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Cerebrovascular lesions in acquired immune deficiency syndrome (AIDS)

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Summary. Cerebrovascular lesions were seen in 28 of 83 cases (34%) of acquired immune deficiency syndrome (AIDS). Cerebral hemorrhage was noted in 4 cases, cerebral infarct in 23 cases and both in 1 case. Cerebral hemorrhage was in various locations such as intraparenchymal, subarachnoid space, subdural space and epidural space. Large, clinically evident hemorrhage was noted in 2 of 5 cases and bleeding tendency was noted in 2 cases. Most of the 24 cases with cerebral infarcts were not clinically evident; they were multiple, small and mainly involved the striatum, cerebral cortex and brain stem. Mural thickening of occasional small blood vessels was seen in 12 of the cases (50%) with infarcts. Other changes in blood vessels included vasculitis in one case and perivascular lymphocytic infiltration in another. In addition to thrombo-embolism and systemic ischemia/anoxia, these blood vessel changes may have a role in the development of cerebral infarcts in AIDS.

Key words: AIDS – Cerebral hemorrhage – Cerebral infarct – Mural thickening of small blood vessels

Neurological complications are frequent in acquired immune deficiency syndrome (AIDS). Approximately 80% to 90% of AIDS cases show neuropathology at autopsy [1, 5, 9, 14, 20, 24]. Lesions are various and include several opportunistic infections and a recently recognized lesion in AIDS, subacute encephalitis, which is reported to be caused by human immunodeficiency virus (HIV) [13]. In an autopsy series of 83 AIDS cases, we confirmed the incidence of these pathological entities. In addition, we noted a much higher incidence of cerebrovascular lesions than that in several AIDS series [1, 5, 17, 19, 28]. In addition to anoxia/ischemia and thromboembolism, etiological factors for cerebrovascular lesions in AIDS patients include pathology of the cerebral blood vessels [8, 33] and demonstration of HIV within endothelial cells of cerebral blood vessels [25, 30, 32]. In this report, the cases with cerebrovascular lesions are analyzed and their pathogenetic factors are discussed. In addition, hitherto undescribed pathological changes in small blood vessels associated with the infarcts are illustrated.

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Materials and methods

Autopsies were performed on 83 cases with AIDS or AIDS-related complex. Formalin-fixed sections of frontal lobe, temporal lobe, occipital lobe, parietal lobe, basal ganglia, thalamus, midbrain, pons, medulla, cerebellum and pituitary as well as macroscopically noted lesions were embedded in paraffin and stained with hematoxylin and eosin. As warranted in each case, sections were stained with luxol fast blue-periodic acid-Schiff, modified Bielschowsky, Gram's, Ziehl-Nielsen, Grocott's methenamine silver stains and for toxoplasma using immunostaining kits provided by Bio Genex Laboratories (Dublin).

Results

The clinical features and neuropathological findings in 83 cases of AIDS are summarized in Tables 1 and 2. Of the five cases with cerebral hemorrhage, two had large, clinically diagnosed hemorrhages and three had small, incidental ones. The hemorrhages had various locations, namely, intraparenchymal, subarachnoid, subdural or epidural. One case with a few putaminal infarcts showed mild mural thickening of small vessels in the putamen and another case showed diffuse mild perivascular lymphocytic infiltration. Thrombocytopenia was clinically noted in two cases. No case had a history of hypertension and two cases were intravenous drug abusers (IVDAs).

Table 1. Some clinical features of 83 AIDS cases with or without cerebral infarct

	Cases with infarct 24 (29%)	Cases without infarct 59 (71%)	Total 83 (100%)
Age, mean (range):			
adult (years)	23 38.7 (25–67)	53 35.7 (20–82)	76 36.8 (20–67)
child (months)	1 44	6 19 (5–52)	7 22.6 (5–52)
Sex:			
male	20	42	62
female	4	17	21
Risk factors of AIDS:			
IVDA	11	28	39
homo- or bisexual	5	16	21
(IVDA + homosexual)	(2)	(2)	(4)
parent with AIDS or IVDA	1	5	6
spouse with AIDS or IVDA	2	3	5
blood transfusion	3	0	3
unknown	4	9	13

IVDA = Intravenous drug abuse

Table 2. Neuropathological findings of 83 AIDS cases with or without cerebral infarct[a]

	Cases with infarct 24 (29%)	Cases without infarct 59 (71%)	Total 83 (100%)
Subacute encephalitis	12	22	34 (41%)
with MGC	12	12	24
without MGC[b]	0	10	10
Opportunistic infections	9	18	27 (33%)
CMV infection	2	6	8
taxoplasmosis	2	5	7
cryptococcosis	2	5	7
PML	1	2	3
Herpes virus infection	1	1	2
Aspergillosis	1	0	1
tuberculosis	0	1	1
histoplasmosis	0	1	1
Malignant lymphoma	0	6	6 (7%)
Cerebral hemorrhage	1	4	5 (6%)
Other abnormalities[c]			5 (6%)
Normal[d]			13 (16%)

[a] Many brains had more than one type of pathology
[b] With microglial nodules and without apparent opportunistic infection
[c] Focal rarefaction (one case), and gliosis (one case) and calcospherites (three cases) in the white matter
[d] Five cases had generalized, acute anoxic or ischemic changes
MGC: Multinucleated giant cell; CMV: Cytomegalovirus; PML: progressive multifocal leukoencephalopathy

Tables 1 to 4 summarize the findings on the 24 cases with cerebral infarcts. Eleven of 24 cases were IVDAs (Table 1). Associated findings included subacute encephalitis with multinucleated giant cells (12 cases) and various opportunistic infections (9 cases) (Table 2). Most infarcts were small and multiple (Table 3). They were of various age and were found frequently in the putamen, caudate, cerebral cortex and brain stem. A large recent infarct in the territory of the posterior cerebral artery was present only in a 67-year-old patient who had an aortic valve replacement. There was severe systemic atherosclerosis and popliteal artery thrombus in a 61-year-old patient, and organized bacterial endocarditis in a 39-year-old IVDA. Emboli were, however, not observed in the brain of these three patients.

Five patients had clinical ischemic or anoxic episodes such as severe hypotension, cardiorespiratory

Table 3. Pathological features of cerebral infarcts

Size		
Large		1/24 cases
Small, macroscopically noted		7
Small, microscopic		20
Number		
Single		2/24 cases
A few		10
Many		13
Location of small infarcts		
Putamen		17/24 cases
putamen + caudate	8	
brain stem		10
Cerebral cortex		10
Cerebellum		5
Globus pallidus		2
Cerebral white matter		2
Pituitary gland		2
Thalamus		1

arrest and anoxic encephalopathy. Three of these five showed definite ischemic changes at least in Ammon's horn. Two other cases without apparent clinical history of ischemia or anoxia showed similar pathological findings. Border zone infarct was not observed. Although diffuse neuronal loss and astrocytosis of the cerebral cortex were seen in one case, laminar necrosis of the cerebral cortex was not observed.

Arteries of the circle of Willis were unremarkable in 22 cases and had slight atherosclerosis in 2 aged patients (61 and 67 years). Mild to moderate thickening of the wall of small blood vessels, which were probably arterioles, was noted in 11 cases (Fig. 1A, B), and severe stenosis with occlusion was found in one case (Fig. 1C); this case also had subacute encephalitis with multinucleated giant cells and a cytomegalic cell in a microglial nodule. A few thrombi were noted within small vessels in three cases without any source of emboli (Fig. 1D); two of which also had blood vessels with mural thickening. The brain of a 34-year-old woman had a small infarct in the occipital periventricular area associated with vasculitis (Fig. 2) and a few microinfarcts in the putamen, in addition to subacute encephalitis with multinucleated giant cells and microglial nodules but without evidence of opportunistic infections. A small cystic infarct between caudate and putamen and diffuse, mild lymphocytic cuffing were noted in a case with progressive multifocal leukoencephalopathy.

Calcification of vessel wall, and calcific deposits in the perivascular area and parenchyma were frequently found (Table 4). Nine of 13 cases with calcification in the putamen and/or globus pallidus showed infarcts in the region. Three cases with calcification in the cerebral white matter had subacute encephalitis in the same area. One of these three cases also showed calcification in the cerebral cortex (Fig. 3A). One case with a few recent microscopic infarcts in the globus pallidus, internal capsule and a cerebral peduncle, showed mild calcification of vascular wall in and around the lesion in the cerebral peduncle (Fig. 3B), in addition to moderate calcification in the basal ganglia. The other cerebral peduncle had no calcification. Ferrugination of neurons and their processes were found in and around the infarcts, particularly in the basal ganglia in four cases.

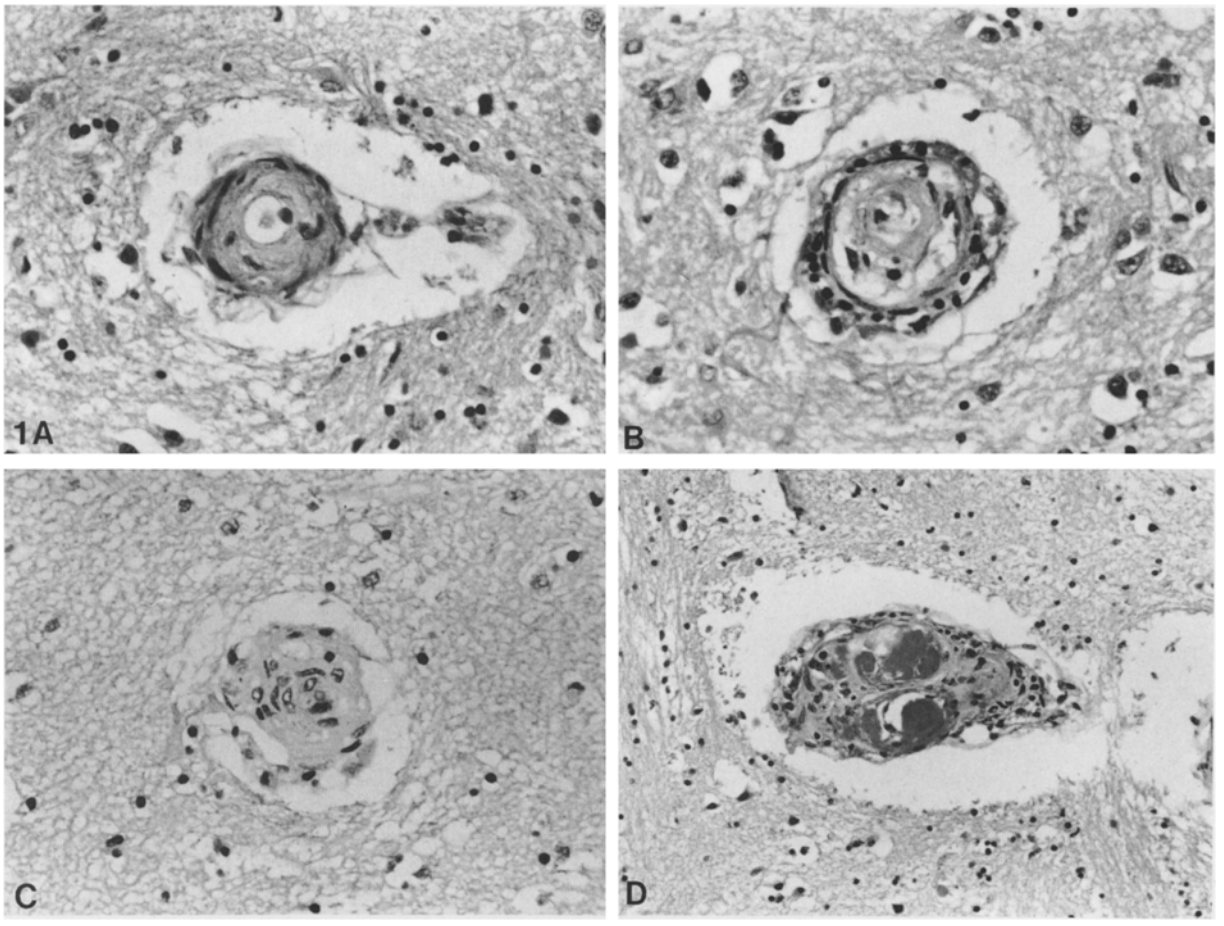
Discussion

The noteworthy finding of this study is the relative frequency (34%) of cerebrovascular lesions, consisting of hemorrhages and infarcts. Similar lesions were noted in 2%–21% of some series [1, 5, 17, 19, 28].

The incidence of hemorrhage (6%) is within the range of the reported frequency from 0.8% to 15% in the literature (Table 5) [1, 17, 19, 28]. We confirmed that the hemorrhages are of various locations [1] and severity [19]. The etiology of hemorrhage is unclear in most cases except for thrombocytopenia, which was noted in two of our cases and two cases in the literature [28]. Lack of significant change in blood vessels and absence of history of hypertension in our series support bleeding tendency as the main pathomechanism, although it was not always diagnosed clinically. Drug abuse itself has been reported as a risk factor for stroke [4, 7, 23]. However, abnormalities such as mycotic aneurysm or narrowing of the leptomeningeal arteries were not found in any of IVDAs with hemorrhages or infarcts in our series.

Cerebral infarcts were seen in 29% of our cases, much higher than the 0.8% to 8% incidence rate of other series (Table 5) [1, 17, 19, 28]. Most of the infarcts in our series were small. In the literature, such microinfarcts were identified only in four cases: two with disseminated intravascular coagulopathy (DIC) or diffuse venous thrombi [19] and two with microglial nodules in the brains [1]. The most common etiological factors for cerebral infarcts in AIDS are non-bacterial thrombotic endocarditis and DIC as reported in 11 of 23 cases (Table 5). In our series, there were no cases with DIC or non-bacterial thrombotic endocarditis, while three cases had thrombus formation in cerebral blood vessels and three other cases had possible sources of thromboembolism such as bacterial endocarditis, aortic valve replacement and marked atherosclerosis in systemic blood vessels.

Generalized ischemia or anoxia is a usual event in AIDS. However, it was pathologically evident only in five cases as definite changes in the Ammon's horn, which is known to be most vulnerable to generalized



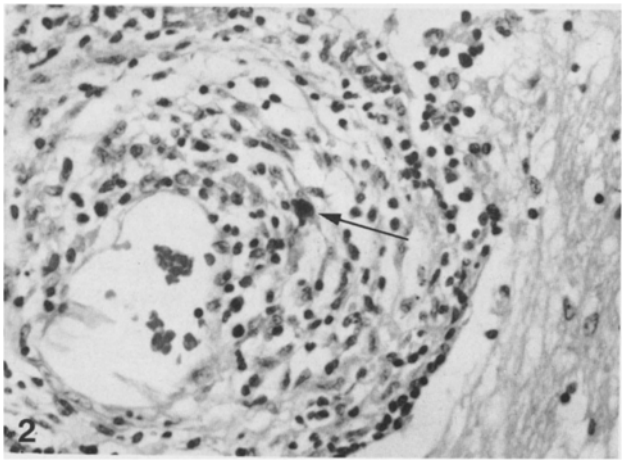


Fig. 1A–D. Blood vessel changes in the putamen with microinfarcts. **A**, **B** and **D** are in a 32-year-old man and **C** is in a 47-year-old man. **A** Moderate mural thickening of a small blood vessel, probably an arteriole. **B** Moderate subintimal thickening and mild perivascular infiltration of mononuclear cells. **C** Occlusion of the lumen by thickening of the vessel wall, probably in an arteriole. **D** Thrombi in recanalized blood vessel. H&E; **A, B, C,** ×317, **D** ×158

Fig. 2. Vasculitis with a multinucleated giant cell (*arrow*) in the inflammatory infiltrate. H&E; ×280

ischemia or anoxia, while the striatum, which is also relatively vulnerable to ischemia or anoxia, was most frequently affected in this series [3, 29].

Pathology of the blood vessels, although rare, is one of the etiological factors cited for cerebral infarcts in AIDS. These include granulomatous angitis in one case [33] and an intimal proliferative lesion involving leptomeningeal arteries in four cases [8]. These findings were not seen in our series. Instead, pathology of small intraparenchymal blood vessels were noted in 63% of our cases with infarcts. In most cases, the blood vessels, which appeared to be arterioles, had fibrous thickening of the wall, with or without infiltration by inflammatory cells. Although occlusion of

such blood vessels was seen only in one case, they may have contributed to the development of ischemic lesions. Many of the cases with these blood vessel changes had subacute encephalitis and one case showed a multinucleated giant cell in a perivascular infiltrate (Fig. 2). Microinfarcts have been described in two AIDS brains with microglial nodules [1], and fibrinoid necrosis of the wall of a putaminal blood vessel was noted in another AIDS brain with microglial nodules [10]. HIV has been demonstrated in vascular endothelial cells in AIDS brain [25, 30, 32], even in the regions devoid of inflammatory cells [32]. This remains a possibility in our series, which did not have in situ hybridization and immunohistochemical study for HIV.

Among the common opportunistic infections, the possible etiological agents to be considered for blood vessel changes include cytomegalovirus (CMV), Toxoplasma, Herpes zoster and Aspergillus.

Table 4. Blood vessel changes associated with cerebral infarcts

Blood vessel changes in the brain		15/24 cases
mural thickening of small vessel		12
with subacute encephalitis	8	
with thrombus formation	2	
thrombus formation		1
vasculitis		1
perivascular lymphocytic infiltration		1
Calcification of blood vessel wall and parenchyma		17/24 cases
putamen and/or globus pallidus		13
with infarcts in this region	9	
Ammon's horn or dentate nucleus		3
cerebral white matter		3
cerebral cortex		1
cerebral peduncle (unilateral)		1

CMV has been associated with a variety of lesions such as microglial nodules, isolated CMV inclusion-bearing cells, focal parenchymal necrosis, ventriculoencephalitis, radiculomyelitis [18] and multiple infarcts due to vasculitis [15]. However, it has not been reported in association with mural thickening of the blood vessels similar to our findings.

In addition, although 10 of 30 patients with CMV lesions in the brain were found to have CMV inclusions in isolated capillary endothelial cells, none of them showed parenchymal vasculitis [18]. Convincing CMV inclusions were not seen within the vascular endothelium in a case of CMV infection, multiple infarcts and vasculitis [15]. Therefore, it is not likely that CMV infection is the major etiology of the multiple infarcts and vascular pathology in this study, which had only two cases with isolated inclusion-bearing cells. On the other hand, a normal-appearing cell could still be infected by CMV [31].

Toxoplasmosis usually induces necrotizing encephalomyelitis and abscess formation with demonstrable organisms [1, 21]. Blood vessels may show fibrinoid necrosis with perivascular inflammatory response [1]. One of our cases had a few scattered cysts around infarcts and another had a single abscess far from the infarcts. Although Herpes zoster and Aspergillus preferentially affect blood vessels [16, 22], these etiological agents were not found in and around the infarcts of our two cases with focal periventricular infection by Herpes and Aspergillus.

Similar to a series of pediatric AIDS cases [2, 27] a striking finding in our cases is the calcification of blood vessels and parenchyma. Since calcification in the basal ganglia was not found in half of the cases with infarcts in these structures (9 of 18 cases) and four cases showed calcification but no infarcts in the

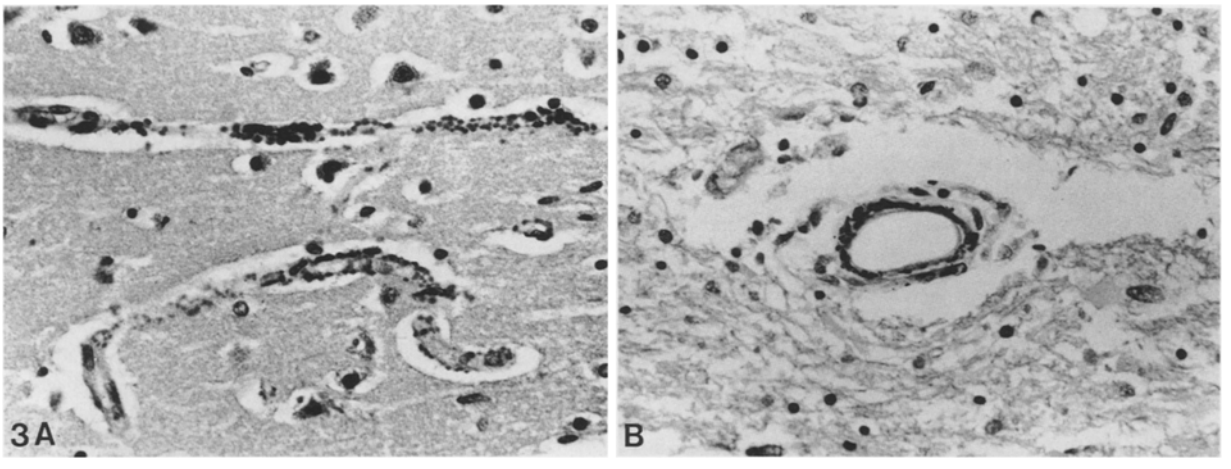


Fig. 3. A Calcification of small cortical vessels. **B** Mural calcification of a small artery in an infarct of a cerebral peduncle. H&E; ×317

Table 5. Cerebrovascular lesions in AIDS

	Total no. of cases	Cerebral hemmorrhage	Cerebral infarct (causes, comments)
This series (1987)	83	5	24
Anders et al. [1]	89	13	6 (4 NBTE or DIC, 2 microinfarcts)
Budka et al. [5]	100	11[a]	
Moskowitz et al. [19]	52	4	4 (1 DIC, 1 venous thrombosis, 2 pituitary infarct)
Snider et al. [28]	50	3	2 (NBTE)
Cho et al. [8]	4		4 (intimal proliferation of leptomeningeal artery)
Cammarosano and Lewis [6]	41		2 (NBTE)
Garcia et al. [11]	1		1 (NBTE)
Guarda et al. [12]	13		1 (NBTE)
Yankner et al. [33]	1		1 (granulomatous angitis)
Levy et al. [17]	128	1	1
Sharer et al. [26]	8		1

[a] Eleven cases with cerebral hemorrhages or infarcts
NBTE: Non-bacterial thrombotic endocarditis; DIC: disseminated intravascular coagulation

basal ganglia, a direct relationship between calcification and infarct seems unlikely. However, these calcifications are clearly abnormal in this young population.

Among several factors that may have contributed to the development of the microinfarcts in our series, the mural thickening of the small cerebral blood vessels is the most intriguing and requires further investigation, particularly regarding its etiology and pathomechanism in relation to HIV infection.

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