From Cavern-Dwellers to Cavernoma Science
Towards a New Philosophy of Cerebral Cavernous Malformations

Christian Stapf, MD; Dominique Hervé, MD

Since the introduction of noninvasive imaging tools roughly 30 years ago, vascular malformations of the brain have attracted increasing interest. Among them, cerebral cavernous malformations (CCM) appear to be the most frequently diagnosed entity with current prevalence estimates ranging from 100 to 500 cases per 100,000 in the general population. They may come to clinical attention after epileptic seizures, progressive neurological syndromes, or symptomatic hemorrhage, but overall, asymptomatic lesions seem to be most frequently encountered since the introduction of highly sensitive gradient echo (T2*) weighted sequences in routine MR imaging protocols.

Despite increasing detection rates and growing insight into underlying molecular and genetic mechanisms, many practical issues remain as yet unsolved, particularly when it comes to actual patient care and counseling:

First, no standardized imaging protocols exist. Brain MRI with the aforementioned T2*-weighted images are now considered the diagnostic standard, but the absence of contrast-enhanced T1 sequences may miss an associated developmental venous anomaly and vice versa, which may for example impact on the strategy of any neurosurgical intervention (Figure 1).

Also, no treatment standards for specific CCM interventions are readily available. If indicated, neurosurgical excision is the treatment of choice as stereotactic radiotherapy appears to have less favorable results. Therapeutic decisions are ideally based on a multidisciplinary discussion considering cavernoma characteristics (such as size, location, bleeding status, etc) and the patient’s overall profile (including age, neurological symptoms, family history, etc). However, no controlled clinical data exist so far to guide treatment strategies based on prospective natural history versus surgical outcome predictions.

Most important, the long-term bleeding risk has been insufficiently studied. Recent estimates from familial (ie, multiple CCM) cases suggest crude spontaneous hemorrhage rates may be as low as 0.6% per year and lesion, but the potential risk of otherwise indicated antiplatelet treatment and oral anticoagulation is currently unclear (Figure 2), and the impact of pregnancies and hormonal treatment remains highly controversial.

The culmination of these continuing clinical dilemmas is that the literature does not even provide a consistent definition of what CCM hemorrhage actually is. Quite commonly, available case series lump together symptomatic and asymptomatic bleeding, intracavernous and extracranial hemorrhage extension, acute bleeding and “chronic” hemosiderin, etc, to name but a few categories.

In this confusing situation, the Angioma Alliance and its scientific advisory board should be congratulated for their welcome initiative to develop a consensus proposal for CCM reporting standards as published in the current issue of Stroke. Based on an extensive literature review, Al-Shahi Salman and coauthors develop a publication-based, clinical definition of CCM hemorrhage and offer pragmatic recommendations for CCM reporting terminology in clinical practice and future research protocols.

Scientific consensus in the medical community is often achieved through authoritative agreement among a panel of established contributors. Sometimes, writing groups may simply agree on already-existing practice, as has been the case for the proposed standards defining reporting terminology for AVM research. More often, however, the path to agreement among specialists is more complex, as evidence from appropriately designed studies, but also common experience, overlapping strategies, etc may serve as a basis for final editing of appropriate consensus statements. Some recommendations may eventually have legal implications, define current standards of care, and inspire the content of continued medical education programs and future curricula of academic medical schools. The methodological downside of “authoritative” consensus is that its content may be susceptible to extrascientific interests, political considerations, and personal ambitions of individual panel members or groups.

By comparison, Al-Shahi Salman et al chose a different, almost “democratic,” approach: Based on a systematic literature review with transparent, up-to-date methodology, the authors develop a publication-based definition of CCM hemorrhage along with consensus recommendations for reporting variables in CCM clinical research. Whether defining consensus via an arithmetic majority of published sources is appropriate or not may be subject to future methodological discussions—the validity of a given hypothesis may not correlate with the number of reports or cited references. In the end, the principle of majority remains an appropriate (if not the most appropriate) tool for political decision-making, but it
does not necessarily lead to what may be called scientific truth.

These theoretical considerations aside, the major advantage of the new CCM reporting standards is not only the filling of an important gap. Moreover (and different from the widespread temptation of premature conclusions), they are but the starting point to future research and remain open to further testing in prospective studies. Jerzy Neyman, the mathematician to whom we owe the concept of confidence intervals, comes to mind as he wrote: “Not all the revolutionary developments in science or technology are initiated by the identification and rejection of a dogmatic assumption so that not all such developments are Copernican in character.

Occasionally it happens that, through apparently minor contributions of many scholars, all the pieces of a complicated jigsaw puzzle are accumulated but no comprehensive overall picture is available.”

Thanks to the initiative of the Angioma Alliance, the pieces in the jigsaw puzzle of clinical CCM research will eventually have a standardized size, and future contributors will finally speak the same language.

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