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Human immunodeficiency virus and carotid artery disease – single center experience and literature review

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ABSTRACT

INTRODUCTION: People infected with the human immunodeficiency virus (HIV) - People living with HIV/AIDS (PLWHA) - seem to have an increased risk of incidence and prevalence of cardiovascular diseases, namely stroke of ischemic nature. Additional etiological mechanisms, in addition to aging, appear to lie in chronic virus-mediated inflammation as well as in antiretroviral therapy (ART).

The aim of this study was to carry out a retrospective review with descriptive analysis of cases of PLWHA and with a diagnosis of carotid atherosclerotic disease in a tertiary referral center as well as a non-systematic review of the literature.

METHODS: All patients diagnosed with HIV infection and concomitantly diagnosed with carotid atherosclerotic disease, in a tertiary center, between October 2007 and December 2019, were selected. A descriptive analysis of the sample and additionally a non-systematic review of the literature using the MEDLINE database, were performed.

RESULTS: Nine patients who met the inclusion criteria were selected, 7 (78%) being male. The mean age at diagnosis of carotid disease was 59 years. The diagnosis of HIV infection preceded, on average, 12 years before the diagnosis of carotid disease, while the start of ART preceded this diagnosis by about 11 years. The most common cardiovascular risk factors are dyslipidemia (89%), high blood pressure (56%) and smoking (56%). Approximately 33% had peripheral arterial disease and 22% had coronary artery disease.

Only two (22%) patients underwent carotid endarterectomy over a median follow-up of 5 years, both for asymptomatic stenosis. Since the diagnosis of carotid disease, there have been no major cardiovascular events (stroke or acute myocardial infarction). During follow-up there were two deaths.

CONCLUSION: PLWHA have a high prevalence of multisite artery disease, manifesting it at a relatively earlier age compared to the general population. These patients benefit from multidisciplinary follow-up for therapeutic optimization in order to obtain better results. However, larger prospective studies are needed to clarify the results in these patients and to improve the therapeutic approach, particularly in those with concomitant carotid disease.

Keywords: HIV; AIDS; carotid artery disease; carotid endarterectomy.

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INTRODUCTION

People diagnosed with Human Immunodeficiency Virus (HIV)/ Acquired Immune Deficiency Syndrome (AIDS) (PLWHA) have experienced an increase of their life expectancy, mainly due to the advent of high active anti-retroviral therapy (HAART) and adjunctive therapies, permitting similar life span when compared to the general population (non-HIV-infected individuals) once an excellent therapeutic adherence and immunological response are achieved.[1] Although this allowed a significant reduction of AIDS incidence, non-AIDS defining illness has increased in PLWHA since the effects of ageing have begun to manifest, of which diabetes mellitus, dyslipidemia or hypertension are some examples.[2]

Furthermore, PLWHA seem to have an increased risk of cardiovascular disease, even among those who are compliant to HIV-treatment.[3] Coronary artery disease (including acute myocardial infarction) has been the most fully understood comorbidity in these patients. Nevertheless, this increased risk is now being reported to the extent of other cardiovascular events such as heart failure, peripheral artery disease and ischemic stroke.[4] Moreover, this excessive risk might extend beyond traditional risk factors for atherosclerosis and, although the underlying mechanisms are still not totally clear, current research points towards a combination of pre-existing risk factors, inflammatory processes HIV-related and metabolic changes induced by HAART.[1,5]

Although association between HIV infection and ischemic stroke has been widely reported, literature concerning its association with carotid disease is scarce. Therefore, the aim of this study is to report a single center experience of PLWHA diagnosed with carotid artery disease and to perform a descriptive analysis alongside with a non-systematic literature review.

METHODS

A single center retrospective review was performed resorting to ICD-9 codification, which allowed to identify all patients diagnosed with HIV infection and that interacted with the vascular surgery department in a tertiary hospital through its several sectors (including emergency department, outpatient clinic, hospitalization and surgery), in a time-frame between October 2007 and December 2019. Among these, only patients with confirmed carotid disease were included. Other vascular pathologies were excluded or patients in which HIV infection was not confirmed. Demographic profile of the patients was collected alongside outcomes at the time of the carotid disease diagnosis. A descriptive statistical analysis was performed resorting to SPSS (IBM Corp., released 2019. IBM SPSS Statistics for Windows, version 26.0, Armonk, NY, USA). The study protocol (number 235-19) was approved by the local Ethics Committee and respected the Helsinki Declaration.

For the purpose of the non-systematic literature review, a MEDLINE search was performed in order to identify articles focused on HIV infection and its effects on carotid artery disease. Keywords used for research included “HIV”, “AIDS”, [mesh terms] “carotid artery disease” and “carotid endarterectomy”. Additional articles of scientific interest were added by cross-referencing.

RESULTS

A total of nine patients met the inclusion criteria. Among these, seven (78%) were male. The mean age was 64±11 years old. Additionally, mean age of patients at the time of carotid disease diagnosis was 58±12 years.

By the time of carotid disease diagnosis, the most common cardiovascular risk factors identified were dyslipidemia (89%), hypertension (56%) and active or previous smoking (56%). Additionally, 33% of patients were also diagnosed with peripheral artery disease and 22% with coronary artery disease. (Table 1a)

The diagnosis of HIV infection occurred with a mean of 13±7 years before carotid disease diagnosis. Furthermore, PLWHA were under HAART for 11±7 years before carotid disease diagnosis. The degree of carotid disease in this set of patients was between 50-69% in 4 patients, 80-99% in 2 patients while 2 patients present carotid occlusion. (Table 1b) The median follow-up was 5.0 [confidence interval (CI) 3.5-9.0] years. During this period, only two patients (22%), with 87 and 68 years old, were submitted to carotid endarterectomy

Table 1a - Demographics and comorbidities of the patients

Patient	Hypertension	Dyslipidemia	CHF	CKD	DM	Smoking status	Drug-user	Obesity	CAD	PAD	Co-infection
1	0	1	0	0	1	1	0	0	0	0	0
2	1	1	0	0	0	0	0	0	0	0	0
3	1	1	0	1	0	0	0	0	0	0	0
4	0	1	1	0	1	1	0	0	1	1	0
5	1	1	1	0	1	1	0	0	0	1	HBV
6	0	0	0	0	0	0	0	0	0	0	0
7	1	1	0	0	0	1	0	0	0	0	0
8	1	1	0	0	0	0	0	0	0	0	0
9	0	1	0	0	0	1	1	0	1	1	HCV

CAD – coronary artery disease; **CHF** – congestive heart failure; **CKD** – chronic kidney disease; **HBV** – hepatitis B virus; **HCV** – hepatitis C virus; **PAD** – peripheral artery disease.

Table 1b - Demographics and comorbidities of the patients

Patient	Gender	HIV-infection diagnosis (year)	HIV vírus-type	HAART initiation (year)	Carotid disease diagnosis (year)	Age at carotid disease diagnosis	Right Side carotid stenosis	Ipsilateral carotid stenosis (%)	Contra-lateral carotid stenosis (%)
1	Male	2003	2	2003	2017	65	Não	50-69	-
2	Female	1995	1	-	2014	47	Não	-	-
3	Male	1994	1	1994	2014	82	Não	80-89	-
4	Male	1996	1	1996	2010	49	Não	60-69	50-59
5	Male	1994	1	1998	2012	68	Sim	60	100
6	Male	2013	1	2016	2014	56	Não	60-69	<50
7	Male	2016	1	2016	2019	52	Sim	100	-
8	Female	1999	1	1999	2011	58	Não	100	<50
9	Male	1997	1	1997	2010	45	Sim	>80	50-60

HAART - high active anti-retroviral therapy; **HIV** – human immunodeficiency virus.

(CEA), both due to asymptomatic carotid stenosis with stenosis >80%. No postoperative adverse events occurred.

Moreover, during follow-up, no major cardiovascular events, including stroke and acute myocardial infarction, were observed. Nonetheless, two patients died during these time-frame, one of each related to cardiovascular disease (decompensated heart failure). None of them was submitted to CEA during follow-up.

DISCUSSION

In these series, PLWHA with concomitant carotid disease seem to be younger than patients diagnosed with carotid disease alone and, even though we do not provide a control group, according to the current literature, mean age of patients with asymptomatic carotid stenosis is 60.5±12.1 years.[6] This goes in line with the finds by Linc TC et al.[7] that HIV infection was associated with younger age at the time of carotid intervention (59 years [SE 0.29] vs 71 years [SE 0.01], p<0.001) alongside a predominance for male gender as in this study. Moreover, another review states that its prevalence is progressively increased to 10% above 80 years of age, whilst a prevalence only 0.5% is described in patients younger than 60 years for more than 50% carotid stenosis.[7] The finding in this report could be explained by the fact that patients with HIV infection are more prone to dyslipidemia, similarly verified in this group, which plays a role in the physiopathology of carotid disease and other cardiovascular comorbidities.[8-10] Furthermore, HIV-infection has been described to be associated both to accelerated growth of carotid intima-media thickness[11] and to a greater relative risk of developing new focal plaque.[12]Additionally, these patients typically are under HAART, that is another additional factor related to dyslipidemia and lipodystrophy that has been extensively described in the literature.[8,13] The role of statins to counterbalance HAART effects has been studied for many research groups, however, their benefit did not show significant differences regarding prevention of cardiovascular and cerebrovascular events.[14] Actually, standard medical therapy may not provide the same risk reduction for PLWHA as in the general population,[14] eventually due to possible pharmacological interactions nonetheless in the CARE study[16] aggressive best medical treatment for traditional cardiovascular risk factors was effective at slowing atherosclerotic progression.

On the other hand, smoking habits appear to be prevalent in this group of patients as found in our results. Xi Ji et al. reported smoking as significantly related to atherosclerotic plaque in carotid vessel, with an OR of 1.52 (95% CI: 1.14–2.03, I2=59%, P=0.03).[10] In fact, smoking status exposes patients to chronic inflammation, inducing endothelial activation and consequently more damage in the vessels, which could lead to poor outcomes such as stroke and myocardial infarction.[14] Moreover, when in synergism with hypertension and dyslipidemia, prompts patients to higher risk of atherosclerosis.[15] Thus, these patients carry multiple risk-factors that might contribute to amplify the incidence of carotid disease.[10]

Although PLWHA usually have higher rates of stroke, and it incidence also showed to increase (67%) in the last decade,[16] such complication was not observed in this report. The same study described that stroke affects younger PLWHA patients, comparing with non-HIV population. The reason behind its high incidence lies in the fact that HIV-infection itself or the applied therapeutic might play a role in the pathophysiology of stroke. The implied mechanisms that might be responsible for this are the endothelial activation by the induced atherosclerosis and chronic inflammation in the vessels together with the opportunistic infections, neoplasms or cardiovascular disease.[16,17] T cells seem to play an important role by promoting arterial stiffness which lead to functional and structural vascular changes.[20] According to Jericó C. et al, HAART has a potential role in the endothelial and metabolic disfunctions that might predispose to higher rates of ischemic events, accounting with an OR of 10.5 (95% CI: 2.8-39) in a cohort with 132 patients, therefore labeled as an independent risk-factor for atherosclerosis.[18] Another report has shown an incidence of 5.7 per 1000 person-years,

concerning the first cardiovascular event (including stroke) in PLWHA, whereas a longer exposure of HAART had a RR of 1.26, 95% CI 1.14-1.38; P<0.0001.[18,19] Therefore, carotid disease might not be the strongest factor responsible for stroke in this set of patients, which could explain the absence of this complication in the present report. Furthermore, Chow et al.[20] performed a study to evaluate the distribution of ischemic stroke subtypes among PLWHA predominantly under treatment and comparing versus the general population (60 vs 60). It was described a higher proportion of undetermined strokes in PLWHA compared to general population. Another interesting result was a trend toward a greater proportion of strokes attributable to large artery atherosclerosis [relative risk ratio (RRR): 6.7, 95% CI: 0.8-57.9, P=0.08) in those with virologically suppressed infection.

This study has some limitations to consider. The sample is very small which makes difficult to extrapolate results (lack of external validity). Additionally, only two patients were submitted to surgical intervention, and so the likelihood of worse outcomes, even though no complication was occurred, should not be inferred in this set as well if the effectiveness of CEA in PLWHA is similar to general population.[21] Another limitation is the absence of control group alongside with the inherent limitations to its retrospective nature.

CONCLUSION

HIV-infection and its underlying therapeutic approaches might influence the predisposition of carotid disease, since endothelial and metabolic disturbances seem to be accentuated in this subset of patients. This predisposes to an earlier presentation of carotid disease in PLWHA compared to the general population and so, these patients should be managed by a multidisciplinary team. Nonetheless, larger prospective cohorts and trials are needed to clarify the potential hard outcomes and the appropriate management of PLWHA and concomitant carotid stenosis.

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