cause for acute symptomatic seizure in the future. Male predominance in this cohort is consistent with the patient demography of the HIV seropositive patients with neurological illnesses admitted to NIMHANS, which was also mainly male.

In our series, seizure was the presenting symptom in 4 % of HIV patients, and in 20.1% of HIV patients with seizures. Sempere *et al*[7] reported that 8.2% among their 98 HIV patients had seizure as the initial manifestation. Finelli *et al*[8] reported 2 female patients with seizures first time in their life during the peri-partum period. Some authors have advocated HIV screening in all adult patients with new onset seizures.[9] This may be cost effective in communities where prevalence of

Table 1: Neurological disorders associated with HIV infection: Patient characteristics

Parameters	with seizures (n=99)	without seizures (n=401)
Age at presentation in years	32.1 +7.5	33.3 + 7.9
Male : Female	11.4 : 1	8.3 : 1
Duration of illness in days	23.7 $\pm$ 52.1	45 $\pm$ 87.4
Duration of seizures in hours	35.5 $\pm$ 59.4	not applicable
Mortality	25/99 (25.3%)	95/401(23.7%)

Table 2: Subtypes of new onset seizures associated with HIV and neurological disorders

Types of seizures	n (%)
Generalized tonic-clonic	62 (62.6)
Partial seizures	37 (37.4)
Status epilepticus	8 (8.1)
Generalized clonic status epilepticus	5
Complex partial status epilepticus	2
Epilepsia partialis continua	1

Some patients had more than one subtypes

Table 3: Acute symptomatic seizures and their underlying illness associated with HIV infection

Underlying illness	n (%)
Central nervous system tuberculosis	44 (44.4)
Cryptococcal meningitis	41 (41.4)
Cerebral toxoplasmosis	23 (23.2)
HIV encephalitis	3 (3.1)
Neurosyphilis	2 (2.1)
Herpes zoster	2 (2.1)
Progressive multifocal leukoencephalopathy	1 (1.1)
AIDS dementia complex	2 (2.1)
Ischemic stroke	2 (1.1)
Non Hodgkin's lymphoma	1 (1.1)

Some patients had more than one illness.

HIV infection is high. We had earlier reported EEG changes in asymptomatic HIV seropositive individuals.[10] Whether EEG changes would be able to predict future development of clinical seizures is uncertain and requires further study.

Similar to the present study, Chadha *et al* [4] reported generalized seizures to be common (65.2%). Pesola *et al* reported only new onset generalized seizures in 26 AIDS patients.[11] Thus, though these symptomatic seizures were due to underlying focal brain lesions, clinically generalized seizures were more common. This may be due to rapid secondary generalization or inaccurate eyewitness account and reporting. Status epilepticus were encountered in 8.8% of patients and generalized convulsive status epilepticus accounted for the majority. Other studies also reported similar finding.[1,3,12,13] One of our patients had epilepsia partialis continua. The seizure was probably from primary HIV infection of the brain as there were no underlying opportunistic infections. Epilepsia partialis continua secondary to HIV encephalitis and progressive multifocal leukoencephalopathy had been previously reported.[14,15]

In the present study, opportunistic infections were the commonest underlying cause for the seizures accounting for 93.9% of patients, mainly from tuberculosis, cryptococcosis and toxoplasmosis affecting the central nervous system. Wong *et al*[16] of USA, reporting 100 patients with seizures, also found opportunistic infections to be the predominant underlying cause. The infections were: herpes simplex encephalitis (46%), toxoplasmosis (28%), and bacterial meningitis (10%). Holtzmann *et al*[17] from USA also reported similar findings, with infections from herpes simplex encephalitis (45.7%), toxoplasmosis (15.7%), bacterial meningitis (10%). Pesola *et al* [11] on the other hand, reported 30.7% of their AIDS patients with seizures to have HIV encephalopathy, 19.2% with toxoplasmosis, 8% from alcohol withdrawal, and another 30.7% to be idiopathic. Modi *et al*[18] in their 60 HIV infected patients with new onset seizures, found 55% with space occupying lesions, 22% had meningitis, and in the remaining no aetiology was evident. Dal Pan *et al*[1] reported that among the drug abusers with HIV infection, administering cocaine was an important cause of acute symptomatic seizures. In the present series, the mode of acquiring HIV infection was predominantly by heterosexual transmission and none were intravenous drug related. Another important difference is that HIV infection in India is primarily due to clade-C subtype. This is unlike the West, where the infection is from clade-B.[19] The difference in microorganism ecology of the local environment may also influence the etiologies of the opportunistic infections.

There was no difference in mortality among HIV patients with (25.3%) or without seizures (23.7%). None of the patients in this cohort received anti-retroviral drugs, as they were not able to afford the same. This might be responsible for increased mortality noted in present series.

Whether granulocytopenia noted in this series occurred secondary to AEDs or due to primary HIV infection is not certain, but none of our patients had systemic opportunistic infections. The overall rate of neutropenia was 1.2 (0.5-2.3)/ 100,000 prescriptions, compared with 0.9 (0.3-1.9) for thrombocytopenia and 0.4 (0.1-1.3) for hemolytic anemia in a study on a cohort of epilepsy patients by Blackburn *et al*.[20] Dal Pan *et al*[1] reported skin rashes and leucopenia with phenytoin and carbamazepine in HIV seropositive patients. However, Chadha *et al*[4] did not find any adverse effects with phenytoin among their 23 cases. Romanelli *et al*[2] opined that, when AEDs are used with antiretroviral therapy, interactions are more frequently seen. CD4 counts and viral load data is not available in this cohort. However the patients in the present series are drug naive with regards to antiretroviral therapy.

In summary, a new onset acute symptomatic seizure was noted in a fifth of all HIV patients (Clade C, drug naïve) with associated neurological involvement in a cohort of patient from south India. This was associated with opportunistic CNS infections in majority. Future study should be directed to survivors with or without antiretroviral drugs regarding long-term seizure recurrence.

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