Moyamoya Syndrome in South African Children With HIV-1 Infection

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Abstract
A national multicenter study identified 17 South African children with vertically acquired HIV-1 infection and HIV-associated vasculopathy. Five of the children (all indigenous African ancestry) had progressive vascular disease, consistent with moyamoya syndrome. Median presentation age 5.8 years (range 2.2-11). The children with moyamoya syndrome presented with abnormal CD4 counts and raised viral loads. Clinical features included motor deficits, neuroregression, and intellectual disability. Neuroimaging supported progressive vascular disease with preceding clinically silent disease course. Neurologic recovery occurred in 1 patient with improved CD4 counts. Four of the 5 children presented during the era when access to antiretroviral therapy was limited, suggesting that with improved management of HIV-1, progressive vasculopathy is less prevalent. However the insidious disease course illustrated indicates that the syndrome can progress “silently,” and manifest with misleading phenotypes such as cognitive delay or regression. Sub-Saharan Africa has limited access to neuroimaging and affected children may be underdiagnosed.

Keywords
moyamoya syndrome, HIV infection, cerebrovascular disease, HIV vasculopathy, Africa, children

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Over the last decade children with HIV-infection acquired perinatally through vertical transmission are surviving longer.1 This correlates with improved access to health care, nutritional support and antiretroviral therapies. As children live longer, complications that were previously not recognized in this age group are becoming apparent.2

Stroke occurs in people with HIV infection due to opportunistic infections, vasculopathy, cardioembolism, and coagulopathy. The term “HIV-associated vasculopathy” relates to various cerebrovascular changes, which include stenosis and aneurysm formation, vasculitis, and accelerated atherosclerosis.3 This complication may be caused directly or indirectly by HIV infection. The pathogenesis remains a subject of debate.

Moyamoya disease is a rare cerebrovascular disorder of unknown origin due to an occlusion or narrowing of the distal internal carotid, or proximal middle, or anterior cerebral arteries, associated with the development of collateral network at the base of the brain.4 There is a bimodal age distribution with pediatric patients presenting around 5 years of age mainly with ischemic stroke, and in adults around 40 years of age with ischemic events and or intracranial bleeding. Clinical signs can be diverse including headache, seizures, motor, sensory, speech and visual deficits, syncope, personality changes, involuntary movements, disturbances of consciousness, and intellectual disability.5-7 A radiographic picture resembling the disease and referred to as “moyamoya syndrome” occurs with systemic infections, autoimmune, hematological, metabolic or genetic disorders, neoplasm, head trauma, or irradiation to the head.4

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While there are several reports of adults with HIV-1 infection who developed moyamoya syndrome, only 2 case reports were identified in HIV-infected children. Awareness of the presentation and evolution of moyamoya syndrome in children with HIV-1 infection, and the therapeutic implications are important to permit early intervention and improve outcome.

This report describes the South African experience of children presenting with HIV-associated vasculopathy and delineates a subgroup with moyamoya syndrome.

**Methodology**

The 7 tertiary centers in South Africa with pediatric neurology units were enrolled in a multicenter national study. These hospitals provide the referral routes for complex neurology patients and have the capacity to screen children with cerebrovascular disease. Each center reviewed their patient databases for children managed between 2000 and 2015 with HIV infection and vascular disease. Children with HIV-associated vasculopathy were included based on the finding of any combination of clinical presentation and vascular disease. Children with HIV-associated vasculopathy were identified in HIV-infected children. Awareness of the vasculopathy was important to permit early intervention and improve outcome.

This report describes the South African experience of children presenting with HIV-associated vasculopathy and delineates a subgroup with moyamoya syndrome.

**Table 1. Summary of the Study Cohort of Children With HIV-Associated Vasculopathy Referred to Pediatric Neurology Services in South Africa Between 2000 and 2015.**

<table>
<thead>
<tr>
<th></th>
<th>N = 17</th>
<th>Sex, M:F</th>
<th>Age presented median (range)</th>
<th>Impaired viral suppression</th>
<th>Indirect causes and other etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moyamoya syndrome</td>
<td>5</td>
<td>1:4</td>
<td>5.8 years (27 months-11 years)</td>
<td>5/5</td>
<td>Down syndrome n = 1</td>
</tr>
<tr>
<td>HIV-associated vasculopathy</td>
<td>10</td>
<td>7:3</td>
<td>7 years (27 months-11 years)</td>
<td>7/10</td>
<td>n = 9/10 post-Varicella n = 4</td>
</tr>
<tr>
<td>Arterial dissection</td>
<td>2</td>
<td>2:0</td>
<td>7 years, 17 months</td>
<td>1/2</td>
<td>↑ TG and chol n = 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ protein S levels n = 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ C3 levels n = 1 IRIS n = 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Epidermal nevus syndrome n = 1</td>
</tr>
</tbody>
</table>

Abbreviations: Chol, cholesterol; C3, complement C3; F, female; IRIS, immune reconstitution inflammatory syndrome; M, male; TG, triglyceride.

The authors describe the demographics, past medical history, HIV-1 management including age at HIV diagnosis, antiretroviral therapy, and viral load and CD4 count responses, presenting clinical features of moyamoya syndrome, neuroimaging findings, and ongoing clinical and imaging outcomes to understand the course of this condition.

**Results**

Between 2002 and 2015, 17 children presented with cerebral HIV-associated vasculopathy from 3 out of the 7 centers. The remaining 4 centers did not identify any cases referred to their neurology units. The study group are summarized in Table 1. Five children had moyamoya syndrome, 10 had isolated stroke which did not progress to moyamoya syndrome and 2 children had dissections of the carotid artery. No children had cerebral aneurysms at presentation with stroke.

Table 2 details the key features of the children with moyamoya syndrome. All 5 children (4 girls) with moyamoya syndrome were of indigenous African ancestry and acquired HIV-1 infection through vertical transmission. Median age of presentation was 5.8 years (range 2.2 - 11 years). Four presented between 2002 and 2010, and 1 in 2015, when their HIV infection was inadequately suppressed, because either HIV-1 infection was not diagnosed (n = 3) or treatment with antiretroviral therapy was suboptimal (n = 2). Four of the children had evidence of another cause for their vascular complications, the fifth had dual pathology. Patient 1 presented at 11 years of age with acute right hemiplegia, preceded by transient ischemic attacks. She developed neuroregression 1 year later. Antiretroviral therapy was not available in the government sector at that time and her mother declined antiretroviral therapy enrolment into available research studies and nongovernment organization care programs. She defaulted further intervention and follow-up. Patient 2 presented at 10 years of age, having received antiretroviral therapy from age 3.5 years. His course was characterized by recurrent systemic illnesses and failure to thrive, and he experienced frequent periods of poor viral suppression. He was converted to second-line antiretroviral therapy at 7 years of age and from this point onward his viral load and CD4 count results improved. Persistent global developmental delay and behavioral issues led to neurology referral at 10 years of age. Neuroimaging at this age confirmed
<table>
<thead>
<tr>
<th>Patient details, region</th>
<th>Present study</th>
<th>Published cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1, Western Cape</td>
<td>Female Indigenous African</td>
<td>Male European</td>
</tr>
<tr>
<td>Patient 2, Western Cape</td>
<td>Male Indigenous African</td>
<td>Not stated</td>
</tr>
<tr>
<td>Patient 3, Western Cape</td>
<td>Female Indigenous African</td>
<td>Vertical</td>
</tr>
<tr>
<td>Patient 4, Kwa-Zulu-Natal</td>
<td>Female Indigenous African</td>
<td>Vertical</td>
</tr>
<tr>
<td>Patient 5, Western Cape</td>
<td>Female Indigenous African</td>
<td>Vertical</td>
</tr>
</tbody>
</table>

**Demographics**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Ancestry</th>
<th>Mode of HIV infection</th>
<th>Diagnosis age</th>
<th>At presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Indigenous African</td>
<td>Vertical</td>
<td>11 years</td>
<td>Right hemiplegia (face, arm, and leg)</td>
</tr>
<tr>
<td>Male</td>
<td>Indigenous African</td>
<td>Vertical</td>
<td>1.7 years</td>
<td>Right hemiplegia (face, arm, and leg)</td>
</tr>
<tr>
<td>Female</td>
<td>Indigenous African</td>
<td>Vertical</td>
<td>2.6 years</td>
<td>Right arm hemiplegia</td>
</tr>
<tr>
<td>Female</td>
<td>Indigenous African</td>
<td>Vertical</td>
<td>3 years</td>
<td>Trisomy 21. Left hemiplegia (face, arm, and leg)</td>
</tr>
<tr>
<td>Female</td>
<td>Indigenous African</td>
<td>Vertical</td>
<td>2.2 years</td>
<td>Trisomy 21. Left hemiplegia (face, arm, and leg)</td>
</tr>
<tr>
<td>Male</td>
<td>European</td>
<td>Vertical</td>
<td>15 months</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

**Diagnosis age**

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>Presentation</th>
<th>ART</th>
<th>Duration of ART</th>
<th>CD4 count</th>
<th>Viral load</th>
<th>Infection screen</th>
<th>Cardiac review</th>
<th>Coagulation and hematology studies</th>
<th>Autoimmune screen</th>
<th>Metabolic assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 years</td>
<td>Right hemiplegia (face, arm, and leg)</td>
<td>No</td>
<td>N/A</td>
<td>770 cells/mm³ (low)</td>
<td>LDL</td>
<td>CSF: ↑ lymphocytes (7/mm³ on day 1, 30/mm³ on day 3), ↑ protein (0.62 g/L on day 1, 0.5 g/L on day 3), normal glucose, negative for bacteria, AFB, HSV, and mycoplasma</td>
<td>Normal ECG and echocardiogram</td>
<td>Normal clotting screen, protein S, protein C, antithrombin III</td>
<td>Negative ANF, ANCA, anti-dsDNA, RF</td>
<td>Normal CSF lactate and glucose, serum amino acids, urine amino acids, and organic acids.</td>
</tr>
<tr>
<td>10 years</td>
<td>Global developmental behavioral issues</td>
<td>Yes (on second line due to virologic failure)</td>
<td>33 months</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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</tr>
<tr>
<td>5.8 years</td>
<td>Left hemiplegia (face, arm, and leg)</td>
<td>Yes (poor compliance. ART stopped month prior to presentation)</td>
<td>34 months</td>
<td>785 cells/mm³ (low)</td>
<td>CMV neg, CSF not done</td>
<td>—</td>
<td>—</td>
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<tr>
<td>3 years</td>
<td>No</td>
<td>N/A</td>
<td>620 00 copies/ml (log 2.9)</td>
<td>—</td>
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<td>—</td>
<td>—</td>
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</tr>
<tr>
<td>2.2 years</td>
<td>Right arm hemiplegia</td>
<td>N/A</td>
<td>—</td>
<td>↑ 100 copies/ml (log &lt; 2.00)</td>
<td>—</td>
<td>—</td>
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</tr>
<tr>
<td>7 years</td>
<td>Trisomy 21. Left hemiplegia (face, arm, and leg)</td>
<td>N/A</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>10 years</td>
<td>Global developmental behavioral issues</td>
<td>N/A</td>
<td>—</td>
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<tr>
<td>5.8 years</td>
<td>Left hemiplegia (face, arm, and leg)</td>
<td>N/A</td>
<td>—</td>
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<tr>
<td>3 years</td>
<td>No</td>
<td>N/A</td>
<td>—</td>
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<td>—</td>
<td>—</td>
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<tr>
<td>2.2 years</td>
<td>Right arm hemiplegia</td>
<td>N/A</td>
<td>—</td>
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<td>—</td>
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<tr>
<td>15 months</td>
<td>Not stated</td>
<td>N/A</td>
<td>—</td>
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<td>—</td>
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</tr>
<tr>
<td>13 years</td>
<td>Right hemiplegia (face, arm, and leg)</td>
<td>Not stated</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>7 years</td>
<td>Recurrent TIA</td>
<td>N/A</td>
<td>—</td>
<td>—</td>
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</table>

**Table continued...**
<table>
<thead>
<tr>
<th>Patient details, region</th>
<th>Present study</th>
<th>Published cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1, Western Cape</td>
<td>Patient 2, Western Cape</td>
<td>Patient 3, Western Cape</td>
</tr>
<tr>
<td>Lipid profile</td>
<td>Normal</td>
<td>Abdominal USA</td>
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<tr>
<td>Abdominal USA</td>
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</tbody>
</table>

**Neuroimaging**

<table>
<thead>
<tr>
<th>Present study</th>
<th>Published cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT/MRI presentation:</td>
<td>CT/MRI presentation:</td>
</tr>
<tr>
<td>CT: Bilateral basal ganglia infarcts of varying ages. MRI: left head of caudate, anterior limb of internal capsule, posterior limb of internal capsule extending into corona radiata subacute infarcts with restricted diffusion. Multiple smaller chronic infarcts in frontal lobes. MRA: significant stenosis supraciloid portion right ICA and attenuation of segments of the right MCA, ACA and PCA. Focal stenosis left MCA.</td>
<td>CT: (7 years) lacunar infarct left caudate nucleus. MRI: ectatic changes and narrowing bilateral supraciloid ICA and MCA. Follow-up MRI/MRA: increased narrowing right MCA with poststenotic fusiform dilatation. MRA (10 years) occlusion right ACA and MCA. Cerebral angiogram: prominent collaterals developing from the external carotid system.</td>
</tr>
<tr>
<td>CT (1 year later): new left frontal lobe encephalomalacia, old left caudate, corona radiata and right basal ganglia infarcts.</td>
<td>CT: Bilateral asymmetrical severe encephalomalacia and atrophy due to bilateral chronic infarcts with exvacuo dilation of the ventricles. The basal ganglia and posterior fossa are spared. There are extensive net-like collaterals seen on T2 in the circle of Willis. No acute infarcts MRA: complete occlusion supraciloid ICAs, proximal MCAs, and ACAs with some reconstitution of the right MCA and left ACA via collaterals but very attenuated vessels. Basilar artery and PCAs patent but attenuated.</td>
</tr>
<tr>
<td>MRI presentation: (limited study with no MRA). Brain atrophy, exvacuo dilatation of the ventricles. Multiple chronic infarcts - basal ganglia, deep white matter and cerebral cortex. T2 axial - attenuation distal right ICA and MCA, and left ACA. Intense formation of &quot;net-like&quot; collateral vessels around circle of Willis and ambient wing cisterns extending into basal ganglia and corona radiata bilaterally (Figure 1a).</td>
<td>MRI presentation: Bilateral asymmetrical severe encephalomalacia and atrophy due to bilateral chronic infarcts with exvacuo dilation of the ventricles. The basal ganglia and posterior fossa are spared. There are extensive net-like collaterals seen on T2 in the circle of Willis. No acute infarcts MRA: complete occlusion supraciloid ICAs, proximal MCAs, and ACAs with some reconstitution of the right MCA and left ACA via collaterals but very attenuated vessels. Basilar artery and PCAs patent but attenuated.</td>
</tr>
<tr>
<td>CT, MRI presentation: Right frontal subacute to chronic enhancing ACA territory cortical infarct undergoing laminar necrosis. Multiple smaller chronic infarcts—basal ganglia, corona radiate, centrum semiovale, and superficial and deep white matter (Figure 1b). MRA: bilateral distal carotid artery attenuation, right worse than left, complete occlusion right MCA and both ACAs with attenuation left MCA segments (Figure 1c). Collaterals in circle of Willis (T2 axial imaging).</td>
<td>CT/MRI presentation: CT: R ACA/MCA watershed subacute infarct with associated luxury perfusion. Multiple—basal ganglia and deep white matter hypodensities (R&gt;L), consistent with chronic ischemic changes. MRI: R ACA/MCA watershed subacute infarct confirmed with luxury perfusion. Multiple basal ganglia and deep white matter hyperintensities on T2 and FLAIR consistent with chronic ischemia. MRA: Bilateral attenuated distal ICAs. Complete occlusion of proximal MCAs bilaterally with reconstitution of vessels distally via collaterals. Both A1 segments are attenuated L&gt;R. A2 segments and PCAs patent but attenuated. Multiple</td>
</tr>
<tr>
<td>CT/MRI presentation: CT: R ACA/MCA watershed subacute infarct with associated luxury perfusion. Multiple—basal ganglia and deep white matter hypodensities (R&gt;L), consistent with chronic ischemic changes. MRI: R ACA/MCA watershed subacute infarct confirmed with luxury perfusion. Multiple basal ganglia and deep white matter hyperintensities on T2 and FLAIR consistent with chronic ischemia. MRA: Bilateral attenuated distal ICAs. Complete occlusion of proximal MCAs bilaterally with reconstitution of vessels distally via collaterals. Both A1 segments are attenuated L&gt;R. A2 segments and PCAs patent but attenuated. Multiple</td>
<td>CT/MRI presentation: CT: (7 years) lacunar infarct left caudate nucleus. MRI: ectatic changes and narrowing bilateral supraciloid ICA and MCA. Follow-up MRI/MRA: increased narrowing right MCA with poststenotic fusiform dilatation. MRA (10 years) occlusion right ACA and MCA. Cerebral angiogram: prominent collaterals developing from the external carotid system.</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Patient details, region</th>
<th>Present study</th>
<th>Published cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1, Western Cape</td>
<td>Present study</td>
<td>Hsiung and Sotero de Menezes, USA</td>
</tr>
<tr>
<td>Patient 2, Western Cape</td>
<td>Published cases</td>
<td>Narayan et al, USA</td>
</tr>
<tr>
<td>Patient 3, Western Cape</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 4, Kwa-Zulu-Natal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 5, Western Cape</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment received</th>
<th>Present study</th>
<th>Published cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin Prophylaxis</td>
<td>Continued ART, aspirin prophylaxis</td>
<td>ART, aspirin prophylaxis and bilateral synangiosis procedures</td>
</tr>
<tr>
<td>ART reinitiated, aspirin prophylaxis</td>
<td>ART</td>
<td></td>
</tr>
<tr>
<td>ART</td>
<td>Rehabilitation. Revascularization surgery pending aspirin after surgery ART</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome/comment</th>
<th>Present study</th>
<th>Published cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother declined ART. Defaulted follow-up. Represented 1 year later with right hemiplegia and neuroregression.</td>
<td>Prior to presentation chronic course with frequent poor viral suppression. Remained virologically suppressed on ART. No change in clinical condition after 1.5 years. Transferred back to referral hospital</td>
<td>Had further strokes/TIAs. Improved after surgery.</td>
</tr>
<tr>
<td>Remained virologically suppressed on ART and hemiplegia resolved. Transferred back to referral hospital aged 10 years with normal neurological examination.</td>
<td>Learning difficulties and behavioral difficulties.</td>
<td></td>
</tr>
<tr>
<td>Continues in rehabilitation.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACA, anterior cerebral artery; AFB, acid fast bacilli; ANCA, antineutrophil cytoplasmic autoantibodies; ANF, antinuclear factor; ART, antiretroviral therapy; ASOT, anti-streptolysin O titre; CD4, number of CD4 T lymphocyte cells; CMV, cytomegalovirus; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computed tomography; dsDNA, double stranded DNA; ECG, electrocardiogram; ECHO, echocardiogram; ESR, erythrocyte sedimentation rate; HB, hemoglobin; HSV, herpes simplex virus; ICA, internal carotid artery; Ig, immunoglobulin; IgG, immunoglobulin G; IgM, immunoglobulin M; L, left; LDL, viral load that is below the lower detection limit (<400 copies/mL); MCA, middle cerebral artery; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; N/A, not applicable; PCA, posterior cerebral artery; R, right; RF, rheumatoid factor; RPR, rapid plasma reagent screening for syphilis; TB, tuberculosis; TIA, transient ischemic attack; USA, United States of America; VDRL, Venereal Disease Research Laboratory test for syphilis.
long-standing moyamoya syndrome (Figure 1a). He remained static following this presentation with no new neurologic events. Patient 3 was able to access antiretroviral therapy from 3 years of age. Her antiretroviral therapy was discontinued when she was 5 years and 9 months old and she presented a month later when no longer virally suppressed with a left hemiplegia. Neuroimaging confirmed moyamoya syndrome while her clinical profile was limited to focal motor dysfunction (Figures 1b and 1c). Following the reintroduction of antiretroviral therapy and viral suppression her focal neurology improved and no further events have occurred. Patient 4 presented at 3 years of age with a right arm monoparesis, HIV infection was diagnosed on this admission and she was not virally suppressed. She commenced antiretroviral therapy and became virally suppressed with no further stroke-like events but she did have learning difficulties and behavioral problems. Patient 5 presented in 2015 aged 2.2 years. She was known to have Down syndrome. Her mother had tested HIV positive at birth. Accordingly the child received prevention of mother to child transmission therapy and was HIV polymerase chain reaction negative at 3 months of age. But her mother stopped her own antiretroviral therapy and continued to exclusively breastfeed, she died in September 2015 without divulging these medical issues to the child’s father. The father assumed his daughter’s developmental delay and hypotonia was related to Down syndrome. His daughter had never had any AIDS defining illnesses until she presented acutely at 2.2 years with a left hemiplegia and HIV infection was then diagnosed. In addition to the compounding aspects of her Down syndrome and HIV infection she was also anemic. She is awaiting surgical intervention after commencing antiretroviral therapy.

Neurosurgical intervention of burr holes and synangiosis of the brain via the external circulation was considered indicated based on experience in children with Down syndrome and moyamoya syndrome. All the children with moyamoya syndrome had neuroimaging evidence of preceding vascular events, which appeared to be silent. Manifestations were not restricted to the motor system but included cognitive impairment and/or regression.

Between 2002 and 2011 10 additional HIV-1-infected children (7 male; median age 7 years, range 2 years and 3 months to 11 years of age) presented with acute ischemic stroke (3 left and 6 right hemiplegias, and another child with regression). These children did not progress to moyamoya syndrome and were diagnosed with isolated cerebral HIV-associated vasculopathy. The children with moyamoya did not have other HIV related factors which could have predisposed them to stroke, their main common factor was poor viral suppression. While the children with isolated events and no evidence of progression in vasculopathy, had more variable viral suppression, and 9 out of the 10 had additional factors which could have predisposed them to stroke (Table 1). While the study group of children with Moyamoya syndrome is small, improvement or stable course was evident for patients 2, 3 and 4 following maintained viral suppression.

Discussion

The authors describe 17 children with HIV-associated vasculopathy, 5 of this cohort had moyamoya syndrome, a serious and rarely reported complication of HIV-1 infection (Table 2). Two
other pediatric cases of moyamoya syndrome are published and
t heir details are also summarized in Table 2.9,12

Most children in this report presented to neurology services
between 5 and 13 years ago. From April 2004 the South
African National Department of Health rolled out antiretroviral
therapy in the public sector and antiretroviral therapy became
widely available to HIV-infected children. No further cases of
moyamoya syndrome have presented in the last 5 years, except
for the child with the additional risk factor of Down syn-
drome.15 The implication could be that improved access to
antiretroviral therapy restricted the development of HIV vas-
culopathies and their progression to moyamoya syndrome.
Beyond HIV-1 infection, there were no other causes evident
for their vascular presentation.

The children in this series had evidence of silent disease
progression before their acute presentation(patients 3-5) and
well as illustrating misleading phenotypes such as HIV ence-
phalopathy (patient 2). Vascular progression can be ongoing in
HIV-infected children who are not adequately virally sup-
pressed.9,12 There should be a low threshold for performing
isolated and even serial MRI in the “work-up” of children with
HIV-1 to enable early detection and intervention.

Without widespread access to neuroimaging it is not possi-
ble to provide an accurate estimate of the prevalence and inci-
dence of moyamoya syndrome in HIV-infected children.
Furthermore, with improving HIV care, the incidence of pro-
gressive HIV-1 vasculopathy may be lower in settings with
high antiretroviral coverage. Across sub-Saharan Africa
while the incidence of pediatric HIV-1 infection has declined
appreciably because of the widespread use of interven-
tions to prevent mother-to-child transmission, HIV prevalence
among children has remained high (340,000 HIV-infected
children less than 15 years of age in South Africa at the end of
2014), access to antiretroviral therapy is not reliable and screen-
ing by MRI a scarce resource. There may be other children with
HIV-1 not assessed who lack diagnostic closure.

Where moyamoya syndrome is identified, serial imaging
should be considered because it can evolve “silently.”9,12 Chil-
dren with neurocognitive regression are often considered to
have HIV encephalopathy but patients 1 and 2 illustrated that
this assumption is not always true. Without neuroimaging their
progressive vascular disease would have been missed. Even in
South Africa where MRI is available, there are resource limita-
tions which affected the completeness of the neuroimaging
performed in the authors’ patients.

There was overlap in the clinical presentations of the 10
children with isolated acute ischemic strokes compared to the
children with moyamoya disease, in that these children pre-
mitted with isolated motor deficits. Without access to neuroi-
maging patients 1, 3, 4, and 5 could have been considered to
have acute ischemic stroke, and the underlying moyamoya not
suspected until the children re-presented with further
manifestations.

Patient 5 was also complex and illustrated the layering effect
often seen in Africa where dual pathologies are common, in
this case it cannot be definitively stated which was the primary
cause for the moyamoya syndrome, the Down syndrome, or the
HIV-1 infection. It is possible that both played a part in the
clinical expression.15 This most recent patient with progressive
vascular disease was not diagnosed with HIV until her presenta-
tion with stroke because her mother elected not to disclose
her status to her family or to comply with antiretroviral therapy.
The time of the child’s seroconversion is not known and she
may have had poor viral suppression for some time before
presentation with stroke.

The underlying pathogenesis of HIV vasculopathy is not
elucidated but immune dysregulation including proinflam-
atory cytokine imbalances induced by HIV-1 infection may alter
endothelial function and induce endothelial cell damage.8 In
addition antiretroviral therapy may induce dyslipidaemia and is
implicated in endothelial damage and the acceleration of ather-
osclerotic disease.8 Whether these effects contribute to the
development of moyamoya syndrome remains unclear.

Limitations of this study are that this it is a retrospective
study and as such lacked prospective recruitment following
standardized screens of large populations of children with HIV.
Rather the study related to the reactive responses to children
presenting to specialized services, which required recognition
of cerebrovascular disease and referral pathways to be in place.
These are lacking and a major challenge across the country.
Further the capacity of centers to comprehensively screen
patients is another challenge in itself. Even tertiary centers in
South Africa have limited access to neuroimaging, often with
long waiting lists. Children with subtle hemiplegia can be
missed in the context of busy infectious diseases services where
the main focus relates to control of viral load and more global
health care.2

While overall health and adequate blood CD4 count and
viral load are important in the care for children with HIV-1
and moyamoya syndrome, there are novel interventions in the
field of moyamoya disease and syndrome that could be con-
sidered.16 Therapies have been evaluated in patients with other
etiologies for moyamoya syndrome, or moyamoya disease, but
are yet to be trialed in affected children with HIV-1 disease.
Establishing whether interventions such as burr holes are ben-
eficial would be important for developing consensus manage-
ment recommendations in these patients.16

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