

Cerebrovascular Complications of HIV in Children

Smruti S. Shah, Robert A. Zimmerman, Lucy B. Rorke, and Louis G. Vezina

Summary: Two uncommon but important cerebrovascular manifestations of human immunodeficiency virus (HIV) infection in children are arteritis with formation of fusiform aneurysms and arterial sclerosis with vascular occlusion. We studied the CT and MR imaging features of HIV in two girls and one boy (9 to 18 years old) and compared them with autopsy findings in two patients. One of the children had findings consistent with small areas of subacute infarction and the other two had fusiform dilatation of the major vessels of the circle of Willis. The ischemic lesions and arteriopathy were confirmed at autopsy. In one patient, an incidental B-cell lymphoma (not visible on the imaging studies) was diagnosed.

Index terms: Acquired immunodeficiency syndrome; Aneurysm, cerebral; Children, diseases

An increase in the frequency of human immunodeficiency virus (HIV) infection coupled with the lack of an absolute cure has resulted in an increasing number of HIV-infected children. The morbidity and mortality rates are high in the pediatric group; about 20% of HIV-infected infants will get acquired immunodeficiency syndrome (AIDS) in the first year of life and about 90% by 12 to 18 months of age. The frequency of cerebrovascular complications in children with AIDS is 1.3% (1).

We studied the imaging features in three children with HIV infection in whom vascular lesions (ischemia/hemorrhage) were identified; two of these patients also had postmortem examinations. An interesting finding in two of the children was formation of fusiform aneurysms of the major vessels of the circle of Willis. This finding has been described previously (1), and it may be a feature specific to AIDS. Nonetheless, vascular involvement, per se, should be recognized as a cause of neurologic deterioration in children with HIV infection.

Subjects and Methods

Three patients (two girls and one boy) with AIDS were studied. Antibodies against HIV were measured by enzyme-linked immunosorbent assay and confirmed by the western-blot technique.

All patients had unenhanced and contrast-enhanced computed tomography (CT) of the brain with 5- to 8-mm-thick sections. One patient (patient 3) had unenhanced and contrast-enhanced magnetic resonance (MR) imaging and MR angiography on a 1.5-T unit. A follow-up CT scan was available for one patient (patient 2). The imaging studies were evaluated with reference to the parenchymal and vascular abnormalities. A complete autopsy was performed in two cases.

The brain was preserved in 10% formalin solution and cut in the coronal plane. Sections were then taken and processed in a routine manner using hematoxylin-eosin stains. Sections of blood vessels were also stained with elastin and trichrome stains. Selected sections were evaluated for presence of bacteria, fungi, and acid-fast bacilli by using Gram's stain, Gomori's methenamine silver stain, and Kinyoun carbolfuchsin stain, respectively.

Case 1

An 18-year-old boy with hemophilia, found to be infected with HIV via a blood transfusion at age 12 years, presented with a catastrophic event (headache, vomiting, disorientation, lethargy). His head CT scan revealed a right frontal intracerebral hematoma and ectasia of the anterior cerebral artery and middle cerebral artery (Fig 1A). The hematoma was evacuated, but the patient died in the postoperative period. Autopsy disclosed multiple fusiform aneurysms involving the major cerebral vessels (Fig 1B). Multiple intracerebral hemorrhages and a residual, partially evacuated cavity in the right frontal lobe were found, along with massive cerebral edema with multiple herniations and Duret lesions. Microscopic study of the major vessels disclosed massive thickening of the wall, primarily related to subintimal fibrosis (Fig 1C). The internal elastic lamina was partially destroyed. Only a few lymphocytes remained in the adventitia of these aneurysmally dilated

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From the Departments of Radiology (S.S.S., R.A.Z.) and Pathology (L.B.R.), the Children's Hospital of Philadelphia (Pa); and the Department of Radiology, Children's National Medical Center, Washington, DC (L.G.V.).

Address reprint requests to Robert A. Zimmerman, MD, Department of Radiology, the Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104.

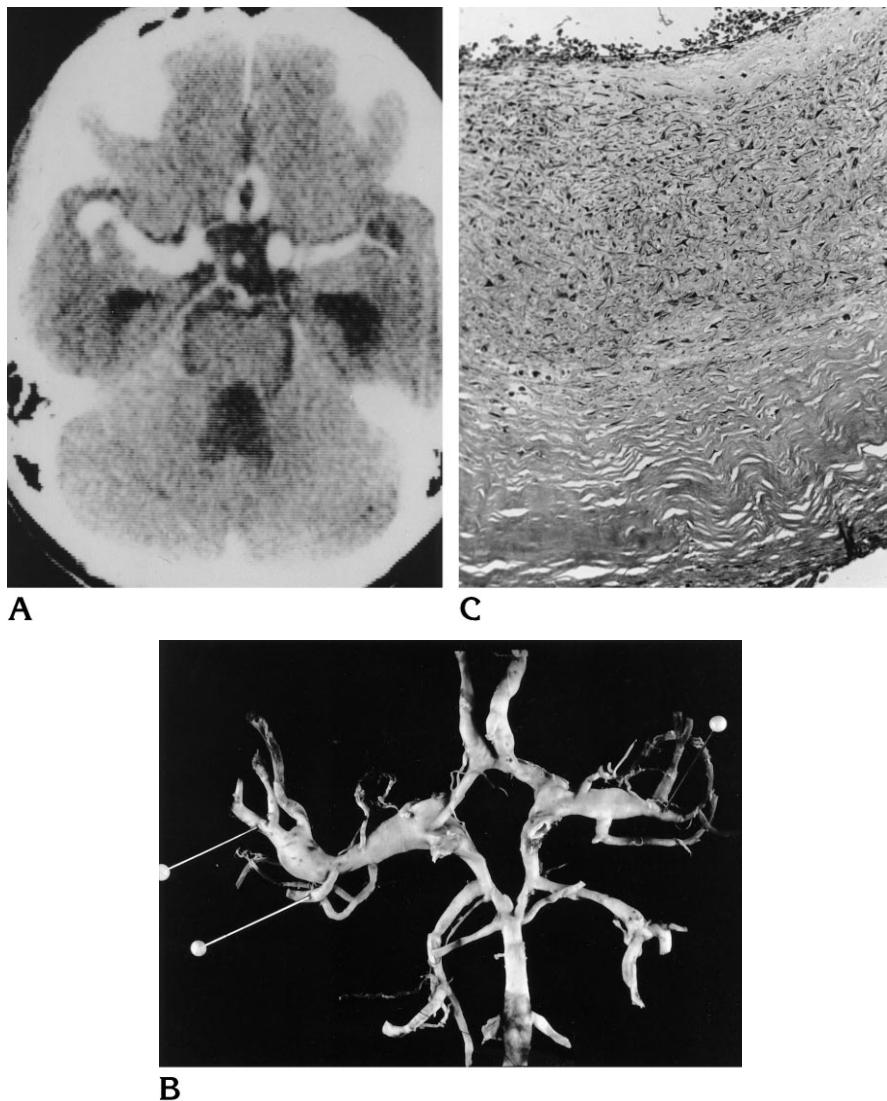
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Fig 1. Patient 1: 18-year-old boy with hemophilia and HIV infection contracted via blood transfusion at age 12.

A, Contrast-enhanced CT scan of the brain shows aneurysmal dilatation of the vessels of circle of Willis. The dilated temporal horns and fourth ventricle are a part of the HIV-related encephalopathy.

B, Autopsy shows major basal cerebral blood vessels, including both internal carotid arteries, circle of Willis, the A2 division of the anterior cerebral arteries, the middle cerebral arteries and branches at bifurcation, the posterior cerebral arteries and several branches, as well as the basilar artery with the superior cerebellar and anterior inferior cerebellar arteries. All vessels are thickened and distended, but fusiform aneurysms of both middle cerebral arteries are especially striking.

C, Trichrome-stained photomicrograph of enormously thickened wall of middle cerebral artery shows fibrocollagenous, redundant thickening of media and extraordinary mesenchymal proliferation of endothelium.



vessels, whereas medium-sized subarachnoid arteries displayed a striking panarteritis, indicating presence of both acute and chronic vasculitis.

Case 2

A 9-year-old girl had contracted AIDS in the perinatal period but did not manifest signs and symptoms of disease until age 8. She presented with decreased level of consciousness and a left hemiparesis. A head CT scan revealed generalized cerebral atrophy with hypodense enhancing lesions in the basal ganglia involving the external capsule and thalamus on the left (Fig 2A). A follow-up scan showed a decrease in the enhancement and mass effect (Fig 2B). Disseminated *Mycobacterium avium-intracellulare* infection and cryptosporidiosis were found. The patient died within 3 days. At autopsy, severe cerebral atrophy was noted, with multiple areas of necrosis of various ages. These were distributed throughout the cerebral hemispheres with more severe involvement of the basal

ganglia. The circle of Willis vasculature was of normal formation, but the right A1 division and left A2 division of the anterior cerebral arteries had a somewhat fibrotic appearance pathologically. The arteries of the circle of Willis were involved by a panvasculitis characterized by endothelial proliferation, medial thickening, and inflammation of the media and adventitia. An incidental B-cell lymphoma was also found.

Case 3

A 12-year-old girl with congenital AIDS manifested signs and symptoms of the disease at age 10 years, when she presented with a fungal infection of the skin. Two years later she presented with fever, seizures, mild weakness of the upper extremities, and drowsiness. A head CT scan revealed multiple nonenhancing hypodense lesions in the cerebral hemispheres, predominantly involving the frontal lobes. The arteries of the circle of Willis and some sylvian vessels were ectatic (Fig 3A). A contrast-enhanced MR

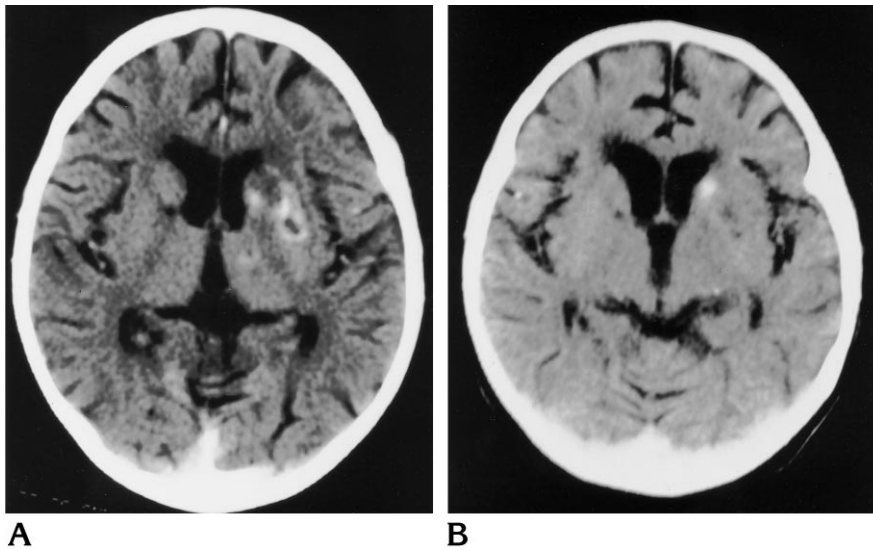


Fig 2. Patient 2: 9-year-old girl with AIDS contracted perinatally.

A, Contrast-enhanced CT scan of the brain shows hypodense, peripherally enhancing lesions in the left basal ganglia.

B, Follow-up contrast-enhanced CT scan 2 weeks after A shows a decrease in the size of the left basal ganglia infarct.

image showed multiple nonenhancing isointense nodular lesions in the brain stem, left thalamus, and supratentorial white matter (Fig 3B). These lesions were isointense on T2-weighted images and were accompanied by perilesional edema (Fig 3C and D). The MR angiogram revealed diffuse aneurysmal dilatation of the internal cerebral arteries, anterior cerebral arteries, middle cerebral arteries, and right posterior cerebral artery. This dilatation extended distally to involve the sylvian branches of the middle cerebral artery bilaterally (Fig 3E). The patient died within 2 months; the family refused to have an autopsy performed.

Discussion

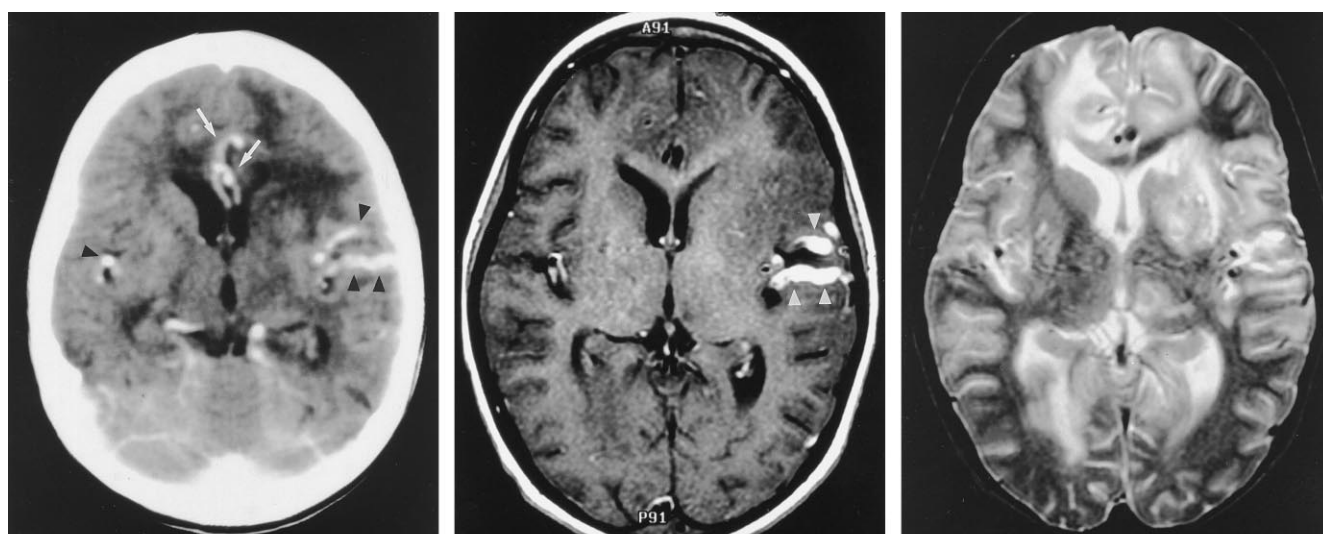
Vertically transmitted HIV infection accounts for about 85% of reported cases of AIDS in children. Another mode of transmission is by blood transfusion. The presence of HIV antibodies passively acquired from the mother until about 15 months (2) makes the diagnosis of AIDS difficult in infants.

The central nervous system (CNS) manifestations of AIDS in children differ markedly from those in adults. These differences have been attributed to an immature immune system (3). Vascular complications in adults usually consist of occlusion associated with emboli, hemorrhage into a neoplasm, or a complication of thrombocytopenia. A basilar tip aneurysm has also been reported (4). Granulomatous angiitis with diffuse segmental narrowing of large and medium-sized vessels in the territories of the anterior, middle, and posterior cerebral arteries associated with ischemic lesions has also been described (5).

It is estimated that ischemic and hemorrhagic strokes occur in 1.3% of children with AIDS (1). Inflammatory vasculopathy with and without calcification is seen (6), with probable infection of the endothelial and perithelial cells. Joshi et al (7) have suggested that elastases from repeated infections may injure the elastic lamina of vessels. We postulate that the inflammation begins in the adventitia and involves the vasa vasorum, which leads to ischemia of the arterial wall, resulting in the destruction of elastic lamina and subintimal fibrosis. This panarteritis with ischemia resulting from damage of the vasa vasorum could then lead to the aneurysmal arterial dilatation and/or sclerosis/stenosis.

An unusual presentation of the arteriopathy is aneurysmal dilatation of the arteries of the circle of Willis. We have read one previously reported case (1) and we are describing two more. One of us has also seen two young adults with HIV who also had vasculitis and fusiform aneurysms at autopsy.

Park et al (1) did immunohistochemical studies of affected blood vessels using a mouse monoclonal antibody to the major transmembrane glycoprotein of HIV, gp41, which revealed positive staining of mononuclear cells throughout the full thickness of the intima but not in the media or adventitia. The abnormal arteries showed marked intimal fibroplasia with medial thinning and elastic lamina destruction or duplication. The histopathologic observations in our patient (patient 1) are similar to these findings. In addition, we observed medium-sized vessels



A

Fig 3. Patient 3: 12-year-old girl with congenital AIDS.

A, Contrast-enhanced CT scan of the brain reveals nonenhancing hypodensities in both frontal lobes and dilatation of the anterior cerebral arteries (arrows) and middle cerebral artery branches in the sylvian fissure (arrowheads).

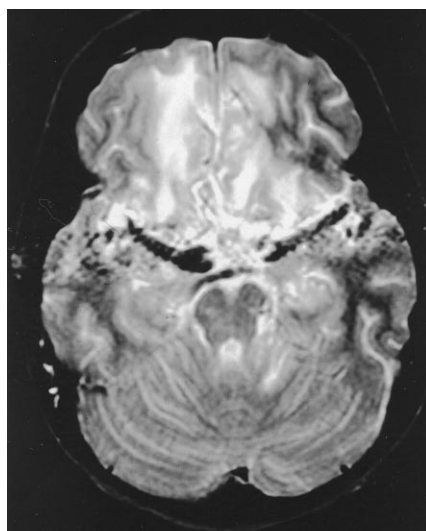
B, Contrast-enhanced axial T1-weighted MR image shows enhancing, dilated middle cerebral artery branches in the left sylvian fissure (arrowheads).

C, Axial T2-weighted MR image shows nodular lesions isointense to cortex in the left basal ganglia with perilesional edema and other poorly defined lesions in the frontal and parietal cortex.

D, Axial T2-weighted MR image shows aneurysmal dilatation of the middle cerebral arteries bilaterally with poorly defined frontal lobe lesions.

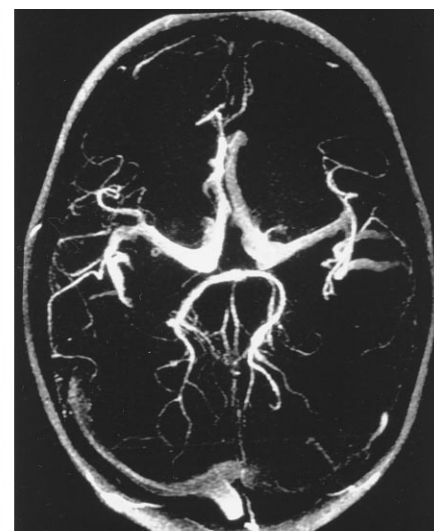
E, Collapsed image of a three-dimensional time-of-flight MR angiogram reveals ectasia of the internal cerebral arteries, anterior cerebral arteries, and middle cerebral arteries bilaterally.

B



D

C



E

that tended to display a more obvious panarteritis.

Park et al (1) proposed that while ischemic lesions are sequelae of intrinsic vascular disease and thrombotic rather than embolic vascular occlusions, hemorrhagic strokes are usually related to a hemorrhagic diathesis. Although hemorrhage was seen in the setting of a vasculopathy in one of our patients (patient 1), this boy had hemophilia as well. The second

patient (patient 3) with aneurysmal dilatation of the vessels had coexistent parenchymal lesions that accounted for her neurologic deficit.

The most common CNS presentation of AIDS in children is encephalitis. It is characterized by generalized parenchymal atrophy, white matter lesions that spare the U-fibers, and symmetric vascular calcifications in the basal ganglia (8). The vascular calcification can be observed as early as 2 months of age and is infrequent in adults.

In adult patients, opportunistic and reactivated latent infections have constituted the largest single category of neuropathologic abnormalities in the various reported series (9). Reactivation is not often seen in pediatric patients, owing to their lack of prior exposure to pathogens (10), which results in a lower rate of infections. However, because of immunosuppression, serious bacterial infections, such as sepsis and meningitis, are encountered. Congenital CNS infections, such as toxoplasmosis, cytomegalovirus, and syphilis, are rare, but they have been reported (9, 10). Seroconversion to JC virus occurs in late childhood or adolescence, accounting for a small number of pediatric patients with progressive multifocal leukoencephalopathy. Three cases have been reported with imaging features identical to those in adult patients with this disease (11–13).

Since patients are now surviving longer, infections that are common in HIV-infected adults can be expected in children as well. One of our patients (patient 3) had imaging findings suggestive of an infection (Fig 3C and D); however, the pathogenesis of these changes was never ascertained because of the lack of autopsy.

Primary CNS lymphoma represents the most common CNS mass lesion in pediatric HIV disease (14). Its frequency in this group is 3% (15), compared with 6% in the adult population (16). Epstein-Barr virus has been implicated as its causative agent. Histologically, these lesions are either small- or large-cell tumors of B-cell origin, similar to those in adults (14). The imaging features of primary CNS lymphoma in children are akin to those described in adults. Usually, they are multicentric tumors, hyperdense on plain CT scans, with frequent enhancement after contrast administration (14, 15, 17). Uncommonly, they may be hypodense with ring enhancement simulating granulomas or abscesses (15, 17). One of our patients had a B-cell lymphoma diagnosed at autopsy that was not visible on the imaging studies.

Conclusion

Cerebral vasculopathy in the pediatric AIDS patient may take the form of vascular ectasia resulting from a destructive-proliferative pro-

cess probably associated with a panarteritis and involvement of the vasa vasorum.

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