Cavernous angiomas: deconstructing a neurosurgical disease

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Cavernous angioma (CA) is also known as cavernoma, cavernous hemangioma, and cerebral cavernous malformation (CCM) (National Library of Medicine Medical Subject heading unique ID D006392). In its sporadic form, CA occurs as a solitary hemorrhagic vascular lesion or as clustered lesions associated with a developmental venous anomaly. In its autosomal dominant familial form (Online Mendelian Inheritance in Man #116860), CA is caused by a heterozygous germline loss-of-function mutation in one of three genes—CCM1/KRIT1, CCM2/Malcavernin, and CCM3/PDCD10—causing multifocal lesions throughout the brain and spinal cord.

In this paper, the authors review the cardinal features of CA's disease pathology and clinical radiological features. They summarize key aspects of CA's natural history and broad elements of evidence-based management guidelines, including surgery. The authors also discuss evidence of similar genetic defects in sporadic and familial lesions, consequences of CCM gene loss in different tissues at various stages of development, and implications regarding the pathobiology of CAs. The concept of CA with symptomatic hemorrhage (CASH) is presented as well as its relevance to clinical care and research in the field. Pathobiological mechanisms related to CA include inflammation and immune-mediated processes, angiogenesis and vascular permeability, microbiome driven factors, and lesional anticoagulant domains. These mechanisms have motivated the development of imaging and plasma biomarkers of relevant disease behavior and promising therapeutic targets.

The spectrum of discoveries about CA and their implications endorse CA as a paradigm for deconstructing a neurosurgical disease.

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ABBREVIATIONS CA = cavernous angioma; CASH = CA with symptomatic hemorrhage; CCM = cerebral cavernous malformation; CD14 = cluster of differentiation 14; DCEQP = dynamic contrast enhanced quantitative perfusion; DVA = developmental venous anomaly; FDR = false discovery rate; MEKK = mitogen-activated protein kinase kinase; QSM = quantitative susceptibility mapping; sCD14 = soluble form of CD14; sROBO4 = soluble form of Roundabout 4; SRS = stereotactic radiosurgery; SWI/VenBold = susceptibility weighted imaging/BOLD venographic imaging; TLR4 = toll-like receptor 4; T2*/GRE = gradient recalled echo acquired; VEGF = vascular endothelial growth factor.


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The lesion is histologically identical in association with all genotypes, characterized by grossly dilated vascular spaces (known as “caverns”) lined by a single layer of endothelium, lacking mature vessel wall angiarchitecture, and manifesting features of chronic hemorrhage in adjacent neuroglial parenchyma (Fig. 1). The gross appearance of the lesion has been likened to a mulberry. Familial lesions have been shown to harbor biallelic mutations in endothelial cells (ECs) lining the pathological vascular lumen. This observation is consistent with a Knudsonian mechanism that involves a homozygous loss of function in the lesion endothelium, while all cells in the body are heterozygous for the inherited gene. Lesions surgically resected from sporadic cases lacking inherited germline mutations harbor somatic mutations of the same three CCM genes. This indicates identical molecular mechanisms related to CCM gene loss of function in both familial and sporadic lesions.

In this review, we have applied conventional and distinct rules of nomenclature for disease, lesion, human gene, mouse gene, and protein. Both the human disease and the vascular lesion characterizing the phenotype are designated as cavernous angioma (CA), which is also known as cerebral cavernous malformation (CCM). Human genes associated with familial CA are fully capitalized and italicized as CCM1, CCM2, and CCM3, whereas murine genes are italicized with both upper- and lower-case letters and appear as Ccm1, Ccm2, and Ccm3. To avoid confusion, we refer to the respective gene products by their protein database names: KRIT1, Malcavernin (or OSM), and PDGCD10, respectively. By following these rules, referencing the disease, a vascular lesion, a gene (mouse or human), or a protein should be interpretable.

Histologically identical CA lesions arise in the brain after irradiation, which is not surprising in view of the propensity of radiation to cause somatic mutations. Vascular hyperpermeability in the irradiated brain may also play a role, as may radiation-induced hemorrhagic microangiopathy—both described in the spectrum of pathology leading to radionecrosis. Other extradural lesions with the histological features of CA have been described, but those lesions do not occur with the genetically inherited disease nor have they been related to its mechanisms. In this review, we will not address radiation-induced nor extradural CAs.

Historical Paradigms Defining the Cavernous Angiomaf

There is no evidence that cerebrovascular angiomas were recognized in antiquity. With the advent of postmortem examinations and clinical pathological correlations, vascular lesions became recognized in association with seizures or apoplexy (hemorrhagic stroke). Virchow first attempted to classify cerebrovascular malformations. Subsequent pathologists, mostly in the German schools, struggled with the lesions’ classification as angiomatic tumors versus developmental anomalies. Others avoided this controversy and employed the term “hamartoma” or “tumor-like anomalies” (geschwulstartige fehlbildungen). Cushing and Bailey commented extensively on cavernomas (angioma cavernosum) in their classical treatise. With the introduction of cerebral angiography and the growing recognition of, and interest in, arteriovenous malformations, cavernomas were understood in the context of “cryptic” or angiographically occult vascular malformations, as described by Russell. The currently recognized pathological features of CAs were further clarified by McCormick, before being more conclusively defined, with a clearer correlation with MRI features.

Imaging Features

The advent of MRI ushered in an era of better detection and more precise definition of cerebrovascular pathologies including CA. While CT had revealed CAs as nonspecific ill-defined calcifications, MRI clearly defines the typical “popcorn appearance” of the lesion, which highlights larger caverns, with mixed signals of blood at different stages of organization and calcifications, and surrounding hemosiderin (Fig. 1B). The latter “hemosiderin ring” is best appreciated on T2-weighted sequences. Acute hemorrhage may mask underlying cavernomas on MRI as on CT, but the typical lesion emerges on serial MRI with clearance of acute blood. In all, MRI allows the diagnosis of asymptomatic lesions as well as those associated with epilepsy and recent bleeding, and reveals multifocal lesions in familial cases and associated venous anomalies (Fig. 2).

Gradient recalled echo acquired (T2*/GRE) sequences reveal the “blooming” effect of hemosiderin, increasing the sensitivity of detection of CAs. Susceptibility weighted imaging (SWI/VenBold) sequences, particularly those obtained at 3 Tesla, can reveal a greater number of multifocal lesions in familial cases, which do not appear on more conventional and T2*/GRE images. These sequenc-
es reveal more than twice the lesion burden identified on conventional MRI as well as a greater number of lesions with advancing age in familial cases. Some of these occult lesions may progress to larger lesions or hemorrhages. This enhanced sensitivity has created a differential diagnostic challenge with hemorrhagic microangiopathy or cerebral microbleeds, particularly in the aging brain, and with some cases of hemorrhagic metastases that need to be considered in the appropriate clinical context.

MRI also allows functional imaging of primary sensorimotor, speech, and visual cortical areas, and their white matter connectome by diffusion tensor imaging, which has enhanced surgical planning. New MRI techniques of quantitative susceptibility mapping (QSM) and dynamic contrast enhanced quantitative perfusion (DCEQP) have been developed to measure iron deposition and vascular permeability in CAs (Fig. 3), and are being assessed as potential biomarkers of clinically relevant disease activity.

**Natural History and Why CASH Matters**

Patients with CA typically present with a broad range of symptoms, most often during the 2nd to 5th decades of life. The most frequent clinical manifestations of CAs include seizures (50%), symptomatic hemorrhage (25%), and focal neurological deficits without radiographic evidence of recent hemorrhage (25%) (Fig. 4). Nevertheless, 20%–50% of CA patients have no symptoms, and their disease is identified incidentally due to the widespread accessibility and utilization of brain MRI. Early natural history studies reported a wide range of hemorrhage frequencies, in part due to variances in definition. Thus, the
The definition of symptomatic hemorrhage was standardized in 2008 as “requiring acute or subacute onset of symptoms...accompanied by radiological, pathological, surgical, or rarely only cerebrospinal fluid, evidence of recent extra- or intrallesional hemorrhage.”

In population studies and in case series without selection criteria, the risk of first symptomatic hemorrhage has been found to be extremely low (0.08% per patient-year) among incidentally identified CAs. However, once a symptomatic hemorrhage has occurred, the annual risk of a subsequent episode of bleeding is dramatically increased—at least 10-fold by most estimates. This elevated risk is greatest soon after a hemorrhage but persists thereafter, with a 5-year risk estimated at 42% (95% CI 27%–58%). Brainstem lesions are also associated with a greater risk of initial bleeding and recurrent symptomatic hemorrhage, although it is unclear if this is related to a sensitivity bias, in which tiny bleeds are more likely symptomatic in an eloquent location. Bleeding is also more frequent and occurs earlier in CCM3 familial cases with PDCD10/CCM3 mutations, but this appears to be related to the development of exceptional lesion burden at an early age, rather than the greater risk of bleeding associated with individual lesions.

There are fewer than 200,000 cases of CA with symptomatic hemorrhage (CASH) among the more than 1 million patients with CA in the United States. Hence, CASH represents a singular clinical entity, distinguishing lesions that impact a patient’s life and merit clinical intervention. Given their high risk of rebleeding and the high cost and potential risks of their surgical excision, particularly when identified in brainstem locations, CASHs are currently the primary focus of therapeutic development aimed at stabilizing and preventing rebleeding.

Evidence-Based Management Guidelines

Despite many publications about CAs, there remains controversy regarding optimal diagnostic and management strategies. The Angioma Alliance, which is the primary patient support group in the US advocating on behalf of patients and research in CA, assembled a multidisciplinary writing group with expert clinicians to help summarize the existing literature in the clinical care of CA, focusing on five topics: 1) epidemiology and natural history, 2) genetic testing and counseling, 3) diagnostic criteria and radiology standards, 4) neurosurgical considerations, and 5) neurological considerations. Participants of the writing group reviewed literature, rated evidence, developed recommendations, and established consensus, controversies, and knowledge gaps according to a prespecified protocol. Of 1,270 publications (January 1, 1983, to September 31, 2014), they selected 98 based on methodological criteria and identified a further 38 recent or relevant publications. These publications were used by topic editors to summarize current knowledge about CA and to make 23 management recommendations, which were rated by class (size of effect) and level (estimate of certainty) according to the American Heart Association/American Stroke Association criteria. The guidelines were peer-reviewed and published in 2017, with more detailed content available online (www.angioma.org/ccmguidelines).

Surgical Opportunities and Challenges

The recently compiled guidelines for evidence-based CA management note that there have been no reports of randomized controlled trials comparing resection to conservative treatment and that most case series contributing to systematic reviews harbor substantial biases and lack adjudicated outcomes. A population-based study revealed poorer outcome over the 5 years following surgery or initiation of medical/conservative management, and a higher risk of symptomatic hemorrhages and focal neurological deficits in CA cases treated surgically than in those treated medically. However, that study was not randomized and, clearly, the patients treated surgically were sicker and more likely to experience bleeding from the CA prior to surgery. Nevertheless, the benefits of surgery...
for CA cannot be taken for granted, and it is important to weigh the risk of surgery versus the natural history of CAs in specific clinical scenarios and lesion locations.

Case series generally report low rates of surgical morbidity and mortality for supratentorial CAs, but much higher rates for brainstem lesions. Surgical complication rates, however low, clearly exceed the low risks from hemorrhage in lesions that have never bled. Hence surgical excision of asymptomatic lesions, particularly those lying deep or in brainstem locations are almost never justified. Nevertheless, this same risk appears more favorable when compared to the risk of recurrent intracranial hemorrhage following a CA hemorrhage. Depending on the location of the CA, the risk of resection can vary widely, and this is taken into account when making surgical decisions. Thus, resection is generally recommended for symptomatic, easily accessible CAs, given the increased risk of repeated bleeding after the first hemorrhage and the low level of morbidity associated with surgery.

Deeper CAs located in the insula, basal ganglia, or thalamus require a more technically challenging surgery involving critical structures, including deep nuclei and white matter tracts, and the risk of injury to small perforating arteries. For very experienced teams, the postoperative morbidity rate associated with these CAs is 5%–18%, with the rate of mortality approaching 2%; many patients ultimately attain recovery from severe disability. Surgical resection is not recommended for asymptomatic CA, especially if located in eloquent, deep, brainstem or spinal location, nor in cases with multiple asymptomatic lesions (class III, level B).

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There are conflicting data on resection of a DVA associated with CA, with most authors advocating DVA preservation to prevent serious complications such as edema, hemorrhage, and/or venous infarctions. In general, a DVA can only be resected if it is very small, or if the brain it drains is also being resected (as in rare cases of modified lobectomies for regional venous dysmorphism and seizures).

Stereotactic radiosurgery (SRS) has been suggested as an alternative treatment for symptomatic CA located in eloquent areas, with most series identifying a decline in the hemorrhage rate more than 2 years after SRS treatment. Causality cannot be inferred, however, as most natural history studies also demonstrate decreasing rebleeding rates after 2 years posthemorrhage. Recently, authors conducted a retrospective study of SRS comparing patients treated for their first brainstem hemorrhage with patients treated for a second hemorrhage; the authors found no significant difference in annual bleeding rates between the two groups. There is legitimate concern whether radiation exposure may enhance the genesis of new CAs in children and in familial cases. Complications from SRS are not trivial, particularly with lesions in eloquent areas deemed at high risk for resection, and the optimal SRS dose to reduce hemorrhage is not known.

The following consensus recommendations regarding CA surgery were proposed based on current evidence, following vetting using the Delphi technique (the classes and levels of evidence are listed according to the American Heart Association criteria):

1. Surgical resection is not recommended for asymptomatic CA, especially if located in eloquent, deep, brainstem or spinal location, nor in cases with multiple asymptomatic lesions (class III, level B).
2. Surgical resection may be considered in solitary asymptomatic CA if easily accessible in noneloquent area, to prevent future hemorrhage, because of psychological burden, expensive and time-consuming follow-ups, to facilitate lifestyle or career decisions, or in patients who might need to be on anticoagulation (class IIb, level C).

3. Early surgical resection of CA causing epilepsy should be considered, especially when medically refractory epilepsy, in the absence of uncertainty about lesion epileptogenicity (class Ila, level B).

4. Surgery may be considered in symptomatic easily accessible CA lesions, with mortality and morbidity equivalent to living with the lesion for about 2 years (class IIb, level B).

5. Surgical resection may be considered in deep CA lesions if symptomatic or after prior hemorrhage, with mortality and morbidity equivalent to living with the lesion for 5–10 years (class IIb, level B).

6. After reviewing the high risks of early postoperative mortality and morbidity and impact on quality of life, it may be reasonable to offer complete surgical resection of brainstem CA after a second symptomatic bleed as those lesions have a more aggressive course (class IIb, level B).

7. Indications for resection of brainstem CA after a single disabling bleed, or for spinal CAs, are weaker (class IIb, level C).

8. Radiosurgery may be considered in solitary CA lesions with previous symptomatic hemorrhage if the lesion lies in eloquent areas that carry an unacceptable high surgical risk (class IIb, level B).

9. Radiosurgery is not recommended for asymptomatic CAs, for lesions which are surgically accessible, and in familial CA disease with concern about de novo lesion genesis (class III, level C).


**Lesion Pathobiology**

Beyond their salient histopathological features, human CA lesions harbor evidence of enhanced angiogenic activity and a proliferative index of ECs lining the caverns. They exhibit defective interendothelial junctions, and the peri-endothelial layer lacks mature smooth muscle cells, with the lesions exhibiting iron deposits, gliosis, and a robust inflammatory cell infiltration, including B-cells, plasma cells, and B- and T-cell clusters as well as oligoclonal immunoglobulins. Microdissected B-cells from CA lesions demonstrate antigen-driven clonal expansion and complement activation. Additionally, human CA lesions have recently been shown to involve clonal expansion of a fraction of ECs in the walls of caverns harboring the CCM mutations. These features are common to all lesion locations and genotypes.

Murine models have been developed in *Ccml*, *Ccml2*, or *Ccml3* heterozygous mice, in a background of genetic instability favoring somatic mutations (*Trp53* or *Msh2* loss). Consistent with Knudson’s two-hit hypothesis, these mice develop a rich repertoire of CA lesions that increase throughout life, recapitulating the human disease. The *Ccml3* models have a more robust lesion burden, as with the human disease. Mature multicavernous lesions exhibit all of the known phenotypical signatures of the human lesion, including ECs lining the caverns lacking the respective CCM protein, a defective EC barrier, a high EC proliferative index, chronic bleeding with iron deposition, and a robust inflammatory response. Primitive single caverns (ballooned capillaries) are also seen in these models (Fig. 5), indicating the primordial CA lesion. The latter is consistent with capillary telangiectasia, with ECs lacking the CCM protein but not manifesting any bleeding, iron deposit, or inflammation. The evolution of CAs from capillary telangiectasias, previously proposed based on pathological observations, now seems confirmed by lesion genesis in mice.

Robust development of clustered CA lesions can also be induced in the mouse hindbrain with a conditional endothelial homozygous knockout of *Ccml, Ccm2*, or *Ccml3* genes in the first postnatal days, during ongoing active vasculogenesis in the early postnatal mouse hindbrain (Fig. 5). These acute models allow rapid testing of signaling aberrations and rescue of lesion development while the more chronic models are better suited for preclinical testing of pharmacotherapy, including therapeutic effects on lesional hemorrhage and inflammation. Both models can be imaged using micro-CT, allowing a high-throughput assessment of lesion burden and quantitative analyses (Fig. 5).

**Consequences of CCM Gene Loss**

Homozygous loss of *Ccml*, *Ccml2*, or *Ccml3* in endothelium is lethal to the embryo, resulting in gross defects in the heart and aortic development. This is mediated by endothelial gain of MEKK3-KLF2/4 signaling in early embryonic development. CA lesions arise from the same gain of MEKK3-KLF2/4 signaling in brain microvascular endothelium with postnatal loss of CCM genes, bypassing embryonic lethality. This leads to a number of consequent signaling aberrations, including downstream Rho-A kinase (ROCK) activation, which provokes endothelial barrier dysfunction. ROCK inhibition can rescue the CCM phenotype in endothelium and prevents lesion formation, maturation, and hemorrhage. Other signaling aberrations involve dysangiogenesis, endothelial-mesenchymal transition, proinflammatory state, oxidative stress, and autophagy. Loss of TSP1 and thrombomodulin-associated local anticoagulant domains. Lesion development is also driven by lipid polysaccharide signaling through CD14/TLR4 receptors on brain microvascular ECs, and this has been related to a robust impact of gram-negative bacteria in the gut microbiome on lesion development.
and vascular lesions, highlighting the role of the neurovascular unit in the human disease. Loss of Ccm function in the epithelium has been shown to provoke intestinal leak and vulnerability to inflammatory bowel disease. This may, in turn, impact the gut microbiome and affect CA disease severity.

Figure 6 illustrates a number of signaling aberrations correlated with Ccm gene loss and CA lesion development. A recent study catalogued the comprehensive transcriptome of the human CA lesion neurovascular unit and differentially expressed genes in association with induced loss of Ccm1 and Ccm3 genes in cultured murine brain microvascular ECs and the Caenorhabditis elegans nematode, reflecting a rich network of connected genes related to these signaling aberrations.

**Implications for Biomarker Development**

Imaging or molecular signatures of biological processes have been proposed for the diagnosis, etiological categorization, severity assessment, and prognostication of disease. The U.S. Food and Drug Administration and National Institutes of Health have designated a Biomarkers Working Group aimed at categorizing contexts of use and defining standards of rigor in biomarker development (https://www.ncbi.nlm.nih.gov/books/NBK326791). Vascular leak is a fundamental feature of CAs, facilitating hemorrhage and the accompanying accumulation of nonheme iron. A novel MRI application that assesses iron deposition using QSM has been implemented in human CAs (Fig. 3). Mean lesional QSM was shown to recapitulate actual iron concentrations measured by mass spectroscopy in surgically resected human CA lesions. Researchers in Chicago and New Mexico optimized DCEQP, another MRI technique that reflects mechanistically postulated vascular hyperpermeability. Both QSM and DCEQP were applied during longitudinal follow-up, with strong interobserver agreement, stability of repeated measurements in clinically stable lesions, and reproducibility across MRI instrument platforms. Mean lesional QSM and DCEQP increased significantly in CAs manifesting interval symptomatic hemorrhage during longitudinal follow-up, with highly sensitive and specific thresholds. Therefore, QSM and DCEQP were proposed as monitoring biomarkers of lesional bleeding and responses to therapy. Projects are underway to validate these biomarkers at multiple sites as part of the CASH Trial Readiness initiative and to test their change as affected by ROCK inhibition using atorvastatin in the first Phase I–IIa proof-of-concept (AT CASH EPOC) trial.

Greater CA disease severity has been identified in association with genetic modifiers causing proinflammatory states. Chronic CA disease aggressiveness during a patient’s lifetime has also been associated with plasma Vitamin D deficiency, an index proinflammatory state. Other research has assessed plasma proteins with a reported role in the pathology of CA and brain hemorrhage, including angiogenesis, inflammation, EC integrity and permeability, response to stress, cell adhesion, and extracellular matrix remodeling. Plasma levels of vascular endothelial growth factor (VEGF) and endoglin (ENG) [both p < 0.04, false discovery rate (FDR) corrected] were lower in pa-
patients who had suffered a symptomatic hemorrhage in the previous 3 months. Hierarchical clustering analysis demonstrated a cluster of four plasma inflammatory cytokines (interleukin [IL] 2, interferon gamma, tumor necrosis factor alpha, and IL1β) characterizing patients with a “high” inflammatory state associated with seizures (p = 0.02) and more than one prior symptomatic hemorrhage during a patient’s lifetime (p = 0.04). More recently, higher plasma levels of IL1β (p = 0.008) and sROBO4 (p = 0.03), and lower levels of sCD14 (p = 0.05), IL6 (p = 0.04), and VEGF (p = 0.0003) were reported in patients who suffered a subsequent symptomatic hemorrhage in the year following the plasma sampling. The individual predictions had only modest sensitivities and specificities (receiver operating characteristic–areas under the curve 0.66–0.82) for individual significant biomarkers after FDR correction. However, a best-weighted combination of the levels of four of these molecules accomplished 86% sensitivity and 88% specificity in predicting a symptomatic hemorrhage in the next year, and this was further confirmed in a separate prognostic sample and by rigorous Monte Carlo simulations. Such a level of prognostication had never been shown in brain hemorrhage from any cause. Hence, the combination of multiple biomarkers emerging from mechanistic studies is likely to enhance the rigor of diagnostic and prognostic associations in CA.

Implications for Therapeutic Targeting

The endothelial phenotype resulting from CCM loss can be rescued by inhibition of mechanistically linked signaling aberrations and the pathogenetic immune response. As discussed previously, familial cases with autosomal dominant inheritance involve one mutated copy of the gene in every cell of the body, while CA lesions develop from somatic biallelic mutations in the second copy of the gene. Sporadic CA lesions also manifest somatic mutations in the same genes, indicating similar pathobiology. Hence mechanistic therapies targeting the CA lesion are likely operative in both familial and sporadic forms of the disease. In recent experiments, the ROCK inhibitor, statins (with pleiotropic effects including Rho inhibition), and B-cell depletion were shown to decrease hemorrhage in murine CA lesions. Table 1 summarizes the status of development of candidate therapies, based on mechanistic discoveries and preclinical results, that are potentially aimed at testing in the human disease. Preclinical effects have been demonstrated (fasudil, statins, B-cell depletion) or planned (BA-1049) in mouse models using contemporary randomized treatment assignment versus placebo, and blinded outcome assessment per the US National Institute of Neurological Disorders and Stroke guidelines.

The rates at which a new CA develops in familial cases...
and first symptomatic hemorrhage in asymptomatic CAs are far too low to allow meaningful testing or compel primary prevention strategies. CASH lesions, for which resection is not undertaken because the majority are in deep and brainstem locations, are the most likely to be followed expectantly according to current evidence-based guidelines. There is a clinical equipoise for testing novel therapies with the goal of preventing rebleeding in such cases. It would be appropriate to develop a drug that stabilizes the CASH lesion. This would mitigate the costs and neurological sequelae of repeated hemorrhage and of resection in many patients. Based on data from natural history studies, the therapeutic benefit for secondary prevention (symptomatic rebleed) would be maximal within 2–3 years after a recent symptomatic bleed.

The clearest pathway for drug repurposing involves currently approved statin drugs, with ROCK inhibition pleiotropic effect at high doses. Statins may be ready for Phase III multisite trials in about 5 years, pending the results of an ongoing Phase I–IIa single-site trial (AT CASH EPOC, NCT02603328; registered at clinicaltrials.gov) aimed at a biomarker proof-of-concept effect and preliminary safety data in brain CA, albeit without mechanistic studies or preclinical evidence to date. A pragmatic propranolol trial was initiated in Italy (Treat_CCM, NCT03589014; registered at clinicaltrials.gov), although it is admittedly underpowered and any signal of favorable results will be considered exploratory, requiring a more definitive Phase III study. Biologics affecting B-cell depletion may generate interest in the development for a new indication in CASH. While new drug developments of ROCK-2 inhibitor BA-1049 (US Patent #10106525) and Tempol may benefit from respective commitments by BioAxone and Recursion Pharmaceuticals, these new drugs still require completion of preclinical testing, toxicology, pharmacological optimization, and Phase I–II studies. There has also been expressed interest by teams in the European Union to develop the drug sulindac sulfone for CA.

Cavernous Angioma as a Paradigm Disease

CA is a paradigm of a common neurovascular lesion with uncommon but consequential clinical sequelae. With Mendelian inheritance of familial cases, identical somatic mutations in sporadic cases, and faithful murine models of disease, several mechanisms of lesion genesis and progression have been elucidated. The disease has emerged as a paradigm of a commonly inherited neurovascular lesion with rare but significant clinical sequelae.
model of pathology involving vascular proliferation and dysmorphism, hemorrhagic angiopathy, brain iron deposition, lesional epileptogenesis, neurovascular immune disorder, and gut-brain axis. Investigations from many fields of science have been translated to help elucidate CA pathology and to develop biomarkers and putative therapies. These have included molecular genetics, vascular biology, immunology, microbial ecology, MR physics, biomedical engineering, transcriptomics, computational biology, biomarker science, pharmacology, genetic and population epidemiology, and trial readiness and design. It is a model of translational neuroscience with neurosurgical leadership, leveraging clinical programs, human subjects research, the mining of surgical tissue, and collaborations with “big science” teams.

Research on CA has contributed novel concepts in medicine. It is the first disease shown to be caused by genes essential for embryonic cardiovascular development, in which mutation later in life, on brain microvascular ECs, causes a focal neurovascular pathology. It is also the first disease in which gene heterozygosity, in the absence of lesions, causes diffuse systemic vascular and epithelial hyperpermeability. And it is the first disease where a gut-brain axis has been mechanistically linked to specific signaling on brain microvascular ECs. Spectacular discoveries and benefit to patients await similar deconstruction of other neurosurgical diseases.

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