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Moyamoya syndrome causing stroke in young women with type 1 diabetes

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Abstract

Context—Moyamoya syndrome is an idiopathic brain vasculopathy characterized by stenosis of major intracranial arteries. It often presents in patients with type 1 diabetes or thyroid disease and may have an autoimmune etiology. Moyamoya-related stroke poses a diagnostic challenge as initial symptoms and deficits vary greatly from classic ischemic stroke to encephalopathy, psychiatric, or seizure disorder.

Case Description—We report 4 patients with type 1 diabetes and other autoimmune diseases who developed moyamoya-related stroke at a young age. Despite having long-term diabetes, these patients exhibited no evidence of dyslipidemia or other typical risk factors for atherosclerosis which might contribute to premature stroke. Three of the four patients underwent revascularization surgery while one patient received conservative management. All patients had improved neurologic function after treatment, some with residual deficits.

Conclusion—We highlight the importance of recognizing moyamoya syndrome in patients with pre-existing autoimmune diseases such as type 1 diabetes, as prompt diagnosis and treatment can have major impact on patient outcome and quality of life.

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Keywords

moyamoya; stroke; autoimmunity

1. INTRODUCTION

Moyamoya syndrome is an idiopathic brain vasculopathy characterized by stenosis or occlusion of major cerebral arteries particularly within the circle of Willis, with accompanying proliferation of small collateral vessels that give its namesake “puff of smoke” finding on angiography. While moyamoya is recognized as a major cause of premature stroke among neurology and surgical subspecialties, it remains unfamiliar to endocrinologists and diabetes providers. This disorder was first described in Asians and has since been reported in American and European populations. In North America, moyamoya tends to affect young women and present as transient ischemic attacks or stroke, with accompanying sensory-motor deficits or cognitive impairment (Bower et al., 2013; Starke et al., 2012); rarer presentations may include personality or behavioral changes that mimic psychiatric illness (Lubman et al., 2003; Scott and Smith, 2009). Moyamoya can develop in association with radiation exposure, certain genetic disorders, or immunological disorders and is inclusively named “moyamoya syndrome,” while the term “moyamoya disease” is reserved for idiopathic cases without associated risk factors (Scott and Smith, 2009). Regardless of terminology, treatment of moyamoya focuses on restoring cerebral blood flow. Mild cases are treated medically with anti-platelet agents, while those with severe occlusions or inadequate collateral compensation may require surgical revascularization (Hallemeier et al., 2006; Scott et al., 2004).

We are particularly interested in autoimmunity as a factor in moyamoya syndrome, as our patient base exhibits frequent type 1 diabetes (T1D) and Graves’ disease. The Mayo Clinic moyamoya cohort shows dramatically higher prevalence of autoimmune diseases in moyamoya patients than in the U.S. population (22.3% vs. 3.2%, respectively, $P<0.0001$), which echoes findings from Asian studies (Bower et al., 2013; Chen et al., 2015). The risks associated with individual diseases are variable, with 8.4% of U.S. moyamoya patients having concurrent T1D and 17% having thyroid disease (Bower et al., 2013). In most of these cases, diagnosis of moyamoya follows the onset of T1D or thyroid disease, suggesting that established autoimmunity may be a priming factor for moyamoya.

We report 4 cases of moyamoya in young Caucasian women with preexisting T1D. Two of the patients also had Graves’ disease, and another had systemic lupus erythematosus (SLE). We highlight the association of moyamoya with autoimmune endocrinopathies and discuss challenges in distinguishing moyamoya symptoms from classic T1D-associated neurologic events, including hypoglycemia and atherosclerotic stroke.

2. METHODS

Four cases of moyamoya with coexisting type 1 diabetes are reviewed from two institutions. Patients were interviewed in conjunction with a focused medical record review. All signed HIPAA authorization, permitting presentation of their case histories in a de-identified

manner according to guidance from the Washington University Human Research Protection Office.

3. RESULTS

The clinical histories of four patients included in the study are presented in Table 1. All four patients were women who had type 1 diabetes prior to moyamoya diagnosis, with mean age of T1D onset being 12.8 ± 4.3 years, and 25.5 ± 7.5 years at moyamoya onset. Mean duration of diabetes was 12.8 (1.0-24.0) years. Three of the patients had additional autoimmune disease, including Graves' disease in two and SLE in one. Diabetes was generally well-controlled with average hemoglobin A1c $7.1 \pm 0.9\%$. Serum lipid profile showed no evidence of dyslipidemia with average LDL 61 ± 0.7 mg/dL.

At presentation, three patients experienced acute-onset hemiparesis and weakness in upper or lower extremities, while a fourth patient presented with syncope and psychosis but no focal sensory-motor deficits. Hypoglycemia was not present during symptomatic episodes. MRI demonstrated varying degrees of cerebral infarcts in each case. Moyamoya diagnosis was established after angiography revealed occlusion or severe stenosis of major intracranial arteries (Figure 1), with pial collateral compensation. Cerebral venography showed no thrombosis, and hypercoagulability workup was negative. Three of the four cases showed involvement of bilateral internal carotid arteries (ICA), while a fourth had focal occlusion of the middle cerebral artery (MCA). One patient received revascularization surgery within months of diagnosis, while two others had postponed surgery until symptoms recurred several years later and corroborated by worsening findings on angiography. One mild case had adequate collateral blood flow and was managed medically with anti-platelet and statin therapy. All patients had improved symptoms after treatment, and most were able to return to full-time work. Residual symptoms include headaches, memory impairment, and mental fatigue.

4. DISCUSSION

Type 1 diabetes is associated with higher risk for cardiovascular disease and, in particular, ischemic stroke, usually due to metabolic abnormalities including hyperlipidemia, hypertension, renal disease, insulin resistance, and inflammation (Soedamah-Muthu et al., 2006). A subtype of T1D patients, however, suffer stroke not because of these traditional factors but from the rare vasculopathy of moyamoya syndrome, which can present as classic ischemia with focal symptoms, or as atypical neurologic or even psychiatric manifestations (Festa et al., 2010; Leypoldt et al., 2015). Such pleiotropy in clinical presentation can delay the diagnosis of moyamoya-related stroke in T1D patients, as symptoms are often mistakenly attributed to hypoglycemia or diabetes-related atherosclerosis (Bower et al., 2013, 2012). While dyslipidemia can be found in moyamoya patients (Duan et al., 2012) and, indeed, atherosclerosis has not been excluded as a potential contributor to the moyamoya vascular phenotype, this does not appear to be a major factor in our patients, as all had well-controlled diabetes and serum lipids.

A prominent feature in our case series was the presence of autoimmunity. All four patients had type 1 diabetes prior to moyamoya onset, and two had Graves' disease while another had SLE. Moyamoya syndrome is frequently associated with autoimmune diseases and in fact has been suggested to have an autoimmune component in its pathogenesis. Mechanistically, circulating anti-endothelial cell antibodies have been identified in moyamoya patient sera (Ogawa et al., 2003), which provides a potential explanation for how an autoimmune inflammatory process might result in endothelial injury. Other autoantibodies including CAMK2A, CD79A, and EFNA3 have also been described in association with neurological disease and inflammation (Sigdel et al., 2013). Genetic polymorphism in HLA DR/DQ has been found in Korean children with familial moyamoya, suggesting possible immune dysregulation (Hong et al., 2009). Yet another link between autoimmune thyroid disease and moyamoya involves thyroid antibodies cross-reacting with cerebral artery-derived antigens, resulting in autoimmune arteritis, where treatment of the underlying thyroid disorder may in fact ameliorate the cerebrovascular disease. In our cases, Patients 1 and 4 presented with moyamoya shortly after their Graves' diagnosis, similar to previously reported moyamoya-Graves' cases. However, it is notable that moyamoya symptoms recurred in one of our patients despite definitive treatment for hyperthyroidism.

In conclusion, moyamoya remains an under-recognized disease entity, and concurrent moyamoya with T1D even more so. When evaluating a young T1D patient with stroke or new psychiatric or neurologic symptoms, moyamoya syndrome should be part of the differential diagnosis as it requires a specific management approach. Angiography is required to establish the diagnosis of moyamoya and to inform treatment and follow-up. Lifestyle modifications such as blood pressure control and lipid reduction are recommended, but recurrences are likely driven by the underlying pathologic process and may require surgical treatment.

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Figure 1. Cerebral angiography of Patient 1 showing severe narrowing of the bilateral supraclinoid internal carotid arteries (black arrows), which caused slow flow through the more distal pericallosal arteries.

Table 1
Clinical characteristics of four moyamoya patients with preexisting type 1 diabetes

Patient	Age at Diagnosis, y		Other Autoimmune Diseases	Presentation Leading to Diagnosis of Moyamoya	Angiography Finding	Moyamoya Treatment	Residual Symptoms
		T1D	Moyamoya				
1	9	25	Graves' disease, positive ANA 1:80	Progressive tingling and muscle weakness in left upper and lower extremities	Bilateral supraclinoid ICA stenosis	Anti-platelet therapy, statins	Memory impairment
2	12	36	Family history of T1D and thyroid disease	Acute-onset left arm and leg weakness, headache, decreased right eye vision	Right MCA occlusion	Right STA-MCA bypass 6 years after diagnosis; repeat revascularization anterior to prior bypass	Memory impairment, mental fatigue, left side weakness
3	11	20	SLE	Acute-onset left hemiparesis	Bilateral supraclinoid ICA stenosis	Bilateral encephaloduroarteriosynangiosis (EDAS) within 1 year of diagnosis	Mild left side weakness
4	19	20	Graves' disease	Syncope, panic attacks, psychiatric symptoms followed by seizures with acute right hemiparesis, word-finding difficulty	Bilateral ICA stenosis	Right ICA angioplasty, left STA-MCA bypass 2 years after diagnosis	Residual mild word-finding difficulty