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Frequency of seizures and epilepsy in neurological HIV-infected patients

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Summary

Background: Infection with the human immunodeficiency virus (HIV) is associated both with infections of the central nervous system and with neurological deficits due to direct effects of the neurotropic virus. Seizures and epilepsy are not rare among HIV-infected patients. We investigated the frequency of acute seizures and epilepsy of patients in different stages of HIV infection. In addition, we compared the characteristics of patients who experienced provoked seizures only with those of patients who developed epilepsy.
Methods: The database of the Department of Neurology, University of Münster, was searched for patients with HIV infection admitted between 1992 and 2004. Their charts were reviewed regarding all available sociodemographic, clinical, neurophysiological, imaging and laboratory data, therapy and outcome. Stage of infection according to the CDC classification and the epileptogenic zone were determined.
Results: Of 831 HIV-infected patients treated in our department, 51 (6.1%) had seizures or epilepsy. Three of the 51 patients (6%) were diagnosed with epilepsy before the onset of the HIV infection. Fourteen patients (27%) only had single or few provoked seizures in the setting of acute cerebral disorders (eight patients), drug withdrawal or sleep withdrawal (two patients), or of unknown cause (four patients). Thirty-four patients (67%) developed epilepsy in the course of their HIV infection. Toxoplasmosis (seven patients), progressive multifocal leukencephalopathy (seven patients) and other acute or subacute cerebral infections (five patients) were the

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most frequent causes of seizures. EEG data of 38 patients were available. EEG showed generalized and diffuse slowing only in 9 patients, regional slowing in 14 patients and regional slowing and epileptiform discharges in 1 patient. Only 14 of the patients had normal EEG. At the last contact, the majority of the patients (46 patients = 90%) were on highly active antiretroviral therapy (HAART). Twenty-seven patients (53%) were on anticonvulsant therapy (gabapentin: 14 patients, carbamazepine: 9 patients, valproate: 2 patients, phenytoin: 1 patient, lamotrigine: 1 patient). Patients with only provoked seizures had no epilepsy risk factors except HIV infection, and were less likely to be infected via intravenous drug abuse.

Conclusions: Seizures are a relevant neurological symptom during the course of HIV infection. Although in some patients seizures only occur provoked by acute disease processes, the majority of patients with new onset seizures eventually develops epilepsy and require anticonvulsant therapy. Intravenous drug abuse and the presence of non-HIV-associated risk factors for epilepsy seem to be associated with the development of chronic seizures in this patient group.

Introduction

Infection with the human immunodeficiency virus (HIV) carries a risk for seizures through opportunistic infections of the central nervous system (CNS). Toxoplasmosis, CNS lymphoma, cryptococcal or tuberculous meningitis, and progressive multifocal leukencephalopathy (PML) are strongly associated with the occurrence of acute or chronic repeated seizures.[1–4] In addition, the HIV is neurotropic and thus may have direct harmful effects on the CNS itself.[5] Moreover, drugs used for treatment of the HIV infection[6] or opportunistic infections,[7] and metabolic abnormalities associated with renal or hepatic failure[8] may predispose for seizures.

Data about the frequency of seizures among HIV-infected patients are limited by the retrospective design and small sample sizes of most studies. New onset seizures were found in 3–17% of the investigated patient group.[1,4,8–11] Since most studies have focussed on new onset seizures, even less is known about the frequency of pre-existing epilepsy in HIV-infected persons. The prevalence of epilepsy in the normal population is age dependent. In the age group 20–40 years, estimated prevalence for epilepsy in the normal population is 20–40/100,000.[12] The few studies documenting all patients with seizures in a defined group of HIV-infected patients found that in 1–4% of the cases the seizures clearly predated the HIV infection.[9,10,4] However, these patients were recruited in hospitals and not in the community where the prevalence of epilepsy among HIV-infected persons may be lower.

In most studies, the majority of patients suffered primarily from generalized seizures with only 25–30% showing focal symptoms.[1,4] Focal seizures were not necessarily associated with focal space-occupying lesions.

Seizures in HIV-infected patients seem to have a high chance of recurrence,[9] therefore, it has been recommended to start anticonvulsant therapy even after the first seizure.[13] Phenytoin and carbamazepine are strong inducers of the hepatic cytochrome p450 system. Since many antiretroviral agents are substrates of this enzyme system, administration of these drugs results in unfavorable pharmacokinetic interactions and thus in failure of antiretroviral therapy.[14] The newer anticonvulsant agents like gabapentin, lamotrigine and levetiracetam do not have most of these disadvantages and are therefore recommended for use in HIV-associated seizures.[13] With our study, we wanted to investigate the characteristics of HIV-infected patients with seizures or epilepsy, and to compare those patients who only had provoked seizures with patients who eventually developed epilepsy, and to document the treatment that had been prescribed.

Methods

The database of the Department of Neurology, University of Münster, was searched for patients with HIV infection treated as in-patients or out-patients between 1992 and 2004. The Department of Neurology is a referral center for HIV-infected patients with neurological symptoms and part of the 'competence network HIV' in Germany. Patients with a history of seizures or with seizures during treatment were identified by searching for the keyword 'seizure/seizures' and 'epilepsy' in the computerized database as well as in the patients' discharge summaries. The charts of all identified patients were reviewed using all available historical, sociodemographic, clinical, neurophysiological, imaging and laboratory data. The diagnosis of seizures or epilepsy was verified, patients with inconclusive data

that did not allow certain diagnosis were excluded. Information about seizure therapy and outcome was gathered. Stage of infection according to the Center of Disease Control (CDC) classification, time of infection and way of infection, the seizure type, the epileptogenic zone and the etiology of epilepsy were determined using all available information. HIV-associated encephalopathy was diagnosed when the appropriate clinical features were present and other causes for encephalopathic symptoms could be excluded.

Statistical analysis was performed with a commercial software package (SPSS 12.0 for windows, SPSS Inc., Chicago, IL, USA). Interval- and ordinal-scaled data were compared using the Mann–Whitney *U*-test for inter-group comparison, nominal-scaled data with the χ^2-test or Fisher's exact test (2×2 tables). Significance level was set at $p < 0.05$ for two-tailed tests.

Results

During the study period, 831 HIV-infected patients were treated as in-patients in our department. Fifty-one of them (6.1%) had seizures or epilepsy and will be described further. Their median age was 37 years, and more than two-third of them were male (Table 1). In three patients (6%), seizure onset clearly predated the HIV infection. Fourteen patients (27%) had single or few seizures only in the setting of acute disease (eight patients), drug withdrawal or sleep withdrawal (two patients), or of unknown cause (four patients). The other 38 patients (67%) eventually developed epilepsy. Thus, the incidence of new onset seizures in our patient cohort was 5.8%. The patients' characteristics are presented in Table 1. The most frequent underlying cerebral diseases were HIV-associated encephalopathy (11 patients), PML (7 patients) and toxoplasmosis (7 patients).

Eight patients (17%) had simple partial seizures only, three patients (6%) had complex partial seizures only. Partial seizures with secondary generalization were seen at least once in 14 patients (27%). In 26 patients (51%), the seizure was generalized without definite partial component. Electroencephalography (EEG) data was available for 38 patients. The other 13 patients had undergone EEG at other institutions. Fourteen patients (27%) had a normal EEG, in nine patients (17%) only generalized slowing was detected. The EEG of 3 patients (6%) showed generalized as well as regional slowing, 11 patients (22%) had only regional slowing, 1 patient showed additional regional epileptiform discharges. Cerebral imaging data computed tomography (CT) and magnetic resonance imaging (MRI) was available for 44 patients. The majority of them had a cortical lesion, only 10 had no visible lesion in the CT or MRI scan (see Table 2). Out of the 37 patients with (pre-existing or new onset) epilepsy, the epileptogenic zone could be localized to a certain brain region in only 6 patients. The diagnosis of non-localizable focal epilepsy was made in 11 patients. In 20 patients, the epilepsy could not be further classified.

The patients with new onset epilepsy did not differ from the patients who only had single or few provoked seizures regarding age and gender distribution, CDC stage at time of first seizure, CD4+ lymphocyte count, highly active antiretroviral therapy (HAART) at time of first seizure, EEG or imaging abnormalities or seizure classification (see Table 3). No patient with only provoked

Table 1 Demographic and clinical characteristics of all HIV-infected patients with seizures

	HIV-infected patients with seizures or epilepsy ($n = 51$)
Age in years (median, 25/75 percentile)	37, 31/41
Sex (female/male)	13/38
CDC stage at time of first seizure	
A	0
B	2
C	29
Epilepsy onset before infection	3
Not classifiable	17
Way of infection	
Sexual contact	13
i.v. drug abuse	10
Blood/transplantation	6
Other	1
Unknown	21
CD4+ lymphocytes at time of first seizure	
>500	6
200–500	9
<200	18
Unknown	18
HAART at time of first seizure	
Yes	37
No	4
Not applicable	3
Unknown	7
CNS complications at time of first seizure	
HIV-associated encephalopathy	11
Toxoplasmosis	7
PML	7
CNS-tuberculosis	1
None/unknown/not applicable	25

Table 2 Classification and seizure-related data in all HIV-infected patients with seizures

	HIV-infected patients with seizures or epilepsy (n = 51)
Epilepsy classification	
Epilepsy (unclassifiable)	20
Focal epilepsy (non-localizable)	11
Focal epilepsy (extratemporal)	6
Single seizure	14
Seizure classification	
Simple partial seizure	8
Complex partial seizure	3
Partial seizure with secondary generalization	14
Generalized seizure (unclassifiable)	26
Risk factor for epilepsy besides HIV-associated risks	
No risk factor/unknown	42
Head trauma	2
Positive family history	1
Brain surgery	1
EEG	
Alcohol-/drug abuse	5
Normal	14
Generalized slowing only	9
Focal slowing only	11
Focal and generalized slowing	3
Focal slowing and epileptiform discharges	1
No original EEG data available	13
Imaging (MRI, CT scan)	
No lesion	20
Cortical lesion	21
Subcortical lesion only	3
No imaging data available	7

seizures was infected via intravenous drug abuse ($p < 0.05$) or had other than HIV-associated risk factors for epilepsy ($p = 0.09$), and only one of them had HIV-associated encephalopathy as the only CNS manifestation of HIV infection.

At the time of last contact to our center, 29 of the 51 patients (57%) were on anticonvulsant therapy (see Table 4). The most frequently used substance was gabapentin (14 patients) followed by carbamazepine (9 patients).

Discussion

Seizures and epilepsy are a relevant neurological symptom or sequela in HIV-infected patients that frequently occur in acute disease setting. In most patients, cerebral imaging shows cortical lesions. However, not all patients who develop acute seizures eventually develop epilepsy. Common epilepsy risk factors and intravenous drug abuse were associated with recurrent chronic seizures. Although the majority of the patients were treated with anticonvulsants, a significant number did not receive the best-suited substances.

The prevalence of seizures or epilepsy in our study cohort is similar to the more recently published reports. Pascual-Sedano and coworkers reported 3% patients with new onset seizures among HIV-infected patients of an internal medicine referral center in Spain.[1] A study performed in a tertiary care hospital in India documented new onset seizures in 8% of all HIV-infected patients.[9] On the other hand, a study reporting data from the mid-1980s found a significantly higher incidence of 11%,[4] another early study of even 17%.[11] Most likely, the cohorts of earlier series were suffering from more advanced stages of the disease due to the more restricted therapeutic means at that time.

Intracranial cortical lesions were found in more than 40% of our patients. This proportion is slightly higher than reported by Wong et al.[4] and Dore et al.,[10] but approximately similar to that of Van Paesschen et al.[8] Cerebral toxoplasmosis accounted for the majority of identifiable lesion etiologies. This is in accordance with most other studies who reported on lesional seizure etiology.[1,4,8–10,15,16] The prevalence of toxoplasmosis in our as well as other studies is relatively high. This is most likely due to the change in antiretroviral and supporting antiinfective therapy over the last years.[17] Interestingly, PML was found equally frequent in our patients. Other studies found much less PML among their seizure patients.[1,9] Since these studies have been performed in medical departments, PML might have been underdiagnosed, and recruitment bias may play an additional role.

The pathomechanisms causing seizures in PML as a white matter disease remain to be elucidated. Pathological studies have shown that demyelination takes place not only in white matter, but also both in cortical areas and the basal ganglia.[18] Lesions adjacent to the cortex seem to be associated with the occurrence of seizures in patients with PML.[19] Neurons affected by demyelination may alter their electrophysiological properties and become hyperexcitable, thus increasing the likelihood of seizures.[20] However, these hypotheses still need to be verified.

HIV related encephalopathy was found in a relatively large proportion of our patients. Similar results were reported by Pesola and Westfal.[21] and Holtzman et al.[16] from western industrialized countries, whereas two reports from India and South Africa found only few patients with this symptom

Table 3 Comparison of the characteristics in acute seizures vs. epilepsy with onset after infection

	HIV-infected patients with provoked seizures ($n = 14$)	HIV-infected patients with epilepsy ($n = 34$)	Significance
Age in years (median, 25/75 percentile)	31, 28.5/50	37, 32/41	n.s.
Sex (female/male)	4/10	8/26	n.s.
CDC stage at time of first seizure			
A	0	0	n.s.
B	0	2	
C	11	18	
Not classifiable	3	14	
CDC at last contact			
A	0	4	n.s.
B	0	3	
C	12	23	
Not classifiable	2	4	
Way of infection			
Sexual contact	6	6	$p < 0.05$ (i.v.-drug abuse vs. no i.v. -drug abuse)
i.v. drug abuse	0	10	
Blood/transplantation	2	3	
Other	0	1	
Unknown	6	14	
CD4+ lymphocytes			
>500	0	6	n.s.
200-500	2	7	
<200	7	11	
Unknown	5	10	
HAART at time of first seizure			
Yes	9	26	n.s.
No	2	2	
Not applicable/unknown	3	6	
MRI lesion			
No lesion	3	17	n.s.
Only subcortical	1	2	
Cortical lesion	8	11	
No imaging data available	2	4	
Etiology of cerebral lesions			
Toxoplasmosis	5	2	n.s.
PML	3	3	
HIV-encephalopathy	1	10	
Unknown/not applicable	5	19	
EEG			
Normal	4	10	n.s.
Generalized slowing only	5	4	
Focal slowing, no ED	3	8	
ED	0	1	
No EEG data available	2	11	
Seizure classification			
Simple partial seizure	1	6	n.s.
Complex partial seizure	2	1	
Partial seizure with secondary generalization	4	9	
Generalized seizure (unclassifiable)	7	18	
Risk factor for epilepsy besides HIV-associated risks			
No/unknown	14	27	n.s. ($p = 0.09$)
Risk factor present	0	7	

Table 4 Anticonvulsant therapy

	HIV-infected patients with seizures and epilepsy (n = 51)
Anticonvulsant therapy at time of last contact	
Yes	29
No	22
AED	
Gabapentin	14
Valproate	2
Carbamazepine	9
Lamotrigine	1
Clonazepam	2
Phenytoin	1

complex. HIV related encephalopathy usually occurs in later stages of the infection, and patients in non-industrialized countries may not live long enough to develop this condition.

Although most patient had unspecific EEG abnormalities, epileptiform discharges were seen only in one patient. This supports the notion mentioned in earlier studies[9,16,4] that EEG is relatively insensitive in the setting of seizures associated with HIV infection.

A clear focal semiology was seen in almost 50% of our patients. Most other reports found focal semiology in 15—30% of the cases,[15,1,8,4] although the proportion of identifiable focal brain lesions was roughly similar. This discrepancy may be due to recruitment bias. However, in our study, all chart documents were reviewed by a trained epileptologist who might have been more aware of evidence that proves partial seizure onset. Anyway, generalized seizures predominate in HIV patients.

Patients with provoked seizures differed from patients who developed epilepsy only in some aspects. Intravenous drug abuse was found only in patients who developed epilepsy. This could be explained by a higher proportion of opportunistic, drug-related comorbidity in those patients, which may predispose to the development of epilepsy. Acknowledged risk factors for epilepsy in otherwise healthy persons such as previous head trauma or positive family history of epilepsy are of course associated with the development of epilepsy also in HIV-infected patients.

Anticonvulsant therapy was initiated in nearly two third of our patients. Almost half of them were on gabapentin, an anticonvulsant drug that is no substrate or inducer of the cytochrome p450 system, is not relevantly protein-bound and exclusively renally eliminated, and therefore has essentially no interactions with other drugs.[22] In addition to its anticonvulsant properties, it is anxiolytic and has analgesic effects in neuropathic pain.[23] Therefore, it is recommended for use in HIV-infected patients.[13,24] However, its effect on seizures in this patient group has never been investigated in controlled trials. Pregabalin and Levetiracetam are new anticonvulsant agents with equally favorable pharmacokinetics. Carbamazepine is effective in focal epilepsy, but — as inducer as well as substrate of the cytochrome p450 system — potentially has unfavorable pharmacokinetic properties, particularly when used in combination with HAART. On the one hand, HAART failure due to carbamazepine interaction has been reported.[14] On the other hand, carbamazepine toxicity may be increased by antiretroviral agents.[25,26] Two of eight HIV-infected patients treated with carbamazepine had to switch therapy because of side effects.[15] Phenytoin has the same unfavorable pharmacokinetic properties. In patients with HIV-associated seizures, 14% of the patients treated with phenytoin had to discontinue due to side effects.[16] Other studies[1,9] did not find serious side effects from phenytoin treatment but had only limited follow-up. Thus, a relevant number of patients were treated with agents with high potential of complications although more favorable drugs are available. In most cases, initial anticonvulsant treatment was initiated by a general practicioner or internal medicine specialist. These clinicians may not be aware of the high potential for adverse effects of these drugs among HIV-infected patients. In addition, a relevant number of cases were treated before gabapentin or one of the other favorable agents became available.

Valproate acid is used in focal as well as generalized epilepsy. It was administered in two of our patients. Until recently, its use has been discouraged because of in vitro data suggesting a drug-induced increase of viral replication.[27] However, it has been discovered that valproate inhibits a chromatin remodeling enzyme responsible for maintenance of latent HIV infection in CD4+ T-cells.[28] A small pilot study could show that three of the four patients had significant decrease of latent HIV infection in resting T-cells under valproate therapy in combination with HAART.[29] If these preliminary results can be reproduced in larger studies, valproate could become an anticonvulsant of first choice in HIV-infected patients.

Our study has several limitations. As a retrospective chart review, it suffers from the typical disadvantages of this kind of studies like missing information and non-standardized way of documentation. Since the patients were identified by being treated in a neurological department, the incidence of seizures is probably overestimated and cannot be easily compared to that of patients

recruited from emergency wards or departments of internal medicine.

We were not able to follow the patients over a significant time period, therefore our study does not have relevant outcome data. To further enhance our knowledge about adequate diagnosis and therapy of HIV-associated seizures, prospective studies focussing on therapy and outcome are needed.

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