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Role of pre-stroke immunity in ischemic stroke mechanism among patients with HIV

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Abstract

Individuals with HIV are at a higher risk of stroke compared to uninfected populations. The role of HIV-related immunosuppression in stroke mechanism is uncertain. Our aim is to test the hypothesis that stroke mechanisms among HIV+ individuals vary according to preceding CD4 counts. We carried out a retrospective chart review of inpatient admissions for ICD-9 defined ischemic events (TIA or stroke) in HIV+ individuals from 2002–2016 at a tertiary care center. Stroke mechanisms were ascertained based on radiographic and clinical presentation, and adjudicated by the treating team and confirmed separately by a vascular neurologist. Vascular risk factors, use of antiretroviral drugs (ARVs), nadir CD4 and current CD4 counts (cells/mm³) were captured to build logistic regressions and generalized linear models to calculate the odds ratios (OR) and beta estimates with their respective 95% confidence intervals. We found that among 115 cases (median age 52, 64% men), stroke mechanisms were 22% due to large artery atherosclerosis (LAA), 17% small artery disease, 16% infectious, 8% cardioembolic, 21% cryptogenic, and 16% other etiologies. The median nadir CD4-count was 153 (IQR 22–274), and 312 (IQR 88–518) at the time of stroke, and 53% were on ARVs. LAA was more common with longer HIV infection (OR 1.1 per year, 1.0–1.2) and nadir CD4 counts <200 (OR 6.7, 1.4–31.9). Stroke due to LAA was associated with higher CD4 count the year prior to stroke (B=0.009, P=0.06 for the interaction) independent of CD4 nadir <200 (B=1.88, P=0.035). We concluded that in this sample, LAA was the most frequent stroke mechanism among HIV+ individuals with nadir CD4 <200 but higher CD4 counts near the time of stroke. Determining the association between pre-stroke immune status and stroke mechanisms may allow a targeted approach to stroke prevention.

SUMMARY:

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LAA was more common among individuals with HIV who had nadir CD4 counts < 200 cells/mm³ but who had higher CD4 counts one year prior to stroke. Strokes caused by infections were more common among those with immunosuppression. Preventing immunosuppression through early diagnosis and treatment of the HIV infection in addition to aggressive vascular risks control may impact the stroke disparity in HIV populations.

Keywords

hiv; stroke; atherosclerosis; stroke mechanism; small artery disease

INTRODUCTION:

Prior to the widespread use of effective combined antiretroviral therapy (cART), opportunistic infections and central nervous system neoplasias were often cited as stroke mechanisms.(Levy, Bredesen, & Rosenblum, 1985; Morgello, Block, Price, & Petito, 1988) After the introduction of cART, stroke mechanisms related to large artery atherosclerosis (LAA), small artery disease (SAD) and cardioembolism became more prevalent.(Morgello, Mahboob, Yakoushina, Khan, & Hague, 2002; Ortiz, Koch, Romano, Forteza, & Rabinstein, 2007; Vinikoor et al., 2013) For example, LAA and SAD account for only 30% of the strokes in study samples in which the majority of study subjects have CD4 counts < 200 cell/mm³ but account for 76% of the strokes in study samples in which the majority has of subjects have CD4 counts > 400 cell/mm³.

Stroke prevention depends on the stroke etiology.(Esenwa & Gutierrez, 2015) Consequently, it is important to move on from defining stroke as a homogenous outcome to focus on stroke subtypes pathophysiology. With this in mind, we explored the mechanisms of stroke in a sample of HIV+ patients to test the hypothesis that stroke etiology varies with the pre-stroke immunological status.

METHODS:

Patients 18 years and older were identified using validated ICD-9 codes for HIV (042 [Human Immunodeficiency Virus Diseases] and V08 [Asymptomatic Human Immunodeficiency Virus Infection] and stroke (435 [ischemia, cerebral, transient], 432 [hemorrhage, intracranial], 433.1 [embolism/thrombosis, carotid], 434 [embolism/thrombosis, cerebral], 436 [disease, cerebrovascular]). The data collection was performed between January 1, 2002 to December 31, 2016. The study was approved by the local IRB, including reviewing medical notes and charts with identifiable patient information under the assurance that the identifiable data would not be disclosed and that it will be stored in encrypted local systems.

From each identified case we extracted age, sex, self-reported ethnicity, clinical characteristics and continuous measures related to vascular risks such as hemoglobin A1c %, low density lipoprotein (LDL) cholesterol and triglycerides levels preceding the stroke. We calculated the time of HIV infection as documented in the admission or consult notes. Nadir CD4, viral loads and CD4 counts up to the time of stroke were collected from the laboratory

data or typed reports. For cART, we collected each medication individually and by class at the time of stroke.

Stroke ascertainment:

The stroke mechanism was determined by the admitting team. Separately, a vascular neurologist carried out a detailed review of each case and extracted stroke related variables. Stroke mechanisms were classified as LAA (intra- or extracranial), SAD (penetrating artery infarct with no parent artery luminal irregularities), infectious, others (heterogeneous mechanisms not fitting the categories above), and cryptogenic (no identified etiology). We defined a stroke workup as “thorough” if the work included brain parenchymal imaging (brain CT or MRI), neck and brain arterial imaging, echocardiogram, blood tests (lipid panel, hemoglobin A1c, hypercoagulable tests [i.e. protein C & S activity, antiphospholipid antibodies, etc]) and lumbar puncture.

Statistical analyses: We used the variables reported in table 1 and 2 to construct logistic regression models. First, we assessed for collinearity between reported variables. Nadir CD4 counts correlate with CD4 prior to stroke ($R=0.60$), so we categorized nadir CD4 to <200 versus >200 cell/mm³ and used CD4 count prior to stroke in increments of 50 to allow for larger point estimates. For vascular risk, we chose continuous versus categorical variables depending on which variable provided the best goodness of fit for LAA stroke defined by the change of -2 log. With the final variables, we ran multivariable logistic regression with backward and forward variable elimination to select the top 10 variables. Finally, we used a multilevel generalized linear model to test whether changes in CD4 counts near the time of stroke related differently to stroke mechanisms. A P value <0.05 was considered statistically significant with the exception of interactions, for which we tolerated a P value <0.10 . The statistical analyses were carried out with SAS version 9.4.

RESULTS:

The sample characteristics are described in table 1 and 2. We identified 122 HIV+ patients admitted with stroke (115 ischemic events [103 ischemic strokes and 12 transient ischemic attacks] and 7 hemorrhagic events). Only patients with ischemic events were included in subsequent analyses. Of the 115 ischemic events, 26 (22%) were due to LAA (25 had intracranial LAA and one cervical LAA), 19 (17%) due to SAD, 18 (16%) due to infectious etiologies (six with bacterial endocarditis, five varicella zoster, two cryptococcal meningitis, two toxoplasmosis, one syphilis, one bacterial meningitis, and one mucormycosis), nine (8%) due to cardiac embolism (five atrial fibrillation, four intracavitary clot), and 18 (16%) due to various etiologies (seven with hypercoagulable state [four due to cancer], six due to cocaine use, two due to dissection, one due to sickle cell crisis, and one due to avastin use). Twenty-five patients (21%) had cryptogenic strokes, but among these, only three had a thorough workup.

The median time of follow-up prior to stroke was 2 years (IQR 1–7, range 0–13). Cross-sectional associations were reported in table 3. Using longitudinal data on CD4 counts, we found a persistent association between nadir CD4 <200 cells/mm³ and higher CD4 count the year prior to stroke with LAA but not with SVD (table 4 and supplementary data). The

largest beta estimate for LAA was found among those that had nadir CD4 < 200 cells/mm³ but CD4 > 400 cell/mm³ at the time of or immediately before stroke (B=2.88 ± 0.87, P=0.001) compared with those with nadir CD4 counts < 200 cells/mm³ and CD4 < 200 cells/mm³ at the time of stroke.

DISCUSSION:

The three most important stroke mechanisms in this HIV population were LAA, SAD and infectious etiologies. We found that a CD4 nadir < 200 cells/mm³ may relate to LAA. These results replicate a finding in a sample of autopsied brains in which pathologically defined LAA was more common with pre-mortem low nadir CD4 counts but higher CD4 counts at the time of death.(Gutierrez et al., 2015) Given that some previous findings have indicated that low CD4 nadir also relates to incident MI and ischemic cardiomyopathy,(Silverberg, Leyden, Quesenberry, & Horberg, 2009) it is possible that a low nadir CD4 increases the systemic arterial susceptibility to atherosclerosis beyond traditional vascular risks. It is worth noting, nonetheless, that dyslipidemia remained associated with LAA, thus highlighting the importance of aggressively managing traditional vascular risks in this population. The persistence of infectious etiologies in a cART era adds on to the argument that although cART is readily available, a significant proportion of the HIV population is unaware of the infection and/or do not use cART.(Bradley et al., 2014)

Lower CD4 nadir and higher CD4 count near death have been associated with brain arterial inflammation localized to the intima and closely related to the presence of atheroma. (Gutierrez et al., 2016) Similarly, a nadir CD4 count < 200 cells/mm³ has been associated with faster progression of carotid artery intima-media thickening,(Hsue et al., 2004) a marker of atherosclerosis. We have argued before that it is possible that HIV proteins in the arterial wall may function as perpetual antigenic stimuli, (Gutierrez, et al., 2016) similarly to what has been reported in coronary arteries.(Eugenin et al., 2008) In this context, severe immunosuppression may favor seeding of the arteries with the virus itself or its proteins.

We also reported that SAD is more common in men and among those with Hepatitis C co-infection, and less common among patients with nadir CD4 count < 200 cells/mm³. Co-infections with Hepatitis C has been previously associated with SAD to a greater extent than HIV *per se*, and when compared to uninfected controls.(Morgello, Murray, Van Der Elst, & Byrd, 2014) Epidemiologically, there is evidence that hepatitis C is a risk factor for vascular events among those with HIV,(Bedimo et al., 2010) including coronary heart disease and stroke. Whether HIV accentuates this risk even further merits further analysis.

This report represents to date one of the largest case series of patients with stroke and HIV. We considered a strength of this report the effort to disclose the thoroughness of stroke workup, which evidently influences the final stroke mechanisms. In this context, it is possible that atrial fibrillation and opportunistic infections were underestimated in the absence of long term cardiac monitoring or lumbar puncture, particularly among those with “cryptogenic strokes”. Stroke mechanism ascertainment is a probabilistic exercise and often there are conflicting or overlapping stroke etiologies. It is important, however, for clinicians

to carry out a minimally acceptable workup for patients with HIV and stroke to assess for etiologies with specific treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

REFERENCES:

- Bedimo R, Westfall AO, Mugavero M, Drechsler H, Khanna N, & Saag M (2010). Hepatitis C virus coinfection and the risk of cardiovascular disease among HIV-infected patients. *HIV Med*, 11(7), 462–468. doi: 10.1111/j.1468-1293.2009.00815.x [PubMed: 20163481]
- Bradley H, Hall HI, Wolitski RJ, Van Handel MM, Stone AE, LaFlam M, et al. (2014). Vital Signs: HIV diagnosis, care, and treatment among persons living with HIV--United States, 2011. *MMWR Morb Mortal Wkly Rep*, 63(47), 1113–1117. [PubMed: 25426654]
- Esenwa C, & Gutierrez J (2015). Secondary stroke prevention: challenges and solutions. *Vasc Health Risk Manag*, 11, 437–450. doi: 10.2147/vhrm.s63791 [PubMed: 26300647]
- Eugenin EA, Morgello S, Klotman ME, Mosioian A, Lento PA, Berman JW, et al. (2008). Human immunodeficiency virus (HIV) infects human arterial smooth muscle cells in vivo and in vitro: implications for the pathogenesis of HIV-mediated vascular disease. *Am J Pathol*, 172(4), 1100–1111. doi: 10.2353/ajpath.2008.070457 [PubMed: 18310503]
- Gutierrez J, Goldman J, Dwork AJ, Elkind MS, Marshall RS, & Morgello S (2015). Brain arterial remodeling contribution to nonembolic brain infarcts in patients with HIV. *Neurology*, 85(13), 1139–1145. doi: 10.1212/WNL.0000000000001976 [PubMed: 26320196]
- Gutierrez J, Menshaw K, Gonzalez M, Goldman J, Elkind MS, Marshall R, et al. (2016). Brain large artery inflammation associated with HIV and large artery remodeling. *AIDS*, 30(3), 415–423. doi: 10.1097/QAD.0000000000000927 [PubMed: 26765935]
- Hsue PY, Lo JC, Franklin A, Bolger AF, Martin JN, Deeks SG, et al. (2004). Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection. *Circulation*, 109(13), 1603–1608. doi: 10.1161/01.CIR.0000124480.32233.8A, 01.CIR.0000124480.32233.8A [pii] [PubMed: 15023877]
- Levy RM, Bredesen DE, & Rosenblum ML (1985). Neurological manifestations of the acquired immunodeficiency syndrome (AIDS): experience at UCSF and review of the literature. *J Neurosurg*, 62(4), 475–495. doi: 10.3171/jns.1985.62.4.0475 [PubMed: 2983051]
- Morgello S, Block GA, Price RW, & Petito CK (1988). Varicella-zoster virus leukoencephalitis and cerebral vasculopathy. [Case Reports]. *Arch Pathol Lab Med*, 112(2), 173–177. [PubMed: 3337629]
- Morgello S, Mahboob R, Yakoushina T, Khan S, & Hague K (2002). Autopsy findings in a human immunodeficiency virus-infected population over 2 decades: influences of gender, ethnicity, risk factors, and time. *Arch Pathol Lab Med*, 126(2), 182–190. doi: 10.1043/0003-9985(2002)126<0182:AFIAHL>2.0.CO;2 [PubMed: 11825115]
- Morgello S, Murray J, Van Der Elst S, & Byrd D (2014). HCV, but not HIV, is a risk factor for cerebral small vessel disease. *Neurol Neuroimmunol Neuroinflamm*, 1(3), e27. doi: 10.1212/nxi.0000000000000027 [PubMed: 25340079]
- Ortiz G, Koch S, Romano JG, Forteza AM, & Rabinstein AA (2007). Mechanisms of ischemic stroke in HIV-infected patients. *Neurology*, 68(16), 1257–1261. doi: 68/16/1257 [pii], 10.1212/01.wnl.0000259515.45579.1e [PubMed: 17438215]
- Silverberg MJ, Leyden W, Quesenberry CP, Jr., & Horberg MA (2009). Race/ethnicity and risk of AIDS and death among HIV-infected patients with access to care. *J Gen Intern Med*, 24(9), 1065–1072. doi: 10.1007/s11606-009-1049-y [PubMed: 19609624]
- Vinikoor MJ, Napravnik S, Floris-Moore M, Wilson S, Huang DY, & Eron JJ (2013). Incidence and Clinical Features of Cerebrovascular Disease Among HIV-Infected Adults in the Southeastern United States. *Aids Research and Human Retroviruses*, 29(7), 1068–1074. doi: DOI 10.1089/aid.2012.0334 [PubMed: 23565888]

Table 1:

Demographic, clinical and ancillary characteristics of the sample studied.

	All ischemic events (N=115)	LAA (N=26)	Small artery disease (N=19)	Infectious etiologies (N=18)
Age (in years), median, IQR	52, 46–58	56, 49–68	57, 54–63	47, 40–56
Male sex (%)	64	54	74	67
Ethnicity (%)				
Non-Hispanic white	10	4	5	6
Non-Hispanic black	57	62	73	50
Hispanic	28	27	21	39
Other/mixed	5	8	0	6
Hypertension (%)	60	77	68	39
Left ventricular hypertrophy	36	42	32	38
Diabetes (%)	24	31	21	28
Hemoglobin A1c %, (median, IQR)	6, 5.2–6.3	6.2, 6.2–6.9	5.5, 5.3–5.9	5.7, 5.0–7.2
Dyslipidemia (%)	36	62	32	11
LDL cholesterol (median mg/dl, IQR)	103, 68–125	118, 83–139	83, 67–119	79, 47–113
Triglycerides (median mg/dl, IQR)	189, 96–247	167, 103–220	98, 85–164	221, 67–257
Active smoking (%)	24	23	37	11
Drug use	27	19	42	17
Hepatitis C	22	31	48	22
Hepatitis B	8	4	5	11
Prior stroke	20	34	21	11
Prior cardiac disease	20	35	5	11
Chronic kidney disease	17	27	11	11
Cancer	10	8	5	0
Concurrent asymptomatic carotid stenosis > 40%	14	24	11	7.7
Concurrent asymptomatic intracranial stenosis	32	65	6	50
NIHSS on admission	3, 3–6	3, 1–6	2, 1–5	11, 3–22

Abbreviations: N, number; LAA, large artery atherosclerosis; IQR, interquartile-range; NIHSS, National Institute of Health Stroke Scale; LDL, low density lipoprotein.

Table 2:

Immunological and HIV related characteristic of the sample studied

	All ischemic events (N=115)	LAA (N=26)	Small artery disease (N=19)	Infectious etiologies (N=18)
Median length of HIV infection (in years), IQR	12, 4–18	15, 9–23	9, 4–21	5, 0–16
Median CD4 count prior or at the time of the stroke, IQR	312, 88–518	412, 317–412	400, 252–780	51, 13–247
Median nadir CD4 count, IQR	153, 22–274	155, 62–155	239, 100–780	50, 5–155
Nadir CD4 < 200 cells/mm ³ (%)	63	64	32	89
Median viral load prior to stroke	434, 20–19512	20, 20–1216	400, 20–18709	11267, 548–98050
History of prior opportunistic infections (%)	44	39	37	56
Median number of prior OI	0, 0–2	0, 0–2	0, 0–1	1, 0–2
Candida (%)	26	27	11	33
HSV (%)	8	8	0	17
VZV (%)	6	8	5	6
Tb (%)	5	4	11	6
PCP (%)	21	19	11	17
Mac (%)	8	0	11	6
Antiretroviral use (%)	64	89	58	39
Median number of ARV medications	3, 0–3	3, 3–4	3, 0–3	0, 0–3
NRTI (%)	53	77	58	28
NNRTI (%)	17	19	21	0
PI (%)	34	50	32	28
INSTI (%)	14	19	5	28
FI (%)	2	4	0	6
CCR5 (%)	0	0	0	0
Lumbar puncture done (%)	46	50	21	89
WBC > 4 [*] (%)	42	15	25	75
Median protein	71, 46–106	45, 35–75	86, 55–137	116, 77–156
Median glucose	63, 52–78	69, 61–85	57, 50–63	56, 42–72

Abbreviations: N, number; LAA, large artery atherosclerosis; IQR, interquartile-range; OI, opportunistic infections; HSV, herpes simplex virus; VZV, Varicella Zoster; Tb, Tuberculosis; PCP, Pneumocystis Carinii; Mac, Mycobacterium Avium-Intracellulare; ARV, antiretroviral therapy; NRTI, Nucleoside Reverse Transcriptase Inhibitors; NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitors; PI, protease inhibitors; INSTI, integrase strand transfer inhibitors; FI, fusion inhibitors; CCR5, Chemokine Co-receptor Antagonists.

* Adjusted by red blood cell count at expected ratio of 1WBC:750 RBC.

Table 3:

Multivariable logistic regression predictors of ischemic stroke mechanism

	Large artery atherosclerosis OR (95% CI)	Small artery disease OR (95% CI)	Infectious etiologies OR (95% CI)
Male sex	-	5.80, 1.07–31.52	-
Non-Hispanic black	1.76, 0.40–7.82	3.18, 0.72–14.24	0.48, 0.14–1.61
Dyslipidemia	5.01, 0.99–25.25	0.63, 0.14–2.79	-
Smoking	2.51, 0.47–13.55	3.75, 0.78–18.10	0.17, 0.03–0.93
Prior stroke	10.34, 1.72–62.27	3.36, 0.58–19.63	0.31, 0.05–1.96
Prior cardiac disease	2.43, 0.55–10.60	0.10, 0.09–0.99	0.80, 0.14–4.68
Chronic kidney disease	4.25, 0.70–25.73	0.93, 0.13–6.74	0.92, 0.15–5.43
HbA1c (per 1 % change)	1.62, 0.99–2.63	-	-
Length of HIV infection	1.12, 1.01–1.24	-	-
CD4 count at the time of stroke (per 50 cell-increments)	1.08, 0.97–1.21	-	0.74, 0.61–0.88
Nadir CD4 count < 200 cells/mm ³	10.44, 1.64–66.26	0.07, 0.01–0.33	-
Hepatitis C co-infection	-	10.89, 2.10–56.41	-

Analytic note: variables for each model were selected if the p value was ≤ 0.20 in multi-adjusted backwards logistic regression using table 1 and 2 variables.

Table 4:

Longitudinal retrospective analysis of CD4 counts preceding stroke

	Model 1	Model 2	Model 3	Model 4	Model 5
	LAA (Beta estimate $\pm$ SE)	LAA (Beta estimate $\pm$ SE)	LAA (Beta estimate $\pm$ SE)	LAA (Beta estimate $\pm$ SE)	SAD (Beta estimate $\pm$ SE)
Nadir CD4 count < 200 cells/mm³	1.88 $\pm$ 0.89, P=0.035	4.27 $\pm$ 3.02, P=0.16	3.16 $\pm$ 1.21, P=0.009	6.89 $\pm$ 4.71, P=0.14	-2.94 $\pm$ 0.92, P=0.001
CD4 count over time (per 50 cell-increments)	0.001 $\pm$ 0.022, P=0.95	-0.041 $\pm$ 0.207, P=0.20	-0.07 $\pm$ 0.07, P=0.29	-0.131 $\pm$ 0.191, P=0.49	0.095 $\pm$ 0.062, P=0.12
CD4 count over time*year prior to stroke	0.009 $\pm$ 0.005, P=0.067	0.142 $\pm$ 0.048, P=0.003	0.060 $\pm$ 0.016, P=0.003	0.120 $\pm$ 0.044, P=0.044	-0.011 $\pm$ 0.017, P=0.49

Model 1: Using variables listed in Table 3 as predictors

Model 2: Using all variables listed in Tables 1 and 2 as predictors

Model 3: Comparing LAA only to non-infectious stroke mechanisms

Model 3: Comparing LAA only to non-infectious stroke mechanisms AND using all variables listed in Tables 1 and 2 as predictors

Model 5: Using small artery disease as outcome instead of LAA.

Abbreviations: LAA, large artery atherosclerosis; SE, standard error; SAD, small artery disease.