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Stroke and transcranial Doppler in children with human immunodeficiency virus

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ABBREVIATIONS

ACA	Anterior cerebral artery
HIV	Human immunodeficiency virus
ICA	Internal carotid artery
MCA	Middle cerebral artery
TAMMV	Time-averaged maximum mean velocity
TCD	Transcranial Doppler

[abstract]

AIMS To describe stroke syndromes and transcranial Doppler (TCD) findings in children with human immunodeficiency virus (HIV) and examine the associations between TCD and clinical and laboratory data.

METHOD We enrolled 42 children (24 males, 18 females) with HIV (median age=7y 6mo; 2y 7mo–15y 6mo), with and without stroke who underwent a TCD examination of the anterior and posterior circulations to derive time-averaged maximum mean velocity (TAMMV) measurements for comparison with previous studies. Clinical and laboratory variables were extracted from the medical records.

RESULTS Of the 42 children with HIV, five had right-sided hemiparesis; three had chronic lung disease; two occurred post-varicella infection; one after herpetic oral

ulceration; and one had a poorly functioning left ventricle. Neuroimaging showed middle cerebral artery (MCA) TAMMV greater than 200cm/s, moyamoya-like arteriopathy, left basal ganglia infarction with ipsilateral stenosis, hygroma consistent with venous thrombosis, and a hyperdense left MCA. Eight neurologically asymptomatic children had atypical TCD. The CD4 cell count was non-significantly lower in 6 out of 30 children with atypical TCD (median=21.5; interquartile range=16.1–26.5) compared with the remainder (median=29; interquartile range=21.3–35.0; p=0.09).

INTERPRETATION A variety of stroke syndromes occur in children with HIV. TCD suggests atypical intracranial vessels and/or haemodynamics in some children with HIV infection, consistent with vasculopathy, possibly related directly to immunodeficiency and/or infection.

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What this paper adds

- A range of stroke syndromes are found in children with human immunodeficiency virus (HIV).

- Transcranial Doppler (TCD) velocities in HIV are commonly outside the range for typically developing children.
- TCD and neuroimaging data in children with HIV suggest intracranial vasculopathy as one mechanism for stroke.
- CD4 cell count is non-significantly lower in children with HIV and atypical TCD.

[main text]

The availability and use of new drug therapies in human immunodeficiency virus (HIV) have had a significant impact on mortality. Therefore, reducing the neurological burden with appropriate treatment and preventative strategies is a priority, although the range and complexity of the mechanisms involved has hampered progress.[1] Stroke is aetiologically different in HIV-positive children and adults. In children, mechanisms include coagulopathy, cardioembolism, aneurysm, transient cerebral arteriopathy, and subacute necrotizing encephalopathy.[2–5] The relative importance and natural history of arteriopathy is uncertain, at least in part because repeated invasive vascular imaging has been difficult to justify;[2] however, non-invasive techniques may shed light on the mechanisms involved.

Evidence for the importance of vascular changes provoked by the HIV infection itself[1] includes changes in vasomotor reactivity with HIV infection without cerebrovascular symptoms,[6] and reports of transient cerebral arteriopathy[4] and aneurysm formation[5] in HIV-infected children with and without evidence for infection by other organisms. A T cell-mediated vasculitis/perivasculitis has been recognized in children with HIV

encephalopathy and concurrent ischaemic stroke.[7] The metabolic and immune effects of antiretrovirals may confer additional stroke risk.[1,8]

Transcranial Doppler (TCD) ultrasound enables non-invasive measurement of blood flow velocity in the basal cerebral arteries. Distal internal carotid artery (ICA)/middle cerebral artery (MCA) time-averaged maximum mean velocity (TAMMV) is rarely less than 50cm/s or more than 140cm/s in typically developing European[9] or African[10] children, while in those with sickle cell anaemia, an ICA/MCA TAMMV less than 70cm/s or more than 190cm/s identifies vessel occlusion or stenosis.[11,12] Adults with HIV have lower mean blood flow velocities in the MCA and a reduction in cerebral reserve capacity when compared to adults without HIV,[6] but there are few published data in children with HIV. The aims of this study were to report a series of children with HIV and stroke, describe TCD findings in children with HIV with and without stroke, and examine the associations between atypical TCD and clinical and laboratory factors.

METHOD

Population and study design

Patients with a laboratory-confirmed diagnosis of HIV were eligible for the study. Ethical approval was obtained from the Red Cross War Memorial Children's Hospital and the University of Cape Town, South Africa. Over a 6-week period in April to May 2008, we prospectively recruited children aged 2 to 16 years attending the hospital-based HIV clinic at the Red Cross War Memorial Children's Hospital, Cape Town, for a study examining the aetiology of stroke and the role of TCD in children with HIV with and without stroke. Using the World Health Organization clinical definition of acute

spontaneous focal neurological signs lasting more than 24 hours, children without neurological complications and those with a history of previous stroke were invited to participate. Those with a history of HIV encephalopathy, tuberculous meningitis, or other known neurological disorder were excluded after screening. Parents and/or guardians, and where appropriate children, interested in participating were given an information sheet (made available in Xhosa, Afrikaans, and English) if the child was eligible and informed consent and/or assent (via an interpreter where appropriate) was sought.

Biological data and TCD studies

All enrolled children with HIV with and without stroke underwent a single, routine complete TCD examination of the anterior and posterior circulation by the first author using the portable EZ-Dop system (Scanmed, Evesham, UK). Data from other studies of typically developing children[9,10,13] are included for comparison (Table 1). Since there are few data on TCD in childhood stroke, in addition to reporting TAMMV in each vessel and side-to-side differences, atypical TCD was also defined using the criteria defined by Adams et al.,[11,12] which were originally used to diagnose intracranial stenosis confirmed on conventional arteriography in children with sickle cell disease: (1) mean TAMMV equal to or greater than 190cm/s in any artery; (2) low TAMMV in the MCA defined as a TAMMV less than 70cm/s and an MCA ratio (lower/higher) of 0.5 or less; (3) an anterior cerebral artery (ACA)/MCA ratio greater than 1.2 on the same side; or (4) the inability to document an MCA in the presence of a demonstrated ultrasound window.

We considered this justifiable because stenosis in transient cerebral or post-varicella arteriopathies in children with stroke without sickle cell disease is also

intracranial. In addition, the features that Adams et al. described are rarely seen in otherwise typically developing African children, even if they are anaemic.[10]

TAMMV was measured in the ICA/MCA, as well as the anterior and posterior cerebral and basilar arteries of the circle of Willis, in children with HIV and were compared with previously published data.

TAMMV in each artery of the circle of Willis

The TAMMV in each artery of the circle of Willis was documented in children with HIV with and without prior stroke.

Asymmetry

Asymmetry for side-to-side difference, defined as a coefficient of variation (ratio of the SD to the mean) between right and left TAMMV greater than 8%,[9] or asymmetry (left MCA-right MCA) greater than 30%,[14] was compared in children with HIV and previously published data.

Criteria set out by Adams et al.

We documented the number of children with HIV fulfilling the criteria set by Adams et al. for arteriopathy based on data in children with sickle cell disease[11,12,15] and their[13] and others' experience[9,10] with typically developing children.

Weight and head circumference were available from the visit to the clinic. Blood pressure measurements were available from the time of the stroke or from clinic in those without stroke. Heart rate, respiratory rate, peripheral oxygen saturation, and end-tidal

exhaled carbon dioxide were measured over 5-minutes sitting at rest using the Tidal Wave capnograph (Respironics, Murrysville, Pennsylvania, USA). Clinical history, biological and laboratory data including viral load, CD4 cell count, full blood count, and exposure to antiretroviral therapy were collected retrospectively from the medical records.

Statistical analysis

SPSS v16 (SPSS Inc., Chicago, USA) was used for the statistical analysis. A two-sided *t*-test was used to compare the means of two independent groups and the Wilcoxon signed-rank test was used for non-parametric continuous variables. Fisher's exact test was used for categorical variables. The *F*-test was used to test for equality of variance. The pooled *t*-test was used for variables with equal variance and the Welch–Satterthwaite test was used for variables with unequal variance. Correlation between variables was examined using Pearson's and Spearman's correlation coefficients for parametric and non-parametric variables respectively.

RESULTS

Forty-two children (24 males, 18 females; median age=7y 6mo, range=2y 7mo–15y 6mo) were enrolled, 37 with no known neurological history and a normal neurological examination (21 males, 16 females) and five (four males, one female) with a history of an acute focal neurological episode (all right-sided) without a precipitating event between 6 months and 10 years (median age=4y, at a median of 1y 2mo before the TCD study; Figs. 1 and 2).

Of those without stroke, two had computed tomography (CT) scans: one had a right temporoparietal subdural haematoma following a road traffic accident and one had global atrophy. Four children with stroke had neuroimaging confirmation. The neuroimaging characteristics were varied but three had evidence of involvement of the basal cerebral arteries in association with an arterial stroke, while venous pathology was not excluded in the fourth (Figs. 1 and 2).

The child who did not have neuroimaging was male and born at 28 weeks' gestation. He was diagnosed with HIV at the age of 1 year. He was globally developmentally delayed and had recurrent gastroenteritis, ear infections, and chickenpox. He was not on antiretroviral treatment when he presented with vomiting, a seizure, and right-sided hemiparesis at the age of 3 years. His CD4 cell count was 16 at diagnosis and 20.9 at the time of the stroke. TCD at the age of 5 years showed left MCA TAMMV greater than 200cm/s and right MCA TAMMV of 140cm/s (coefficient of variation=22%, asymmetry=36%).

TCD studies

TAMMV in children with HIV with and without stroke

Full cohort

The TAMMV in each artery of the circle of Willis was higher in the five children with stroke than the comparable artery in the non-stroke group (n=37) and for the right MCA (p=0.049) and right posterior cerebral artery (p=0.03), which was statistically significant. Interestingly, there was flow in both MCAs on TCD in the children with previously diagnosed moyamoya and cardiac embolism (Fig. 2), suggesting recanalization.

Asymmetry

Four of five children with stroke had a coefficient of variation for the two sides greater than 8%[9] and three had asymmetry greater than 30%,[14] while 16 out of 37 of those without stroke also had a coefficient of variation between right and left MCA TAMMV greater than 8%[9] and six had asymmetry greater than 30%.[14]

Criteria set out by Adams et al.

All vessels were insonated on both sides in all 42 children. One child with a stroke had a left MCA TAMMV of 200cm/s,[11,12] while the remaining MCA velocities were within the 70cm/s to 190cm/s range, although one child had an ACA/MCA TAMMV ratio equal to or greater than 1.2. Six of the 37 children without stroke had unilateral ICA/MCA TAMMV equal to or less than 70cm/s, three right and three left; three of the six children were also within an ACA/MCA TAMMV ratio equal to or greater than 1.2[12] and four also had asymmetry greater than 30%.[14] Of the seven children with atypical TCD according to the criteria set out by Adams et al.,[11] including the one with a stroke, three were not on antiretroviral therapy, compared with five of 35 of those with no TCD abnormality using this system (Fisher's exact test, p=0.1). For the 30 children with data available, there was a trend for a lower CD4 cell count in the six with atypical TCD (median=21.5; interquartile range=16.1–26.5) compared with the rest (median=29; interquartile range=21.3–35.0; p=0.09).

Resting peripheral oxygen saturation, end-tidal exhaled carbon dioxide, and z-score for weight and head circumference were not significantly correlated with TAMMV. In 30 children whose CD4 cell count was available, there were trends for direct correlation of

CD4 cell count with TAMMV in the left MCA (r=0.34, p=0.07) and basilar arteries (r=0.34, p=0.07).

Twenty-three children were followed up for a median of 2 years 10 months (range=5mo–8y 10mo); there were no further strokes. One death occurred in a child without stroke and epilepsy was more common in those with stroke (2 out of 3 vs 3 out of 20; p=0.046).

DISCUSSION

There are few data on the mechanism of or outcome for stroke in HIV-positive children, although it may occur spontaneously or in the context of additional infection.[5,16] Previous studies have suggested that intracranial arteriopathy, potentially detectable by TCD, plays a role. The prevalence rates of cerebral infarction (ischaemic or haemorrhagic) in paediatric and adult autopsy series of HIV-infected brains ranges between 6% and 34%, but in life the majority of these patients were clinically asymptomatic.[2] In a longitudinal study of children with HIV, the clinical incidence of stroke was 1.3% per year.[16] In a retrospective study of 567 children, 426 of whom had neuroimaging, 11 (2.6%) had cerebrovascular lesions, only one of whom had presented with focal neurological signs.[17] In another large study nested within a randomized controlled trial, the incidence was calculated as 3.4 cases per 10 000 person-years (95% confidence interval=1.8–6.0) compared with 0.23 to 0.27 per 10 000 person-years for North American children.[5]

Our data show that TCD is rarely normal in children with HIV and a history of clinical stroke. In this series, we specifically selected those children with spontaneous focal neurological signs because we were interested in whether children with HIV and arterial

ischaemic stroke without an immediate precipitating cause had vasculopathy. We found an abnormal TCD with unilateral TAMMV greater than 200cm/s in one child, which was consistent with stenosis. All but one of those children with stroke had a coefficient of variation between the two sides greater than that previously reported in typically developing children[9] and three had asymmetry considered to be related to vasculopathy in adults.[14] TAMMV was higher in the stroke group than in the non-stroke group and significantly higher on the side contralateral to the infarct, particularly in the posterior circulation. This may represent a compensatory response via the circle of Willis in an attempt to perfuse the ischaemic penumbra on the side ipsilateral to the infarct and maintain perfusion to the unaffected parenchyma.

Three children with stroke, including the one with abnormal TCD, had evidence of vasculopathy. Two were hypertensive (Fig. 1). One male child presented with recurrent boils and chickenpox with vesicular skin lesions at the age of 5 years, was diagnosed with vertically transmitted HIV at the age of 10 years, and was treated with antiretroviral treatment from 1 month after diagnosis. He presented with a left-sided headache and right-sided hemiparesis 6 months later. His blood pressure was high at 124/88mmHg. Magnetic resonance imaging (MRI) showed a left basal ganglia infarct and magnetic resonance angiography showed attenuation of the left proximal MCA consistent with varicella-related angiopathy and possible occlusion of a perforator artery. His CD4 cell count was 0.6 at diagnosis and 5 at the time of the stroke. TCD 6 months later showed a TAMMV of 120cm/s on the left and 98cm/s on the right (coefficient of variation=11%; asymmetry=14%). The other male child was diagnosed with vertically transmitted HIV at the age of 2 months and had persistent whooping cough, chronic lung disease (lymphoid

interstitial pneumonia), chronic suppurative otitis media, and behavioural difficulties. He was on antiretrovirals but was poorly adherent. At the age of 8 years and in the context of new mouth ulcers, he experienced acute onset of weakness of the right hand and left foot. The right-sided hemiparesis progressed and persisted; he developed difficulty swallowing and right upper motor neuron facial weakness. His blood pressure was high at 135/94mmHg. The MRI scan showed bilateral cortical atrophy and multifocal infarcts of different ages bilaterally in the MCA and left ACA territory. The magnetic resonance angiography scan showed an absent right M1 and attenuation of the sylvian branches and stenosis of the M2 on the left with an ivy sign. TCD a month later showed left MCA TAMMV of 97cm/s and right MCA TAMMV of 107cm/s (coefficient of variance=7%, asymmetry=9%).

The pattern of basal ganglia infarction seen in one patient (Fig. 1a,b) may have been a result of occlusion of a perforator artery. Transient cerebral arteriopathy-associated basal ganglia infarction has been reported in association with HIV infection[4] and Varicella zoster and other herpetic viruses have been reported in association with HIV-related vasculopathy and stroke[16] as well as being demonstrated in histopathological samples of arteries of the circle of Willis. However, manifestations of varicella-mediated infarction may differ in the immunocompromised, conferring a plausible risk of varicella-associated stroke beyond the conventional 12 months. HIV-associated moyamoya-like vasculopathy has been previously reported in one child[18] and a few adults.[19] Given that moyamoya has not been reported in two large series of children with HIV, including those with ~~with the prevalence of~~ symptomatic and asymptomatic stroke and cerebrovascular disease ~~in~~ [16,17] it is interesting that we had one case in our series (Fig. 1c,d), although the TCD study

suggested that the ICA/MCA remained patent or recanalized. Follow-up studies are needed to determine the natural history of HIV-associated moyamoya.

Mechanisms other than vasculopathy were also seen in those with stroke. Embolic stroke in the context of poor cardiac function appears to have been the mechanism in one patient (Fig. 2a,b), who presented with right upper motor neuron facial weakness and hemiparesis at the age of 4 years. He had a past medical history of recurrent lower respiratory tract infection and gastroenteritis but was not known to have had a herpes virus infection. He was diagnosed with vertically transmitted HIV. His CD4 cell count was 18 at the time of presentation and echocardiography showed poor cardiac function with an ejection fraction of less than 20%. His blood pressure was 105/69mmHg.

Venous ischaemia has not been reported in children with HIV, although it has been reported in adults[20] and could be an explanation for the diffuse atrophy and hygroma seen in one female patient who had had a focal deficit previously (Fig. 2c,d). She was diagnosed with vertically transmitted HIV at the age of 5 years and was treated with antiretrovirals but suffered from tuberculosis, chronic lung disease, and herpes zoster. She presented with high temperature, vomiting, and right upper motor neuron facial weakness at the age of 8 years. Her blood pressure was 111/71mmHg and her CD4 cell count was 14.4 at diagnosis and 36.2 at the time of the stroke. The CT scan showed gross brain shrinkage and a small left frontoparietal hygroma. TCD at the age of 8 years showed left MCA TAMMV of 120cm/s and right MCA TAMMV of 88cm/s (coefficient of variation=22%, asymmetry=36%).

As was also demonstrated in a study of adults with HIV and stroke in South Africa,[21] the variety of stroke syndromes we document in this article are also seen in children

without HIV but much more work is needed in this area since data from the African continent are scarce.

TCD may also be atypical in those with HIV without stroke, suggesting that the large vessels are involved in the pathological process in neurologically asymptomatic patients. We documented slightly higher TAMMV and an increase in asymmetry compared with previously reported data in typically developing children. In addition, using the criteria set out by Adams et al.,[12] 6 out of 37 asymptomatic children with HIV had evidence of vasculopathy and an additional two had asymmetry greater than 30%,[14] consistent with asymptomatic intracranial cerebrovascular disease in 22%. This suggests that subclinical cerebrovascular abnormalities may be common, but further evaluation of the significance of these findings requires neuroimaging and longitudinal follow-up, particularly since cerebral arteriopathy in childhood commonly improves. HIV has been implicated as a direct and facilitative agent in HIV-associated vasculopathy, while pan-intimal thickening and fibroplasia with medial thinning and distortion or duplication of the elastic lamina have also been reported.[22] As in studies in adults, the range of clinico-radiological findings in our study is supportive of multiple pathophysiological mechanisms involving small-to-large-vessel stenotic and occlusive arterial and perhaps venous disease.

In their TCD study comparing adults with and without HIV, Brilla et al.[6] suggested that in the absence of severe cardiac or steno-occlusive cerebrovascular disease, lower mean MCA blood flow velocities may represent alteration in cerebral arteriolar resistance or vascular dysfunction related to direct invasion by HIV or other infectious agents. Our data also provide some evidence for an effect of HIV itself, either related to reduction in cerebral blood flow, as suggested by the direct correlation between CD4 cell count and

left ICA/MCA and basilar velocities in our data, or due to direct infection of the blood vessels leading to vasculopathy, for which our small data set provides some evidence in that there was a trend for CD4 cell count to be lower in those with atypical TCD according to the criteria set out by Adams et al. However, a larger group of children with HIV and a control group of children without HIV for whom a CD4 cell count is available is required before any firm conclusions can be drawn. From the Doppler equation, basal cerebral artery velocities are determined by the diameter of the vessel as well as cerebral blood flow, limiting the conclusions that can be drawn, but these questions could be addressed with MRI, magnetic resonance angiography, and non-invasive magnetic resonance measurement of cerebral blood flow.

The observation of all right-sided hemiparesis, four in male patients, in this series is of potential interest. Cerebral lateralization of immune function has been demonstrated, with worse immune function in those with left hemisphere abnormality,[23] which should be explored in prospective studies.

There is no evidence from our data to suggest a link between stroke and antiretroviral therapy;[8] in fact, there was a trend for atypical TCD to be more common in the untreated. Protease inhibitors have been shown to have effects on carotid intimal thickness and endothelial-derived arterial function,[6] partly explained by the induction of a metabolic syndrome with insulin resistance. However, our data in mainly preadolescent children, suggest that HIV itself plays a role and that vasculopathy is less common in those on antiretrovirals.

Limitations of our study include: (1) the clinical World Health Organization definition of stroke was used in the developing world setting, as for previous studies in African

adults with HIV,[1] whereas most recent paediatric stroke studies have included imaging abnormality as a criterion for separating stroke from transient ischaemic attack; (2) the study was conducted over an 8-week period when the TCD was available and the strokes and neuroimaging had occurred previously; (3) the study is small and not all children were followed up, so the results require confirmation; (4) the study did not include a non-HIV control group, so we compared our data with published TCD data in children of African and European ancestry without HIV and in North American children with intracranial vasculopathy in the context of sickle cell disease; (5) we did not undertake TCD of the neck vessels: the observation of symmetrically low mean blood flow velocities seen in adults with HIV compared to those without was not replicated in our study; it is possible that this is related to extracranial vasculopathy that might explain the unilateral low velocities in six of these children with HIV. Asymmetrical MCA velocities appear to be more common in children with stroke and HIV compared with those with HIV without stroke and typically developing children.[9]

Risk factors for stroke in HIV are multiple, additive, and sometimes unavoidable. Recognition of different mechanisms of HIV-associated stroke is important since treatment options vary. Patients with HIV vasculitis may need immunosuppressive therapy in contrast to those with a more adult atherosclerotic profile, who may benefit from management of stroke risk factors such as hypertension, salt intake, and cholesterol levels. If varicella zoster is causally implicated, addition of acyclovir and prednisolone may be warranted. The potential utility of a low-cost, portable ultrasound device for the detection and follow-up of vasculopathy, and the evaluation of primary and secondary stroke risk, warrants prospective studies in this field. We propose that such a study should

be conducted in collaboration with the International Paediatric Stroke Study group, which could allow for the prospective identification of significant vasculopathic risk factors in HIV-associated stroke in childhood.

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Table 1: Population characteristics

	TCD in typically developing North American children[13] *n*=64	TCD in typically developing European children[9] *n*=112	TCD in typically developing African children[10] *n*=115	Children with HIV *n*=37	Children with HIV and stroke *n*=5
Age (y:mo), mean (range)	-	-	-	7:10 (2:7–15:7)	7:3 (4:5–10:1)
Male:female	-	-	-	20:17	4:1
Latest CD4 cell count, mean (IQR)	-	-	-	26 (20–34)	21 (5–36)
Haemoglobin	-	-	-	11.2 (10.9–11.9)	12.1 (11.9–12.2)
Peripheral oxygen saturation 10, mean (range)	-	-	-	98.9 (94–100)	97.6 (97–100)
Antiretrovirals (%)	-	-	-	30/34 (88%)	4/5 (80%)
WCC, mean (range)	-	-	-	9.3 (4.2–27.3)	12 (11.2–12.7)
Platelets, mean (range)	-	-	-	401 (118–868)	366 (258–474)
Average of right and left MCA	-	-	-	-	-
-Age 1-2.9 years[9]	-	85±10	-	-	-
-Age 5 years[13] (3-5.9 years)[9]	87±6	94±10	-	-	-
-Age 7 years[13] (6-9.9 years)[9]	85±5		-	-	-
-Age 9 years[13]	83±7	97±9	-	-	-
-Age 11 years[13]	72±8		-	-	-
-Age 13 years[13] (10-18 years)[9]	71±5	81±11	-	-	-
-Age 15 years[13]	70±6		-	-	-
Left MCA	-	-	92.1±24.6	101 (96–114)	115 (84–120)
Right MCA	-	-	91.5±26	94 (84–105)	113 (98–124)
Left ACA	-	-	58.5±19.8	82 (72–96)	93 (71–98)
Right ACA	-	-	63.4±19.5	83 (70–94)	86 (61–98)
Left PCA	-	-	34.2±8.8	57 (48–66)	84 (65–90)
Right PCA	-	-	33.4±10.5	55 (47–61)	73 (69–75)
Basilar artery	-	-	59.1±10.6	60 (47–70)	62 (56–65)
-Age 1-2.9 years[9]	-	51±6	-	-	-
-Age 5 years[13] (3-5.9 years)[9]	66±6	58±6	-	-	-
-Age 7 years[13] (6-9.9 years)[9]	66±6	58±9	-	-	-
-Age 9 years[13]	55±7		-	-	-
-Age 11 years[13]	57±8		-	-	-
-Age 13 years[13] (10-18 years)[9]	51±4	46±8	-	-	-
-Age 15 years[13]	46±7		-	-	-
Coefficient of variation (%)	-	2–8	10±21	12±14	19±11
Asymmetry (left MCA-right MCA/left MCA) × 100	12±10	-	11±16	16±20	29±21

Distributions are given as the mean±SD or as the median (interquartile range [IQR]), unless otherwise stated. Latest CD4 cell count: latest CD4 cell count before the TCD study; peripheral oxygen saturation 10: haemoglobin oxygen saturation recorded over 10 minutes with a Masimo pulse oximeter; antiretrovirals (%): percentage of children on antiretroviral medication. TCD, transcranial Doppler; HIV, human immunodeficiency virus; WCC, white cell count; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery.

Figure legends

Figure 1: Magnetic resonance imaging (MRI) (a) and magnetic resonance angiography (MRA) (b) scans of a male patient who presented with recurrent boils and chickenpox with vesicular skin lesions at the age of 5 years, and was diagnosed with vertically transmitted human immunodeficiency virus (HIV) at 10 years of age. The MRI scan shows a left basal ganglia infarct. The MRA scan shows attenuation of the left proximal MCA consistent with varicella-related angiopathy and possible occlusion of a perforator artery. MRI (c) and MRA (d) of a male patient diagnosed with vertically transmitted HIV at the age of 2 months. The MRI shows bilateral cortical atrophy and multifocal infarcts of different ages bilaterally in the MCA and the left anterior cerebral artery territory. The MRA shows an absent right M1 and attenuation of the sylvian branches and stenosis of the M2 on the left with an ivy sign.

Figure 2: Head computed tomography (CT) scan (a,b) of a male patient who presented with right upper motor neuron facial weakness and hemiparesis at the age of 4 years. It shows a hyperdense left middle cerebral artery but no definite infarct (yellow circle and arrow). (c,d) Head CT scan of a female patient diagnosed with vertically transmitted human immunodeficiency virus at the age of 5 years. The CT scan shows gross brain shrinkage and a small left frontoparietal hygroma.