

HIV-associated Intracranial Aneurysmal Vasculopathy in Adults

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ABSTRACT. Diffuse fusiform intracranial aneurysms have been reported in children with human immunodeficiency virus (HIV) for over 2 decades, but have only recently been reported in adults with HIV. Although these aneurysms have important clinical implications, their etiology and optimal therapy are unknown. We present a systematic review of diffuse intracranial fusiform aneurysmal vasculopathy in patients who are HIV-positive. We conducted a comprehensive literature search for relevant case reports and reviews published before February 2009. Patients were included if they had HIV infection and radiographic imaging consistent with fusiform aneurysmal vasculopathy. We identify 11 published adult cases of intracranial fusiform aneurysmal vasculopathy and describe 1 unpublished case from our own institution. Available data regarding clinical presentation, characteristic imaging findings, and treatment of this complex syndrome are reviewed. Adults with HIV-associated intracranial aneurysmal vasculopathy typically are significantly immunosuppressed and present with gross neurologic dysfunction. Characteristic radiographic findings include diffuse cerebral fusiform aneurysms with hemorrhage or infarct. Treatment of any active infection followed by the initiation of antiretroviral therapy and corticosteroids may be a reasonable approach in this complex syndrome. (First Release Dec 15 2009; *J Rheumatol* 2010;37:226–33; doi:10.3899/jrheum.090643)

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HUMAN IMMUNODEFICIENCY VIRUS
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 VARICELLA ZOSTER VIRUS

Intracranial aneurysmal vasculopathy has been identified in children with human immunodeficiency virus (HIV) since the 1980s¹, but only in the past several years have cases of diffuse fusiform intracranial aneurysms been reported in HIV-positive adults. Although these aneurysms have important clinical significance, the etiology of these lesions is unclear and their optimal therapy is unknown. There is abundant literature on infectious etiologies of cerebral aneurysms²⁻⁴; this review will be limited to the syndrome of HIV vasculopathy characterized by adult intracranial fusiform vasculopathy. We identify 11 published adult cases of intracranial fusiform aneurysmal vasculopathy and describe 1 unpublished case from our own institution (Table 1). Available data regarding clinical presentation, characteristic imaging findings, and treatment of this complex syndrome are reviewed.

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MATERIALS AND METHODS

Case reports and literature review. In February 2009, we performed a Medline® search without time limits with the following subject headings: “HIV and intracranial aneurysm,” “HIV and intracerebral aneurysm,” “HIV and fusiform aneurysm,” and “HIV and vasculopathy” to identify pertinent literature and case reports. We supplemented this search by consulting all the references of interest cited in these articles. Patients were included in the study if they had HIV infection and radiographic imaging consistent with fusiform aneurysmal vasculopathy. For the analysis, we included only references in English. We summarized data from selected reports using a standardized data form.

RESULTS

We identified 11 published cases of intracranial fusiform aneurysmal vasculopathy in adults and describe 1 unpublished case from our own institution.

A 38-year-old African American woman presented to our institution with slurred speech and right hemiparesis; a head computed tomography (CT) scan showed multiple ischemic and hemorrhagic foci and her cerebral angiogram revealed multiple intracranial fusiform and saccular aneurysms throughout all vascular territories of the anterior and posterior circulations (Figure 1). She reported a negative HIV test in the past. Initial laboratory studies revealed the following values: white blood cell count 8.9 cells/l, with 89.5% neutrophils; hematocrit 29.8%; platelet count 304×10^9 platelets/l; normal coagulation study findings; erythrocyte

Table 1. Characteristics of patients with fusiform intracranial vasculopathy and HIV infection.

Study	Age (yrs), Sex	CD4 (cells/mm ³) Viral Load (copies/ml)	History	Presentation	Laboratory Findings	Imaging	Therapy	Clinical Outcome
Our Patient	38 F	CD4 < 1, viral load 79,074	None	Right hemiparesis	See text	Head CT: ischemia of bilateral basal ganglia, hemorrhage of right frontal and occipital lobes. Angiogram: multiple intracranial fusiform and saccular aneurysms in anterior and posterior circulation	Steroids, started ARV, anti-CMV therapy for retinitis	New hemorrhage on day 39. Followup angiogram showed resolution. No new events at 18 mo followup
Modi ⁹	37 M	CD4 = 164	None	Severe cognitive impairment	CSF: protein 1.06 g/l, glucose 2.7 mmol/l, 3 neutrophils/ml, 41 lymphocytes/ml. CSF India ink negative, adenosine deaminase normal, syphilis serology negative, MTB culture negative	Angiogram: fusiform aneurysmal dilatation of bilateral ACA and MCA	Treated for presumed TB meningitis. No ARV	Lost to followup
	43 M	CD4 = 172	On therapy for pulmonary TB	Headache, meningismus, confusion	—	Head CT: SAH. Angiogram/surgery: Bilateral MCA fusiform aneurysms	Unable to repair right MCA aneurysm. No ARV	Died of renal failure
	43 M	CD4 = 17	On therapy for pulmonary TB	Generalized tonic-clonic seizures	CSF: protein 0.82 g/l, glucose 2.0 mmol/l, no cells. CSF adenosine deaminase normal. Serum ESR 130 mm/h	CT angiogram: multiple fusiform intracranial aneurysms. + aneurysmal dilatation of ascending aorta	Started ARV	Lost to followup
Hamilton ¹²	34 M	CD4 = 66, viral load “undetectable”	Endstage renal disease	Headache, fever left hemiparesis	—	Head CT: diffuse SAH. CT angiography: diffuse vasculopathy of all major cerebral vessels with multiple fusiform and giant saccular aneurysms	Unclear treatment	Discharged after 7 days
Ake ¹¹		CD4 = 15, VL 191,429	Recurrent VZV infections	Cognitive and language deficits	CSF: WBC 44 cells/mm ³ (86% neutrophil, 11% lymphocyte, 1% monocyte, 2% eosinophils), RBC 305,000 cells/mm ³ , glucose 24 mg/dl, protein < 2.0 g/dl. Negative CSF bacterial culture, fungal culture, AFB culture. Negative CSF DNA PCR for CMV, Epstein-Barr virus, human herpes virus-6 and -8, herpes simplex virus, VZV. CSF HIV RNA <30 copies/ml. CSF VDRL and cryptococcal antigen negative. ESR 38 mm/h	Head CT: hemorrhage in Sylvian fissure, lateral ventricle; SAH. Angiogram: Diffuse fusiform aneurysms and stenoses in anterior and posterior circulations	Continued noncompliance with ARV	Fatal subarachnoid hemorrhage 3 weeks after presentation

Table 1. Continued.

Study	Age (yrs), Sex	CD4 (cells/mm ³) Viral Load (copies/ml)	History	Presentation	Laboratory Findings	Imaging	Therapy	Clinical Outcome
Tipping ⁵	27 F	CD4 = 14	None	Right hemiparesis	CSF: 7 lymphocytes/mm ³ , 3 polymorphs/mm ³ , protein 1.0 g/l, glucose 41 mg/dl. Negative CSF cryptococcal antigen, rapid plasma reagin, and cultures for bacteria, fungi, and tuberculosis	CT: left basal ganglia infarct and fusiform dilation of L MCA, L ACA and distal basilar artery	—	Died of pneumonia 25 days after presentation
Kossorotoff ⁶	23 M	CD4 = 496	2 previous MCA strokes	Recurrent left MCA stroke	CSF normal	MRI: recurrent L MCA infarct. Angiogram: large L terminal ICA aneurysm; multiple ectasias alternating w/stenotic lesions on medium-size arteries	Continued ARV	Alive at 9 yrs
	32	CD4 = 338	Recurrent VZV infections	Chronic headache	CSF: WBC 13/mm ³ , protein 1.09 g/dl, glucose 2.1 mmol/l. CSF PCR VZV negative. Serologies positive for Epstein-Barr virus, human herpes virus-8, and CMV	MRI: R MCA infarct. Angiogram: multiple ectasia and focal stenoses on medium and small cerebral arteries	Aspirin. Continued ARV	Alive at 1 year. Followup MRA at 1 yr unchanged
O'Charoen ⁷	36 M	CD4 = 43, VL 298,000	Polycystic kidney disease	Dysarthria, right-side weakness	CSF: WBC 1/mm ³ , RBC 8/mm ³ , protein 65 mg/dl, glucose 49 mg/dl. Negative CSF India ink, bacterial culture, VDRL, cryptococcus agglutination, CMV DNA PCR, VZV DNA PCR. ESR 95 mm/h, CRP 8.2 mg/dl	MRI: L internal capsule.lateral thalamus infarct. MRA: fusiform aneurysmal dilation in A2 segments of bilateral ACA, MCA, postcerebral and basilar arteries	Did not receive	—
Berkefeld ⁸	37 M	—	MCA infarct 3 mo prior to presentation	Progressive L hemiparesis and visual field disturbances	CSF: 7 WBC/ μ l protein 0.85 g/l. Microbiology examinations of CSF and serum normal. ESR 65 mm/h, CRP 0.9 mg/dl	MRA: RICA and MCA showed moderate arterial dilation, thickening, and contrast enhancement of walls. MRI: R MCA infarct	Penicillin G, corticosteroids (dose not given), azathioprine. Started ARV	Alive at 3 mo
	31 M	—	Serum VZV antibody elevated, serum VZV PCR positive	Recurrent TIA, aphasia, right hemiparesis	CSF: WBC 9/ μ l. Serum VZV antibody elevation and positive serum VZV PCR	MRI: L MCA infarcts. MCA aneurysmal dilation, thickening, and contrast enhancement of arterial wall	Improved with acyclovir and corticosteroids (decortine 1000 mg for 4 days). Started ARV	Alive at 4 mo

Dash denotes information not given. CT: computed tomography; CMV: cytomegalovirus; CSF: cerebrospinal fluid; MCA: middle cerebral artery; ARV: anti-retroviral; TB: tuberculosis; ESR: erythrocyte sedimentation rate; SAH: subarachnoid hemorrhage; PCR: polymerase chain reaction; HIV: human immunodeficiency virus; CRP: C-reactive protein; ACA: anterior cerebral artery; MRI: magnetic resonance imaging; MRA: magnetic resonance angiogram; WBC: white blood cells; RBC: red blood cells; ICA: internal carotid artery; VZV: varicella zoster virus; TIA: transient ischemic attack; MTB: mycobacterium tuberculosis.

sedimentation rate 95 mm/h, and C-reactive protein 3.5 mg/dl.

Surgical intervention was deferred because of the peripheral locations of her multiple aneurysms. She was prescribed empiric broad-spectrum antibiotics in case of mycotic aneurysms. Multiple blood cultures prior to the administration of antibiotics remained negative, and echocardiogram was negative for vegetations. She underwent lumbar puncture on hospital day 6: the cerebrospinal (CSF) fluid contained 0 leukocytes/ μ l, 51 erythrocytes/ μ l, protein 38 mg/dl, and glucose 56 mg/dl. CSF bacterial culture, oligoclonal bands, and cytology were all negative. Serum tests for syphilis, Lyme, Rickettsia, Bartonella, and cryptococcus were negative. Following lumbar puncture, she received intravenous dexamethasone 6 mg every 6 hours to treat possible autoimmune vasculitis. Her mental status improved significantly and she was transitioned to a prednisone taper.

The patient's HIV ELISA and confirmatory Western blot were subsequently positive, giving a new diagnosis of HIV with CD4 cell count < 1 cells/mm³, CD4 cell percentage 1%, and HIV viral load 79,074 copies/ml. To evaluate additional infectious causes of central nervous system (CNS) vasculitis, she underwent repeat lumbar puncture on hospital day 15, with CSF revealing 0 leukocytes/ μ l, 2 erythrocytes/ μ l, and protein 49 mg/dl. CSF testing for cytomegalovirus (CMV) polymerase chain reaction (PCR) and herpes simplex virus PCR was indeterminate as there were no white blood cells in the CSF for HLA testing. CSF testing for syphilis, cryptococcus, and bacterial and fungal cultures were negative. An extensive evaluation for underlying autoimmune etiologies was negative. Contrast CT of the chest, abdomen, and pelvis did not reveal vascular abnormalities. Abdominal arteriogram did not show aneurysms.

This patient had a lengthy hospital course complicated by *Pneumocystis jirovecii* pneumonia, CMV retinitis, and disseminated mycobacterium avium complex; she recovered from these opportunistic infections and began antiretrovirals (ARV) with emtricitabine/tenofovir and lopinavir-ritonavir. On hospital day 39, she suffered a new left basal ganglia hematoma with mass effect upon the left lateral ventricle, so her steroids were changed to intravenous methylprednisolone 20 mg every 12 hours. She was also given a prolonged course of valganciclovir for CMV retinitis. Repeat angiogram on hospital day 85 showed improvement in all areas (Figure 2), and she has continued receiving ARV and completed a 12-month prednisone taper. At the 18-month followup, she remains alive with no new neurologic events and a CD4 count of 216 cells/mm³, CD4 cell percentage 24%, and viral load 170 copies/ml.

The 12 adult patients we identified had a mean age of 34.1 years (range 23–43), male:female ratio 3:1, mean CD4 count 132.5 cells/mm³ (range < 1–496), and mean viral load 142,138 copies/ml (range from undetectable to 298,000;

Table 1). Clinical presentation in adults with HIV-associated intracranial aneurysmal vasculopathy includes altered mental status, cognitive impairment, acute hemiparesis, and dysarthria. Cerebral infarcts and hemorrhages are common in this syndrome. Six adults presented with isolated infarct⁵⁻⁸, 3 with subarachnoid hemorrhage, 1 with combined infarct and hemorrhage (our patient), and 2 with neither infarct nor hemorrhage⁹. Two cases were found to have contrast enhancement of arterial walls⁸. Cerebral angiography revealed multiple and often bilateral fusiform aneurysms, which are symmetrical spindle-shaped enlargements of the entire artery circumference¹⁰.

Clinical outcomes are fairly poor for this syndrome and longterm followup is often unavailable (Table 1). Three of 12 adult patients were taking ARV at the time of presentation of vasculopathy; 1 died shortly after presentation¹¹ and 2 survived (for 9 years and 1 year)⁶. Of note, the 2 survivors had preserved CD4 counts at presentation (496 and 338 cells/mm³, respectively)⁶. Four adults started ARV at presentation; 3 remain alive (at 18 months, 3 months, and 4 months)⁸ and 1 was lost to followup⁹. Of the 5 adults who never started ARV therapy, 2 died^{9,5}, 1 was discharged at 7 days with no longterm followup available¹², and the remaining 2 were lost to followup or not reported^{7,9}. Additional therapy for these patients included steroids, acyclovir, presumptive tuberculosis meningitis therapy, penicillin G, and azathioprine.

DISCUSSION

Diffuse intracranial fusiform aneurysmal vasculopathy is a complex syndrome affecting young adults with significant immunocompromise from HIV disease, similar radiographic imaging findings, and similar clinical presentations. These patients tend to have CD4 counts below 200 and high HIV viral loads. Radiographic findings include characteristic diffuse fusiform aneurysms often with hemorrhage or infarct. Clinical presentations among adults include confusion, cognitive deficits, dysarthria, and hemiparesis. While adults present with significant neurologic impairment, several pediatric cases of HIV-associated intracranial vasculopathy were discovered on routine surveillance imaging in asymptomatic patients¹³. There is one pediatric report of cerebral vasculopathy as the presenting manifestation of undiagnosed HIV¹⁴; our case is the third in the adult literature of intracranial fusiform aneurysmal vasculopathy presenting in a patient not previously known to be HIV-positive^{7,9}. Based on these 4 cases, the presence of fusiform intracranial aneurysms in younger patients without typical atherosclerosis risk factors should prompt a search for underlying HIV infection.

Childhood HIV-associated intracranial fusiform aneurysmal vasculopathy has been reported in 1.6% of children with HIV¹³. There are over 32 case reports of HIV-positive children, mostly severely immunocompromised in the era

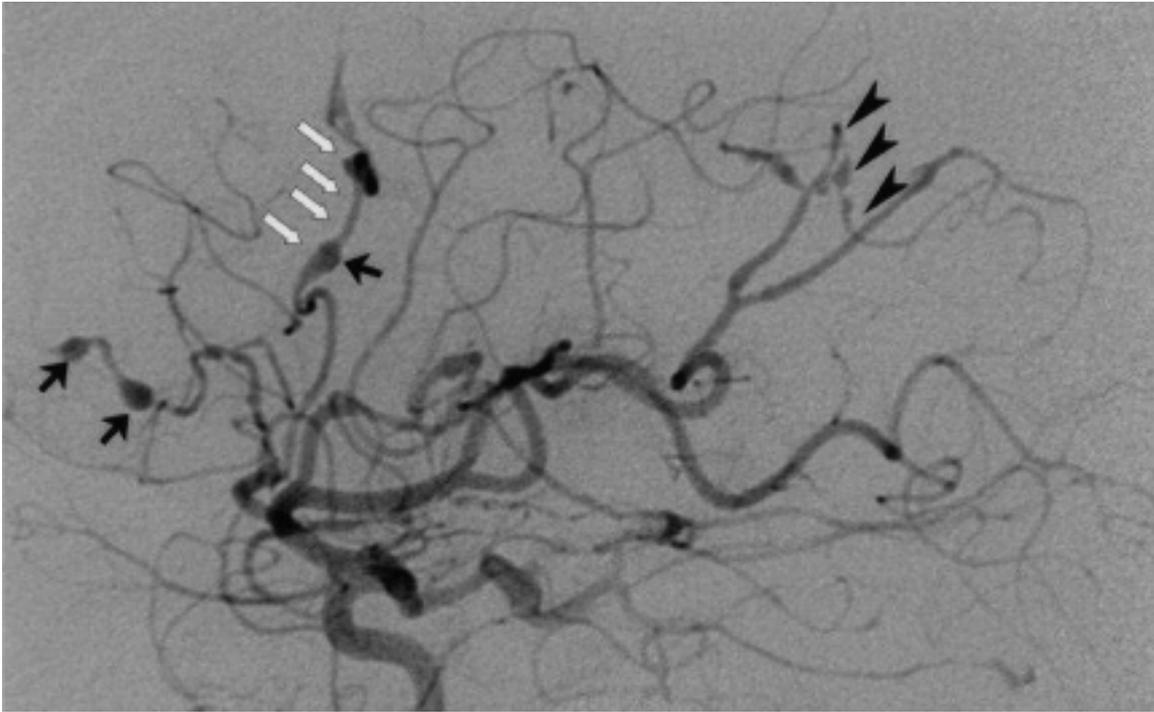


Figure 1. A lateral view of the internal carotid artery distribution from the initial cerebral angiogram shows vasculopathic changes. Black arrows indicate saccular aneurysms on branches of the anterior cerebral artery. White arrows indicate vasculopathic changes on another branch of the anterior cerebral artery. Black arrowheads indicate the pattern of vascular narrowing and fusiform aneurysms on a branch of the middle cerebral artery.

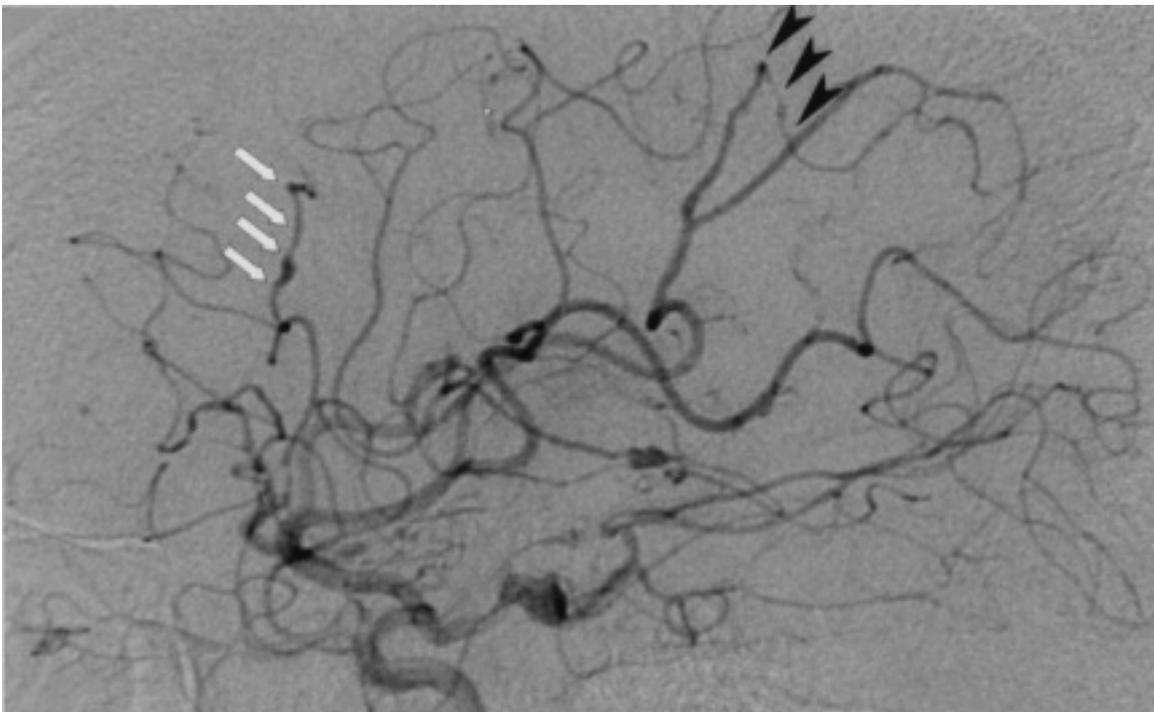


Figure 2. A lateral view of the internal carotid artery distribution from the followup cerebral angiogram done 91 days after the initial study shows marked improvement of the vasculopathic changes. White arrows indicate substantial improvement in the vasculopathic changes on a branch of the anterior cerebral artery compared to Figure 1. Black arrowheads indicate improvement of the vasculopathic changes in the branch of the middle cerebral artery compared to Figure 1.

before highly active antiretroviral therapy, with fusiform aneurysms on arteries of the circle of Willis resulting in ischemic and hemorrhagic strokes, and leading to death in 6 months^{5,15-18}. Pediatric autopsies revealed aneurysmal dilatation confined to the large arteries of the circle of Willis, sparing the leptomeningeal and intraparenchymal arteries. Histopathologic specimens showed medial fibrosis with loss of the muscularis layer, disruption or destruction of the internal elastic lamina, and intimal thickening with sparse or absent vascular inflammation^{1,17}. Only 1 of the 12 reported adult cases underwent autopsy⁵, showing fusiform dilation of left internal carotid artery and middle cerebral artery with luminal thrombosis, concentric intimal fibrosis, atrophic media, and elastic lamina thinning and fragmentation; these findings are consistent with pediatric reports.

The etiology of HIV-associated intracranial vasculopathy remains unclear. The HIV along with other pathogens may play a role but the exact mechanism of vessel damage remains undefined. Reported causes of infective intracerebral aneurysms in patients with HIV include salmonella, mycobacterium tuberculosis (MTB), meningovascular syphilis, CMV, and varicella zoster virus (VZV), among others^{19,20}. However, in many reported cases an infective cause other than HIV is not found. Mycotic aneurysms from bacterial or fungal organisms are usually fusiform and located in distal arterial branches. In the antibiotic era, mycotic aneurysms are typically due to hematogenous seeding of previously damaged arteriosclerotic vessels. Multiple blood cultures and echocardiographic assessment are needed to rule out bacteremia and infective endocarditis.

Others have suggested a role for MTB or atypical mycobacterial infection in causing these intracranial aneurysms, because mycobacteria are a known cause of infective vasculitides in patients with HIV, and several pediatric cases had concurrent mycobacterial infection^{1,21}. Intracranial tuberculous aneurysm rupture has been described in a single case report of a patient with tubercular meningitis²². Of the 12 adult cases of diffuse cerebral vasculopathy reviewed here, 2 were on therapy for pulmonary TB at the time of presentation⁹; 5 patients had CSF examined for acid-fast bacillus or adenosine deaminase, and all were negative^{5,7,9,11}, although 1 was still subsequently treated for presumed tubercular meningitis⁹; and only our patient had atypical mycobacterial infection near the time of presentation.

The most common form of syphilitic vasculitis is Heubner's arteritis, endarteritis obliterans affecting large and medium-size arteries in the circle of Willis, characterized by fibrous and inflammatory changes in the adventitia, along with thinning of the media and fibroblastic proliferation of the intima. Meningovascular syphilis is now mainly seen in patients with HIV who are untreated or inadequately treated with penicillin²³; these patients have faster disease progression and worse outcomes than their HIV-negative

counterparts. Single saccular intracranial aneurysms have been reported in patients with meningovascular syphilis, but diffuse intracranial aneurysms have not been described³.

In patients with acquired immunodeficiency syndrome (AIDS), CMV vasculitis of the CNS has been documented in 2%–13% of autopsy specimens²⁴. Vasculitis may involve meningeal vessels as well as extradural vessels of the brain and spinal cord. Koeppen, *et al* described a man who developed blindness, deafness, and paraplegia after intrathecal methotrexate for presumed CNS lymphoma²⁵. Autopsy revealed chorioretinitis, arteritis of the ophthalmic artery with infarcted optic nerve, occlusive arteritis with multiple infarcts of the brain and spinal cord, and small and medium vessel vasculitis in the brain and thoracic cord. Electron microscopy of the brain and retina revealed abundant intranuclear inclusion bodies compatible with CMV. Single or multiple intracranial aneurysms, however, have not been reported in CMV infection.

Productive VZV infection of cerebral arteries is another possible cause of cerebral fusiform vasculopathy in patients with HIV. VZV infects large and small cerebral arteries, causing aneurysms and necrotizing angiitis²⁶. Pathology of affected larger cerebral arteries has revealed necrotizing arteritis or intimal proliferation occluding the lumina with stenosis or thrombosis, often with positive VZV immunostaining²⁷.

Unifocal, large-vessel infarction from VZV occurs in elderly, immunocompetent persons with recent zoster, and is likely due to transaxonal migration of VZV from trigeminal nerve afferent fibers to vessels of the anterior cerebral circulation²⁸. Multifocal VZV vasculopathy affects branches of large or small cerebral arteries in immunocompromised patients. Saraya, *et al* described an HIV-positive adult with multiple intracranial aneurysms along smaller peripheral arteries, suggesting viral spread via cerebral arteries, not the trigeminal nerve²⁹.

Nagel, *et al* described 30 patients with VZV CNS vasculopathy, 5 of whom were HIV-positive and 37% of whom lacked a history of varicella zoster infection or rash³⁰. The absence of CSF pleocytosis was noted in 33% of patients. Anti-VZV IgG antibody in the CSF was a more sensitive marker of cerebral VZV infection than CSF VZV DNA (93% vs 30%)³⁰. Others have also shown that a reduced ratio of the concentration of anti-VZV IgG in serum to that in CSF as compared with the ratios of total IgG and albumin supports the diagnosis of active VZV CNS infection²⁶.

Several cases of CNS vasculopathy in HIV-infected children cite VZV as a possible causative agent. Fulmer, *et al* report a child with AIDS and fusiform dilatation of the anterior and posterior cerebral arteries with positive immunohistochemical staining against VZV of the dilated vessels¹⁴. In a series of 13 pediatric cases of cerebral aneurysmal arteriopathy, 4 had a history of VZV infection and 2 had elevated serum VZV antibody titers, but none had

VZV infection confirmed in the CNS; 2 postmortem CNS examinations with VZV immunostaining were both negative¹⁸. Of the 12 adult cases, CSF VZV DNA PCR was negative in 3 patients and not reported in the remainder^{6,7,11}. A fourth patient had an elevated VZV serum antibody level and a positive serum VZV PCR but no reported CSF studies; this patient had clinical and radiographic improvement that authors attributed to high-dose intravenous acyclovir and steroids⁸. VZV immunostaining was not performed on the single adult case that went to autopsy⁵.

HIV itself has been implicated as the cause of intracranial vasculopathy. One theory holds that HIV or opportunistic infection causes immune activation with cytokine and growth factor production, causing vascular remodeling⁵. Others postulate that HIV directly invades and damages cerebrovascular endothelium. With only 2 exceptions, all reported adult and pediatric cases, including patients on ARV, had highly elevated HIV viral loads upon presentation with aneurysmal disease^{12,16}. However, in only 1 pediatric case were HIV sequences detected by PCR in an affected intracerebral artery¹⁷. Kure, *et al* described a pediatric case with positive anti-gp41 antibody staining of cells in the organizing thrombi and the thickened intima of the involved artery from the circle of Willis, and suggested that positive-staining cells in the intima were not endothelial cells but rather were derived from hematogenous cells involved in ongoing thrombi¹. The single published adult autopsy reported a negative p24 antigen staining of vessel sections⁵.

If an opportunistic infection is the etiologic agent for the intracranial vasculopathy, one theoretical concern is that initiating ARV would prompt immune reconstitution inflammatory syndrome (IRIS) and possibly worsen the underlying vasculopathy. Bonkowsky, *et al* described a 12-year-old boy with perinatally acquired HIV infection and poor compliance on numerous ARV regimens who, 6 months after switching to a new ARV regimen with excellent immunologic recovery and suppression of his viral load, developed acute neurologic symptoms with diffuse fusiform aneurysms in large cerebral vessels and acute infarction¹⁸. While no adult case reports document IRIS in the setting of cerebral vasculopathy, our patient suffered a basal ganglion hemorrhage several weeks after initiating ARV and reducing her decadron dosing; she was retreated with high-dose methylprednisolone and then transitioned to a 12-month prednisone taper.

Adults with HIV-associated intracranial aneurysmal vasculopathy tend to be significantly immunosuppressed, with CD4 counts below 200 cells/mm³ and viral loads greater than 100,000 copies/ml. They present with significant neurologic dysfunction and characteristic radiographic findings of diffuse cerebral fusiform aneurysms. Clinicians must be aware that the presentation of intracranial aneurysmal vasculopathy may be the initial presentation of HIV disease in both children and adults. It is important to exclude active

infection such as bacterial pathogens, MTB, meningovascular syphilis, CMV, and VZV.

Despite over 30 case reports in the pediatric literature and now 12 reported adult cases, optimal therapy for this syndrome remains undefined. There is some suggestion that initiating ARV or optimizing a previous ARV regimen will stabilize or reverse intracranial aneurysmal vasculopathy. In the adult literature, survival to discharge has been documented in 2 of 3 patients who were already receiving ARV at presentation with vasculopathy; in 3 of 4 patients who started ARV after presentation with vasculopathy; and in 1 of 5 patients who never received ARV^{5-9,11,12}. Martinez-Longoria, *et al* described a child whose intracerebral aneurysm underwent complete radiographic resolution on an optimized ARV regimen, but her initial presentation was atypical in that she initially had only a single aneurysm as well as angiographic evidence of arteritis¹⁵. Elfenbein, *et al* described a child with progression of neurologic symptoms despite immune recovery with ARV³¹, and Mazzoni, *et al* described a pediatric case with clinical improvement and radiographic stabilization of vasculopathy after optimization of ARV¹⁶.

Based on our limited experience and literature review, initiation of ARV may be a reasonable approach for treatment of fusiform vasculopathy in patients infected with HIV. There is no evidence that supports one ARV regimen over another, but the following factors should be considered when selecting a regimen: the HIV genotypic and/or phenotypic resistance profile in the patient, the toxicity profile and the tolerability of an ARV regimen, and the ability of an ARV regimen to penetrate the blood-brain barrier. Some ARV that penetrate the CNS include zidovudine, lopinavir/ritonavir, and nevirapine³². While it is unclear whether CNS drug penetration is necessary for this patient population, the CNS has been documented to be a reservoir site for HIV replication³³.

Steroids have an undefined role in treating this vasculopathy and in preventing IRIS. Pediatric cases of HIV-associated intracranial fusiform vasculopathy have been treated with ARV and aspirin, but not with steroids^{6,15,17,18}. Of the 5 adult patients who survived at least 1 month after hospital discharge, 100% received ARV and 60% received both steroids and ARV. Of the 3 adult patients who received steroid therapy following vasculopathy diagnosis, 1 received unspecified dose and duration of corticosteroids, 1 received dexamethasone 1000 mg for 4 days, and the patient at our institution received dexamethasone and then, after repeat intracranial hemorrhage, methylprednisolone and a prolonged prednisone taper⁸. All 3 of these patients survived (3 months, 4 months, and 18 months, respectively). Of note, each also began an ARV regimen around the time of steroid initiation. Defining the mechanism of benefit of steroids is problematic because the mechanism of vasculopathy is unknown. Autopsy studies have not revealed vasculitis,

therefore we do not feel high-dose steroids for prolonged duration are indicated, as for CNS vasculitis. However, an abbreviated course of steroids may be a consideration during the initiation of the ARV therapy for the prevention of IRIS. An example of such a steroid regimen would be prednisone started at 1 mg/kg given as a single dose followed by a taper and discontinuation of the drug over a 3-month period.

Despite these limited data, in patients with HIV and the characteristic radiographic findings of diffuse cerebral vasculopathy, we recommend treating any active infection, then initiating ARV and steroids in a timely manner. Special attention should be given to the possible development of IRIS. Additional autopsy data are needed, with emphasis on the evaluation of VZV and HIV in affected cerebral arteries.

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