pediatric stroke

WHEN RARE MEETS RARE: MOYAMOYA ARTERIOPATHY IN A PEDIATRIC PATIENT WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA TYPE 2 (HHT-2) - A CASE REPORT AND OVERVIEW

Silva Lõo, Felix Ratjen, Pradeep Krishnan, Elizabeth Pulcine, Mahendranath Moharir, Prakash Muthusami, Manohar Schroff, Adriana Carolina Vargas Nino, Amanda Robertson, Nomazulu Dlamini

ABSTRACT

Background: Hereditary Hemorrhagic Telangiectasia (HHT) is known to cause multisystemic vascular disease, and risk for intracranial hemorrhage, thromboembolic stroke, and brain abscess in children. Moyamoya arteriopathy (MMA) is a progressive steno-occlusive arteriopathy, which has not previously been described in children with HHT.

Case Presentation: We describe unilateral MMA in an asymptomatic 8-year-old female with a pathogenic variant in the activin A receptor type II-like I (ACVRL1) gene and a positive family history of HHT-type 2. Expanded genetic testing with whole genome sequencing did not yield additional known contributory genetic variants to MMA. Due to radiographic evidence of MMA progression, impaired cerebral perfusion and compromised hemispheric hemodynamics, she underwent uneventful indirect revascularization with pial synangiosis, and continues on Aspirin for primary stroke prevention without complications.

Conclusions: Aberrant signaling through transforming growth factor-β (TGF-β) and its effects on angiogenesis and endothelial function is a possible common molecular mechanism in HHT and MMA. A better understanding of the pathogenesis of both vasculopathies, as well as possible associations, is needed to accurately guide estimation of risk for ischemic and hemorrhagic cerebrovascular complications, balancing the risks and benefits of antithrombotic therapy, frequency, and timing of cerebrovascular and systemic surveillance, as well as surgical and non-surgical treatment approaches for pediatric patients with HHT and MMA.

Background

Hereditary Hemorrhagic Telangiectasia (HHT) or Rendu-Osler-Weber Syndrome is a rare autosomal dominant multisystemic vascular disease characterized by recurrent epistaxis, mucocutaneous telangiectasias, and arteriovenous malformations (AVMs). HHT is clinically diagnosed based on the Curaçao criteria, which have low sensitivity but high

specificity for the diagnosis of HHT in young children (Govani & Shovlin, 2009; Faughnan et al., 2020, Table 1; Pollak et al., 2023; Danesino et al., 2023; Table 2). Secondary to arteriovenous shunting through pulmonary AVMs and paradoxical embolism, HHT is known to cause thromboembolic stroke, hemorrhage, and brain abscess in children. Children, including infants,

Genes and proteins associated with Hereditary Hemorrhagic Telangiectasia

TABLE 1

Gene	Affected Protein	Location	Phenotype	Classic Symptoms	Frequency
HHT					
ENG	Endoglin	9q34.11	HHT-1	Nosebleeds, telangiectasia, AVMs Increased rates of brain and pulmonary AVMs	39-59%
ACVRL1	ALK1	12q13.13	HHT-2	Nosebleeds, telangiectasia, AVMs Increased rates of liver AVMs	25-57%
MADH4	Smad4	18q21.1	HHT-juvenile polyposis syndrome	Nosebleeds, telangiectasia, AVMs Juvenile polyposis syndrome	1-2%
HHT-like syndromes					
GDF2	BMP9	10q11.22	HHT-like	Nosebleeds, telangiectasia, family history	<1%
RASA-1	P120-Ras GAP	5q14.3	Rasa-1 related disorders (CM-AVM)	Dermal telangiectasia, cerebral AVMs	Unknown

Govani & Shovlin, 2009; Viteri-Noël et al., 2022

Curaçao Diagnostic Criteria for Hereditary Hemorrhagic Telangiectasia

TABLE 2		
Criteria	**Epistaxis**	Spontaneous, recurrent nosebleeds
	Telangiectasias	Multiple at characteristic sites (lips, oral cavity, nose, fingers)
	Visceral Lesions	Gastrointestinal telangiectasia, pulmonary AVM, hepatic/cerebral/spinal AVM
	Family History	First degree relative with HHT diagnosis according to criteria
Diagnosis	**Definite**	3 or more criteria are fulfilled
	Possible/ Suspected	2 criteria are present
	Unlikely	1 or none criteria are present

Govani & Shovlin, 2009; Faughnan et al., 2020

with a positive family history of HHT, are at an increased risk of sudden and devastating intracranial hemorrhage from cerebrovascular malformations (Beslow et al., 2020), however the risk of ischemic stroke in this population is unknown.

Given the risk of serious complications affecting multiple systems, current HHT guidelines recommend that children undergo contrast-enhanced magnetic resonance imaging (MRI) of the brain to screen for AVMs, and a contrast echocardiogram to detect pulmonary right-to-left shunting at the time of diagnosis (Faughnan et al., 2020). Contrast-enhanced brain MRI is considered to have good specificity and sensitivity for identifying cerebral AVMs, however without dedicated cerebrovascular imaging, such as magnetic resonance angiography (MRA) or catheter-directed cerebral digital subtraction angiography (DSA), additional vascular abnormalities might be missed.

Moyamoya arteriopathy (MMA) is defined by chronic progressive steno-occlusion of the terminal segment of the internal carotid artery (ICA) and contiguous middle cerebral artery (MCA) and anterior cerebral artery (ACA) with formation of a compensatory network of lenticulostriate collateral vessels that bypass the occlusion and appear as a “puff of smoke” on catheter-directed DSA (Suzuki & Takaku, 1969; Ihara et al., 2022). Moyamoya disease refers to idiopathic disease, whereas moyamoya syndrome refers to patients in whom the arteriopathy occurs in association with a known disease or condition such as sickle cell disease, neurofibromatosis type-1 or trisomy 21 (Dlamini et al., 2019). MMA is a known cause of recurrent stroke in children and adults but is also increasingly being detected during surveillance screening in children with comorbid inherited diseases (Kuroda, 2015; Lin et al., 2011; Lehman et al., 2022). While the etiopathogenesis of MMA remains largely unknown, the proposed mechanisms include angiogenic and vasculogenic imbalance, and aberrant vascular

remodeling in association with genetic susceptibility and inflammation in segmentally vulnerable cerebral vasculature (Tinelli et al., 2020; Dorschel and Wanebo, 2023).

Here we describe MMA in a previously healthy, asymptomatic 8-year-old female with a pathogenic variant in the activin A receptor type II-like I (ACVRL1) gene and a positive family history of HHT-type 2 and discuss possible overlapping etiopathogenetic mechanisms of the two rare cerebrovascular diseases.

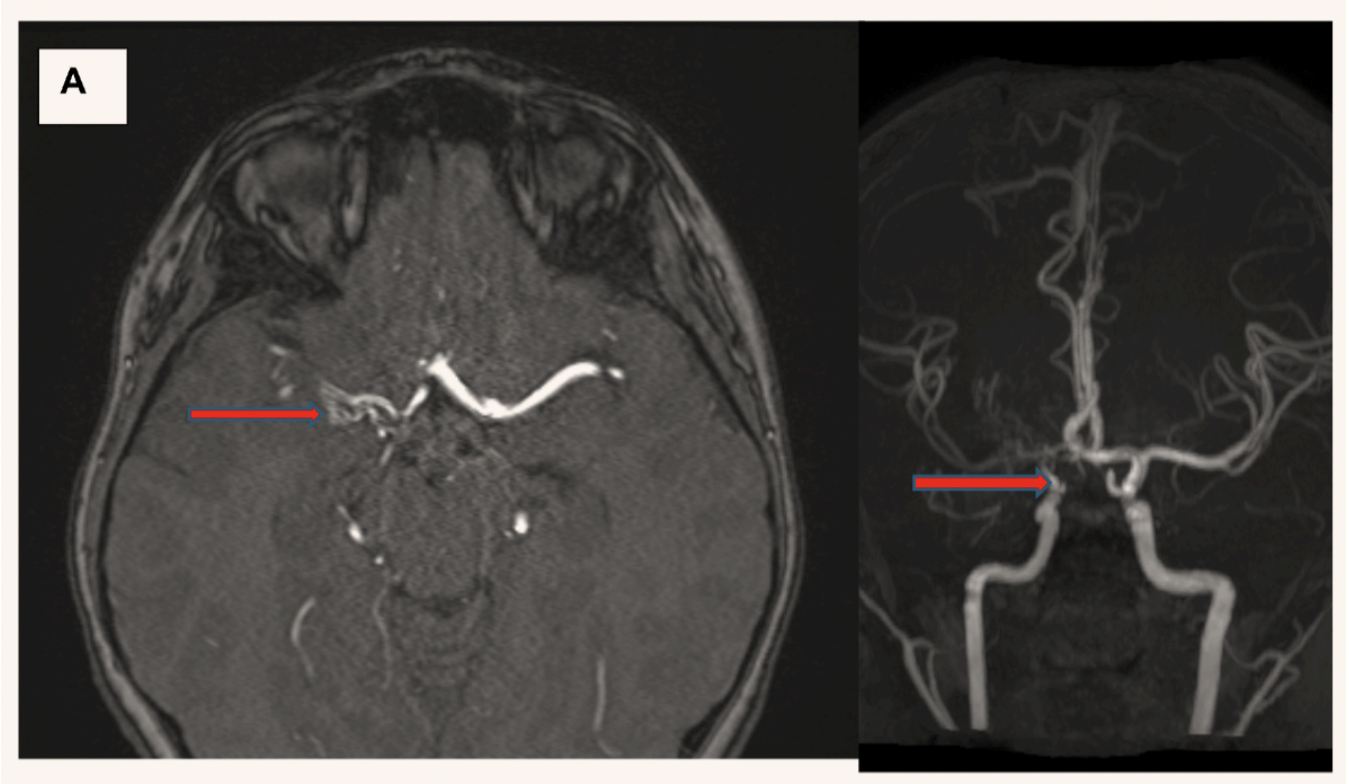
Case Description

An 8-year-old, developmentally appropriate female was diagnosed with HHT-2 following genetic testing due to a positive family history of the disease and familial heterozygous pathogenic variant in the ACVRL1 gene (GRCh38, NM 000020.3, c.150G>A, p.Trp50*). She was asymptomatic and had a normal physical examination.

Initial screening brain MRI with and without contrast revealed normal brain parenchyma, developmental venous anomalies in the right frontal and left occipital lobes, no AVMs, arteriovenous fistulae, or capillary malformations. Vascular imaging with time-of-flight and contrast-based MRA revealed unilateral MMA with marked signal attenuation of the terminal segment of right ICA, narrowing of the right A1 segment of the ACA, and the right M1 segment of the MCA, and proliferative collaterals at the inferior aspect of right basal ganglia. The left ICA, MCA and ACA, and the main arteries in the posterior circulation were normal. T2-weighted fluid-attenuated inversion recovery (FLAIR) images showed foci of hyperintense signal in the sulci of the right cerebral hemisphere in keeping with an ivy sign (see Figure 1, Aa, Ba). Systemic vascular workup included normal abdominal ultrasound and normal echocardiography. Intracardiac and intrapulmonary shunting were excluded using the triple CO2 agitated saline bubble test. The patient underwent expanded genetic testing with whole genome sequencing which confirmed the ACVRL1 pathogenic variant in the proband and did not yield additional known contributory genetic variants to MMA. Antithrombotic therapy with Aspirin 81mg once daily (approximately 3mg/kg) was initiated for primary stroke prevention.

Follow-up brain MRI and MRA at 6 months demonstrated stable parenchymal findings and a prominent P4 segment of the right posterior cerebral artery (PCA) in keeping with pial collateral formation. Blood oxygen level-dependent functional MRI (BOLD-fMRI) with breath-hold hypercapnic challenge showed abnormal negative cerebrovascular reactivity (CVR) in the right hemisphere, suggestive of steal phenomenon. Catheter-directed DSA confirmed unilateral MMA with steno-occlusion of the terminal segment of the intracranial right ICA with proliferative basal and pial collaterals to the MCA territory (see Figure 1C-D).

After multidisciplinary discussions, the patient underwent right-sided indirect revascularization with pial synangiosis on the basis of (1) radiographic evidence of progression of the MMA; (2) presence of the ivy sign as a radiographic biomarker of impaired cerebral perfusion (Montaser et al., 2022); and (3) compromised right-sided hemispheric hemodynamics with evidence of steal phenomenon on CVR as a known prognostic indicator of risk for ischemic complications (Dlamini et al., 2020; Gupta et al., 2012; Reinhard et al., 2008).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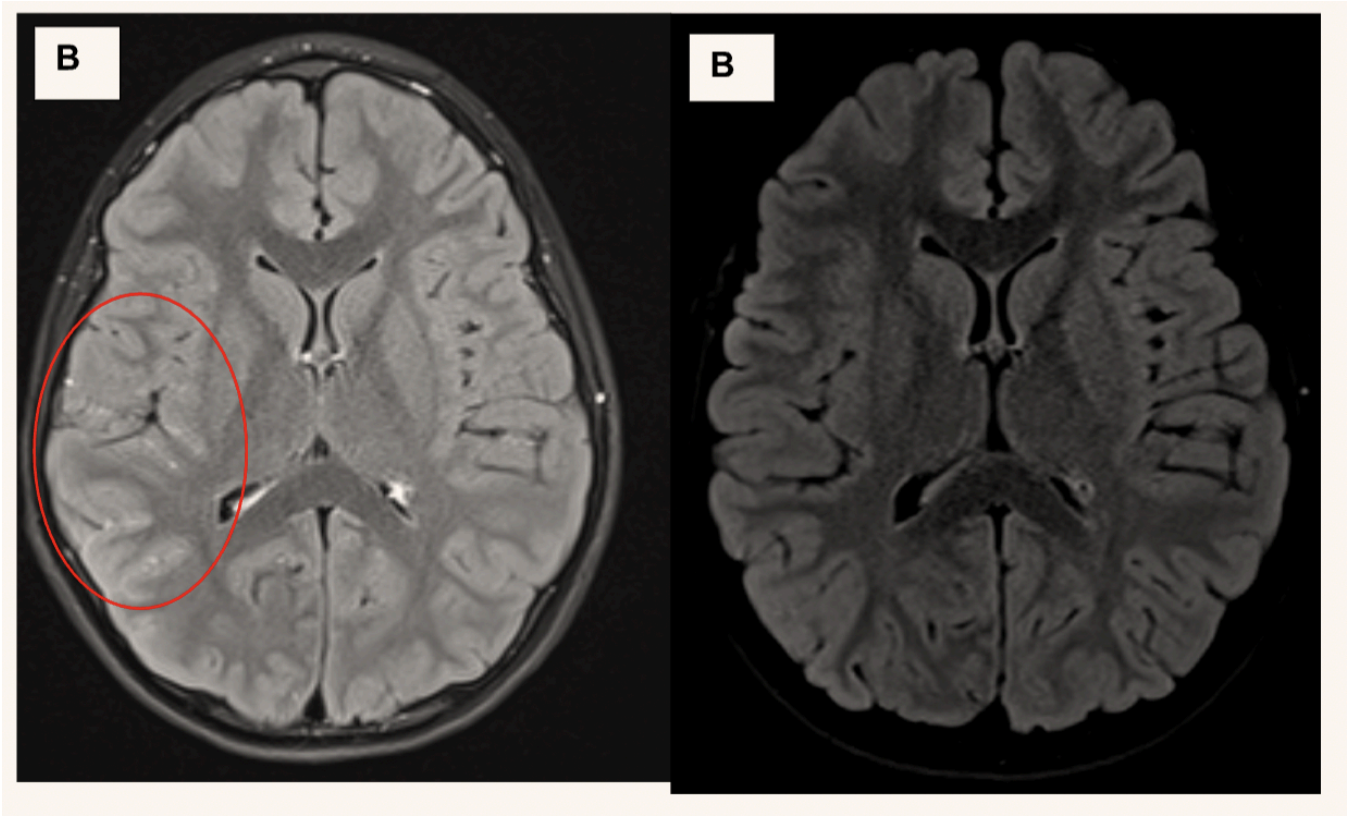
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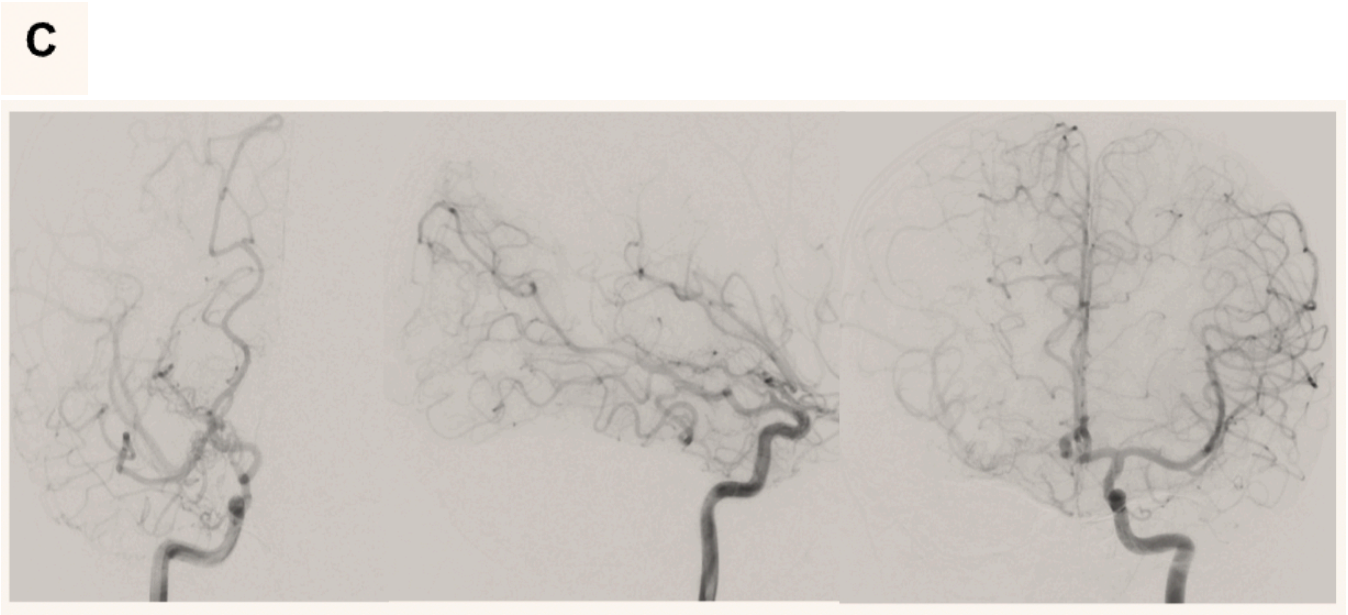
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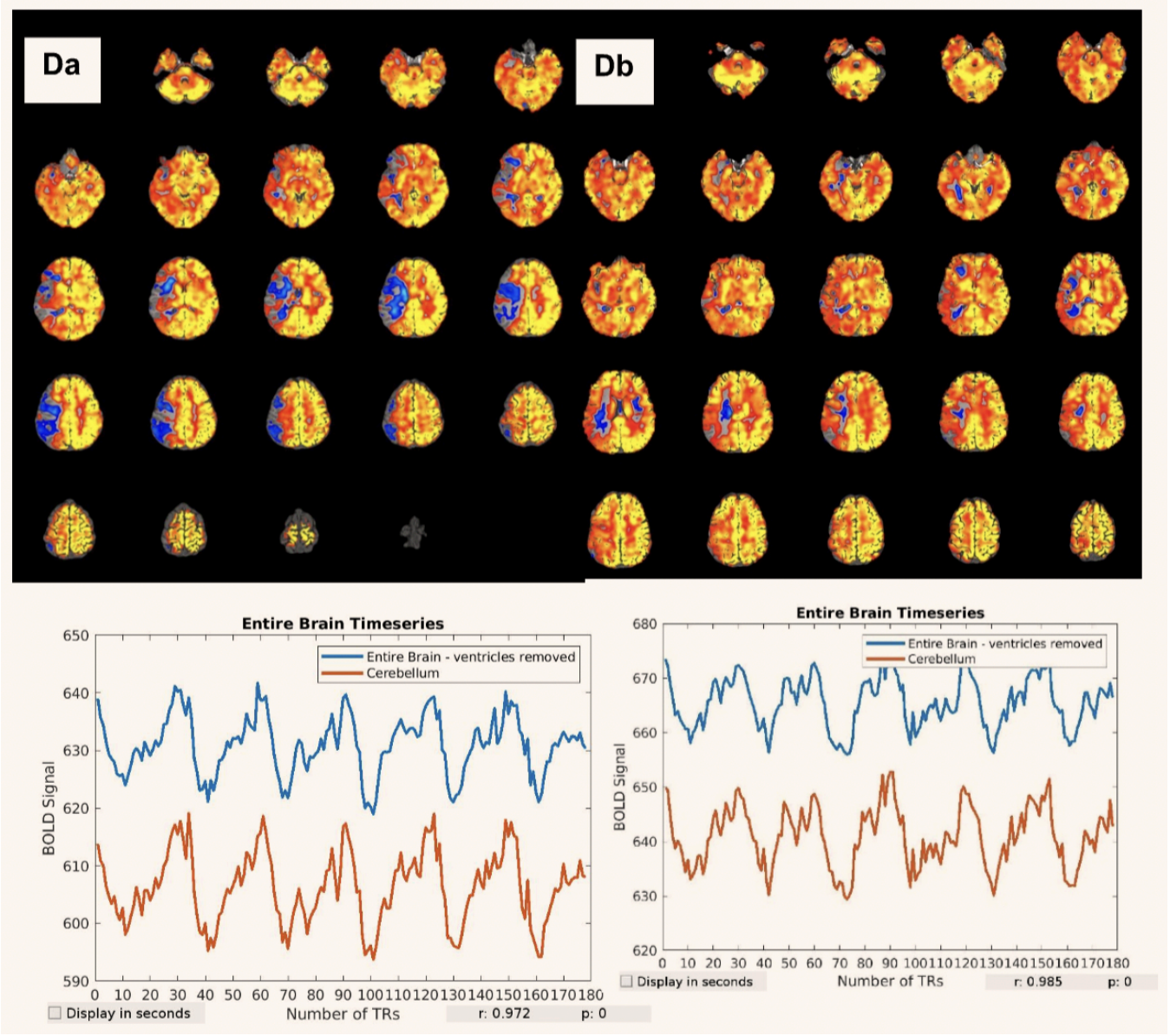

Figure 1. (A) Three-dimensional maximum intensity projection of time-of-flight magnetic resonance angiography (MRA, TOF) shows right terminal ICA occlusion, significant narrowing of proximal MCA and ACA with proliferative collaterals (Aa at the time of diagnosis, Ab 7 months post-surgery; (B) Axial Fluid-attenuated Inversion Recovery (FLAIR) MRI shows diffuse leptomeningeal hyperintensities, in keeping with 'ivy' sign in the sulci of the right cerebral hemisphere at the time of diagnosis (Ba), and resolved 'ivy' 7 months post-surgery (Bb); (C) Catheter-directed cerebral angiography shows occlusion of right terminal ICA with multiple collaterals from the terminal segment of the right ICA and hypertrophied anterior choroidal artery , and normal appearance of left ICA supplying bilateral ACA-s, and right MCA; (D) Blood oxygen level-dependent functional MRI (BOLD-fMRI) with hypercapnic challenge of cerebrovascular reserve (CVR) reveals abnormal negative cerebrovascular reactivity in the right hemisphere (blue area beyond the ventricle) at the time of diagnosis (Da), and 7 months post-surgery (Db). (E) Whole brain and cerebellar BOLD (as regressor) signal changes during hypercapnic challenge pre- and post-surgery.

Seven months post revascularization surgery, follow-up brain MRI/MRA showed stable unilateral steno-occlusion with patent pial synangiosis through the frontal branch of the right superficial temporal artery, and resolution of the ivy sign in the right hemisphere. CVR showed reduced negativity within the right

cerebral hemisphere compared to the pre-surgery CVR (see Figure 1C-D).

Discussion

In this report, we describe the co-occurrence of two rare cerebrovascular diseases, HHT-2 and moyamoya arteriopathy, in an 8-year-old asymptomatic female, and discuss possible common etiopathogenetic mechanisms.

Central nervous system complications in patients with HHT can result from vascular malformations in the brain and spinal cord, or occur secondary to embolism from right-to-left shunting in the pulmonary vascular bed (from AVMs), causing hemorrhagic, ischemic, or infectious complications (Brinjikji et al., 2015; Agarwal et al., 2022; White et al., 2023). Up to 29% of patients with HHT develop cerebral vascular malformations, including brain AVFs, nidus-type AVMs, and capillary malformations, with the latter being the most common phenotype (Fulbright et al., 1998; Krings et al., 2015; Beslow et al., 2020; Azma et al., 2022). Given the risk of serious ischemic and hemorrhagic complications, the current consensus-based International HHT Guideline recommends brain MRI with and without contrast for screening of AVMs in asymptomatic children with HHT at the time of diagnosis (Faughnan et al., 2020). While a Position Statement of the European Reference Network for Rare Vascular Disorders (VASCERN-HHT) recommends against widespread cerebral AVM screening of asymptomatic HHT patients due to lack of evidence to favour the treatment of unruptured cerebral AVMs (Eker et al., 2020), the international guideline received a strong agreement, and was supported by a majority of patient and provider representatives as an important component for decision making and patient counseling (Geithoff, 2021; Clancy et al., 2021).

Compared with the gold standard catheter-directed DSA, MRI is relatively sensitive and specific when used to find cerebral AVMs in patient with HHT, with a sensitivity of 80%, specificity of 94.4%, and a negative predictive value of 65.4% (Vella et al., 2020). Catheter-directed DSA is typically not performed in individuals with normal MRI and MRA findings, thus likely underestimating the number of potential cerebral vascular malformations. Without luminal vascular imaging, steno-occlusive arteriopathies might also be missed (Lehman et al., 2024). Conventional stroke risk factors have not been studied in HHT, and the main proposed mechanism of ischemic stroke is thought to be aseptic thromboembolism through pulmonary AVMs, and hyperviscosity secondary to chronic hypoxemia from right-to-left shunts.

To our knowledge, this is the first case report describing MMA as an incidental finding in the setting of HHT-2. Previous studies of children and adults with HHT that have reported results of catheter-directed DSA, have not described steno-occlusive cerebrovascular findings (Krings et al., 2015; Azma et al., 2022). The HHT Project of the Brain Vascular Malformation Consortium reported neurovascular manifestations with imaging features and genotype-phenotype correlations in a cohort of 75 patients with HHT-1 and -2 (average age at enrollment 37 years), who underwent MR imaging with contrast-enhanced sequences, and catheter-directed DSA. MMA was not described in any of the participants (Krings et al., 2015).

As moyamoya has not been previously reported in patients with HHT, and mechanisms of both diseases are a matter of ongoing research, it is of interest to consider possible common etiopathogenetic pathways.

Abnormal vascular development in HHT results from disturbances in the transforming growth factor-β (TGF-β) signaling pathway, affecting the endothelium of small cerebral blood vessels.

Over 90% of patients with HHT harbor a pathogenic mutation in a transforming growth factor TGF-β type III receptor endoglin (ENG) or ACVRL1 genes, and HHT-1 refers to patients carrying mutations in ENG, while variants in ACVRL1 defines HHT-2 (McDonald et al., 2015; Fernandez-L et al., 2005; Viteri-Noel et al., 2022). Both pathogenic variants result in haploinsufficiency, which refers to a reduction of the functional protein levels by 50%, causing imbalance in the TGF-β signaling pathway. Mutations in ACVRL1 cause production of aberrant endothelial transmembrane kinase receptors of TGF-β which fail to be expressed in the cell membranes of endothelial cells, causing disorganized cytoskeleton and fragility of vessels, as well as abnormal angiogenesis after injuries (Fernandez-L et al., 2005; Viteri-Noel et al., 2022). Although HHT-1 and HHT-2 are both related to aberrant angiogenesis and vascular remodeling due to TGF-β signaling defects, the phenotype is slightly different with increased incidence of pulmonary AVMs, brain AVMs, and gastrointestinal bleeding in HHT-1, and liver vascular malformations as well as high output cardiac failure in HHT-2 (Brinjikji et al., 2015; Pahl et al., 2018; Viteri-Noel et al., 2022; Azma et al., 2022).

Endoglin and ALK1 are not only expressed in endothelial cells but are also found in mononuclear cells and have been proposed to serve as adhesion molecules for leucocyte infiltration. Leukocyte infiltration mediated by the expression of adhesion molecules and chemokines synthesized by the endothelium could be impaired, affecting vascular repair and remodeling in HHT (Rossi et al., 2015).

In MMA, the histopathological hallmarks of the vascular disease are extensive fibrocellular intimal thickening caused by proliferation of smooth muscle cells (SMC), irregular undulation of the internal elastic lamina, and significant thinning of media (Kuroda et al., 2008; Fukui et al., 2000; Takagi et al., 2007). Pathologically increased angiogenesis, vasculogenesis and arteriogenesis in MMA result in dilatation of preexisting perforating arteries, and development of new fragile collaterals (Bersano et al., 2016; Bedini et al., 2016; Tinelli et al., 2020). The newly formed vessels show impaired blood-brain barrier function, loss of endothelial cell integrity and various histopathological changes including fragmented elastic lamina, attenuated media, fibrin deposits in the wall and microaneurysms due to increased flow (Kuroda et al., 2008; Lim et al., 2006). The basal and cortical collateral vessels are thought not only to represent compensatory mechanisms for the reduced cerebral blood flow, but also the aberrant active neo-vascularization which can occur before significant hemodynamic impairment (Kim et al., 2014).

The exact pathophysiology of MMA remains unclear, as the disease is heterogeneous and complex, comprising various genotypes and phenotypes. Several angiogenic and cellular proliferative proteins have been associated with the disease and correlated with the histopathological appearance of the diseased vessels (Bedini et al., 2016; Bang et al., 2016; Dorschel & Wanebo, 2023). The circulating biomarkers that may be involved with MMA pathogenesis include endothelial progenitor cells (EPCs) and different cytokines and their polymorphisms (Jung et al., 2008; Rafat et al., 2009; Kim et al., 2010). Although the exact cellular mechanisms involved in EPC mobilization, recruitment, and homing are unclear, this regenerative process is thought to be regulated by (1) growth factors - vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF); (2) cytokines related to vascular remodeling and angiogenesis – matrix metalloproteinases (MMPs) and their inhibitors, hypoxia inducible factor-1α (HIF-1α), and cellular retinoic acid-binding protein-1 (CRABP-1); as well as (3) cytokines related to inflammation (Jung et al., 2008; Bang et al., 2016).

Both MMA and vascular dysplasia in HHT exhibit altered endothelial integrity and vascular remodeling as key pathophysiological processes despite affecting different types of vascular beds. Endothelial dysfunction is further responsible for the dysregulation of vascular tone, cellular adhesion, thrombus formation, smooth muscle cell proliferation, and vessel wall inflammation. Aberrant signaling through TGF-β and its effect on angiogenesis is a possible common molecular mechanism in these diseases.

The level of TGF-β has been found to be elevated in CSF, and expression in arteries of patients with MMA (Hojo et al., 1998). Yamamoto and colleagues (Yamamoto et al., 1997) demonstrated that accumulation of elastin via the TGF-β pathway is also responsible for the intimal thickening in moyamoya. Another link in the overlapping pathologies might be Hypoxia-Induced Factor-1α (HIF-1α), which is one of the major transcriptional activators involved in tissue-oxygen homeostasis. HIF-1 α has been shown to be up-regulated as a result of reduced cerebral blood flow and hypoxia, causing upregulation of TGF-β3 transcription (Nishi et al., 2004; Schaffer et al., 2003). Interestingly, while HIF-1α and endoglin have been demonstrated to be overexpressed in the intima of MCA in patients with MMA (Takagi et al., 2007), ALK1 has not been specifically studied.

While the role of inflammation in the pathogenesis of these vasculopathies remains elusive, there is evidence of common convergent molecular pathways which regulate angiogenic and inflammatory responses associated with abnormal vascular remodeling in both diseases (Hojo et al., 1998; Mahmoud et al., 2010). Upregulation of endoglin and ALK1 on activated monocytes is impaired in HHT-1 and -2, suggestive of their essential role in inflammatory response and tissue repair (Sanz-Rodriguez et al., 2004; Dingenouts et al., 2015). There is a growing body of molecular and clinical evidence which point towards immune-related and inflammatory responses as second hits to trigger moyamoya arteriopathy onset in the background of segmental vascular susceptibility (Asselman et al., 2022; Dorschel & Wanebo, 2023). Inflammatory and vasoactive substances (e.g. prostaglandins and leukotrienes), normally inactivated in the lungs (Said, 1982), have been hypothesized to contribute to the development of MMA by escaping inactivation through potential right-to-left shunting (via patent foramen ovale, atrial or ventricular septal defects, or pulmonary AVMs) and acting upon the endothelium in at risk patients (Xu et al., 2023).

Conclusions

HHT and MMA are two rare vascular diseases which can cause severe cerebrovascular complications in children. Both disorders affect the endothelium of blood vessels in the brain leading to aberrant angiogenesis. While systemic and cerebrovascular complications of HHT have been mostly attributable to AVM rupture or shunting, the role of steno-occlusive pathology remains unclear.

We report an 8-year-old asymptomatic female with HHT-2 and MMA who was diagnosed on the basis of a pathogenic familial heterozygous variant in the ACVRL1 gene. As both systemic vascular diseases affect endothelial integrity and vascular remodeling, disease mechanisms and possible common etiopathogenetic pathways are discussed.

A better understanding of the pathogenesis of both disorders is needed to accurately guide estimation of risk for ischemic and hemorrhagic cerebrovascular complications, balancing the risks and benefits of antithrombotic therapy, frequency, and timing of cerebrovascular and systemic surveillance, as well as surgical and

non-surgical treatment approaches for pediatric patients with HHT and MMA.

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Affiliations:

Silva Lõo MD, MSc
Division of Neurology, Department of Pediatrics, Children's Stroke Program, Research Institute, University of Toronto, Hospital for Sick Children, Toronto, Ontario, Canada
University of Helsinki, and Helsinki University Hospital, Helsinki, Finland

Felix Ratjen MD, PhD, FRCPC, FERS
Division of Respiratory Medicine, Department of Pediatrics, Translational Medicine, Research Institute, University of Toronto, Hospital for Sick Children, Toronto, Ontario, Canada

Pradeep Krishnan MD, MBBS
Department of Diagnostic Imaging and Interventional Radiology, University of Toronto, Hospital for Sick Children, Toronto, Ontario, Canada

Elizabeth Pulcine MD, MSc, FRCPC, CSCN (EEG)
Division of Neurology, Department of Pediatrics, Children's Stroke Program, Research Institute, University of Toronto, Hospital for Sick Children, Toronto, Ontario, Canada

Mahendranath Moharir MBBS, MD, MSc, FRACP
Division of Neurology, Department of Pediatrics, Children's Stroke Program, Research Institute, University of Toronto, Hospital for Sick Children, Toronto, Ontario, Canada

Prakash Muthusami,4 MD, MBBS
Department of Diagnostic Imaging and Interventional Radiology, University of Toronto, Hospital for Sick Children, Toronto, Ontario, Canada

Manohar Schroff,4 MD, DMRD, FRCPC
Department of Diagnostic Imaging and Interventional Radiology, University of Toronto, Hospital for Sick Children, Toronto, Ontario, Canada

Adriana Carolina Vargas Nino MD, MSc
Division of Neurology, Department of Pediatrics, Children's Stroke Program, Research Institute, University of Toronto, Hospital for Sick Children, Toronto, Ontario, Canada

Amanda Robertson,5 MSc
Neurosciences and Mental Health, Stroke Imaging Lab for Children, Hospital for Sick Children, Toronto, Ontario, Canada

Nomazulu Dlamini MBBS, MRCPCH, MSc (Lon), PhD
Division of Neurology, Department of Pediatrics, Children's Stroke Program, Research Institute, University of Toronto, Hospital for Sick Children, Toronto, Ontario, Canada

Corresponding Author
Nomazulu Dlamini,
Division of Neurology, Hospital for Sick Children, 175 Elizabeth Street, M5G 2G3 Toronto, Ontario, Canada; email address nomazulu.dlamini@sickkids.ca