Cerebrovascular disease in children with HIV-1 infection

CHARLES K HAMMOND | BRIAN ELEY | NICKY WIESELTHALER | ALVIN NDONGO | JO M WILMSHURST

1 Department of Paediatric Neurology, Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town; 2 Paediatric Infectious Disease Unit, Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town; 3 Department Paediatric Radiology, Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town, South Africa.

Correspondence to Jo M Wilmshurst, Department of Paediatric Neurology, Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital, Rondebosch, Cape Town 7700, South Africa. E-mail: jo.wilmshurst@uct.ac.za

An estimated 3.2 million children worldwide have human immunodeficiency virus (HIV) infection. Antiretroviral therapy (ART) has resulted in prolonged survival, leading to an increase in complications previously recognized in adults. Children with HIV infection have increased risk of cerebrovascular disease from multiple aetiologies including HIV-associated vasculopathy, opportunistic vasculitis, cardioembolism or coagulopathy, all of which may be secondary to the infection. Prevalence of cerebrovascular disease in HIV-infected children is underestimated because of limited neuroimaging in low and middle income countries, silent events without overt motor manifestations, and mislabeling as HIV encephalopathy for non-motor manifestations such as behavioural and cognitive difficulties. No management guidelines for cerebrovascular disease in HIV-infected children exist but common practices target risk factors for stroke in low and middle income countries. Where capacity permits, screening for opportunistic infections, vasculitis, coagulopathy and cardioembolism is important. Optimising virological suppression, correction of anaemia, control of seizures and aspirin prophylaxis are management priorities. Neurosurgical interventions may have a role.

INTRODUCTION

By the end of 2013, 3.2 million children who were less than 15 years of age worldwide had human immunodeficiency (HIV) infection. Access to antiretroviral therapy (ART) correlated with prolonged survival of children with vertically acquired HIV infection into adolescence and adulthood, and with this the development of complications previously associated with adults infected with HIV.

Stroke is a recognized complication of HIV infection. Both ischaemic and haemorrhagic strokes occur in infected individuals. In the USA, between 1997 and 2006 stroke admissions declined by 7% in the general population but increased by 60% in individuals infected with HIV.

For children with HIV infection and cerebrovascular disease, the prevalence, aetiologies, pathogenesis, clinical spectrum, and optimal management remain unclear. This report reviews the published literature, specifically focusing on HIV vasculopathy. It does not address diverse factors which can also result in cerebrovascular disease in children, such as perinatal events and post-meningitis sequelae.

METHOD

Search engines PubMed, Medline, and Cochrane Central Register of Controlled Trials were accessed using the keywords: ‘stroke’, ‘cerebrovascular disease’, ‘HIV’, ‘AIDS’, ‘children’, and ‘adolescents’. Conference proceedings (abstracts) and the International Registers of ongoing clinical trials related to neurology, child neurology, and infectious diseases were also accessed. Additional articles were identified through the reference list of selected publications.

Using the American Heart Association and American Stroke Association updated definition of stroke, the term stroke was broadly used to include central nervous system (CNS) infarction based on clinical, pathological, or imaging findings. This encompasses ischaemic stroke, which includes arterial ischaemic stroke and cerebral sinus venous thrombosis, and haemorrhagic stroke, which includes intracerebral haemorrhage (ICH), subarachnoid haemorrhage, and intraventricular haemorrhage. Articles describing silent CNS infarctions and transient ischaemic attacks were also included. Children up to 18 years of age were included. The literature was searched from 1980 to June 2015. Throughout the following text, the term stroke refers to the clinical manifestation with imaging correlation, while cerebrovascular disease relates to the inherent process which may not have clinical correlation.

Twenty-seven case reports and series (including four autopsy studies) and four larger patient cohorts (inclusive of children with cerebrovascular disease) were identified. In total, there were 74 cases of cerebrovascular disease in children infected with HIV reported to date from North and Central America (USA, Mexico), South America (Columbia, Brazil), and Europe (Netherlands, France, Spain, Italy, Germany, United Kingdom, Norway, Sweden, Denmark, and Italy).
RESULTS

Prevalence of stroke in children infected with HIV

Between 1.3% and 2.6% of children infected with HIV develop stroke in clinical series, although a higher prevalence (4–36%) of cerebral ischaemic lesions is reported at autopsy. Limited access to neuroimaging in low and middle income countries (LMIC), where the majority of children infected with HIV reside, may underestimate the extent of cerebrovascular disease; for example, in a South African paediatric HIV-infection clinic, 6% of those evaluated had hemiplegia. These children were assessed as part of a prospective study and were not previously identified to have neurological complications.

Aetiology and pathogenesis of cerebrovascular disease in children infected with HIV

In the pre-ART era, cerebrovascular disease in people living with HIV infection was attributed to opportunistic infections, such as varicella zoster virus and cytomegalovirus, or malignancies such as CNS lymphomas and disseminated Kaposi sarcoma (Table II). Following the introduction of ART in 1996 the incidence of opportunistic infections and neoplasms declined, but cerebrovascular disease did not. HIV-1 may directly infect the wall of cerebral vessels or indirectly damage the vascular wall through an inflammatory or autoimmune response, a condition termed ‘HIV-associated cerebral vasculopathy’.

HIV-associated cerebral vasculopathy

HIV-associated cerebral vasculopathy is defined as cerebral vasculopathy/arteriopathy affecting predominantly medium-sized cerebral vessels with radiological evidence of vessel stenosis, occlusion, or aneurysmal dilatation without any identifiable cause other than the HIV infection. This vasculopathy may be asymptomatic or cause stroke, encephalopathy, or cognitive impairment. In some cases,

Table I: Summary of published cross-sectional and retrospective studies of children with human immunodeficiency virus (HIV) infection and neurological disease which include cerebrovascular disease

<table>
<thead>
<tr>
<th>Publication (Author, year, country)</th>
<th>Type of study</th>
<th>N (%)</th>
<th>Demographic characteristics</th>
<th>Types of cerebrovascular disease (n)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Izbudak et al. 2013, USA37</td>
<td>Retrospective longitudinal study</td>
<td>8/179 (4.5)</td>
<td>5 males, 3 females, mean age: 18.5y</td>
<td>Ischaemic infarcts (8)</td>
<td>Mean CD4 count&lt;96 cells/mm³, mean viral load&lt;19 770 copies/mL patients underwent MRA. All 6 had segmental occlusion, narrowing or narrowing/dilatation in the circle of Willis. Three had fusiform aneurysms and 1 had a saccular aneurysm. Comorbidities included thrombocytopenia, VZV, and disseminated MAC. Serial imaging showed asymptomatic progression of the CVD in 7 patients.</td>
</tr>
<tr>
<td>Mariam and Assefa 2012, Ethiopia36</td>
<td>Retrospective review</td>
<td>1/22 (4.5)</td>
<td>–</td>
<td>Ischaemic infarcts (1)</td>
<td>1 out of 22 children with HIV-1 encephalopathy had an ischaemic stroke. In the other children, other features of HIV-1 encephalopathy were identified.</td>
</tr>
<tr>
<td>Govender et al. 2011, South Africa2</td>
<td>Cross-sectional study</td>
<td>5/78 (6.4)</td>
<td>2 males, 3 females, age range: 4y 3mo–10.5y (median 7y 2mo)</td>
<td>Not stated</td>
<td>3/5 patients were not on ART (median viral load&lt;45 000 copies/mm³). 2/5 on ART (median viral load&lt;400 copies/mL). Comorbidities included pneumococcal meningitis (n=1), tuberculous meningitis (n=1) and disseminated MAC. Serial imaging showed asymptomatic progression of the CVD in all patients.</td>
</tr>
<tr>
<td>Patsalides et al. 2002, USA38</td>
<td>Retrospective review</td>
<td>11/426 (2.6)</td>
<td>6 males, 5 females, age range: 8mo–15y (median 9.3y)</td>
<td>Ischaemic infarcts only (4), infarcts and aneurysms (4), aneurysms only (3)</td>
<td>Only 1/11 had a focal neurologic symptom. The remaining 10/11 were asymptomatic despite extensive lesions. On neuroimaging, 3/11 had aneurysms only, 4/11 had infarctions only, and 4/11 had both infarctions and aneurysms. 10/11 patients had advanced HIV disease with severe immune suppression (CD4 count&lt;200 cells/mm³), VZV infection (n=6), protein S deficiency (n=2), protein C deficiency (n=1).</td>
</tr>
</tbody>
</table>

VZV, varicella zoster virus; MAC, Mycobacterium avium complex; CVD, cerebrovascular disease.
HIV-associated cerebral vasculopathy

Due to direct infection of HIV (Direct)\textsuperscript{43,44}
Due to vasculitis/perivasculitis (Indirect)\textsuperscript{46,47}

Secondary causes
Opportunistic vasculitis\textsuperscript{38,41,48}
Varicella zoster virus
Cytomegalovirus
Mycobacterium
Candida albicans
Cryptococcus
Treponema
Malignancies\textsuperscript{11,21,41,48}
Primary CNS lymphoma
Secondary tumours
Coagulopathies\textsuperscript{8,27,33,38}
Protein S deficiency
Protein C deficiency
Thrombocytopenia
Cardioembolism\textsuperscript{11,39,43}
Bacterial endocarditis
Marantic endocarditis
HIV-associated cardiac dysfunction
Antiretroviral drugs\textsuperscript{8,51}
Protease inhibitors

\textsuperscript{a}In the direct mechanism, the vasculopathy is due to vessel wall invasion by the HIV. In the indirect mechanism, the vasculopathy is due to autoimmune/inflammation within the vessel wall secondary to a systemic HIV infection. CNS, central nervous system.

Table II: Aetiology of cerebrovascular disease in children infected with human immunodeficiency virus (HIV)

Aneurysmal dilatation of the vessels results from medial thinning and loss of muscularis and internal elastic lamina within the vascular wall. This dilatation increases the risk of thrombosis and ischaemic stroke in children infected with HIV.\textsuperscript{22,44} Both fusiform or saccular aneurysms of the major vessels in the circle of Willis are described.\textsuperscript{14,37}

Aneurysms of the cerebral vessels, stenosis, occlusion, or dilatation of the vessels may be the outcome due to the resultant endothelial dysfunction, medial fibrosis, and thinning, damage, or loss of the muscularis and internal elastic lamina, and intimal hyperplasia of the vascular wall.\textsuperscript{33,44} The identification of HIV viral antigen in the intima of affected parenchymal and leptomeningeal arteries using monoclonal antibodies to gp41 further supports the direct role of HIV in vascular disease.\textsuperscript{21}

Opportunistic infections, malignancies, and comorbidities

In LMIC, the pathogenesis of cerebrovascular disease in children infected with HIV is complicated by the layering effect of multiple comorbidities associated with HIV infection, including the role of ART, co-infections, malnutrition, and iron-deficiency anaemia.\textsuperscript{43}

Opportunistic infections causing meningitides/vasculitides leading to stroke commonly occur in the setting of advanced acquired immunodeficiency syndrome, which still occurs in settings with limited access to ART.\textsuperscript{3,21} The commonly identified pathogens include Streptococcus pneumoniae, Haemophilus influenzae, varicella zoster virus, Mycobacterium tuberculosis, cytomegalovirus, and Cryptococcus neoformans.\textsuperscript{38,41,48} Vasculitis occurs either by direct infection of the vascular wall, leading to direct vascular injury and thrombosis in the cerebral vessels, or by a systemic immune mediated mechanism.\textsuperscript{39,49}

Primary CNS lymphoma is the most common tumour associated with stroke in children infected with HIV.\textsuperscript{11,21} Focal tumour infiltration of blood vessel walls results in direct vascular injury, invasion of the lumen, and focal thrombosis.\textsuperscript{39} Other tumours, such as lymphomatoid granulomatosis and disseminated Kaposi sarcoma, are associated with stroke in adults infected with HIV in pre-ART era reports.\textsuperscript{41}

Coagulopathies which occur in some children with HIV infection include deficiencies of protein S\textsuperscript{38} and protein C,\textsuperscript{31} immune thrombocytopenia,\textsuperscript{21} and thrombotic thrombocytopenia.\textsuperscript{9} Systemic HIV infection is thought to trigger with initiation of ART.\textsuperscript{34} HIV-associated cerebral arteriopathy is more frequently reported in individuals with active infection (low CD4 count or high viral load).\textsuperscript{45}

Indirect mechanisms suggested to lead to vascular disease in children with HIV-1 infection include autoimmune or inflammatory responses to systemic HIV infection.\textsuperscript{46} An autoimmune mechanism for the vascular disease was proposed, based on separate post-mortem brain tissues of six children with HIV-1 infection.\textsuperscript{47} Perivascular and transmural infiltrates of inflammatory cells – predominantly CD3+ and CD8+ T-cells – were detected, with no clinical or immunohistochemical evidence of opportunistic viral infections.\textsuperscript{47} The authors proposed that the CD3+ T-cell infiltrates in the CNS of children infected with HIV may represent oligoclonal expansion of cytotoxic T-cells in the context of a vigorous anti-HIV-1 response, even though the viral loads in the CNS during this T-cell perivasculitis were low, raising the possibility of an autoimmune basis for the T-cell response. Molecular mimicry (cross-recognition of common epitopes on HIV-1 and the host protein) was suggested as a mechanism for the endothelial cell injury, the ensuing vasculopathy, and the subsequent ischaemic stroke in these children.\textsuperscript{47} Inflammatory markers correlated with common carotid intima-media thickness in young adults with perinatally acquired HIV-1 infection, considered an increased risk for stroke, and further support an inflammation mediated mechanism.\textsuperscript{46}
consumptive coagulopathies and immune mediated mechanisms.43,50

Cardioembolism from various causes occur in children infected with HIV with stroke.11,43 In adults with HIV infection, cardioembolism accounts for 4% to 15% of ischaemic strokes.39 Bacterial endocarditis, opportunistic infections (marantic endocarditis), or cardiac infection with HIV itself, a condition termed HIV-associated cardiac dysfunction, may be the explanation.39

The role of ART in the aetiology of stroke
Stroke is described in adults with HIV infection following adverse effects of ART.43 Combination ART may increase the risk of stroke by elevating cholesterol and triglyceride levels. This indirect effect occurs more with protease inhibitors than other classes of antiretrovirals and is more pronounced after prolonged use.51 No paediatric cases of stroke in HIV infection attributable to the adverse effect of ART were identified.

Types of cerebrovascular disease and clinical manifestations
Both ischaemic and haemorrhagic strokes occur in children with HIV infection. In the more common ischaemic strokes, infarcts occur frequently in the cerebral cortex, basal ganglia, or internal capsule usually in the territories of the middle cerebral arteries or the anterior cerebral arteries.37,38 Haemorrhagic strokes are mostly intracerebral9 but subarachnoid haemorrhage is reported.14 Of the 74 reported cases of stroke in children with HIV infection in the literature, 54 were ischaemic strokes,10,12,13,15–27,29–33,35–38 six caused by ICH,9,18,21,31,34,35 five caused by ischaemic strokes and ICH,11,21,31 four due to subarachnoid haemorrhage,14,16,17,28 and in five cases the type of stroke is not stated.2

Identification of cerebrovascular disease is challenging especially in LMIC.40 Manifestations may be subtle or silent, or consist of neurobehavioural problems, learning difficulties or regression, which can be confused with HIV encephalopathy.37 Others may present as transient ischaemic attacks and not be investigated, missing the vasculopathy due to limited resources and lack of recognition of events. Neuroimaging has identified moyamoya syndrome which was clinically silent or presented with recurrent transient ischaemic attacks.15

Cerebrovascular disease in children with HIV infection does not differ from the presentation in uninfected children. Most cases are asymptomatic or present with soft signs, such as behaviour and mild cognitive impairment or transient ischaemic attacks, which do not come to medical attention and may only be recognized on neuroimaging or at autopsy.21,38 In overt stroke, the common clinical presentations include hemiparesis, facial weakness, seizures, aphasia, headache, or loss of consciousness.19,38

Stroke due to vasculopathy may be the initial presentation of HIV infection in children.35 The age of vasculopathy presentation in children with HIV infection may vary from early infancy35 to late adolescence.9,38 Cerebrovascular complications in children with HIV infection are more common in those who acquired their HIV infection during the perinatal period, thus prophylactic ART administered to pregnant females infected with HIV may provide a line of defence against HIV infection and cerebrovascular complications in their offspring.38

Investigation of stroke in children infected with HIV
The diagnosis of stroke is through history, clinical signs, and neuroimaging. Once a diagnosis of stroke is verified, management is directed towards acute stroke treatment, establishing the cause of stroke, management of HIV infection and related comorbidities, and secondary prevention. There are no published guidelines for managing stroke in children with HIV infection. Table III lists important investigations that are reported in the published cases of cerebrovascular disease in children infected with HIV. The investigation of stroke in children with HIV infection overlaps with that of the non-infected children, except there are additional risk factors in the HIV-infected group. In LMIC access to neuroimaging and many other investigations are limited or unavailable. The South African stroke guideline,52 though designed for adult patients, provides guidance for basic stroke care in these settings. For children with HIV infection, screening for the viral load and the presence of opportunistic infections are priorities.

Basic investigations
Irrespective of the underlying cause, the minimum battery of tests listed in Table III should be completed. Counselling and HIV testing are required if the HIV status of the child is unknown, as stroke may be the initial presentation of HIV infection in some children.37 For children with HIV infection, CD4 count and viral load are necessary to establish the extent of immunosuppression and the degree of virological control.11,49 A chest radiograph may assist the investigation of infections (particularly tuberculosis), tumours, emboli from cardiac disease, and vascular abnormalities.19

Infectious screen
Evaluation of infectious causes of vasculitis and stroke mimics include testing for tuberculosis, varicella, mycoplasma, syphilis, toxoplasmosis, cryptococcosis, herpes simplex virus infection, and cytomegalovirus infection using serological-, polymerase chain reaction-, or antigen-based tests. These are of special relevance to LMIC where opportunistic infections in children with HIV infection are prevalent.

The role of neuroimaging
Neuroimaging modalities including computed tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance angiography (MRA) and conventional cerebral angiography are useful in diagnosing or confirming the stroke and in investigating the aetiology (Figs. 1–3). While
a limited resource in most LMIC, access to neuroimaging can be pivotal to understanding the aetiology and further investigations that are needed. In a cohort of perinatally infected children who underwent sequential neuroimaging over a 14-year period, eight developed cerebrovascular events, all due to infarction. Progression of the infarct occurred in seven of the eight patients on subsequent neuroimaging. In five of these seven patients, there were no clinical signs or symptoms suggestive of progression. This would support a low threshold for proceeding to neuroimaging, since the early identification of cerebrovascular disease can have implications on patient management.

Common radiological findings in ischaemic stroke are basal ganglia–thalamic infarction, focal cerebral cortical infarction, and internal capsule infarction. MRA often reveals stenosis, segmental occlusion, or aneurysmal dilatation of the major vessels of the circle of Willis especially the M1 segment of middle cerebral arteries, distal internal carotid artery, and proximal anterior cerebral arteries. Serial imaging studies may reveal progressive occlusion of the vessels with the development of collateral circulation. Radiological features of HIV-1 encephalopathy, namely cortical atrophy, ventricular dilatation, basal ganglia calcifications, and periventricular white matter hyperintense T2 signals may be seen.

### Other specific investigations
The patient’s history, physical findings, and results of initial investigations may direct what further investigations are done. In most regions of Africa, these additional inves-

### Table III: Investigations in children infected with human immunodeficiency virus (HIV) with cerebrovascular disease. These are investigations as performed in the published cases. The table separates them into basic investigations for low and middle income countries (LMIC) and further investigations (a), where availability of resources permit. Screens which are of especial relevance in LMIC settings with high prevalence of HIV are noted (b)

<table>
<thead>
<tr>
<th>Test modality</th>
<th>Standard</th>
<th>Specific to children infected with HIV</th>
<th>Further investigationsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Full blood count &amp; peripheral smear</td>
<td>CD4 count and HIV RNA viral loadb</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blood glucose, urea, creatinine &amp; electrolytes</td>
<td>Infectious screen (bacterial and tuberculosis cultures), PCR or antigen test for VZV, mycoplasma, syphilis (RPR, TPHA or VDRL), toxoplasma, Cryptococcus, HSV, CMVb</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liver function tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erythrocyte sedimentation rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fasting lipid profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CT scan</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MRI/MRA of the head and neck</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroimaging</td>
<td>CSF cell counts and chemistryb</td>
<td>Test for acid fast bacilli</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bacterial cultures</td>
<td>PCR testing for VZV, HSV, CMV, JC virus, HHV (types 6 and 7), enteroviruses and adenovirusb</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CSF tuberculosis cultures and PCRb</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CSF should also be tested for aspergillus, Cryptococcus, toxoplasma, treponema, and borreliab</td>
<td></td>
</tr>
<tr>
<td>CSF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>4-limb blood pressure monitoring</td>
<td>Echocardiogram</td>
<td></td>
</tr>
<tr>
<td>assessment</td>
<td>Electrocardiogram</td>
<td>Abdominal Doppler ultrasound</td>
<td></td>
</tr>
<tr>
<td>Autoimmune</td>
<td></td>
<td>According to accepted guidelines (e.g. antiphospholipid antibodies) and as guided by history and clinical findings,43,50</td>
<td></td>
</tr>
<tr>
<td>screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulation</td>
<td>Platelet count</td>
<td>Protein S (perform 3 months’ post event)</td>
<td></td>
</tr>
<tr>
<td>screening</td>
<td>Basic clotting screen (PTT, PT, INR)</td>
<td>Protein C (perform 3 months’ post event)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fibrinogen level</td>
<td>Antithrombin III</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thrombin time</td>
<td>Factor V Leiden</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bleeding time</td>
<td>Nuclear medicine (SPECT, PET scans)c</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lactate (CSF/blood)d</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Urine dipstick, microscopy &amp; culture</td>
<td>Urinary organic and amino acidsd</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brain biopsy (rarely)</td>
<td></td>
</tr>
</tbody>
</table>

aFurther investigations undertaken as guided by outcomes of basic investigations, history, and clinical examination. In most regions of Africa these investigations would not be accessible, due to capacity, availability, and cost. bOf especial relevance in LMIC where HIV is prevalent. To support features consistent with systemic lupus erythematosus. To screen for evidence of mitochondrial pathology, such as mitochondrial encephalopathy with lactic acidosis and stroke-like events. To exclude homocystinuria. PCR, polymerase chain reaction; VZV, varicella zoster virus; RPR, rapid plasma reagent test for syphilis; TPHA, Treponema pallidum hemagglutination assay test for syphilis; VDRL, venereal disease research laboratory test for syphilis; HSV, herpes simplex virus; CMV, cytomegalovirus; CSF, cerebrospinal fluid; HHV, human herpes virus; PTT, partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; SPECT, single-photon emission computed tomography; PET, positron emission tomography.
Investigations may not be accessible due to capacity, availability, and cost. Further cardiovascular workup, when indicated, include an MRA of the neck to outline the carotid and vertebral arteries, and abdominal ultrasound to identify renal vessel abnormalities. Further cardiovascular workup, when indicated, include an MRA of the neck to outline the carotid and vertebral arteries, and abdominal ultrasound to identify renal vessel abnormalities. For suspected thromboembolic events, coagulation screen should include protein S, protein C, antithrombin III, factor V Leiden, antiphospholipid antibodies, and anticardiolipid antibodies. Brain biopsy can identify emboli, features of vasculitis, or additional pathology, such as concomitant mycobacterial or fungal infection, lymphoma, or viral inclusions. While undertaking this invasive investigation is unusual, when other screens have failed to elucidate an etiology, this intervention can be considered.

**Treatment of stroke in children with HIV infection**

Ideally, affected children should be managed in a stroke unit equipped with skilled personnel and facilities for comprehensive assessment of medical problems, impairments, and disabilities. Established pathways and management protocols are needed for the acute and post-acute management of stroke coordinated by a multidisciplinary team of physicians, nursing staff, therapists, social workers, and psychologists. In resource-limited settings, such as in sub-Saharan Africa, shortages in skilled personnel and pressure for hospital beds preclude such an establishment even at tertiary level hospitals. In South Africa, adult stroke units exist which could serve as models for the reorganization of existing resources to provide more effective stroke care without necessarily incurring additional cost.

**Basic interventions**

Basic supportive interventions include temperature control, normalization of oxygenation and serum glucose concentra-
treatments, correction of anaemia, and rehydration. Systemic hypertension and seizures should be controlled. Low platelet counts and factor deficiencies should be corrected and vitamin K administered for vitamin K-dependent coagulation disorders. Children with HIV infection often suffer macro- and micronutrient deficiencies due to chronic illness and poor social circumstances requiring comprehensive management.

**Acute thrombolysis for ischaemic stroke**

There are no reports on the use of intravenous tissue plasminogen activator for acute ischaemic stroke in children with HIV infection. Experience of using intravenous tissue plasminogen activator in adults with HIV infection with ischaemic strokes indicate that their risk of death is similar to patients without HIV infection treated with intravenous tissue plasminogen activator.

**Anticoagulation**

The safety and efficacy of low molecular weight heparins has not been evaluated in children with HIV infection with ischaemic stroke. The concomitant use of warfarin and ART requires monitoring of the international normalized ratio, because warfarin is metabolized by the CYP450 system and interactions are reported with protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

**Antiplatelet agents**

Aspirin may decrease the risk of further infarctions. There are no specific interactions with ART but Reye syndrome remains a concern. Other antiplatelet agents have not been trialled in children with HIV infection.

**Initiation of ART**

The initiation of ART leads to a decreased viral load and sometimes an improvement in the arteriopathy, with or without corticosteroids. Prior to initiating ART, opportunistic infections should be treated to prevent immune reconstitution inflammatory syndrome occurring.

**Surgical procedures**

Surgical evacuation of intracranial haematomas is undertaken to reduce intracranial pressure. Ventricular drainage and, if indicated, ventriculo-peritoneal shunting for progressive hydrocephalus may be necessary. More complex neurosurgical interventions are not routine. Surgical revascularization procedures could be an option for children with moyamoya syndrome and those who continue to have cerebrovascular dysfunction despite optimal medical management. In young children, where direct anastomosis procedures are technically difficult due to the small scalp donor vessels, or the middle cerebral arteries recipient vessels, an indirect revascularization procedure is reported to be effective in non-infected children, through drilling burr holes, without vessel synangiosis and craniotomy, with inversion of the dura in order to enhance new dural revascularization of the brain.

Focused vascular surgeries are reported with successful outcome. Pipeline embolization device, a recently approved wire mesh cylindrical implanted device which is placed within an artery in the brain to treat aneurysms, successfully treated an adult patient with HIV who presented with ischaemic stroke and three fusiform cerebral aneurysms. The pipeline embolization device allows flow diversion in patients when aneurysm location precludes parent vessel sacrifice or surgical bypass.

**Stroke rehabilitation**

Early initiation of rehabilitation is recommended by a multidisciplinary team of experienced therapists. The ultimate goal of rehabilitation is to enable children to resume their premorbid function within their families, communities, and schools. In children with significant permanent disabilities, goals target reduction of the burden of care for the family and helping the child to become as independent as possible. In those with severe strokes and poor recovery, caregivers should be trained by the multidisciplinary team. Institutionalization may be required for children with very poor prognosis. Such crucial decisions should involve all parties and consider financial and social circumstances.

In LMIC, community-based rehabilitation or step-down facilities are employed especially in patients who are stable.

**Clinical outcome of stroke in children with HIV infection**

Variable outcomes are reported in children with HIV infection with stroke. In some patients with ischaemic stroke who are treated with aspirin and initiated on ART, improvement with no new infarcts is reported, but ongoing focal neurological deficits, progression of symptoms, and stroke recurrence are also documented. Fatal outcomes at presentation are more commonly reported with haemorrhagic stroke. Among four reported cases of subarachnoid haemorrhage, three died at presentation.

Two patients with ICH who had surgical evacuation of the haematoma died during the post-operative period.

**SUMMARY**

Children with HIV infection are at increased risk of stroke. The frequency is underestimated because access to neuroimaging is limited and cerebrovascular disease may be clinically silent or subtle, manifesting as behavioural change or cognitive regression and mislabelled as HIV encephalopathy.

The pathogenesis of cerebrovascular disease in HIV is complex. HIV-associated cerebral vasculopathy may result from direct HIV-1 infection of cerebral vessels or be caused by an indirect process of an autoimmune vasculitis secondary to the systemic infection. The effects of co-infections, comorbidities, and the side effects of ART are important.

Management should focus on optimizing HIV virological control and exclusion of opportunistic infections. Where possible, ART with adverse atherosclerotic side effects should be avoided. Basic interventions are important in the
across management. In the long term, secondary aspirin pro-
phylaxis may be protective. The role of more complex inter-
ventions, such as neurosurgery, is unclear.

ACKNOWLEDGEMENTS

The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

REFERENCES


9. Rychmanina N, Wong EC, Davis JC, Ray PE. Hemor-


11. Narayan P, Samuels OB, Barlow DL. Stroke and pediat-

12. Bonkowski JL, Christenson JC, Nixon GW, Pavia AT. Cerebral aneurysms in a child with acquired immune deficiency syndrome during rapid immune reconstruc-

13. Elfenbein DS, Emmanuel PJ. Radiological case of the month. Aneurysmal dilatation of cerebral arteries associ-

14. Mazzoni P, Chiriboga CA, Miller WS, Rogers A. Intrac-
erebral aneurysms in human immunodeficiency virus infection: case report and literature review. Pediatr Neu-

15. Hsiung GY, Sotero de Menezes M. Moyamoya syn-
drome in a patient with congenital human immuno-
deficiency virus infection. J Child Neurol 1999; 14: 268–70.


18. Shah SS, Zimmerman RA, Roche LB, Veizina LG. Cere-

19. Moriarty DM, Haller JO, Loh JP, Fikre S. Cerebral infarction in pediatric acquired immunodeficiency syn-


23. Frank Y, Lin W, Kahn E, Farmer P, Gorey M, Pahwa S. Multiple ischemic infarcts in a child with AIDS, vari-

24. Cho E, Sharrer L, Peress N, Little B. Intimal prolifera-
tion of leptomeningeal arteries and brain infarcts in sub-


29. Carvalho Neto A, Bruck I, Coelho LO, et al. Cerebral arterial aneurysm in a child with acquired immunodefici-


32. Lang C, Jacob I, Kreuz W, et al. Rapid development of giant aneurysm at the base of the brain in an 8-year-

33. Goyal A, Shah I. HIV-associated thromboembolic phe-

34. Mahadevan A, Tagore R, Siddappa NB, et al. Giant ser-


36. G Mariam A, Asseg A. Clinical and neuroimaging pro-

37. Ishuduk I, Chulian M, Hutton N, et al. Perinatally HIV-infected youth presenting with acute stroke: pro-

38. Pantaleides AD, Wood LV, Atac GK, Sandifer E, Butman JA, Patronas NJ. Cerebrovascular disease in HIV-

39. Benjamin LA, Bryer A, Emsley HCA, Khoo S, Solomon T, Connor MD. HIV infection and stroke: current per-


42. Connor MD. Treatment of HIV associated cerebral vas-


44. Gutierrez J, Glenn M, Isaacsen RS, Marx AD, Mash D, Petito C. Thinning of the arterial media layer as a possi-

45. Chow FC, Bacchetti P, Kin L, Price RW, Huey PY. Effect of CD4+ cell count and viral suppression on risk


---

New from Mac Keith Press

**Tics and Tourette Syndrome**

Key Clinical Perspectives

Roger Freeman

- Extensive discussion of tic disorders that occur alone or in other conditions such as ADHD, DCD, anxiety, and mood disorders.
- Practical advice for clinicians who may encounter tics and Tourette syndrome to improve management of their patients.
- With numerous illustrative vignettes and clinical practice points, an excellent resource for paediatricians, child and adolescent psychiatrists, neurologists, and other health professionals.

Contact us at admin@mackeith.co.uk to receive full table of contents and further details.


www.mackeith.co.uk