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Effect of CD4 cell count and viral suppression on risk of ischemic stroke in HIV infection

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Abstract

Objectives—Evidence from the current era of combination antiretroviral therapy supports an association between HIV and cerebrovascular disease. In addition to traditional vascular risk factors, HIV-specific factors including immunodeficiency and viral replication may also predict stroke risk. The aim of this study was to determine the relationship between CD4 cell count, viral suppression and validated ischemic stroke outcomes.

Design—Single-center, case-control study

Methods—We identified ischemic stroke cases in HIV-infected adults from an HIV clinic using International Classification of Diseases codes for cerebrovascular disease followed by validation of each case. Controls from the same HIV clinic were selected by incidence density sampling. Demographic and clinical data, including most recent CD4 count and plasma HIV RNA concentration, were abstracted from hospital and HIV clinic electronic medical records. Matched conditional logistic regression models were used to evaluate the association between CD4 cell count, viral suppression and ischemic stroke.

Results—In an adjusted model, viral suppression decreased the odds of ischemic stroke by a factor of 0.16 (95% CI 0.05-0.50, p=0.002). This association, although attenuated (OR 0.31, 95% CI 0.09-1.06, p=0.062), remained after restricting the analysis to ischemic strokes due to true atherosclerotic mechanisms (i.e., excluding infection and malignancy-related strokes).

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Conclusion—Achieving viral suppression may reduce ischemic stroke risk, including risk of atherosclerotic strokes, in HIV-infected individuals.

Keywords

HIV; immunodeficiency; viral suppression; ischemic stroke; cerebrovascular disease

Introduction

HIV-infected individuals are at growing risk for comorbid conditions more prevalent in an aging population, including cerebrovascular disease[1-3]. While several stroke risk factors are common to HIV-infected individuals and the general population[4], HIV-specific factors including immunodeficiency and viral replication may predict cerebrovascular risk in this unique patient population[1-3,5]. Whether the observed association between these factors and stroke is mediated by opportunistic infections and other conditions in uncontrolled HIV infection that predispose to stroke, or via distinct biological mechanisms, including HIV-related immunologic abnormalities and inflammation, remains unclear. Furthermore, in contrast to cardiovascular disease, the heterogeneity of stroke renders it more challenging to rigorously evaluate cerebrovascular risk factors in HIV infection, especially as careful validation of each outcome is required. The primary goal of this study was to examine the relationship between CD4 cell count, viral suppression and validated ischemic stroke outcomes. We secondarily evaluated the impact of restricting the analysis to ischemic strokes due only to true atherosclerotic mechanisms.

Methods

We conducted a single-center, case-control study of HIV-infected patients followed in an HIV clinic at San Francisco General Hospital (San Francisco, California). We included all individuals ≥ 18 years with a first-ever ischemic stroke diagnosed between January 1, 2000 and December 31, 2012. Potential ischemic stroke cases were identified by documentation of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) cerebrovascular codes (433, 434, 436, 437, 443.21, 443.24) in at least one encounter from the hospital or HIV clinic electronic medical records (EMR), which are linked by a unique patient identifier. A board-certified neurologist (F.C.C.) validated all ischemic stroke diagnoses using adapted World Health Organization MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Project[6] criteria. EMR admission notes, discharge summaries and clinic notes were reviewed. Results of brain imaging, carotid ultrasounds, electrocardiograms, echocardiograms and Holter monitoring were also examined to determine stroke mechanism, categorized as large-artery (atherothrombotic), small vessel (lacunar), cardioembolic (other than endocarditis), cryptogenic or other based on Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria[7]. The index date was defined as the date of stroke symptom onset or, if unknown, the date the stroke first came to clinical attention. Potential cases were excluded if the index date preceded the HIV diagnosis.

Controls were selected using incidence density sampling based on the case index date. Controls, defined as HIV-infected individuals followed in the same HIV clinic as cases with an encounter on the case index date but no history of ischemic stroke during the study period, were matched by index date in a 1:1 ratio with cases.

We abstracted demographics, stroke risk factors, health-related behaviors, medications and laboratory results before the index date from the hospital and clinic EMR. Stroke risk factors were identified from admission notes and clinic problem lists. Substance use was identified from HIV clinic notes and categorized as current, past/never used or unknown. Most recent laboratory results before the index date, including CD4 count (FACSCanto II Flow Cytometer, BD Biosciences, San Jose, CA), CD4 nadir (limit of detection 1.0 cells/μl) and plasma HIV RNA concentration (Versant HIV-1 RNA 3.0 bDNA Assay, Bayer, Tarrytown, NY from 2000-2010; RealTime HIV-1 PCR, Abbott Molecular, Des Plaines, IL from 2010-present) were collected. Cases and controls were considered virally suppressed in the six months before the index date if all plasma HIV RNA measurements for at least six months before the index date (with a minimum of one measurement during the time period) were below the laboratory limit of detection (Versant: 75 copies/ml; RealTime: 40 copies/ml).

We used matched conditional logistic regression models to evaluate the association between CD4 count, viral suppression and ischemic stroke adjusted for age and clinically relevant variables chosen with forward stepwise selection. In a secondary analysis, we excluded all ischemic strokes due to non-atherosclerotic mechanisms (e.g., infection-related strokes) and reapplied the selected model. 2-sided p values <0.05 were considered statistically significant. Analyses were performed using Stata (StataCorp 2012. Release 12; Stata Corporation, College Station, TX). The institutional review board of the University of California, San Francisco, approved the study.

Results

Among 165 potential cases of first-ever ischemic stroke in HIV-infected adults, we identified 60 confirmed strokes along with 60 controls. Mean age was 49 years, and 27% were women. Hypertension, dyslipidemia and smoking were prevalent. Additional characteristics are detailed in Table 1.

Of the 60 first-ever ischemic strokes, 14 were due to large-artery atherothrombotic disease, 12 to small vessel disease, 10 to cardioembolic disease other than endocarditis and 10 to other mechanisms: infectious meningitis (4), endocarditis (3), hypercoagulable state in the setting of HIV-related malignancy (2) and carcinomatous meningitis (1). No mechanism was identified in 14 cases, of whom 2 had incomplete stroke evaluations and 6 had unavailable results. Median HIV RNA concentration (p=0.62) and CD4 count (p=0.47) were not significantly different between those with complete versus incomplete or unavailable stroke evaluations.

Several stroke risk factors, including hypertension, dyslipidemia and coronary heart disease, were associated with higher ischemic stroke odds in unadjusted analyses (Table 2). Current alcohol use (versus past use/never used) also predicted statistically significantly higher odds

of ischemic stroke. Viral suppression in the six months before the index date was associated with lower odds of ischemic stroke, while higher HIV RNA concentrations increased ischemic stroke odds. We did not find a statistically significant association between either recent or nadir CD4 count and ischemic stroke odds (Table 2).

In an age-adjusted multivariate matched logistic regression model, dyslipidemia was independently associated with higher odds of ischemic stroke, as was hypertension although this did not reach statistical significance (Table 2). In the adjusted model, viral suppression lowered the odds of ischemic stroke by a factor of 0.16 (95% CI 0.05-0.50, p=0.002). When plasma HIV RNA concentration was included in the model in lieu of viral suppression, it was associated with 1.36 higher odds (95% CI 1.05-1.76, p=0.018) of ischemic stroke per $\log_{10}$ increase in concentration. The two variables were not included in the model together due to collinearity.

After limiting the analysis to ischemic strokes due to an established atherosclerotic or cardioembolic (non-endocarditis) mechanism, we applied the same multivariate model. Viral suppression in the six months before the index date remained protective against ischemic stroke, although confidence intervals were too wide to rule out no effect (OR 0.31, 95% CI 0.09-1.06, p=0.062)(Table 2).

In a sensitivity analysis, we restricted the model to virally suppressed individuals. Given fewer observations (n=17 strokes), we tested the addition of single predictors to an age-adjusted model to identify factors associated with ischemic stroke. A history of hypertension showed a trend toward a statistically significant increase in the odds of ischemic stroke in these individuals with well-controlled HIV (OR 5.28, 95% CI 0.89-31.13, p=0.066). We again did not find a statistically significant association between CD4 count and ischemic stroke odds.

Discussion

In this case-control study of validated ischemic strokes in HIV-infected adults, we demonstrated an association between viral suppression and ischemic stroke risk. Our results are concordant with previous studies of ischemic stroke in HIV-infected cohorts[1,3,8], many of which relied on ICD-9 codes rather than rigorous validation of strokes, as in this study. We did not find a statistically significant association between recent or nadir CD4 count and ischemic stroke risk, although existing data are conflicting on the effect of CD4 count on stroke risk[1-3,5,8,9].

The mechanism underlying the association between viral replication and ischemic stroke is unknown. While a distinct biological mechanism unique to HIV infection may play a role (e.g., HIV-related chronic inflammation and immune activation), the association may be mediated through opportunistic infections and other HIV-related illnesses that also predispose to stroke. To address this question, we tested the association between viral suppression and stroke risk after excluding strokes due to infection and other advanced HIV-related illnesses. Viral suppression remained protective against ischemic stroke, although this effect was attenuated and no longer reached statistical significance. While viral

suppression may play a greater role in protecting against non-atherosclerotic strokes, viral suppression also protected against atherosclerotic strokes. Additionally, after both removing non-atherosclerotic strokes and restricting the analysis to virally suppressed individuals, traditional vascular risk factors (i.e., hypertension, dyslipidemia) remained associated with ischemic stroke. Taken together, these findings underscore the importance of achieving viral suppression and treating traditional risk factors to reduce stroke risk in HIV-infected individuals.

In the Data Collection of Adverse Events of Anti-HIV Drugs (D:A:D) cohort, a two-fold increase in CD4 count was associated with a lower adjusted relative risk of stroke[5]. After excluding stroke-like events, the strength of the observed association was diminished although still statistically significant. We found a similar effect on the association between viral suppression and ischemic stroke risk after excluding strokes due to infection and other advanced HIV-related illnesses. The D:A:D study, however, used a composite stroke outcome and relied on central validation of strokes using a definition that was not designed to distinguish atherosclerotic from non-atherosclerotic mechanisms. In contrast, we examined one specific cerebrovascular outcome—namely, ischemic stroke—given major differences between ischemic and hemorrhagic stroke mechanisms and risk factors. Furthermore, one neurologist with HIV expertise and access to primary stroke evaluation data validated all events with the prespecified purpose of distinguishing between stroke mechanisms.

Our results support an association between viral suppression and validated ischemic strokes in HIV-infected individuals. Despite the heterogeneity of stroke and diverse mechanisms that underlie stroke subtypes (e.g., atherosclerotic vs. cardioembolic vs. infection-related), our study was able to evaluate the impact of immunodeficiency and viral suppression on ischemic stroke risk. While bias due to missing data remains possible, stroke misclassification or inclusion of stroke mimics is unlikely to have occurred. Study limitations include the small number of cases and our inability to validate ischemic strokes without evaluations in the EMR. Strokes classified as cryptogenic may have, in fact, been due to an established mechanism. However, we found no statistically significant difference in median HIV RNA concentration or CD4 count between those with complete versus incomplete or unavailable stroke evaluations.

Our findings provide additional evidence that viral replication is associated with ischemic stroke risk in HIV-infected individuals. While this association may be mediated, in part, by infections and illnesses more common in uncontrolled HIV that predispose to stroke, viral suppression also reduced the odds of atherosclerotic ischemic strokes, independent of traditional vascular risk factors. In HIV-infected individuals, achieving viral suppression may reduce ischemic stroke risk. Moreover, focused attention on treating traditional risk factors is also essential to decrease stroke risk in HIV-infected individuals. Other clinically relevant questions regarding the mechanisms underlying stroke risk in HIV infection remain unanswered, including whether inflammation and immune activation 1) mediate the association between viral replication and ischemic stroke and 2) result in accelerated vascular aging and increased cerebrovascular risk over time, even among virally suppressed individuals. Large-scale observational studies and clinical trials aimed at answering these

questions will position the field to investigate novel interventions to modify stroke risk in this aging population.

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F.C.C. participated in the study conception and design, performed data analysis and interpretation and drafted the manuscript. P.B. performed data analysis and interpretation and provided critical revisions of the manuscript. A.S. participated in the study design and data interpretation and provided critical revisions of the manuscript. R.W.P. participated in data interpretation and provided critical revisions of the manuscript. P.Y.H. participated in data interpretation, provided critical revisions of the manuscript and supervised the study. All co-authors reviewed and accepted the final version of the manuscript.

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Table 1
Clinical characteristics of HIV-infected individuals with and without ischemic stroke

Clinical characteristic (number (%), unless noted)	Cases (n=60)	Controls (n=60)
Age (years), mean (SD)	50.1 (8.3)	48.2 (7.0)
Female	12 (20)	20 (33)
Race		
White	26 (43)	20 (33)
Black/African-American	28 (47)	31 (52)
Latino/Hispanic	1 (2)	0 (0)
Other	5 (8)	9 (15)
Hypertension	44 (73)	28 (47)
Dyslipidemia	25 (42)	9 (15)
Diabetes mellitus	10 (17)	7(12)
Coronary heart disease	15 (25)	1 (2)
Heart failure/Cardiomyopathy	9 (15)	1 (2)
Atrial fibrillation/flutter,	4 (7)	1 (2)
Hepatitis C virus	20 (33)	41 (67)
Current alcohol use	22 (37)	12 (20)
Past alcohol use/never used	35 (58)	48 (80)
Current smoker	36 (60)	48 (80)
Past smoker/never smoked	16 (27)	10 (17)
Current methamphetamine use	10 (17)	9 (15)
Past methamphetamine use/never used	41 (68)	50 (83)
Current cocaine use	23 (38)	23 (38)
Past cocaine use/never used	27 (45)	36 (60)
Current heroin use	5 (8)	8 (13)
Past heroin use/never used	47 (78)	52 (87)
Aspirin use	11 (18)	5 (8)
Statin use	14 (24)	3 (5)
CD4 count (cells/mm^3), median (IQR)	276 (122, 419)	303 (190, 510)
CD4 nadir (cells/mm^3), median (IQR)	102 (36, 208)	44 (12.5, 194)
HIV RNA (log, copies/ml), median (IQR)	3.24 (0, 4.35)	0 (0, 3.59)

Clinical characteristic (number (%), unless noted)	Cases (n=60)	Controls (n=60)
ART use	39 (65)	44 (73)
Virally suppressed in 6 months before index date	22 (37)	40 (67)

Abbreviations: ART, antiretroviral therapy

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Table 2

Odds ratios for predictors of ischemic stroke

	All ischemic strokes (n=60) Bivariate analysis		All ischemic strokes (n=56)‡ Multivariate model		Ischemic strokes after excluding non-atherosclerotic, non-cardioembolic strokes (n=47)§	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Age (per 10 years)*	1.52 (0.88-2.62)	0.13	1.07 (0.53-2.18)	0.84	1.15 (0.55-2.38)	0.72
Female sex	0.50 (0.21-1.17)	0.11	---	---	---	---
Hypertension*	3.00 (1.35-6.68)	0.007	2.66 (0.91-7.81)	0.075	3.18 (0.98-10.31)	0.053
Dyslipidemia*	3.67 (1.49-9.04)	0.005	4.11 (1.27-13.37)	0.019	3.46 (1.03-11.58)	0.044
Diabetes mellitus	1.60 (0.52-4.89)	0.41	---	---	---	---
Coronary heart disease	15.00 (1.98-113.56)	0.009	---	---	---	---
Atrial fibrillation/flutter	4.00 (0.45-35.79)	0.22	---	---	---	---
Alcohol use†	2.83 (1.12-7.19)	0.028	---	---	---	---
Smoking†	0.46 (0.18-1.21)	0.12	---	---	---	---
Methamphetamine use†	1.14 (0.41-3.15)	0.80	---	---	---	---
Cocaine use†	1.56 (0.67-3.59)	0.30	---	---	---	---
Heroin use†	0.667 (0.19-2.36)	0.53	---	---	---	---
CD4 count (per 100 cells/mm^3)	0.92 (0.79-1.08)	0.29	---	---	---	---
CD4 count > 500 cells/mm^3	0.54 (0.21-1.35)	0.19	---	---	---	---
Nadir CD4 count (per 100 cells/mm^3)	1.05 (0.81-1.36)	0.72	---	---	---	---
HIV RNA (per 1 log copies/ml)	1.24 (1.00-1.54)	0.047				
Virally suppressed 6 months before index date*	0.23 (0.09-0.60)	0.003	0.16 (0.05-0.50)	0.002	0.31 (0.09-1.06)	0.062

*Covariates included in multivariate models.

†All alcohol, tobacco and substance use is current use versus never/past use.

‡4 cases excluded due to missing data on viral suppression in the 6 months before index date

§3 cases excluded due to missing data on viral suppression in the 6 months before index date