Greater Risk of Stroke of Undetermined Etiology in a Contemporary HIV-Infected Cohort Compared with Uninfected Individuals

Felicia C. Chow, MD, MAS,* Richard W. Price, MD,* Priscilla Y. Hsue, MD,† and Anthony S. Kim, MD, MAS*

Background: Although ischemic stroke risk is increased among people living with HIV infection, little is known about the epidemiology of ischemic stroke subtypes in contemporary HIV-infected cohorts. We examined the distribution of ischemic stroke subtypes among predominantly treated HIV-infected individuals to determine if and how the distribution differs from that of the general population. *Methods:* We studied 60 HIV-infected and 60 HIV-uninfected adults with a history of first-ever ischemic stroke between 2000 and 2012. Ischemic strokes were classified as 1 of 5 subtypes based on established criteria. We used multinomial logistic regression models to compare the relative frequency of ischemic stroke subtypes by HIV status. *Results:* Large artery atherosclerosis (23%) and stroke of undetermined etiology (23%) were the most common stroke subtypes among HIV-infected individuals. The most recent plasma HIV viral load before the stroke event differed by subtype, with a median undetectable viral load for individuals with large artery stroke and stroke of undetermined etiology. Using cardioembolic stroke as the reference subtype, HIV-infected individuals were at higher proportional risk of stroke of undetermined etiology compared with uninfected individuals (relative risk ratio [RRR]: 8.6, 95% confidence interval [CI]: 1.2-63.7, $P = .04$). Among HIV-infected individuals with virologically suppressed infection, we observed a trend toward a greater proportion of strokes attributable to large artery atherosclerosis (RRR: 6.7, 95% CI: .8-57.9, $P = .08$). *Conclusions:* HIV-infected individuals may be at greater proportional risk of stroke of undetermined etiology compared with uninfected individuals. Further investigation is warranted to confirm this finding and determine underlying reasons for this greater risk. **Key Words:** HIV infection—cerebrovascular disease—ischemic stroke subtype—cerebral infarction.

From the *Department of Neurology, University of California, San Francisco, San Francisco, California; and †Department of Medicine (Division of Cardiology), University of California, San Francisco, San Francisco, California.

Received December 22, 2016; accepted February 3, 2017.

Grant support: This work has been supported by the National Center for Advancing Translational Sciences of the NIH under Award Number KL2TR000143. Support for statistical analysis was provided through the UCSF Clinical and Translational Science Institute (UL1TR000004).

Work was conducted at the Department of Neurology, University of California, San Francisco, Zuckerberg San Francisco General Hospital, San Francisco, CA, USA.

Address correspondence to Felicia C. Chow, MD, MAS, Zuckerberg San Francisco General Hospital, Department of Neurology, University of California, San Francisco, 1001 Potrero Avenue, Building 1, Suite 101, San Francisco, CA 94110. E-mail: felicia.chow@ucsf.edu.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2017.02.010

Introduction

In recent large cohort studies, the risk of stroke is increased for people living with HIV infection compared with uninfected individuals.[1-3] Although several studies have evaluated the distribution of ischemic and hemorrhagic strokes in HIV infection, less is known about the epidemiology of ischemic stroke subtypes. Understanding the distribution of ischemic stroke subtypes in HIV would aid in focusing future investigations of the pathogenesis of this elevated stroke risk and to develop potential novel interventions to modify stroke risk in HIV infection. Many of the prior studies investigating ischemic stroke subtypes in HIV infection were performed in cohorts from either before the introduction of antiretroviral therapy (ART) or of largely untreated HIV-infected individuals with advanced disease,[4-7] and are not generalizable to people living with HIV infection in the modern era of widely available and highly effective combination ART.

In this study of a contemporary cohort of people living with HIV infection and HIV-uninfected patients followed in outpatient clinics from an urban safety net hospital, we examined the distribution of ischemic stroke subtypes to determine if and how, among predominantly ART-treated HIV-infected individuals, the distribution differs from that of the general population.

Methods

Study Design

We identified all HIV-infected individuals 18 years of age and older with a first-ever ischemic stroke diagnosed between 2000 and 2012 who were seen on at least two occasions by a medical provider in an HIV clinic at an urban safety net hospital in San Francisco. Potential cases were first identified by the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes for cerebrovascular disease (433, 434, 436, 437, 443.21, or 443.24). The diagnosis of ischemic stroke was then validated by medical record review by a board-certified neurologist (F.C.C.) using criteria adapted from the World Health Organization MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) project and the Multi-Ethnic Study of Atherosclerosis (MESA).[8,9] Cases were excluded if the stroke event occurred before the diagnosis of HIV. The majority of HIV-infected stroke cases were included in a previously published case-control study with a different HIV-infected comparator group.[10]

The HIV-uninfected cohort was frequency-matched in a 1:1 ratio to the HIV-infected cohort based on the calendar year of ischemic stroke diagnosis from among individuals followed in a primary care clinic in the same urban hospital with an ICD-9-CM code for cerebrovascular disease but no ICD-9-CM code for HIV infection. Ischemic stroke diagnoses in the HIV-uninfected cohort were also validated by medical record review.

Covariates

Demographics, stroke risk factors, health-related behaviors, and laboratories were abstracted from medical records. The presence of vascular risk factors was defined based on problem lists in the primary care or HIV clinic documentation and neurology admission notes. All health-related behaviors (e.g., smoking, alcohol, and substance use) were categorized as current versus never or prior use. Individuals for whom no information was available regarding health-related behaviors were classified as unknown. The most proximate CD4 count and plasma HIV RNA level prior to the stroke event for the HIV-infected cases were recorded. HIV RNA levels below the limit of detection were coded as 0 log copies/mL.

Ischemic Stroke Mechanism

The stroke evaluation performed for each case was reviewed in detail by a board-certified neurologist (F.C.C.) following protocols from MESA.[9,11] The records reviewed included discharge summaries; follow-up neurology, cardiology, primary care and HIV clinic notes; and all available brain magnetic resonance imaging and computed tomography images. The results of electrocardiograms, echocardiograms, Holter monitoring, carotid ultrasound, and conventional angiography were also examined. Based on available data, ischemic strokes were categorized as large artery atherosclerosis (extra- and intracranial), small vessel occlusion (lacunar), cardioembolism, other known etiology, or undetermined etiology based on MESA and TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria.[12] According to TOAST criteria, individuals for whom a complete ischemic stroke evaluation was not performed were classified as stroke of undetermined etiology. To be considered complete, an ischemic stroke evaluation had to include a minimum of brain imaging (computed tomography or magnetic resonance imaging), extra- and intracranial vascular imaging, electrocardiogram, and echocardiogram.[11]

Statistical Analysis

We compared demographic and clinical characteristics between HIV-infected and uninfected stroke cases using Student's *t*-test or chi-square test and HIV-related laboratories by stroke subtype using the Kruskal–Wallis test. We used multinomial logistic regression to determine the relative risk of ischemic stroke subtypes by HIV status after first adjusting for demographics (Model 1) and then for demographics plus additional vascular risk factors identified by forward stepwise selection (Model 2). *P* values were two-sided, with <.05 considered