

3. Pratt SG, Beyer CK, Johnson CC: The Marcus Gunn phenomenon. A review of 71 cases. *Ophthalmology* 1984;91:27-30.
4. Chattopadhyay A, Srinivas K, Sharatchandra B, Kannan N: The Marcus Gunn phenomenon: Discussion and report of three cases. *Quintessence Int* 1995;26:563-566.
5. Mrabet A, Oueslati S, Gazzah H, et al: Clinical and electrophysiological study of 2 familial cases of Marcus Gunn phenomenon. *Rev Neurol* 1991;147:215-219.
6. Rana PV, Wadia RS: The Marin-Amat syndrome: An unusual facial synkinesis. *J Neurol Neurosurg Psychiatry* 1985;48:939-941.
7. Marin-Amat, in Geeraets WJ (ed): *Ocular Syndrome*. Philadelphia, Lea & Fibiger, 1978, p 282.
8. Wartenberg R: Inverted Marcus-Gunn phenomenon (so called) Marin-Amat syndrome. *Arch Neurol* 1948;60:584-586.
9. Koike M, Yoshioka H: Case of Marin Amat syndrome. *Ganka* 1969;11:230-233.
10. Kinoshita M, Nakazato H, Satoyoshi E: A case of sarcoidosis with Marin-Amat syndrome. *Nippon Naika Gakkai Zasshi* 1976;65:1437-1440.
11. Lubkin V: The inverse Marcus Gunn phenomenon. An electromyographic contribution. *Arch Neurol* 1978;35:249.
12. Pavesi G, Medici D, Macaluso GM, et al: Unusual synkinetic movements between facial muscles and respiration in hemifacial spasm. *Mov Disord* 1994;9:451-454.

## 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 nevirapine. 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), starvudine (d4T), and ritonavir, 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.

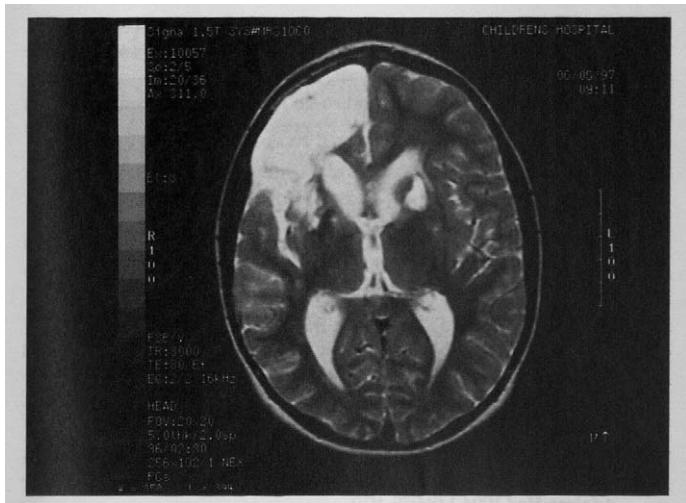


Figure 1.  $T_2$ -weighted magnetic resonance image ( $T_R$ -3000,  $T_E$ -80) showing a large right frontal lobe infarct with associated encephalomalacia, and a smaller infarct in the left caudate nucleus.

Laboratory data showed normal complete blood count, electrolytes, and coagulation profile. His CD4 count had increased to 344/ $\mu$ L, and his serum HIV viral load remained less than 500 copies/ $\mu$ L. Cerebrospinal fluid showed three red blood cells/ $\mu$ L, four white blood cells (monocytes)/ $\mu$ L, protein level of 16 mg/dL, and glucose level of 89 mg/dL (serum glucose 118 mg/dL). Polymerase chain reaction for herpes simplex virus 1 and 2, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and human herpes virus-6 were all negative. Additional studies were done (including protein C, protein S, antithrombin III, the Venereal Disease Research Laboratory test, factor V DNA, antimicrobial antibodies, rheumatoid factor, lupus inhibitor, and anticardiolipin antibodies), but did not identify any other causes for strokes. However, the serum level of triglyceride was found to be elevated to 282 mg/dL, although serum cholesterol levels were normal. An MRI showed a large right frontal lobe infarct with encephalomalacia from his stroke during his last intensive care unit stay (Figure 1). A magnetic resonance angiogram showed occlusion of right anterior and middle cerebral arteries. The cerebral angiogram confirmed these lesions and showed that there were prominent collaterals

developing from the external carotid system (Figure 2). The patient was placed temporarily on heparin and was treated with warfarin adjusted to an INR between 2 to 3. After 3 months, he experienced recurrence of transient ischemic attacks with left face and arm hemiparesis and dysesthesia. A single photon emission computed tomographic scan and transcranial Doppler with acetazolamide challenge showed a limited vascular reserve; therefore, a right superficial temporal artery synangiosis procedure was offered as an experimental treatment. Six months after the operation, the patient had a transient ischemic attack involving the right side, and repeat MRI showed progressive narrowing of his left middle cerebral arteries. He was offered a second synangiosis procedure on the left side. Currently, 6 months after the second operation, the patient is stable with no new neurologic symptoms.

### Discussion

Moyamoya disease is a rare, chronic occlusive disease of the cerebrovascular system involving the circle of Willis. The diagnostic guideline as defined by the Ministry of Health and Welfare of Japan involves four criteria<sup>11</sup>: (1) stenosis or occlusion of the intracranial internal carotid artery or the adjacent anterior and middle cerebral arteries, (2) abnormal vascular network adjacent to the stenosed artery identified during the arterial phase of angiography, (3) bilateral findings on angiography, and (4) no other identifiable cause. Because of the 4th criterion, the term moyamoya syndrome, or phenomenon, is used to distinguish from moyamoya disease caused by the presence of other associated diseases. These include neurofibromatosis, post-irradiation, tumor, Down syndrome, atherosclerosis, antiphospholipid syndrome, autoimmune vasculitis, and leptospiral infections.<sup>8,12</sup> One pathologic case was described in a patient with AIDS and quaternary neurosyphilis.<sup>13</sup> In the case of our patient, we have looked exhaustively for any other cause that could explain his cerebrovascular disease. There is no evidence of any of the previously described associated diseases in our patient. However, our patient did have a history of varicella infection, which has been described to be associated with acute hemiplegia of childhood and strokes in adults,<sup>14,15</sup> but we were unable to find evidence of active infection with repeated normal cerebrospinal fluid that was negative PCR for varicella-zoster virus. Other possible confounding variables include the unknown long-term effects of the antiretrovirus medications and the effects of intravenous immunoglobulin, which he received monthly for about 5 years, but these have never been reported to cause changes in the cerebral vasculature. Another abnormality noted in our patient's work-up was the elevated triglyceride level. Some recent studies suggest that hypertriglyceridemia can be an independent risk factor for atherothrombotic cerebrovascular disease in adult patients.<sup>16,17</sup> However, recent reports suggest that the elevated triglycerides could be an effect of the protease inhibitor rather than a primary endocrine abnormality.<sup>18</sup> This would make atherosclerosis an unlikely cause of strokes in a 10-year-old boy with no other evidence of cardiac or peripheral vascular disease. One could argue that he could have moyamoya disease independent of his HIV infection, but based on the low incidence of the disease, especially in the Caucasian population, this would be an unlikely coincidence. We suspect that active HIV infection, either independently or with influence from a past varicella-zoster virus infection, played a significant role in the cause of the cerebrovascular changes in our patient. Nevertheless, it is possible that the etiology is multifactorial, with influence from the long-term use of multiple medications, his

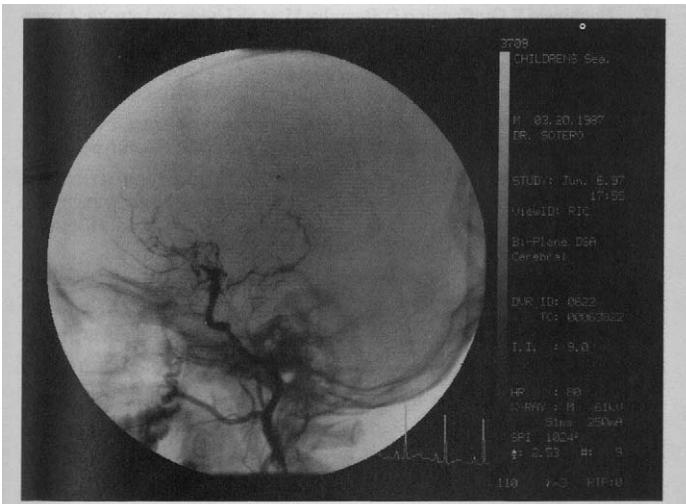


Figure 2. Digital subtraction angiogram of right internal carotid artery, lateral view, showing ectatic changes of the supraclinoid internal carotid artery, occlusion of both right anterior and middle cerebral arteries, and partial reconstitution of the right middle cerebral artery by branches of the lenticulostriate arteries.

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 vaso-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 synangiosis 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.

Ging-Yuek R. Hsiung, MD

Marcio Sotero de Menezes, MD

Departments of Neurology and Pediatrics  
University of Washington  
Seattle, Washington

Received May 27, 1998. Received revised Sept 22, 1998. Accepted for publication Sept 28, 1998.

Address correspondence to Dr Sotero de Menezes, Children's Hospital and Medical Center, Department of Neurology, Seattle, WA 98105. Tel: 206-526-2078; fax: 206-528-2649.

## References

1. Snider WD, Simpson DM, Nielsen SL, et al: Neurological complications of acquired immunodeficiency syndrome: Analysis of 50 patients. *Ann Neurol* 1983;14:403-418.
2. Pinto AN: AIDS and cerebrovascular disease. *Stroke* 1996;27:538-543.
3. Park YD, Belman AL, Kim TS, et al: Stroke in pediatric acquired immunodeficiency syndrome. *Ann Neurol* 1990;28:303-311.
4. Burns DK: The neuropathology of pediatric acquired immunodeficiency syndrome. *J Child Neurol* 1992;7:332-346.
5. Philippet P, Blanche S, Sebag G, et al: Stroke and cerebral infarcts in children infected with human immunodeficiency virus. *Arch Pediatr Adolesc Med* 1994;148:965-970.
6. Moriarty DM, Haller JD, Loh JP, Fikrig S: Cerebral infarcts in pediatric acquired immunodeficiency syndrome. *Pediatr Radiol* 1994;28:611-612.
7. Shah SS, Zimmerman RA, Rorke LB, Vezina LG: Cerebrovascular complications of HIV in children. *Am J Neuroradiol* 1996;17:1913-1917.
8. Fukui M: Current state of study on moyamoya disease in Japan. *Surg Neurol* 1997;47:138-143.
9. Goto Y, Yonekawa Y: Worldwide distribution of moyamoya disease. *Neurol Med Chir (Tokyo)* 1992;32:883-886.
10. Suzuki J: *Moyamoya Disease*. Berlin, Springer-Verlag, 1986.
11. Nishimoto A: Moyamoya disease. *Neurol Med Chir (Tokyo)* 1979;19:221-228.
12. Nichols FT: Moyamoya disease, in *Neurobase CD-ROM*. Detroit, University of Michigan, 1997.
13. Morgello S, Laufer H: Quaternary neurosyphilis in a Haitian man with human immunodeficiency virus infection. *Hum Pathol* 1989;20:808-811.
14. Caekebeke JF, Peters AC, Vandvik B, et al: Cerebral vasculopathy associated with primary varicella infection. *Arch Neurol* 1990;47:1033-1035.
15. Hilt DC, Buchholz D, Krumholz A, et al: Herpes zoster ophthalmicus and delayed contralateral hemiparesis caused by cerebral angiitis. *Ann Neurol* 1983;14:543-553.
16. Pan WH, Chiang BN: Plasma lipid profiles and epidemiology of atherosclerotic disease in Taiwan—a unique experience. *Atherosclerosis* 1995;118:285-295.
17. Hachinski V, Graffagnino C, Beaudry M, et al: Lipids and stroke: A paradox resolved. *Arch Neurol* 1996;53:303-308.
18. Miller KD, Jones E, Yanovski JA, et al: Visceral abdominal fat accumulation associated with use of indinavir. *Lancet* 1998;351:871-875.
19. Kure K, Llena J, Lyman W, et al: Human immunodeficiency virus-1 infections of the nervous system: An autopsy study of 268 adult, pediatric, and fetal brains. *Hum Pathol* 1991;22:700-710.
20. Lang C, Jacobi G, Kreuz W, et al: Rapid development of giant aneurysm at the base of the brain in an 8-year-old boy with perinatal HIV infection. *Acta Histochem* 1992;42(Suppl):83-90.
21. Hosoda Y: Pathology of so-called "spontaneous occlusion of the circle of Willis." *Pathol Annu* 1984;19(Pt 2):221-244.
22. Masuda J, Ogata J, Yatani C: Smooth muscle cell proliferation and localization of macrophages in T-cells in the occlusive major arteries in moyamoya disease. *Stroke* 1993;24:1960-1967.