Stroke and HIV – causal or coincidental co-occurrence?

Stroke is responsible for a large part of the global burden of disease. Worldwide in 1990 it was the second commonest cause of mortality, causing approximately 4.4 million deaths. Two-thirds of these deaths occurred in less developed countries. In South Africa in 2001 it was the fourth leading reported natural cause of mortality.[1]

HIV infection has in the wake of our pandemic become a leading cause of death and dread disease, with an estimated 15% of the population being infected.[1]

A co-occurrence of these two illnesses is therefore expected. The debate rests with regard to whether or not there is a causal relationship.[2]

The first suggestion that there is an association between HIV and stroke came from autopsy and case series from the USA.[2] These were followed by population studies to determine the risk of this association.[2] The first of these was a study from KwaZulu-Natal (KZN) that found an HIV prevalence of 16% in a young stroke population.[2] The prevalence of HIV in that region at that time was also 16%, suggesting that there was no significant increase in the risk of stroke associated with HIV infection. In another population-based study from Baltimore, USA, the incidence of stroke in persons with AIDS was 0.2% per year.[2] In this study AIDS was found to confer an adjusted relative risk of 13.7 for ischaemic stroke (IS) and 25.5 for intracerebral haemorrhage (ICH), indicating that AIDS is strongly associated with both IS and ICH.[2] A criticism directed at this study has been that only patients meeting the Centers for Disease Control (CDC) definition of AIDS were included. In a study from Germany on 772 HIV-infected patients, a prevalence of 1.2% for stroke and an annual incidence rate for IS of 216/100 000 population was reported.[2] The prevalence was highest in young adult patients with advanced HIV infection.[2] This latter finding has been consistently observed in studies reporting on the association between HIV and stroke. The results in this regard thus appear to be inconclusive but favour an increased stroke risk, at least with advanced HIV/AIDS.

These studies and subsequent clinical case series identified the potential causes or mechanisms of stroke in HIV infection to be opportunistic infections, intracranial neoplasms, marantic and infective endocarditis, and coagulation abnormalities.[2] In a prospective study carried out by us at Chris Hani Baragwanath Hospital we found the causes of stroke in HIV-infected patients to be coagulopathies (42%), meningitis (22%), vasculopathy (10%), cardioembolism (7%), hypertension (7%) and cryptogenic (12%).[3] The specific coagulopathy linked to stroke in HIV is protein S deficiency but, as we later showed, this is an epiphenomenon of HIV rather than a cause of stroke.[3] Several other studies from various regions of the world, including Baltimore (USA), KZN and Blantyre (Malawi), reporting on the mechanisms of stroke in HIV obtained results similar to ours.[2,3] These findings are, however, comparable to the causes/mechanisms of stroke reported in HIV-negative patients, arguing once again in favour of a coincidental rather than causal association between HIV and stroke.[3]

In terms of these causes/mechanisms, hypertension, meningitis, cardioembolism and coagulopathies are associated with stroke in HIV-infected patients in the same manner as is described for HIV-negative patients. Vasculitis deserves further mention as it is often empirically or anecdotally described to be a cause/mechanism of stroke in HIV- infected patients, even though vasculitis caused by HIV has yet to be identified in the brain.[4] Vasculitis, when identified in patients with HIV and stroke, is most often due to an underlying or associated opportunistic infection. Vasculopathy, on the other hand, is used to describe involvement of arterial vessels by HIV itself, in the absence of opportunistic infection, aneurysm formation and inflammatory immune diseases, and has been identified at autopsy in HIV-infected brains, antemortem in children with HIV and even in a murine AIDS model.[4,5] Whether or not this vasculopathy causes stroke in HIV has yet to be proven. Aneurysmal vasculopathy has been described in HIV, albeit infrequently. The aneurysms occur intracranially and extracranially, are mostly fusiform, and present with subarachnoid haemorrhage and rarely with ischaemic stroke.[5]

Antiretrovirals (ARVs) are being increasingly used in our health care systems and in terms of toxicity or side-effects have now become topical with respect to being potential risk factors for cardiovascular and cerebrovascular disease. ARVs are expected to increase the burden of stroke and heart attack in HIV. ARVs, in particular the protease inhibitors, cause a metabolic syndrome characterised by lipodystrophy/lipoatrophy, abnormal body fat distribution, dyslipidaemia and insulin resistance.[6] These are associated with endothelial dysfunction. Endothelial dysfunction is a critical initial step of atherogenesis that subsequently contributes to the progression and clinical manifestations of atherosclerosis.[6] It is therefore pivotal to the development of cardiovascular and inflammatory pathology.[6] Whereas there are recent reports of myocardial infarction in young patients receiving protease inhibitor therapy, such evidence with respect to cerebrovascular disease or stroke is still lacking. Furthermore, endothelial dysfunction has been seen in HIV-infected patients without the use of ARVs. Endothelial activation in HIV is thought to occur either by cytokines or by the effects of secreted HIV-associated proteins, gp120 and TAT. The dysfunctional endothelial cells could then potentiate tissue injury, inflammation and remodelling and accelerate the development of cardiovascular and cerebrovascular disease.[6] The question therefore arises as to whether endothelial dysfunction, and the consequent vasculopathy or potential to accelerate

atherosclerosis, are clinically relevant or merely epiphenomena. Case control studies that identify vasculopathies and investigate endothelial function and atherogenicity in HIV-infected patients with and without stroke are needed to resolve these issues.

ICH as a cause of stroke in HIV patients is reported infrequently but is thought to be higher than would be expected in a general population of young adults with stroke.[7] ICH is a late and serious complication of AIDS with a mortality of 62.5%. Potential aetiologies for the ICH that have been described include cerebral toxoplasmosis, thrombocytopenia, hypertension and cerebral tuberculosis.[7]

Cerebral venous thrombosis is a relatively important cause of stroke in the young, but despite the high occurrence of coagulation disorders, has not been widely reported in HIV-associated stroke.

In conclusion, the evidence from the literature with respect to stroke and HIV is that:

1. There is a probable increased risk for stroke in young adults with advanced HIV infection.

2. The causes/mechanisms of stroke in HIV are similar to those in non-HIV stroke populations.

3. Infections presenting as meningitis or a focal brain lesion or causing vasculitis need to be identified and treated. The most pertinent investigations are brain imaging and cerebrospinal fluid analysis – an important issue in resource-limited settings that currently bear the brunt of the HIV epidemic.

4. The introduction of ARVs may increase the risk of stroke in HIV.

5. The molecular mechanism/s of stroke in HIV are yet to be elucidated.

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