De Novo intracerebral aneurysm in a child with acquired immunodeficiency syndrome

Mohamad G. Bakhaidar, *MBBS,* ***Naushad A. Ahamed,*** *MBBS, DMRD,* ***Mohammed A. Almekhlafi,*** *MSc, FRCPC,* ***Saleh S. Baeesa,*** *MD, FRCSC.*

ABSTRACT

يعد فيروس نقص المناعة البشري (HIV) المرتبط بأمهات الدم، اعتلالاً وعائياً نادراً لدى الأطفال والبالغين الحاملين للعدوى. نعرض في هذه الدراسة حالة طفل يبلغ من العمر 7 سنوات سبق تشخيصه بعدوى فيروس نقص المناعة البشرية المكتسبة خلقيا والذي تعرض لنزف تحت العنكبوتية نجم عن تمزق أم الدم مغزلية الشكل في الشريان السباتي الداخلي والتي تم تشخيصها لمدة 6 أشهر بتصوير الرنين المغناطيسي. خضع الطفل لجراحة ناجحة لإعادة بناء الشريان الأوعية الدموية وتعافى بشكل جيد. تعد هذه الحالة من ضمن أولى الحالات الموثقة لطفل مصاب بأم الدم الناجمة عن فيروس نقص المناعة البشرية والتي يتم علاجها جراحياً. نقوم هنا أيضا بمراجعة الأدبيات ذات الصلة بهذه الحالة النادرة.

Human immunodeficiency virus (HIV) infection associated aneurysmal vasculopathy is a rare complication of HIV infection affecting the pediatric and adult population. We present a case of a 7-year-old male child known to have a congenitally acquired HIV infection presenting with a ruptured left distal internal carotid artery fusiform aneurysm that was diagnosed on MRI scans 6 months prior to his presentation. He underwent craniotomy and successful aneurysm reconstruction. He had uncomplicated postoperative course and experienced a good recovery. This case is among the few reported pediatric cases of HIV-associated cerebral arteriopathy to undergo surgery. We also reviewed the relevant literature of this rare condition.

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From the Division of Neurosurgery (Bakhaider, Baeesa), Department of Surgery, Department of Radiology (Ahamed) and Division of Neurology (Almekhlafi), Department of Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. Saleh S. Baeesa, Department of Neurosurgery, Faculty of Medicine, King Abdulaziz University, PO Box 80215, Jeddah 21589, Kingdom of Saudi Arabia. E-mail: sbaeesa@kau.edu.sa

Neurological involvement frequently complicates the course of human immunodeficiency virus (HIV) infection in both pediatrics and adults.[1] Cerebrovascular complications are rarely encountered in these setting and are attributed either, to the primary HIV infection or secondary complications of immunodeficiency.[2,3] The incidence of cerebrovascular events in pediatric patients with HIV infection is estimated to be 3.4 cases per 10000 person-years.[4] Human immunodeficiency virus–associated arteriopathy encompasses several forms of arterial diseases occurring in the absence of any cause other than HIV infection. The HIV–associated aneurysmal arteriopathy is a rare cerebrovascular complication of acquired immune deficiency syndrome (AIDS) and has been the subject of several case reports and case series involving children, and more recently adults, with AIDS.[2,3,5-10] This aneurysmal arteriopathy is characterized by multiple, diffused aneurysmal dilatations confined to the major arteries of the circle of Willis.[1,11] The mechanism by which HIV results in CNS arterial damage is still not clearly understood.[2] Most patients with this condition present with cognitive changes and motor deficits associated with infarction or hemorrhage.[12] Our objective in presenting this particular case is to report a documented de novo left fusiform carotid bifurcation aneurysm in a child with maternally acquired-HIV infection who presented with subarachnoid hemorrhage and underwent surgical clipping of the aneurysm.

Case Report. A 7-year-old boy who was known to have congenital HIV infection presented with a sudden onset of severe headache and altered level of

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consciousness of 2 days duration. Two years earlier, he tested positive for HIV infection when he presented with severe dyspnea and cough due to pulmonary tuberculosis. His HIV-1 RNA quantitative polymerase chain reaction (PCR) was carried out and showed 15042 copies/ml. Brain MRI and angiography (MRA) studies during that admission showed no abnormal intracranial or vascular findings (**Figure 1**). The CSF analysis revealed normal cell count, glucose and protein in a normal range, and negative latex agglutination test and culture. He had a remarkable recovery and was discharged on an 18-month course of anti-tuberculosis therapy and antiretroviral therapy: zidovudine, lamivudine, and lopinavir/ritonavir combination. He presented to the emergency department 18 months after with a new onset of generalized tonic-clonic convulsion. He was not compliant to antiretroviral therapy, and the HIV-1 RNA quantitative PCR showed a higher viral load of 310798 copies/ml. Brain MRI and MRA scans showed a 10 x 8 mm fusiform aneurysm in the left distal internal carotid artery (ICA) (**Figure 2**). He was managed with antiretroviral therapy and monitoring of the aneurysm with MRI after 3 months. At the current presentation, 6 months after, his general examination revealed low-grade fever (37.8°C), and his Glasgow coma score (GCS) was 14. There was neck stiffness, positive Kerning's and Brudzinski's signs but no papilledema or any focal neurological deficit.

Early and confirmed diagnosis. Brain CT scan revealed left Sylvian hyperdensity consistent with subarachnoid hemorrhage (SAH) with associated hydrocephalus (**Figure 3A**). The MRI scan demonstrated subacute blood products in the left Sylvian fissure with intraventricular extension and hydrocephalus. No basal leptomeningeal enhancement was noted on post-contrast images. Brain MRA scans demonstrated that the previously visualized fusiform aneurysm increased in size and included the proximal segments of the

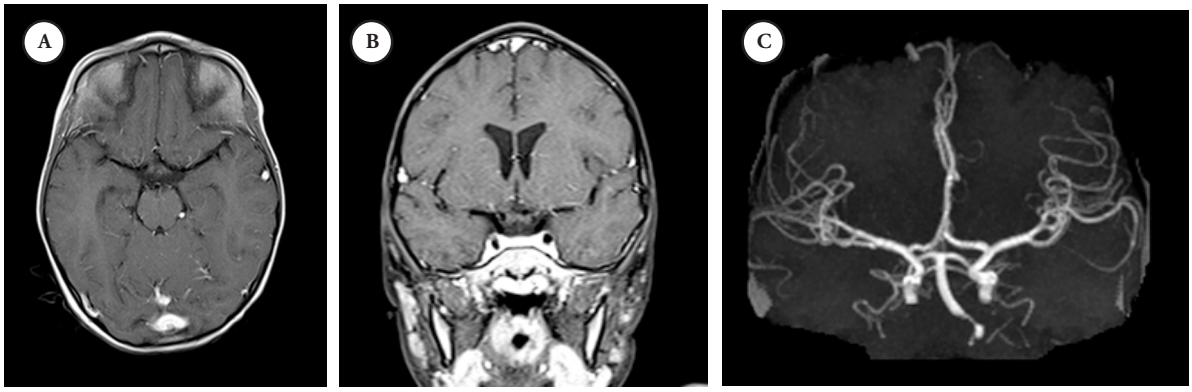

Figure 1 - Initial presentation study **A**) post-contrast T1-wighted MRI and **B**) at the level of the Circle of Willis and maximum-intensity projection reconstruction MRI image **C**) demonstrating normal flow void and vascular anatomy at the circle of Willis, particularly at the left ICA and MCA. MCA - middle cerebral arteries, ICA - internal carotid artery

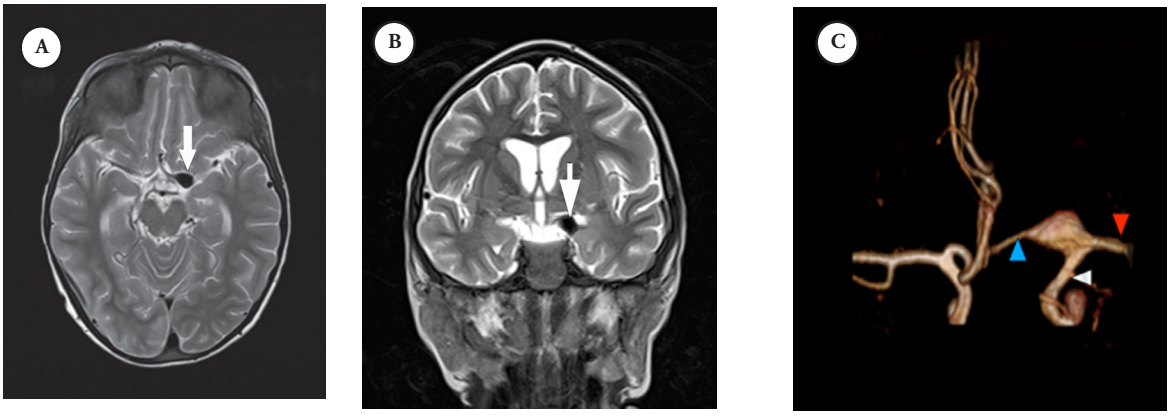

Figure 2 - Second presentation MRI study: selected axial **A**) and coronal **B**) T2-weighted MRI at the region of circle of Willis showing an aneurysm at the junction between the distal ICA, M1-segment of MCA and the A1-segment of ACA, demonstrated as a flow void. This was well demonstrated with a **C**) 3D-reconstruction of the MRA. ICA - internal carotid artery, MCA -middle cerebral arteries, ACA - anterior and middle cerebral arteries

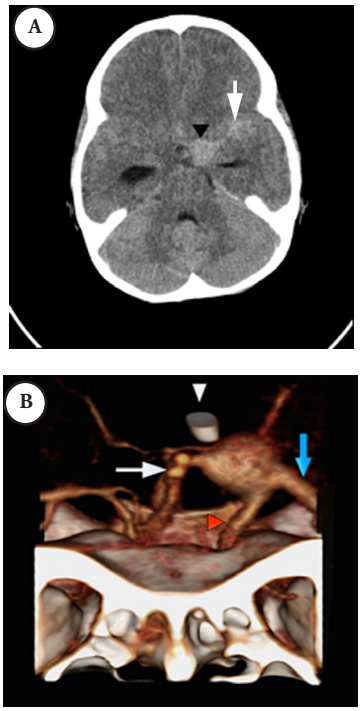

Figure 3 - Third presentation CT study selected axial non-contrast enhanced CT of the brain **A)** showing interval increase in the dimensions of the aneurysm and SAH due rupture of the aneurysm. There was hydrocephalus seen as marked dilatation of the temporal horns of the temporal horns of the lateral ventricles. 3D-reconstruction of a contrast-enhanced CTA **B)** after insertion of EVD, demonstrating the large fusiform aneurysm at the junction between the distal ICA, M1-segment of MCA and the A1- segment of ACA. The bony landmarks of the cranial fossa and the anterior cloned process are also shown. MCA - middle cerebral arteries, ICA - internal carotid artery, EVD - external ventricular drain, ACA- anterior and middle cerebral arteries, CTA - CT angiography, SAH - subarachnoid hemorrhage

anterior and middle cerebral arteries (ACA and MCA). The chest x-ray and CT scans of the chest and abdomen were within normal limits. He was admitted to the ICU and an external ventricular drain (EVD) was inserted. The CSF analysis showed 31 WBCs, 91% of which were lymphocytes. Otherwise, CSF was unremarkable. He had remarkable improvement of his level of consciousness. Subsequent aneurysm delineation with CT angiography (CTA) was carried out and revealed a large 13 mm x 16 mm fusiform aneurysm at the left ICA bifurcation, which involves the proximal segments of ACA and MCA (**Figure 3B**). Investigations ruled out concurrent infections such as cytomegalovirus, Epstein-Barr virus, or varicella.

Treatment. He underwent left pterional craniotomy and successful reconstruction of the aneurysm at the ICA/MCA using 2 fenestrated aneurysm clips and sacrificing the proximal part of the ACA. A clip of the

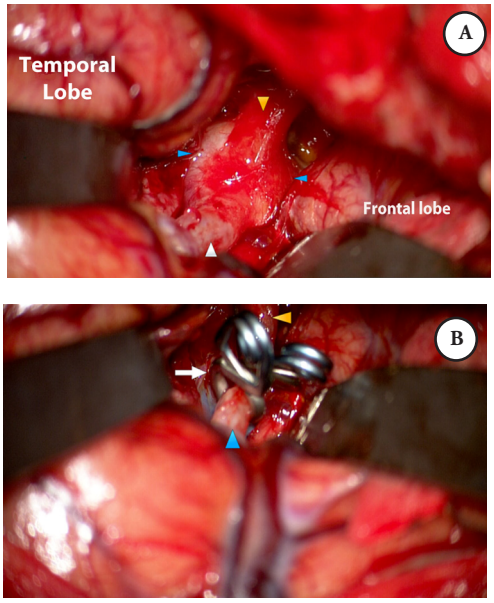

Figure 4 - Intraoperative microscopic photograph through **A)** left frontotemporal craniotomy and transsylvian approach demonstrating the extent of the aneurysm, **B)** Repair of the fusiform ICA/MCA aneurysm was reconstructed with 2 fenestrated aneurysm clips. MCA - middle cerebral arteries, ICA - internal carotid artery.

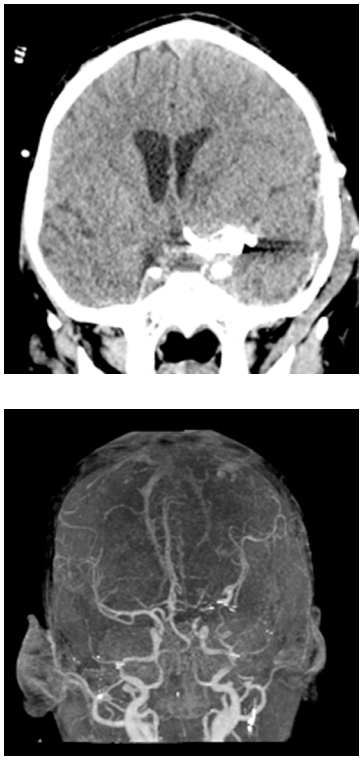

Figure 5 - Selected coronal non-contrast CT image of the brain **A)** showing the clip applied across the aneurysm. Maximum-intensity projection reconstruction **B)** and 3D reconstruction of the postoperative contrast-enhanced MRA, demonstrates the reconstruction of the aneurysm and the patent distal circulation.

remaining aneurysmal ACA was applied proximal to the takeoff of Huebner's artery (**Figure 4**).

Follow-up. He had an uneventful postoperative period. He could not be weaned of EVD, and required the insertion of a ventriculoperitoneal shunt. His postoperative CTA revealed adequate ICA/MCA reconstruction (**Figure 5**). He was discharged on a highly active anti-retroviral therapy (HAART) regimen of zidovudine 9 mg/kg by mouth, twice a day (PO BID), lamivudine (3TC) 4mg/kg PO BID, and Kaletra® (lopinavir/ritonavir) 15mg/kg PO BID.

Discussion. Cerebral vasculopathy has been described as an unusual manifestation of AIDS in several case reports and case series in pediatric and adult medical literature.[13] Kure et al in 1989,[14] reported the first case of HIV-associated cerebral aneurysmal arteriopathy in a pediatric patient. Since then, at least 23 reports (44 cases) of pediatric patients with HIV-associated cerebral aneurysmal arteriopathy have been published. These are summarized in **Table 1**.

The HIV-positive pediatric patients have an increased incidence of cerebral aneurysms. Aneurysms associated with HIV infection are typically fusiform in shape.[11] However, saccular aneurysms secondary to HIV infection have been reported in the literature.[13,15] As in our case of a large fusiform aneurysm of ICA bifurcation with involvement of the proximal MCA and ACA, most of the cerebral aneurysms associated with HIV infection are located in the arteries of the circle of Willis.[1-3,13,16]

The HIV-associated cerebral vasculopathy usually presents with cognitive changes and motor deficits secondary to infarction or hemorrhage.[2,15] Most patients with cerebral aneurysms secondary to HIV in the reported cases presented with seizures, headache, localized neurological deficits, and fatal subarachnoid hemorrhage.[1] Cerebral aneurysms were reported as an incidental finding in asymptomatic patients with HIV-infection.[5,13,17]

The classical microscopic findings of autopsy examination of patients diagnosed with HIV-associated vasculopathy include medial fibrosis with the loss of the muscularis, destruction of the internal elastic lamina, and intimal hyperplasia.[14,18] Many mechanisms were proposed in the literature to explain how HIV infection results in CNS arterial damage.[1,2,11] The exact mechanism is still undefined.[16,17] Whether cerebral vasculitis is directed primarily to HIV infection or secondary to associated infections such as varicella zoster virus, cytomegalovirus, or other opportunistic infections is still a matter of debate.[1,2,15] Direct HIV invasion of the endothelium of cerebral arteries is one of the mechanisms that may explain the vasculopathy.[16] The transmigration of certain HIV-infected monocytes through the blood-brain barrier during the phase of neural tissue invasion and the release of local and systemic toxins are among the proposed mechanisms.[16] With the known tropism of those monocytes to the brain tissue, this might also explain the isolated cerebral vasculopathy in the absence of systemic vascular involvement.[13,16]

Petropoulou et al,[17] reported the development of the cerebral aneurysm during a period with high circulating viral load. In the current case, we demonstrated the same observation as our patient was discovered to have the aneurysm at the time with his higher reported viral load (310798 copies/ml) and while he was not adhering to his antiretroviral medications. The high viral load is associated with the viral activity and could lead us to support the theory of a direct relation of the virus activity to the formation of these aneurysms. Husson et al[13] reported a case with a formation of cerebral arteriopathy during a period of high p24 antigen levels signifying high viral replication. Kure et al[14] has positively stained the cells of the wall of the affected arteries with antibodies against HIV transmembrane glycoprotein (gp-41) thorough immunohistochemistry. Dubrovsky et al[2] and Mahadevan et al[16] used PCR to amplify HIV-1 DNA from the dilated arteries of their reported cases. These observations support the direct contribution of the virus to the pathogenesis of the arteriopathy. Bonkowsky et al, in 2002,[11] reported a case that presented during the immune reconstitution status. The CNS event occurred 5 months after the initiation of HARRT. Demopolous et al, in 2009,[18] reported another 3 cases that presented after an average of 6 months of initiation of HAART.[18] Both reports reported the clinical manifestations while the number of CD4 lymphocytes was increasing, and the HIV viral load was decreasing. The immune reconstitution inflammatory syndrome could be implicated in the pathogenesis of HIV-associated arteriopathy.[18]

The occurrence of aneurysmal vasculopathy during periods of higher viral load and profound immunosuppression has led investigators to consider the possibility of the presence of infective etiology acting in synergy with HIV.[16] Associations between infections with varicella zoster virus, cytomegalovirus, and herpes simplex virus encephalitis with the development of the aneurysmal vasculopathy were reported in the literature.[2,3,13] Our patient tested negative for active varicella zoster virus and cytomegalovirus infections through serum immunoglobulin.

The optimal management of patients with cerebral

Table 1 - Summary of all reported pediatric cases of HIV-related aneurysmal vasculopathy.

Year /No. of cases	Age at aneurysm diagnosis (years)/gender/HIV source	Presentation	Radiological modality/ Radiological findings/vessels involved	Management	Outcome
Kure et al, 1989[14]	6 yrs/ male / congenital	Aphasia and quadriplegia	Fusiform dilatation of circle of Willis	NS	Death after 25 days in the hospital
Lang et al, 1991[19]	8 yrs/ male / congenital	NS	Fusiform dilatations of left ICA, MCA, and ACA	AZT 5 years before CNS event	Died after one month secondary to cardiomyopathy
Husson et al, 1992[13]					
1	11 yrs/ male/ blood transfusion	Asymptomatic	Multiple saccular aneurysms of right MCA and fusiform aneurysm of left ACA and MCA	DDI one year prior to the presentation changed to AZT after aneurysm diagnosis	CNS symptoms after 16 months
2	12 yrs/ male/ blood transfusion	Asymptomatic	multiple aneurysmal dilatations of the right MCA and ACA	DDI was continued after the diagnosis	Remained asymptomatic
3	12 yrs / female/ congenital	Fever, lethargy, seizure and upper limbs weakness	Multiple fusiform ICA, ACA, MCA and right PCA aneurysms	NS	Death within 2 months of presentation
Dubrovsky et al, 1998[2] 1	13 yrs/ male/ uncertain	Acute right hemiparesis	Fusiform dilatations of left supraclinoid ICA and proximal ACA and MCA	AZT 18 months prior to the presentation, continued after diagnosis of the aneurysm	Death after 3 months secondary to cerebral infarction
2	11 yrs/ female/ congenital	Acute change in mental status	Fusiform aneurysms of left ICA and proximal MCA and bilateral PCA	AZT started one year prior to the presentation	Death after 6 months secondary to infection
3	6 yrs/ female/ Congenital	Seizure	Multiple fusiform aneurysms of the right ICA and proximal right MCA	AZT since 2-year-old. Radiotherapy for brain lymphoma	Neurological status worsened gradually. Died later secondary to HIV-enteropathy
4	12 yrs/ male/ blood transfusion	Headache and left-sided weakness	Fusiform aneurysms of left ICA, MCA, and ACA	ART (DDI 2 years before the presentation	Multiple opportunistic infections after the presentation died after 36 months
5	10 yrs/ male/ perinatal	Collapsed at school	Not carried out	DDI started 2 years prior to the presentation	Death at presentation
Fulmer et al, 1998[5]	11 yrs / female / congenital	Asymptomatic	Multiple ICA, MCA, and ACA fusiform aneurysms	Observation	Death after 3 years was secondary to other AIDs complications
Mazzoni et al, 2000[15]	8 yrs/ female/ congenital	Sudden loss of consciousness followed by seizure and mild hemiparesis	multiple saccular and fusiform aneurysms in the proximal arteries, predominantly, in the left MCA	AZT was replaced with DDI at the age of 3 years. HAART (AZT, 3TC, RTV) was initiated after aneurysm diagnosis	Patient recovered after one month. After 4 months, repeated MRA showed no changes in the aneurysms
Carvalho neto et al, 2001[6]	6 yrs/ male / congenital	Seizure	Aneurysmal dilatation of circle of Willis, more in the right.	AZT and DDI were started at the age of 2 years. Supportive management for the CNS event	The seizures stopped, and the patient was discharged with follow up in the clinic
Nunes et al, 2001[3]	2 months old/ female/ congenitally-acquired	Right hemiparesis and coma	Saccular aneurysm of left basilar artery.	IV AZT at birth. She was on AZT and DDI at presentation. Conservative management for SAH	Death after 12 days of SAH

Table 1 - Summary of all reported pediatric cases of HIV-related aneurysmal vasculopathy continued.

Year /No. of cases	Age at aneurysm diagnosis(years)/ gender/ HIV source	Presentation	Radiological modality/ Radiological findings/vessels involved	Management	Outcome
Patsalides et al, 2002[20]	7 cases, (7yrs – 15 yrs), 5 males and 2 females, 4 perinatal and 3 through blood transfusion	NS	Aneurysms involved ICA, MCA, ACA, PCA, basilar and vertebral arteries	All were taking ART before the diagnosis of aneurysmal arteriopathy	2 cases were alive through out the observation period; 4 cases died secondary to other AIDS-related complications and a single case died secondary to CNS complications
Petropolous et al, 2003[17]	12 yrs/ male /NS	Asymptomatic	Multiple saccular aneurysms of proximal right ICA and proximal basilar artery	Continued the earlier started HAART (AZT, 3TC, NVP) with follow-up of the aneurysms	After 2 years follow-up, no new CNS symptoms, and MRI showed no changes
Martinez-Longoria et al, 2004[1]	12 yrs /female/ congenital	Headache, transient left hemiparesis, blurred vision	Left ICA obstruction, stenosis in infraclinoid right ICA and fusiform dilatations of the right ICA bifurcation extends to right MCA and ACA	Initially on AZT. SQV and 3TC were started 3 month before CNS event. HAART regime (Kaletra® (LPV/RTV), 3TC and D4T) and aspirin was started after the CNS event	MRI after 15 months showed complete resolution of the aneurysm. No neurological event was occurred over 2 years follow-up
Mahadevan et al, 2007[16]	16 yrs / male / not known	Headache, vomiting, slurred speech and weakness	Fusiform dilatations of bilateral vertebral, basilar artery, right ICA, and MCA	A twist drill and ventricular tap did reduce the intracranial pressure	Death within hours of presentation
Thakker and Bhatia 2009[10]	12 yrs/ male/ congenital	Headache and right hemiparesis	Fusiform aneurysms of the left supraclinoid ICA	ART 4 months prior to the presentation. Conservative management of the aneurysm	No reported the death or other CNS manifestations
Demopolous et al, 2009[18]					
1	12 yrs/ male/ NS	Right hemiparesis	Fusiform right ICA aneurysm	ART for 5 years prior to the presentation	Complete neurological recovery
2	6 yrs/ female/ NS	Left hemiparesis	Fusiform dilatations of right ICA, right vertebral, and basilar artery	ART for 6 months prior to the presentation	The residual weakness with neurocognitive impairment
3	7 yrs/ Male/ NS	Right hemiparesis	Multiple aneurysms of vessels of the circle of Willis	Did not receive ART	Death
Savitr sastri et al, 2011[8]	13 yrs / Male /NS	Aphasia and right hemiplegia	Fusiform dilatations of bilateral supraclinoid ICAs	External ventricular drain inserted	Death within hours of presentation
Schieffelin et al, 2013[4]					
1	7 HIV-infected pediatric cases were reported to have cerebral aneurysm with no specific demographic	CNS symptoms	Aneurysmal dilatation of arteries in the circle of Willis	DDI at the time of CNS event	Alive
2		blurred vision	Multiple aneurysms, multiple infarcts	HAART at the time of CNS event	Died
3		seizures, right hemiparesis	Internal carotid artery aneurysm	HAART at the time of CNS event	Died
4		CNS symptoms	Aneurysm of left ACA and narrowing of right MCA	HAART at the time of CNS event	Alive
5		Hemiplegia	Fusiform CNS aneurysm	HAART at the time of CNS event	Alive
6		CNS symptoms	Multiple CNS aneurysms	HAART at the time of CNS event	Alive
7		CNS symptoms	Diffuse CNS aneurysms with ectasia	D4T, NVP at the time of CNS event	Died
Current Case	7 yrs/ Male/ Congenital	Headache and altered level of consciousness	fusiform aneurysm at left ICA bifurcation, and proximal ACA and MCA	Clipping of the aneurysm. Started on HAART before discharge	Discharged in a stable neurological condition to be followed up in the clinic

CT - Computed tomography, MRI - Magnetic resonance imaging, MRA - Magnetic resonance angiography, CTA - Computed tomography angiography, ICA - Internal carotid artery, ACA - Anterior carotid artery, MCA - Middle cerebral artery, PCOM - Posterior communicating artery, ACOM - Anterior communicating artery, SCA - Superior cerebellar artery, AICA - Anterior inferior cerebellar artery, CNS - Central nervous system, IEL - Internal elastic lamina, ART - Antiretroviral treatment, HAART - Highly active antiretroviral treatment, AZT - Azidothymidine/Zidovudine, DDI - Didanosine, 3TC - Lamivudine, RTV - Ritonavir, D4T - Stavudine, ABC - Abacavir, EFV - Efavirenz, NVP - Nevirapine, NFV - Nelfinavir, SQV - Saquinavir, LPV - Lopinavir, IDV - Indinavir, APV - Amprenavir , TDF - Tenofovir, DRV - Darunavir, RAL - Raltegravir

aneurysmal arteriopathy is still not well established.[1] Older case reports, before the initiation of the highly active anti-retroviral therapy (HAART), have showed fatal outcomes in most patients either due to stroke or severe intracranial hemorrhage.[2] While some reports have demonstrated ongoing progression of the disease despite the initiation of HAART, others have shown a stop of the disease progression,[11,15,17] and even resolution of the arteriopathy after the initiation of HAART.[1] These reports of improvement of arteriopathy after the initiation of HAART can also support the hypothesis of the direct role of HIV infection to the causation of this condition.[16] Surgical intervention is rarely reported in pediatric patients with HIV-associated cerebral aneurysmal arteriopathy. The diffuse distribution and fusiform architecture of most of the aneurysms reported have hindered neurosurgical or endovascular treatment.

In conclusion, HIV-associated vasculopathy is a rare complication of HIV affecting pediatrics and adults. Cerebral aneurysms secondary to HIV-associated arteriopathy have been reported as an incidental radiological finding while most patients reported symptoms ranging from mild headache to sudden death secondary to subarachnoid hemorrhage. The early initiation of HAART seems to decrease the incidence of aneurysms and other cerebrovascular complications of HIV infection. Secondary etiologies, most importantly VZV vasculopathy, should be considered in the differential diagnosis of stroke and other cerebrovascular abnormalities in patients with HIV-infection. Appropriate investigations with early treatment for secondary etiologies should be pursued to decrease the complications of vasculopathy. Surgical and endovascular management are appropriate options when indicated, for both adults and pediatric patients with HIV-associated aneurysmal arteriopathy.

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