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## Moyamoya Syndrome in a Patient With Congenital Human Immunodeficiency Virus Infection

### ABSTRACT

A 10-year-old boy with congenital human immunodeficiency virus (HIV) infection developed recurrent episodes of left hemiparesis at age 7 years. The progression of his disease was followed by computed tomography, magnetic resonance imaging, magnetic resonance angiography, and cerebral angiography. The series of images showed progressive stenosis of both carotid arteries at the suprasellar origin with involvement of his anterior and middle cerebral arteries, while prominent collateral vessels developed from his external carotid supply through ophthalmic and middle meningeal arteries. The pattern of cerebrovascular disease is consistent with moyamoya syndrome. We suggest that further studies on the pathophysiology of cerebrovascular disease in patients with HIV could be helpful in understanding the cause of moyamoya disease as well. Also, with the various advances in treatment of HIV, neurovascular complications could be seen more frequently as the long-term survival in these patients improves. (*J Child Neurol* 1999; 14:268-270).

Stroke has been recognized as a complication of acquired immune deficiency syndrome (AIDS) since the beginning of the epidemic.<sup>1</sup> The incidence of stroke in AIDS in both adults and children is estimated to be about 1.3% per year.<sup>2,3</sup> However, the mechanisms of ischemic stroke in the two populations are felt to be different. Ischemic cerebral infarcts in adults usually are due to nonbacterial thrombotic endocarditis or concomitant opportunistic central nervous system infections,<sup>2</sup> whereas infarcts in children are more likely to be related to arteriopathy of the cerebral vessels.<sup>3-7</sup> On the

other hand, moyamoya disease is much rarer, with an estimated incidence of 0.0001% (1 case in 1 million) per year in Japan<sup>8</sup> and worldwide of about 4000 cases reported over 25 years,<sup>9</sup> although the actual incidence could be higher because of underrecognition. Autopsy studies show that there is intimal and medial thickening of the affected intracerebral vessels without evidence of an inflammatory process,<sup>10</sup> but the cause of the vasculopathy of either disease remains mostly unclear. We describe a patient with moyamoya syndrome with congenital human immunodeficiency virus (HIV) infection without evidence of any other previous or concurrent central nervous system infection, and compare the literature on the histopathology in pediatric patients with AIDS with HIV and moyamoya. Perhaps by learning more about the pathophysiology of cerebrovascular diseases in AIDS, we can gain some insight into the pathophysiology of moyamoya disease as well.

### Case Report

We have followed a 10-year-old Caucasian boy with congenital HIV infection since the age of 7 years because of recurrent episodes of left hemiparesis involving the face, arm, and leg. He was first diagnosed with HIV at 15 months of age. Prior to his neurologic presentation, he was treated with various experimental protocols, including zidovudine (AZT), pentamidine, intravenous immunoglobulin, and didanosine (ddI). He had an episode of chicken pox at age 5 years, and an attack of perianal zoster at age 6 years; both responded well to acyclovir.

At age 7, he came to our attention because of three episodes of transient ischemic attacks over a period of 1 month; one episode involved right arm and face hemiparesis with expressive aphasia, and the other two episodes involved left face, arm, and leg hemiparesis and numbness. He had no evidence of active zoster at that time and his neurologic examination was unremarkable. A head computed tomographic (CT) scan was done and revealed a lacunar infarct in the left caudate nucleus. His cerebrospinal fluid cultures and analyses were unremarkable. His CD4 count was 0/ $\mu$ L. His sedimentation rate was 16, and an antinuclear antibody screen was negative. His serum protein C, protein S, and antithrombin III levels were all normal. His carotid duplex and transthoracic echocardiograms were also normal. A magnetic resonance angiogram showed ectatic changes and narrowing in bilateral supraclinoid internal carotid arteries and middle cerebral arteries. He was placed on aspirin (81 mg/day) for stroke prophylaxis, and his HIV treatment was changed to AZT, ddI, and zalcitabine. During the next year, he was still experiencing about one episode of left hemiparesis exacerbated by exercise every 3 to 6 months. Two follow-up magnetic resonance imaging (MRI) and magnetic resonance angiogram scans showed increased narrowing of his right middle cerebral artery with post-stenotic fusiform dilation.

At age 9 years, the patient had a severe *Pneumocystis carinii* pneumonia infection and dehydration with giardiasis, and he also suffered a stroke with left face, arm, and leg hemiparesis. A repeat work-up showed normal cerebrospinal fluid with polymerase chain reaction (PCR) negative for all herpes viruses. A repeat echocardiogram was also normal. His antiretroviral regimen was changed to lamivudine (3TC), stavudine (d4T), and zalcitabine, and his opportunistic prophylaxis included azithromycin, ganciclovir, trimethoprim/sulfamethoxazole, and fluconazole. His stroke prophylaxis remained 81 mg per day of aspirin. Six months after he began this regimen, his CD4 count improved to 50/ $\mu$ L, and his serum HIV ribonucleic acid (RNA) viral load was less than 500 copies/ $\mu$ L. After this, he was medically stable, was gaining weight and height to the 50th percentile of his age, and was attending mainstream school in grade 4. Neuropsychologic testing showed that his IQ was normal.

At age 10 years, he was re-admitted because of crescendo transient ischemic attacks with left hemiparesis and paresthesia involving his face, arm, and leg. On examination, his blood pressure was 110/70 mm Hg with a regular pulse rate of 84 beats per minute. There were no carotid bruit or cardiac murmurs. Neurologic evaluation was remarkable only for a pronator drift on the left arm, and an extensor plantar response on the left foot.



hypertriglyceridemia, or a combination of the various factors in his complicated history.

Although the epidemiology of strokes in association with AIDS in adults is still unclear,<sup>2</sup> the association in the pediatric population appears to be more definitive.<sup>3-7</sup> In the few available autopsy reports, there seems to be a characteristic histopathologic pattern of vascular changes. Park et al<sup>3</sup> described arteriopathy affecting large vessels of the circle of Willis with intimal fibroplasia with medial thickening and elastic lamina destruction or reduplication. Similar pathologic changes also were described by other groups.<sup>7,19,20</sup> These vascular changes were speculated to be due to HIV itself or HIV-infected cells, because a major HIV transmembrane glycoprotein (gp41) has been detected in the walls of the abnormal arteries of the circle of Willis.<sup>3,16</sup> However, Lang et al<sup>20</sup> did not detect gp41 in such lesions. Interestingly, the pathologic description on moyamoya disease vessels also reveals thickening from smooth muscle cell proliferation in the media and reduplication of the elastic lamina.<sup>10,21,22</sup> This suggests that HIV can induce a central nervous system vasculo-occlusive process that is similar to moyamoya disease. However, it is important to realize that these pathologic changes are nonspecific responses to injury and cannot be regarded as pathognomonic for a specific process. Since many diseases can produce the radiologic findings seen in moyamoya disease, it is not unreasonable to suggest that moyamoya disease is a specific pattern of vascular changes with development of collateral vascular supply in response to a particular insult that resulted in a progressive occlusive disease of the vessels of the circle of Willis. There is active research underway in Japan focusing on the genetic basis of moyamoya disease.<sup>8</sup> Perhaps an occult infectious cause such as HIV with minimal inflammatory response also could be a basis for the disease.

As for the management of our patient, the temporal artery syngangiosis was offered only as an experimental treatment and a last resort, as his symptoms were progressing despite maximum medical treatment. One needs to be aware that data on the long-term effectiveness of the procedure are still very limited. Prior to the recent advances in HIV treatment, neurologic complications were often seen at the terminal stage of AIDS. With the introduction of protease inhibitors, the natural history of HIV-infected patients has changed significantly. Cerebrovascular complications could become more frequent as these patients live longer, and early diagnosis and aggressive management are warranted. Further research on the mechanisms of stroke in AIDS is necessary to improve our understanding and management of these patients' illness.

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