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Case Reports

Intracerebral Aneurysms in Human Immunodeficiency Virus Infection: Case Report and Literature Review

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We describe a child with human immunodeficiency virus infection who presented with a large subarachnoid hemorrhage. She had multiple saccular and fusiform aneurysms in the proximal cerebral arterial circulation and no evidence of bacterial or fungal infection. The arteriopathy coincided with a high human immunodeficiency virus RNA load. Human immunodeficiency virus may cause cerebral arteriopathy with potentially life-threatening complications.

Mazzoni P, Chiriboga CA, Millar WS, Rogers A. Intracerebral aneurysms in human immunodeficiency virus infection: Case report and literature review. Pediatr Neurol 2000;23:252-255.

Introduction

Intracranial arterial aneurysms are rare in children [1,2]. Mycotic aneurysms are even less common and, with the exception of human immunodeficiency virus (HIV), are rarely observed in the absence of congenital heart disease. Intracranial hemorrhage is a well-documented complication of aneurysms [3-5]. We report a case of an HIV-infected child with multiple cerebral aneurysms who presented with a large subarachnoid hemorrhage (SAH) and review several studies that suggest a possible causal role of HIV in the development of intracranial aneurysms in patients with acquired immunodeficiency syndrome.

Case Report

The patient was an 8-year-old female with congenital HIV infection and sickle cell trait who was born at term with a normal weight, height, and head circumference. She had two episodes of pneumonia and one of oral thrush in her first year after birth. By 15 months old, she manifested microcephaly (head circumference less than the 5th percentile), diffuse hypotonia, global developmental delay, and failure to thrive (weight less than the 5th percentile). At 7 years old, she was nonverbal and was unable to sit or grasp objects. She had been treated with zidovudine beginning at 13 months of age, which was replaced with didanosine at 3 years of age. Bactrim was added at 7 years of age. Three weeks before admission, a cranial computed tomographic scan revealed diffuse atrophy and periventricular white matter hypodensities, consistent with HIV encephalopathy.

She presented to the emergency room at 8 years, 4 months of age with a sudden loss of consciousness followed by a generalized tonic-clonic seizure. Her weight was 17 kg and her head circumference was 41 cm (both less than the 5th percentile). She had a fluctuating level of consciousness, limited upgaze, axial hypotonia, moderate hypertonicity of her legs accompanied by clonus, and mild hemiparesis involving her left face, arm, and leg. Funduscopic examination revealed normal discs and vasculature.

A cranial computed tomography scan revealed extensive SAH, right greater than left, extending throughout the right suprasellar, prepontine, and ambient cisterns, with dilation of the lateral and third ventricles. A ventricular drain was placed. Contrast cerebral angiography revealed multiple arterial aneurysms (Fig 1), both fusiform and saccular. Most of these aneurysms were located near or in the circle of Willis.

Her serum hematocrit was 32.5%, and the leukocyte and platelets counts and prothrombin and partial thromboplastin times were normal. The erythrocyte sedimentation rate was 45 mm/hr. The cerebrospinal fluid contained 284,000 leukocytes/μL (91% lymphocytes and 1% neutrophils) and 145,000 erythrocytes/μL. The cerebrospinal fluid protein concentration was 276 mg/dL; glucose was 91 mg/dL. The serum HIV viral RNA load was undetectable (less than 400 copies/mL). Serum antibody tests for cytomegalovirus and varicella-zoster virus (VZV) were negative. She was a chronic hepatitis B carrier. Bacterial, fungal, and viral cultures of blood and cerebrospinal fluid failed to identify additional infectious sources. Echocardiography revealed no vegetations, and renal ultrasound demonstrated no aneurysms.

After a brief course of antibacterial therapy, treatment was initiated with zidovudine, lamivudine, and ritonavir. Because of the shape and multiplicity of the aneurysms, the child was not considered a candidate for surgical aneurysmal repair. She received supportive treatment in the intensive care unit, and within 1 month she had recovered to her baseline examination and level of functioning.

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Received November 12, 1999; accepted April 26, 2000.

PII S0887-8994(00)00179-X • 0887-8994/00/$20.00

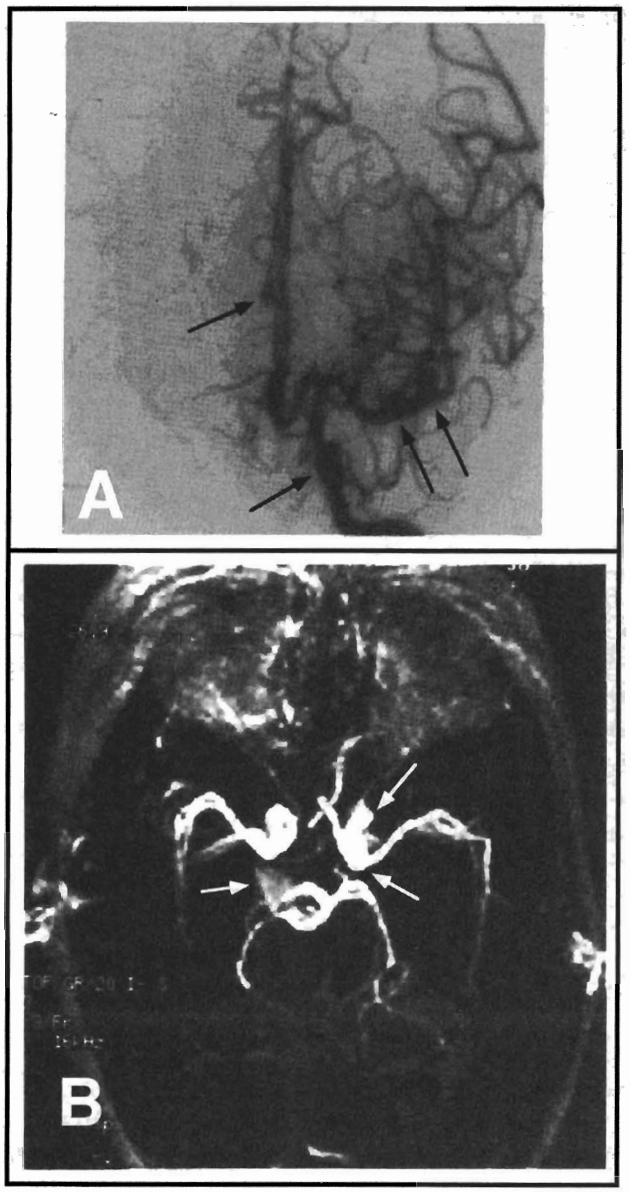

Figure 1. (A) Contrast cerebral angiography obtained 1 day after admission and (B) magnetic resonance angiography obtained 2 weeks later. Both techniques revealed ectasia of the M2 segment of the left middle cerebral artery, with slightly better visualization of the distal M2 wide-necked saccular aneurysm by contrast angiography (A) than by magnetic resonance angiography (B). All but the smallest aneurysm (arrows) in this patient with contrast angiography were visible by magnetic resonance angiography.

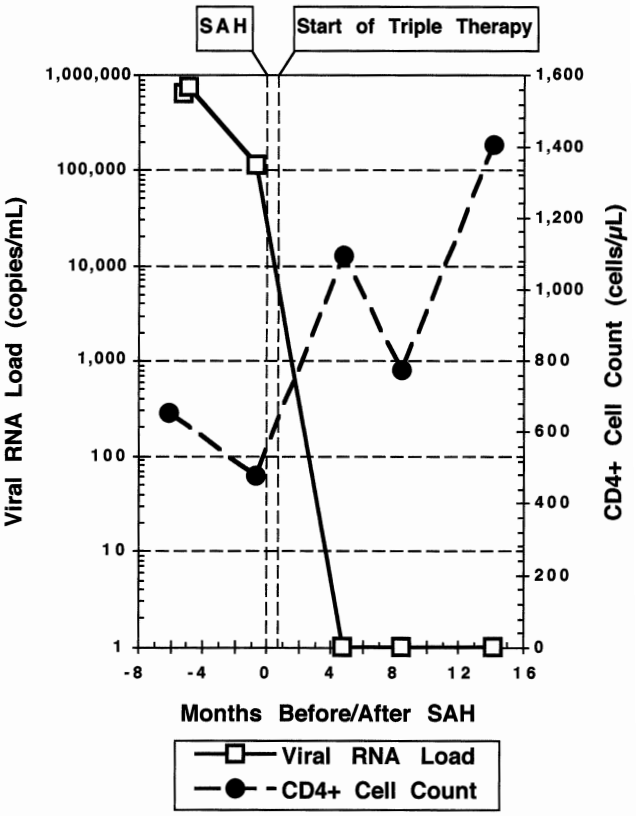

Figure 2. Viral RNA load (open squares) and CD4+ cell count (filled circles) in our patient, at various times before and after occurrence of the subarachnoid hemorrhage (SAH). Triple therapy (zidovudine, lamivudine, and ritonavir) was initiated 21 days after the SAH.

Five months before presentation, the patient's CD4 count was 650 cells/μL and her viral RNA load was greater than 750,000 copies/mL (Fig 2). Four months after beginning triple antiretroviral therapy, the CD4+ count increased to 1,092 cells/μL, and the viral RNA load was undetectable. A second magnetic resonance angiogram (not presented) done at this time revealed no new aneurysms and no clear change in the existing ones.

Discussion

Our patient had multiple aneurysms in the proximal cerebral arterial system in the setting of HIV encephalopathy. Her aneurysms were clinically silent until she had acute SAH, probably from the right posterior cerebral artery aneurysm. The proximal location and large size of this child's aneurysms are atypical for mycotic aneurysms, which tend to be fusiform and located in distal arterial branches.

Cerebral arterial aneurysms have previously been demonstrated in patients with HIV infection. Maniker and Hunt [6] described berry aneurysms of the circle of Willis in six adults with acquired immunodeficiency syndrome. Husson et al. [7] prospectively identified multiple fusiform and saccular aneurysms of large intracranial vessels in two HIV-infected children by magnetic resonance imaging. In one case, contrast cerebral angiography did not reveal additional small or medium-vessel aneurysms, and chest and abdomen magnetic resonance imaging revealed no extracranial large-vessel aneurysms. In the second case the aneurysms appeared (as observed on serial magnetic resonance angiograms) over an interval during which the serum p24 antigen load increased dramatically, without evidence of an inflammatory or congenital process. Both patients had no signs referable to their aneurysms.

HIV infection has been associated with arteriopathy of small, medium, and large cerebral arteries, both in isolation and in the presence of cerebral aneurysms and

infarcts. Aneurysmal dilation of the circle of Willis was found at postmortem examination in one of six HIV-infected children with stroke [8,9]. The affected arteries exhibited marked intimal fibroplasia with medial thinning and elastic lamina destruction or reduplication. The intima of this patient's cerebral arteries stained positive for the major transmembrane glycoprotein of HIV, gp41. Another patient in this series had a healed arteriopathy of large to medium-size meningocerebral and leptomeningeal arteries, with intimal hyperplasia and endothelial prominence. Inflammation was absent. In another series of six children with acquired immunodeficiency syndrome, Joshi et al. [10] described fibrosis of the intima with fragmentation of elastic tissue and fibrosis and calcification of media with variable luminal narrowing in multiple organs. In five patients the brain was involved; the cerebral arteries were the only vessels that also exhibited inflammation, supporting a relationship between HIV encephalopathy and arteriopathy. Intimal fibrosis with thickening of the media was also observed in the aorta's vasa vasorum of a child with HIV infection [11].

The mechanism by which HIV results in central nervous system arterial damage is unknown. Postulated mechanisms include direct HIV invasion of cerebrovascular endothelium, damage resulting from exposure to toxic cytokines produced systemic (blood) or local (central nervous system) perivascular infiltrates [12], or less likely from recurrent non-HIV systemic infection [10]. In favor of a direct HIV-related pathogenesis for the arteriopathy is its association with high viral titers (as in our patient) and viral antigens [7] and the positive HIV antigens present in affected vessels [8]. Recently, staining of an aneurysmal brain vessel was positive for antigen in an HIV-infected child who died of SAH [13]. This finding, coupled with the frequent coinfection of HIV with VZV found in one series of children with HIV arteriopathy (four of 13 patients), has linked VZV to HIV arteriopathy [14]. However, a greater number of VZV staining studies of unaffected vessels are needed to interpret the causal relevance of this association.

The known tropism of certain HIV strains for brain mononuclear cells [15], coupled with the transendothelial migration postulated to occur during HIV neuroinvasion and its accompanying immune activation [16], may explain the formation of aneurysms in cerebral arteries in the absence of systemic arterial aneurysms [7,10] and account for the frequent co-occurrence of HIV encephalopathy and HIV vasculopathy.

One of the patients reported by Husson et al. [7] developed multiple intracerebral aneurysms during a period of increase in his serum p24 antigen concentration. Our patient's viral load was very high (greater than 600,000 copies/mL; Fig. 2) 5 months before the hemorrhage occurred and was still high (greater than 100,000) 1 month before the event. Her arteriopathy was probably progressing during this period, given the subsequent spontaneous aneurysmal rupture. The viral load was reduced to undetectable levels a few weeks after initiating antiretroviral therapy. Whether early antiretroviral therapy can alter the development and natural history of HIV-related aneurysms is unknown. In our patient, no change in aneurysm size was observed by magnetic resonance imaging 4 months later, suggesting a possible arrest in the progression of arteriopathy after beginning antiretroviral therapy.

The pathologic, imaging, and clinical studies discussed above suggest that HIV infection may be associated with damage to the wall of the large cerebral arteries, leading to aneurysm formation. These aneurysms can rupture and lead to devastating SAH. Cranial computed tomography performed only 3 weeks before the hemorrhage in the current patient did not reveal any aneurysms, illustrating the limitations of computed tomography in assessing their presence. Magnetic resonance imaging may be a useful tool in identifying the incidence of HIV-related arteriopathy and in monitoring the course of arteriopathy in individual patients—perhaps indicating the time when neurosurgery or interventional angiography is indicated. It may also help monitor the effectiveness of antiretroviral therapy. We suggest that magnetic resonance imaging or magnetic resonance angiography (or both) may be indicated in HIV-infected children with sustained high viral loads, especially those refractory to treatment or with evidence of encephalopathy. Early identification of HIV arteriopathy may help change the risk stratification, may guide antiretroviral therapy, and may prevent intracranial hemorrhage.

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