A Tangled Web: Dual Diagnosis of Hereditary Hemorrhagic Telangiectasia and Familial Cerebral Cavernous Malformation

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ABBREVIATION KEY

AVM	**Arterio Venous Malformation**
CCM	**Cerebral Cavernous Malformation**
FH	**Family History**
GC	**Genetic Counselor**
HHT	**Hereditary Hemorrhagic Telangiectasia**

AVM	**Arterio Venous Malformation**
HTC	**Hemophilia Treatment Center**
ISSVA	**International Society for the Study of Vascular Anomalies**
MRI	**Magnetic Resonance Imaging**
TTCE	**Trans Thoracic Contrast Echocardiography**

To the Editor:

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Management of complex vascular anomalies is rapidly evolving towards addition of targeted therapies as we increase our understanding of the various mutations identified in affected tissues. Few vascular anomalies also have pathognomonic germline mutations. We describe a child with dual diagnosis of hereditary hemorrhagic telangiectasia (HHT) and familial cerebral cavernous malformation 1 (CCM1). Family history (FH) revealed 4 affected generations. Importance of a thorough FH and genetic counselors (GCs) key role in a comprehensive vascular anomalies program is highlighted.

A 5-year-old boy developed right hemiparesis, facial droop, focal seizures with generalization, and slurred speech. Brain Magnetic Resonance Imaging (MRI) demonstrated a 2.5 cm left parietal intraparenchymal hematoma with hemosiderin staining and surrounding vasogenic edema. Numerous other foci of hemosiderin staining were present, suggesting multiple cavernous malformations (Fig. 1A). He received levetiracetam and steroids with resolution of neurological deficits. FH (Fig. 2) at initial evaluation revealed an asymptomatic 35-year-old mother (III-6), maternal grandfather (II-7) with a "blip" on brain MRI and history of nose bleeds, and maternal uncles with epistaxis (III-7), frequent headaches (III-8), and "lesions" on spine MRI (III-9). Patient's 34-year-old father (III-5) was well with normal annual chest X Ray screening required for his profession. Paternal grandmother (II-5) stroked at age 5 years, had a brainstem vascular lesion resected in young adulthood, and her brother (II-1) had brain surgery at age 13 years. This great-uncle also has two children who have cerebral vascular lesions on MRI (III-2, III-3). Paternal uncle (III-4) had 8-10 brain "vascular lesions" being monitored. Paternal grandfather (II-4) died from skin cancer at 38 years. Paternal great-grandfather (I-1) had a seizure disorder at least throughout his adulthood. No one had undergone genetic testing previously. Patient's 11 and 9-year-old sisters were well. CCM and HHT genetic testing panels on the proband revealed a heterozygous pathogenic variant [c.1201_1204del (p. Gln40TThrfs*10)] in the KRIT1 gene and a heterozygous likely pathogenic variant [c.598C>T (p. Arg200Trp)] in the ACVRL1 gene, indicating dual diagnosis of CCM1 and HHT. Subsequent family testing showed his mother, two maternal uncles, and maternal grandfather have the ACVRL1 variant, and father, paternal uncle and paternal grandmother have the KRIT1 variant. The eleven-year-old sister has negative genetic testing, but the 9-year-old possesses both variants (Fig. 2). Patient's serial brain imaging showed resolution of the large left frontoparietal subcortical bleed over time and re-demonstrated multiple "cavernomas". Spine MRI and pulmonary arteriovenous malformation (AVM) screening by transthoracic contrast echocardiography (TTCE) were negative. He does not have epistaxis or oral-cutaneous telangiectasias. No neurosurgical or neuro-interventional procedure are planned currently. His affected sister has multiple small cerebral "cavernomas" with a large lesion in the right cerebellum (Fig. 1B).

CCMs occur in the brain and spinal cord and consist of clustered, enlarged capillary channels. They can occur sporadically in isolation, or as part of familial CCM, an autosomal dominant disorder caused by pathogenic variants in one of 3 known genes: KRIT1, CCM2, PDCD10. Familial CCM is not a fully penetrant genetic condition and only 50% of individuals will be symptomatic of seizures, cerebral hemorrhage, headaches, or retinal "cavernomas". Of the asymptomatic patients, about 50% will have an identifiable CCM on imaging. The Angioma Alliance has published consensus guidelines regarding diagnostic and management strategies[1]. HHT is also an autosomal dominant vascular disorder, causing AVMs in the brain, lungs, and liver, as well as skin and mucosal telangiectasias. Unlike familial CCM, HHT is nearly fully penetrant. It is caused most often

by an alteration in one of three genes: ACVRL1, ENG, or SMAD4. Diagnosis and management guidelines are well established[2]. CCMs are classified as venous malformations and HHT as an arteriovenous malformation disorder, per the International Society for the Study of Vascular Anomalies (ISSVA) classifiction[3].

The estimated prevalence of HHT and familial CCM is 1/5000 to 1/10,000[1,2] and chance of inheriting both is rare at 1/100,000 to 1/400,000. Our two pediatric patients are unique in that they carry genes for both conditions, a first report of its kind. Involvement of genetic counselors in our vascular anomalies program allowed for establishment of a 4-generation pedigree, genetic counseling, and testing for all family members as desired. Earlier genetic diagnosis in the extended family could potentially have led to timely diagnosis and preemptive screening with intervention for our patient and other family members. The adult family members now diagnosed with HHT or CCM1 have established with adult hematologists at our Hemophilia Treatment Center (HTC). The HTC model of care with all its resources is very applicable to comprehensive care of patients with HHT and other vascular anomalies. Additionally, it provides for seamless transition from pediatric to adult care and enables comprehensive care for the whole family, as in our patient's case. Large, deep posterior fossa vascular lesions (Fig 1B) at risk for bleeding can be challenging to manage by surgical or interventional approaches. In this context, we note a recent publication demonstrating augmented mTOR signaling in CCM endothelial cells and use of mTOR inhibitor Rapamycin in mouse models, showing effective blocking of CCM formation[4], with hope for translation to targeted therapies in such patients.

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`Figure 1A, B.docx` available at https://authorea.com/users/624680/articles/646932-a-tangled-web-dual-diagnosis-of-hereditary-hemorrhagic-telangiectasia-and-familial-cerebral-cavernous-malformation