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Cerebrovascular Ischemic Events in HIV-1-Infected Patients Receiving Highly Active Antiretroviral Therapy: Incidence and Risk Factors

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Key Words
Stroke · HIV · Antiretroviral therapy · Atherosclerosis

Abstract
Background: Stroke risk is increased in AIDS patients, and highly active antiretroviral therapy (HAART) may accelerate atherosclerosis, but little is known about the incidence and risk factors for ischemic stroke in patients under HAART. We have studied the incidence, types of stroke and possible risk factors for cerebrovascular ischemic events in a large cohort of HIV-1-infected patients treated with HAART. ***Methods:*** We conducted a retrospective review of ischemic strokes and transient ischemic attacks occurring in a cohort of HIV-1-infected patients treated with HAART from 1996 to 2008. As a control group, consecutive unselected patients from the same cohort were included. Patients and controls were compared for demographic, clinical and laboratory variables, including vascular risk factors, data on HIV infection and duration of HAART. Variables with significant differences were included in a backward logistic regression model. ***Results:*** Twenty-seven cerebrovascular ischemic events occurred in 25 patients, with an incidence of 189 events (166 strokes) per 100,000 patients/year. Independent factors associated with cerebrovascular events were: history of high alcohol intake (OR 7.13, 95% CI 1.69–30.11; p = 0.007), a previous diagnosis of AIDS (OR 6.61, 95% CI 2.03–21.51; p = 0.002) and fewer months under HAART (OR 0.97, 95% CI 0.96–0.99; p < 0.001). Six patients (24%) had large artery atherosclerosis: they had a similar HAART duration to controls. ***Conclusions:*** Stroke incidence is high in patients with HIV-1 infection treated with HAART. Duration of HAART exerted a global protective effect for cerebrovascular ischemic events, and our results do not support a major role in large artery atherosclerosis stroke. High alcohol intake is a major risk factor for stroke in these patients.

Introduction

Stroke is a frequent neurological problem in patients with HIV-1 infection, with ischemic stroke being far more common than hemorrhagic stroke [1]. Patients with HIV-1 infection may suffer a stroke due to a wide spectrum of mechanisms and etiologies [1–3]. Ischemic stroke may be caused by AIDS-associated disorders, such as vasculitis associated with opportunistic meningitis or vari-

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cella zoster disease, and AIDS-related cardiomyopathy. In addition, HIV-1 per se may cause aneurysmatic and non-aneurysmatic cranial vasculopathy. Other causes include infectious or non-bacterial thrombotic endocarditis and coagulation disorders. Neurosyphilis and cocaine abuse may be a cause of stroke in certain patients with HIV-1 infection. Atherothrombotic stroke is also common, especially in older patients [2]. In a population-based study, the relative risk of ischemic stroke among AIDS patients was increased more than 9 fold (9.1; 95% CI 3.4–24.6) as compared with the general population matched for age, after excluding patients with opportunistic infections of the central nervous system and HIV-associated dementia [4].

In recent years, there has been concern about a possible risk of accelerated atherosclerosis associated with highly active antiretroviral therapy (HAART), particularly with protease inhibitors (PI), which may cause dyslipidemia and insulin resistance. In a large prospective cohort study, the incidence of cardio- and cerebrovascular events increased with longer exposure to HAART, after excluding those patients associated with other concomitant central nervous system diseases [5]. However, in another study, the global incidence of cardiovascular or cerebrovascular disease was shown to be decreased in the short term in AIDS patients after treatment with HAART, excluding cases of cerebrovascular disease associated with drug dependence and HIV-1-related infections [6]. In neither study was the impact of HAART on the incidence of ischemic stroke analyzed as a specific endpoint. Moreover, mechanisms of stroke were not specified and, while HAART might reduce stroke caused by AIDS-associated disorders, it might in the long term increase atherothrombotic strokes. Nevertheless, an increase in the frequency of atherotrombotic strokes in patients receiving HAART could not be demonstrated in a recent clinical series [2].

In the present study, we have reviewed all cases of ischemic stroke and transient ischemic attacks (TIA) occurring in a large cohort of HIV-1-infected patients treated with HAART, with the aim of studying the incidence, types of stroke and possible risk factors for cerebrovascular ischemic events in this population.

Patients and Methods

A prospective cohort of HIV-1-infected patients attended at the HIV outpatient clinic of the Ramón y Cajal University Hospital in Madrid, Spain, was analyzed. All HIV-1-infected patients diagnosed with ischemic stroke and TIA between March 1996 and March 2008 while under treatment with HAART were selected. All patients had been attended during the acute phase of stroke or TIA by at least 1 neurologist with experience in cerebrovascular disorders and had at least 1 cranial computed tomography (CT) or magnetic resonance imaging (MRI) performed in the acute phase. Patients with other neurological disorders mimicking stroke were excluded.

Patients' charts were retrospectively reviewed, and the following data were recorded: age, sex, past medical history, risk factors for HIV infection, HIV infection stage according to the Centers for Disease Control, concomitant or recent (<3 months) CD4+ cell count and RNA HIV-1. Plasma HIV-1 RNA levels were determined by the branched DNA amplification technique (Quantiplex HIV RNA, version 2.0; Chiron Corporation, Emeryville, Calif., USA). Other items recorded were: history of antiretroviral treatments, cigarette smoking, alcohol intake >50 g/day, arterial hypertension, diabetes mellitus, hypercholesterolemia, active intravenous drug use (IDU) or cocaine consumption. Fasting serum cholesterol, with its low-density lipoprotein and high-density lipoprotein cholesterol fractions, and triglyceride levels immediately after stroke were also recorded. Clinical features of the stroke episode and the results of vascular, cardiological and other studies performed were registered. In patients with more than 1 stroke episode, data were obtained from the first occurring event.

Stroke mechanism was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria in large artery atherosclerosis, small artery occlusion (lacune), cardioembolism, as well as other determined and undetermined etiology [7]. We included large artery atherosclerosis cases with atherosclerosis with arterial stenosis <50%, according to the Lausanne Stroke Registry criteria [8].

To investigate possible risk factors for cerebrovascular ischemic events among HIV-1-infected patients receiving HAART, we included a control group of 100 consecutive unselected HIV-1-infected patients attending the same outpatient HIV clinic for rutinary follow-up in November 2007. The only inclusion criterion was previous treatment with HAART. The same data as in patients with ischemic events were obtained by chart review and patient interview. Analytical data were obtained from the most recently performed analysis (within the previous month).

Statistical Analysis

In the univariate analysis, patients with ischemic events and controls were compared for the following variables: sex, age, history of IDU, history of hypertension, diabetes, hypercholesterolemia, severe alcohol intake and cigarette smoking, diagnosis of AIDS (history of an AIDS-defining illness), CD4+ cell count, viral replication measured as viral load <1.7 log, time in months receiving HAART, PI and non-nucleoside analogue retrotranscriptase inhibitors, fasting serum cholesterol and triglycerides, active IDU, and current cocaine use. When computing the duration of HAART, time of drug withdrawal due to adverse effects or patients' lack of adherence was discounted. Categorical variables were compared by the χ^2 test or Fisher's exact test, as needed. The Mann-Whitney test was used for continuous variables. Colineality between variables was explored by Belsey's criteria. Variables with significant differences among patients with and without stroke in the univariate analysis were included in a backward logistic regression model. Discrimination of the mod-

el was assessed by the area under the receiving operating characteristics curve. Statistical analysis was performed with SPSS version 14. p values <0.05 were considered statistically significant.

Results

In the study cohort, 2,012 patients initiated HAART during the study period, with a total follow-up of 13,228 patients/year. Twenty-seven cerebrovascular ischemic events occurred in 25 patients, resulting in an incidence of first-ever ischemic events of 189 per 100,000 patients/year (95% CI 115–263). Of the 27 episodes, 5 were TIA and 22 ischemic strokes, with an incidence of first-ever stroke of 166 per 100,000 patients/year (95% CI 97–235).

All patients had at least 1 cranial neuroimaging study (64% had cranial MRI) performed in the acute phase of the ischemic event and underwent routine analytical studies, electrocardiography, chest X-ray and syphilis serology. Other investigations included carotid ultrasonography (76%), transcranial Doppler (24%), cervical and cranial MRI, CT or digital angiography (16%), echocardiography (64%), antiphospholipid antibody determination (16%), cerebrospinal fluid analysis (16%), and search for prothrombotic coagulation disorders (4%).

Stroke etiology was classified as large artery atherosclerosis in 6 patients (24%), small artery occlusion (lacunar) in 6 (24%), cardioembolism in 2 (8%), as due to other determined causes in 3 (12%) and of undetermined cause in 8 (32%). Among patients with large-artery atherosclerosis, 4 (67%) had extracranial internal carotid stenosis >50%. Cardioembolic strokes were caused by rheumatic mitral stenosis and paroxysmal atrial fibrillation. Other specific causes of stroke were: HIV-associated aneurysmatic vasculopathy, vasculitis due to tuberculous meningitis and stroke associated with cocaine abuse (1 patient each).

Among the patients with stroke of undetermined etiology, in 3 of them (38%), no cause could be demonstrated despite a complete investigation. The remaining 5 cases (62%) had an incomplete etiological investigation. In 2 of them, a possible cardioembolic source was documented but no carotid imaging studies were performed. Other possible causes in this group (not confirmed) were varicella zoster vasculopathy and marantic endocarditis associated with lung cancer (2 patients).

Table 1 shows the main clinical characteristics of patients with cerebrovascular events and controls. No colinearity was found between the variables studied. Patients with cerebrovascular events had a significantly more frequent history of previous AIDS, cigarette smoking and heavy alcohol intake than control patients. They had a lower CD4+ cell count, less frequent undetectable viral load and had received HAART for a shorter period of time. No differences were found in the frequency of other risk factors for ischemic stroke.

The following variables were included in the maximal model for logistic regression analysis: cigarette smoking, alcohol intake >50 g/day, previous diagnosis of AIDS, CD4+ cell count, HIV-1 viral load <50 copies/ml, and months under HAART. Only a history of high alcohol intake (OR 7.13, 95% CI 1.69–30.11; p = 0.007), a previous diagnosis of AIDS (OR 6.61, 95% CI 2.03–21.51; p = 0.0017) and fewer months under HAART (OR 0.97, 95% CI 0.96–0.99; p = 0.002) were independent factors for cerebrovascular ischemic events in this population.

Table 1. Demographic and clinical characteristics and laboratory findings of patients with cerebrovascular ischemic events and controls

	Patients (n = 25)	Control group (n = 100)	p value
Males	18 (72)	77	0.607
Age, years	46 ± 11.01	45 ± 7.94	0.556
Former IDU	13 (52)	56	0.823
Active IDU	2 (8)	2	0.178
Cigarette smoking	22 (88)	63	0.017
Cocaine use	4 (16)	8	0.256
Alcohol abuse	8 (32)	5	<0.001
Arterial hypertension	5 (20)	10	0.179
Hypercholesterolemia	6 (24)	17	0.401
Hypertriglyceridemia	0	13	0.069
Diabetes mellitus	2 (8)	7	1
Previous AIDS	17 (68)	37	0.007
CD4+ cell count/mm^3	355 ± 252	473 ± 242	0.032
HIV-1 RNA <50 copies/ml	12 (48)	82	0.003
Months under HAART	52 ± 39.3	89 ± 37.81	<0.001
Months under PI-based therapy	36 ± 30.35	53 ± 42.59	0.060
Months under NNRTI-based therapy	17 ± 27.62	28 ± 31.05	0.079
Total cholesterol levels, mg/dl	196 ± 51.69	185 ± 48.44	0.336
LDL cholesterol levels, mg/dl	113 ± 40.72	112 ± 35.78	0.916
HDL cholesterol levels, mg/dl	41 ± 15.29	40 ± 12.5	0.726
Triglyceride levels, mg/dl	174 ± 83.22	167 ± 136.65	0.795

Data are given as the mean ± SD or number of subjects, with figures in parentheses as percentages. NNRTI = Non nucleoside analogue retrotranscriptase inhibitors; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

Nagelkerke's R^2 was 0.401. The area under the receiving operating characteristics curve was 0.848, which shows a good discrimination of the model. Results were similar after excluding from the maximal model variables related with effectiveness of HAART therapy, such as CD4+ cell count and undetectable plasma RNA HIV levels. This reduction in the variables included in the maximal model provides a more appropriate model, given the low number of events included in the present study.

Comparison of patients with large artery atherosclerosis with the control group showed only differences in the frequency of hypertension (50 vs. 10%; p = 0.024) and undetectable plasma RNA HIV levels (33 vs. 82%; p = 0.016), but not in the duration of HAART.

Discussion

The present study demonstrates a high incidence of stroke in patients with HIV-1 infection treated with HAART. This incidence is within the range described for the general population in developed countries, including Spain, but much higher than in the age range (35–55 years) where the majority of our patients and controls are included [9, 10]. In 1 study, AIDS patients have more than a 9-fold increase in ischemic stroke risk when compared with the general population after matching for age [4]. In this cohort with a high frequency of IDU as risk factor for acquiring HIV-1 infection, patients also bear a heavy load of some vascular risk factors, such as smoking, cocaine abuse and heavy alcohol intake. The relatively high frequency in patients and controls (7–24%) of other classical vascular risk factors, such as hypercholesterolemia, hypertension and diabetes, is also remarkable. Surprisingly, of all vascular risk factors studied, the only independent risk factor for stroke in our cohort of patients treated with HAART was a history of high alcohol intake. Heavy alcohol consumption has been shown to be an independent risk factor for stroke in men [11–13]. Mechanisms involved in this increased risk among our patients might be the presence of alcoholic cardiomyopathy, the association with other toxic habits with increased risk of stroke, such as smoking and cocaine abuse, and a lower adherence to HAART.

In the present study, the duration of HAART exerted a global protective effect on the incidence of cerebrovascular ischemic events in HIV-1-infected patients. As far as we know, no study has yet explored the influence of duration of HAART on the risk of ischemic stroke. Previous studies have shown apparently contradictory results regarding the influence of HAART on the incidence of cardio- and cerebrovascular events, but stroke incidence was not separately analyzed. While Bozzete et al. [6] found that the rate of admissions from these disorders decreased from 1995 to 2001, the D:A:D cohort study showed an increasing incidence of cardio- and cerebrovascular events with cumulative duration of HAART [5]. Thus, while HAART might lower the risk associated with uncontrolled HIV-1 infection, in the long term, it may favor atherosclerosis. Both studies excluded cases associated with opportunistic infections, although other HIV-1-associated disorders with an increased risk of cerebrovascular events, such as coagulopathy, myocardiopathy or HIV-1 cerebral vasculopathies, might not have been excluded.

The association of ischemic events with a shorter HAART duration may be explained by several factors. The main factor is the increased risk of AIDS-associated disorders which may cause cerebral ischemia secondary to cerebral vasculitis in patients with recent introduction of HAART or with low treatment adherence. In the present series, only 1 patient had an opportunistic infection (tuberculous meningitis) as cause of stroke, but another had a stroke temporally associated with herpes zoster infection and possibly had varicella zoster-associated vasculopathy. HIV-1-associated vasculopathy represents as much as 20% of stroke in HIV-1-infected patients [3]. The intracranial form of HIV-1-associated vasculopathy occurs in immunocompromized patients, with low CD4+ cell counts, and HAART probably also protects against it. The fact that a previous diagnosis of AIDS was an independent risk factor for ischemic events in our study may be related with previous arterial damage due to HIV vasculopathy. On the other hand, it seems possible that adherence to HAART might be associated with a more healthy lifestyle and a favorable health-related behavior concerning risk factors for stroke. In this cohort with a high proportion of former IDU, patients with active intravenous drug, alcohol or cocaine abuse are probably more likely to have a lower adherence to HAART. These patients are also more frequently smokers and would have lower adherence to dietary and pharmacological treatment of hypertension and dyslipidemia.

Regarding stroke caused by large artery atherosclerosis, the present study does not support a major role of HAART duration in the pathogenesis of this event. However, no definite conclusion can be drawn, given the low number of cases with this stroke mechanism. Other limitations of our study are its retrospective nature, although based on a prospective cohort, and the relatively short

duration of the follow-up of patients under HAART (mean 6.6 years for the whole cohort). The development of HAART-induced atherosclerosis is likely to take many years to develop. Thus, while this study shows that HAART probably reduces early stroke, presumably by reducing the impact of HIV infection, it cannot provide reassurance that HAART will not result in an increase in stroke after many years or decades of treatment. Further studies with a larger number of HIV-1-infected patients with stroke caused by large artery atherosclerosis are needed to clarify the role of HAART duration as a risk factor for this type of stroke.

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