CLINICAL VIGNETTE

Moyamoya and SLE

Tamara Dahhan, DO and Benedict Tiong, MD

Introduction

Moyamoya Syndrome is a progressive cerebrovascular disorder from narrowing of the internal carotid arteries and its branches, which can result in ischemic stroke or hemorrhagic disease. Moyamoya syndrome is associated with Lupus. It is unclear Lupus associated disease is related to Lupus disease activity.

Case

A 49-year-old female with a systemic lupus erythematosus (SLE) and Sjogren's syndrome presented to Rheumatology with intermittent episodes of severe dizziness and left-sided facial parasthesias for two months. The episodes had acute onset and were often triggered by rapid positional changes. They were not associated with vertigo. Each episode would last a few minutes, followed by nausea and lightheadedness. They occurred multiple times a day, interfered with activities. She denied any associated headache, seizures or hearing or vision changes.

She was diagnosed with lupus in 2009. She presented with Idiopathic Thrombocytopenic Purpura (ITP) with a positive antinuclear antibody (ANA) of 1:640 and anti-ribonucleoprotein (RNP) antibody, as well as alopecia, Raynaud's and inflammatory arthritis. Her ITP had been treated with high dose glucocorticoids followed by a taper as well as mycophenolate mofetil (MMF). Her lupus was also treated with hydroxychloroquine. After four years, she was tapered off MMF with no recurrence of her ITP.

Prior to her episodes of dizziness, she noted increased joint pains and fatigue, despite treatment with hydroxychloroquine. She was intolerant to methotrexate and leflunomide and was started on belimumab injections. She had been on treatment for one month before her new symptoms started. She was concerned her symptoms were medication related and discontinued both hydroxychloroquine and belimumab.

She initially presented to the Emergency Department after onset of symptoms. MRI Brain showed no ischemic process, intracranial hemorrhage, or mass effect. She was discharged home after being given ondansetron and intravenous fluids and referred to Neurology for further evaluation. ED labs were unremarkable, including comprehensive metabolic panel, complete blood count, troponin, brain natriuretic peptide, lipase, and erythrocyte sedimentation rate (ESR).

At outpatient Neurology consultation, she was afebrile with normal blood pressure, heart rate and oxygen saturation. She was alert and oriented, pupils were equal round and reactive to light. Extraocular movements were full and intact without nystagmus. Sensation on the face was intact to light touch, cranial nerves 2-12 were intact. Dix-Hallpike maneuver was negative bilaterally. Muscle strength was normal in all 4 extremities, and sensation to light touch was intact. Gait was normal. No rashes or petechia were noted. Cardiovascular and respiratory exams were normal. The only finding was mild tenderness in some proximal interphalangeal (PIP) joints.

Neurology ordered a videonystagmogram and vestibular evoked myogenic potential which were within normal limits. MRA Brain and Neck imaging demonstrated high grade, near occlusive stenosis of the right supraclinoid internal carotid artery (ICA), extending into the right M1 and A1 segments with suggestion of adjacent collaterals. These radiographic findings raised concern for Moyamoya disease or other vasculopathy. MRI Brain with perfusion studies showed a mild asymmetric delay of Tmax within the right MCA territory, without associated decreased blood volume or cerebral blood flow.

Additional lab testing included CBC, which was notable for white blood cell count of 3.52/µL and an absolute lymphocyte count of 400/µL with no anemia or thrombocytopenia. Chemistries included normal creatinine, electrolytes and liver enzymes. Double stranded DNA antibody (dsDNA) and complement levels were normal. Antiphospholipid antibodies were negative. Antineutrophilic cytoplasmic antibody (ANCA) was positive for Anti-proteinase 3 (PR-3) antibody of 40.5 CU (normal less than 20 CU). ESR and C-reactive protein were normal. Urinalysis and spot urine protein to creatinine ratio were normal. Chest X-ray showed no significant cardiopulmonary findings.

On follow-up visits, the patient had no signs or symptoms of small vessel vasculitis, including petechia or purpura, ocular inflammation, epistaxis, hemoptysis, shortness of breath, or focal weakness and ANCA vasculitis was felt to be less likely.

She was evaluated by Neurosurgery, who requested a cerebral angiogram by Interventional Radiology, which showed Suzuki grade III Moyamoya in the right ICA. There was underlying progressive stenosis and intensification of collaterals seen in the sylvian branches off the right MCA. Collateral flow was

supplied principally by the right posterior cerebral artery and left ICA via the anterior communicating artery. No collaterals were seen of the right external carotid artery. The right superficial temporal and occipital arteries were normal caliber.

Given lack of prior stroke on imaging and no neurologic deficits on exam, Neurosurgery elected to start medical management with cilostazol and aspirin 81mg daily. The patient was unable to tolerate cilostazol due to stomach discomfort but continued on aspirin. Two months after starting medical management her symptoms progressed. During exercise, she developed an acute episode of left side facial numbness, tongue numbness, bilateral vision loss and decreased hearing. The symptoms resolved after 5 minutes of rest. She was sent to the ED to rule out acute stroke versus transit ischemic attack. MRI Brain showed no infarctions or mass effect, and MRA Brain showed the previously noted right ICA stenosis and collaterals without change. It was suspected that her ischemic symptoms were triggered by exertion, likely related to change in perfusion in the context of flow-limiting lesions in the brain. There was low concern for active CNS vasculitis, as the presentation of collaterals would be highly uncommon and more likely related to a slow onset, progressive vascular occlusion, not seen in vasculitis causing acute vessel inflammation.

The patient continued to have episodes of exertional dizziness and facial paresthesias despite aspirin and was seen by an outside neurosurgeon for a second opinion. Given her ongoing symptoms of orthostasis, dizziness with physical exertion, as well as left-sided parasthesias, it was felt that her symptoms were related to Moyamoya vasculopathy affecting the right side of her anterior intracranial circulation. The patient was considered to be a high risk for stroke or hemorrhage with medical management alone as symptoms of hemodynamic insufficiency continued. MRI Brain with perfusion demonstrated delayed circulation in the right MCA territory, despite spontaneous collaterals that were formed. While her symptoms could not clearly be attributed to the right MCA territory, it was possible that a steal phenomena from her posterior circulation to the carotid circulation was exacerbated by exercise.

Surgical intervention with revascularization was recommended. She underwent a right Encephaloduroarteriosynangiosis (EDAS) without complication. A few months after surgery, she reported near complete resolution of symptoms. She has since restarted regular exercise without any limitations. She is followed by neurosurgery, with serial imaging monitoring the new mild stenosis in the left ICA. Her previous symptoms of lupus activity, including fatigue and inflammatory arthritis, improved despite remaining off belimumab and hydroxychloroquine.

Discussion

Moyamoya syndrome and SLE have been long associated, with unclear relationship.[1] Moyamoya syndrome (MMS) is defined as presence of moyamoya angiographic findings in the setting of an associated medical condition. Moyamoya disease (MMD) is defined as moyamoya angiographic findings in patients who have no underlying risk factors but may have a genetic predisposition.[2]

Moyamoya syndrome has been associated with multiple medical conditions, including brain radiation, brain tumors, meningitis, sickle cell disease, neurofibromatosis type 1, Down syndrome, as well as autoimmune disease.[3] Autoimmune diseases associated with MMS include SLE, antiphospholipid syndrome, polyarteritis nodosa and Sjogren's syndrome.[3] In autoimmune disease, it is unknown if the underlying autoimmunity predisposes to the vascular changes.[1] Presence of positive autoantibodies including ANA, anti-dsDNA, anti-SSA, lupus anticoagulant and anticardiolipin antibodies have been reported in MMS, which suggests immunologic factors are involved in pathogenesis.[4] On the other hand, Moyamoya disease is not associated with an underlying medical condition, and some cases have been attributed to a genetic polymorphism of the RNF213 gene on chromosome 17q25.3. This has been found to be a susceptibility factor for MMD in East Asian countries.[5]

Moyamoya syndrome and moyamoya disease can occur in any ethnic group but are most commonly described in patients of East Asian descent. They can occur in both pediatric and adult patients with a bimodal age distribution at 10 years and at 40 years of age with female predominance.[6] Moya moya vasculopathy is a rare progressive cerebrovascular disorder that causes constriction of large intracranial brain vessels, specifically the internal carotid arteries, resulting from arterial wall thickening and stenosis followed by angiogenesis of small vessel collaterals. The vascular changes can be unilateral or bilateral.[2] "Moyamoya" is the Japanese word for puffy or hazy and is used to describe the appearance of the collateral vessels on angiography.[2] These vascular changes can result in ischemic stroke or transient ischemic attack (TIA), and less commonly cerebral hemorrhage. Other less common presentations include headache, neurocognitive impairment and seizures.[3] Patients may be asymptomatic despite vascular changes noted on imaging consistent with moyamoya vasculopathy.

The gold standard imaging to diagnosis moyamoya vasculopathy is digital subtraction angiography. This is cerebral angiography that digitally subtracts radio-opaque structures such as bone, allowing for clear depiction of blood vessels.[3] The Suzuki staging system characterizes the stage of disease, which can be monitored over time with serial cerebral angiography. The staging system evaluates changes in the development and intensification of collateral vessels, as well as reduction or disappearance of moyamoya vessels due to progressive stenosis consistent with worsening disease.[3] Magnetic resonance imaging and angiography can also be used to aid in diagnosis and are more commonly used for surveillance.

Medical management and surveillance imaging is recommended for asymptomatic patients with preserved cerebral blood flow on imaging. Medical management includes antiplatelet therapy with aspirin 81mg daily.[7] Cilostazol, a

phosphodiesterase III inhibitor, can be an alternative. Antiplatelet agents are contraindicated with hemorrhagic manifestations of the moyamoya vasculopathy. No studies have evaluated therapeutic anticoagulation in Moyamoya, and it is generally avoided.[7]

Patients with moyamoya vasculopathy with cerebral hemodynamic insufficiency benefit from surgical revascularization to improve cerebral blood flow and prevent the exhaustion of moyamoya collaterals.[3] Treatment with medical management alone in patients with hemodynamic insufficiency is associated with high risk of stroke and hemorrhage. Patients with ischemic symptoms have risks of recurrent stroke, with five-year risk of ischemic events nearly 65% in individuals with unilateral disease and 82% in individuals with bilateral disease.[8] Interestingly up to 20% of patients with unilateral disease progress to bilateral disease in the anterior and posterior circulation. These patients have an associated increased risk of ischemic or hemorrhagic symptoms.[9]

Surgical revascularization for moyamoya consists of direct versus indirect bypass. Direct revascularization involves a direct extracranial-intracranial anastomosis between the superficial temporal artery and middle cerebral artery. Indirect revascularization is performed by applying tissue such as dura, muscle or a branch of an artery that is perfused by a branch of the external carotid artery to the area of the ischemia to promote revascularization of the underlying cortical vessels over time.[3] While direct bypass allows for prompt revascularization, it is technically more difficult with increased risk of procedural complications including cerebral hyperperfusion syndrome.[3] Indirect bypass allows for angiogenesis to occur over days to weeks. No randomized controlled trials have demonstrated superiority between direct or indirect bypass.[3]

In our patient, neurosurgery elected to perform an indirect extracranial-intracranial bypass revascularization procedure with Encephaloduroarteriosynangiosis (EDAS) surgery in an attempt to form collaterals from the extracranial vasculature to her hypoperfused cerebral territory. An indirect bypass was preferred because it did not require temporary clamping of the recipient vessel, reducing the risk of ischemia of the affected territory and reducing the risk of proximal thrombosis and stroke due to competitive flow from a direct bypass. Our patient did well with surgical revascularization via an indirect bypass resulting in resolution of her symptoms of exertional dizziness and facial paresthesias previously caused by cerebral hypoperfusion from moyamoya vasculopathy in the setting of SLE. This patient demonstrates the relationship between Moya Moya disease and SLE.

REFERENCES

1. **Wang R, Xu Y, Lv R, Chen J**. Systemic lupus erythematosus associated with Moyamoya syndrome: a case report and literature review. *Lupus*. 2013 May;22(6):629-33. doi: 10.1177/0961203313485828. Epub 2013 Apr 10. PMID: 23574743.
2. **Suwanwela NC**. Moyamoya disease and moyamoya syndrome: Etiology, clinical features, and diagnosis. In: *UpToDate*, Conner RF (Ed), Wolters Kluwer. (Accessed on May 14, 2024.)
3. **Gonzalez NR, Amin-Hanjani S, Bang OY, Coffey C, Du R, Fierstra J, Fraser JF, Kuroda S, Tietjen GE, Yaghi S; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology**. Adult Moyamoya Disease and Syndrome: Current Perspectives and Future Directions: A Scientific Statement From the American Heart Association/American Stroke Association. *Stroke*. 2023 Oct;54(10):e465-e479. doi: 10.1161/STR.0000000000000443. Epub 2023 Aug 23. PMID: 37609846.
4. **Jeong HC, Kim YJ, Yoon W, Joo SP, Lee SS, Park YW**. Moyamoya syndrome associated with systemic lupus erythematosus. *Lupus*. 2008 Jul;17(7):679-82. doi: 10.1177/0961203307087375. PMID: 18625642.
5. **Bang OY, Chung JW, Kim DH, Won HH, Yeon JY, Ki CS, Shin HJ, Kim JS, Hong SC, Kim DK, Koizumi A**. Moyamoya Disease and Spectrums of RNF213 Vasculopathy. *Transl Stroke Res*. 2020 Aug;11(4):580-589. doi: 10.1007/s12975-019-00743-6. Epub 2019 Oct 24. PMID: 31650369.
6. **Sato Y, Kazumata K, Nakatani E, Houkin K, Kanatani Y**. Characteristics of Moyamoya Disease Based on National Registry Data in Japan. *Stroke*. 2019 Aug;50(8):1973-1980. doi: 10.1161/STROKEAHA.119.024689. Epub 2019 Jun 25. PMID: 31234758.
7. **Suwanwela NC**. Moyamoya disease and moyamoya syndrome: Treatment and prognosis. In: *UpToDate*, Conner RF (Ed), Wolters Kluwer. (Accessed on May 14, 2024.)
8. **Hallemeier CL, Rich KM, Grubb RL Jr, Chicoine MR, Moran CJ, Cross DT 3rd, Zipfel GJ, Dacey RG Jr, Derdeyn CP**. Clinical features and outcome in North American adults with moyamoya phenomenon. *Stroke*. 2006 Jun;37(6):1490-6. doi: 10.1161/01.STR.0000221787.70503.ca. Epub 2006 Apr 27. PMID: 16645133.
9. **Kuroda S, Ishikawa T, Houkin K, Nanba R, Hokari M, Iwasaki Y**. Incidence and clinical features of disease progression in adult moyamoya disease. *Stroke*. 2005 Oct;36(10):2148-53. doi: 10.1161/01.STR.0000182256.32489.99. Epub 2005 Sep 22. PMID: 16179571.