

## Case of Moyamoya Disease in a Patient With Advanced Acquired Immunodeficiency Syndrome

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**Background:** Moyamoya disease is an occlusion of the terminal portion of internal carotid arteries and proximal portion of middle and anterior cerebral arteries of unknown origin. Moyamoya syndrome is associated with meningitis, tuberculosis, syphilis, head trauma, head irradiation, brain tumor, von Recklinghausen's disease, tuberous sclerosis, Marfan syndrome, sickle cell anemia, arteriosclerosis, hypertension, and oral contraceptive use. To our knowledge, acquired immunodeficiency syndrome (AIDS) as a cause of moyamoya syndrome has not been reported in an adult population. **Objective:** We report a case of moyamoya syndrome in a patient with AIDS and without other conditions associated with occlusion of the circle of Willis and formation of collateral network at the base of the brain and basal ganglia. **Methods:** We present a case report. **Results:** A 29-year-old woman with an 8-year history of AIDS on multiple antiretroviral medications presented with recurrent tingling of the left extremities which 1 month later progressed to mild hemiparesis and dysarthria. During the next few months the patient developed progressive cognitive decline and on-and-off fluctuations in the degree of hemiparesis. Brain magnetic resonance imaging showed multiple small subcortical infarct's in both parietal lobes. Magnetic resonance angiography showed occlusion of middle cerebral arteries distal internal carotid arteries, with prominent collateral network. Cerebral angiography confirmed moyamoya pattern. Lumbar puncture showed: white blood cell count 1, red blood cell count 418, protein 56, glucose 53, negative bacterial and acid-fast bacilli smear and culture, negative VDRL test, India ink, cryptococcal antigen, cytology and negative polymerase chain reaction for cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, and herpes simplex virus type 1 and 2. Electroencephalography showed diffuse background slowing. **Conclusions:** We hypothesize that human immunodeficiency virus (HIV) caused central nervous system vasculitis, which eventually led to formation of moyamoya pattern. No other definite causes of central nervous system vasculitis were found in our patient. Cerebrovascular disorders should be considered in patients with HIV/AIDS with focal neurologic deficit. Moyamoya syndrome as a cause of stroke should be considered in patients with HIV/AIDS, especially as survival improves. **Key Words:** Stroke—moyamoya disease—acquired immunodeficiency syndrome.

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Moyamoya disease is an occlusion of the circle of Willis of unknown origin associated with the formation of collateral network at the base of the brain and basal gan-

glia.<sup>9-11</sup> Occlusion of the terminal portion of internal carotid arteries (ICAs) and proximal portion of middle cerebral arteries (MCAs) and anterior cerebral arteries are

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characteristic.<sup>12,15</sup> The posterior circulation involvement is not typical but is reported.<sup>29</sup> It is diagnosed primarily by magnetic resonance (MR) angiography, cerebral angiography, or both. A similar radiographic picture is found in certain systemic infections, autoimmune, hematologic, metabolic, genetic/chromosomal disorders, and neoplasms. This condition is called "moyamoya syndrome." Disorders associated with moyamoya syndrome are: leptospirosis, tuberculosis, sickle cell anemia, thalassemia, aplastic anemia, lupus anticoagulant, glycogen storage disease (type 1), hyperlipoproteinemia (type 2A), hyperthyroidism, pseudoxanthoma elasticum, neurofibromatosis, tuberous sclerosis, retinitis pigmentosa, sellar and parasellar tumors (craniopharyngioma, optic glioma), Sjögren's syndrome, fibromuscular dysplasia, cranial trauma, cranial irradiation, and oral contraceptive use.<sup>13,15,16,18</sup>

The age of onset of moyamoya disease peaks at 5 years (juvenile type) and 30 to 40 years (adult type).<sup>15</sup> It presents with cerebral infarct (CI) at an early age because of hypoperfusion of certain areas of the brain through stenotic cerebral vessels, and intracerebral hemorrhage (ICH) later in life as a result of a rupture of the collaterals.<sup>11,15</sup> It may manifest with a variety of symptoms and signs: headache; seizures; motor, sensory, and speech deficits; involuntary movements; disturbance of consciousness; psycho-organic syndrome; and mental retardation.<sup>14,15,19</sup>

Pathology of moyamoya disease is unclear. It was found that basic fibroblast growth factor (bFGF) is increased in the vessels of patients with moyamoya disease. bFGF concentration in cerebrospinal fluid (CSF) is significantly higher in patients with moyamoya disease than in patients with arteriosclerotic cerebrovascular occlusive disease and spinal disk disease.<sup>15,21</sup> There is increased activity of bFGF and bFGF receptors in the superficial temporal artery obtained during bypass surgery in moyamoya disease. It is possible that bFGF induces smooth-muscle proliferation with inflammatory response and progressive narrowing of the vessels of the circle of Willis.<sup>12</sup> Stenosis of intracranial arteries leads to the development of collaterals at the base of the brain and basal ganglia.<sup>12</sup> When collaterals become insufficient, cerebral ischemia develops. Hemodynamic stress leads to the formation of microaneurysm and berry aneurysm formation.<sup>12</sup> Cerebral aneurysm is found in 4% to 14% of patients with moyamoya disease.<sup>15</sup> Rupture of the microaneurysm and berry aneurysm causes ICH and subarachnoid hemorrhage.<sup>12</sup>

There are reports that elastin synthesis is increased in patients with moyamoya disease compared with control subjects.<sup>24</sup> Yamamoto et al<sup>24</sup> suggest that moyamoya disease results from abnormal regulation of extracellular matrix metabolism with increased steady levels of elastin messenger RNA, elastin accumulation, and intimal thickening. Elastin accumulation is a

marker of vascular smooth-muscle cell change in patients with moyamoya disease.<sup>24</sup> Possible genetic predisposition to moyamoya disease may be marked by major histocompatibility complex HLA antigen 2. DRB1 1601 is significantly higher in the age group younger than 10 years, and DRB1 0201 is significantly higher in the age group older than 10 years.<sup>25</sup>

Treatment of moyamoya disease consists of antithrombotic medications that prevent ischemic events by influencing progression of vascular stenosis. Surgical treatment consists of revascularization procedures aimed at augmenting cerebral blood flow.<sup>9,11,12,15</sup>

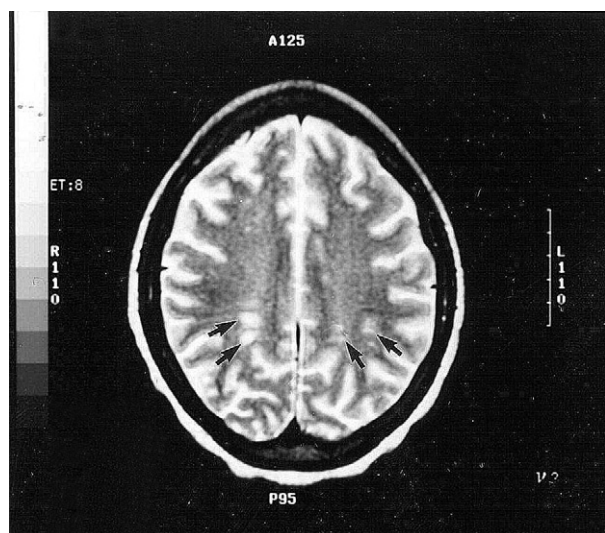
We describe a case of moyamoya disease in a patient with (human immunodeficiency virus) HIV/AIDS. No other definite causes of moyamoya syndrome had been identified in our patient. To our knowledge, association between moyamoya disease and acquired HIV infection in adult patient has not been reported. Hsiung et al<sup>5</sup> described a case of moyamoya syndrome in a 10-year-old child with congenital HIV infection, manifested by recurrent hemiparesis.

Morgello and Laufer<sup>1</sup> reported a case of 22-year-old Haitian man with a 15-month course of chronic progressive meningitis associated with multiple CIs. He died 5 months after he had been given the diagnosis of moyamoya syndrome by cerebral angiography. The autopsy showed that the patient had meningovascular syphilis with necrotizing encephalitis and massive treponemal invasion of the brain, which is consistent with "quaternary" neurosyphilis. On postmortem examination he was also found to have HIV DNA in the brain by dot blot hybridization and retrovirus-like particles by electron microscopy. Moyamoya disease in this case was ascribed to an advanced syphilis that is an established cause of moyamoya syndrome. Diagnosis of postmortem HIV infection in this patient was considered to be a provoking factor for massive central nervous system (CNS) involvement by syphilis.<sup>1</sup>

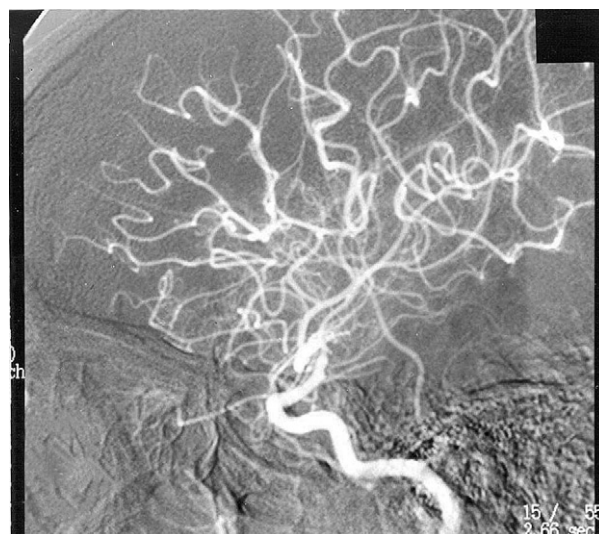
## Case Report

A 29-year-old African American woman with HIV infection of 9 years' duration and advanced AIDS, with CD4 count fluctuating between 8 and 31  $\mu$ L for the last 6 months, was admitted to the HIV service of our hospital with hemolytic anemia and vaginal bleeding. The patient also had history of syphilis diagnosed 4 years before this presentation and treated with intravenous ceftriaxone (2 g every 12 hours) for 4 weeks (she was treated as having neurosyphilis despite negative test results on multiple CSF VDRL tests). A neurology service consult was requested 3 days after current admission for patient's symptom of left arm tingling and tingling of the left half of her tongue. According to the patient, it had started 3 weeks before admission and was episodic in nature,

lasting from minutes to hours and recurring weekly. Her medications included ritonavir, stavudine, lamivudine, azithromycin, and erythropoietin. Her physical examination was significant for systolic murmur, splenomegaly, and hepatomegaly. Neurologic examination revealed normal findings, as did noncontrast computerized tomography of the head. The patient was given the diagnosis of simple partial sensory seizures, and phenytoin (300 mg/day) was started. Electroencephalography and contrast-enhanced MR imaging of the brain were suggested but not performed because the patient left the hospital against medical advice. She was readmitted to HIV service 3 weeks later with generalized weakness, diarrhea, and abdominal discomfort. Above symptoms were self-limited, resolved in 2 days, and no further work-up was necessary because diarrhea, generalized weakness, and abdominal discomfort are frequent in patients with HIV. Neurologic examination at that time revealed mild left hemiparesis (4/5) and left hemisensory loss. Spinal tap was performed at that time. CSF analysis showed 1 white blood cell and 418 red blood cells – traumatic tap, protein 56, glucose 53, negative bacterial and acid-fast bacilli smear and culture, negative VDRL test, India ink, cryptococcal antigen, cytology and negative polymerase chain reaction for cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, and herpes simplex virus type 1 and 2. Electroencephalography showed diffuse background slowing and no epileptiform activity. Brain MR imaging (Fig 1) showed multiple small subcortical infarcts in both parietal lobes. MR angiography of intracranial vessels showed occlusion of proximal MCAs and distal ICAs, with prominent collateral network. Cerebral angiography (Fig 2) confirmed a moyamoya pattern. The patient was given the diagnosis of moyamoya disease and aspirin (325 mg/day) was started.



**Figure 1.** T2-weighted MR imaging of brain shows multiple subcortical infarcts (arrows) in both parietal lobes.



**Figure 2.** Conventional cerebral angiography, lateral view, shows occlusion of distal ICAs, MCAs, and prominent collateral network.

She was re-evaluated 3 weeks later in the neurology clinic. Neurologic examination at that time showed flat affect, diminished attention and concentration, decreased short-term memory 1/3 at 3 minutes, and difficulty with abstract thinking and spelling. Our patient did not have aphasia or dysarthria but was extremely slow in her answers and was inattentive. In addition to previously noted mild left hemiparesis and left hemisensory loss, she had mild left central facial palsy, dysmetria on left finger-nose test out of proportion to weakness, and dystonic posturing of the left hand. The patient was lost for follow-up in our clinic and reappeared on our HIV service 4 months later with worsening of anemia and bronchitis. At that time she was not taking antiretroviral medications as a result of noncompliance. Her neurologic examination showed progressive cognitive decline in addition to left hemiparesis. The patient's cognitive impairment and inattention, and left hemiparesis, fluctuated in severity. She had episodes of worsening of left hemiparesis and stupor.

During this admission she refused blood transfusions for anemia and was transferred to a nursing home because she could no longer take care of herself.

Two months later she was readmitted to our hospital for repair of rectovaginal fistula. Her neurologic examination at that time showed further progression of cognitive deficit, increased left hemiparesis, and periods of stupor lasting hours to days. She died suddenly 4 months later in the nursing home while watching television. Autopsy was not performed.

## Discussion

Association between AIDS and cerebrovascular disorders (CVD) is uncertain.<sup>2-6,8,22,23</sup> Forty percent of patients

with AIDS, have neurologic complications, and only 1.3% of them have cerebrovascular disorders.<sup>2</sup> True incidence of cerebrovascular complications in AIDS is difficult to establish because of a high rate of association of HIV infection with opportunistic bacterial, viral, and spirochetal infections of the CNS that also produce cerebral vessel involvement.<sup>7,17,26-28</sup> The CNS in AIDS is affected by direct infection of CNS cells with HIV, and by opportunistic infections or neoplasms. There is also clinical and histopathologic evidence suggesting that HIV infection may cause inflammatory vascular disorders.<sup>20,26</sup> HIV infection can cause CNS vasculitis with subsequent strokes.<sup>1,5-8,26,27</sup> Different mechanisms are implicated in pathogenesis of CNS vasculitis in HIV/AIDS, including infection of endothelial cells by HIV or other infectious agents, immune complex deposition, and dysregulation of cytokines and adhesion molecules. It is not clear whether vasculitis is caused by HIV itself, some associated viral structure, or unusual endothelial reaction to the virus.<sup>27</sup> Besides vascular inflammation, protein S deficiency and vasospasm may be other pathogenetic mechanisms of cerebrovascular complications in AIDS.<sup>8</sup> Expression of CVD in AIDS consists of CI, transient ischemic attacks, and ICH.<sup>2,3,8</sup> CI seems to be more frequent than ICH.<sup>2</sup> ICHs are usually associated with thrombocytopenia, primary CNS lymphoma, and metastatic Kaposi's sarcoma. CIs are associated with nonbacterial thrombotic endocarditis and opportunistic CNS infections. The role of antiphospholipid antibodies, including anticardiolipin antibodies, in pathogenesis of stroke in HIV/AIDS is uncertain.<sup>2</sup> To our knowledge, moyamoya syndrome as a complication of AIDS has not been reported in an adult patient population.

We hypothesize that in our case HIV infection induced CNS vasculitis that eventually led to moyamoya pattern formation. HIV infection has been described previously as a cause of CNS vasculopathy.<sup>2,4,8,26,27</sup> No other definite causes of CNS vasculitis were found in our patient. Polymerase chain reaction for DNA of cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, and herpes simplex virus type 1 and 2 in CSF revealed negative findings. Acid-fast bacilli smear and culture results had been negative in CSF as well. Even though our patient was given the diagnosis of syphilis 4 years before diagnosis of moyamoya syndrome, VDRL test in CSF had produced negative results on multiple occasions in the past and during recent admissions. In addition, despite negative CSF VDRL test results, the patient was treated with intravenous ceftriaxone for 4 weeks in the past because of AIDS and the possibility of developing CNS syphilis. Serum rapid plasma reagin (RPR) was always reactive at a very low titer (1:1), including time of initial diagnosis and after treatment, and never increased to higher numbers. It is common practice to consider a patient treated if RPR titers do not increase, because treatment of syphilis is difficult in AIDS populations, and, in the experience of

our HIV service, RPR titers usually do not reverse to zero even after treatment. Anticardiolipin antibodies were in a normal range and lupus anticoagulant was negative in the patient's serum. Our patient had hemolytic anemia presumably as a result of AIDS and antiretroviral medications. To our knowledge, hemolytic anemia is not listed as a cause of moyamoya syndrome. Besides, our patient's anemia was not long standing and it is long-standing anemia that is necessary for moyamoya pattern formation.

It is possible that, in our patient, HIV infection had caused CNS vasculopathy, which eventually led to the formation of moyamoya pattern. Despite 9 years of HIV diagnosis and aggressive treatment with the addition of new available antiretrovirals to the regimen, it is possible that our patient did not receive optimal treatment because she did not adhere to the regimen. Besides, antiretroviral medications were periodically stopped because of worsening of hemolytic anemia (it was thought that worsening of patient's anemia was at least partially related to antiretroviral medications). CVD should be considered in patients with HIV/AIDS with focal neurologic deficit. Moyamoya syndrome as a cause of stroke should be considered in patients with HIV/AIDS, especially as survival improves. More research is necessary on vascular presentation of HIV infection, cerebral vasculitis, its causes, and natural course in patients with HIV/AIDS.

At this point, our impression is that HIV infection caused cerebral vasculopathy, which led to moyamoya syndrome. It is quite possible that in future, as knowledge about AIDS accumulates, we will find that cerebral vasculopathy leading to moyamoya syndrome is caused by another agent, similar to the story of Kaposi's sarcoma, which was thought to be caused by HIV, but now we know that it is caused by human herpesvirus 8. It is also possible that we will see more cases of moyamoya syndrome in patients with AIDS as survival increases, and diagnosis of moyamoya disease improves.

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