Unilateral Moyamoya Disease in an Adolescent Female of Non-Asian Descent: A Case Report

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Radiology Case. 2026 January; 20(1):1-7 :: DOI: 10.3941/jrcr.5942

AUTHORS' CONTRIBUTIONS

Aaron Peterson wrote the introduction, case presentation, and discussion sections. Trinity Puno and Joshua Levy oversaw final edits and drafted the final manuscript once it was written. Angus Cheng and Jabre Millon obtained patient consent and allowed for data abstraction. Tim Stone, Isaac Wang, Rajpaul Gill, and Millie Pal helped with initial structuring and conception of the manuscript. Kyle Mefferd, Denise Vidal, Angelina Rodriguez, and Upinder Singh approved the final manuscript.

DISCLOSURES

None.

PATIENT CONSENT

Yes, written consent was obtained.

HUMAN AND ANIMAL RIGHTS

No human or animal experiments were conducted.

ABSTRACT

Moyamoya disease is an idiopathic occlusive cerebrovascular disease that affects the internal carotid artery, middle cerebral artery or anterior cerebral artery forming a smoke-like collection of blood vessels seen on digital subtraction angiography or magnetic resonance imaging/angiography. Moyamoya disease most frequently occurs in East Asian populations and is worsened by physical stressors, often leading to headaches, seizures, speech/visual deficits, and transient ischemic attacks or strokes. The cause of moyamoya disease has yet to be fully explained, but several studies have shown genetics play a factor in the development of the disease. The characteristic puff of smoke sign is most easily visualized with direct angiography and can be treated surgically with direct or indirect revascularization techniques. This article presents a unique case of moyamoya disease in a Hispanic pediatric patient involving the left middle cerebral artery who was treated with an indirect revascularization technique, encephaloduroarteriosynangiosis.

CASE REPORT

CASE REPORT

Imaging Findings

A 15-year-old Hispanic female with a history of chronic migraines for several years and attention-deficit/hyperactivity disorder (ADHD) presented to a family medicine clinic with an acute on chronic headache and associated LUE weakness, gait instability, and visual changes. When asked about location, she described the pain as most intense in the left occipital region and affirmed it was different in nature from her typical migraines. The patient has a family history of seizures including her mother, and a rupture of a brain aneurysm leading to early death of her paternal grandfather at age 30. She was sent to an emergency department for further evaluation and workup. CT angiography of the brain showed left M1 middle cerebral artery (MCA) stenosis consistent with possible MMD. The patient subsequently had an MRI of their brain which was unremarkable. Interestingly, the pediatric radiologist at that time stated the MRI of the brain was not indicative of moyamoya disease, so the patient was initially discharged with plans for outpatient follow-up with neurosurgery.

Upon seeing neurosurgery, the patient was recommended to return to the ED for further imaging to reevaluate the cause of her persistent symptoms. Her cerebral angiogram in (Figure 1) demonstrated a left MCA M1 occlusion with extensive lenticulostriate collaterals and pial collaterals. The Suzuki staging system for moyamoya disease has been previously used to correlate with the degree of collateralisation of blood vessels seen in children, but not adults [1]. There are a total of 6 stages that range from Stage 1 to Stage 6 as seen in (Table 1), describing the progressive steno-occlusive changes at the terminal internal carotid artery and the eventual development and subsequent regression of basal moyamoya collateral vessels, eventually manifesting as the reliance on external carotid artery collaterals in the most advanced disease stages. However, despite having distinct stages for disease progression and monitoring, its practical application remains limited when only a single angiographic image and/or time point is available, as in our case.

Management

After cerebral angiography was completed, the patient was discharged with verapamil, acetylsalicylic acid and clopidogrel for further outpatient follow-up. Two months later, the patient underwent encephaloduroarteriosynangiosis (EDAS) for revascularization of the left MCA without any significant complications. She was admitted to the intensive care unit for overnight monitoring and only experienced mild nausea with food consumption.

Follow-Up

The patient was stable for discharge on post-op day 1 and discharged on aspirin, levetiracetam for 1 week as seizure prophylaxis, and clopidogrel to start on post-op day 5. She had resolution of her symptoms immediately after EDAS, but no clinical information about further follow-up was able to be obtained. Follow-up intervals for patients with similar clinical pictures tend to be every 6-12 months during the first several years after surgery, then annually or as clinically indicated.

DISCUSSION

Moyamoya is a rare, chronic cerebrovascular disorder characterized by unilateral or bilateral progressive narrowing and occlusion of the terminal portions of the intracranial internal carotid arteries and Circle of Willis distal to the anterior choroidal arteries, with compensatory collateral vessel neovascularization, often described as a “puff of smoke” on angiography [2-6]. It is typically classified into two types: moyamoya syndrome (MMS) and moyamoya disease (MMD) [7]. MMS is characterized by its association with an underlying medical condition with vascular changes secondary to another primary condition, whereas MMD is an idiopathic and sometimes familial occlusive cerebrovascular disease with characteristic imaging findings without underlying risk factors [7,8]. While the pathophysiology of MMD is not fully established, it is associated with several genetic mutations [9]. The RNF213 gene and its variant, p.R4810K, has been implicated as a major susceptibility gene in MMD [10,11]. Although the disease is more common in patients of East Asian ancestry and was initially described in Japanese patients, it has been documented across all populations, including the present case of a Hispanic adolescent [8,12,13].

Epidemiologically, MMD has a bimodal age distribution, peaking in childhood and adulthood at approximately 10 years old and 30-40 years old, respectively [12]. The annual incidence in the United States is 0.57 per 100,000 persons with a female predominance of 1.9:1 [12]. The typical presentation is more common in adults with transient ischemic attack, ischemic stroke, and hemorrhagic strokes affecting the terminal internal carotid artery and its major branches of the middle cerebral artery or anterior cerebral artery [8, 14]. Although classically known to affect the internal carotid artery, studies demonstrated 40-50% of patients also have posterior cerebral artery involvement [15]. Additional symptoms include headaches, seizures, visual impairments, and sensory motor deficits [14]. In children, hemispheric ischemic strokes are more prominent, presenting as either hypoperfusion from watershed infarctions or an artery-to-artery thromboembolism [11]. In the present patient, the initial symptom was an acute on chronic headache, ultimately found to be associated with underlying MMD.

Diagnosis relies on the detection of unilateral or bilateral stenosis in the distal internal carotid arteries or proximal anterior or middle cerebral arteries with characteristic collateral vessel networks on imaging [6]. The gold standard imaging modality is cerebral angiography, but diagnosis may also be accomplished via less invasive methods, such as computed tomography angiography (CTA) and magnetic resonance angiography (MRA) [16]. The term "moyamoya" means "puff of smoke" in Japanese, describing the appearance of the collateral blood vessels that form to compensate for blockages found in the basal ganglia and thalamus also referred to as “ivy sign” and “brush sign”, which serve as major diagnostic criteria [3,4,6]. Histologically, MMD is characterized by fibrocellular thickening of the intima, especially in the internal carotid artery and vessels of the Circle of Willis [5]. It is notable that the present patient’s MMD was undetected on MRI despite positive findings on CTA, leading to increased time to confirmatory imaging via cerebral angiogram and subsequent treatment.

MMD is typically bilateral, but unilateral disease is a relatively uncommon variant with an estimated incidence of approximately 14-15%, and is more common in younger individuals, like the present patient [17]. Its clinical characteristics are not fully described, and there is ongoing debate regarding whether unilateral disease represents an early stage of bilateral MMD or a distinct entity altogether [18-20]. Some studies suggest that unilateral MMD may exhibit unique characteristics, such as an association with ipsilateral carotid canal hypoplasia or increased blood flow relative to bilateral disease [19,20]. It may carry a lower risk of stroke and share a

stronger association with atherosclerosis [19]. However, further comprehensive characterization of unilateral MMD through larger-scale studies is needed. Our patient's case highlights this less common presentation of MMD and contributes to a better understanding of the spectrum of MMD manifestations.

Treatment approaches vary depending on patient age, symptoms, and disease severity. Symptomatic patients generally require surgical revascularization, while asymptomatic patients may be managed conservatively with antiplatelet therapy [8]. Most surgical therapies for MMD aim to bypass the occlusive arterial segments which can be accomplished by either direct artery-to-artery anastomosis or indirect revascularization. Several indirect revascularization techniques have been described and are generally preferred in pediatric patients due to the smaller vasculature not allowing for direct surgical anastomosis [21]. Examples of indirect revascularization include encephalomyosynangiosis (EMS), encephaloduroarteriosynangiosis (EDAS), and encephaloduroarteriomyosynangiosis (EDAMS). The most common procedure is EDAS, an indirect revascularization bypass surgery in which superficial temporal artery branches with surrounding galea are placed under the dura directly onto ischemic cortical areas [22]. This approach promotes the angiogenesis of new vasculature over time [23]. The present patient underwent EDAS with neurosurgery and had no major complications and no recurrence of disease to date.

TEACHING POINT

Moyamoya disease remains an uncommon cause of stroke, but it should be considered in patients who present with headache, weakness, seizures, and speech/visual deficits, even in patients who are not of East Asian descent. Most cases present with bilateral internal carotid artery or internal carotid artery branch occlusion, but this case highlights a rare unilateral presentation of moyamoya disease; therefore, it is advisable for all providers to familiarize themselves with and promptly manage this disease process for proper treatment.

QUESTIONS

Question 1: Which of the following are considered common presenting symptoms of Moyamoya disease?

A. Transient ischemic attacks (applies)

B. Hemorrhagic strokes (applies)

C. Hemispheric ischemic strokes (applies)

D. Peripheral neuropathy

E. Chronic cough

Explanation:

Moyamoya disease typically presents with transient ischemic attacks, ischemic strokes, or hemorrhagic strokes, especially in adults. In children, hemispheric ischemic strokes are more common, either from hypoperfusion or artery-to-artery thromboembolism. Peripheral neuropathy and chronic cough are not typical features of Moyamoya disease. [see Discussion, second paragraph]

Question 2: Which statements accurately describe the Suzuki staging system for Moyamoya disease?

A. It has 4 distinct angiographic stages

B. It ranges from Stage I to Stage VI (applies)

C. Stage I involves narrowing of the ICA apex with minimal abnormal vessels (applies)

D. Stage VI involves disappearance of Moyamoya vessels with reliance on ECA and vertebrobasilar collaterals (applies)

E. It is primarily based on histopathologic findings

Explanation:

The Suzuki staging system consists of 6 stages, ranging from Stage I (initial ICA narrowing with minimal abnormal vessels) to Stage VI (disappearance of Moyamoya vessels, complete ICA occlusion, and dependence on ECA and vertebrobasilar collaterals). It is angiography-based, not histopathology-based. [see Table 1]

Question 3: Which statement(s) are true regarding the epidemiology of Moyamoya disease?

A. It has a bimodal age distribution with peaks at ~10 years and 30–40 years (applies)

B. It is more common in males

C. It has an annual incidence in the U.S. of 0.57 per 100,000 persons (applies)

D. It demonstrates a female predominance of ~1.9:1 (applies)

E. It is exclusively found in East Asian patients

Explanation:

Moyamoya disease has a bimodal age distribution (childhood and adulthood at ~10 years and 30–40 years). In the U.S., the annual incidence is 0.57 per 100,000 persons with a female predominance of 1.9:1. While it is more common in East Asian patients, it has been documented across all populations, including Hispanic patients. [see Discussion, second paragraph]

Question 4: Which of the following statements about treatment of Moyamoya disease are correct?

A. Symptomatic patients generally require surgical revascularization (applies)

B. Asymptomatic patients are typically treated with antiplatelet therapy (applies)

C. Indirect revascularization techniques are commonly used in pediatric patients (applies)

D. EDAS is the most common indirect revascularization procedure (applies)

E. Direct bypass techniques are always preferred in children

Explanation:

Symptomatic patients typically undergo surgical revascularization, while asymptomatic patients may be treated conservatively with antiplatelet therapy. Indirect procedures are preferred in children due to smaller vasculature, with EDAS being the most common. Direct bypass is generally not preferred in pediatric patients. [see Discussion, 4th paragraph]

Question 5: Which imaging modalities are used in the diagnosis of Moyamoya disease?

A. Cerebral angiography (applies)

B. CT angiography (applies)
C. MR angiography (applies)
D. CT brain without contrast
E. Transcranial doppler ultrasound

Explanation:

The gold standard for diagnosing Moyamoya disease is cerebral angiography, though CTA and MRA may also be used as less invasive options. CT brain without contrast may be able to detect sequelae of moyamoya disease, but it is not used in diagnosis of the disease. Transcranial doppler ultrasounds have no diagnostic role in Moyamoya disease. [see Discussion, second paragraph]

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FIGURES

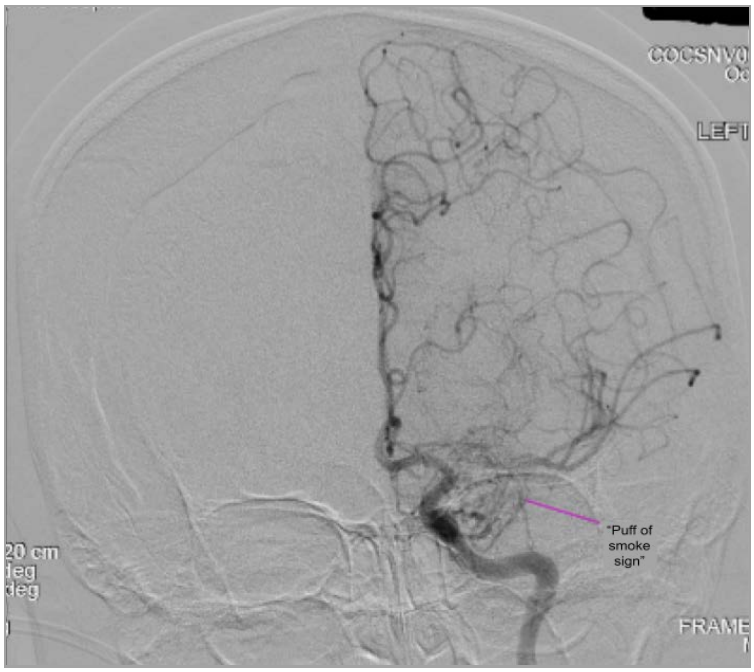

Figure 1: Cerebral angiography with the characteristic “puff of smoke sign” which describes the appearance of small, abnormal net-like vascular collateral networks in moyamoya disease. Occlusion of the middle cerebral artery M1 segment at its origin with extensive lenticulostriate collaterals with an angiographic appearance typical of a "puff of smoke" is visualized.

Table 1: The Suzuki staging system for moyamoya disease

Suzuki Stage	Angiographic Features	References
I	Narrowing of distal internal carotid artery (ICA) apex/carotid fork; none/minimal abnormal vessels	[1,11,25-28]
II	Beginning of Moyamoya vessels (small abnormal collaterals at base of brain)	[1,11,25-28]
III	Intensification of Moyamoya vessels; further ICA stenosis; prominent basal collaterals	[1,11,25-28]
IV	Minimization of Moyamoya vessels; beginning of reduction in basal collaterals; development of external carotid artery (ECA) and leptomeningeal collaterals	[1,11,25-28]
V	Further reduction of Moyamoya vessels; marked reliance on ECA and leptomeningeal collaterals	[1,11,25-28]
VI	Disappearance of Moyamoya vessels; complete ICA occlusion; cerebral perfusion dependent on ECA and vertebrobasilar system collaterals	[1,11,25-28]

KEYWORDS

Moyamoya disease (MMD), Moyamoya syndrome (MMS), Puff of smoke sign, Encephaloduroarteriosynangiosis (EDAS), Suzuki staging system, Cerebral angiography

ABBREVIATIONS

MMD = Moya Moya Disease
MMS = Moya Moya Syndrome
RNF213 GENE = Ring Finger Protein 213 GENE
P.R4810K VARIANT = Arginine (R) At Position 4810 Of Rnf213 Protein Replaced By Lysine (K)
MRI = Magnetic Resonance Imaging
CTA = Computed Tomography Angiography
MRA = Magnetic Resonance Angiography
ADHD = Attention Deficit Hyperactivity Disorder
LUE = Left Upper Extremity
EDAS = Encephalo Duro Arterio Synangiosis
MCA = Middle Cerebral Artery
EMS = Encephalo Myo Synangiosis
EDAMS = Encephalo Duro Arterio Myo Synangiosis

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