pediatric stroke

Moyamoya Arteriopathy in a Child with Hereditary Hemorrhagic Telangiectasia: a pathogenic link or bad luck?

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ABSTRACT

Background*:* Individuals with hereditary hemorrhagic telangiectasia (HHT) may be afflicted by vascular malformations in various organs including the brain. Arteriovenous malformations, arteriovenous fistulas, and capillary malformations are the most common brain vascular malformations in patients with HHT. Moyamoya arteriopathy has not been previously described in association with HHT.

Methods: Patients ≤ 18 years old seen at our HHT Clinical Center of Excellence who had neuroimaging obtained between 1/1/2003 and 3/15/2024 were identified. Brain MRI/MRAs were retrospectively reviewed.

Results: A single case of moyamoya arteriopathy was identified in our pediatric cohort of 100 children with HHT. We describe the case of a 2-year-old with HHT with a pathogenic variant in the *ACVRL1* gene and unilateral asymptomatic moyamoya arteriopathy that was incidentally discovered on screening MRI obtained for HHT. The child intermittently tolerated low-dose aspirin, but it had to be discontinued at times due to worsening epistaxis. She underwent uncomplicated unilateral pial synangiosis. Special management considerations highlighted by this case include the role of aspirin and anemia in patients with HHT and moyamoya.

Conclusions: Moyamoya and HHT are both vascular dysplasias that may share common pathogenic mechanisms, but further research is needed to understand this link.

MANUSCRIPT

Introduction

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disease that can be caused by pathogenic variants in one of several genes including Endoglin (*ENG*), Activin A Receptor Like Type (*ACVRL1*), SMAD family member 4 (*SMAD4*), and Growth Differentiation Factor 2 (GDF2).[1,2] Individuals with HHT have mucosal telangiectasia, which may predispose to epistaxis and gastrointestinal bleeding, and vascular malformations in various organs including the lungs, liver, and brain. Brain vascular malformations, including arteriovenous malformations (AVMs), arteriovenous fistulas (AVFs), and capillary malformations, occur in about 10-20% of individuals with HHT.[3,4] There are no cases of moyamoya arteriopathy associated with HHT reported in the literature. Here, we report a case of a 2-year-old with HHT and unilateral asymptomatic moyamoya arteriopathy and estimate the frequency of occurrence in children with brain MRI/MRA at our HHT Clinical Center of Excellence.

Methods

A database was extracted through Johns Hopkins Clinical Research Data Acquisition after IRB approval of expedited research using the keyword “HHT” or “hereditary hemorrhagic telangiectasia” with neuroimaging, including brain MRI without and with contrast and brain MRA between 1/1/2003 and 3/15/2024. After exclusion of those who had an alternative or unlikely diagnosis of HHT, a subset of 100 patients ≤ 18 years of age seen at

Johns Hopkins Clinical Center of Excellence were identified and their brain MRIs were retrospectively reviewed.

Results

Of 100 pediatric patients with HHT who had brain MRI and MRA seen at our HHT Center of Excellence between 1/1/2003 and 3/15/2024, a single case of comorbid moyamoya arteriopathy was identified.

A 2-year-old girl with HHT was found to have unilateral moyamoya on a brain MRI/A obtained as part of routine HHT care, a single case in our retrospective review of a cohort of 100 pediatric patients ≤ 18 years. She was the healthy product of a non-consanguineous union. Her mother had been diagnosed with HHT with an *ACVRL1* gene mutation after she presented with significant nosebleeds that worsened during her pregnancy with the patient. Genetic testing was performed on the child at age 22 months of age and showed the same pathogenic variant in the *ACVRL1* gene (c.1231C>T or p.Arg411Trp), leading to her HHT diagnosis. The patient had occasional, mild epistaxis at the time of diagnosis but was otherwise healthy. Her routine HHT screening included a normal saline contrast transthoracic echocardiogram (no evidence of pulmonary AVMs) and a brain MRI and MRA at 2 years of age. The neuroimaging showed normal parenchyma without cerebral AVM or stroke, but it did reveal severe stenosis of the terminal ICA and proximal right M1 and A1 segments with evidence of collateralization, consistent with moyamoya arteriopathy (Figure 1). The neuroimaging was also notable for right sulcal FLAIR hyperintensity, known as the "ivy sign," which signifies dilated leptomeningeal vessels with slow flow, indicative of impaired tissue perfusion. Digital subtraction angiogram confirmed severe right internal

carotid artery terminus stenosis with lenticulostriate collateral vessels (Figure 2). The child did not experience headaches, seizures, or any episodic or ongoing neurologic deficits, and her neurologic examination was normal.

After discussion of risks and benefits, a trial of low-dose aspirin (1.5 mg/kg/d) was initiated. After she tolerated that dose well, her aspirin dose was increased to 3 mg/kg/d. However, she developed multiple daily nosebleeds, so her dose was decreased to 1.5 mg/kg/d and ultimately discontinued due to ongoing epistaxis. Epistaxis improved significantly upon aspirin discontinuation.

Uncomplicated right pial synangiosis was performed. Five days before surgery, aspirin 3 mg/kg/d was initiated to provide perioperative stroke protection. She had no perioperative clinical or radiographic ischemic or hemorrhagic events. A follow-up brain MRI and MRA at 7 months after surgery showed persistent stenosis of distal right ICA, ACA and MCA (Figure 3) with a suggestion of progression. Right superficial temporal artery was robust in caliber but no definite engraftment was seen at this time. The child was doing well clinically at follow-up 7 months after surgery without interval ischemic events. She remained on aspirin without any significant interval epistaxis.

Discussion

Brain vascular malformations are common in individuals with Hereditary Hemorrhagic Telangiectasia. AVMs, AVFs, and capillary malformations occur most frequently.[5] There have been case reports of vein of Galen malformations associated with *ENG* and *ACVRL1* mutations,[6,7] suggesting a pathologic link between HHT and a broader

range of intracranial vascular malformations. Despite this, an association with moyamoya arteriopathy has not been previously described, and the index case is unique based on our single center experience.

Whether moyamoya is rarely associated with HHT or two rare diseases coincidentally occurred in the same patient remains unknown at this time. However, as both diseases involve abnormalities in cerebral arterial vasculature, an overlap in the pathways leading to each disease may be hypothesized. The mechanisms leading to brain vascular malformations in patients with HHT are incompletely understood. The *ACVRL1* gene, which was mutated in our patient, encodes ALK1, a transmembrane serine/threonine kinase receptor in the transforming growth factor-beta (TGFβ) receptor family that is important for vascular morphogenesis, response to shear stress, and vascular quiescence.[8,9] Similar pathways have been implicated in the pathogenesis of moyamoya, though there is no clear molecular link between ALK1 and moyamoya, and the malformations due to aberrant endoglin/ALK1 signaling pathways are that of vascular telangiectasia and anomalous vascular development lacking a capillary bed rather than arterial steno-occlusive disease. Interestingly, in one study of 12 patients with moyamoya, endoglin was found to be overexpressed in the intima of the middle cerebral artery compared with healthy controls.[10] In the cohort, there was an absence of immunoreactivity for endothelial growth factor, a key regulator in angiogenesis and vessel repair. Endoglin and ALK-1 are both components of the TGFβ receptor complex and both can cause HHT when mutated, typically causing a loss of function. Whether such mutations, potentially coupled with other factors resulting in a gain of function, may also predispose to moyamoya is unknown. HHT may also predispose to moyamoya via other mechanisms. Shunting of blood through pulmonary AVMs, for example, could permit

passage of vasoactive substances that would otherwise be inactivated in the pulmonary vascular bed; this has been hypothesized as a potential “second hit” mechanism that could lead to moyamoya in patient with predisposing conditions.[11] Our patient had no evidence of pulmonary AVM or interatrial shunt on transthoracic echocardiogram, making this mechanism unlikely to contribute to the moyamoya pathogenesis of the current case.

There are some special considerations with regards to moyamoya management in a patient with HHT. First, antithrombotic agents are typically avoided in patients with HHT due to risk of epistaxis and gastrointestinal bleeding. In this case, these risks were weighed against the potential benefits of aspirin in preventing thromboembolism in the stenotic vessel, and the aspirin dose was adjusted based on emergence of epistaxis at higher doses. Perioperative antiplatelet therapy was prioritized, as the stroke risk is relatively high perioperatively.[12,13] Second, iron-deficiency anemia is a common complication of HHT,[14,15] and is a risk factor for perioperative stroke in children with moyamoya.[16-18] Therefore, evaluation for and treatment of anemia in children with HHT and moyamoya may help reduce stroke risk. Finally, children with HHT and moyamoya may require more frequent neuroimaging surveillance following surgical revascularization. In addition to standard postoperative moyamoya neuroimaging to assess for adequate revascularization, additional surveillance for *de novo* vascular malformations may be needed, particularly because data in both animal models and humans have indicated that trauma, wounds, and inflammatory insults can trigger development of vascular malformations.[19-21]

This report has important limitations. The singular nature of this case limits our ability to determine if there is in fact a pathogenic link between HHT and moyamoya, or if

this is simply a case of bad luck. Only targeted evaluation of the *ACVRL1* gene was performed. Whole exome sequencing to evaluate for genetic variants associated with moyamoya was recommended but never sent due to exorbitant cost to the family. Finally, given the unilateral nature of the findings and the limited duration of follow up at this time, we cannot confirm the diagnosis of moyamoya. Though the disease distribution and progression over about 14 months is most consistent with moyamoya arteriopathy, there was no clear evidence of engraftment at 7 months after surgery, though engraftment may take up to one year in pediatric moyamoya arteriopathy. Alternate explanations for the radiographic findings, such as an intracranial dissection, focal cerebral arteriopathy, and ICA terminus thrombosis, were considered less likely given radiographic appearance, disease progression over time, and otherwise benign clinical history.

Neuroimaging to screen for brain vascular malformations is recommended for children with HHT at the time of diagnosis.[1] Special attention to the carotid termini to evaluate for early steno-occlusive disease is reasonable. Further evaluation of larger cohorts of children with HHT who have screening neuroimaging may help to elucidate the link between moyamoya and HHT.

Figure Legend

Figure 1. A) Axial maximal intensity projection (MIP) MRA images of the circle of Willis show stenosis of the right internal carotid terminus and proximal A1 and M1 segments, with prominent collateral vessels highlighted in circles. B) 3D MIP in the oblique AP projection of the right internal carotid artery again demonstrates marked focal narrowing of the carotid terminus and proximal A1 and M1. Hypertrophied lenticulostriate collateral vessels project upward, characteristic of moyamoya (block arrow). C) 3D MIP in the oblique AP projection of the normal left internal carotid artery as a comparison. D) Serial axial FLAIR images show asymmetric curvilinear hyperintensities (block arrows) reflecting slow flowing leptomeningeal vessels along the cortical surface of the right cerebral hemisphere, compatible with 'ivy sign' in the setting of moyamoya arteriopathy. *MIP, maximal intensity projection. MRA, magnetic resonance angiography. 3D, 3-dimensional. AP, anterior-posterior. FLAIR, fluid attenuated inversion recovery.*

Figure 2. Digital subtraction cerebral angiography. A) Oblique lateral view of right carotid injection shows marked stenosis at the right ICA and origin of A1 segment of ACA (arrows). The lenticulostriate and ICA terminus perforators are hypertrophied (block arrow). B) Oblique AP projection of the right internal carotid artery shows stenosis of the right ICA terminus and origin of M1 and A1, with moyamoya (puff of smoke) appearance of the lenticulostriate collateral vessels (block arrow). C) Oblique AP projection of the left carotid injection shows normal caliber of the ICA, ACA and MCA as a comparison. *ICA, internal carotid artery. ACA, anterior carotid artery. AP, anterior-posterior. MCA, middle cerebral artery.*

Figure 3. A) Pre-surgical coronal (whole brain) and axial (16 mm thickness) MIP MRA images of the circle of Willis. B) Post-surgical MRA at 7 months following pial synangiosis shows increased prominent visualization of the right superficial temporal artery (open arrows). However, the distal right ICA, A1 segment of ACA and entire MCA are poorly visualized (dashed circles), indicating progression of steno-occlusive disease, although the degree of stenosis is likely exaggerated by technical differences (post-surgical MRA performed at lower spatial resolution and lower magnetic field strength at 1.5 T v. 3.0 T for the baseline study). Note the persistent presence of lenticulostriate collateral vessels (arrowheads). C) Post-surgical axial FLAIR images show persistent slow flowing leptomeningeal vessels along the cortical surface of the right cerebral hemisphere ('ivy sign') but no evidence of parenchymal ischemia. D) Post-surgical ASL shows decreased CBF throughout the right MCA territory (white arrow) and marked hypertensity in the right MCA vasculature (block arrows) related to a delayed transit. *MIP, maximal intensity projection. MRA, magnetic resonance angiography. FLAIR, fluid attenuated inversion recovery. ICA, internal carotid artery. ACA, anterior carotid artery. MCA, middle cerebral artery. ASL, arterial spin labeling. CBF, cerebral blood flow.*

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AUTHOR CONTRIBUTIONS:

Lisa R. Sun conceptualized / designed the study, contributed to data interpretation, drafted the manuscript, critically edited the manuscript, and approved the submission.

Vedmanvitha Ketireddy performed data collection / radiographic database review, critically edited the manuscript, and approved the submission.

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Doris D.M. Lin, MD designed the study, performed data collection / radiographic database review, contributed to data interpretation, critically edited the manuscript, and approved the submission.

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