Vasculopathy in HIV-infected children – a case series

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We report on 6 HIV-infected South African children who presented with vasculopathy involving medium and large vessels. Four patients presented with a stroke, one with heart failure and one with gangrene. Five patients had aneurysms and one patient had an occlusion. The arteries of the circle of Willis and the aorta and its major branches were extensively involved. The precise mechanisms of vascular injury in HIV require further study.

Vasculopathy in HIV-infected children is increasingly recognised (frequency 1 - 2%).[1] A wide range of vascular disease can be encountered, from vasculitis caused by specific infective agents to nonspecific vasculitis. Cytomegalovirus and tuberculosis are leading infective causes,[2] with small and medium-sized vessels commonly involved. Aneurysm formation or occlusive disease of large elastic arteries (aorta, femoral, popliteal, carotid and subclavian) is less frequently described.

According to Chetty,[2] vasculopathic processes in HIV- infected patients can be classified as infective, necrotising systemic, hypersensitivity, angiocentric, immunoproliferative, primary angiitis of the central nervous system, large-vessel vasculopathy and miscellaneous. The disease may be associated with a known pathogen or trigger, or may occur in the absence of an obvious identifiable agent.[2] Theories as to the cause include direct vascular endothelial infection with HIV, secondary opportunistic infections, secreted viral proteins such as gp120 (envelope protein) or Tat (transactivator of viral transcription), and cytokine-mediated damage.[3]

Pathological studies[4] have suggested that elastases from repeated infections may injure the elastic lamina of vessels. Other authors describe increased secretion of vascular endothelial cell growth factor A (VEGF-A) by T lymphocytes in HIV-1-infected individuals that may induce vascular leakage and stimulate proliferation of vascular endothelial cells.[5] Postmortem studies of HIV-infected children showed a 64% prevalence of large-vessel arteriopathy. Most of the pathological findings were in the vasa vasorum, and they mainly consisted of medial hypertrophy and chronic inflammation.[6]

Case reports

Small-vessel disease in HIV-infected children is seen fairly frequently in hospitals and clinics, but larger-vessel disease is less frequent. We review 6 patients with medium- and large-vessel vasculopathy seen at Coronation Hospital for Women and Children and Chris Hani Baragwanath Hospital between 2000 and 2006. All presented with complications arising from medium- and/or large-vessel involvement. Details of clinical presentation, radiological and serological investigations, management, treatment and outcome of these patients are set out in Table I.

Discussion

Vasculopathy in an HIV-positive child is an uncommon but important disease. A large-vessel (aorta and femoral and carotid arteries) vasculopathy is rarely described in children. The prevalence of cerebrovascular disease has been reported as 2.6% in children with HIV.[7] Medium- and large-vessel involvement can result in either multiple aneurysm formation or occlusive disease, as seen in our patients. Unusual sites such as the descending aorta, subclavian vessels, and renal and internal carotid arteries can be affected.

Previously reported cases[8] of vascular disease in children were associated with severe immunosuppression. These cases were reported before the widespread use of highly active antiretroviral therapy (HAART) but, in our series, patients 1, 2 and 3 had been on a standard HAART regimen for an average of 6 months before presenting. Patients 1 and 3 were virally suppressed. The immune-reconstitution inflammatory syndrome (IRIS) could be implicated in the pathogenesis of their vascular complications.[9] IRIS occurs within a few weeks to months after the start of HAART; patients most often present with clinical manifestations while the number of CD4 lymphocytes is increasing and the HIV viral load decreasing, as was probably the case in these 3 patients.

All our patients had been treated for pulmonary tuberculosis on the basis of clinical suspicion and investigations. The similarities in pathology to Takayasu's arteritis (aetiology unknown) with regard to large-vessel involvement and multiple aneurysm formation have been noted previously.[10] The diagnosis of Takayasu's arteritis can be confirmed by angiography, which often outlines a massively dilated aortic arch with aneurysmal dilatation and stenosis of various large vessels – carotid and

TABLE I. A CASE SERIES OF HIV VASCULOPATHY IN CHILDREN

Features	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (yrs)	12	10	6	7	3	1.5
Gender	Male	Male	Female	Male	Male	Female
Clinical presentation	Right hemiparesis	Right hemiparesis	Systemic hypertension Left hemiparesis	Right hemiparesis	Systemic hypertension Cardiac failure Left hemiparesis	Gangrene both arms (Fig. 6)
CD4 Absolute number (cells/μl)	593	Unknown	373	Unknown	325	451
CD4 %	17%	Unknown	15.1%	Unknown	Unknown	Unknown
Viral load (copies/μl)	<400	Unknown	130	Unknown	Unknown	Unknown
Duration of antiretroviral therapy	5 yrs	3 mo.	6 mo.	None	None	None
Associated conditions	Pulmonary tuberculosis, Lymphocytic interstitial pneumonitis, Molluscum contagiosum, Herpes zoster	Pulmonary tuberculosis	Pulmonary tuberculosis Cardiomyopathy with left ventricle thrombus (Fig. 3)	Pulmonary tuberculosis Lymphocytic interstitial pneumonitis Cor pulmonale Herpes zoster Cataract (left)	Pulmonary tuberculosis Lymphocytic interstitial pneumonitis	Pulmonary tuberculosis
CT/MRI/ other findings	Right internal carotid artery aneurysm (Fig. 1)	Left internal carotid artery occlusion (Fig. 2)	Right internal carotid, right vertebral and basilar artery aneurysms	Aneurysms of vessels of the circle of Willis (Fig. 4)	Right frontoparietal infarct Aortogram showing aneurysmal dilatation of the arch at the junction of the transverse and descending aorta and the brachiocephalic trunk (Fig. 5)	Abd. aortogram showing irregularity of descending aorta below the coeliac plexus (Fig. 7)
Outcome	Almost complete neurological recovery	Improved neurological function	Residual left-sided weakness Neuro-cognitive impairment	Died	Unknown	Unknown Family requested discharge
Pathology	Not done	Not done	Not done	Medial fibrosis, destruction of internal elastic lamina hyperplasia of branches of circle of Willis aneurysms	Organising thrombus of left brachiocephalic trunk on carotid Doppler	Not done

CT = computed tomography scan; MRI = magnetic resonance imaging.

subclavian arteries and abdominal aorta – or, rarely in children, lesions of the coronary artery.[11] In patients with large-vessel vasculopathy (e.g. aortic involvement), multiple aneurysms and a diagnosis of tuberculosis, Takayasu's arteritis cannot be excluded with certainty. Future studies need to investigate a possible link between Takayasu's arteritis and tuberculosis in the pathogenesis of large-vessel vasculopathy.

The possibility that children with HIV may have large-vessel vasculopathy should always be kept in mind. Echocardiography[12] and carotid artery Doppler are useful screening tools. The optimal management of these patients has not yet been well established. Surgery for large-vessel disease is performed in selected patients. A low CD4 count is associated with poor surgical outcome, but pre-operative HAART has

improved surgical outcomes. Medical management, including HAART, has been used in children with good results.[12] It still needs to be determined whether early treatment with HAART will prevent the occurrence of HIV vasculopathy. In addition, the precise mechanisms of vascular injury in HIV require further study.

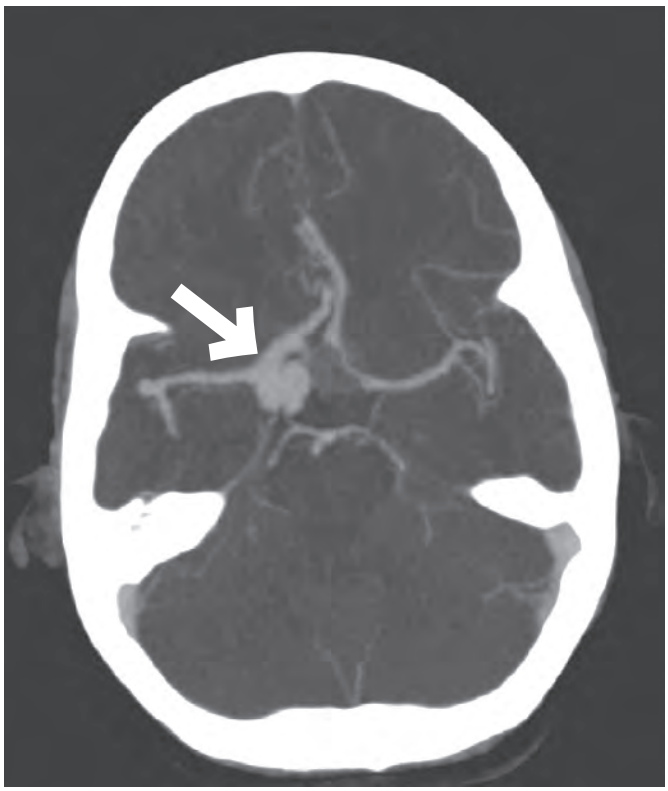

Fig. 1. Patient 1. Contrast CT scan of brain showing right internal carotid artery aneurysm (arrow).

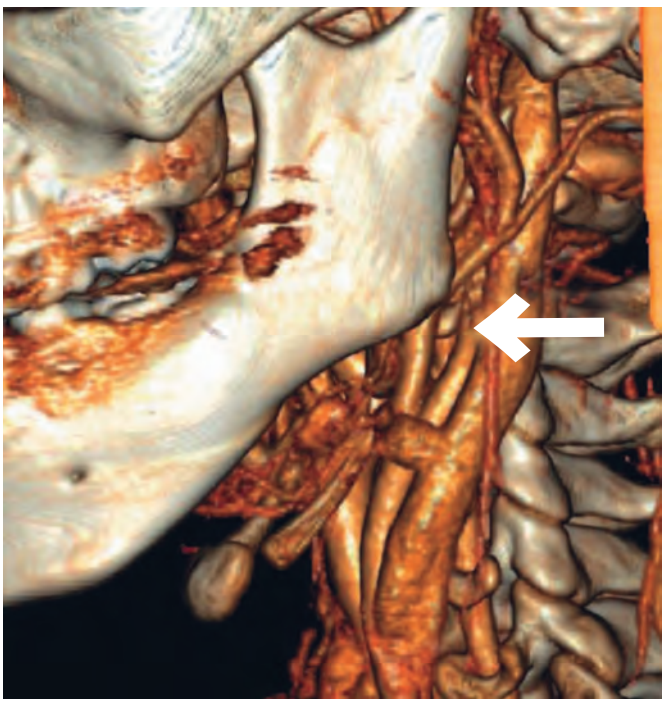

Fig. 2. Patient 2. CT reconstruction angiogram with left internal carotid artery occlusion (arrow).

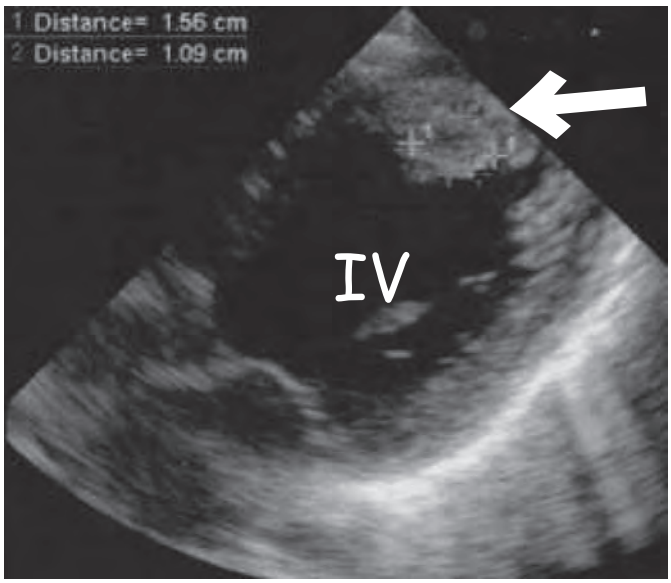

Fig. 3. Patient 3. Apical 4-chamber echocardiogram showing dilated left ventricle with apical thrombus (arrow).

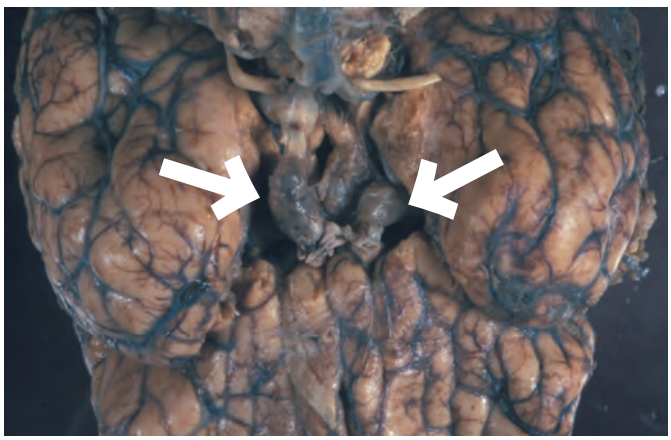

Fig. 4. Patient 4. Postmortem specimen showing aneurysms of posterior communicating arteries (arrows) in the circle of Willis.

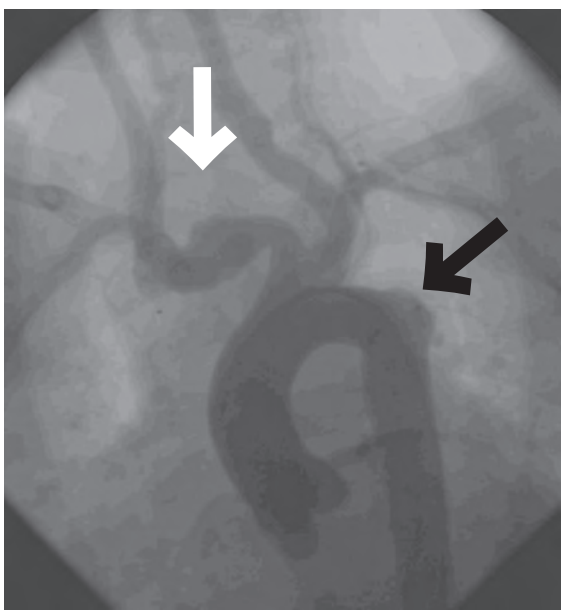

Fig. 5. Patient 5. Aortogram showing aneurysmal dilatation of the arch at the junction of the transverse and descending aorta (black arrow) and the brachiocephalic trunk (white arrow).

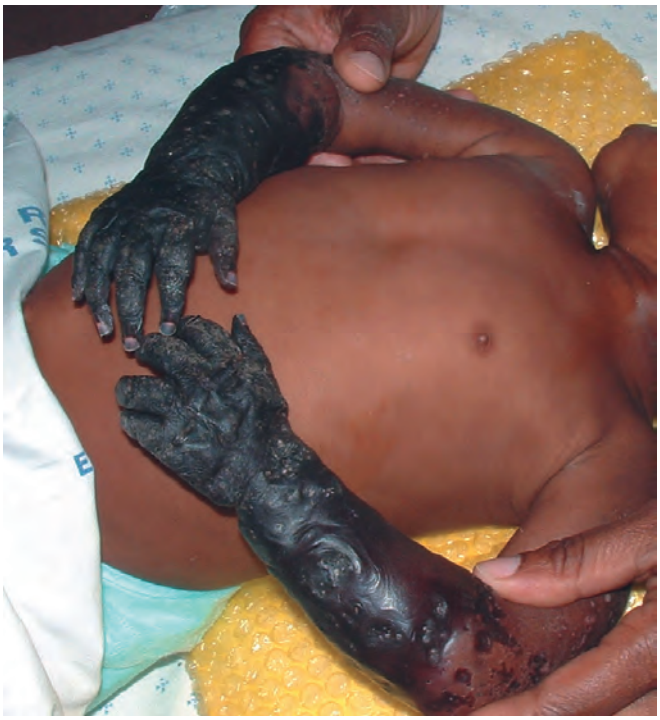

Fig. 6. Patient 6. Gangrene of both arms.

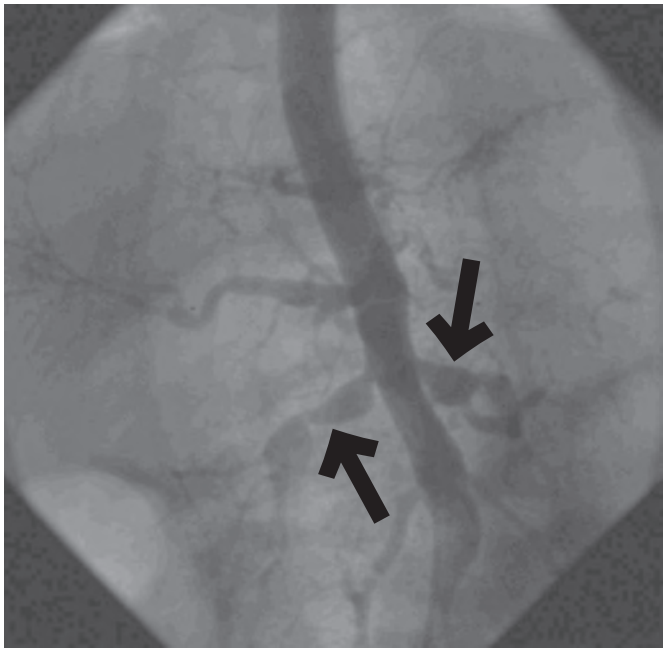

Fig. 7. Patient 6. Abdominal aortogram showing irregularity of the descending aorta below the coeliac plexus. The superior mesenteric artery is dilated and irregular; both renal arteries are stenosed and aneurysmal (arrows).

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