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Publication Date
2021-07-01

DOI
10.1016/j.clinimag.2021.01.020

Peer reviewed

HHS Public Access

Author manuscript

Clin Imaging. Author manuscript; available in PMC 2022 July 01.

Published in final edited form as:

Clin Imaging. 2021 July ; 75: 55–66. doi:10.1016/j.clinimag.2021.01.020.

Systemic and CNS Manifestations of Inherited Cerebrovascular Malformations

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1. Introduction

Cerebrovascular malformations have important clinical implications. A subset are syndromic, inherited conditions with involvement of multiple other systems in the body. In the past decade, rare genetic brain disorders analysis advanced remarkably due to multi-institutional, multi-disciplinary funded research and improved basic science and neuroradiology, with unexpected links emerging between cerebrovascular malformations and gut bacteria [1] and cortical maldevelopment [2]. This paper provides a review of systemic and CNS manifestations of familial cerebral cavernous malformation (CCM), arteriovenous malformation (AVM), capillary malformation-AVM (CM-AVM), and associated cerebrovascular malformations. New insights into pathobiology and sporadic malformation somatic mutations have implications for developing treatments.

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Author disclosures: Drs. Hart, Mabray and Morrison report no disclosures. Dr. Kim reports consulting for Recursion Pharmaceuticals. Dr. Whitehead reports contract work for DSG Therapeutics.

2. Cerebral Cavernous Malformation

CCMs are low-flow, thin-wall vascular malformations of the brain, also known as cavernomas or cavernous angiomas, with a tendency for repeated hemorrhage. Prevalence in the general population is estimated at roughly 0.5% [3,4]. Although having relatively lower morbidity than high-flow AVMs, CCMs can result in significant complications, including seizures, focal neurologic deficits, and even death [5]. However, 20–50% of incidentally discovered CCM patients may be asymptomatic [6]. They fall into 3 groups: (1) sporadic (SCCM), no familial nature, about 80% of all cases, many associated with developmental venous anomalies; (2) familial (FCCM), approximately 20% of cases, with a genetic origin, usually with multiple CCMs present; and (3) radiation-induced. Familial CCM is found in all populations throughout the world, although the effect of founder mutations has led to higher prevalence in certain ethnic/geographic areas [7,8].

2.1. Imaging of CCMs

The common forms are familiar to radiologists on MRI. The classification initially described by Zabramski et al. is often used (Table 1) [9]. Larger lesions have a characteristic reticulated or “popcorn” appearance, with peripheral hemosiderin deposition showing susceptibility effects and mixed signal intensity interior, including combinations of both low and high T2 signal intensity and often areas of T1 hyperintensity, reflecting various stages of blood breakdown products (Figs. 1 and 2). They can range from a few mm to multiple cm. Some lesions, mostly smaller, reflect chronic hemorrhage, with hypointense signal on T2 and susceptibility effect. Lesions seen only on gradient-based sequences may represent punctate CCMs, microhemorrhages, or intravascular blood within telangiectasias that are the earliest form of CCM. A key feature is the dynamic nature of these vascular malformations. Serial imaging may reveal new (or de novo) lesions, growth, internal hemorrhage, or peripheral hemorrhage. Although growth is usually slow, large hematomas can occur. If acute hemorrhage is the initial clinical presentation, the underlying malformation may be initially obscured by hematoma.

Gradient-based MRI is important because of its greater sensitivity to blood-breakdown products, and susceptibility-weighted imaging or equivalent is the most sensitive and preferred gradient-echo sequence to optimally detect small CCMs (Fig. 1) [10]. This is especially important in the case of suspected FCCM since detecting more than 1 CCM makes FCCM much more likely. The exception is SCCM associated with DVA, in which case more than 1 CCM can occur around the periphery of a single DVA, still considered a single albeit combined malformation complex. Note that susceptibility-weighted imaging is helpful in either case: detecting multiple, separate lesions makes FCCM likely, with implications for family counseling, and SWI or equivalent can depict associated DVAs in the case of SCCM. Brain MRI that uses only fast spin echo technique may entirely miss small lesions that are obvious on gradient-based sequences.

Contrast enhancement is variable and is usually mild or not present. CCMs are classically considered occult on standard catheter angiography. On CT, larger CCMs often demonstrate variable increased attenuation relative to brain from internal calcification or blood. Small CCMs are often not visible on CT.

Reporting considerations: In order to avoid blooming artifacts, measurements of large CCMs are more accurate on spin-echo T2 than gradient-based sequences. The presence of multiple lesions on SWI or other gradient-based sequences should be noted. A current consensus statement defining and reporting CCMs recommends that CCMs be described as a clinical hemorrhagic event if there is both an acute or subacute clinical event and radiographic or additional evidence of recent hemorrhage [11]. Radiographic evidence of hemorrhage includes increased attenuation on CT or altered signal intensity on MRI with evolution on follow-up studies. Asymptomatic hemorrhage, CCM growth or new lesion on imaging studies without clinical symptoms is not considered a clinical hemorrhagic event.

Familial CCMs are uncommonly associated with DVAs [12]. In FCCM disease, although young patients with mutations may have no lesions, these commonly appear and increase over time and are usually seen in adulthood, occasionally even hundreds of lesions.

Sporadic CCMs are often associated with a DVA (Fig. 2) [12,13]. Multiple CCM de novo cases around a pre-existing DVA strongly suggest DVAs are present at birth due to anomalous venous system development with CCMs occurring later [14,15]. Although the pathophysiology is not completely understood, the CCM etiology likely relates to venous stenosis and higher pressures [16,17]; oxidative stress and inflammation may also contribute [18,19].

If a solitary CCM is identified with no known family history, especially if hemorrhage has occurred, it is important to look carefully for a DVA, either with contrast or SWI, because of surgical implications. Neurosurgeons usually avoid resecting the DVA itself because of risk of venous infarct [20], although there are differing viewpoints [15].

CCMs, telangiectasias and hemorrhage may occur within a radiation therapy field, and the risk is greater with higher doses [21,22]. Children are reportedly more susceptible than adults, with a median latency of 8–12 years, with considerable variation. Risk of hemorrhage from radiation-induced CCMs is similar to that from other CCMs [22].

Follow-up MRI is indicated based on development of new neurological symptoms or worsening epilepsy. In the current absence of medical therapy, there are no strong evidence-based recommendations for surveillance imaging of CCMs, and decisions are based on clinical judgment [23]. Differential diagnostic considerations of multiple, small hemorrhagic lesions, in addition to FCCM, include conditions such as hypertension, cerebral amyloid angiopathy, hemorrhagic metastases, and coagulopathy. This can be especially challenging in FCCM patients with additional diseases, such as hypertension. Multiple small calcifications, such as may be seen in neurocysticercosis, may present a confusing picture on SWI if CT is not available. Infrequently, a hemorrhagic neoplasm may present with a reticulated appearance resembling a CCM.

2.2. Cavernous Malformations in the Spinal Cord

Cavernous malformations (CMs) can occur in the spinal cord in both sporadic and familial settings [24], with a risk of hemorrhage in those symptomatic at presentation or with history of previous hemorrhage close to 9% per person year [25]. Spinal cord CMs are not

uncommon in familial disease, up to 70% using highly sensitive sequences (such as 3D MEDIC), many of which are small lesions with likely low risk of symptoms [26]. CMs can uncommonly occur in nerve roots [27]. Radiation-related CMs of the spinal cord have also been reported [22].

Finding a spinal cord CM should prompt MRI of the brain and investigation of family history. Acute spinal cord hemorrhage may be confusing (Fig. 3); the differential diagnosis includes CM as well as AVM, AVF, and hemorrhagic tumor. Follow-up imaging can be essential to identify the typical lesions after resolution of acute hemorrhage. If there is any suspicion of spinal cord CM, gradient-based sequences are critical, especially for the thoracic and lumbar spine, where clinical MRI often relies on multi-spin-echo sequences [26].

2.3. Systemic Manifestations of Familial CCM Disease

As an inherited condition with manifestations in the CNS, eyes, skin, bone, and adrenal glands, FCCM has features of a neurocutaneous disorder. Although most symptoms come from brain disruption, radiologists are important in identifying the multisystem findings.

Eye: A prospective French study of 60 FCCM patients found 5% had retinal cavernomas on fundoscopic examination [28]. All were asymptomatic regarding the retinal lesions, and each of the 3 genes was represented among the affected patients.

Skin: In surveys of large cohorts of FCCM patients, 9–20% were found to have skin lesions, which are capillary-venous lesions of various subtypes [29,30]. Most occur in the extremities. Deeper lesions may occasionally be evaluated by MRI for diagnosis or presurgical planning, and multiple lesions can sometimes be seen (Fig. 4).

Adrenal gland: Small calcifications without an associated mass can be seen on CT in FCCM, more often on the left than the right, and increasing in number with age (Fig. 5) [31]. These are suspected to be due to small vascular lesions in the adrenal gland, although no histologic correlation is yet available. No clinical implications are known. These are unusual enough that a characteristic appearance of small adrenal calcifications on CT, not associated with a mass, should encourage obtaining family history and possibly cranial MRI.

Bone: Osseous vascular malformations occur in the spine in FCCM patients [32,33], with a higher prevalence of MRI-atypical vascular malformations (low T1 and high T2 signal) [33]. Histologic analysis of tissue from 2 patients who had pathologic fractures showed combined capillary-venous malformations in the marrow with little fat in the lesions. These MRI-atypical malformations may be larger and perhaps more aggressive than typical osseous vascular malformations (Fig. 6). MRI-atypical vascular malformations in the vertebra are not as specific as adrenal gland calcifications for FCCM.

A suggested association of liver hemangiomas with FCCM [34] is not clearly confirmed at this time [35]. Further investigation might add information regarding possible visceral organ involvement.

2.4. Molecular Mechanisms: Of Mice and Men and Microbes

Familial CCM disease is an autosomal dominant condition that results from mutations in any of 3 genes: *CCM1 (KRIT 1), CCM2*, and *CCM3 (PDCD10)*, in descending order of frequency in the population [36]. *CCM3* tends to have earlier and more severe manifestations and more multisystemic involvement than FCCM caused by the other 2 genes, with reported association of meningioma [37]. There is an unusually high prevalence of CCM1 in the southwestern United States Hispanic population because of a founder effect, likely a spontaneous mutation in one of the early Spanish settlers in what is now northern New Mexico [7,38]. Individuals move, of course, and the CCM1 Common Hispanic Mutation is now more widely found. Familial clusters, and new cases due to de novo mutations, are found scattered throughout the world. FCCM follows a two-hit mechanism, with one germ-line defect and a second, somatic hit [39,40]. Mosaicism has been demonstrated within murine and human cavernous lesions, supporting a model in which a postzygotic mutation leads to clonal expansion of mutant cells incorporated with wild-type endothelial cells into the malformation [41,42]. There is also evidence that sporadic cases have 2 somatic hits in one of the same 3 genes, demonstrating a genetic basis for both SCCM and FCCM [43]. Since the Rho kinase pathway has been shown to be activated in both sporadic and familial patients, the presence of common genetic factors and molecular pathways offers hope that information gained from studies of familial disease may be applicable to sporadic cases.

How is it that mutations in any of 3 genes can lead to similar disease? The underlying mechanisms for formation and growth of CCMs constitute an active area of study, and more detailed review is available elsewhere [44]. The 3 proteins encoded by these genes interact with multiple partners and participate in multiple signaling pathways. Notably, however, the 3 proteins form a heterotrimeric complex that affects especially endothelial cell binding, particularly for the CNS. Loss of any of the 3 results in increased RhoA and RhoA kinase (ROCK) activation, making drugs that affect ROCK signaling of interest for potential CCM therapy. For example, statins and other drugs that inhibit ROCK activation reduce CCM formation in mouse models [45,46] and there is currently a phase I/II trial testing safety and dosing of atorvastatin for use in patients with SCCM/FCCM with recent symptomatic hemorrhage (NCT02603328). Other pathways dysregulated with loss of CCM genes include MEKK3-KLF2/4 and endothelial-to-mesenchymal transition [47,48]. Vitamin D is an important modulator of CCM activity in both animal models and patients [49,50].

Following unexpected experimental results after changes in an animal facility, the gut microbiome has more recently been implicated as playing an important role in CCM lesion formation in a neonatal mouse model. Specifically, CCM knock-out mice exposed to lipopolysaccharide challenge developed hemorrhagic CCM lesions with greater severity and also had greater relative abundance of gram-negative bacteria, *B. fragilis*, in stool samples. Lipopolysaccharide coating on gram-negative bacteria is a known ligand of TLR4 receptors on endothelial cells. TLR4 in turn activates MEKK3-KLF2/4 signaling, which was previously shown to mediate CCM lesion formation in this mouse model [1]. Human data from the Brain Vascular Malformation Consortium study confirmed a positive correlation of TLR4 risk allele with numbers of CCMs and with gene expression levels [1,18]. In addition,

a specific role of CCM3 in the gut has emerged in a mouse model, likely accounting for the more severe disease course of *CCM3* mutations [51]. Specific dietary factors may lead to more CCM formation. In humans, CCM cases had greater relative abundance of gram-negative bacteria compared to healthy controls.

These studies are the first clear link of the microbiome with CNS vascular malformations and illustrate a mechanism by which bacteria, without crossing the blood-brain barrier, can still have a major effect on the brain. There are intriguing implications for possible CCM treatment, including possibility of dietary change, fecal transplantation or other manipulation of the microbiome.

2.5. Future Directions in CCM Diagnosis and Treatment

Imaging: Tools being used for research include quantitative susceptibility mapping, dynamic contrast-enhanced permeability imaging, and automated detection techniques [52–54].

Biomarkers: A combination of 4 molecules in plasma has shown promise as a biomarker in predicting symptomatic hemorrhage in the next year [55].

Treatment: Evidence-based guidelines for clinical management of FCCM disease have been published [23]. So far treatment has been either surgical removal, with accompanying risk, especially for deep or critical location lesions, or symptomatic treatment of seizures and headaches and rehabilitation for neurological deficits. Lesions that have bled are at higher risk of repeat hemorrhage. Stereotactic radiosurgery has sometimes been used for hemorrhagic lesions in deep locations, although a meta-analysis showed very similar outcomes of death, intracranial hemorrhage, and focal neurologic deficit after stereotactic radiosurgery compared to patients who did not receive it [56]. Therapeutic radiation may accelerate CCM formation [57].

With improved understanding of pathobiology, a number of drugs are now being explored. These include atorvastatin and other ROCK inhibitors, tempol, vitamin D, propranolol, sulindac and others [58]. As mentioned above, the microbiome is another promising field for possible treatment options.

A recent population-wide, retrospective study revealed a perhaps paradoxical finding that antiplatelet therapy or anticoagulation was not a risk but may actually be beneficial in patients with CCM [59]. Controlled trials are necessary before recommending this for treatment, but it may be that, in the absence of recent hemorrhage, anticoagulation or antiplatelet therapy indicated for usual clinical reasons need not be withheld in CCM patients.

3. Developmental Venous Anomaly

DVAs are reviewed here because of the association with CCMs and an uncommon genetic condition. The DVA is the most common cerebrovascular malformation, with a prevalence of about 2.5–3%. As the name implies, it is more properly considered an anomaly of venous

development than a vascular malformation. The etiology of this congenital variant is unclear, hypothesized to be due to fetal venous thrombosis or disturbed angiogenesis and regression [60,61]. Most DVAs are benign and are considered “don’t touch” lesions; however, on closer examination, a variety of complications or other features can exist.

DVAs consist of multiple medullary veins which join to a larger draining collector vein that may drain superficially or less often into the deep venous system. Normal brain tissue is present between the veins and there is no abnormal shunting. Large DVAs may have more than one collector vein. The caput medusae appearance is readily identified on contrast-enhanced MRI, SWI MRI, or angiography (Fig. 2). They occur anywhere in the brain and are frequently incidental findings on cranial MRI.

The most common clinically significant finding associated with a DVA is a CCM in its drainage bed, as noted above (Fig. 2). Hemorrhage adjacent to a DVA is likely from a nearby CCM, or in rare cases a hemorrhagic infarction from DVA venous thrombosis, or high inflow from an AVM or AVF [61]. Rarely does a DVA with hemorrhage have no definitive etiology, however hemorrhage can obscure an underlying CCM [62]. Imaging findings include regional atrophy, white matter lesions, and dystrophic calcification on CT [60,63,64]. Uncommonly, hydrocephalus or nerve compression syndromes occur secondary to compression from the collector vein [61]. DVAs may show perfusion abnormalities including a prolonged MTT on perfusion MRI and decreased metabolic activity on 18F-FDG-PET [64–66].

Multiple DVAs may be seen in some patients with **blue rubber bleb syndrome**, a sporadic condition characterized by multiple cutaneous and mucous venous malformations caused by somatic activating mutations of *TEK*, the gene encoding TIE2 [67].

4. AVMs and Genetic Conditions Associated with AVMs of the CNS

AVMs result from abnormal, high-flow connections between arteries and veins, without an intervening capillary bed. On histology, normal brain tissue is not present within the nidus. The tangle of vessels is seen on multiple imaging studies. AVMs are characterized on CT and MRI by enlarged, tortuous feeding arteries and draining veins. Gliosis and evidence of prior hemorrhage may be seen in the brain parenchyma. Angiography is definitive, demonstrating multiple enlarged feeding arteries, the hallmark of shunting to the venous system through the nidus, and the pattern of venous drainage (Fig. 7). Aneurysms may be present in the enlarged, rapidly flowing arterial supply, and venous varices may be present. AVMs are distinguished from AVFs, which also have shunting from direct connections but no nidus (dural AVFs, acquired conditions, are not discussed further in this review). Most AVMs are sporadic, while some are part of genetic syndromes. Multiple AVMs are strongly suggestive of genetic origins, most commonly hereditary hemorrhagic telangiectasia (HHT) [68,69].

Risk of hemorrhage from brain AVMs is 2–4% per year [70,71]. Seizures or neurologic deficits can also occur. Treatment options include surgical resection, stereotactic radiosurgery, embolization, or a combination. The Spetzler-Martin grading scale is the most

common method used for estimating risks of surgery (Table 2) [72], although other scales have shown improved prediction, including the SM-Supplemented score [73].

5. Hereditary Hemorrhagic Telangiectasia

HHT, also known as Osler-Weber-Rendu syndrome, is an autosomal dominant condition due to a mutation of 1 of 3 genes: *endoglin (ENG)* in HHT1, *ACVRL1* in HHT2, and *SMAD4* in juvenile polyposis/HHT overlap syndrome. Vascular malformations occur in multiple locations in the body, with associated clinical manifestations. Clinical diagnostic criteria are listed in Table 3 [74].

5.1. Brain Vascular Malformations in HHT

Brain AVMs occur in 10–20% of HHT patients, more frequently in HHT1 than in HHT2 [69,75]. They tend to be supratentorial and superficial, usually <3 cm, Spetzler-Martin grade 1 or 2, although serious hemorrhage or larger AVMs can occur. In HHT new AVMs may develop in childhood [76]; de novo appearance in adulthood has not been described. Rarely, a pial AVF shunting lesion with direct arterial-venous shunting and no nidus may occur (Fig. 8). The most common, and least dangerous, brain malformation in HHT is a capillary vascular malformation, formerly termed micro-AVM, <1 cm in diameter, with faint MRI post contrast enhancement and a blush in the angiographic capillary phase (Fig. 9), with a feeding artery and vein that may be visible and not enlarged [68,69]. These differ from brain capillary telangiectasias (BCTs); BCTs are angiographically occult and lack an identifiable feeding artery. DVAs, CCMs, and vein of Galen of malformations are also reported in HHT [69]. Cerebral aneurysms are reported, although the incidence may not be higher than the general population, especially when accounting for AVM feeding arteries.

The risk of hemorrhage from brain AVMs is controversial and likely lower with HHT, 0.3–0.7% per year per lesion, than in sporadic AVMs overall [77,78]. The combination of MRI and MRA with contrast, especially at 3T, has advantages for screening for brain AVMs [79]. HHT capillary vascular malformations have a benign clinical course. One study found no hemorrhage or other symptoms related to capillary malformations in 222 lesion years of follow-up [80].

5.2. Cortical Malformations in HHT

Malformations of cortical development, most often polymicrogyria, have been found on brain MRI in 5–12% of HHT patients. They are often perisylvian, unilateral, and subclinical. This subgroup of HHT patients has a higher prevalence of brain or pulmonary AVMs, sometimes with a brain AVM near the polymicrogyria [2,81]. The cases appear related to *ENG* mutations, leading to hypotheses about the relationship of abnormal angiogenesis and corticogenesis [81].

5.3. Spinal Cord Vascular Malformations in HHT

Spinal vascular malformations in HHT are rare, usually present at a young age, and consist of perimedullary AVFs [82]. Treatment is usually endovascular embolization (Fig. 10).

5.4. Systemic Manifestations of HHT

Mucocutaneous telangiectasias: Epistaxis is the most common symptom of HHT, eventually in up to 96% of HHT patients [83]. Anemia can be a significant clinical problem, sometimes requiring chronic iron infusions or blood transfusions [84]. Visible telangiectasias of the mouth, face or hands usually appear later, most commonly in early adulthood [84,85].

Lungs: Pulmonary AVMs are found in 15–50 % of HHT patients (Fig. 11) [84,85]. Complications include hemoptysis and hemothorax, hypoxemia, and dyspnea, as well as CNS complications of stroke and cerebral abscess due to paradoxic embolization. Contrast echocardiography is highly sensitive for screening; chest CT is an alternative but could be avoided if there is minimal or no shunt by echocardiography [86]. Pulmonary angiography may be used for diagnosis and embolization [84,85].

GI tract: Telangiectasias in the stomach or small intestine are very common in HHT, with symptomatic hemorrhage in 25–30% of patients, usually after age 40 [84]. Patients with juvenile polyposis in the *SMAD4* overlap syndrome also have an increased risk of GI malignancies.

Liver: AVMs are not uncommon in the liver in HHT, with symptoms in about 8%, including high-output heart failure, portal hypertension and biliary necrosis [87]. Screening for these complications is important, and more clinically relevant in most patients, than imaging the malformations. These lesions can be visualized by ultrasound, CT, or MRI.

5.5. Molecular Mechanisms and Future Directions in HHT Treatment

The products of the genes involved in HHT are all part of the BMP9/10 signaling pathway. ACVRL1 and endoglin are members of an endothelial receptor complex for BMP9 and BMP10. Binding of this complex activates transcription factors, including SMAD4, and furthers regulation of angiogenesis. Dysregulation of this pathway in HHT results in abnormal angiogenesis [88]. HHT lesions also show some evidence of a two-hit mechanism with one inherited germ-line mutation and one somatic mutation in HHT genes [89]. Brain and spinal cord AVM lesions from non-HHT (sporadic) cases have somatic mutations in *KRAS* and other RAS/MAPK pathway genes affecting angiogenesis [90,91].

Thus, drugs that affect angiogenesis are promising for treatment of HHT. These include bevacizumab, pomalidomide, and tyrosine kinase inhibitors such as pazopanib. The BMP9/10 pathway may be activated by some immunosuppressive drugs, including tacrolimus and sirolimus. The latter has also demonstrated promise for treatment of blue rubber bleb nevus syndrome and other venous and lymphaticovenous malformations [88]. As with CCM, treatment of HHT is likely to benefit from increasing understanding of the underlying mechanisms.

6. CM-AVM

Capillary malformation-arteriovenous malformation (CM-AVM) syndrome is a relatively recent addition to known genetic conditions which include cerebrovascular malformations.

CM-AVM is most notably characterized by multiple capillary malformations, often 1–2 cm in diameter but occasionally large, mostly on the face and limbs. AVMs or AVFs are seen in 18–24% of patients in brain or spine, skin, muscle, and bone, but much less likely in visceral organs, unlike HHT. Inheritance is also autosomal dominant, and caused by germ-line mutations in *RASA1* (CM-AVM1) and *EPHB4* (CM-AVM2) [92,93]. Parkes Weber syndrome, in which limb overgrowth occurs in association with a capillary stain and multiple arteriolovenular microfistulas, is present in some CM-AVM patients. Vein of Galen aneurysmal malformation has been reported in patients with both mutations [94,95]. There is considerable overlap in the phenotype of CM-AVM2 with HHT [96].

Cutaneous or deeper vascular malformations, such as occur in CM-AVM, can be evaluated by various imaging techniques, including ultrasound, CT, MRI, and catheter angiography. Contrast-enhanced MRA can classify venous malformations according to venous drainage pattern without radiation risk [97]. Time-resolved, contrast-enhanced MRA can assess both arterial and venous features of soft tissue AVMs, aiding treatment planning [98]. Clinical and imaging features of other, nonfamilial vascular neurocutaneous disorders are discussed in detail elsewhere and may arise in the differential diagnosis [99]. For example, both Parkes-Weber syndrome and Klippel-Trenaunay syndrome, a sporadic condition usually arising from a somatic mutation in *PIK3CA*, involve limb overgrowth and capillary skin lesions [100,101]. However, the former involves high-flow lesions, but Klippel-Trenaunay lesions show only low flow [101].

7. Capillary Telangiectasia

BCTs consist of clusters of dilated, thin-walled capillaries interspersed with normal brain parenchyma. Prevalence is difficult to determine because of the specific sequences needed for imaging but is reported at <1% [102]. The most common location is the pons [103]. MRI findings typically include mild contrast enhancement and either normal routine T1 and T2-weighted appearance or mild T2 prolongation [103,104]. There is susceptibility effect, with SWI more sensitive than T2 gradient echo [105]. Histologically these lesions do not contain thrombus, and the susceptibility effect is most likely due to deoxygenated blood in the slowly flowing vessels. A draining vein is seen in over a third of cases (Fig. 12) [103].

Most BCTs are clinically benign and are detected incidentally. Reported rare, symptomatic BCTs may be due to other, associated vascular formations [102]. Routine follow-up is not recommended for isolated, incidentally detected BCTs.

Note that BCTs differ from capillary vascular malformations of HHT discussed above, and from the cutaneous capillary malformations of CM-AVM.

7. Conclusions

Key features of these syndromes are summarized in Table 4.

Research in a variety of fields is increasing understanding of the clinical, imaging, and molecular aspects of cerebrovascular malformations. Optimal imaging sequences should be utilized if brain or spine vascular malformations are found or suspected. FCCM, HHT, and

CM-AVM often involve multiple other systems in the body. Recognizing the varied manifestations may improve diagnosis of the disease, with potential value to both individual patients and their families.

Continued elucidation of molecular mechanisms may eventually lead to treatment with medication or even manipulations of the gut microbiome. Even for sporadic CCMs, very frequently associated with a nearby DVA, evidence of somatic mutations gives promise that medical therapies that emerge for FCCM may also apply to SCCM. For both inherited and sporadic cerebrovascular malformations, understanding the imaging manifestations and clinical risks will improve patient care.

Acknowledgments

Funding: This work was supported in part by the National Institute Institutes of Health grant U54 NS065705

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Highlights:

- Radiologists can play an important role in diagnosis and assessment of inherited cerebrovascular malformation disease by recognizing systemic manifestations in different tissues.
- Features suspicious for CCM or HHT in brain, spinal cord, or elsewhere in the body should lead to optimized imaging for each.
- Understanding genetic and molecular mechanisms underlying these diseases will likely lead to new treatment options
- Molecular mechanisms in these diseases may prove relevant to sporadic vascular malformations that involve somatic mutations.

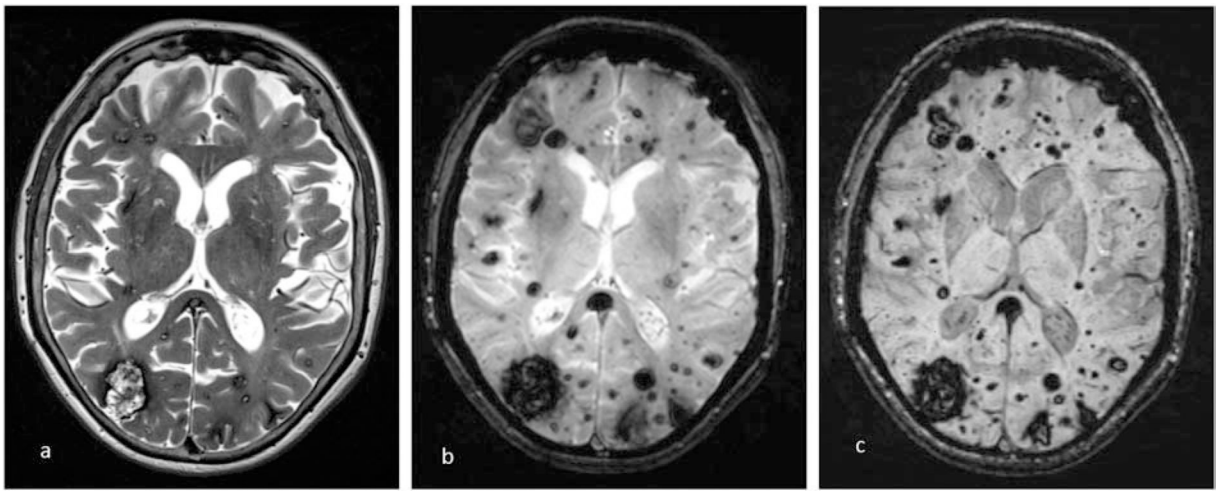

Fig. 1—.

Familial cerebral cavernous malformations (CCMs). 63-year-old woman with hemiplegia and gait difficulties. Axial MRI, FSE T2 (**A**), T2 GR (**B**), and SWI (**C**), show numerous CCMs, ranging from a large, reticulated type right occipital CCM to multiple small, mixed-signal-intensity CCMs to a large number of smaller lesions, including one in the splenium of the corpus callosum, with progressively more seen on GR and SWI.

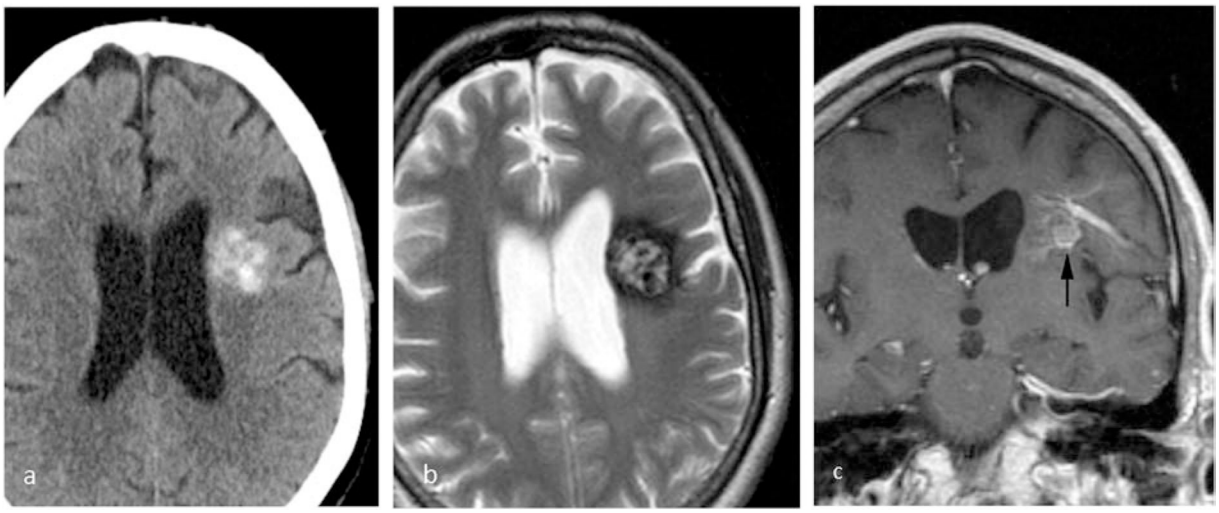

Fig. 2--

Sporadic cerebral cavernous malformation and developmental venous anomaly. 65-year-old man with acute mental status change. **A**. Nonenhanced CT revealed irregular left frontal lobe calcification. **B**. MRI, axial TSE T2 performed soon after showed no acute hemorrhage but typical reticulated appearance of CCM with hemosiderin rim. **C**. MRI, coronal post gadolinium T1 shows that the CCM (arrow) lies at the inferior margin of a DVA with superficially draining collector vein.

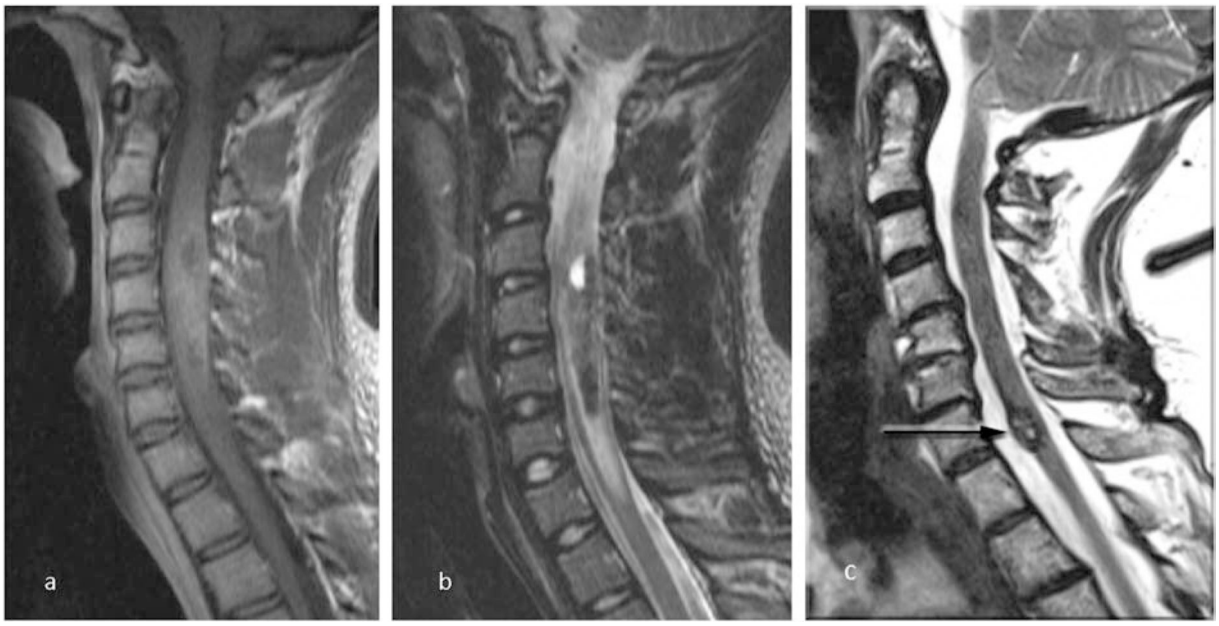

Fig. 3—.

Spinal cord cavernous malformations. 17-year-old male with left shoulder and arm pain. Sagittal T1 (**A**) and TSE T2 (**B**) MRI shows complex region of hemorrhage including fluid-fluid layer, swelling, and edema, originally suspected to be neoplasm. Brain MRI showed several small cavernous malformations. Spinal cord cavernous malformation was resected, with good outcome. *CCM1* mutation confirmed after initial presentation. Compare with cavernous malformation without acute hemorrhage in the ventral spinal cord (arrow) at C7 in a 58 year-old-woman with right upper extremity weakness and numbness (**C**, sagittal T2). Brain MRI revealed multiple cavernous malformations.

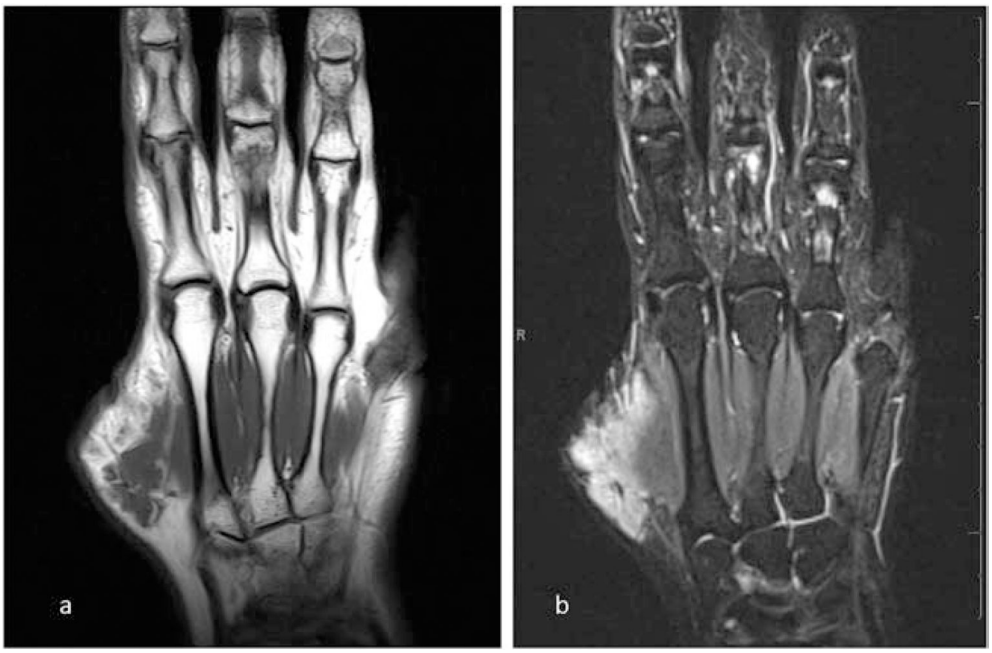

Fig. 4—.

Skin vascular malformation in familial CCM. 29-year-old woman with familial cerebral cavernous malformations and lobulated vascular lesion in dorsal soft tissues of right hand had MRI. Coronal T1 (**A**) and T2 STIR (**B**), demonstrate lobulated lesion in the soft tissue. Multiple CCMs were present on brain MRI and there was a family history of CCMs.

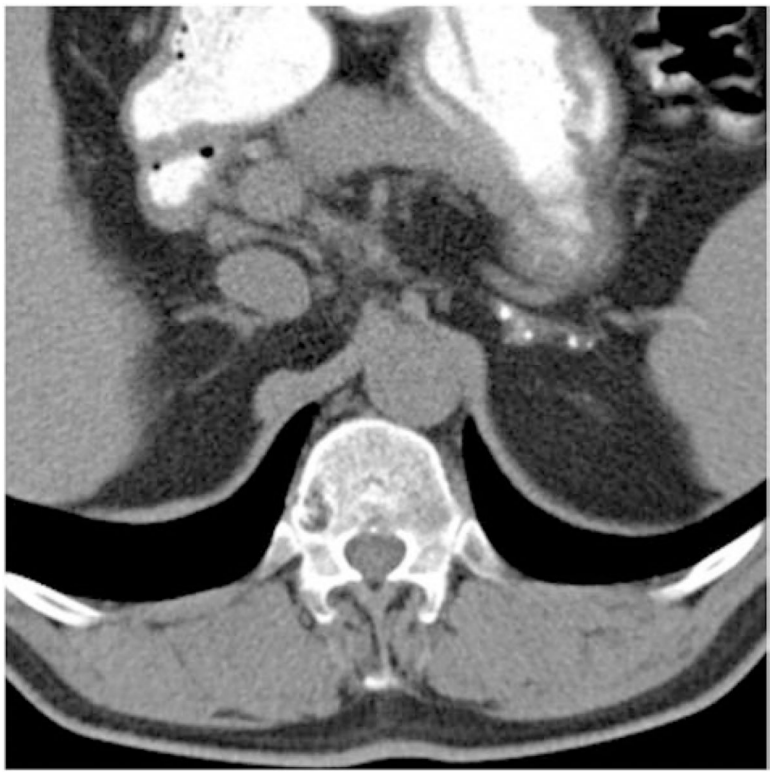

Fig. 5--

Adrenal calcifications in familial cerebral cavernous malformations. 59-year-old man with documented *CCM1* mutation, multiple brain CCMs, and unrelated cirrhosis. CT abdomen without intravenous contrast administration. There were 2 right (not pictured on this slice) and 5 left adrenal calcifications, incidental findings. A vertebral vascular malformation is visible in the right side of the T12 vertebral body (see below regarding osseous vascular malformations).

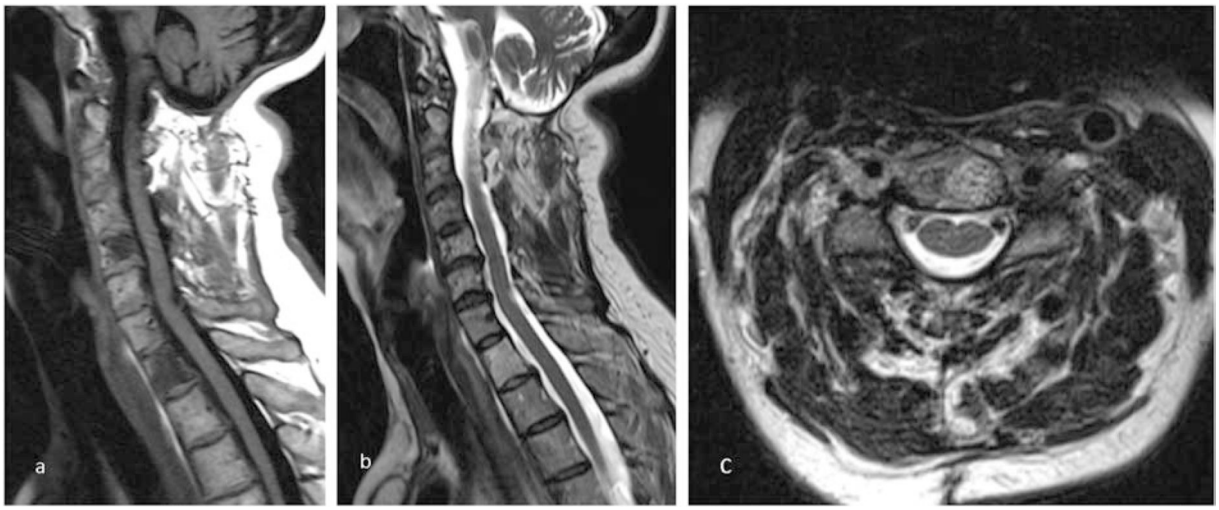

Fig. 6.

MRI-atypical vertebral osseous vascular malformations in FCCM. 50-year-old woman with documented *CCM1* mutation and numerous cavernous malformations in the brain, MRI cervical spine done for unsteadiness. MRI, sagittal T1 (**A**), sagittal TSE T2 (**B**) and axial TSE T2 (**C**) of the cervical spine shows low T1/high T2 lesions in C5 and T1, stippled appearance on axial T2 through the C5 lesion. They remained stable for years.

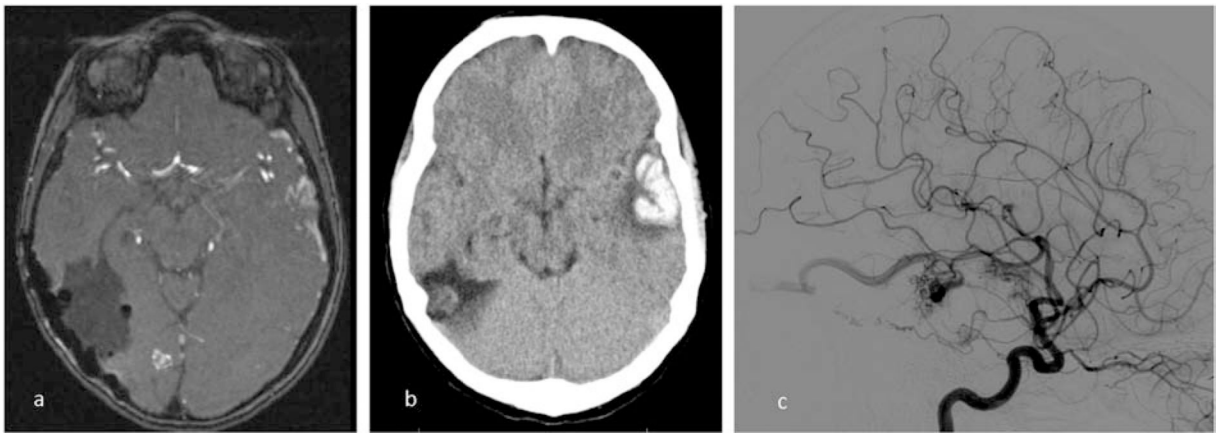

Fig. 7—.

Cerebral AVMs in HHT. 10-year-old girl with hereditary hemorrhagic telangiectasia. **A**. Axial source image from MRA shows right occipital and left temporal lobe small AVMs, as well as resection site of previous posterior right temporal AVM. **B**. At age 17, acute left temporal hemorrhage is visible on nonenhanced CT. **C**. Angiogram, lateral view of left ICA injection shows anterior left temporal AVM with enlarged feeding arteries, tangle of vessels, and early shunting into venous system.

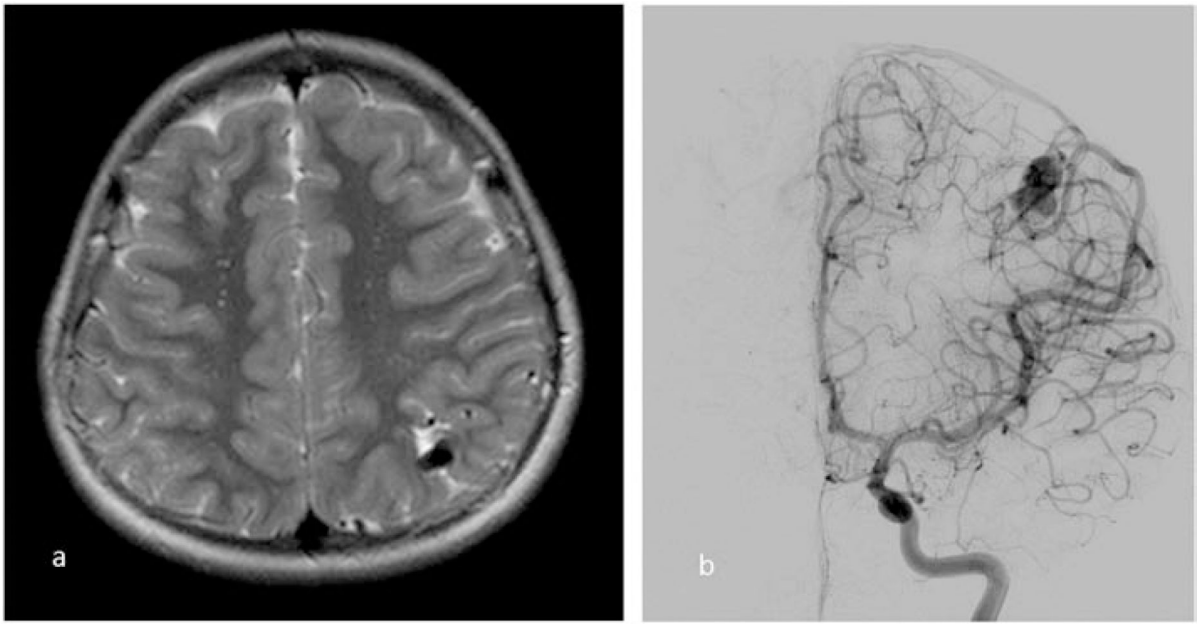

Fig. 8—.

Pial AVF in HHT. 9-year-old boy with HHT, screening MRI of brain performed. **A**. MRI axial TSE T2 shows left parietal malformation. **B**. Angiogram, AP view LICA injection, shows left parietal enlarged arteries and veins with a venous varix but no discernable nidus, consistent with pial arteriovenous fistula.

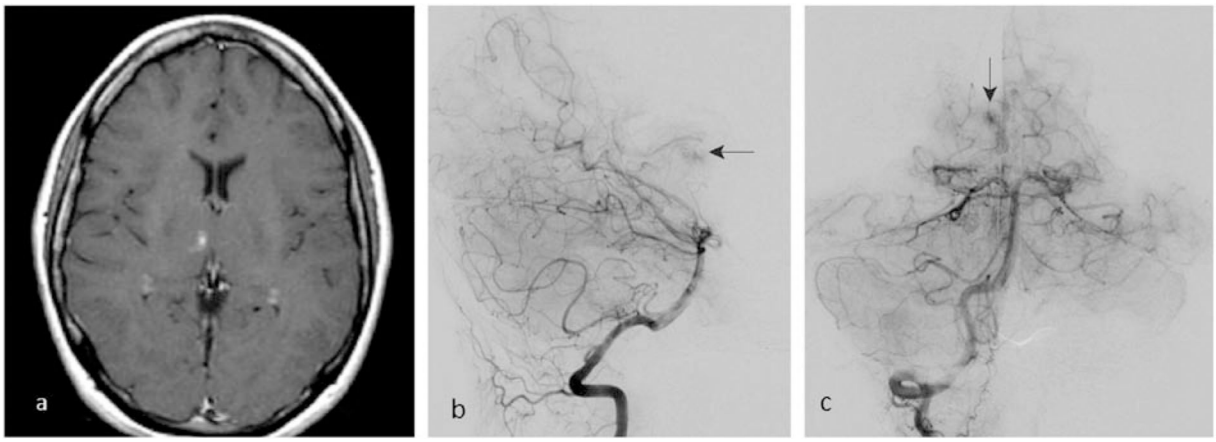

Fig. 9—.

Capillary vascular malformation in hereditary hemorrhagic telangiectasia. 24-year-old woman with hereditary hemorrhagic telangiectasia. **A**. Contrast-enhanced axial T1 MRI of a 24 year old woman shows focus of enhancement <1 cm in the medial right thalamus. Subsequent angiogram, right vertebral injection, lateral view (**B**) and AP view (**C**), shows a blush without enlarged feeding or draining vessels (arrows). Location in the thalamus is unusual; subcortical location is much more common.

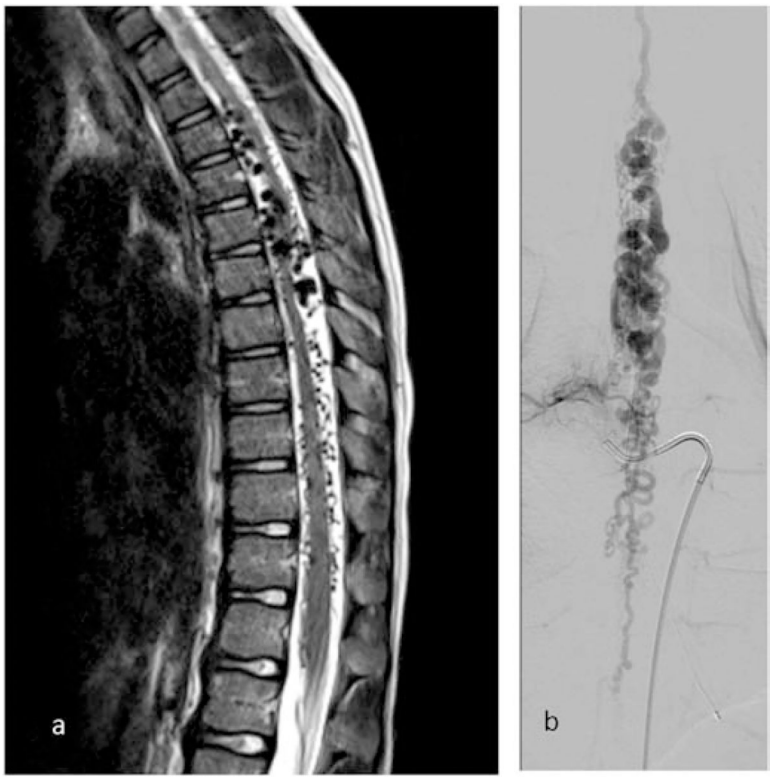

Fig. 10—.

Spinal arteriovenous fistula in HHT. 8-year-old boy with hereditary hemorrhagic telangiectasia had spinal vascular malformation detected incidentally, when partially visualized on MRI brain. **A**. MRI, sagittal TSE T2 shows numerous dilated, tortuous vessels seen in the thoracic spine. **B**. AP view of spinal angiogram, injection at T7, shows tortuous vessels of spinal arteriovenous fistula. Treated with embolization.

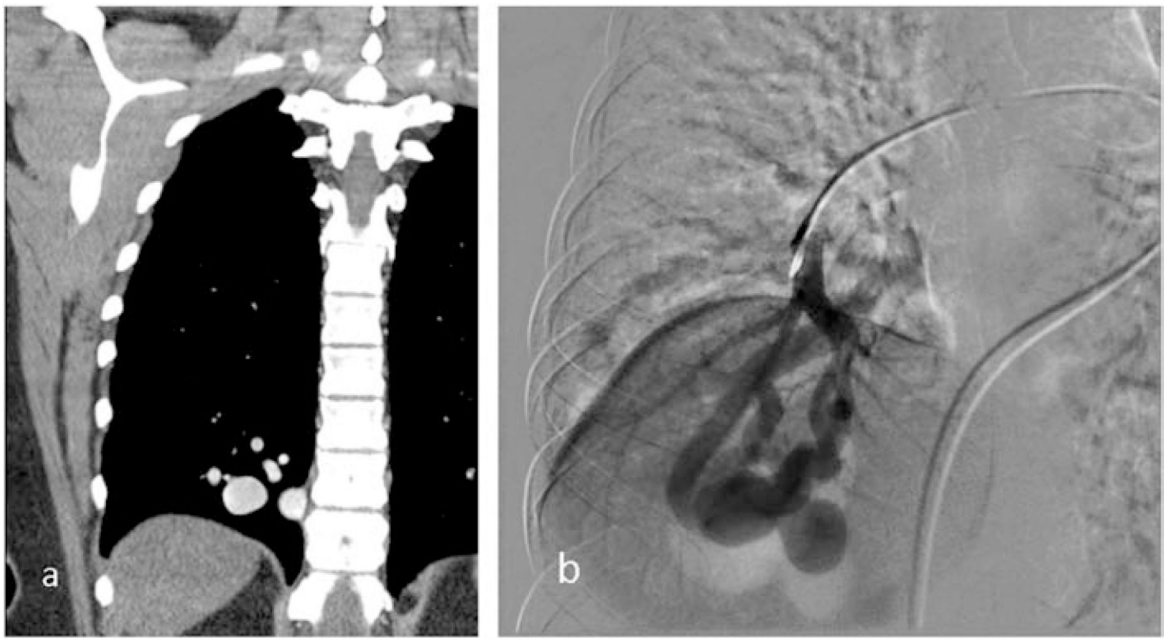

Fig. 11—.

Lung AVMs in HHT. 45-year-old woman with hypoxia and family history of hereditary hemorrhagic telangiectasia. Basilar lung AVMs demonstrated on both CT (**A**, coronal reformat) and pulmonary angiography (**B**). These and others not illustrated were embolized.

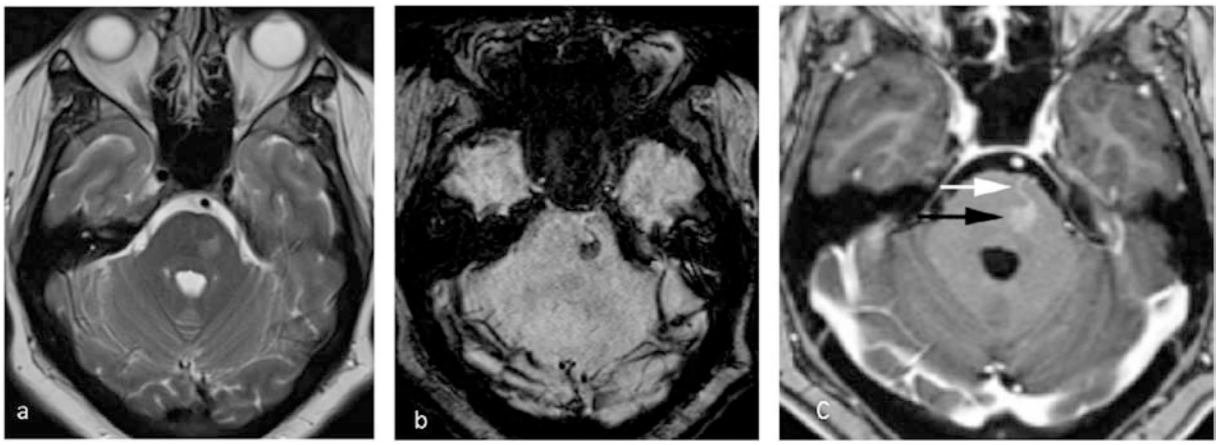

Fig. 12—.

Capillary telangiectasia. 31-year-old woman with hemianopsia, incidental finding of **c**apillary telangiectasia. Left pontine capillary telangiectasia (black arrow) visible on MRI TSE T2 (**A**), SWI (**B**), and post gadolinium T1 (**C**). Slightly increased T2 signal intensity (**A**) and draining vein (white arrow) are not uncommon.

Table 1.

Zabramski classification of CCMs

Type 1	T1 hyperintense core, T2 hyperintense or hypointense core
Type 2	Classic “popcorn” or reticulated appearance, hemorrhage of varying ages: mixed on T1 and T2 centrally with periphery of T2 hypointensity
Type 3	Prior hemorrhage: mostly T2 hypointense from hemosiderin staining, T1 hypointense to isointense center
Type 4	Punctate lesions: seen well only as low signal on gradient-based T2 imaging

Table 2.

Spetzler-Martin grading system for AVMs. The grade is the sum of the points assigned for the 3 features.

Feature	Points
Size of AVM	
<3 cm	1
3–6 cm	2
>6 cm	3
Eloquence of site	
Noneloquent	0
Eloquent	1
Venous drainage pattern	
Superficial only	0
Deep	1

Table 3.

Curaçao diagnostic criteria for HHT

1. Epistaxis – spontaneous, recurrent
2. Telangiectasias – multiple at characteristic sites (lips, oral cavity, fingers, nose)
3. Visceral lesions – such as gastrointestinal telangiectasia; pulmonary, hepatic, cerebral, spinal AVMs
4. Family history – first degree relative with HHT according to these criteria

Definite if 3 or more criteria present, possible or suspected if 2 present

Table 4.

Summary features of inherited cerebrovascular malformation syndromes.

Condition	Cerebrovascular malformations	Other tissues involved	Genes involved	Pathways involved	Prevalence estimates
Familial cerebral cavernous malformations	Cavernous malformations in brain and spinal cord	Eyes: retinal cavernous malformations Skin: capillary-venous malformations Bone: capillary-venous malformations Adrenal gland: calcifications (possibly malformations)	*CCM1, CCM2, CCM3* *	Rho kinase (ROCK), TLR4-MEKK3-KLF2/4, endothelial cell binding, EndMT, others	16 to 50 per 10,000
Hereditary hemorrhagic telangiectasia	Brain: AVM, capillary vascular malformation, pial AVF, (others reported) Spinal cord: AVFs Brain: polymicrogyria	Mucocutaneous: telangiectasias Lung: AVMs GI tract: telangiectasias Liver: AVMS	*endoglin (ENG)* (HHT1), *ACVRL1* (HHT2), and *SMAD4* (juvenile polyposis/HHT overlap syndrome) **	BMP9/10, regulation of angiogenesis	1 to 2 per 10,000
Capillary malformation-AVM	AVM, Vein of Galen aneurysmal malformation	Skin, muscle, spine AVMs and AVFs Skin: capillary malformations Limb overgrowth (Parkes Weber)	*RASAI* (CM-AVM1), *EPHB4* (CM-AVM2)	Ras/MAPK signaling	0.1 to 0.8 per 10,000

* Somatic mutations of each of the 3 CCM genes found in some sporadic CCMs

** Somatic mutations in *KRAS* and other RAS/MAPK pathway genes found in some sporadic AVMs

EndMT = endothelial-to-mesenchymal transition