Cerebral Infarction in Adult AIDS Patients
Observations From the Edinburgh HIV Autopsy Cohort

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Background and Purpose—Autopsy series of patients with AIDS have found a 4% to 29% prevalence of cerebral infarction. Little is known of the prevalence of cerebral infarction when not associated with non-HIV central nervous system (CNS) infection, lymphoma, or cardioembolic sources. Clinical correlation has seldom been available. We describe the pathological and clinical features of patients from the Edinburgh HIV Cohort Study found to have had cerebral infarcts without evidence of non-HIV CNS infection, CNS lymphoma, or cardioembolic sources at autopsy.

Methods—From 183 autopsy cases, 26 without evidence of opportunistic cerebral infection or lymphoma were selected. These 26 cases went through a second selection process in which the presence of cerebral infarction, in the absence of the conditions mentioned, was verified. Histology and clinical records for the remaining patients were reviewed.

Results—Ten (5.5%) cases fulfilled the inclusion criteria and demonstrated similar hypoxic-ischemic lesions. Small-vessel thickening was seen in all cases, and perivascular space dilatation, rarefaction, and pigment deposition, with vessel wall mineralization and perivascular inflammatory cell infiltrates, were seen in some cases. Vasculitis was not found. One patient had had a transient ischemic attack, and no patient had had a stroke.

Conclusions—Cerebral infarcts in HIV-infected patients are not common in the absence of cerebral non-HIV infection, lymphoma, or embolic sources. We found an HIV-associated vasculopathy with similar features in all risk groups. In AIDS patients presenting with stroke or transient ischemic attack, potentially treatable causes, such as cerebral coinfection or tumor, should be sought. (Stroke. 2000;31:2117-2126.)

Key Words: acquired immunodeficiency syndrome ▪ cerebral infarction ▪ pathology

Human immunodeficiency virus (HIV) invades the central nervous system (CNS) early.1,2 Any neurological manifestations may result from opportunistic infections, neoplasia, the immunological and metabolic response to HIV, iatrogenic causes, or corisk factors (eg, injection drug use), or they may be related directly to HIV itself.2,3 Indeed, postmortem neuropathological series reveal that CNS abnormalities occur in up to 90% of patients with advanced AIDS.2,4,5 In a clinical series, up to 70% of HIV-infected patients eventually develop neurological manifestations.6 Cerebral infarction in an HIV-infected patient may, at least in theory, result from any one of the causes listed in Table 1,7,8 but a stroke-like clinical presentation is unusual, occurring in ≈1%, with cerebral hemorrhage constituting 32% of the cases.9 On the other hand, autopsy series in adults have found a much higher prevalence of cerebral infarction (4% to 29%).9,12,16,28,43–46 but the majority of studies do not distinguish between cerebral infarcts associated with, and therefore potentially caused by, non-HIV CNS infection, CNS lymphoma, or cardioembolic sources and cerebral infarcts occurring in the absence of these conditions.9,11,12,14,44–50 Furthermore, patient risk factors for cerebral infarction, including drug misuse, are seldom described,17,22,45,47,48,50 and no clinical correlation has been available or very little is known about the patient’s clinical course before death.11,12,14,16,17,22,28,44–47,49–51 Therefore, it is far from clear whether HIV itself causes cerebral infarction and (if it does) whether the patients experience a stroke, transient ischemic attack (TIA), or other neurological symptoms that are indicative of neurovascular disease before death.8

The principal aims of the present study were (1) to establish whether cerebral infarcts occurred in the Edinburgh HIV autopsy cohort, in the absence of causes other than possibly HIV infection itself; (2) to describe the pathological characteristics of any cerebrovascular lesions; and (3) to retrospectively correlate the autopsy findings with relevant clinical features (in particular, symptoms and signs that would have been in keeping with neurovascular disease) and vascular risk factors.

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Subjects and Methods

Study Design and Population

We performed an observational pathology study of patients from the Edinburgh HIV Cohort Study, with clinical correlation. The Edinburgh HIV Cohort at the time of the study consisted of 1372 HIV-infected patients (28% homosexual patients, 48% intravenous drug users, 4% patients with blood product–related HIV, 17% heterosexual patients, and 3% patients with other or unknown risk factors for HIV infection), all prospectively followed up, of whom 535 had died. One hundred eighty-three (34%) of the patients (25% homosexual patients, 65% intravenous drug users, 5% heterosexual patients, and 5% other) had a full neuropathological post mortem. Forty-four of the 183 cases in the autopsy cohort were pre-AIDS cases; ie, they had not developed AIDS. Autopsies were requested on all patients, and results were not biased by dementia or other underlying clinical illness. There is virtually no overlap between the 2 major “at-risk” groups, with only 1 homosexual patient having been an injection drug user.

Methods

After formalin fixation, the brain was coronally sliced and blocked according to an established protocol to include all areas of the cerebrum, brain stem, and cerebellum. Sections of the frontal lobe (in all cases) and additional blocks including temporal and occipital cortex and basal ganglia (in most cases) were stained immunohistochemically by use of an antibody to HIV p24 core protein (Du Pont; diluted 1:200 and with microwave pretreatment, immersed in 0.01 mol/L citric acid for 3 minutes).

Case selection was performed in 2 stages. First, all 183 autopsy reports were screened, and 157 cases were not selected for further detailed review if (1) the report clearly documented normal brain tissue; (2) an opportunistic cerebral infection was detected, such as toxoplasmosis, fungal infection, cytomegalovirus, varicella-zoster virus, herpes simplex virus, or mycobacterium; or (3) cerebral lymphoma was found. Cases with criteria 2 and 3 above were excluded because these conditions are all accepted causes of cerebral infarction in HIV-infected patients. Second, the CNS histology in the remaining 26 cases then went through another selection process, in which we checked that cases indeed had pathologically verified cerebral infarcts without pathological evidence of non-HIV cerebral infection, lymphoma, hemorrhage, traumatic injury, or potential sources of cerebral emboli. Sixteen cases were excluded for the following reasons (number of cases in parentheses): no infarcts or ischemic lesions seen on CNS pathology review (n = 9), primary intracerebral hemorrhage (n = 2), non-HIV-related cerebral infarction (n = 4), cerebral lymphoma (n = 3), and cerebral hemorrhage (n = 1).

Methods

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Table 1. Potential Causes of Cerebral Infarction in HIV-Infected Patients

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<tr>
<th>General</th>
<th>Specific</th>
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<tr>
<td>Cardiac</td>
<td>Nonbacterial thrombotic endocarditis, infective endocarditis (injection drug use), HIV myocarditis with thrombus</td>
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<tr>
<td>Vascular (vasculitis/vasculopathy)</td>
<td>Cytomegalovirus, varicella-zoster virus, herpes simplex virus, mycobacterium tuberculosis, syphilis, cryptococcosis, mucormycosis, aspergillosis, candida albicans, candida tropicalis, coccidioidomycosis, toxoplasmosis, trypanosomiasis, HIV vasculopathy, or vasculitis (eosinophilic, necrotizing, granulomatous)</td>
</tr>
<tr>
<td>Abnormalities of coagulation</td>
<td>Protein S deficiency, antiphospholipid antibodies, disseminated intravascular coagulation</td>
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<tr>
<td>Cerebral opportunistic infection/neoplasms</td>
<td>Toxoplasmosis, lymphoma</td>
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<tr>
<td>Injection drug use</td>
<td>Cocaine, heroin</td>
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<tr>
<td>Other associations</td>
<td>Hepatitis B antigenemia</td>
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Table 2. Summary of Number and Distribution of Cerebral Infarcts, Small Cerebral Vessel Lesions, and HIV Pathology

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<th>Case</th>
<th>Risk Group</th>
<th>CX</th>
<th>BG</th>
<th>Th</th>
<th>BrS</th>
<th>CBM</th>
<th>WM</th>
<th>Total No. of Infarcts</th>
<th>Hyaline Thickening</th>
<th>Perivascular Space</th>
<th>Vessel Mineralization</th>
<th>Perivascular Pigment</th>
<th>Perivascular Lymphocytes and Macrophages</th>
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<td>1 H</td>
<td>1 0 0 0 0 0 0 0 1 Mild Mild + + -</td>
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* H indicates homosexual; DU, drug user; Hem, hemophiliac; CX, cortex; BG, basal ganglia; Th, thalamus; BrS, brain stem; CBM, cerebellum; WM, white matter; MNGC, multinucleate giant cell; IHC, immunohistochemistry; PCR, polymerase chain reaction; GM, grey matter; M/S, moderate/severe; +, present; - , absent; and ND, not determined.

** Proviral load/µg DNA in frontal lobe.

† In case 6, PCR was not performed separately in GM and WM.
viral encephalitis (n=1), basal meningitis (n=1), cerebral abscess (n=1), bacterial endocarditis with vegetations (n=1), and extensive head trauma (n=1). All histology on the remaining 10 cases was reviewed in detail, with the site and number of infarcts, their morphological features, any associated vessel abnormalities, and evidence of HIV encephalitis documented.

HIV-1 proviral load was determined in fresh, frozen, frontal lobe tissue from 9 of the 10 cases by nested polymerase chain reaction with the use of conserved primers from the pol region, followed by competitive polymerase chain reaction with the use of templates constructed from pol sequences. In 8 cases, this was performed separately on gray and white matter.

Clinical Review
For the 10 selected cases, all hospital and clinical records were reviewed, including general practitioner (family doctor) letters, clinical notes, inpatient notes, nursing notes, and laboratory and radiology reports. The following clinical details were elicited: patient demographic details, length of clinical follow up, risk factors for HIV, intravenous and other drug misuse at the time of death, prescribed medications, disease stage, vascular risk factors including family history of vascular disease, documented diagnosis of ischemic heart disease, cardiac failure or arrhythmia, peripheral vascular disease, hypertension (defined as requiring treatment or based on a clinical diagnosis made during the final admission), diabetes mellitus (based on treatment or diagnosis documented in the clinical record), and hypercholesterolemia (requiring treatment, dietary modification, or documented in the clinical record). Furthermore, any history of pulmonary embolism, deep venous thrombosis, emboli to any site, or significant hypoxia (PaO₂ <50 mm Hg on arterial blood gas measurement) during the last admission was noted. Detail was then sought on any history of neurological problem at any time, including the nature of the onset, history and examination findings, investigations performed, neurological and psychiatric opinion sought, and relation to the onset of a diagnosis of AIDS dementia complex. Records of investigations were reviewed with emphasis on inflammatory markers (erythrocyte sedimentation rate and C-reactive protein), tests of blood coagulation, cholesterol levels, serology for any of the infective conditions listed in Table 1, and chest x-ray reports. ECGs were reviewed, and all neuroradiological reports performed at any time were reviewed in the context of any documented neurological signs and symptoms.

Results
Ten cases out of 183 autopsies (5.5%) fulfilled all the inclusion criteria. Relevant pathological findings and frontal lobe viral load estimates are shown in Table 2.

Gray Matter Lesions
The histological appearance of gray matter lesions (Figure 1) was similar in all but one case (case 1). Typical lesions were multiple and small, composed of palely stained and rarefied brain tissue, with loss of neurons and variable numbers of associated reactive astrocytes and microglial cells. Some lesions were noncavitated, whereas others were completely cavitated, with other lesions exhibiting a spectrum of degrees of cavitation between these 2 extremes. Foamy macrophages were seen in small numbers in a proportion of lesions, depending on the histological age of the lesion and the degree of tissue damage. Thus, macrophages were most conspicuous in subacute or resolving lesions with extensive tissue necrosis and cavitation. The histological age of lesions varied from old (at least 3 months) to acute (≤1 day); this variation was apparent both between and within cases. Thus, in some cases, lesions were of a similar histological age; in some, the appearances suggested ≥2 “crops” of lesions; and in others, a wide range of lesion ages was seen. The number of lesions per brain varied, with a clear predilection for neocortex and basal ganglia. Neocortical lesions were relatively evenly distributed throughout all 4 lobes. In 2 cases, there was an apparent clustering of lesions in superficial cortical layers 2 and 3 (cases 4 and 9), whereas in others, there was an apparent preference for deeper cortical layers (cases 3 and 7). Less commonly, lesions were identified in the thalamus (4 cases), cerebellum (2 cases), and brain stem (1 case). In case 1, the appearances were somewhat different, in that there was a small, old, solitary, linear, cavitated infarct in the parietal cortex.

In no case was there evidence of global, hemorrhagic, or regional vessel territory infarction, wedge-shaped cortical infarction, or intracerebral or subarachnoid hemorrhage. In 3 cases (cases 1, 6, and 10), focal lesions were superimposed on recent, more widespread, hypoxic-ischemic changes, which were interpreted as being due to agonal global cerebral circulatory insufficiency. These were most severe in case 6, in which a dilated cardiomyopathy, congestive cardiac failure, and hypoperfusion were dominant clinical features latterly.

White Matter Lesions
Generalized white matter rarefaction and gliosis with U-fiber sparing was a conspicuous feature in case 8, whereas white matter pallor and edema were seen in case 6 as a manifestation of agonal hypoperfusion. All other cases exhibited a mild to moderate degree of focal white matter rarefaction. There was a single focal white matter infarct in case 10.

Vessel Pathology
Leptomeningeal vessels and main arteries on the circle of Willis showed either no atherosclerosis (8 cases) or mild intimal thickening only (cases 1 and 10). Penetrating intracerebral vessels showed a mild to moderate degree of...
concentric hyaline thickening in 9 of the 10 cases; thickening was most severe in case 5. This was patchily distributed: in 3 cases, it was most conspicuous in the basal ganglia (cases 1, 4, and 9); in 2 cases, it was most conspicuous in the deep white matter (cases 3 and 8); and in 4 cases, it appeared evenly distributed in the cortex, white matter, and deep gray structures (cases 2, 5, 6, and 7). The cerebellum in all cases was relatively spared, and in case 10, there was no significant small-vessel thickening. These relatively mild structural vessel wall changes were accompanied by variable degrees of perivascular space dilatation and parenchymal rarefaction, the severity of which paralleled the severity and distribution of small-vessel thickening. Similarly, small perivascular deposits of pigment were a feature in all cases; their presence was again correlated with a small-vessel thickening and perivascular space dilatation and rarefaction. Microvessel mineralization was observed in 4 cases (cases 1, 6, 7, and 9), particularly in the basal ganglia, with 3 of these 4 patients being drug users. Small numbers of perivascular inflammatory cells, both lymphocytes and macrophages, were present in 5 cases, with 4 of them being drug users. Representative vessel pathology is shown in Figure 2.

In no case was there evidence of vasculitis. Small-vessel occlusion was not observed, with the exception of one possible intravascular thrombus in a small penetrating artery in the basal ganglia of case 2 and in a single neocortical penetrating artery in case 5. Fibrinoid necrosis of occasional neocortical and basal ganglia microvessels was a feature only in case 6; this brain was unusual in that it showed severe agonal global hypoxic-ischemic damage.

Other Brain Pathology
By definition, no brain harbored pathology due to trauma, tumor, or opportunistic infection. Multinucleate giant cells were identified in the brains of 1 homosexual patient, 4 drug users, and the sole hemophiliac patient. In these 6 cases, HIV was identified by use of p24 immunohistochemistry, thus fulfilling the criteria for the histological diagnosis of HIV encephalitis. Other features included focal leptomeningeal thickening and varying degrees of cerebral atrophy, which were present in all cases.

Clinical Features
Patient characteristics are summarized in Table 3. In case 10, the only hemophiliac patient, despite a detailed general practitioner’s summary of the past medical history, hospital/clinic follow-up notes were available for only 2 weeks before death, whereas for the remaining 9 cases, lengthy follow-up (20 to 224 months, mean 75 months) was available. Vascular risk factors were not common for the group as a whole (Table 3). Cardiac disease was present in only 1 patient (case 6), in whom there was no evidence of intracardiac thrombus or vegetation at post mortem. Despite 5 patients having been previous injection drug users, only 2 (cases 6 and 8) were misusing drugs at the time of death. One patient (case 6) had been using oral dihydrocodeine and diazepam, and another (case 8) had been using injection as well as oral drugs (dihydrocodeine, temazepam, diazepam, and methadone). None of the 10 patients had used heroin or cocaine during the 6 months before death. All patients died before the introduction of protease inhibitors into clinical practice in Edinburgh, and anti-retroviral medication was limited to zidovudine and didanosine, although only 2 patients were on anti-retroviral medication at the time of death (cases 1 and 7). Patients were on numerous prescribed medications in the months before

Figure 1. Photomicrographs illustrating the typical, small, predominantly gray matter, hypoxic/ischemic brain lesions. A, Small well-circumscribed basal ganglia infarct (case 2). The bulk of the lesion is composed of necrotic tissue debris and macrophages, surrounded by a thin rim of edema with scattered reactive astrocytes. Had the patient survived, this lesion would have evolved into a classic cavitated (type Ia) lacunar infarct. Original magnification 95 (hematoxylin and eosin). B, Small area of cortical rarefaction and neuronal loss, of presumed hypoxic/ischemic pathogenesis (case 8). Original magnification 190 (hematoxylin and eosin). C, Detail of small thalamic rarefied lesion (case 5) similar to that illustrated in panel B. The tissue is rarefied, gliotic, and devoid of neurons but does not show frank caviation. Such lesions have been termed incomplete (type Ib) lacunar infarcts. Original magnification 380 (hematoxylin and eosin).
death, but none of these have been associated with cerebral infarction or vasculopathy. All patients had advanced AIDS (Table 3). Two patients had positive syphilis serology (although neither had evidence of vasculitis or meningitis at autopsy), and 7 had positive cytomegalovirus serology, although only 1 patient had circulating IgM antibodies. Hepatitis B or C serology was positive in 7 patients, and low platelet counts were present in 5, but none had histological evidence of intravascular thrombi, hemorrhage, or other tissue changes in keeping with cryoglobulinemia or disseminated intravascular coagulation. A full coagulation profile, including proteins C and S, was available for 1 patient (case 4) only. Plasma fibrinogen was raised in 1 patient (case 9) but was measured only in 5. Cholesterol levels were not available for any of the patients. No obvious source of emboli was found at post mortem in any patient.

Five of the 10 patients had no neurovascular symptoms or signs. In the remaining 5 patients (Table 4), a clinically evident stroke did not occur, and a diagnosis of TIA was made in only 1 patient (case 4). One other patient (case 9) had radiological evidence of basal ganglia infarction but no clinical stroke syndrome. Cognitive changes were noted in 3 patients (cases 6, 8, and 9), and diagnoses of AIDS dementia complex were made 2, 1, and 4 years before death, respectively.

Discussion

We found histopathological evidence of cerebral infarction in 1 in 20 of a large autopsy series of adult HIV cases (7% if one considers only AIDS patients), after patients with cerebral opportunistic infections, lymphoma, non-HIV infections, or sources of cerebral emboli (all potential causes of cerebral infarction) had been excluded. They all (drug users, homosexuals not using drugs, and 1 hemophiliac patient) had evidence of a nonvasculitic vasculopathy with the same histopathologic features. The presence of the vasculopathy and the extent of cerebral infarction were not associated with viral load. Despite these pathological findings, only 1 patient had had a TIA clinically, and no patient had had a clinically evident stroke. All patients with evidence of cerebral infarction had AIDS and were thus severely immunocompromised.

Reviews of AIDS neuropathology have documented cerebral infarction in 4% to 29% of HIV-infected patients,9,12,16,17,28,44–46 but few studies have assessed how many patients had cerebral infarction in the absence of potential causes, such as cerebral opportunistic infections, lymphoma, or emboli from nonbacterial infective endocarditis.9,23 Some studies, however, have described their histopathologic findings, patient characteristics, and selection criteria in sufficient detail to enable us to work out the proportion of their patients with “isolated” cerebral infarcts and would have fulfilled (as far as we can assess) our selection criteria.16,28,43,51 The combined total of the 4 studies51 (22 of 356 patients fulfilling our selection criteria) gives a proportion of HIV-associated cerebral infarct cases (6%) that closely approximates our own. Variations in individual studies may reflect population differences, variation in patient selection for autopsy, or the small number of cases.

The vascular lesions in all our 10 cases were characterized by hyaline small-vessel thickening, perivascular space dilatation, rarefaction, and pigment deposition, with vessel wall mineralization and perivascular inflammatory cell infiltrates also seen in some cases. There were only occasional intravascular thrombi. Such changes are similar to those described by Mizusawa et al.,28 although in their study opportunistic cerebral infection was a feature in 9 of 24 brains. Similar
Several of the neuropathological features we describe are consistent with the effects of focal or diffuse blood-brain barrier breakdown, such as hyaline vessel wall thickening, perivascular space dilatation, rarefaction, and pigment deposition. Damage to the blood-brain barrier in HIV brains with leakage of serum protein has been reported, usually as a chronic diffuse phenomenon but also as a fatal, acute, relapsing variant.64 These vessel features are also commonly seen in aging non-HIV brains (cerebral arteriolosclerosis), exacerbated principally by hypertension and diabetes mellitus. However, none of the patients in this series were elderly, hypertensive, or diabetic.

Although small-vessel pathology similar to what we describe may be seen in HIV-negative drug-abuser brains (authors’ unpublished data, 1999), the fact that no vascular lesion was seen exclusively in any one HIV risk group suggests that in this series the changes are more likely a consequence of HIV infection itself. It has been claimed that HIV infects vascular endothelial cells, although this is a disputed. Indeed, infection of endothelial cells with consequent blood-brain barrier breakdown has been advanced as at least a theoretically possible mechanism of HIV entry into the CNS. More specifically, HIV infection of vessel walls has been linked to focal blood-brain barrier breakdown and to vessel mineralization. Similar, though not identical, vascular changes have been found in HIV-infected patients in the pre-AIDS stage; these changes are possibly the result of a lymphocyte T-cell reaction during early infection with HIV. In our series, neither the presence and distribution of HIV encephalitis nor the viral load was correlated with the number or distribution of the cerebral infarcts, although the small number of cases makes this correlation uncertain.

Altered vasoreactivity, alone or in combination with any of the above-mentioned factors, may, at least in theory, have contributed to the development of microinfarcts. Disturbed vasoreactivity in patients with HIV has recently been reported. Temporary vasospasm was one of the possible mechanisms involved in a recent study describing incomplete lacunar infarcts in non-HIV brains; incomplete lacunar

**TABLE 3. Patient Details**

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<tr>
<th>Patient No.</th>
<th>Age at death, y</th>
<th>Sex</th>
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<th>Risk Factors for Cerebral Infarction</th>
<th>Duration Known HIV Positivity/ AIDs, mo</th>
<th>Disease Stage* (CD4 Count)†</th>
<th>Stroke/TIA Symptoms</th>
<th>Laboratory Data‡</th>
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<td>H</td>
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<td>DU</td>
<td>CS, family history</td>
<td>58/18</td>
<td>C3 (38)</td>
<td>–</td>
<td>Platelet count 34×10^9/L, HBV core and surface antigen positive, CMV IgG and IgM positive</td>
</tr>
<tr>
<td>6</td>
<td>33</td>
<td>M</td>
<td>DU</td>
<td>CS, congestive heart failure</td>
<td>63/14</td>
<td>C3 (31)</td>
<td>–</td>
<td>HCV positive, VZG IgG positive</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
<td>M</td>
<td>DU</td>
<td>CS</td>
<td>93/19</td>
<td>C3 (40)</td>
<td>–</td>
<td>Platelet count 74×10^9/L, HCV positive, CMV IgG positive</td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>F</td>
<td>DU</td>
<td>CS, alcohol</td>
<td>105/6</td>
<td>C3 (23)</td>
<td>–</td>
<td>HBV core antibody positive, HCV positive, CMV IgG positive</td>
</tr>
<tr>
<td>9</td>
<td>34</td>
<td>M</td>
<td>DU</td>
<td>CS</td>
<td>114/24</td>
<td>C3 (8)</td>
<td>+?</td>
<td>Platelet count 76×10^9/L, CMV IgG positive, plasma fibrinogen elevated (5.3 g/L)</td>
</tr>
<tr>
<td>10</td>
<td>22</td>
<td>M</td>
<td>Hem</td>
<td>CS</td>
<td>122/36</td>
<td>C3 (0)</td>
<td>–</td>
<td>Platelet count 70×10^9/L, HCV positive</td>
</tr>
</tbody>
</table>

CS indicates cigarette smoking; alcohol, alcohol excess; VZV, varicella-zoster virus; HBV, hepatitis B virus, CMV, cytomegalovirus; HCV, hepatitis C virus; NA, not available; +, present; and -, not present.

*1993 classification by Centers for Disease Control and Prevention.
†At time of death.
‡Results are listed if available and abnormal: full blood count, international normalized ratio, partial thromboplastin time, plasma fibrinogen levels (all performed during last admission or clinic visit), antinuclear factor, syphilis serology, HBV and HCV serology, CMV serology, VZV serology, and toxoplasmosis serology (all performed at some time before death).
infarcts are small foci of incompletely infarcted brain in deep gray structures that are similar in many respects to the microinfarcts that we describe in the brains of AIDS patients.

What else may have contributed to the cerebral infarcts in our patients? Two patients had positive syphilis serology, but in the absence of meningitis or vasculitis, this is unlikely to be relevant. None of the patients had significant atherosclerosis of their medium or large vessels, and there were no other arterial or cardiac sources of cerebral emboli detected during life or at autopsy. Other investigators have associated cerebral infarcts in HIV-infected patients with hepatitis B42 (hepatitis B or C serology was positive in 6 of our patients), as well as with a prothrombotic state related to protein S deficiency,35,36 antiphospholipid antibodies,39,40 or disseminated intravascular coagulopathy.4,11,12 We have protein S levels, which were normal, for only 1 patient, and none of our patients had antiphospholipid antibodies measured. Thus, the theoretical possibility of “hypercoagulability” remains, although intravascular thrombi, recent or organized, were seen only rarely in this and other autopsy series, even in those cases with very recent infarcts. The fact that “crops” of small cerebral infarcts of similar histological age were seen in some brains might suggest showers of microemboli or a transient hypercoagulable state, but this remains speculative. Infarcts were not a feature in other organs at autopsy, militating against cardiac embolism or a generalized hypercoagulable state.

We could not demonstrate a clear correlation between the pathological changes and clinical features of stroke or TIA in our patients. Five patients had no neurovascular symptoms at any stage. One patient had experienced recurrent anterior circulation TIAs that started 11 months before death, but no etiology was found on investigation on 2 separate occasions, although an angiogram was not performed. The diagnosis was changed to migraine on review by a neurologist because the attacks were slow in onset and were associated with headache, but the diagnosis was reversed again after a typical left partial anterior circulation TIA. As the TIAs resolved after the introduction of ganciclovir, one might speculate that the patient had a cytomegalovirus-induced vasculitis that was treated with ganciclovir. Alternatively, the cessation of the TIAs may have been entirely coincidental. None of our patients received highly active anti-retroviral therapy because they came to autopsy before the introduction of the newer anti-retroviral agents.

Several patients presented diagnostic difficulty not only to the attending physicians (cases 1, 2, 3, and 9) but also to the neurologists to whom they were referred (cases 1, 3, and 9). All 4 patients (cases 1, 2, 3, and 9) had recurrent transient neurological symptoms. One patient was diagnosed as having atypical migraine, and in the other 3 patients, the symptoms were thought to be seizure-related, although in 2 of them, a diagnosis of atypical migraine was entertained at some point. Recently, recurrent transient neurological deficits similar to those noted in our patients have been found to occur in clinical cohorts and have been linked to antiphospholipid antibodies or protein S deficiency.
Six years before death, the patient developed transient numbness in the distribution of the right trigeminal nerve. MRI head scan was normal, and the numbness resolved spontaneously over a few weeks.

Three years before death, 1 week after discontinuing benzodiazepines, there were 2 episodes of transient expressive dysphasia lasting ~1 h, preceded by flashing lights in visual field and acrid smell. An associated recurrence of previous homonymous hemianopia resolved off AZT. EEG showed generalized paroxysmal abnormality, and patient was treated with carbamazepine.

One year before death, there was an episode of paresthesia radiating down the left arm. No abnormality was detected on examination.

Five months before death (witnessed) there was a generalized seizure, attributed to hypocalcemia. CT was normal. Two months before death, there were 3 episodes of unilateral facial numbness, spreading to one or both arms, lasting 5 min to 5 h. Migraine was considered and sumatriptan was prescribed.

One month before death, a possible episode of amaurosis fugax lasted 30 min. Variable visual field loss was found on formal testing, with no active CMV retinitis clinically. Nine months before death, there was an episode of expressive dysphasia and right hemiparesis lasting 20 hours. Full workup again revealed only a raised CSF protein. The patient developed diarrhea and questionable CMV retinitis and was started empirically on ganciclovir, after which, the above episodes resolved.

Eleven months before death there were 2 episodes of acute onset dysarthria, followed by numbness of the whole left side of the body, which resolved over 2 h. CT brain, EEG, ECG, carotid and vertebral Doppler studies, transsphenoidal echo with contrast, and full coagulation profile were all normal. CSF showed no cells, and protein was raised at 0.72 g/L. Aspirin treatment yielded no resolution.

Ten months before death, there was a neurological review. Because further similar attacks were thought to be of slow onset and were followed by headaches, a diagnosis of migraine was made. There was no resolution with sumatriptan and propranolol.

Nine months before death, there was an episode of expressive dysphasia and right hemiparesis lasting 20 h. Full workup again revealed only a raised CSF protein. The patient developed diarrhea and questionable CMV retinitis and was started empirically on ganciclovir, after which, the above episodes resolved.

Six years before death, the patient developed transient numbness in the distribution of the right trigeminal nerve. MRI head scan was normal, and the numbness resolved spontaneously over a few weeks.

Five years before death, there was intermittent right-sided numbness, which lasted a year. No clear diagnosis was made, but at the time of neurological review, patient was thought to be anxious or possibly to have seizures related to drug withdrawal. Over the 4 y before death, the patient developed progressive AIDS dementia complex. Initially migraine, then after episodes of dysphasia, diagnosis as seizure possibly related to benzodiazepine withdrawal

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Clinical Features</th>
<th>Clinical Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Four years before death, the patient developed intermittent episodes of homonymous hemianopia affecting either side. There was no associated headache, nausea, or positive visual phenomena, and the episodes lasted for ~20 min at a time. Symptoms resolved on pizotifen.</td>
<td>Initially migraine, then after episodes of dysphasia, diagnosis as seizure possibly related to benzodiazepine withdrawal</td>
</tr>
<tr>
<td>2</td>
<td>Five months before death (witnessed) there was a generalized seizure, attributed to hypocalcemia. CT was normal. Two months before death, there were 3 episodes of unilateral facial numbness, spreading to one or both arms, lasting 5 min to 5 h. Migraine was considered and sumatriptan was prescribed. One month before death, a possible episode of amaurosis fugax lasted 30 min. Variable visual field loss was found on formal testing, with no active CMV retinitis clinically.</td>
<td>Seizure related to hypocalcemia</td>
</tr>
<tr>
<td>3</td>
<td>Eleven months before death, there was a 2-mo history of intermittent visual disturbance lasting 20 minutes, diagnosed as migrainous aura without headache or other features of migraine. It resolved spontaneously.</td>
<td>Possible migraine</td>
</tr>
<tr>
<td>4</td>
<td>Eleven months before death there were 2 episodes of acute onset dysarthria, followed by numbness of the whole left side of the body, which resolved over 2 h. CT brain, EEG, ECG, carotid and vertebral Doppler studies, transsphenoidal echo with contrast, and full coagulation profile were all normal. CSF showed no cells, and protein was raised at 0.72 g/L. Aspirin treatment yielded no resolution. Ten months before death, there was a neurological review. Because further similar attacks were thought to be of slow onset and were followed by headaches, a diagnosis of migraine was made. There was no resolution with sumatriptan and propranolol. Nine months before death, there was an episode of expressive dysphasia and right hemiparesis lasting 20 hours. Full workup again revealed only a raised CSF protein. The patient developed diarrhea and questionable CMV retinitis and was started empirically on ganciclovir, after which, the above episodes resolved.</td>
<td>TIAs</td>
</tr>
<tr>
<td>9</td>
<td>Six years before death, the patient developed transient numbness in the distribution of the right trigeminal nerve. MRI head scan was normal, and the numbness resolved spontaneously over a few weeks. Five years before death, there was intermittent right-sided numbness, which lasted a year. No clear diagnosis was made, but at the time of neurological review, patient was thought to be anxious or possibly to have seizures related to drug withdrawal. Over the 4 y before death, the patient developed progressive AIDS dementia complex.</td>
<td>? Seizures related to drug withdrawal</td>
</tr>
</tbody>
</table>

AZT indicates azidothymidine; CSF, cerebrospinal fluid.

In conclusion, the present study suggests that cerebral infarcts in HIV-infected patients are not common in the absence of cerebral opportunistic infection, lymphoma, non-HIV infection, or embolic sources. We confirm the existence of an HIV-associated vasculopathy but highlight that this vasculopathy shows similar histopathologic features in all risk groups irrespective of drug use, hepatitis serology, or even syphilis serology. The possible relation of this vasculopathy to direct HIV infection of vessel walls should be further investigated. Finally, the present study supports the approach that in AIDS patients presenting with a stroke or TIA, potentially treatable causes, such as cerebral coinfection or tumor, be excluded before assuming that the cause is HIV itself, be that as a result of a vasculopathy or some as yet unrecognized pathogenic mechanism.

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References


Cerebral Infarction in Adult AIDS Patients: Observations From the Edinburgh HIV Autopsy Cohort

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