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Acquired Immunodeficiency Syndrome and the Risk of Stroke

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Background and Purpose—Although acquired immunodeficiency syndrome (AIDS) is thought to increase the risk of stroke, few data exist to quantify this risk. This is the first population-based study to quantify the AIDS-associated risk of stroke.

Methods—We identified all incident ischemic stroke (IS) and intracerebral hemorrhage (ICH) cases among young adults 15 to 44 years of age in central Maryland and Washington, DC, who were discharged from any of the 46 hospitals in the study area in 1988 and 1991. Using data from the medical records, 2 neurologists reviewed each case to confirm the diagnosis. Cases of AIDS among these patients with stroke were defined using Centers for Disease Control and Prevention criteria (1987). The number of cases of AIDS in the central Maryland and Washington population during 1988 and 1991 was determined from regional health departments working with the Centers for Disease Control and Prevention. Poisson regression was used to estimate the age-, race-, and sex-adjusted relative risk of stroke associated with AIDS.

Results—There were 385 IS cases (6 with AIDS) and 171 ICH cases (6 with AIDS). The incidences of IS and ICH among persons with AIDS were both 0.2% per year. AIDS conferred an adjusted relative risk of 13.7 (95% confidence interval [CI], 6.1 to 30.8) for IS and 25.5 (95% CI, 11.2 to 58.0) for ICH. After exclusion of 5 cases of stroke in AIDS patients in whom other potential causes were identified, AIDS patients continued to have an increased risk of stroke with an adjusted relative risk of 9.1 (95% CI, 3.4 to 24.6) for IS and 12.7 (95% CI, 4.0 to 40.0) for ICH.

Conclusions—This population-based study found that AIDS is strongly associated with both IS and ICH. (*Stroke*. 2004; 35:51-56.)

Key Words: acquired immunodeficiency syndrome ■ epidemiology ■ HIV ■ stroke

Stroke has often been reported as a complication of acquired immunodeficiency syndrome (AIDS). However, few data exist to quantify the risk of AIDS-associated stroke. Furthermore, most existing studies fail to distinguish between strokes associated with medical conditions known to be associated with HIV infection such as lymphoma, opportunistic infections, and endocarditis and strokes resulting from an as-yet-undetermined HIV-related process.^{1,2} Several possible mechanisms have been hypothesized to account for stroke in association with AIDS, including a prothrombotic state² or a covert HIV-induced vasculopathy.^{3,4} Currently, there are no reported population-based studies regarding the association of AIDS with stroke; therefore, the actual magnitude of AIDS-associated stroke risk remains in question. To address these issues, we report the first study to quantify the

overall AIDS-associated risk of stroke within a defined population. In addition, the analysis was repeated excluding strokes thought to be a result of AIDS-associated medical conditions to approximate the risk of stroke associated solely with AIDS.

Methods

Identification of Individuals With Stroke

The Baltimore-Washington Cooperative Young Stroke Study (BW-CYSS) is a regional, hospital-based registry initiated to study the incidence and cause of stroke in young adults.⁵ The study region encompasses Baltimore; Washington, DC; and 5 central Maryland counties (Anne Arundel, Baltimore, Howard, Montgomery, and Prince Georges). The total population of this region in 1990 was 3 935 910. The population that was 15 to 44 years of age was

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2 077 825; 58% of this group were white, 36% were black, 3% were Asian, and 3% were from other racial and ethnic groups.

All 44 acute-care hospitals and both rehabilitation hospitals in this region participated in the study. Institutional Review Board approval was obtained at all participating institutions. Because of referral patterns, it was considered unlikely that persons who lived in the study region would be admitted to hospitals outside this area. Data were available for 1988 and 1991, during which there were 2470 hospital discharges of persons 15 to 44 years of age with a primary or secondary diagnosis reflecting a possible cerebral infarction (1988 and 1991) or intracerebral hemorrhage (ICH; 1991) (*International Classification of Diseases*, 9th revision [ICD-9], codes 431.00 through 438.00, indicating cerebrovascular disease other than subarachnoid hemorrhage; 671.50 through 671.54, indicating cerebral venous thrombosis; and 674.00 through 674.04, indicating cerebrovascular complications of the puerperium). Of these cases, medical records from 2309 (93%) were available for review by a nurse who had experience in caring for patients with stroke and who had been trained in the study procedures. From our case-control studies in the same population using both discharge surveillance and direct referral from regional neurologists, we estimate that 3% of cases are not hospitalized.

The abstracting process yielded a narrative summary for each patient that described past strokes and episodes of transient ischemic attacks, neurological symptoms and signs at presentation, and their evolution. In addition, the data recorded included demographic characteristics; risk factors (for ICH, only the 1991 data included this information); laboratory data, including the results of neuroimaging; all ICD-9 codes at discharge; and autopsy data if available.

The abstracted information on each possible acute stroke was reviewed by 2 neurologists who classified the event as a cerebral infarction, ICH, or other medical condition. Stroke was defined according to the criteria of the World Health Organization as a focal neurological deficit of sudden onset with symptoms lasting >24 hours or leading to death before this period with no other cause than cerebrovascular disease.⁶ This definition therefore excludes patients with subarachnoid hemorrhage and transient ischemic attack. The definitions of cerebral infarction and ICH were based on the criteria of the Stroke Data Bank of the National Institute of Neurological Disorders and Stroke.⁷ We chose to include strokes resulting from cerebral venous thrombosis in the category of cerebral infarction because central venous thrombosis is often misdiagnosed and because any unrecognized cases would be included as cerebral infarctions. Probable and possible causes were also assigned during the review process.⁸ Disagreements between the neurologists were resolved by consensus in meetings with a third neurologist. Strokes that occurred as immediate consequences of trauma were excluded. Cerebral infarction associated with subarachnoid hemorrhage was also excluded. Only first stroke occurring in persons who lived in the study region were included in the present analysis.

Identification of Stroke Cases With AIDS

First-ever stroke patients (both sexes, all races, with ages between 15 to 44 years) in the BWCYSS registry were screened as possible AIDS cases using the following characteristics: ICD-9-CM codes for HIV infection or other AIDS-associated illness defined in the 1987 AIDS case definition,^{9,10} a blood test positive for HIV, intravenous drug abuse identified by history or admission physical examination findings, low white blood count (<3000) at admission, low platelets (<100 000) at admission, and suggestive findings in a narrative description of "other medical problems." For all stroke patients who met the above criteria, the narrative summaries and written descriptions of other medical problems were reviewed, and patients were classified in accordance with the 1987 Centers for Disease Control and Prevention (CDC) definition for AIDS.¹⁰ Patients with HIV infection who did not fulfill the criterion for AIDS were included in the non-AIDS group. Of note, this study was performed in the era before highly active antiretroviral therapy (HAART); therefore, AIDS patient were treated, at most, with zidovudine (AZT).

Identification of Strokes Caused by AIDS-Related Medical Conditions or Other Concomitant Etiologies

Each case was critically reviewed for AIDS-related medical conditions or other concomitant etiologies. Radiological studies were analyzed for findings considered atypical for brain-related ischemia or hemorrhage. This review sought to identify AIDS patients with stroke in whom other known stroke etiologies existed, including endocarditis, and/or intracerebral AIDS-related pathologies, including opportunistic infections, primary central nervous system lymphoma, metastatic Kaposi sarcoma, meningoencephalitis, progressive multifocal leukoencephalopathy, cerebral abscess, and tuberculoma. These individuals were then excluded from the AIDS case group during secondary analysis. This procedure was performed to quantify the effect of AIDS on the risk of stroke exclusive of the effects of AIDS-related causes of stroke and other stroke etiologies.

Determination of Person-Time at Risk

Law mandates physician reporting of AIDS cases. Data on AIDS cases residing in the study region were obtained from both the District of Columbia and the State of Maryland. The data for Washington was provided by the Agency for HIV/AIDS, Commission of Public Health, Department of Human Services of the Government of the District of Columbia through the CDC HIV/AIDS Reporting System (HARS). New cases were sent to the CDC to be checked for duplication against confidential identifiers of name, address, and date of birth to prevent overreporting and to determine residence history. The CDC then returned the corrected numbers to the agency.⁹

For the appropriate Maryland counties, data were provided by the AIDS Administration of the Maryland Department of Health and Mental Hygiene, which maintains its own AIDS Registry. Maryland also uses the HARS system and checks all new records through the CDC.

The person-time at risk for stroke among AIDS cases was estimated as the simple average of the number of AIDS cases alive at the beginning of each study year and the number of AIDS cases alive at the end of each study year. The person-time at risk for stroke among persons without AIDS was estimated by subtracting the person-time calculated for AIDS exposure from the total person-time in the study population.

We determined the distribution of the population according to sex, age, and race on the basis of estimates for 1988 and 1991 for the region of Maryland under study^{11,12} and on the basis of the 1990 US census for Washington.¹³ Persons were categorized according to sex, 10-year age groups, and 2 racial categories (white and all other). The "all other" category was 86% black.

Statistical Analysis

The incidence of stroke was determined by dividing the number of strokes by the number of years of person-time for both the AIDS and non-AIDS populations. The crude relative risks of AIDS as a risk factor for each stroke was calculated as the ratio of the incidence rates; the non-AIDS stroke population served as the reference group. Relative risks adjusted for age, sex, and race and 95% confidence intervals (CIs) were obtained by fitting Poisson regression models that predicted the incidence of stroke according to age, sex, race and whether the person had AIDS.

To assess the statistical differences in demographic characteristics and risk factors between stroke patients with AIDS and stroke patients without AIDS, we used Student's *t* test for age and Fisher's exact test for all other factors. Two-tailed probability values are reported.

Results

Analysis of All Strokes Among AIDS Versus Non-AIDS Patients

Within the BWCYSS, there were 386 ischemic stroke (IS) cases (6 with AIDS) and 171 ICH cases (6 with AIDS).

Among the 557 stroke patients included, only 2.2% had AIDS. There were 380 cerebral infarctions and 165 ICHs during 4 104 734 non-AIDS-exposed person-years. During the 2829 person-years of AIDS exposure in the study population, there were 6 ISs and 6 ICHs. Table 1 lists these cases by stroke type, general demographic data (sex, age, race), known risk factors for AIDS, previous medical history, risk factors for stroke, clinical stroke syndrome, and infarction location per imaging.

Tables 2 and 3 summarize the demographic and risk factor data for IS and ICH cases, respectively, with patients categorized according to their AIDS or non-AIDS status. Stroke risk factors included in the analysis were history of hypertension, diabetes mellitus, elevated cholesterol, and ischemic heart disease; current cigarette use; current illicit drug use; and alcohol abuse. Although there were no statistically significant differences for these factors between AIDS and non-AIDS patients for either IS or ICH, non-AIDS cases had a greater prevalence of vascular risk factors.

Table 4 shows the crude and age-, race-, and sex-adjusted relative risks for both IS and ICH strokes among all AIDS patients within the BWCYSS. The incidences of IS and ICH among persons with AIDS were each 0.2% per year. The adjusted relative risk for both stroke types was high, 13.7 for cerebral infarction (95% CI, 6.1 to 30.8) and 25.5 for ICH (95% CI, 11.2 to 58.0). The combined adjusted relative risk was 17.8 (95% CI, 10.0 to 31.6).

Analysis of Stroke Cases Excluding Strokes Caused by AIDS-Related Medical Conditions or Other Concomitant Etiologies

The 12 strokes among AIDS patients were reviewed for both AIDS-related causes of stroke and other possible concomitant causes of stroke. This review revealed 2 cases in the IS group and 3 cases in the ICH group that were consistent with the stated exclusion criteria. Among the IS cases, 1 patient (patient 3) was found to have brain MRI findings that were read as "unusual for pure ischemia," and other AIDS-related pathologies were suggested. The second IS patient (patient 5) was found to have been admitted in sickle cell crisis with a markedly depressed hematocrit of 21.6. Among the ICH cases, 1 patient (patient 8) was found to have a large pericardial effusion with an increased echogenicity in the area of the aortic valve in which a vegetation could not be excluded. The second case (patient 9) excluded was a hemodialysis patient who received streptokinase to open an occluded imbedded catheter the day before developing bilateral multifocal ICH. The third ICH case (patient 11) involved a known intravenous drug abuser. The patient had a positive blood culture for *Staphylococcus aureus* with head CT showing bilateral involvement consistent with an embolic phenomenon, including a left parietal ICH with abnormalities also reported in the right parietal lobe.

Table 5 reports the crude and age-, race-, and sex-adjusted relative risks for both IS and ICH strokes among the AIDS patients after exclusion of the 5 cases found to have AIDS-related medical conditions or other concomitant etiologies for stroke. The incidence of IS and ICH among persons with AIDS was 0.14% and 0.11% per year for IS and ICH,

respectively. The adjusted relative risk for both stroke types was high, 9.1 for cerebral infarction (95% CI, 3.4 to 24.6) and 12.7 for ICH (95% CI, 4.0 to 40.0). The combined adjusted relative risk was 10.4 (95% CI, 4.9 to 22.0).

Discussion

Our results demonstrate that AIDS is strongly associated with both IS and ICH. Although we were unable to find any epidemiological studies quantifying the degree of stroke risk in AIDS patients, several studies suggest potential mechanisms for such a risk. Of 183 cases within the Edinburgh HIV Autopsy Cohort, an intensive screening procedure identified 10 cases of cerebral infarction that had no evidence of opportunistic cerebral infection, lymphoma, hemorrhage, traumatic injury, or potential sources of emboli.³ Detailed histological examination revealed small-vessel thickening in all 10 cases, with some cases demonstrating perivascular space dilation, rarefaction, and pigment deposition, with vessel wall mineralization and perivascular cell infiltrates but no evidence of vasculitis. These histopathologic findings were seen regardless of drug use, hepatitis serology, or syphilis serology. An HIV-associated vasculopathy was proposed. In South Africa, where intravenous drug use is less commonly associated with HIV infection, analysis of data from the Durban Stroke Data Bank showed the percentage of cryptogenic strokes, based on Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, was higher (91%) among young adult stroke patients with HIV infection than among age- and sex-matched stroke patients without HIV infection (36%).² Available angiographic investigations showed no evidence of vasculitis. These findings support the possibility of an intrinsic predisposition to stroke among HIV-infected patients. A transcranial Doppler study compared HIV-infected patients and healthy control subjects. Patients with preexisting stenotic or occlusive lesions were excluded. HIV-infected patients had reduced baseline cerebral blood flow and decreased cerebrovascular reserve capacity in response to acetazolamide challenge, suggesting altered vasoreactive responses in HIV infection.⁴

Except for studies based on both clinical and pathological evidence, it is quite difficult to isolate strokes caused by intrinsic AIDS-associated pathophysiology in the absence of AIDS-related medical complications or other concomitant etiologies. Any clinical approach to this issue is fraught with difficulties. Nevertheless, the implications of our findings would differ if the excess risk of stroke in AIDS patients were due to endocarditis or nonvascular AIDS-related intracranial pathology. Thus, we performed a secondary analysis, excluding patients with other concomitant etiologies. Of note, no brain biopsy or autopsy data were available. Despite a reasonable approach to these exclusions, AIDS infection was still strongly associated with stroke.

Our study possesses other limitations and sources of potential bias. One limitation is the small number of AIDS cases among women. Only 2 of 12 strokes cases with AIDS, 1 IS and 1 ICH, occurred among women. Similarly, only 10% of the reported AIDS cases in our study area were women. For these reasons, our study findings may not be generalizable to women. However, if women are excluded from

TABLE 1. Demographics, Risk Factors, Clinical Syndrome, Testing, and Etiology Among AIDS Patients With IS and ICH Within the Young Stroke Data Bank

Patient	Stroke Type	Sex	Age, y	Race	Risk Factors for AIDS	Previous Medical History	Risk Factors for Stroke	Clinical Stroke Syndrome	Stroke Location per Imaging
1	IS	M	40	Black	IVDA	PCP Anemia Leucopenia AZT therapy	Alcohol abuse DM HTN	R hemiparesis	L IC lacune
2	IS	M	37	Black	IVDA	Splenectomy Thrombocytopenia Polyclonal gammopathy Herpes zoster infection	Cocaine abuse	Aphasia R facial palsy R hemiparesis	L parietal involving L basal ganglia
3	IS	M	43	Black	IVDA		Alcohol abuse DM High cholesterol HTN Smoking	Vertebrobasilar syndrome with dizziness, dysphagia, and ataxia	L thalamus L occipital L cerebellum (Pattern unusual for pure ischemia)*
4	IS	M	27	Black	Homosexual	CMV pneumonia	None	Slurred speech L-sided ataxia	R fronto parietal R basal ganglia R caudate
5	IS	M	32	Black	IVDA Transfusion	Thrombocytopenia Herpes zoster infection TB-treated	Alcohol abuse Sickle cell disease/crisis*	R hemiparesis R hemisensory deficit	L basal ganglia
6	IS	F	33	Black	Transfusion	Chronic candidiasis Aplastic anemia	DM Smoking	Slurred speech L homonymous Hemianopsia L hemiparesis	R parietal-occipital R cerebellum R parietal R centrum semiovale
7	ICH	M	36	Black	IVDA	AIDS dementia AZT therapy PCP	Unknown	Lethargy R hemiparesis	L frontal/parietal/ temporal
8	ICH	M	35	Black	IVDA	Thrombocytopenia Herpes zoster infection AZT therapy Bacterial endocarditis	DM HTN Smoking Bacterial endocarditis*	Coma	L parietal cisternal and intraventricular
9	ICH	F	33	Black	IVDA	Neurosyphilis-treated, with FTA positive and RPR negative	Cocaine abuse DM High cholesterol HTN Smoking Recent tx with streptokinase*	Lethargy R hemiparesis	R parietal/occipital L frontal
10	ICH	M	36	Black	Unknown	Kaposi's sarcoma PCP Hepatic failure Thrombocytopenia	High cholesterol Smoking	R hemiparesis	L frontal/parietal and SAH
11	ICH	M	36	Black	IVDA Homosexual transfusion	AZT therapy Thrombocytopenia Cirrhosis	Alcohol abuse DM High cholesterol HTN Smoking <i>Staphylococcus aureus</i> in blood culture*	Seizures Coma	L parietal/occipital R parietal
12	ICH	M	30	White	Transfusion	PCP CMV retinitis Thrombocytopenia Hepatitis	DM High cholesterol HTN Smoking	Lethargy R hemiparesis	L frontal/parietal and SAH

IVDA indicates intravenous drug abuse; PCP, pneumocystis carinii pneumonia; HTN, hypertension; DM, diabetes mellitus; IC, internal capsule; CMV, cytomegalovirus; TB, tuberculosis; FTA, free treponemal antibody; and RPR, rapid plasma reagin.

*Case was removed from secondary analysis.

TABLE 2. Risk Factor Comparison for IS

Risk Factor	IS		2-Tailed <i>P</i>
	AIDS Patients (n=6)	Non-AIDS Patients (n=380)	
Mean age, y	35.3	36.4	
Male, %	83	70	0.115
Nonwhite, %	100	44	0.671
Hypertension, %	16	48	0.218
Diabetes mellitus, %	16	20	1.0
Elevated cholesterol, %	17	41	0.408
Ischemic heart disease, %	0	8	1.0
Current Cigarette Use, %	33	47	0.690
Current illicit drug use, %	50	22	0.135
Alcohol abuse, %	33	21	0.608

analysis, the relative risk of AIDS does not change appreciably. The recalculated crude relative risks excluding females are 21.5 for cerebral infarction (95% CI, 6.9 to 51.2) and 39.2 for ICH (95% CI, 12.5 to 94.7).

A potential source of bias is the possibility of underreporting of AIDS cases in the population under study, which would underestimate the person-time at risk for stroke among AIDS patients and inflate the relative risk associated with AIDS. Available data suggest a high degree of completeness for the CDC AIDS surveillance in the study region during the years of this study. A national study reported a completeness of 92% for 1988,¹⁴ and internal analyses by the Maryland AIDS Registry reported a completeness of 94% for 1991 (personal communication). These evaluations of the reporting rate relied on hospitalization records. Therefore, to the extent that AIDS patients did not receive any hospital inpatient care, the number of cases could be underestimated. Nevertheless, we believe it is unlikely that the magnitude of the underreporting of AIDS cases in the study population would appreciably alter our results. It is also possible that we did not

TABLE 3. Risk Factor Comparison for ICH

Risk Factor	ICH		2-Tailed <i>P</i>
	AIDS Patients (n=6)	Non-AIDS Patients (n=165)	
Mean age, y	34.5	36.1	
Male, %	83	76	0.410
Nonwhite, %	83	58	1.0
Hypertension, %*	25	52	0.36
Diabetes mellitus, %*	0	5	1.0
Elevated cholesterol, %*	50	28	0.575
Ischemic heart disease, %*	0	3	1.0
Current cigarette use, %*	0	23	0.572
Current illicit drug use, %*	75	38	0.296
Alcohol abuse, %*	0	30	0.318

*Only ICHs occurring in 1991 were compared (4 AIDS cases, 79 non-AIDS cases).

TABLE 4. Crude and Adjusted Relative Risk of Stroke for All AIDS Cases

	Crude Relative Risk	95% CI	Adjusted* Relative Risk	95% CI
IS relative risk	23.0	8.4–50.4	13.7	6.1–30.8
ICH relative risk	52.9	19.1–117.6	25.5	11.2–58.0
Either type of stroke relative risk	32.0	16.4–56.3	17.8	10.0–31.6

*Age-, sex-, and race-adjusted.

identify every AIDS patient among our stroke cases. Additionally, some AIDS patients with stroke may not have received ICD-9 codes for stroke at discharge because of a large number of other important medical problems. Both of these circumstances would lead to an underascertainment of AIDS patients with stroke, which would tend to underestimate the association between AIDS and stroke.

Because of the design of our study, it was not possible to adjust relative risks for factors other than age, race, and sex. However, the prevalence of hypertension, diabetes mellitus, and cigarette smoking was lower among AIDS patients with stroke than among stroke patients without AIDS or in the general population, according to data from the Maryland Behavioral Risk Factor Survey for the same region during the same years.¹⁵ Thus, adjustment for these factors would have produced a stronger association between AIDS and stroke.

Our study was conducted in the pre-HAART era, although 4 of our patients were on AZT therapy, as indicated in Table 1. Therefore, our findings are relevant to most AIDS patients worldwide who do not have access to HAART therapy. In addition, our study provides an excellent baseline for the stroke risk of AIDS, which will allow comparison to future studies of stroke risk in the era of HAART therapy.

One strength of our study was that only patients who met the strict 1987 CDC AIDS definition¹⁰ were included in the exposed group. Thus, 10 HIV-positive patients in the IS group and 5 HIV-positive patients in the ICH group were included in the non-AIDS stroke group. If these HIV-positive patients were more comparable to AIDS patients in terms of stroke risk, then this would have tended to decrease the observed association between stroke and AIDS.

In conclusion, this is the first population-based study to directly quantify the AIDS-associated risk of stroke. We also attempted to address the possibility that pathophysiological mechanisms intrinsic to AIDS may predispose to stroke. Even

TABLE 5. Crude/Adjusted Relative Risk of Stroke Excluding Strokes Caused by AIDS-Related Medical Conditions or Other Concomitant Etiologies

	Crude Relative Risk	95% CI	Age-, Race-, Sex-Adjusted Relative Risk	95% CI
IS relative risk	15.3	4.1–39.5	9.1	3.4–24.6
ICH relative risk	26.4	5.4–78.6	12.7	4.0–40.0
Either type of stroke relative risk	18.6	7.5–38.7	10.4	4.9–22.0

after exclusion of 42% of our cases potentially attributable to other known causes or complications of AIDS, there was a strong association between AIDS and both IS and ICH.

Appendix

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