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Manu K. Arul, BS
State University of New York, Upstate Medical University

Omaditya Khanna
Thomas Jefferson University

Michael R. Gooch, MD
Thomas Jefferson University

A Case Report and Overview of Familial Cerebral Cavernous Malformation Pathogenesis in an Adult Patient

Manu K. Arul, BS[1]; Omaditya Khanna, MD [2]; Michael R. Gooch, MD[2]

[1]State University of New York, Upstate Medical University, College of Medicine, Syracuse, NY
[2]Department of Neurological Surgery, Thomas Jefferson University, Philadelphia, PA

OBJECTIVE

We present a case of a 39 year-old woman who presented with a solitary cavernous malformation hemorrhage without any other lesions, and subsequently presented several months later with a new hemorrhage from a de novo lesion. We discuss mechanisms of paradominant inheritance and haploinsufficiency to describe phenotype expression of familial cavernous malformations.

CASE DESCRIPTION

The patient presented with unremitting headaches, who had a known history of a solitary cerebral cavernous malformation (CCM) for which she underwent resection several months prior with no evidence of any other CCM lesions seen on post-operative MRI. She has no history of whole brain radiation, family history of cavernous malformations, or prior head trauma. During this hospital visit, she was found to have develop two new lesions in the left fronto-parietal lobe and cerebellum. She was treated with surgical resection of the left frontoparietal lesion, and recovered fully. It is of interest that a patient approaching her fourth decade of life would start to develop formation of multiple de novo cavernous malformations, especially with an absent family history. Paradominant Inheritance and haploinsufficiency are two proposed models of inheritance that can be related to this patient's disease progression.

CONCLUSION

The case illustrates an atypical clinical course of a patient with familial cerebral cavernous malformations with delayed formation of de novo lesions.

INTRODUCTION

Cerebral Cavernous Malformation is a vascular disease of the brain with solitary and familial mechanisms.[1] The patient of interest presented to the hospital with headaches and a past history of CCM one year prior, with new hypodense lesions on a head CT scan, most likely cavernous malformations. The possibility of hereditary CCM development during adulthood and lesion multiplicity through the mechanisms of paradominant inheritance and haplo-insufficiency is described. Understanding these modes of inheritance as well as the genetic pathology can aid in genetic counseling as well as developing disease modifying treatments apart from surveillance and surgery.

CASE

The patient is a 39 year-old female with a history of a solitary cavernous malformation for which she underwent a left parieto-occipital craniotomy for resection in 2016. At that time, a post-operative MRI did not reveal any other lesions suspicious for cavernous malformations (including GRE sequence). She presented to an outside hospital with an unremitting headache starting one-week prior. She describes the headache as bifrontal and similar to a headache she had during her prior presentation. She rated the pain as an 8 out of 10. A head CT was performed and a new left frontoparietal intraparenchymal hemorrhage was discovered separate from her previous resection site. When the patient was admitted to our institution for further care and evaluation.

Other than her previous craniotomy for a hemorrhagic cavernous malformation, she has no other significant surgical history. Her family medical history is pertinent for hypertension in her mother. She was not taking any medications, and claims not to smoke, drink alcohol, or use illicit substances. An MRI was performed after her resection in 2016, which did not demonstrate new lesions.

Her physical exam demonstrated that she was awake, alert, and oriented to person, place, and time. She had no gross cognitive or neurologic deficits; cranial nerve testing of CN II-XII showed normal functioning, her strength was 5/5 in upper and lower extremities, and her sensation was intact. Her gait was normal, without disturbances; she did not demonstrate pronator drift. An MRI was performed, revealing new lesions in the right cerebellum as well as left frontoparietal lesion.

The patient was brought to the OR for resection of the lesion the following day. She underwent a left frontoparietal craniotomy and resection of the lesion without complications. Her post-operative recovery had no complications and she was discharged from the hospital on post-operative day[3].

DISCUSSION

Cerebral cavernous malformations (CCM) are low flow, vascular malformations of vessel-like channels, filled with blood in

various stages of degradation. They lack the smooth muscle support of normal vessels without any intervening brain parenchyma, and are generally clustered and dilated.[1,2] Cavernous malformations account for 5 to 15% percent of all vascular malformations in the CNS, and are prone to rupture due to stressors or changes in blood pressure.[2] Cavernous malformations can be hereditary (familial) or sporadic, and are usually discovered through a symptomatic presentation of hemorrhage.[2] The most common presenting symptoms include headache, seizures, and focal neurologic deficits; seizures are the most common symptom in 40-60% of presenting cavernous malformations. The presence of multiple lesions seen on a cerebral magnetic-resonance image is indicative of the familial form of the disease, and 20-50% of affected individuals will develop symptoms between the second and fifth decade of life.[3]

We report a patient approaching her 4th decade of life with a history of one prior symptomatic cavernous malformation the previous year, presenting now for a separate symptomatic, actively bleeding cavernous malformation. Following her previous resection in 2016, post-operative MRI did not reveal new lesions or disease foci. Now, CT and MRI reveals two distinct lesions, newly developed within a year's time, reflecting an atypical clinical course of the familial form of cerebral cavernous malformation disease.

Familial Cerebral Cavernous Malformation Development

Familial or hereditary CCM occurs from mutations involving 3 loci: CCM1, CCM2, and CCM3. CCM1 mutations account for roughly 70% of familial cerebral cavernous malformations.[4] It is proposed that the various mutations within these genes might affect angiogenesis and endothelial cell morphogenesis, deteriorating vascular stability.[4] There are close to one hundred CCM1 mutations that contribute to disease development.[5] In a 2007 review, Brouillard and Vikkula described numerous roles the CCM1 locus plays in cerebral vascular development, as well as its possible significance in arterial-venous differentiation. The main pathogenesis from a CCM1 mutation is derived from the KRIT1 gene, that is suggested to play a role in cell adhesion and migration, directly influencing the endothelial cells which form and support vasculature.[5] CCM2 is described as playing a role akin to that of CCM1, especially in the sequestration and signaling of the KRIT1 involved pathway. This acts through the MGC4607 gene, malcavernin; it has been shown that both loci can act together in a CCM1/2 complex to influence vascular development.[6] CCM3 can be described as "tumor suppressor like," where deletions in CCM3 can lead to proliferation and resistance to apoptosis, shown by Louvi et al in a mouse model.[7] A zebrafish model by Yoruk et al further supports that the CCM3 model behaves separately from the CCM1/2 pathway, and even contributes to a phenotypically different pattern of vascular development.[8] Furthermore, their study showed CCM3 worked in conjunction with GCKIII, which can be implicated in pharmaceutical therapy.

Originally, Zabramski et al described familial cavernous malformation as a dynamic disease, with families exhibiting similar symptomatology among generations.[9] Our patient, however, did not recall family members with her disease or symptomatology. It is possible that family members had asymptomatic lesions, as Zabramski's research points out that actively bleeding cavernomas are most likely to be symptomatic and discovered. In addition, Denier et al had demonstrated that CCM3 genotypes generally had less familial expression of the disease. Though it is understood which genes play a role in disease development, the underlying mechanism of expression is not concretely understood (See figure 1).

De novo Cerebral Cavernous Malformation

De novo cavernomas have been reported to have underlying risk factors, such as cranial radiation, coexistent vascular malformations, and hormonal factors. Head injury, reactive angiogenesis, and viral infections can also play a role in producing cavernomas. [10] However, their exact pathogenesis remains unknown. Gross' meta-analyses proposed that de novo CCMs develop from developmental venous anomalies (DVA), venous stasis, and resultant microhemorrhage due to venous hypertension.[1] Nearly half of sporadic CCMs are associated with an adjacent DVA; in contrast, hereditary CCMs develop in near absence of DVAs.[3]

Our patient had no history of cavernous malformation until her first occurrence one year prior to this presentation. In between that time and now, two new cavernous malformations formed. Her work up and medical history did not have any associated DVA or other vascular abnormality. The question remains to why she had developed a symptomatic cavernoma close to four decades into her life, and then two more within a year's time. There are several cases of multifocal sporadic lesions, where CCM mutations accounted for roughly 60% of observed pathologic findings.[11] Bacigaluppi's review et al sheds light on various molecular pathways that are responsible for vascular development and pathologic variations in cerebral cavernous malformation.[3] Two of the foremost theories on the inheritance of this disease, as well as other vascular malformation pathologies are those of paradominant inheritance and haploinsufficiency.

Haploinsufficiency

Haploinsufficiency is defined by non-inheritance of a gene or loss of function mutation that leads to insufficient genetic expression of a wild-type phenotype. Diseases such as Angelmann syndrome and Ehlers-Danlos Syndrome are characteristic of haploinsufficiency. It has been proposed that haploinsufficiency manifests through various ways in CCM, such as inadequate protein production for endothelial junction formation, causing the pseudovascular formation characteristic of CCM.[12] Though this can be seen as an adequate explanation for disease mechanism, it would not fit the presentation of our patient as haploinsufficiency would indicate disease progression since birth, which was not the case here.

Paradominant Inheritance:

Paradominant inheritance mimics the two hit hypothesis initially described by Knudson to describe the tumor suppressor gene mechanism.[3] Paradominant inheritance constitutes a congenital inheritance of a nonfunctional gene, and

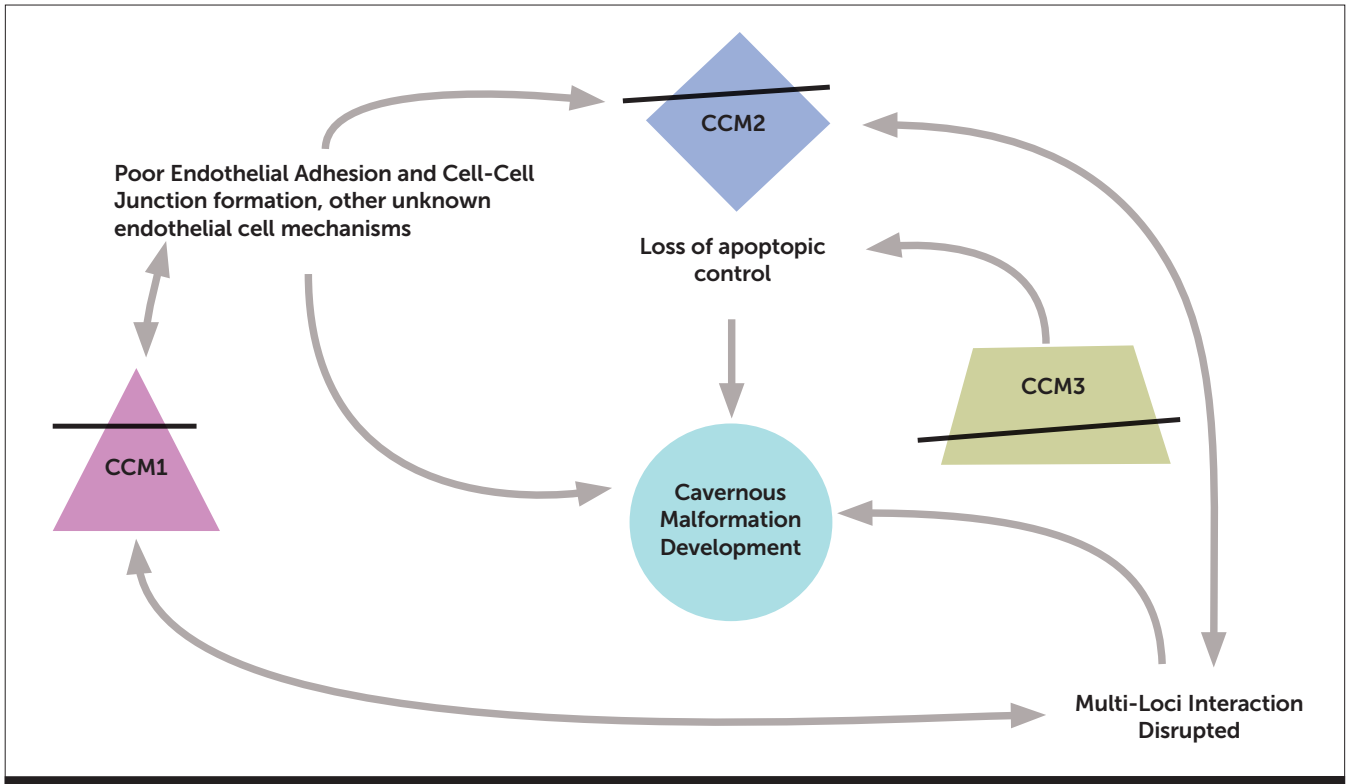

Figure 1.

This simplistic diagram illustrates the individual CCM loci contribution to disease development, as well as the complex pathways that have been shown in various studies. A black bar indicates loss of function. Knockouts or non-inheritance of functional loci have been shown to result in CCM development and other abnormal vascular phenotypes.[6–8,13,14]

then a somatic second hit during life. However, the patient preserves a normal phenotype until the second hit is sequestered, thus the "paradominance." Though there are 3 CCM genes, a loss of function by two hit mechanism to any one gene can lead to lesion development.[3,5,13] Furthermore, it has been pointed out that one hit to any gene can express vascular abnormalities, such as weakened endothelial vascular lining.[6] These genetic disruptions can come to light through any trauma, injury, or radiation the brain vasculature. See figure 2.

Paradominant inheritance could shed light on our patient's disease development as she has no prior evidence of CCM development apart from her prior presentation; her rapid multifocal lesion development imitates similar disease processes of tumor suppressor genes, such as breast tumor multiplicity in BRCA mutations. It should be understood that there is difference between paradominant inheritance and two hit mechanism; the two hit mechanism conveys the disease is autosomal dominant and shows partial penetrance after one hit, while a two hit would show full penetrance.

This patient's development of CCM lesions in the absence of venous anomalies, alongside the manifestation of new lesions in a short period of time mimic a pathologic mechanism resembling that of paradominant inheritance. Her generation of multiple lesions after a year's time could indicate that a second gene was compromised in the past few years, fulfilling a two-hit mechanism. Further genetic testing on tissue sample can illuminate which CCM mutations led to her disease, and could further illuminate the variations in CCM1, CCM2, and CCM3 pathogenesis.

CONCLUSION

Here we have presented the case of a 39 year-old female who was diagnosed and treated for a de novo formation of a symptomatic cavernous malformation, with only one prior cavernous malformation one year prior. The acuity of lesion genesis and her late presentation of the disease can address the reasoning toward the pathogenesis of familial cavernous malformation as resembling a two-hit mechanism, resembling similarities with paradominant inheritance, with the second gene knockout occurring recently. Further genetic analysis of this patient and her family could possibly illuminate her mutations and inheritance pattern.

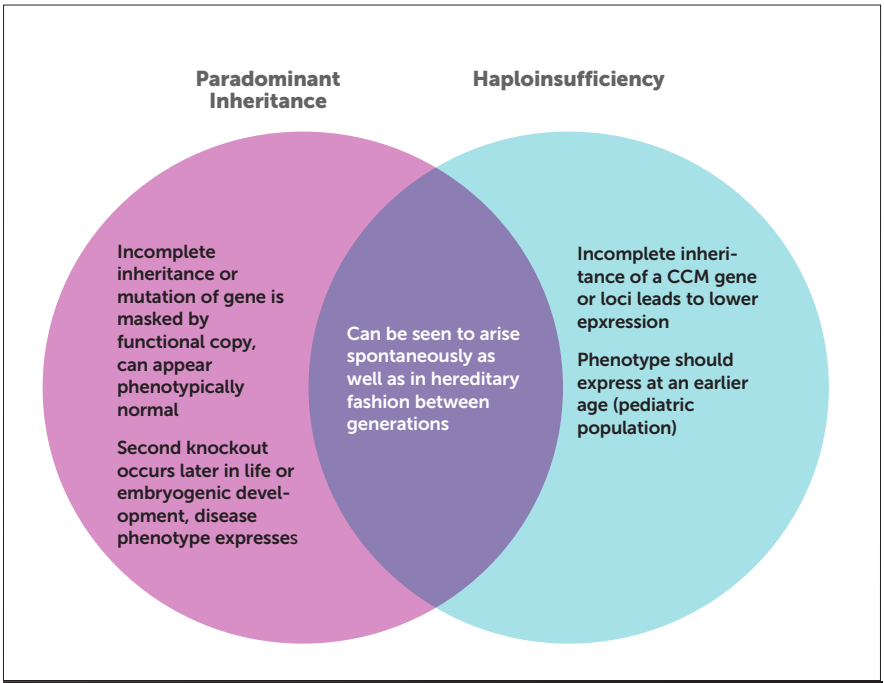

Figure 2.

This Venn Diagram portrays the theoretical differences and similarities between paradominant inheritance and haploinsufficiency. Paradominant inheritance has been theorized to be the underlying mode of inheritance for other anomalies that appear to develop sporadically.[15,16]

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