

Highly Effective Antiretroviral Therapy and Cerebral Aneurysms

Terapêutica anti-retroviral e aneurismas cerebrais

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RESUMO

O óbito de pacientes infectados com o vírus da imunodeficiência humana (HIV) tem sido atribuído a múltiplas causas, incluindo infecções sistêmicas, doença neurológica e falência múltipla de órgãos. Com o advento da terapêutica anti-retroviral altamente eficiente, a sobrevida tem se estendido e processos que não têm tradicionalmente se manifestado começam a desempenhar um papel importante no contexto da infecção por HIV. Embora complicações vasculares em pacientes infectados por HIV e em uso de terapia anti-retroviral tenham sido descritas na literatura, pouca discussão tem ocorrido sobre o papel relativo dos vírus e dos medicamentos na gênese destes eventos. O objetivo desta revisão é discutir estes aspectos.

Palavras-chave: aneurismas cerebrais, infecção, terapêutica anti-retroviral, SIDA.

ABSTRACT

Classically, the death of patients infected with the human immunodeficiency virus (HIV) has been due to multiple causes, including incurable systemic infections, neurological disease and multisystem failure. With the advent of the highly effective antiretroviral therapies (HAART), the survival has been longer and processes that have traditionally not had enough time to play a role in the functional decline of HIV-infected patients are appearing. Although vascular complications in HIV-infected patients in use of HAARTs has been addressed in the literature, there has been limited discussions regarding the possible relationship between infection with HIV, use of HAART and the development of cerebral aneurysms. The aim of the present study is provide insight into the understanding of cerebrovascular complications, especially cerebral aneurysms, associated with the use of HAARTs in HIV-infected patients.

Keywords: aids, antiretroviral therapy, cerebral aneurysms, HIV infection.

INTRODUCTION

The acquired immunodeficiency syndrome (AIDS) is considered a relatively new disease and historically death of patients infected with the human immunodeficiency virus (HIV) has been due to multiple causes, including incurable systemic infections, neurological disease and multisystem failure. The decreased morbidity and mortality from these more classical causes, resulting from the advent of the highly effective antiretroviral therapies (HAART), is giving rise to morbidity and/or mortality from disease processes that have traditionally not had enough time to play a role in the functional decline of HIV-infected patients²⁹.

HIV infection is associated with vascular diseases and an increased incidence of stroke in adults⁷. Although vascular complications in HIV-infected patients in use of HAARTs has been addressed in the literature, there has been limited discussions regarding the possible relationship between infection with HIV and use of HAART and the development of cerebral aneurysms.

HISTORY

The first reports of cerebral aneurysms occurring in association with HIV were documented in three patients from Zimbabwe and one from the USA, in 1989^{10,29}. Since then, there have been a few case reports in which the documented aneurysms have involved extracranial arteries, including the common carotid and its branches, the subclavian arteries, aorta, femoral artery and its branches, and the popliteal arteries^{10,22,23}.

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Until 2006, fusiform dilatations of intracranial arteries have been described in HIV-positive in 32 children^{9,14,26,29}, and until 2007 only 11 HIV-positive patients have been described with intracranial aneurysms^{17,18,20,29}. Seven of these had saccular aneurysms and one had a giant aneurysm^{8,12,14} that could have been coincidental congenital aneurysms. The remaining three patients had fusiform aneurysms and presented with strokes, headache and SAH^{10,29}. Modi et al. also described three further cases of adult HIV patients with intracranial fusiform aneurysms in and around the circle of Willis³¹.

EPIDEMIOLOGY

Infection with the HIV contributes to an increased risk of stroke²¹, and published series of HIV - positive patients demonstrated an incidence of 6-11% of intracerebral hemorrhage^{2,13,17,20,21,22,23,24,27}.

It is interesting to report the apparently increased ratio of fusiform to saccular aneurysms in HIV-infected patients when compared to the ratio of the two seen in the general population, since saccular aneurysms are generally much more common^{2,12,28,30}. Nevertheless, saccular aneurysms are not unheard of in the HIV-infected population, either pediatric or adult^{11,26}. One study reports an incidence of fusiform intracranial artery dilatation of 1,9% in 426 HIV-positive children²⁷.

NATURAL HISTORY

Clinical manifestations varied from cerebral infarcts (frequent), transient ischemic attacks, intracranial hemorrhages, subarachnoid hemorrhages, seizures, and movement disorders^{9,14,26}. Prior to the availability of HAARTs, following the aneurysm diagnosis, there was typically a rapid decline in patient's health secondary to AIDS-related complications, usually culminating in death within a few months from the diagnosis⁹. However, stabilization of intracranial aneurysms has been reported in patients after 4-15 months of treatment with HAARTs.^{7,27} It remains to be seen whether HAART therapy will arrest progression or promote resolution of intracranial aneurysms in adults, thereby confirming the role of HIV in the pathogenesis of intracranial arterial aneurysm formation.

HISTOPATHOLOGY

The poorly defined vasculopathy has been documented in adults as involving either large or medium extracranial or intracranial arteries^{1,14,23,24,28}. The extracranial large arteries may manifest with both aneurysmal and non-aneurysmal disease^{19,30}. Similarly, the intracranial vasculopathy may manifest with both aneurysmal and non-aneurysmal lesions^{4,5,6,19}. This is usually an asymptomatic disease and is characterized by hyaline small vessel wall thickening, rarefaction pigment deposition with vessel wall mineralization, perivascular space dilatation and occasional inflammatory cell infiltrates⁷.

PATHOPHYSIOLOGY

Despite numerous investigations into the cerebral aneurysm formation, the exact mechanism behind this process remains largely unknown. Although the prospect of damage mediated by the virus itself should not be ignored, as HIV glycoprotein 41 has been demonstrated in mononuclear cells within the intima of aneurysmal intracranial arteries in 1 case^{18,32,34}, it is worthwhile to note that there is little evidence that HIV directly damages CNS structures and cells. Accordingly to Mazzoni et al. and Kriznac-Bengez et al.²⁸ the pathogenesis of intracranial aneurysms in HIV-infected patients is postulated to be caused by immune activation in response to transendothelial migration of HIV strains with tropism for cerebral mononuclear cells, and an alteration of dynamic vascular responsiveness to pulsatile blood flow regulated by alterations in circulating cytokines and growth factors leading to vascular remodeling. There is also the possibility that bacterial infection of the vessel wall secondary to immunosuppression by opportunistic infections such as varicella-zoster virus, herpes simplex virus, cytomegalovirus, Epstein-Barr virus, Treponemapallidum, Candida albicans, Cryptococcus neoformans, and Mycobacterium tuberculosis may contribute as has been previously suggested regarding extracranial aneurysms in HIV-positive patients^{3,9}. In addition, at least one study has demonstrated that the HIV protease inhibitor ritonavir at concentrations near clinical plasma levels significantly increases cytotoxicity in human endothelial cells, inducing cell injury at high concentrations^{15,16,22,25,31,32,33,35,36}.

CONCLUSION

In conclusion, cerebral aneurysm is an uncommon life-threatening clinical complication or association observed in HIV-infected patients. In this paper we have presented a review on the relationship between HIV infection and treatment with HAARTs and cerebral aneurysms. It is not clear whether aneurysms are secondary to virus infection or HAARTs. More studies are necessary to clarify this intriguing issue.

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