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CLINICAL VIGNETTE

Moyamoya Disease: An Important Non-Atherosclerotic Cause of Stroke Affecting the Young

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Case

A 31-year-old female was referred for concern for Moyamoya disease (MMD). Two months prior to her visit, she suddenly developed a headache at work, with acute struggling with her speech. She was also nauseous and started vomiting, and a bystander called 911 and she was taken to a local hospital by ambulance. On imaging, she was found to have a 2-3 cm intracerebral hemorrhage centered in the left basal ganglia, and was started on anti-hypertensives; her initial systolic blood pressure was in the 150's mm Hg. She was also started on levetiracetam for seizure prophylaxis. A diagnostic cerebral angiogram showed bilateral Suzuki grade 5 MMD. MRI revealed remote bifrontal ischemic infarcts, and she was discharged to an inpatient rehabilitation facility, with neurologic deficits including mixed aphasia, dysarthria and mild right hemiparesis.

Prior to her presentation, she was generally healthy, though on review, she did have untreated seizures as a child. She had no prior surgeries, and no known family history of MMD. She is a non-smoker and uses no illicit drugs. Her discharge medications included amantadine, citalopram, levetiracetam, atorvastatin and clonidine, to maintain a blood pressure goal of <160/90 mm Hg.

On exam, her vital signs and general exam were normal with a blood pressure of 103/64 mm Hg. Her neurologic examination revealed 3/4 hyper-reflexia at the right patella and decreased sensation to two-point discrimination over the right lateral leg. Otherwise, sensation, reflexes, gait and strength had recovered to near-normal. She had a mixed trans-cortical aphasia including both expressive and receptive components, but with the help of family, she was able to answer questions in Korean. She was relaxed and pleasant. Her family reported that her language deficits were improving slowly at home. Prior to her stroke, she was fully fluent in Korean and English, but in rehabilitation she had re-gained only Korean speech, and her ability to write in English.

Four months after her stroke, she underwent cerebral revascularization via a combined superficial temporal artery (STA) to middle cerebral artery (MCA) bypass on the left side. Three months later, she returned to have a right direct STA-MCA bypass. She tolerated her surgeries well, though she temporarily experienced partial sensorineural hearing loss beginning several days after her second surgery that started on the right side, spread to involve the left side, and then reverted to just the right side again, before dissipating within 2 weeks. She had no new strokes on MRI post-operatively and her donor vessels were patent. She was discharged with low-dose aspirin, as well as lacosamide for seizure prophylaxis. She has since fully regained her language function in both Korean and English, and her hemiparesis has fully resolved. She will have follow-up angiography 6 months, and yearly MRI/MRA thereafter.

Discussion

MMD is a chronic, idiopathic, bilateral, progressive steno-occlusive arteriopathy characterized by stenosis of the terminal internal carotid arteries and the proximal middle and anterior cerebral arteries. As the stenosis progresses, the posterior cerebral arteries can become occluded as well.[1,2] Compensatory dilation of collateral vasculature in the deep nuclei results in a hazy angiographic appearance that inspired the nickname "moyamoya," Japanese for "puff of smoke".[3] MMD is definitively diagnosed by digital subtraction angiography, but MRI/MRA commonly identifies suspected cases. Suzuki and Takaku described six stages of angiographic evolution.[4] While this grading system bears little correlation with clinical outcomes, it is still widely employed to describe disease progression.

Whereas MMD is idiopathic by definition,[5] the terms "quasi-moyamoya" and "moyamoya syndrome" are typically used to describe the angiographic appearance of moyamoya in the setting of an associated disease or condition, such as sickle cell disease, type 1 neurofibromatosis, trisomy 21, cranial irradiation, or an autoimmune disorder, among many others. Atherosclerosis and vasculitis are inconsistently included with these associated conditions, though are often maintained separately in that prognosis and treatment are quite different for these cases. The distinction is critical in that, while MMD is expected to progress in a large majority of cases, certain forms of quasi-moyamoya may be halted with risk factor modification. Atherosclerosis is the most common of these. One area that remains unaddressed is the confluence of genetic predisposition and bone marrow transplantation in sickle cell patients, as affecting the risk of moyamoya syndrome development and progression.

In Korea, the prevalence of MMD was estimated to be 9.1 per 100,000 in 2008, with an incidence of 1 per 100,000. In com-

parison, the annual incidence of MMD in the states of Washington and California was 0.086 per 100,000 in 2005. MMD affects women more than men, at about a 2:1 ratio, and 10-15% of patients have a family history of MMD.[2] There are two peaks of incidence, one in childhood centered around the age of 10, and another around the age of 40.[1,2,6]

MMD can present with transient ischemic symptoms, stroke, intracerebral hemorrhage, seizures, cognitive dysfunction or headaches. Since the anterior circulation is more commonly affected, the ischemic symptoms affecting these patients commonly involve hemiparesis, language dysfunction or sensory deficits.[2] Intracerebral hemorrhage occurs in about 30% of MMD patients, most commonly in adults, due to friable collateral vessels. One identified site of collateralization prone to hemorrhage is the choroidal anastomosis, which, when visualized, portends a dramatically greater risk of bleeding.[7] Seizures occur in about 5% of MMD patients and are related to ischemia. Headaches in MMD are thought to be related to dilation of dural and cortical vasculature, with a mechanism similar to migraine headaches. Some children with MMD can develop choreiform movements, or a "morning glory" optic disk appearance.[8] Posterior circulation disease is associated with a worsened prognosis. MMD should be suspected in young stroke or intracerebral hemorrhage patients with few risk factors for atherosclerotic disease.

A small number of genetic features predispose to MMD, the most important being a p.R4810K variation in the *RNF213* gene on the long arm of chromosome 17.[9] Interestingly, the R4810K variant is largely specific to the East Asian population, while other variants of *RNF213* are associated with MMD, along with a number of other vascular disorders, in other parts of the world.[10] Non-R4810K variants have also been associated with hemorrhagic presentation in MMD,[11] as well as intracranial atherosclerosis.[12]

The natural history of MMD includes a 65-95% risk of stroke recurrence within 5 years of initial stroke.[13] Two-thirds of patients experience significant motor and cognitive decline over ten years' follow-up, if untreated.[13] While low-dose aspirin, permissive hypertension, and aggressive oral fluid hydration are commonly initiated in MMD patients presenting with ischemic symptoms in an effort to mitigate short-term stroke recurrence, the treatment of MMD is surgical revascularization.[4,14] Surgery is typically recommended in otherwise low-risk surgical patients with symptomatic Suzuki grade 2 angiographic moyamoya, or Suzuki grade 3 and above with or without symptoms. Goals of surgery include long-term stroke risk reduction, re-hemorrhagic risk reduction, preservation of motor and cognitive function, and rarely, seizure management. Long-term stroke risk and symptomatic progression are reduced to <5% after revascularization.[15-17]

A variety of techniques for surgical revascularization have been described, all with the goal of blood flow augmentation. In general, these revascularization techniques can be divided into two types: indirect, where an external source of arterial blood is brought into close proximity with the brain in order to promote neoangiogenesis and collateralization; and direct, where an external source of blood is channeled directly into the recipient cerebral artery. While it is generally accepted, though with little evidence in support, that children with MMD likely respond just as well to indirect techniques as to direct,[18] recent literature in adult patients with MMD has heavily favored strategies that include direct revascularization. These include combined revascularization involving both a direct and an indirect technique, in patients with either ischemic or hemorrhagic presentation.[19-23]

It is increasingly clear that treatment at a high-volume center is among the most important predictors of surgical outcome, with patients experiencing shorter lengths of stay, lower costs, greater likelihood of discharge to home, and a 15-fold lower rate of death.[24,25] In addition, while long-term maintenance of revascularization remains excellent,[26] MMD remains a systemic disease wherein disease progression continues despite symptomatic stability. As such, patients require long-term monitoring with surveillance imaging, clinical monitoring, and neuropsychological evaluations.

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