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Perspective

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A brief history of cerebral cavernous malformations: a personal perspective

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Abstract

As is the case in many areas of medicine and science in general, there has been a dramatic acceleration in the acquisition of understanding during the last few decades. This is also the case for cerebral cavernous malformations (CCMs). We like to artificially divide the progress that we have personally witnessed into three phases: pre-magnetic resonance imaging (MRI), post-MRI, and molecular. We highlight the major leaps forward linked to the specific discovery.

Keywords: Cerebral cavernous malformations, history, developments

PRE-MRI PHASE

The histology of cerebral cavernous malformations (CCMs) had been known and described in the classic texts of pathology for many decades. CCM was then called "cavernous hemangioma", "cavernous angioma", or "cavernoma". The description of the CCM stressed the presence of a mass of abnormally dilated vascular channels, with walls made of collagen and lined by endothelium, without evidence of arterial structures, and containing in decreasing order of frequency hemosiderin-laden macrophages, thrombosis, hemorrhage, calcification, and ossification. Because of the contiguity of the dilated vascular channels, the center of the lesion is void of brain parenchyma[1-3].

In the above publications, CCMs were reported as rare compared to other vascular anomalies with an incidence of only 1% of all intracranial vascular lesions and 15% of all cerebral vascular malformations. Their familial occurrence was thought to be exceptional.

A very large retrospective autopsy study suggested a prevalence of around 0.4%[4].

Because of the lack of adequate imaging, the older literature could only report surgically or autopsy-confirmed cases. Large surgical series reported a clinical presentation of seizures in 35%-60% of the cases, focal neurological deficits in about 30% of the cases, and headaches alone or associated with other signs of increased intracranial pressure in about a fourth of the cases[5-11].

A later prospective epidemiological study fundamentally corroborated the older data regarding the clinical presentation[12].

Prior to the advent of computed tomography (CT), a thorough set of diagnostic tests for CCM would include cerebral angiography, which was mostly negative or when positive demonstrating a nonspecific finding. A higher degree of diagnostic sensitivity has been achieved more recently with the use of CT angiography, even though its specificity is still questionable[13].

In reality, cavernous malformations were, for the most part, undetectable during routine angiography. This fact led to the belief, as amply documented in the older literature, that they were AVMs not visible or "angiographically occult" (also referred to as cryptic AVM)[3,14,15]. The unknown association of the CCM and a developmental venous anomaly (DVA), which was clearly visible on angiography, explained management decisions in which DVA was often erroneously considered the source of bleeding, leading to the often disastrous extirpation of the DVA with consequent infarction of the brain drained by it[16,17].

The advent of CT began to shed light into the clinical and epidemiological behavior of this condition. In a seminal study, Hayman *et al.*[18] described a family of 122 individuals studied over five generations; 15 of the 43 people studied with a CT had a finding suggestive of a CCM. Five patients had a confirmed pathological diagnosis. Six individuals had multiple lesions.

POST-MRI PHASE

CT dramatically increased the ability to detect these lesions, even though it lacked sensitivity and specificity when compared to the MRI. False-negative CT occurred in up to a third of the cases visualized on MRI[19].

By means of a rarely used iron-based staining technique, authors were able to effectively and convincingly correlate the histological findings of hemosiderin-laden macrophages surrounding the CCMs and iron depositions within glial cells in the adjacent white matter, with the MRI variations in signal intensity. The very sensitive and fairly specific appearance of a CCM on MRI was described as falling into two distinct categories: larger lesions appear as a reticulated core of mixed signal intensity (SI) with a characteristic rim of decreased SI on T2-weighted images, while the small lesions present as areas of mostly decreased SI on T2-weighted images unless accompanied by a small hemorrhage[19]. Subsequent radiological and pathological characterization in more extensive studies allowed classification into four groups or lesion types.

The possibility to diagnose CCMs without pathological/surgical confirmation allowed clinicians to confirm the CCM prevalence as ranging between 0.16% and 0.9%, corroborating the pathological data of Otten *et al.*[4], Morris *et al.*[20] and Flemming[21].

MRI also made possible the conduction of prospective epidemiological studies that fundamentally corroborated the older data regarding clinical presentation[12].

Furthermore, MRI allowed the definitive recognition of the frequent co-existence of CCM and DVA, also known as venous angiomas. This had the important consequence of avoiding the tragic decision to extirpate the innocent DVA and only focus on the resection of the bleeding CCM[22].

MRI became invaluable to reach a presumptive preoperative diagnosis of the surgically very challenging middle fossa lesion[23].

The exquisite sharpness of MRI pictures made it possible to detect the co-existence of different vascular malformations (anomalies) and to study their respective natural histories in adults as well as children[22,24-30]. MRI also confirmed that CCMs are dynamic lesions: they may remain stable for years, they might grow with or without a hemorrhage, and they may contract in volume. Prospective studies carried out to study the natural history of CCMs demonstrated the dynamic nature of these lesions and confirmed that the majority of CCMs, cranial or spinal, might be in fact characterized by a relatively more benign course than originally feared[31-37].

T2 gradient recalled echo was later introduced as being more sensitive for smaller CCMs than conventional T2 sequences, as well as susceptibility-weighted imaging, which demonstrated detection rates of 1.7× more lesions than gradient recalled echo[38,39].

Rare complex phenomena such as superficial siderosis, obstructive hydrocephalus, hypertrophic olivary degeneration, and the novo lesions have been demonstrated[40-44].

MOLECULAR

It is now very well established that CCMs can occur in either a sporadic or familial form. MRI opened a new chapter in the history of CCMs with the discovery of the prevalence of the familial form characterized by an autosomal dominant pattern of transmission[45]. CCMs can appear *de novo* or after radiation therapy[43].

The natural history of the familial form has been reported by some studies to be more aggressive than that of the sporadic form[37,46,47]. However, some other meta-analyses do not support this statement.

In parallel to the study of their clinical course, better clarification of the pathological ultrastructure of CCMs and their complicated relationship with other rarer and more complex genetically transmitted conditions began to occur[33,34,48,49].

Within a relatively short amount of time after the confirmation of a clear genetic component causing the genesis of CCMs, the study of the molecular biology of the lesion rapidly progressed. Mutations were found in three genes: *CCM1* (*KRIT 1*), *CCM2* (*MGC4607*), and *CCM3* (*PDCD10*)[50-58].

More than 350 distinct *CCM1*/*CCM2*/*CCM3* mutations have been published to date, and, 15 years after the identification of CCM3, no additional genes have been correlated to the remaining almost 5%-15% of cases that are not associated with any of the three[59-62].

CCM protein products collectively interact with each other, as well as with other molecules, proteins, and kinases to regulate various cellular processes, including angiogenesis and intercellular communication. Mutations in any of the genes impairs the functionality of the CCM complex, including the Rho family of the GTPases, which specifically regulate the endothelial barrier leading to altered development and maintenance of the vascular permeability. However, data on why mutations in *CCM* genes commonly affect the cerebral and spinal vasculature remain unclear[63-80].

Research on CCM proteins and their influence on the cellular and molecular pathways and their influence on the disease has been the focus of intense research and controversies that have greatly enhanced our knowledge to the point where several pharmacological therapeutic candidates are under preclinical investigation with promising results in the prevention of lesion formation, maturation, and hemorrhage such as mTOR and ROCK inhibitors, among others[81-84].

Pending questions include why mutations in *CCM* genes predominantly affect blood vessels in the brain and spinal cord, further understanding of lesions without *CCM1-3* mutations; use of laser ablation as a minimally invasive surgical treatment, as well as radiation therapy for deep-seated lesions, and those located in eloquent cortex; and additional clarification regarding the use of antithrombotic/anticoagulant agents for each type and risk of hemorrhage as well as clearer recommendations for the treatment of comorbidities.

There are still many gaps that need to be addressed to include medical therapies as part of the therapeutic options, and, for this reason, as of today, CCMs remain a surgical disease.

CCM patients and their families formed the Angioma Alliance in the United States, which has inspired and funded further research and has helped standardize the management of this condition. Following its stimulating example, similar associations have been established and organized around the world[85].

CONCLUSIONS

Our knowledge of the clinical and epidemiological characteristics of CCMs has been tremendously enhanced with the advent of MRI. Because this imaging modality is very sensitive in regard to the visualization of even the smallest CCMs and specific, epidemiology and clinical features of CCMs were prospectively studied and elucidated. Furthermore, understanding the molecular biology of CCMs and the development of the vascular system in the human patient has allowed for the development of novel biomarkers and therapeutic markers, with the potential to offer medical treatment in the years to come.

DECLARATIONS

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Authors' contributions

Contributed to the planification, literature review, redaction, and critical revision of this manuscript: Rigamonti D, Vivas-Buitrago T

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