How does vascular disease associated with retroviral infection differ from atherosclerosis?

Abstract

In this paper the difference in epidemiology, pathophysiology, natural history, presenting problems and treatment between HIV vasculopathy and atherosclerotic disease will be shown. However, there is some overlap between these two important diseases.

Epidemiology of HIV infection

The acquired immunodeficiency syndrome (AIDS) was first diagnosed in 1981. It is caused by the human immunodeficiency virus (HIV). The virus almost certainly originated from closely-related African primate viruses (simian immunodeficiency virus). Since 1981, AIDS has grown to be the second leading cause of disease burden world-wide and the leading cause of death in Africa, where it accounts for over 20% of deaths.1 In South Africa, the prevalence of HIV infection is about 30% among pregnant women attending antenatal clinics and South Africa accounts for one-third of AIDS deaths globally.2

Epidemiology of atherosclerosis

Cardiovascular disease is the most frequent cause of adult deaths in the Western world. In many developed countries, the incidence of ischaemic heart disease has been falling for the last two or three decades, but it is rising in Eastern Europe, on the Indian subcontinent and in sub-Saharan Africa. This has led to predictions that cardiovascular disease will soon become the leading cause of death on all continents.3

Epidemiology of HIV infection and atherosclerosis in South Africa

The HIV epidemic has stabilised in South Africa since 2004, but cardiovascular disease is rapidly increasing and may overtake HIV as the leading cause of death in South Africa.2

Pathophysiology of HIV infection

HIV infection leads to destruction of the key immune effector cell, the CD4 T-lymphocyte, with resultant immune deficiency and opportunistic infections.

HIV infection affects about every organ system in the human body causing mucocutaneous, pulmonary, gastrointestinal, cerebral, cardiac, renal, rheumatological and vascular pathologies. HIV vasculopathy is not one of the common presenting clinical problems of HIV infection.

HIV-related vasculitis may affect small-, medium- or large-sized arteries. The patient with large-vessel involvement may present with false aneurysms or thrombotic occlusions. The pathogenic mechanisms of this disease are not completely understood. HIV replication or opportunistic infection may induce direct injury of the vessel wall, or an immune mechanism may cause vascular damage. Histological examination of the large vessel walls shows a leucocytoclastic vasculitis of the vaso vasora in the adventitial layer.4 It appears that occlusive disease and aneurysmal disease share a similar basic pathological process, viz. an inflammatory disorder of the arterial wall.

HIV has been widely recognised as a prothrombotic condition, causing deep vein thrombosis (DVT). A systematic review published in 2005 found an incidence of DVT in HIV-positive patients ranging from 0.19% to 18%.5 In an audit performed at Johannesburg Hospital, 84% of patients who presented with DVT were found to be HIV positive.6 Although many pathways have been investigated to determine the mechanism of thrombosis, the only strong evidence available appears to be a protein S deficiency.7 Many other factors appear to play at least some role, and it appears inevitable that the mechanisms underlying thrombosis associated with HIV infection are multimodal.

Pathophysiology of atherosclerosis

Atherosclerosis is a progressive inflammatory disorder of the arterial wall and is caused by endothelial injury of large- and medium-sized arteries. The main chemical irritant causing endothelial injury is smoking, while the main physical cause of injury is the turbulence with altered shear stress at arterial origins and bifurcations. Hypertension, which increases this shear stress, is another important predisposing factor for arterial disease.
The other important risk factors are hypercholesterolaemia and diabetes. The injury increases the permeability of the endothelium to lipids and inflammatory cells (mainly monocytes) which become deposited subendothelially. The monocytes take up oxidised low-density lipoprotein (LDL) from the plasma and become lipid-laden foam cells (macrophages). Extracellular lipid pools (fatty streaks) appear in the intimal space when the foam cells die and release their contents. The reverse relationship between high-density lipoprotein (HDL) and atherosclerosis is probably explained by the influence of HDL in preventing LDL oxidation. In response to the cytokines and growth factors produced by the activated macrophages, smooth muscle cells migrate from the media of the arterial wall into the intima. The lipid core becomes covered by smooth muscle cells and matrix (fibrous cap), producing a stable atherosclerotic plaque that will remain asymptomatic until it becomes large enough to obstruct arterial flow or ruptures. The gradual obstruction of arterial flow causes chronic arterial insufficiency while the sudden rupture of plaque may cause acute thrombotic or acute embolic arterial occlusion.

Stable plaque is typified by a small lipid core covered by a thick fibrous cap with calcification and plentiful collagenous cross-struts. Vulnerable plaques are characterised by a lipid-rich core, a thin cap, an increase in inflammatory cells, and the release of proteolytic enzymes and metallo-proteinases that cause thinning of the fibrous cap. Intraplaque haemorrhage, from immature new blood vessels that infiltrate the lesion (angiogenesis), weakens the plaque. Further chemical and/or physical injury can lead to rupture of this fibrous cap and the exposure of highly thrombotic plaque contents to the flowing blood. The plaque is now unstable and may result in acute thrombotic occlusion at the site of the ruptured plaque and/or distal embolization. It is important to appreciate that it is this complicated unstable plaque that leads to the most serious and dramatic clinical presentations. STEMI (ST-elevation myocardial infarction) and acute on chronic arterial occlusion of a leg are caused by a thrombotic occlusion at the site of the unstable plaque, while non-STEMI, stroke, acute arterial occlusion of a leg and the blue toe syndrome results from an embolic occlusion distal to the ruptured plaque.

Pathophysiology of HIV vasculopathy and atherosclerosis

Both HIV vasculopathy and atherosclerosis are inflammatory conditions of the arterial wall, but with different causes.

Natural history of HIV infection

Primary infection is usually symptomatic and occurs 2-6 weeks after exposure. Patients present with fever, rash, lymphadenopathy, and mucosal ulceration that coincides with a surge in viral load and a fall in CD4 count. Symptomatic recovery parallels the return of the CD4 count and fall in the viral load. The appearance of specific anti-HIV antibodies (seroconversion), usually takes place at 3-12 weeks after exposure (Figure 1). Further chemical and/or physical injury can lead to rupture of this fibrous cap and the exposure of highly thrombotic plaque contents to the flowing blood. The plaque is now unstable and may result in acute thrombotic occlusion at the site of the ruptured plaque and/or distal embolization. It is important to appreciate that it is this complicated unstable plaque that leads to the most serious and dramatic clinical presentations. STEMI (ST-elevation myocardial infarction) and acute on chronic arterial occlusion of a leg are caused by a thrombotic occlusion at the site of the unstable plaque, while non-STEMI, stroke, acute arterial occlusion of a leg and the blue toe syndrome results from an embolic occlusion distal to the ruptured plaque.

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Patients with HIV vasculopathy or DVT usually present at a late stage of their disease and it is controversial whether these manifestations should be considered AIDS-defining diseases.

**Presenting problems in HIV vasculopathy**

HIV-related aneurysms are found in atypical sites with a predilection for the carotid bifurcation and superficial femoral arteries. The aneurysms are usually multiple and almost invariable saccular in nature. The arterial occlusive disease of HIV infection usually affects the distal aorta and its outflow. For obscure reasons, males predominate, and most patients are young, usually in the 4th decade, and predominantly black Africans.

**Presenting problems in atherosclerosis**

Although atherosclerosis is a disorder that begins early in life, clinical manifestations often do no appear until the sixth, seventh or eighth decade. Atherosclerosis may manifest as coronary heart disease, cerebrovascular disease or peripheral vascular disease. These entities often co-exist and the pathogenesis of the disease is similar at the different sites.

**Treatment of HIV vasculopathy**

HIV-related aneurysms usually enlarge rapidly and therefore require repair. Although it is controversial and data are lacking, we manage these aneurysms along the same recommendations for patients with mycotic aneurysms, viz. we resect the aneurysms and restore continuity with an autologous vein bypass. Endovascular placement of a covered stent is a promising alternative option. The results of revasculisation for HIV-related occlusive disease are very disappointing, with high amputation rates. Patients should be carefully selected for intervention, reserving surgery for those with critical limb ischaemia, and opting for lesser invasive procedures, especially in patients with decreased CD4 cell counts. Early results of endovascular management in these patients are promising.

Patients with HIV-related DVT should be treated according to standard protocols as for non-HIV infected patients with DVT.

**Treatment of atherosclerosis**

Prevention and treatment protocols for patients with atherosclerotic cerebrovascular, coronary and peripheral arterial disease are well established.

**HIV infection and atherosclerosis**

HIV infection causes metabolic changes that may accelerate atherosclerosis. The metabolic changes of concern include raised triglycerides, decreased HDL, raised C-reactive protein, raised fibrinogen and increased plasminogen-activating inhibitor activity. Also, a number of studies in Western populations showed a higher prevalence of smoking in HIV-infected people when compared with the general population. The metabolic changes associated with HIV infection have been shown to increase coronary artery disease complications.

**Antiretroviral therapy and atherosclerosis**

Currently available antiretroviral drugs inhibit enzymes of the human immunodeficiency virus. The antiretroviral drug classes are the nucleoside analogues, such as zidovudine (AZT), the non-nucleoside reverse transcriptase inhibitors, such as nevirapine, and the protease inhibitors, such as indinavir and atazanavir.

Protease inhibitors have been associated with a range of metabolic side-effects, including the metabolic syndrome (hyperlipidaemia, central fat accumulation and insulin resistance), that have been implicated in the pathogenesis of atherosclerosis. The nucleoside analogues can cause lipo-atrophy and damage to mitochondria. These metabolic derangements caused by the protease inhibitors and nucleoside analogues have contributed to the rationale that the start of antiretroviral therapy (ART) should be deferred until it is clearly necessary and that protease inhibitors should be avoided as long as possible. Cardiovascular risk is a concern. In a large, multicohort study, combination ART was associated with a 26% increase in the risk of myocardial infarction per year of regimen exposure. Atazanavir, a new protease inhibitor, has the advantage of not inducing lipid elevations, but further study is needed to assess whether this advantage translates into reduced cardiovascular risk with this drug compared with the other protease inhibitors.

**HIV infection, antiretroviral drugs and atherosclerosis**

HIV vasculopathy and atherosclerosis are two different diseases, but with some overlap since HIV infection and its treatment (ART) are both atherogenic.

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