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Frequency and risk factors for cerebral arterial disease in a HIV/AIDS neuroimaging cohort

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Abstract

Background—Infection with HIV predisposes patients to a myriad of neurologic disorders, including cerebrovascular disease. The pathophysiology is likely multifactorial, with proposed mechanisms including infectious vasculitis, HIV-induced endothelial dysfunction, and adverse effects of combination antiretroviral therapy (cART). Epidemiologic data on clinically-evident cerebral vasculopathy in HIV-infected adults is scarce, even though stroke hospitalizations are rising in this patient population.

Methods—6,298 HIV-infected adults (San Francisco General Hospital, 2000 to 2013) were screened to generate a cohort of patients with dedicated neuroimaging of the intra- and extracranial cerebral vasculature. We extracted information regarding the extent of HIV disease (including serial viral load and CD4 counts), cardiovascular disease risk factors, and exposure to cART (cross-referenced with pharmacy records) and performed multivariate logistic regression analysis to identify predictors of vasculopathy.

Results—Of 144 patients, 55 patients (38.2%) had radiographic evidence of cerebral vasculopathy. 20 (13.9%) had a vasculopathy characterized by vessel dolichoectasia and intracranial aneurysm formation. 35 patients (24.3%) had intra- and or extracranial stenosis/occlusion. cART use (OR 2.27, 95% CI 1.03-5) and tobacco abuse (OR 2.35, 95% CI 1.04-5.25) were independently associated with the development of any vasculopathy, whereas cART use was also an independent risk factor for the stenosis/occlusion subtype specifically (OR 2.87, 95% CI 1.11-7.45).

Conclusions—There was a high frequency of cerebral arterial disease in this neuroimaging cohort of HIV/AIDS patients. A history of cART use along with a history of tobacco abuse were independent risk factors for vasculopathy, though these findings should be confirmed in large-scale prospective studies.

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INTRODUCTION

Within the past decade, there has been a substantial rise in the number of stroke hospitalizations for HIV-infected patients, even in the face of a declining rate of stroke hospitalizations overall [1]. And though there is conflicting data, recent studies suggest an increased stroke risk in HIV-infected patients compared with demographically and behaviorally similar uninfected patients [2]. One potential cause of stroke in HIV-infected patients is vascular disease of the cerebral vessels (e.g. cerebral vasculopathy). The earliest studies of vasculopathy as a direct consequence of HIV infection were in various animal models. Approximately 20% of rhesus monkeys infected with simian immunodeficiency virus (SIV) developed an arteriopathy characterized by intimal hyperplasia and fibrosis [3]. In another model, 60% of HIV-1 transgenic mice harbored vascular lesions – including lesions of the cerebral vessels – similar to those observed in the SIV model [4]. Regarding HIV-infected patients, the first reports of clinically-evident cerebral vasculopathy were in the pediatric AIDS population. The intracranial vessels of these children – all with high viral loads and low CD4 counts – were described as tortuous and ectatic, often with aneurysmal dilatations [5, 6]. Case reports of cerebral vasculopathy in HIV-infected adults were subsequently published [7, 8]. Observational studies of stroke in HIV-infected patients again noted the presence of vasculopathy in a subset of patients – intra- and extracranial, including both stenotic and aneurysmal lesions. These cohorts were relatively young and devoid of traditional risk factors for cardiovascular disease (CVD) [9, 10]. The etiology of the arterial cerebrovascular disease in these HIV-infected patients was unclear, though proposed mechanisms included concomitant infectious vasculitides, HIV-induced endothelial dysfunction, and even adverse effects of combination antiretroviral therapy (cART).

In this study, we sought to radiographically characterize and define the prevalence of cerebral arterial disease in a large neuroimaging cohort of HIV-infected adults in San Francisco. We hypothesized a relatively high frequency of vasculopathy in our HIV cohort, and evaluated multiple HIV-related and cART-related factors along with traditional CVD risk factors to try and identify predictors of vasculopathy.

METHODS

Study population

We performed a search via The Health Record Data Service (THREDS) to identify all patients with an International Classification of Diseases, Ninth revision (ICD-9) code of 042 through 044 (HIV disease), V08 (asymptomatic HIV infection status), or 795.71 (non-specific serologic evidence of HIV) in the electronic database of patients treated at San Francisco General Hospital during 2000 to 2013. HIV infection was confirmed by review of diagnostic laboratories (HIV-1/HIV-2 antibody testing and/or detection of HIV-1 nucleic acids by polymerase chain reaction (PCR)). A total of 6,298 HIV-infected patients were identified. We then screened the radiologic records of all HIV-infected patients to delineate our cohort of interest – those with cerebrovascular imaging of the intra- and extra-cranial vasculature via computed tomography (CT) angiography, magnetic resonance (MR) angiography, or conventional angiography. 144 HIV-infected patients with cerebrovascular

imaging were identified and entered into our study. The University of California at San Francisco Committee on Human Research approved this study.

Data extraction

Detailed reviews of electronic medical records were performed for each patient. We extracted information regarding the extent and duration of HIV disease, comorbid cardiovascular conditions and CVD risk factors, inpatient and outpatient pharmacy history, and relevant laboratories. cART regimens and duration were cross-checked with pharmacy records and cocaine and/or methamphetamine use was determined by self-report in conjunction with urine toxicology reports (when available). The radiologic reports of all cerebrovascular imaging studies were reviewed and the actual images were also interpreted retrospectively by an experienced neurologist (N.J.E). We categorized the cerebrovascular findings into three groups: 1) normal vasculature, 2) dolichoectasia and/or intra- or extracranial aneurysms (dolichoectasia/aneurysm), and 3) flow-limiting vascular narrowing or occlusion (stenosis/occlusion).

Statistical analysis

For the univariate analysis, the two vasculopathy subtypes (dolichoectasia/aneurysm; stenosis/occlusion) were individually assessed against the absence of vasculopathy. The Student's t-test was used for continuous variables, and the Mann Whitney U test and Chi-square test were used for categorical variables. We then performed a multivariate analysis to identify those factors independently contributing to any vasculopathy, and a multinomial logistic regression to identify potential risk factors for the two vasculopathy subtypes compared to the absence of vasculopathy. The following variables were considered as candidates for inclusion in our multivariate/multinomial models: demographics, traditional CVD risk factors, HIV-related factors, and all variables with p values < 0.02 on univariate analysis. All analyses were conducted using SPSS, version 21.0. Statistical significance was set at $p < 0.05$.

RESULTS

Prevalence of cerebral arterial disease in our study cohort

Of the 6,298 HIV-infected patients screened, 144 had undergone cerebrovascular imaging of the intra- and extracranial vessels with CT, MR, or conventional angiography. The presence of a focal neurologic deficit (67 patients) was the primary indication for imaging in this cohort, though altered mental status (30 patients), trauma (16 patients), syncope (12 patients), and seizure (9 patients) were also frequent reasons.

84 of 144 patients (58.3%) had normal intra- and extracranial vascular imaging. 20 (13.9%) had a vasculopathy characterized by dolichoectasia – elongated, tortuous vessels – with or without aneurysms. Within this vasculopathy subtype, 10 patients had intracranial aneurysms without additional vessel findings, 9 patients had intracranial aneurysms in conjunction with vessel dolichoectasia, and 1 patient had multi-vessel dolichoectasia without discrete aneurysm formation. 3 patients had multiple aneurysms. All the aneurysms were intracranial, with 76.2% located in the anterior circulation.

The other vasculopathy subtype we identified was essentially the polar opposite of dolichoectasia. This subtype – stenosis/occlusion – was characterized by flow-limiting vessel narrowing or frank vessel occlusion. Within our imaging cohort, 35 patients (24.3%) had evidence of intra- and/or extracranial stenosis/occlusion. 20 of these 35 patients had exclusively intracranial disease, whereas 11 had exclusively extracranial disease; 4 patients had diffuse disease involving both intra- and extracranial vessels. Of those with extracranial vessel involvement, the carotid artery was the stenosed or occluded vessel in 13 (86.7%) patients, with moderate to severe carotid stenosis in 11 of these 13 (84.6%).

5 patients (3.5%) had “other” vascular lesions – 3 patients had arteriovenous malformations and 2 patients had extracranial dissections, likely traumatic in origin.

Association of vasculopathy with HIV-related and cerebrovascular risk factors

The baseline characteristics of our HIV-infected cohort, as stratified by their cerebrovascular imaging findings, are outlined in Table 1. Regarding traditional CVD risk factors, a history of diabetes and hyperlipidemia were relatively infrequent, whereas tobacco abuse and cocaine and/or methamphetamine use (both prior and active use) were fairly prevalent in our study cohort. Univariate analysis identified several variables associated with vasculopathy. Female gender and higher peak viral load were associated with the dolichoectasia/aneurysm subtype, whereas a history of cART use, hypertension, and hyperlipidemia were associated with the stenosis/occlusion subtype. The mean peak viral load in patients with normal vessels was 126,114 copies/mL in contrast to 317,161 copies/mL in those with vessel dolichoectasia and/or aneurysms.

Multivariate analysis was then performed to delineate 1) those variables independently associated with any vasculopathy (as compared to patients without vasculopathy), and 2) those variables predictive of vasculopathy subtype specifically – dolichoectasia/aneurysm versus stenosis/occlusion. The results are provided in Tables 2 and 3. Following adjustment for demographics, HIV-related factors, and traditional CVD risk factors, a history of cART use (adjusted OR = 2.27, 95% CI: 1.03-5) along with a history of tobacco abuse (adjusted OR = 2.35, 95% CI: 1.04-5.25) were independently associated with the development of any vasculopathy. Of those patients with vasculopathy, a history of cART use (adjusted OR = 2.87, 95% CI: 1.11-7.45) was independently associated with the stenosis/occlusion subtype. No variables were independently associated with the dolichoectasia/aneurysm subtype, though female gender approached significance (adjusted OR = 3.09, 95% CI: 0.92-10).

DISCUSSION

Our study is the largest study to date of radiographically-evident cerebral vasculopathy in HIV-infected patients. The frequency of cerebral arterial disease in our study cohort was high: 55 patients, 38.2%, had vascular abnormalities on neurovascular imaging obtained for a variety of indications. These vascular abnormalities were divided into two subtypes given probable contrasting pathophysiologies: 1) dolichoectasia/aneurysm, likely to be characterized pathologically by atrophy of the media and fragmentation of the elastic lamina, and 2) stenosis/occlusion, likely to be secondary to intimal hyperplasia and smooth muscle cell proliferation, akin to atherosclerosis. We discovered the prevalence of both

vasculopathy subtypes to be quite high in our cohort, as 13.9% of patients had dolichoectatic/aneurysmal vessels and 24.3% had stenotic or occluded vessels. This is in sharp contrast to historical prevalence studies of the general population. One systematic review estimated the prevalence of cerebral aneurysms in the general population to be 2% [11]. Even in populations enriched for aneurysm risk factors – such as acute ischemic stroke patients – the prevalence of cerebral aneurysms has been reported as only 6.6-9.3% [12, 13]. Regarding those patients with stenotic/occluded vessels, 11 patients, 7.6% of our cohort, had evidence of moderate to severe carotid stenosis, the mean age of this subset being 51.9 years old. Contrast this to previously published studies of the general population that estimate a 0.5 to 1% prevalence of moderate to severe carotid stenosis in patients under the age of 60 [14].

The high frequency of vasculopathy reported here should be interpreted with several study limitations in mind. First, our study cohort is a cohort of HIV-infected patients referred for neuroimaging; as a result, there may be a degree of selection bias. Nevertheless, the indications for imaging were varied; in fact, 11% of patients received imaging simply due to a history of head and neck trauma. Another caveat to the interpretation of our study is the single site nature, particularly as high rates of drug abuse (cocaine/methamphetamines, tobacco) were noted in our study subjects. Cocaine- and methamphetamine-induced vasculopathy have been previously described, and in one study of stroke in cocaine users, 12 of 45 patients were noted to have carotid stenosis during their stroke evaluation [15]. In the stroke study, though, patients had high rates of concomitant CVD risk factors whereas our study subjects had considerably lower rates of diabetes and hyperlipidemia (and to a lesser degree, hypertension). Furthermore, active and/or prior cocaine/methamphetamine use was prevalent across all our study groups (e.g. patients with and without vasculopathy); only tobacco abuse was independently associated with vasculopathy in our cohort. And lastly, one could argue the prevalence of drug abuse in our cohort reinforces the generalizability of our study results to the greater HIV population. Similar rates of drug abuse were noted in the Fat Redistribution and Metabolic Change in HIV Infection cohort with 16 participating clinical sites across the United States, and studies of HIV-infected patients in Sub-Saharan Africa have also documented equivalently high drug abuse rates [10, 16].

The pathogenesis of cerebral arteriopathy in HIV is likely multifactorial. Hypotheses regarding pathophysiology range from vasculitis due to non-HIV infectious agents, direct viral invasion of vascular cells and/or endothelial injury mediated by HIV proteins, chronic immune dysregulation and inflammation, and toxicities of HIV drug regimens [9, 17-20]. Several patients in our cohort likely had an infectious cerebral vasculitis; 1 patient with vessel dolichoectasia and multiple intracranial aneurysms had biopsy-proven varicella zoster virus (VZV) vasculitis. Though our study was not one of vasculitis per se, we did not find a significant correlation of cerebral arteriopathy with a history of syphilis, clinical history of zoster, hepatitis B and/or C co-infection, or a history of intracranial infection. This should be interpreted with caution, though – as our study was retrospective, we do not have comprehensive infectious serologies and/or cerebrospinal fluid results for all our patients.

Although HIV is unlikely to be vasculotropic, vascular cells are continually exposed to HIV-infected leukocytes, viral proteins, and viral-induced proinflammatory cytokines [21].

Plasma concentrations of multiple inflammatory biomarkers are significantly elevated in HIV-infected patients compared with controls, and several of these biomarkers have been linked to endothelial injury and atherosclerosis [22-24]. For instance, in one study of carotid intima-media thickness (IMT) in HIV-infected patients, higher levels of high sensitivity C-reactive protein (hsCRP) correlated with both higher levels of IMT and faster progression of IMT in the carotid bifurcation region [25]. In the prospective SUN Study, HIV-infected patients with suppressed viral loads throughout the study period had significantly less CIMT progression compared with patients with detectable viral loads [26]. Similarly, we sought to determine whether HIV-related factors such as peak viral load, nadir CD4 count, and duration of HIV correlated with the presence of cerebral vasculopathy in our study subjects. In the univariate analysis, higher peak viral loads were associated with the dolichoectasia/aneurysm vasculopathy subtype, though this was not reproduced in the multivariate analysis. This may in part be due to the relatively small number of patients in the dolichoectasia/aneurysm subtype (20 patients, versus 84 with normal vessels), and therefore warrants further prospective evaluation. In one relatively large study of intracranial arterial samples obtained at autopsy, HIV-infected patients with protracted infection and/or detectable viral loads at death had significantly higher rates of dolichoectasia [27]. Interestingly, in our study subjects, the use of cART was significantly and independently associated with cerebral vasculopathy even when controlling for HIV disease severity, with the use of cART conferring a nearly three-fold increase in the risk of cerebrovascular disease. Furthermore, cART was predictive for the stenosis/occlusion vasculopathy subtype – the subtype whose pathophysiology is likely akin to atherosclerosis. Though controversy exists, several lines of evidence suggest long-term use of cART may contribute to vascular disease, particularly accelerated atherosclerosis [17, 28-30]. Certain antiretroviral drugs (protease inhibitors) may result in metabolic disorders such as insulin resistance and dyslipidemia. Several studies suggest abacavir, a nucleotide reverse transcriptase inhibitor, may upregulate various proinflammatory cytokines (hsCRP, interleukin-6) in patients with HIV [31]. As HIV-infected individuals receiving cART are likely to live longer, they may do so with long-term metabolic challenges and/or the ramifications of chronic systemic inflammation, potentially increasing vascular disease risk. Therefore, vigilance in minimizing additional vascular risk factors in patients receiving cART is likely advisable. In our study subjects, tobacco abuse was the other variable independently associated with vasculopathy; it has yet to be seen if tobacco abuse and cART have additive effects upon cerebrovascular disease and/or events.

CONCLUSION

In conclusion, in this neuroimaging cohort of HIV-infected patients, the frequency of cerebral arterial disease was high. Two types of vasculopathy were identified – dolichoectasia with or without intracranial aneurysms, and stenosis or frank occlusion of intra- or extracranial vessels. The use of cART and tobacco abuse were both independently associated with any vasculopathy, with the use of cART also being an independent predictor of the stenosis/occlusion vasculopathy subtype. Although higher peak viral loads and female gender were also identified in the univariate analysis as predictive of the dolichoectasia/aneurysm subtype, this was not confirmed in the multivariate analysis. Further prospective epidemiological studies are warranted, as are studies exploring the pathophysiology,

progression, and the clinical ramifications of cerebrovascular disease in HIV-infected patients (e.g. stroke, HIV-associated neurocognitive disorders).

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Table 1

Baseline characteristics of HIV-infected patients with and without vasculopathy

Parameter headings	Normal (n = 84)	Dolichoectasia and/or aneurysm (n = 20)	*P* value	Stenosis or occlusion (n = 35)	*P* value
Age	48.4	48	0.87	52	.06
Gender (M:F)	71:13	12:8	0.01*	27:8	0.34
Nadir CD4 (T cells/μL)	237	229	0.90	216	0.63
Peak viral load (copies/mL)	126114	317161	0.02*	99542	0.40
Duration of HIV (y)	9.3	8.9	0.85	9.2	0.93
cART (ever)	42 (50%)	12 (60%)	0.42	26 (74%)	0.02*
Duration of cART (y)	6.5	5.5	0.46	6.9	0.75
PI (ever)	28 (33%)	8 (40%)	1	15 (43%)	0.38
cART CPE	7.3	6.7	0.46	7.5	0.63
Acute stroke identified at the time of vascular imaging	59 (70%)	13 (65%)	0.85	19 (54%)	0.15
Cocaine and/or methamphetamines (ever)	51 (61%)	13 (72%)	0.72	18 (51%)	0.35
Cocaine and/or methamphetamines (current use)	28 (33%)	9 (45%)	0.33	9 (26%)	0.41
Hepatitis B and/or C co-infection	45 (54%)	10 (50%)	0.77	14 (40%)	0.18
Hypertension	31 (37%)	9 (45%)	0.5	20 (57%)	0.04*
Diabetes mellitus	8 (10%)	2 (10%)	1	7 (20%)	0.12
Hyperlipidemia	16 (19%)	4 (20%)	1	13 (37%)	0.04*
Tobacco (ever)	42 (50%)	13 (72%)	0.23	21 (60%)	0.32
History of syphilis	8 (10%)	1 (5%)	1	5 (14%)	0.52
Clinical history of zoster	9 (11%)	3 (15%)	0.70	4 (11%)	1
Intracranial infection (ever)	16 (19%)	3 (15%)	1	6 (17%)	0.81
Intracranial neoplasm (ever)	3 (4%)	1 (5%)	0.58	0 (0%)	0.55

Continuous variables are presented as means.

CART, highly active antiretroviral therapy; PI, protease inhibitor; CPE, CNS Penetration-Effectiveness; y, years.

* $p < 0.05$

Table 2

Multivariable analysis of factors contributing to any vasculopathy

Variable	Adjusted odds ratio (95% CI)	*P* value
Age	1.09 (0.67-1.76)	0.74
Gender	2.49 (0.99- 6.3)	0.05
cART (ever)	2.27 (1.03-5)	0.04*
Peak viral load	1.11 (0.91-1.34)	0.28
Nadir CD4 count	0.96 (0.81-1.12)	0.59
Cocaine and/or methamphetamines (ever)	0.76 (0.33-1.8)	0.52
Hypertension	1.40 (0.6-3.27)	0.43
Diabetes	1.55 (0.44-5.43)	0.49
Hyperlipidemia	1.29 (0.51-3.24)	0.59
Tobacco (ever)	2.35 (1.04-5.25)	0.04*

CI, confidence interval

* $p < 0.05$

Table 3

Multinomial regression analysis of factors contributing to the two vasculopathy subtypes

	Dolichoectasia and/or aneurysm		Stenosis or occlusion	
Variable	**Adjusted OR (95% CI)**	***P* value**	**Adjusted OR (95% CI)**	***P* value**
Age	1.01 (0.49-2.05)	0.99	1.01 (0.61-1.85)	0.82
Gender	3.09 (0.92-10)	0.07	2.1 (0.7-6.33)	0.19
cART (ever)	2.02 (0.64-6.37)	0.23	2.87 (1.11-7.45)	0.03*
Peak viral load	1.22 (0.93-1.6)	0.13	0.82 (0.55-1.21)	0.2
Nadir CD4 count	1.04 (0.84-1.28)	0.72	0.82 (0.65-1.03)	0.18
Cocaine and/or methamphetamines (ever)	0.85 (0.26-2.83)	0.8	0.75 (0.28-1.98)	0.56
Hypertension	1.58 (0.48-5.15)	0.45	1.33 (0.50-3.57)	0.58
Diabetes	1.15 (0.17-7.81)	0.89	1.7 (0.42-6.84)	0.45
Hyperlipidemia	0.88 (0.22-3.5)	0.85	1.7 (0.6-4.8)	0.59
Tobacco (ever)	2.63 (0.81-8.55)	0.11	2.14 (0.84-5.40)	0.11

OR, odds ratio

CI, confidence interval

* $p < 0.05$