A theory for polymicrogyria and brain arteriovenous malformations in HHT

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Abstract

Hereditary hemorrhagic telangiectasia (HHT) is generally considered a disorder of endothelial dysfunction, characterized by the development of multiple systemic arteriovenous malformations (AVMs), including within the brain. However, there have recently been a number of reports correlating HHT with malformations of cortical development, of which polymicrogyria is the most common type. Here we present 7 new cases demonstrating polymicrogyria in HHT, 6 of which demonstrate a brain AVM (bAVM) in close spatial proximity, with the aim of providing a common origin for the association. Upon reviewing patient genetics and imaging data and comparing with previously reported findings, we form 2 new conclusions: (1) polymicrogyria in HHT appears exclusively associated with a subset of mutations in the transmembrane protein endoglin that is involved with blood flow–related mechanotransduction signaling during angiogenesis and (2) the polymicrogyria is characteristically unilateral, typically focal, and correlates with vascular regions experiencing low fluid shear stress during corticogenesis in utero. Integrating these with findings in the literature from genetics and molecular biology experiments, we propose a theory suggesting haploinsufficient endoglin mutations, especially those that are dominant-negative, may predispose focal, aberrant hypersprouting angiogenesis during corticogenesis that leads to the production of polymicrogyria. This hypoxic insult may further serve as the revealing trigger for later development of a spatially coincident bAVM. This hypothesis suggests an essential role for endoglin-mediated hemodynamic mechanotransduction in normal corticogenesis.

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Glossary

ALK1 = activin receptor-like kinase 1; **bAVM** = brain arteriovenous malformation; **BMP** = bone morphogenetic protein; **DN** = dominant-negative; **EC** = endothelial cell; **FSS** = fluid shear stress; **HHT** = hereditary hemorrhagic telangiectasia; **MCD** = malformations of cortical development; **pAVM** = pulmonary arteriovenous malformation; **SC** = stalk cell; **TC** = tip cell; **TGF β** = transforming growth factor β ; **VEGFA** = vascular endothelial growth factor A; **VoGM** = vein of Galen malformation; **vSMC** = vascular smooth muscle cells; **WT** = wild-type.

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is caused by numerous mutations of at least 3 known genes involving mediators of the transforming growth factor β (TGF β) pathway (*ENG* encoding endoglin, *ACVRL1* encoding activin receptor-like kinase 1 [ALK1], and *SMAD4* encoding Smad4, referred to as HHT1, HHT2, and HHT-JP overlap syndrome, respectively).¹ The overall prevalence of HHT is estimated between 1 in 5,000 to 10,000 and approximately 20% of patients with HHT demonstrate a brain arteriovenous malformation (bAVM) using standard imaging modalities.² In contrast, the non-HHT population has a prevalence of bAVMs around 0.01%.³ This significantly increased propensity for bAVMs in patients with HHT reflects their underlying genetic susceptibility to develop erroneous angiogenesis and cerebrovascular remodeling.

Although still a rare entity, detection of cerebral malformations of cortical development (MCD) has significantly increased with advancements in clinical imaging.⁴ Existing on a spectrum of morphologically different malformations related to the timing and location of an applied insult during the phases of normal cortical development,⁵ several recent reports associate MCDs with HHT.^{6,7} In fact, while the prevalence of the most common form, polymicrogyria, is unavailable due to its scarcity, early reports suggest its prevalence among patients with HHT with neuroimaging to be around 5%–10%. Short range spatial coincidence between MCDs and brain vascular malformations has also been frequently observed.^{8,9}

In this Medical Hypothesis, we present 7 new cases from a cohort of 142 patients with HHT assessed by the Brain Vascular Malformation Consortium HHT Investigator Group that demonstrate polymicrogyria on imaging studies, 6 of which demonstrate bAVMs in close proximity. By assessing the morphology (or phenotype) of these lesions and correlating with patient genetics, we propose a theory providing a common origin.

Phenotype and genotype of observed lesions

The methods used are provided in data available from Dryad (Materials, doi.org/10.5061/dryad.ng473mj) and included REB approval and informed written consent for all study participants. The prevalence of polymicrogyria in our cohort

of patients with HHT with available diagnostic imaging was approximately 5% (7/142). Clinical data (table 1) demonstrated no particular sex preference, with *ENG* mutation (HHT1) confirmed on the basis of personal or familial genetic testing in all cases. Only 2 cases presented with symptoms of seizure (secondary to hemorrhage), while pulmonary arteriovenous malformations (pAVMs) were present in 6 cases.

Polymicrogyria was the only form of MCD identified, with 6 patients also demonstrating an adjacent bAVM (table e-1, doi.org/10.5061/dryad.ng473mj). These cases demonstrate 3 phenotypes: (1) focal polymicrogyria with adjacent bAVM ($n = 4$, figure 1, A–C, and figure e-1), (2) unilateral perisylvian polymicrogyria with adjacent bAVM ($n = 2$, figure 1, D–G, and figure e-2), and (3) focal polymicrogyria with no associated bAVM ($n = 1$, figure e-3). The bAVM seen in the infant (patient 4) was a fistulous lesion with one definite feeding artery and several dilated en passage cortical draining veins, while all 5 pericortical bAVMs seen in the adult patients were sharply demarcated with similar angioarchitectural characteristics (table e-1). Coincident lesion location appeared randomly in distal anterior cerebral arterial vascular territory.

Comparison with previous reported findings

These cases add to an emerging literature associating HHT with MCDs. Our findings agree with previous reports, particularly that the in utero effect is unilateral and focal, allowing the polymicrogyria to be clinically occult.⁶ When genetic testing is available, as it was in all of these cases, only *ENG* mutations (HHT1) have been reported with radiologic evidence of polymicrogyria. The 85.7% (6/7 cases) prevalence of spatially coincident polymicrogyria and bAVMs in this cohort raises suspicion for a common insult precipitating the development of both lesions.

Postulate 1: Polymicrogyria in HHT1 reflects in utero cerebral hypoxia

Corticogenesis is often divided into 3 stages: (1) neurogenesis (gestational weeks 4–20), (2) neuronal migration (most between gestational weeks 8–20), and (3) cortical organization (starting around gestational week 20).¹⁰ The presence of isolated polymicrogyria is helpful in narrowing the temporal

Table 1 Clinical and mutation information of patients with hereditary hemorrhagic telangiectasia (HHT) demonstrating polymicrogyria on screening MRI for neurovascular malformations (mutation information from the University of Utah *ENG* database, arup.utah.edu/database/ENG/ENG_display.php, for patients 1–4 and 6, and using Ensembl variant effect predictor, useast.ensembl.org/Homo_sapiens/Tools/VEP, for patients 5 and 7)

Patient	Curacao criteria	Mutation type	Nucleotide change	Protein change	Mother affected	Age at first HHT symptom	Seizure at presentation	Stroke at any time	Pulmonary AVM	Liver AVM	Mucocutaneous telangiectasia
1	4	Nonsense	ENG: c.808C>T	<i>p.Gln270X</i>	Yes	2 y, epistaxis	Yes	Yes	Yes	No	Yes
2	4	Familial, splice site (intron 4)	ENG: c.524-2A>G	—	Yes	5 y, epistaxis	No	No	Yes	Yes	Yes
3	4	Familial, splice site (intron 4)	ENG: c.524-1G>A	—	No	8 y, epistaxis	No	No	Yes	No	Yes
4	4	Familial, nonsense	ENG: c.1522C>T	<i>p.Gln508X</i>	Yes	3 mo, seizure (secondary to hemorrhage)	Yes	Yes	Yes	No	No
5	4	Frameshift deletion	ENG: c.658delA	<i>p.Ile220fs</i>	No	6 y, epistaxis	No	No	No	No	Yes
6	4	Familial, missense	ENG: c.1A>G	<i>p.Met1?</i>	No	13 y, epistaxis	No	No	Yes	No	Yes
7	4	Familial, frameshift deletion	ENG: c.764delG	<i>p.Gly255fs</i>	Yes	28 y, epistaxis	No	No	Yes	No	Yes

Abbreviation: AVM = arteriovenous malformation.

Figure 1 Polymicrogyria with adjacent brain arteriovenous malformations (bAVMs) in patients with hereditary hemorrhagic telangiectasia (HHT)

(A) T2-weighted axial imaging demonstrates abnormally thickened cortex in the posterior parasagittal right frontal lobe (white arrow) in patient 1 at 15 years of age. (B, C) Follow-up imaging when this lesion became symptomatic at 23 years of age demonstrates enhancement of the adjacent bAVM (white arrow) on coronal T1-weighted postcontrast imaging. This vascular malformation (black arrow) and another anterior bAVM (white arrowhead) are present on right ICA injection digital subtraction angiogram. Sagittal T1-weighted images of the right (D) and left (E) Sylvian fissures in patient 5, a 23-year-old man, demonstrate the abnormal, nodular, stippled perisylvian cortex on the right (white arrow). (F) Further demonstration of asymmetry of the Sylvian fissures is evident on T1-weighted axial imaging, with polymicrogyria on the right (white arrowhead). (G) Located within the superior aspect of the right Sylvian fissure is a bAVM (white arrowhead) identified on contrast-enhanced magnetic resonance angiogram.

range for an in utero insult since it is believed to relate to developmental disturbances occurring during late migration or early cortical organization (gestational weeks 16–24). Strict identification of malformation etiology requires histologic or genetic analyses, which are often equivocal.¹¹

Lesion spatial distribution offers some insight about the origins of polymicrogyria in HHT1. Most cases of polymicrogyria with proven etiology are due to congenital infections or hypoxia. A generalized pattern over the entire cortex is the second most common, occurring 13% of the time, with congenital cytomegalovirus infection and peroxisomal disorders the commonest causes.¹² None of the reported cases of polymicrogyria in HHT1 have the generalized form, and therefore, it seems reasonable to attribute its presence to in utero hypoxia. Perisylvian polymicrogyria is the most common pattern, occurring in approximately two-thirds of cases and bilaterally symmetric 85% of the time.¹² However, polymicrogyria identified in HHT1 appears unilateral when perisylvian (figure 1, D–G, and figure e-2 [doi.org/10.5061/dryad.ng473mj]). Therefore, polymicrogyria in HHT1 seems predictably distributed differently compared to other, non-HHT cohorts, and given that its presence reported thus

far is unilateral and more often focal (figure 1, A–C, and figure e-1), the pattern is most suggestive of localized in utero cerebral hypoxia as the underlying cause.

Postulate 2: HHT1 endothelial dysfunction produces a suboptimal response to in utero cerebral hypoxia

HHT1 and HHT2 make up >80%–90% of diagnosed cases of HHT.¹ The related mutations affect either TGF β transmembrane receptor ALK1 (HHT2) or its transmembrane coreceptor endoglin (HHT1). ALK1 is solely expressed in endothelial cells (ECs), forming a heterodimeric complex with BMPR2. Together their activation by bone morphogenetic protein 9 or 10 (BMP9/10) ligands induces phosphorylation of receptor regulated Smad proteins that dimerize with Smad4 before translocating to the nucleus and initiating gene transcription.^{13,14} BMP9/10 signaling plays a critical role in the coordinated endothelial response during angiogenesis. Endoglin is a homodimeric coreceptor known to potentiate ALK1 signaling. To conjecture why to date only some patients with HHT1 demonstrate polymicrogyria radiologically, it is

necessary to consider the role of endoglin in cerebrovascular development.

Cerebrovascular development is defined by 2 different stages: vasculogenesis and angiogenesis.^{15–17} Vasculogenesis produces the primitive embryonic vascular network that covers the closed neural tube in the form of the meninx primitiva at 4 weeks gestational age. All new cerebral vessels angiogenically sprout from this overlying vascular meshwork to perfuse the neural parenchyma. Expression of endoglin and ALK1 is absent during vasculogenesis, but peaks in ECs during developmental angiogenesis.^{15,16,18}

Tissue hypoxia initiates the angiogenic process, beginning in the cortex around gestational week 20 as it converts from anaerobic to aerobic metabolism.¹⁵ Neural tissue releases the ligand vascular endothelial growth factor A (VEGFA) to activate Vegfr2 receptors on nearby ECs. Downstream EC signaling triggers EC proliferation, degradation of the vessel encasing basement membrane, mural cell detachment, and sprouting of endothelial filopodial extensions into the hypoxic parenchyma (figure 2).^{17,19} To ensure this remains a controlled process, countering inhibitory mechanisms to stabilize a vessel are crucial and provided by BMP9/10/ALK1/endoglin signaling that inhibits proliferation of ECs and promotes mural cell recruitment.²⁰

EC sprouting into hypoxic tissue occurs in the form of cords, led by a tip cell (TC) phenotype possessing high expression level of Vegfr2. In response to VEGFA binding on TCs, the surface ligand DLL4 is upregulated. This is an important ligand for Notch receptors on contacting ECs as the resultant

signaling has many similar transcripts as the BMP9/10/ALK1/endoglin pathway, conferring these adjacent ECs to a stalk cell (SC) phenotype.¹⁷ This allows EC cords of SCs to follow VEGFA-sensitive TCs into the hypoxic tissue until anastomosing with other vessels and forming a patent lumen allowing for blood flow. Notch signaling is predominantly exhibited in arterial phenotype ECs and suppressed in venous phenotype ECs, helping assert an arterial–venous vascular hierarchy to sprouting angiogenesis.¹⁷ Antibody suppression of DLL4–Notch EC interactions in tumors is effectively a model where this angiogenic sprouting process is destabilized, producing highly vascularized lesions that are poorly perfused and hypoxic.¹⁷

Developmental angiogenesis represents the initiation of cerebral vascular remodeling that continues throughout life. The process monitors fluid shear stress (FSS) within the epigenetically preset physiologic range determined by vessel phenotype.²¹ FSS within the preset range provides stability to the vascular bed, while high or low levels of FSS initiate remodeling. Recent work identified FSS as necessary for the potentiating coreceptor effect of endoglin on BMP9/10/ALK1 signaling. Blood flow seems to induce physical coupling between ALK1 and endoglin that increases sensitivity to BMP9 (figure 3A).²² Assuming a similar enhanced sensitivity to BMP10 is reasonable since they have a similar effect on ALK1 signaling, with BMP10 mainly expressed during embryogenesis while BMP9 plays a significant role in adult angiogenesis.²³ This may be an important function of FSS, since although BMP9 and BMP10 serum concentrations have been shown to be high at term, it is conceivable their concentrations are low enough at the onset of cortical angiogenesis

Figure 2 Simplified depiction of ALK1, vascular endothelial growth factor A (VEGFA), and notch signaling pathways in angiogenesis

Endoglin, mutated in *HHT1*, is a coreceptor of ALK1 for BMP9/10 ligands, whose signaling inhibits endothelial cell proliferation and mural cell recruitment. This pathway confers a stalk cell endothelial phenotype. VEGFA signaling is proangiogenic, through the PI3K/AKT pathway, and confers a tip cell endothelial phenotype. The tumor suppressor PTEN is a mediator between these 2 pathways. To control angiogenic sprouting, adjacent arterial endothelial cells use cell contact Notch signaling to regulate tip and stalk cell phenotypes. The decoy receptor Vegfr1 is also employed since it competitively binds with VEGFA to lower the relative exposure of Vegfr2 to surrounding VEGFA.

Figure 3 ALK1 mechanotransduction model via its endoglin coreceptor

(A) Under low flow and shear stress conditions, endoglin and ALK1 do not associate (left), with reduced affinity for BMP9/10 ligands compared to when flow-induced coupling occurs (right). (B) A fluid shear stress of 12 dynes/cm² experimentally demonstrated an increase in ALK1 signaling (blue line) at low BMP9/10 concentrations compared with no fluid shear stress applied (red line).²² With decrease in fluid shear stress (FSS) or the amount of surface endoglin expression, the ALK1 signaling curve can be expected to shift to the right, towards the no-flow level of signaling. (C) Although an *HHT2* mutation (*ENG*^{+/+} *ALK1*^{-/-}) produces 50% less ALK1 signaling at high concentration, the potentiating mechanotransduction of endoglin may see its signaling levels still surpass a necessary threshold to suppress hypersprouting angiogenesis, while a dominant-negative *HHT1* mutation (*ENG*^{-/-} *ALK1*^{+/+}) resulting in a low level (<50%) of endothelial cell surface endoglin cannot.

that potentiation of ALK1 signaling via endoglin is essential.^{23,24} Furthermore, cerebral blood flow, and hence FSS, is much lower at the onset of corticogenesis relative to postnatally, with cortical blood flow increasing by threefold alone during the third trimester.²⁵ This increases further still after birth, rising another 1.5–2-fold in the first 2 weeks of life.^{26,27} The work of Baeyens et al.²² demonstrated sigmoid relationships between BMP9 concentration and ALK1 signaling that were left-shifted to lower concentrations when a FSS of 12 dynes/cm² was applied. It is our hypothesis that the effect of decreased endoglin expression in *HHT1* and decreased FSS in utero shifts these curves to the right, reducing endothelial BMP9/10 sensitivity to a level where stabilizing ALK1 signaling fails to meet a threshold level necessary to avoid hypersprouting angiogenesis (figure 3B).

Our cases demonstrate polymicrogyria occurring in regions that are distal along the arterial tree and experience the lowest endothelial FSS at the onset of cortical angiogenesis. Since the overall influence of FSS on promoting ALK1 signaling is mediated by endoglin, this will be further decreased in *HHT1* because it follows a haploinsufficiency model.^{28,29} Endoglin is the most abundant endothelial surface TGF β binding protein and haploinsufficiency (defined as high intolerance to heterozygous loss-of-function mutations and demonstrated by a pLI score of 0.99) produces a change from the wild-type (WT) EC phenotype.³⁰ Thus, in low FSS regions local ALK1 signaling could fail to meet a threshold necessary to keep a functional balance in the TC and SC phenotypes of

angiogenesis, producing focal hypersprouting with hypoxia ensuing. Experimentally, this is seen in studies of vascular development using the retina of *ENG*^{+/-} mice.¹⁹ While arteriovenous malformations preferentially occur proximally involving larger vessels near the optic nerve where blood flow is high, hypervascularization is seen along the distal, low-flow angiogenic front.¹⁹

The importance of *HHT1* dominant-negative haploinsufficiency

We still must consider why polymicrogyria has not been observed in *HHT2* patients. Assuming the likelihood of a patient with HHT being *HHT1* is around 60%,³¹ then the probability of all 7 cases here being *HHT1* is only 3%. If we consider that there are an additional 5 reported *HHT1* cases with polymicrogyria,⁸ this probability drops further to 0.2%. Although haploinsufficiency models of *HHT1* and *HHT2* have been demonstrated,^{13,23,29} the *HHT2* reduction of ALK1 receptors may also not be significant if the benefit of endoglin mechanotransduction outweighs the amount of unpotentiated signaling from a normal expression level of ALK1 receptors in the in utero setting of low BMP9/10 concentration (figure 3C). Furthermore, many endoglin mutants, but not ALK1 mutants, act as dominant-negatives (DNs), where intracellular heterodimerization of mutant with WT endoglin causes functional endoglin expression below 50% of normal on the endothelial surface (theoretically it should be around 25%).^{13,28,29} Mutant

endoglin DNs seem to confine coreceptor to the endoplasmic reticulum, but may also accelerate WT endoglin degradation or silence the WT allele via transcriptional dysregulation.^{28,29} Structural analysis of human endoglin found that the majority of known HHT1 missense mutations involve hydrophobic residues that impair protein folding, hindering its ability to be properly translated to the cell surface, but do not interfere with its ability to interact with WT endoglin.³² Therefore, some heterozygous HHT1 mutations may cause marked decreases in endothelial surface WT endoglin expression that could further increase the propensity for polymicrogyria. This mechanism is unlikely for patient 6, whose mutation interferes with the start translation codon and is unlikely to produce a mutant protein product (table 1). To our knowledge, the mutations for the remaining presented cases have yet to be tested as DNs.

Postulate 3: Focal hypoxia from hypersprouting angiogenesis may also provide a trigger for bAVM development

Unlike the genesis of polymicrogyria, timing for bAVM development is more vague. First, mounting evidence suggests bAVMs are primarily acquired lesions. Of all bAVMs, only 1% are diagnosed within the first 2 years of life, and these seem to be dynamic lesions with increasing numbers of reports of de novo formation and regression.^{33,34} It is possible the one case presented here with no corresponding bAVM may be the result of lesion regression (figure e-3, doi.org/10.5061/dryad.ng473mj). Only 3 rare types of antenatal cerebral arteriovenous lesions are reported in the literature: (1) vein of Galen malformations (VoGMs), (2) dural sinus malformations, and (3) pial arteriovenous shunts.³⁵ All other malformations are considered acquired, following a 2-hit hypothesis, with timing, target, and triggering events predicting the pathomechanical result.^{36,37} In the case of HHT1, focal hypersprouting angiogenesis could provide the hypoxic second hit necessary to produce a somatic mutation for bAVM development postnatally, accounting for the close spatial proximity with polymicrogyria (figure 4).

Three phenotypes of bAVMs have been identified in patients with HHT: (1) pial arteriovenous shunts, (2) nidus-type arteriovenous malformations, and (3) capillary malformations.³¹ While bAVMs demonstrated in infants with HHT have all been pial arteriovenous shunts, the morphology of these malformations likely changes as the lesion matures.³⁸ As part of vessel wall maturation, ECs secrete platelet-derived growth factor B (PDGFB), which disperses into the neighboring extracellular matrix and serves as a chemoattractant for mural cells.¹⁷ β 1-integrins on vascular smooth muscle cells (vSMCs) or pericytes have been shown to bind the Arg-Gly-Asp (RGD) motif of endoglin.²⁶ While other adhesion molecules and receptors are also involved in EC–vSMC adhesion, endoglin–

integrin binding appears the most important to initiate this process.¹⁸ Therefore, reduced surface endoglin in HHT1 can result in suboptimal mural cell coverage of the developing vasculature, producing fragile blood vessels prone to leakage and dilation that may also affect corticogenesis.^{18,39} Furthermore, as blood flow increases during embryogenesis prior to mural cell recruitment, the primitive vessels normally dilate followed by a contraction, the latter representing endoglin-mediated responsive EC shape change and migration to the increased flow.¹⁴ Functional mutations in endoglin impair this contraction, allowing for focal, shunting dilations of the primitive vasculature to persist. The increased blood flow through these dilated segments means normally transient downstream arteriovenous drainage connections are exposed to increased FSS and persist in response, giving rise to a bAVM that may not be apparent until adulthood (figure 4).²²

Other less favored mechanisms for cerebral in utero ischemia

Here we consider several circumstances that could predispose an HHT1 fetus to focal in utero ischemia, later manifesting as focal polymicrogyria, but also offer reasons why these are less plausible explanations for the observed association.

Defective EC TGF β /ALK5 signaling within the yolk sac during vasculogenesis has been demonstrated in *ENG*^{+/-} mice and it affects the differentiation of adjacent mesothelial cells into vSMCs.³⁹ A resultant abnormally dilated segment could act as a shunting lesion and associated physiologic steal phenomenon acting on adjacent cerebral cortex would produce hypoxia that triggers polymicrogyria development. We favor such a pathomechanism less likely since it fails to explain why all of the lesions presently reported appear only along distal arterial low FSS regions.

One of the most feared clinical complications of HHT is paradoxical embolus in the setting of a pAVM. Roughly half of patients with HHT harbor pAVMs and prevalence increases with age.⁴⁰ Fewer than 20 perinatal pAVM cases are presented in the literature, with the earliest diagnosis reported at 16 gestational weeks by Doppler ultrasound.⁴¹ Therefore, in utero presence of these lesions prior to the onset of corticogenesis is possible, so ischemia secondary to paradoxical embolus is a potential pathomechanism. Many, although not all, of our HHT1 cases and those previously reported with polymicrogyria were also diagnosed with at least one pAVM. However, it is important to recognize in utero right-to-left shunting through the ductus arteriosus is physiologically normal for all fetuses, and with the increased transpulmonary pressures, pulmonary blood flow makes a decreased contribution to cerebral blood flow compared with postnatally.

Since there are many molecular mediators of cortical and neurovascular development, as our understanding of their

Figure 4 Proposed sequence of events leading to coincident cortical and cerebral arteriovenous malformations in patients with *HHT1*

Genetic predisposition at conception is related to the heterozygous germline mutation *ENG*^{+/-}, referred to as the pathomechanistic first hit in the developmental theory of arteriovenous malformations according to Lasjaunias.³⁷ Immediate consequence of an *in utero* hypoxic event is a local disruption in normal late neuronal migration or cortical organization, resulting in polymicrogyria cortex. This hypoxic event also serves as the second hit, a somatic mutation to the remaining wild-type endoglin allele, to a segment of endothelial cells of an adjacent vessel (making them *ENG*^{-/-}) and results in focal endothelial dysfunction with poor mural cell recruitment and dilation. Associated hemodynamic changes alter the downstream fluid shear stress (FSS), allowing normally transient vessels to persist and enlarge to a point where the morphology of a brain arteriovenous malformation (bAVM) is apparent on MRI. The development of this bAVM may extend into adulthood depending on the size and location of vessel segment affected by the somatic mutation.

interrelated functions improves, more candidate triggers are likely to be elucidated.⁴² Transmembrane Eph receptor Tyr kinase and ephrins, their membrane-bound ligands, are an example of EC signaling molecules that could serve as another candidate. Despite involvement of ephrins and their receptors in cortical and vascular development, and their recently discovered association with VoGMs,⁴³ no present connection between their dysfunction and HHT is known.

Finally, non-HHT polymicrogyria is known to be caused by multiple genetic and nongenetic causes, with gene mutations linked to neuronal progenitors and migration, centrosome function, and cilia location identified.^{44,45} Most autosomal dominant mutations seem to involve the mTOR pathway, which, unlike HHT1, are associated with overgrowth/megalencephaly syndromes. Similarly, mutations involving the transcription factor *PAX6* have been associated with unilateral polymicrogyria, but these also demonstrate aniridia with anterior commissure and pineal gland absence. Clear connection with a vascular defect has remained elusive, although polymicrogyria lining schizencephalic clefts associated with *COL4A1* mutations has been reported.⁴⁴

Discussion

The flow pattern that develops following the first fetal heartbeat is essential in determining the morphology of the vascular network.¹⁶ Since this remodeling process is faulty in HHT, it serves as a clinical scenario that probes the temporally codependent development of the cerebral cortex with its vascular network. Our small sample size is unfortunate but expected for a series involving a rare disease target population and uncommon findings among affected individuals. We are also limited in detecting MCDs within the capabilities of current radiologic imaging, but may be missing histopathologically present lesions. This may explain why only 1 of 6 bAVMs in patient 1 demonstrated an adjacent MCD. Despite this, 2 important new insights about polymicrogyria observed in patients with HHT have been presented: (1) all cases reported to date appear to only involve HHT1 and (2) the lesions are characteristically unilateral, focal, and correlate with arterial regions exposed to the lowest FSS *in utero*. We have proposed a mechanism whereby the haploinsufficiency model of endoglin and its poor mechanotransduction in regions of low FSS *in utero* predisposes abnormal, focal

hypersprouting angiogenesis. Ensuing hypoxia can produce focal polymicrogyria and also serve as a “revealing trigger” for later bAVM development. This model provides satisfactory timing of in utero events and explains the typically observed short range spatial correlation between polymicrogyria and bAVMs. Finally, it suggests an essential role for endoglin-mediated FSS mechanotransduction in the development of the cerebral cortex.

Author contributions

J.M. Klostanc reviewed the patient imaging, proposed the theory, and drafted the manuscript. L. Chen reviewed the patient imaging and edited the manuscript. S. Mathur provided discussions on the theory and edited the manuscript. J. McDonald provided clinical information and edited the manuscript. M.E. Faughnan provided clinical information and edited the manuscript. F. Ratjen provided clinical information and edited the manuscript. T. Krings did the initial review of patient imaging, proposed the theory, and edited the manuscript.

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Disclosure

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