Moyamoya disease is a chronic, progressive occlusion of the circle of Willis arteries that leads to the development of characteristic collateral vessels seen on imaging, particularly cerebral angiography. The disease may develop in children and adults, but the clinical features differ. Moyamoya disease occurs predominately in Japanese individuals but has been found in all races with varying age distributions and clinical manifestations. As a result, moyamoya disease has been underrecognized as a cause of ischemic and hemorrhagic strokes in Western countries. At this time, there is no known cure, and existing treatment options are controversial. The authors describe the case of a 44-year-old African American woman with a history of hypertension, cervical cancer, breast cancer, and stroke who was diagnosed as having moyamoya disease. A review of the literature for the various facets of this condition is also provided.

Moyamoya disease was first described in Japan by Takeuchi and Shimizu in 1957. Although the disease is most common in Japan, many subsequent cases have been reported elsewhere, including North America and Europe.

Moyamoya disease is deemed a progressive steno-occlusive disease at terminal portions of the bilateral internal carotid arteries with the development of “moyamoya vessels” as collateral channels of circulation. The appearance of these small, multiple vessels at the base of the brain on catheter angiography was originally described by the Japanese term moyamoya, which translates to “puff of smoke.”

According to a 1998 report, which provided the most recent data available, a total of 239 cases of moyamoya disease had been reported in the United States as of 1996. With disease progression, patients—children and adults—are likely to suffer ischemic or hemorrhagic stroke. Although moyamoya syndrome has the same angiographic appearance as moyamoya disease, it is associated with other medical conditions such as arteriosclerosis, autoimmune disease, Down syndrome, head trauma, meningitis, neurofibromatosis type 1, and previous radiation therapy.

In the present report, we describe an African American woman who had a seizure after a surgical procedure. She was later diagnosed as having moyamoya disease. In light of this report, we review the literature on this condition.

Report of Case
A 44-year-old African American woman presented to the hospital for elective surgical placement of a cervical sleeve by her gynecologist-oncologist to allow for radiation treatment of her cervical cancer. After the procedure, while the patient was recovering in the inpatient unit, she suddenly had a seizure. According to the patient’s mother, who was one of the witnesses to the seizure, the patient exhibited tonicoclonic movements of the bilateral arms with concurrent jerking of the head. The seizure lasted approximately 45 seconds. The patient was disoriented and weak after the episode. She did not have associated bowel or bladder incontinence or tongue or cheek biting during the seizure.

On evaluation, the patient stated that she had a similar episode 3 months ago and it was diagnosed as an ischemic stroke. Other than her elective cervical sleeve placement on the day of admission, her surgical history included lumpectomy 10 years ago for breast cancer. The patient’s home medications included nifedipine, lisinopril, and hydrochlorothiazide. She had no known drug allergies. Her family history was notable for hypertension in her mother. The patient denied any family history of stroke, seizure, or cancer. Socially, the patient was unemployed and lived with her husband. She did not smoke cigarettes, consume alcohol, or use illicit drugs.

On physical examination, the patient had a pleasant disposition, was in no acute distress, and was awake, alert, and oriented to person, place, and time. She was obese, with a body mass index of 33.2. Vital signs (blood pressure, 144/88 mm Hg; body temperature, 98.8°F; heart rate, 104 beats per min) were notable for hypertension and tachycardia. Head, neck, and respiratory examinations were unremarkable (respiratory rate, 14 breaths per min; oxygen saturation, 98% on room air). Cardio-
vascular examination revealed tachycardia with regular rhythm. Findings from examinations of the abdomen, skin, extremities, and musculoskeletal system were within normal limits. On neurologic examination, the second through seventh cranial nerves were intact and without focal deficits. Equal sensation and strength was noted in the bilateral upper and lower extremities, and deep tendon reflexes were normal. The patient’s gait was normal with no signs of cerebellar dysfunction.

Results of a complete metabolic panel on admission for the elective cervical sleeve placement were notable for hypokalemia and hypomagnesemia, which were corrected and remained within normal limits for the duration of the patient’s hospital visit. Complete blood cell count showed normocytic anemia with normal leukocyte and platelet counts. Coagulation studies were within normal limits, and hypercoagulable workup was also normal. Specific tests for hypercoagulability disorders included activated protein C resistance, anticardiolipin antibody, antithrombin III, basal homocysteine, complete blood count (with examination of the peripheral smear), D dimer, Factor V Leiden, fibrinogen, lupus anticoagulant, partial thromboplastin time, protein S, prothrombin time, and thrombin time. Results were normal for all of these studies.

Diagnostic studies included a chest radiograph, which was unremarkable, and an electrocardiogram, which showed sinus tachycardia at 115 beats per minute. A magnetic resonance image (MRI) of the brain with and without gadolinium contrast revealed a moderate amount of increased signal in the periventricular white matter regions bilaterally. In addition, there was no evidence of any abnormal enhancement or mass or any acute or subacute infarction.

The radiologic differential diagnoses, given the rather prominent increased signal intensity in the periventricular white matter, suggested the possibility of a demyelinating process such as multiple sclerosis or chronic periventricular white matter leukomalacia secondary to small vessel ischemic disease, and deep white matter infarction commonly seen with hypertension, vasculitis, and diabetes.

A magnetic resonance angiogram (MRA) of the brain later exposed the absence of the middle and anterior cerebral arteries bilaterally. Marked hypertrophy of the lenticulostriate arteries bilaterally was also visible. These arteries were very large in caliber distally, concurrently revealing collateralization of the posterior cerebral arteries to the anterior cerebral artery distribution over the convexity (Figure 1). In addition, a lateral view displayed the occlusion of the middle cerebellar arteries and anterior cerebellar arteries proximally (Figure 2).

On day two of admission, the patient remained asymptomatic without further alteration in mentation or seizure-like activity. A computed tomography angiogram of the head and neck was performed to further delineate the architecture of the patient’s arterial system. Thin axial images of the neck using 150 cm$^3$ of iopamidol demonstrated the right vertebral artery to be much smaller than the left with unremarkable common carotid arteries. Axial images of the brain showed unremarkable cavernous carotid arteries as well as normal appearing basilar artery. Both posterior cerebral arteries were seen. However, the anterior cerebral arteries were not viewed and atresia of the proximal anterior middle cerebral arteries was present.

The constellation of these computed tomography angiogram findings combined with the findings of the brain
studies of patients with moyamoya disease have shown between children and adults. In Japan, children typically present with symptoms attributed to slowly progressive cerebral hypoperfusion and repetitive ischemic symptoms, whereas adults have hemorrhagic events. However, large series studies of patients with moyamoya disease have shown that more than one-third of adults with moyamoya disease present with ischemic events.

In patients with intracerebral hemorrhage, bleeding is commonly observed in the frontal horn of the lateral ventricle, basal ganglia, and thalamus. This is caused by the rupture of abnormal, thin-walled collaterals (moyamoya vessels) or aneurysms. Chiu et al found that 5 of 6 patients with moyamoya disease who presented with intracranial hemorrhage also had an intraventricular bleeding site. Thus, moyamoya disease should be suspected in such patients given this locale of bleeding.

Although the predilection for ischemic strokes in children and hemorrhagic strokes in adults has been reported in Japan, Chiu et al found that at the University of Texas-Houston, ischemic events were the most common presentations in both children and adults.

The differences in presentation between North American and Asian patients may be related to the timing of the vasculopathy. In other words, ischemic symptoms may arise soon after the onset of arterial narrowing or occlusion. These symptoms present later in the US population. It is likely that moyamoya disease has a different clinical expression in the United States than Asia. Furthermore, the studies performed in the United States did not have the preponderance of hemorrhagic stroke that was documented in Japan and South Korea. However, it is possible that a higher percentage of Asian patients in a given region may result in the observed regional prevalence of moyamoya disease.

Neurologic deficits in patients with moyamoya disease are extensive and diverse. Clinically, the presentation of patients with moyamoya disease may include seizures, transient ischemic attacks, ischemic strokes, and hemorrhagic strokes.

In a Washington State and California study of nearly 300 patients—children and adults—with moyamoya disease, 53% of patients had at least one of the following events recorded during hospitalization: seizure, 22%; ischemic stroke, 21%; intracerebral hemorrhage, 15%; subarachnoid hemorrhage, 6%; or transient ischemic attack, 5%. In fact, 13% of the same patient population had two of these events recorded. Visual deficits, speech disturbance, headache, intellectual deterioration, cranial nerve palsies, and disturbance of gait can also be evident.

Possibly as a consequence of cerebral infarcts and hypoperfusion, mental retardation can be seen in children diagnosed as having moyamoya disease. Tobacco smoking and use of oral contraceptives is also associated with moyamoya disease in young women. Activated protein C resistance, congenital heart disease, Down syndrome, fibromuscular dysplasia, neurofibromatosis type 1, and sickle cell disease are medical conditions associated with moyamoya disease. However, the presence of one or more of these conditions yields the diagnosis of moyamoya syndrome.

Etiologic and Pathologic Processes

The exact etiologic process of moyamoya disease is unknown, though myriad bacterial, environmental, genetic, and viral causes have been theorized. The increased incidence among Japanese and other Asian populations—combined with ongoing investigations of occasional family occurrence—suggest that a genetic predisposition is present.
Research has linked familial moyamoya disease to chromosome arms 3p24.2-p26, 6q25, 8p23, 12p12, and 17q25. Alleles of class II genes of the human leukocyte antigen (HLA) have also been associated with moyamoya disease. Elevated levels of cellular retinoic acid-binding protein-I were found in the cerebrospinal fluid of patients with moyamoya disease. This protein leads to a reduced inhibitory effect of retinoic acid on growth factor–stimulated smooth muscle cell proliferation and migration, which in turn may cause intimal thickening in the vasculature. This protein is also associated with increased production of basic fibroblast growth factor (b-FGF), which is found in the vascular intima, media, and smooth muscle and may stimulate arterial growth. High levels of hepatocyte growth factor, a known inducer of angiogenesis, have been found in the carotid fork and cerebrospinal fluid of patients with moyamoya disease.

Antibodies to alpha-fodrin have been associated with moyamoya disease as well. They are a product of endothelial cell apoptosis breakdown, and their involvement in moyamoya disease may be mediated by tumor necrosis factor α and other inflammatory cytokines on endothelial cell activation. This process may play a contributory role in the pathogenesis of the vessel occlusion inherent to moyamoya disease as well. As a consequence, intracranial bleeding may occur because of the rupture of saccular aneurysms in the circle of Willis—resulting in subarachnoid hemorrhage—or because of the rupture of dilated, fragile moyamoya vessels—yielding intracerebral or intraventricular hemorrhage.

Autopsy examination of brain tissue of patients with moyamoya disease often reveals prior infarction in the basal ganglia, periventricular, and intraventricular regions. Furthermore, autopsy specimens from moyamoya vessels expose concentric fibrocellular intimal thickening and a multilayered elastic lamina with concurrent thinning of the media.

Bilateral concentric stenosis—or occlusion—of the distal carotid arteries and the proximal anterior and middle cerebral arteries are consistent pathologic lesions in patients with moyamoya disease. Rarely, the posterior cerebral artery or other vessels of posterior circulation are involved. A diffuse collateral reticulate network of vessels (moyamoya vessels) represent the hallmark of the disease.

Typically, the lenticulostriate arteries enlarge as they become collateralized to allow for adequate cerebral perfusion. In the setting of pathologic stenotic vessels in moyamoya disease, the cerebral circulation is maintained by these collateral vessels. The larger manifestation of this collateral vasculature network often involves the frontal basal regions or the cortical region, yielding ethmoidal moyamoya or vault moyamoya, respectively.

Moyamoya disease also presents with an extracranial involvement of the vasculature. Fibrocellular thickening of the vasculature layers is occasionally observed in the renal, pulmonary, and coronary vessels in addition to the cervical carotid vessels mentioned. Renal artery lesions are the most frequently reported angiographic lesions associated with moyamoya disease and can lead to renovascular hypertension.

**Epidemiology**

Moyamoya disease was first reported in Japan in 1957 and has since been reported worldwide. The disease has a particularly high incidence in Eastern Asia, especially in Japan. The overall prevalence rate of moyamoya disease in Japan in 1995 was 3.16 per 100,000 with an incidence rate of 0.35 per 100,000. The male to female ratio was 1.8:1, and a family history of moyamoya was noted in 10% of cases. Unfortunately, to the best of our knowledge, more recent data is unavailable.

Moyamoya disease has different epidemiologic characteristics in the United States. Uchino et al analyzed data provided from Washington State and California and found the disease incidence to be 0.086 per 100,000, which is lower than the measured value for Japan. However, the incidence rate for Asian individuals in these states was 0.28 per 100,000, which is similar to the incidence rate in Japan. The incidence rates per 100,000 were lower for African American (0.13), white (0.06), and Hispanic (0.03) patients.

Chiu et al also found the clinical expression of moyamoya disease to be different in the United States compared to Asia. They did not find a bimodal age distribution, as the average age of diagnosis was 32 years. However, epidemiology may be influenced by two factors: (1) patients of Asian origin may have an increased tendency to be diagnosed as having moyamoya, and (2) patients presenting with strokes at relatively young ages are more likely to have an aggressive workup, which may lead to a greater sensitivity in the diagnosis of moyamoya disease.

Moyamoya disease is especially rare in African Americans. Chiu et al found only 27 African Americans with moyamoya disease, 13 of whom had sickle cell disease and were thus classified as having moyamoya syndrome. From 1987 to 1998, there were only 14 true accounts of moyamoya disease in the states of Washington and California. If these findings were extrapolated to the 2000 US Census population, there would have been only 44 African Americans diagnosed with moyamoya disease or syndrome each year. However, according to the authors’ research, only about 52% of those individuals would be categorized as having moyamoya disease.

In addition, African Americans were determined to have a median disease onset age of 18 years. As noted earlier, the patient described in the present report was diagnosed much later—at age 44 years.

**Diagnosis**

Moyamoya disease is an important diagnosis to consider in children, young adults, and individuals of Asian ethnicity presenting with stroke. Cerebrospinal fluid results of a lumbar puncture are unremarkable in patients with moyamoya disease. Electroencephalography appearances can be abnormal but are usually nonspecific. Detection by cerebral angiography...
is considered the gold standard, but MRI and MRA are also acceptable methods of diagnosis.3,7

The Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya Disease) of the Japan Ministry of Health, Labour and Welfare8 defined the diagnostic criteria of moyamoya disease as “(Bilateral) stenosis or occlusion of the terminal portion of the internal carotid artery and/or at the proximal portion of the anterior and/or the middle cerebral arteries.”

However, for a definitive diagnosis of moyamoya disease, these findings should be observed in the absence of arteriosclerosis, autoimmune disease, brain neoplasm, Down syndrome, head irradiation, head trauma, meningitis, neurofibromatosis (von Recklinghausen disease), and sickle cell anemia, as similar vascular abnormalities on imaging may occasionally be found in these disease processes.4,7

If the previously mentioned findings are observed in addition to the angiographic imaging typically seen in moyamoya disease, then the patient should be diagnosed as having moyamoya syndrome, not moyamoya disease.7,8,11,16 The patient described in the present report did not have any of these disease processes and was negative for sickle cell disease or trait.

Treatment

Optimal management of moyamoya disease continues to be debated. Unfortunately, no known treatment that is curative or remissive exists.2,12,44,45 Furthermore, treatment in the acute phase is symptomatic with the goal of maintaining cerebrovascular perfusion and function.2,3,12,16,44,45

Various medical management approaches have been researched. Anticoagulant and antiplatelet agents have shown no remarkable benefit.46 The same lack of obvious efficacy has been described for corticosteroids in moyamoya disease.46 McLean et al47 elucidated the use of verapamil hydrochloride to curtail the ischemic symptoms associated with moyamoya disease. Unfortunately, no randomized controlled studies to determine patient outcomes or ischemic infarction recurrence using various surgical revascularization procedures or medical management are available.3,16 However, Chiu et al2 described 20 patients who had surgical revascularization and 15 who were treated medically and found no statistically significant difference in the 5-year stroke recurrence rate between the two groups.

Surgical treatment modalities have been used to manage the hemorrhagic and ischemic consequences of moyamoya disease.2-4,12,13,42,44 Ventricular drainage and hematoma evacuation are often used for hemorrhagic cases.7 In ischemic moyamoya disease, surgical methods have been used to restore and maintain adequate cerebral perfusion.2,3,12,13,19,44

Two main surgical revascularization procedures have been described: direct and indirect. Direct revascularization techniques, which are typically used in adults, include the superficial temporal artery to middle cerebral artery bypass or the middle meningeal artery to middle cerebral artery bypass.12,13,48,49 Wang and Steinberg50 showed the propensity of moyamoya vessels to regress after the former procedure.

The objective of indirect surgical procedures, traditionally used in children, is to increase the volume of circulation in the collateral vasculature. This process requires neovascularization from the extracranial soft tissue to the poorly perfused areas of the brain and occurs within 3 to 6 months.16 Techniques include encephaloduroarteriomyosynangiosis, encephaloduroarteriosynangiosis, encephalomyoarteriosynangiosis, and encephalomyosynangiosis.2,3,14 These procedures aim to increase perfusion in the cerebrovascular territory of the middle cerebral artery. They do not substantially effect the circulation in the fields of the anterior or posterior cerebral arteries.

Serious adverse effects of surgical intervention in moyamoya disease include death, cerebrovascular infarct or hemorrhage, motor or sensory dysfunction, and cognitive decline.2,16,51,52 Regarding the outcomes of indirect revascularization techniques and the role of angiogenesis in the augmentation of necessary collateral circulation, patients with decreased levels of b-FGF in their cerebrovascular fluid had poor results compared with those who had higher levels of b-FGF.16,53 Kim et al54 suggest that a younger age of presentation is associated with increased rates of infarction and an overall worse prognosis. Research3,13 also indicates that the role of early surgical intervention in the abatement of ischemic symptoms may be more effective in children than adults.

In the present report, after the risk, benefits, and alternatives of surgical intervention were explained, it was determined that the patient’s condition would be best managed with conservative medical therapy with lipid control and oral antihypertensive medications. The late detection of moyamoya disease (ie, in adulthood rather than childhood) also played a role in decision making.

Prognosis

Moyamoya disease has a more rapid and worse prognosis in children younger than 3 years than in those aged 3 years or older.54 However, when comparing children with adults, the prognosis is generally worse for adults because they have increased hemorrhagic episodes and thus a higher mortality.16,55

Long-term follow-up research conducted in Japan compared medical and surgical management modalities in adults and found a trend toward a decrease in the incidence of ischemic attacks after direct surgical revascularization.14 Another long-term study56 followed children who underwent surgical intervention and found that they, as adults, had a slowed rate of cognitive decline and fewer ischemic events.

In Japanese subjects, Kuroda et al12 showed disease progression to occur more frequently in women and earlier in those with bilateral moyamoya disease. Furthermore, they quantified the incidence of disease progression to be approx-
CASE REPORT

imately 20%.12 Disease progression can occur in anterior and posterior circulations in symptomatic and asymptomatic patients.12

In the United States, patients with moyamoya disease are often young women who likely develop idiopathic narrowing or occlusion of the distal internal carotid arteries or its proximal branches and thus have the symptomatology of ischemic stroke. In Hallemeier et al,42 patients with bilateral involvement had worse functional outcomes than those with unilateral involvement. Results of the research conducted by Chiu et al2 and Yilmaz et al3 in Houston, Texas, and Indianapolis, Indiana, respectively, show that within the first year of diagnosis of moyamoya, the risk of recurrent stroke was approximately 18% but decreased to 5% per year after that. This finding was interpreted as a benign disease course for patients with moyamoya disease in the United States. Furthermore, both studies2,3 failed to demonstrate a statistically significant difference in the occurrence of ischemic infarction between the medical and surgical intervention subsets of patients. Therefore, the results of US-based studies suggest that moyamoya disease has a different clinical presentation and more benign course in US populations than Asian populations.3

Conclusion
A better understanding of the natural history of patients with moyamoya disease as well as the benefit of the various treatment modalities is needed. Ideally, structured randomized clinical trials would help provide insight into the optimal treatment methods for these patients. In the interim, management of moyamoya disease remains ill-defined and varies depending on the inherent practices of individual institutions.

Surgery can be beneficial, particularly if the diagnosis of moyamoya disease is made early. However, further prospective studies are necessary. Optimization of surgical techniques, perioperative care, and anesthesia will likely improve the benefit of surgical revascularization for future patients. Careful, long-term neurologic and radiologic follow-up is essential in adult patients with moyamoya disease to prevent additional stroke events and improve outcomes.

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References