

Hemorrhage From Cavernous Malformations of the Brain

Definition and Reporting Standards

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Background and Purpose—Cavernous malformations of the brain (CMs) cause intracranial hemorrhage, but its reported frequency varies, partly attributable to study design. To improve the validity of future research, we aimed to develop a robust definition of CM hemorrhage.

Methods—We systematically reviewed the published literature (Ovid Medline and Embase to June 1, 2007) for definitions of CM hemorrhage used in studies of the untreated clinical course of ≥ 20 participants with CM(s), to inform the development of a consensus statement on the clinical and imaging features of CM hemorrhage at a scientific workshop of the Angioma Alliance.

Results—A systematic review of 1426 publications about CMs in humans, revealed 15 studies meeting our inclusion criteria. Although 14 (93%) studies provided a definition of CM hemorrhage, data were less complete on the confirmatory type(s) of imaging (87%), whether CM hemorrhage should be clinically symptomatic (73%), and whether hemorrhage had to extend outside the CM or not (47%). We define a CM hemorrhage as requiring acute or subacute onset symptoms (any of: headache, epileptic seizure, impaired consciousness, or new/worsened focal neurological deficit referable to the anatomic location of the CM) accompanied by radiological, pathological, surgical, or rarely only cerebrospinal fluid evidence of recent extra- or intralesional hemorrhage. The definition includes neither an increase in CM diameter without other evidence of recent hemorrhage, nor the existence of a hemosiderin halo.

Conclusions—A consistent approach to clinical and brain imaging classification of CM hemorrhage will improve the external validity of future CM research. (*Stroke*. 2009;40:000-000.)

Key Words: cerebral cavernous malformation ■ vascular malformations ■ stroke ■ hemorrhagic ■ genetics ■ KRIT1

There is a large reservoir of asymptomatic cerebral cavernous malformations (CMs), affecting 0.2% to 0.4% of the population.^{1,2} A feared complication of CMs is symptomatic intracranial hemorrhage—which tends to be intraparenchymal³—and its potential consequences of death and disability. Given that only $\approx 15\%$ of adults have presented with intracranial hemorrhage at the time of their first CM diagnosis,⁴ clinical practice focuses on identifying which unruptured CMs are most likely to bleed for the first time after diagnosis. Currently, CM location and past hemorrhage are used as predictors of the likelihood of future hemorrhage, and tend to be major determinants of whether CMs are treated. A better understanding of the prognosis for future hemorrhage for an individual with CM(s), and the mechanisms underlying it, are needed from clinical research.

However, the clinical features of CMs are more diverse than the simple occurrence of intracranial hemorrhage. From a clinical perspective, CMs can be confidently said to cause

focal neurological deficits (which cause varying degrees of morbidity, and very occasionally cause death),⁵ as well as epileptic seizures (which may be single, recurrent, or sometimes pharmaco-resistant).⁶ Although patients with CMs complain of headache, CMs have not been proven to cause chronic headache disorders in case-control studies.

Furthermore, the radiological features of CMs are also diverse. Because a hemosiderin halo is the hallmark of CMs on MRI,⁷ and evidence of previous bleeding is a sine qua non of CM histopathology, some consider all CMs to have bled at some point. Although it is important to understand the pathogenesis of hemorrhage—whether symptomatic or not—clinically symptomatic hemorrhage is what is relevant to patients.⁵ At the time of a new or worsened focal neurological deficit, there may be radiological evidence of recent hemorrhage (which may initially obscure the underlying CM which is only diagnosed when visualized on delayed MRI); alternatively, the signal characteristics of the CM may be un-

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Table 1. Definitions of CM Hemorrhage in Studies of the Untreated Clinical Course of ≥ 20 Participants (Organized Chronologically)

| Study | Symptoms/Signs? | Imaging Evidence? | | Acute Blood? | | Growth | Comments |
|--------------------------------|-----------------|-------------------|-----|--------------|------------|--------|--|
| | | CT | MRI | Within CM | Outside CM | | |
| Del Curling et al ¹ | ■ | ... | ? | ... | ... | ... | Clinically significant, radiographically identifiable hemorrhages |
| Robinson et al ¹⁷ | ■ | ... | ■ | □ | ■ | □ | Or prior hemorrhage on lumbar puncture/fresh clot outside CM at surgery |
| Fritschi et al ¹⁶ | ■ | ■ | ■ | ■ | ■ | □ | Or prior hemorrhage on lumbar puncture/fresh clot at surgery |
| Kondziolka et al ¹⁸ | ... | ■ | ■ | ... | ... | ... | Evaluated by referring physicians |
| Aiba et al ¹⁹ | ■ | ■ | □ | ■ | ■ | □ | Or fresh clot outside CM at surgery, or intra-/peri-CM clot density on CT that decreased in size and density on follow-up CT |
| Kim et al ²⁰ | ... | ... | ... | ... | ... | ... | No hemorrhage definition given |
| Porter et al ⁵ | ■ | ■ | ■ | □ | ■ | ■ | Increase in CM size by 20% or more in diameter with associated mass effect or edema and relevant symptoms also qualified |
| Abdulrauf et al ²¹ | ■ | ■ | ■ | ... | ... | □ | Same criteria as Fritschi et al ¹⁶ |
| Porter et al ²² | ■ | ■ | ■ | ■ | ■ | □ | |
| Moriarty et al ¹² | ■ | ... | ■ | □ | ■ | □ | |
| Labauge et al ^{25,26} | ... | ... | ■ | ... | ... | □ | Hemorrhage was distinguished from mere change in size |
| Barker et al ²⁴ | ■ | ■/□ | ■/□ | ... | ... | ■ | Some events without contemporaneous imaging classified as hemorrhages. Lesion growth was a hemorrhage if accompanied by clinical deterioration |
| Kupersmith et al ²³ | ■ | ... | ■ | ■ | ■ | □ | |
| Cantu et al ²⁷ | ■ | □ | ■ | ... | ... | ... | |

■ indicates contributed to hemorrhage definition; □, not required for hemorrhage; ?, unclear; ..., not specified.

changed, or the CM may have grown or changed its MRI signal characteristics when compared with previous imaging.⁸ Moreover, new CMs may appear over time,^{8–10} and edema may appear around CMs.¹¹

Definitions of CM hemorrhage used by researchers have varied,^{5,12} as has the completeness of radiological investigation of new or worsened focal neurological deficits. Our aim, therefore, was to quantify the extent of these variations with a systematic review of the literature, and develop definitions and reporting standards for CM hemorrhage on behalf of the Angioma Alliance, which is an international patient-directed health organization created by people affected by CMs, whose mission is to inform and support individuals affected by CM while facilitating improved diagnosis and management of the illness through education and research (www.angiomaalliance.org). We intended the CM reporting standards to reflect the diversity of CM clinical behavior and to encourage the use of appropriate brain imaging, while accounting for the uncertainties of clinical medicine and the potential incompleteness of brain imaging and neuropathology in large clinical studies. Much the same as previous reporting standards for brain arteriovenous malformations,¹³ the purpose of this endeavor is to improve the homogeneity of

future research into CMs, make systematic reviews easier to do, enhance the external validity (generalizability) of individual studies, and promote appropriate investigation of patients in clinical practice.

Materials and Methods

Literature Review

One author (R.A.-S.S.) systematically reviewed the published literature on CMs in October 2006 (updated in June 2007), by running electronic search strategies (Appendix) in Ovid Medline (from 1950) and Embase (from 1980) looking for any publication about CMs in humans. The titles and available abstracts were read to identify studies of the untreated clinical course of ≥ 20 participants with a sporadic or familial CM, specifically assessing the future occurrence of intracranial hemorrhage attributable to the CM. The relevant reports were read in full, and the definition of CM hemorrhage was extracted from each publication. The components and completeness of these definitions informed the development of our proposed reporting standards, supplemented by review articles, known radiological characteristics of blood degradation products,^{14,15} and the writing committee's personal experience in managing patients with CMs.

Development of Definitions and Reporting Standards

The results of the literature search, illustrations of pertinent brain imaging, and a preliminary set of reporting standards were used to

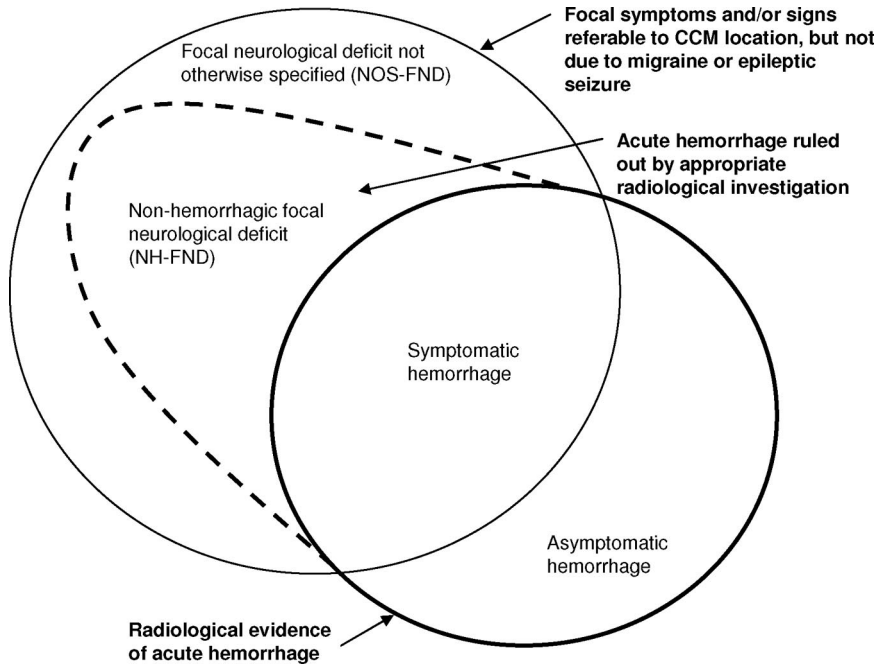


Figure 1. Focal neurological event concepts.

stimulate discussion in a session at the Angioma Alliance Pathobiology of CM Scientific Workshop in Washington DC, USA on November 17, 2006. The reporting standards were modified after feedback and subsequent critical appraisal by the Scientific Advisory Board. Any disagreements were resolved by consensus.

Results

Literature Review

Of 1426 publications about CMs, 15 met the inclusion criteria.^{1,5,12,16–27} A definition of CM hemorrhage was not documented in one (7%) of the studies (Table 1).²⁰ One quarter of the studies did not specify the requirement for relevant clinical symptoms or signs to accompany evidence of recent CM hemorrhage.^{18,20,25,26} Two studies (13%) did not mention the imaging modalities used to confirm CM hemorrhage^{1,20}; more than three quarters (n=12) described the use of MRI, and 7 (47%) mentioned the use of computed tomography (CT), 1 of which included a mixture of hemorrhages both with and without radiological/pathological confirmation.²⁴ Only 7 studies (47%) described whether CM hemorrhage could be within the CM hemosiderin ring or outside it, and 3 studies (20%) specifically excluded intralesional hemorrhages.^{5,12,17} Radiological or surgical evidence of recent hemorrhage was required by the studies that permitted intralesional bleeds to constitute CM hemorrhage.^{16,19,22,23} Two studies (13%) permitted radiological CM growth—if accompanied by relevant symptoms—to constitute CM hemorrhage, without mentioning the requirement for MRI signal characteristics indicating recent hemorrhage.^{5,24} The heterogeneity in published studies' definitions indicated which aspects required specific attention in a set of reporting standards.

Definitions and Reporting Standards

These definitions and reporting standards are based on the recognition of a focal neurological clinical deficit that is anatomically referable to a CM, with clinical assessment and

further investigation determining whether the deficit was caused by recent hemorrhage or some other CM-related mechanism (Figures 1 and 2).

Hemorrhage

Although CM hemorrhage may be asymptomatic (Figure 1), these definitions and reporting standards prioritize the accurate identification of clinically symptomatic hemorrhages with radiological, pathological, surgical, or rarely only cerebrospinal fluid (CSF) evidence of recent extralesional or intralesional hemorrhage (Table 2). Clinical features may include acute or subacute onset of any of: headache, epileptic seizure, impaired consciousness, or new/worsened focal neurological deficit referable to the anatomic location of the CM. Brain imaging should be performed as soon as possible after the onset of clinical symptoms suspicious of hemorrhage. Evidence of acute blood can be easily and accurately identified on CT, which should be performed ideally within 1 week of the onset of a clinical event to reliably demonstrate high density consistent with recent hemorrhage (Figure 3),²⁸ although it may still be apparent for several weeks (Figure 4). To be considered a recent hemorrhage, the high density on CT should be new, when compared to any previous CT imaging of the CM, and should have a Hounsfield value consistent with acute blood, or should resolve on CT imaging performed at least 2 weeks later. MRI can also identify acute and subacute hemorrhage, although its use can be complicated by its impracticability in acutely ill patients, and the time course of the change in appearance of an ageing hemorrhage on different sequences is quite variable (Table 3 and Figure 6).^{29–31} MRI should ideally be performed within 2 weeks of the onset of a clinical event to demonstrate extracellular methemoglobin which is high signal on T₁- and T₂-weighted sequences (Table 3, Figures 4 and 6).¹⁴ Gradient recalled echo (GRE) sequences tend to demonstrate increasing signal dropout as hemosiderin emerges and may be particularly helpful for identifying small hemorrhages. Fluid attenuated inversion recovery (FLAIR) se-

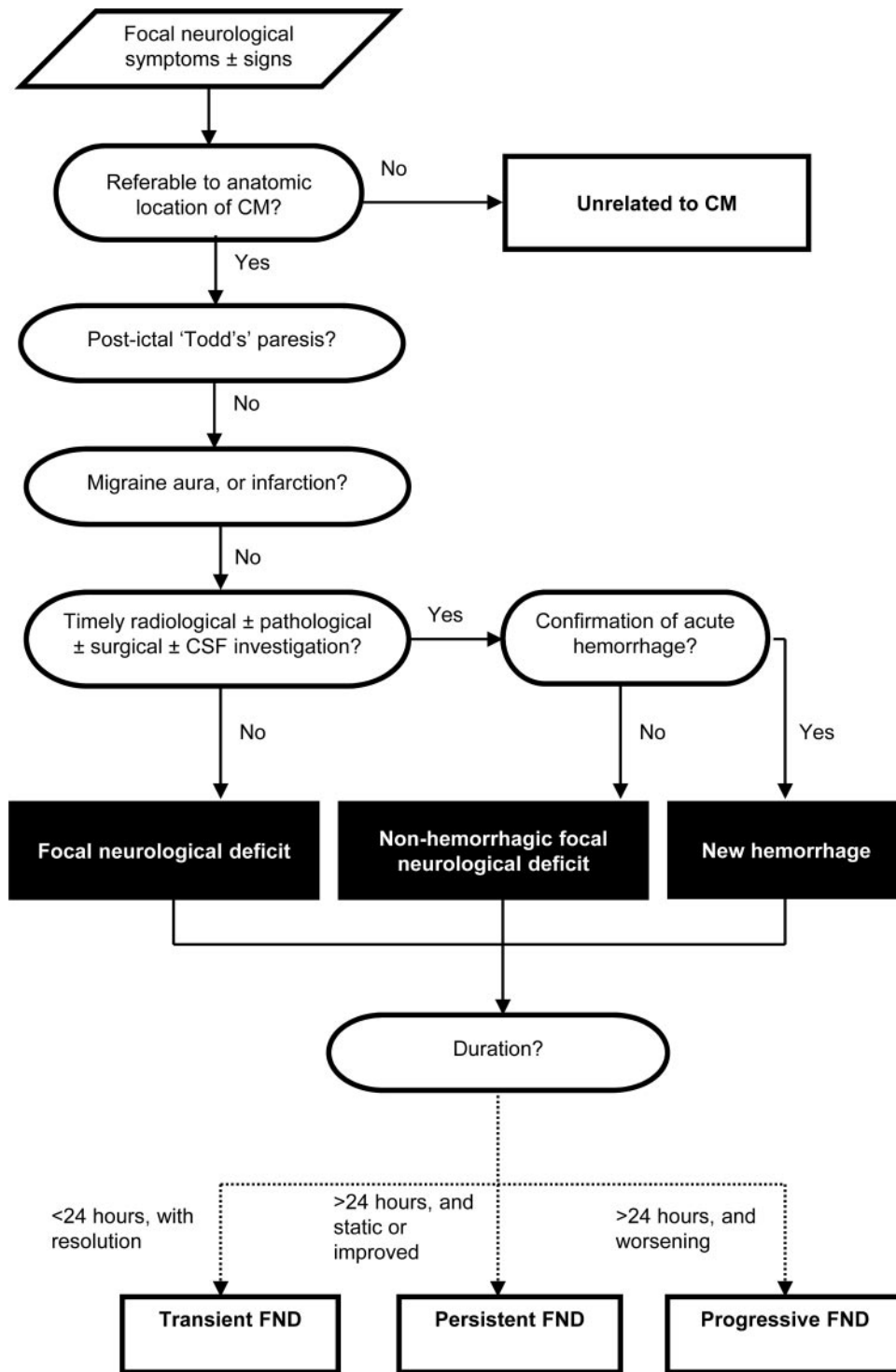


Figure 2. Algorithm for classifying focal neurological events.

quences reflect the appearances of T₂-weighted sequences.¹⁵ The MRI signal changes indicative of recent hemorrhage should be new when compared to previous MRIs, or they should resolve on MRI ≥2 months later. Recent hemorrhage may completely or partially obscure the CM itself on MRI, which is why follow-up MRI is crucial for the diagnosis of a CM underlying an intraparenchymal hemorrhage. The mere existence of a hemosiderin halo, or solely an increase in CM diameter (for example on GRE MRI, with identical TE and TR imaging

parameters as used on previous MRI), without evidence of recent hemorrhage on timely brain imaging, are not considered to constitute hemorrhage. Sufficient pathological confirmation of a recent hemorrhage would include its detection on surgical exposure/excision, biopsy, or autopsy. CSF findings sufficient to support recent hemorrhage from a CM located close to, or has bled toward a pial surface, are heavily—and uniformly—blood-stained CSF (not attributable to a traumatic tap), or visible xanthochromia, or bilirubin on CSF spectrophotometry.

Table 2. CM Hemorrhage Definition

A clinical event involving both:

Acute or subacute onset symptoms (any of headache, epileptic seizure, impaired consciousness, new/worsened focal neurological deficit referable to the anatomic location of the CM).

Radiological, pathological, surgical, or rarely only cerebrospinal fluid evidence of recent extra- or intralesional hemorrhage.

The mere existence of a hemosiderin halo, or solely an increase in CM diameter without other evidence of recent hemorrhage, are not considered to constitute hemorrhage.

Nonhemorrhagic Focal Neurological Deficit

Nonhemorrhagic focal neurological deficit (NH-FND) is defined as a new or worsened focal neurological deficit referable to the anatomic location of the CM, which may present with other clinical features of intracranial hemorrhage, but without evidence of recent blood on timely brain imaging or pathological examination, or examination of the CSF (Figures 1, 2, and 5). These cases may be accompanied by an increase in CM diameter alone (for example on GRE MRI sequences using identical imaging acquisition parameters) or edema on MRI, and these radiological abnormalities should be specified when describing NH-FNDs.

Focal Neurological Deficit not Otherwise Specified

The clinical definition of focal neurological deficits that are not otherwise specified (NOS-FND) is identical to NH-FND, with the exception that the term NOS-FND is used when pathological investigation, CSF examination, or timely imaging have not been performed at all or at the correct time to establish whether hemorrhage, edema, or lesion growth underlie the clinical deterioration. Inevitably, some NOS-FNDs are missed hemorrhages, and the purpose of the distinction between NOS-FND and NH-FND is so that allowance can be made for the local availability and use of brain imaging, and variation between studies' findings can be explored using sensitivity analyses (see below).

Standardized Measure of Impairment/Disability/Handicap

In recognition of the spectrum of severity of the clinical manifestations of CM hemorrhage, NH-FND, and NOS-FND, and the need for standardization to assist comparison between studies, it is essential to use at least one measure of impairment, disability, or handicap at defined time points after symptom onset. Because disease-specific scales are yet to be developed for people with CMs, we recommend the use of generic measures. On the basis of their use in the assessment of people with stroke and epilepsy, we suggest the use of the NIH Stroke Scale (NIHSS) to measure impairment,³² modified Rankin Scale (mRS) to measure disability/handicap,³³ and Short Form 12 or 36 (www.sf-36.org) or EQ-5D (www.euroqol.org) to measure health-related quality of life. These assessments should, ideally, be performed at fixed times after the onset of a clinical event or intervention (1, 6 and 12 months), to facilitate comparison and meta-analysis of studies. Recognizing that some researchers are unable to assess outcome in this way, a less preferable alternative is to



Figure 3. CM hemorrhage on CT. A, T₂-weighted brain MRI demonstrating a right parietal CM (arrow), which was detected incidentally. B, Twenty-one months after diagnosis, sudden left hemiparesis, focal seizures, and headache led to the detection of recent hemorrhage on brain CT (arrow) performed 5 days after symptom onset. C, Four months later, focal seizures accompanied by new daily persistent headache led to the detection of further hemorrhage on brain CT (arrow) performed 1 week after symptom onset.

classify the duration of symptoms as transient (lasting <24 hours), persistent (lasting >24 hours, and staying static or improving), or progressive (lasting >24 hours with further deterioration).



Figure 4. CM hemorrhage on MRI. A, CT brain demonstrating increased density 19 days after the sudden onset of vomiting and ataxia, suggestive of hemorrhage, confirmed by the presence of methemoglobin on coronal T₁-weighted MRI (B), and on axial T₂-weighted MRI (C).

Statistical Approaches to the Analysis of CM Hemorrhage and FNDs

The clear distinctions drawn between CM hemorrhage, NH-FND, and NOS-FND by these definitions are powerful tools to explore reasons for variation between existing studies' findings (for example, because of the imaging modalities

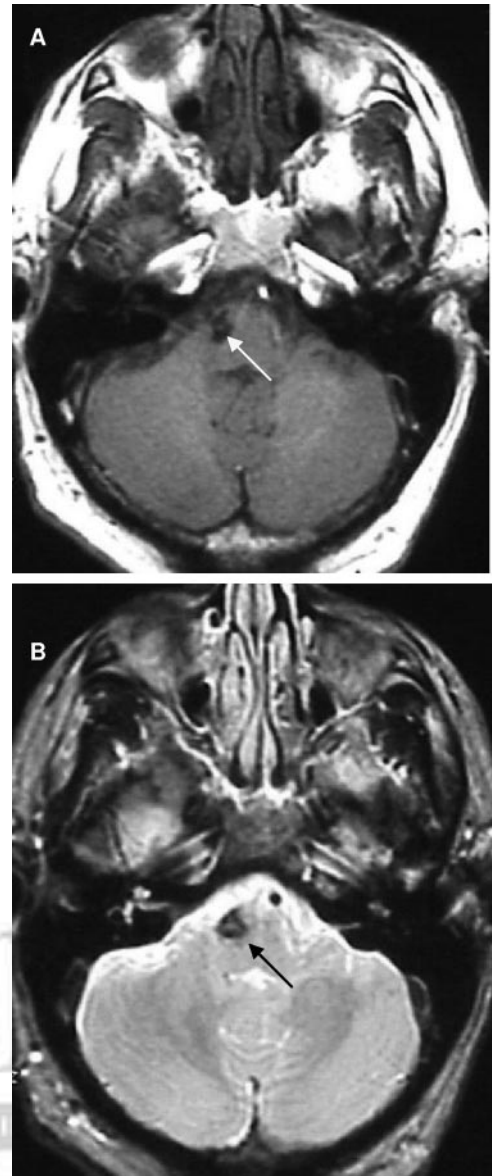


Figure 5. CM nonhemorrhagic focal neurological deficit. This 50-year-old man presented with transient symptoms of right facial numbness, left hemibody numbness and weakness, and vertigo, in the setting of a known right anterolateral pontine CM. Imaging studies included (A) T₁-weighted and (B) T₂-weighted brain MRI, brain CT, and CSF studies (not shown), all failing to confirm any evidence of recent hemorrhage, or change from previous studies. Ultimately, the patient was diagnosed with polycythemia, and the symptoms resolved in conjunction with therapeutic hemodilution.

used). These definitions could compensate for differences between studies using sensitivity analysis (for example, by combining hemorrhage and potentially-hemorrhagic NOS-FND events in studies with delayed or incomplete brain imaging). The power of outcome analyses, using multivariate methods for example, could be improved by combining NH-FND, NOS-FND, and CM hemorrhage to increase the number of outcome events. The use of generic outcome measures can also improve power by being more sensitive than a binary outcome measure; furthermore these measures can improve on the traditional use of CM hemorrhage as an

Table 3. Time Course of Intraparenchymal Hemorrhage on Magnetic Resonance Imaging¹⁴

| | Time After Intraparenchymal Hemorrhage Onset | | | | |
|--|--|---------------------|------------------------|-----------------------|---------------------|
| | Hyperacute ³⁰ <24 Hours | Acute 1 to 3 Days | Early Subacute >3 Days | Late Subacute >7 Days | Chronic >14 Days |
| T ₂ -weighted ¹⁴ | Iso- or hyperintense center, hypointense periphery, and hyperintense rim | Hypointense | Hypointense | Hyperintense | Hypointense |
| T ₁ -weighted ¹⁴ | Iso- or hyperintense | Iso- or hypointense | Hyperintense | Hyperintense | Iso- or hypointense |
| Diffusion-weighted ³⁹ | Hyperintense center, with hypointense foci | Hypointense | Hypointense | Hyperintense | Hypointense |

end point in studies of prognosis and treatment by shifting the focus from events which vary widely in their clinical manifestations, to disability, handicap, and quality of life which are of more relevance to patients.

Recommendations for Reporting Other Variables in CM Clinical Research

Although the focus of this statement has been on clinically symptomatic CM hemorrhage, the consensus process provided an opportunity to consider an ideal minimum baseline dataset for ongoing and future CM clinical research studies (Table 4), which encompass the study of other CM behaviors (such as asymptomatic hemorrhage, Figure 1).

Discussion

This systematic review of the literature confirmed the long-perceived need for clear definitions of CM hemorrhage and other related clinical events. The quality of existing studies' definitions of hemorrhage was heterogeneous (Table 1), and ranged from unclear^{18,20} to explicit.^{5,16} Variation in assessment (including brain imaging use, timing, modalities, sequences, and parameters) and clinical event definitions may partly account for the range of published estimates of CM hemorrhage rates, from 0.4% to 3.1% per year for sporadic CMs,^{12,19} and 4.3% to 6.5% for familial CMs.^{26,34} Furthermore, the lack of distinction between CM hemorrhage, NH-FND, and NOS-FND in some studies (Table 1), emphasizes the need for definitions of all focal neurological events

that are anatomically referable to the location of the CM, not just hemorrhage. We arrived at consensus definitions of CM hemorrhage, NH-FND, and NOS-FND that can easily be applied in several situations: in clinical practice, retrospectively to existing cohorts, and prospectively in future studies (in which NOS-FND should be kept to a minimum).

The challenging complexities of CMs have inevitably contributed to the heterogeneity of the literature, and underpin the need for these definitions. Firstly, the clinical manifestations of CM hemorrhage are varied, and range from no symptoms whatsoever (Figure 1),²⁶ to disabling—and sometimes fatal—stroke (Figure 3). The frequency with which CM hemorrhage may manifest only as an epileptic seizure is unknown; of course, recent hemorrhage is more likely to be detected after the first epileptic seizure experienced by a patient, if a seizure is associated with uncharacteristic symptoms, or if there is a change in seizure pattern. Creating sensitive and specific clinical definitions of CM hemorrhage will be a challenge until further research determines the semiology of associated headaches and epileptic seizures, and which changes in the pattern of preexisting headache and seizure disorders may be indicative of CM hemorrhage. Secondly, CMs are partly composed of hemorrhage of different ages, reflected in the heterogeneity of their MRI signal characteristics³⁴; this existence of subacute or chronic hemorrhage mandates a clear definition of recent hemorrhage. Therefore, we concluded that a clear focus on the clinical and

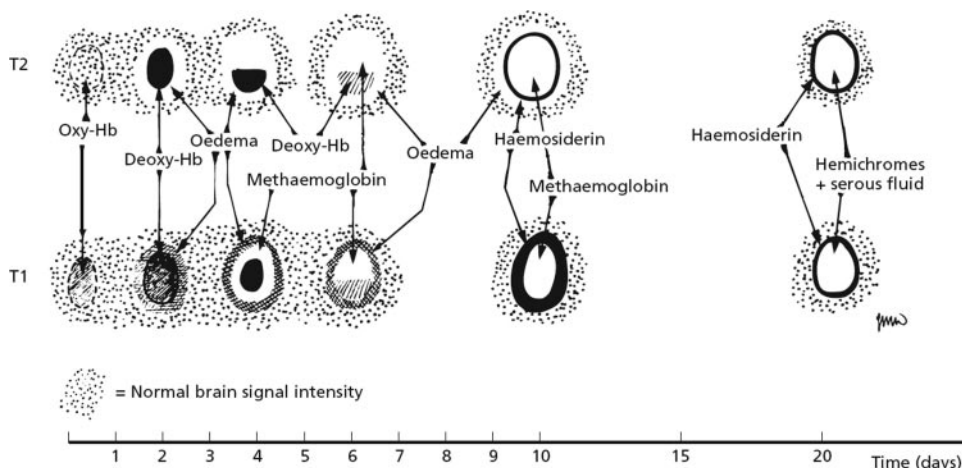


Figure 6. Time course of intraparenchymal hemorrhage on MRI. Normal brain is represented by the stippled background. Reproduced with permission.²⁹

Table 4. Consensus Recommendations for Minimum Reporting Variables in CM Clinical Research

| | |
|---|--|
| Patient baseline characteristics | |
| Date of birth | |
| Sex | |
| Date and mode of clinical presentation leading to CM diagnosis (asymptomatic, hemorrhage, NH-FND, NOS-FND, epileptic seizure, ⁴⁰ headache, ⁴¹ other) | |
| Support for mode of clinical presentation (CT, MRI, CSF, pathology) | |
| Radiological findings at the time of CM diagnosis (recent hemorrhage [TABLE 2], no recent hemorrhage, imaging not performed in a suitable time window to identify recent hemorrhage) | |
| 30-day rating of death/dependence on the modified Rankin Scale following clinical presentation leading to CM diagnosis | |
| Date of onset of first symptom(s) referable to CM (if earlier than date of clinical presentation) | |
| Type of first symptom(s) referable to CM (hemorrhage, NOS-FND, NH-FND, epileptic seizure ⁴⁰) | |
| Family history (≥ 1 symptomatic relative with CM; no symptomatic relatives with CMs, but ≥ 1 asymptomatic relative with CM; ≥ 1 symptomatic relative, but underlying CM not investigated) | |
| Ethnicity | |
| DNA mutation known to cause CM | |
| Characteristics of <i>each</i> CM | |
| Side of brain | |
| Size (maximum diameter, including hemosiderin ring, in millimeters on all brain imaging modalities and sequences) | |
| Location (cortical, subcortical white matter, diencephalic, basal ganglia, internal capsule, brainstem, cerebellum, spinal cord) | |
| Diagnostic confirmation (MRI, pathology) | |
| MRI parameters (field strength, sequences [T ₁ , T ₂ , DWI, FLAIR, GRE, SWI], contrast enhancement) | |
| Date of CM diagnosis | |
| Associated "developmental venous anomaly" | |
| Location (remote or associated with CM) | |
| Diagnostic confirmation (MRI, pathology, digital subtraction angiography) | |
| Date of "developmental venous anomaly" diagnosis | |

imaging characteristics of recent hemorrhage was crucial to a robust definition, whether this was increased density on CT,¹⁹ or the presence of new methemoglobin or deoxyhemoglobin on MRI.²² This approach was central to our decision not to require recent CM hemorrhage to be extralesional, and not to include within our definition a mere increase in CM diameter (to an arbitrarily-defined extent⁵) without evidence of recent hemorrhage. This approach is supported by most existing studies (Table 1), but the pathological basis and clinical consequences of a mere increase in CM size are important priorities for future research.

The challenge of defining a variable manifestation of a complex condition was met by learning from both existing definitions identified by a systematic literature review and the opinions of experts in CM clinical practice and research, who reached a consensus viewpoint. A weakness of these definitions is the lack of knowledge about the imaging correlates of NH-FNDs from CMs, and their underlying causes. However,

part of the purpose of an explicit definition of CM hemorrhage is to encourage research into NH-FND in humans using, for example, higher magnet field strengths and different sequences such as susceptibility-weighted imaging^{35,36} and functional MRI.³⁷ Equally, animal models may offer insights into the pathobiology of some of these yet-to-be understood clinical manifestations.³⁸

In summary, these Angioma Alliance definitions and reporting standards for the principal clinical manifestations of CMs could: influence clinical practice by encouraging appropriate and timely radiological investigation of patients (thereby improving consistency in radiologists' and clinicians' diagnosis of CM hemorrhage); help standardize observational studies of prognosis, clinical trials, and genotype-phenotype correlations, making them easier to compare and meta-analyze; and identify patients with NH-FND and NOS-FND who merit further detailed investigation to understand their underlying pathophysiology. It remains for researchers to prospectively study the inter- and intrarater reliability of the definitions, and to test their validity in routine clinical practice, in the research setting, and in different geographical locations (with varying access to MRI).

Appendix

Electronic Search Strategies

OID MEDLINE

1. Hemangioma, Cavernous, Central Nervous System/
2. Hemangioma, Cavernous/
3. (cavernous adj5 (angioma\$ or hemangioma\$ or malformation\$)).tw
4. cavernoma\$.tw
5. 2 or 3 or 4
6. exp brain/ or central nervous system/ or exp cerebral arteries/
7. exp brain neoplasms/
8. (brain\$ or cerebral or intracerebral or central nervous system or intracranial or cerebellar or intraventricular or supratentorial).tw.
9. 6 or 7 or 8
10. 5 and 9
11. 1 or 10

EMBASE

1. Brain Hemangioma/
2. brain ventricle cavernoma/
3. cavernous hemangioma/
4. (cavernous adj5 (angioma\$ or hemangioma\$ or malformation\$)).tw
5. cavernoma\$.tw
6. 3 or 4 or 5
7. central nervous system/ or exp brain/ or exp brain ventricle/ or exp brain artery/
8. exp brain tumor/
9. (brain\$ or cerebral or intracerebral or central nervous system or intracranial or cerebellar or intraventricular or supratentorial).tw.
10. 7 or 8 or 9
11. 6 and 10
12. 1 or 2 or 11

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Disclosures

None.

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