

Differences between intracranial vascular malformation types in the characteristics of their presenting haemorrhages: prospective, population-based study

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ABSTRACT

Objective: To determine the imaging and demographic characteristics of intracranial haemorrhages, which are subsequently found to be due to an underlying intracranial vascular malformation (IVM).

Methods: We compared the demographic and brain imaging characteristics of adults presenting with intracranial haemorrhage, subsequently found to be due to a brain arteriovenous malformation (BAVM), dural arteriovenous fistula (DAVF) or cavernous malformation (CM) in a prospective, population-based cohort of adults diagnosed for the first time with an IVM (The Scottish IVM Study (SIVMS)).

Results: Of the 141 adults in SIVMS who presented with intracranial haemorrhage, those with CMs presented at a younger age and were less handicapped. A total of 115 (82%) had intracerebral haemorrhage (ICH) with or without subarachnoid, intraventricular or subdural extension. ICH without extension into other compartments accounted for all CM bleeds, but only 50% of BAVM and DAVF bleeds. Median haematoma volumes differed (Kruskal–Wallis, $p < 0.0001$): ICH due to BAVM (16.0 cm³, inter-quartile range (IQR) 4.7 to 42.0) and DAVF (14.1 cm³, IQR 4.9 to 21.5) were similar, but CM haematoma volumes were smaller (median 1.8 cm³, IQR 1.3 to 4.3). These findings were robust in sensitivity analyses. Small haematoma volumes occurred among all IVM types; the largest haematoma volume due to CM was 12 cm³, and volumes of >34 cm³ were only due to BAVM.

Conclusions: Intracranial haemorrhages found to be due to IVMs differ in adults' age of presentation and clinical severity, as well as the volume and distribution of the haematoma within the brain compartments.

About one-fifth of all strokes in white populations are caused by intracranial haemorrhage in the intracerebral, intraventricular, subarachnoid, subdural or extradural compartments. The decision to further image the brain and/or its vasculature is partly influenced by whether an intracranial vascular malformation (IVM) might have caused the haemorrhage. Investigation therefore tends to be targeted at particular clinical subgroups. For example, because IVMs are the leading cause of intracerebral haemorrhage (ICH) in young adults,¹ and brain arteriovenous malformations (BAVMs) are more likely to underlie ICH in previously normotensive young adults,² these individuals are

usually further investigated. However, there are exceptions, and IVMs also occasionally cause ICH deep in the brains of hypertensive elderly people.

The choice of the type of further brain or vascular imaging may also be determined by whether the suspected IVM is an arterial aneurysm, BAVM, cavernous malformation (CM) or dural arteriovenous fistula (DAVF). Because the radiological characteristics of the presenting intracranial haemorrhage might help to indicate the type of underlying IVM, we studied the brain-imaging characteristics of intracranial haemorrhages at the time of first presentation with an IVM, in adults who were prospectively identified in the same time period in the same population; a reference group from the same population with intracranial haemorrhage due to causes other than IVMs was not available for this study.

METHODS

Inclusion criteria

The Scottish Intracranial Vascular Malformation Study (SIVMS) is a prospective, population-based study of all adults (aged ≥ 16 years) resident in Scotland and diagnosed for the first time with an IVM.³ We identified every adult in the cohort who was first diagnosed with a BAVM, DAVF or CM in the years 1999–2003, and whose initial presentation leading to IVM diagnosis had been intracranial haemorrhage. Haemorrhagic presentation was defined as a symptomatic clinical event (any or all of headache \pm seizures \pm global neurological deficit \pm focal neurological deficit), with signs of intracranial blood on brain imaging, in the cerebrospinal fluid or on post-mortem examination. The Multicentre Research Ethics Committee for Scotland approved the study (MREC/98/0/48).

Data collection

We collected demographic data from medical records documenting patients' initial presentation, and graded its severity using the Oxford Handicap Score (OHS).⁴ Hard copies of the first axial brain imaging performed after a haemorrhagic presentation had been reviewed by our two study neuroradiologists (JJB and RJS), who had classified the type and location of intracranial haemorrhage. One author (CC, and RAS in cases of doubt) cross-checked the images, rated them for predominant

ICH location (lobar, deep (basal ganglia, thalamus, internal and external capsules) or infratentorial (cerebellum and brainstem)), classified ICH shape (regular, or irregular if not spherical/ellipsoid), and measured and calculated haematoma volumes blinded to clinical data. Intracranial haemorrhage was attributed to an arterial aneurysm associated with a BAVM when the apparent source of haemorrhage originated in anatomical proximity to the arterial aneurysm; where there was doubt, the bleed was attributed to the BAVM rather than any aneurysm.

Statistical analysis

We calculated haematoma volume in cm^3 using the ABC/2 technique,^{5,6} by identifying the axial imaging slice with the largest area of ICH, and halving the product of the maximum width (A, cm), the width perpendicular to A (B, cm) and the depth (C, cm). We determined depth by multiplying the number of slices on which ICH was visible by the slice thickness of the relevant part(s) of the brain computed tomogram (CT). All measurements for A and B were made with reference to the centimetre scale on the scan. We also performed a sensitivity analysis with the alternative ABC/3 method of calculating the volume of irregular haematomas.⁷ We compared demographic and radiological characteristics between the three mutually exclusive IVM types: BAVM, CM and DAVF. We compared data that did not obey a normal distribution using non-parametric tests.

Intra-observer agreement

Twenty scans were randomly selected, and their A, B and C dimensions were recorded on two occasions 4 weeks apart (by CC), to check intra-observer agreement using Bland and Altman plots.^{8,9}

RESULTS

SIVMS identified 394 adults with a first-in-a-lifetime diagnosis of a definite IVM in the years 1999–2003 inclusive. All 25 adults with a DAVF were diagnosed with digital subtraction angiography (DSA), 197 (86%) of 229 BAVM were diagnosed on pathological examination or using DSA, and all 140 CMs were diagnosed either by MRI or pathological examination (26 (19%) of whom had a BAVM/DAVF ruled out by DSA).

Characteristics of patients with intracranial haemorrhages

Of all 394 adults identified by SIVMS, the numbers presenting with intracranial haemorrhage were: 115 (50%; 95% confidence interval (CI) 44% to 57%) of 229 BAVMs, 17 (12%; 95% CI 8% to 19%) of 140 CMs, and 9 (36%; 95% CI 20% to 56%) of 25 DAVF, giving a total of 141 haemorrhagic presentations. Overall, 69 were female (49%; 95% CI 41% to 57%), their median age was 47 years (inter-quartile range (IQR) 34 to 57.5)

and their median Oxford Handicap Score (OHS) at presentation was 3 (IQR 2 to 5). At the time of presentation, there were significant differences between IVM types in median age and OHS, but not gender (table 1); CMs were diagnosed in younger patients and were clinically less severe.

Characteristics of all presenting intracranial haemorrhages

The occurrence of intracranial haemorrhage was first demonstrated with brain CT (n = 128), MRI (n = 11) or post-mortem examination (n = 2). Brain CT was sometimes performed rather late after the onset of symptoms (table 2), and brain MRI usually confirmed haemorrhage in these cases. Although almost every bleed from a CM and DAVF was intracerebral with or without extension into other brain compartments, 22% of BAVMs presented with haemorrhage confined to the ventricles, subarachnoid space and/or subdural space (table 2); this apparent difference approached statistical significance (Fisher's exact test, $p = 0.06$).

Characteristics of presenting intracerebral haemorrhages

Of the 141 intracranial haemorrhages, 115 (82%) were partly or wholly intracerebral (table 2). Most ICHs were in lobar areas, and there were no significant differences between IVM types in their distribution (Fisher's exact test = 5.8, $p = 0.17$). However, there were significant differences in the pattern of extension of ICH into other brain compartments (table 3): pure ICH accounted for all CM haemorrhages (fig 1A), but only 50% of BAVM and DAVF haemorrhages. Haematoma volume data were available for further analysis in 110 cases (table 3), because an imaging measurement scale was not provided on three scans and two adults were only examined at post mortem. Intra-observer agreement for ICH dimensions was good (see Supplementary figure). Haematoma volumes overlapped between IVM types (table 3; fig 2): $\text{ICH} < 2.4 \text{ cm}^3$ were found in BAVM and CM; $\text{ICH} 2.4\text{--}12.0 \text{ cm}^3$ were found in all IVM types (fig 1A); $\text{ICH} 12.1\text{--}33.6 \text{ cm}^3$ were found in BAVM and DAVF (fig 1E); but $\text{ICH} > 33.6 \text{ cm}^3$ were only found in BAVM. The median volumes of BAVM and DAVF haematomas were not significantly different from each other (Mann-Whitney, $p = 0.622$), but BAVM, DAVF and CM haematomas did differ because of the smaller volume of CM haematomas (table 3). Because forty (36%) ICHs were irregular (fig 1C), we performed a sensitivity analysis using the formula ABC/3 to estimate the volume of the irregular haematomas,⁷ and the formula ABC/2 to estimate the volume of the regular haematomas,^{5,6} but this did not influence our results. Because posterior fossa ICH tends to be smaller than hemispheric ICH, we performed a further sensitivity analysis by excluding adults with posterior fossa ICH, and our findings remained the same: BAVM and DAVF hemispheric haematoma volumes were comparable, whereas

Table 1 Characteristics of adults with intracranial haemorrhage at initial presentation

	BAVM (n = 115)	CM (n = 17)	DAVF (n = 9)	Statistical test
Median age (IQR) (years)	47 (34 to 57)	35 (26 to 44)	62 (52 to 63)	Kruskall Wallis chi-square = 14, $p = 0.001$
% female (95% CI)	47 (38 to 56)	71 (47 to 87)	33 (12 to 65)	ns
Median Oxford Handicap Score (IQR)	3 (2 to 5)	2 (2 to 3)	2 (2 to 4)	Kruskall Wallis chi-square = 12, $p = 0.003$

BAVM, brain arteriovenous malformation; CM, cavernous malformation; DAVF, dural arteriovenous fistula; IQR, interquartile range; 95% CI, 95% confidence interval; ns, not significant.

Table 2 Imaging, types and causes of intracranial haemorrhages

	BAVM (n = 115)		CM (n = 17)		DAVF (n = 9)	
	CT	MRI	CT	MRI	CT	MRI
Brain imaging						
Number	109*	4*	10	7	9	0
Median delay from ICH onset to imaging in days (range)	0 (0–25)	21.5 (0–52)	2 (0–18)	7 (1–26)	0 (0–2)	–
Types of bleed						
ICH ± IVH ± SAH ± SDH (n = 115)	90 (78%)		17 (100%)		8 (89%)	
IVH (n = 11)	11 (10%)		0		0	
SAH (n = 6)	6 (5%)		0		0	
IVH & SAH (n = 8)	7 (6%)		0		1 (11%)	
SDH (n = 1)	1 (1%)		0		0	
Caused by						
IVM	107 (93%)		17		9	
Arterial aneurysm	8 (7%)		0		0	

BAVM, brain arteriovenous malformation; CM, cavernous malformation; DAVF, dural arteriovenous fistula; ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage; IVM, intracranial vascular malformation; SAH, subarachnoid haemorrhage; SDH, subdural haemorrhage.

*Imaging was available for only 113 adults, because two ICHs were diagnosed at post-mortem.

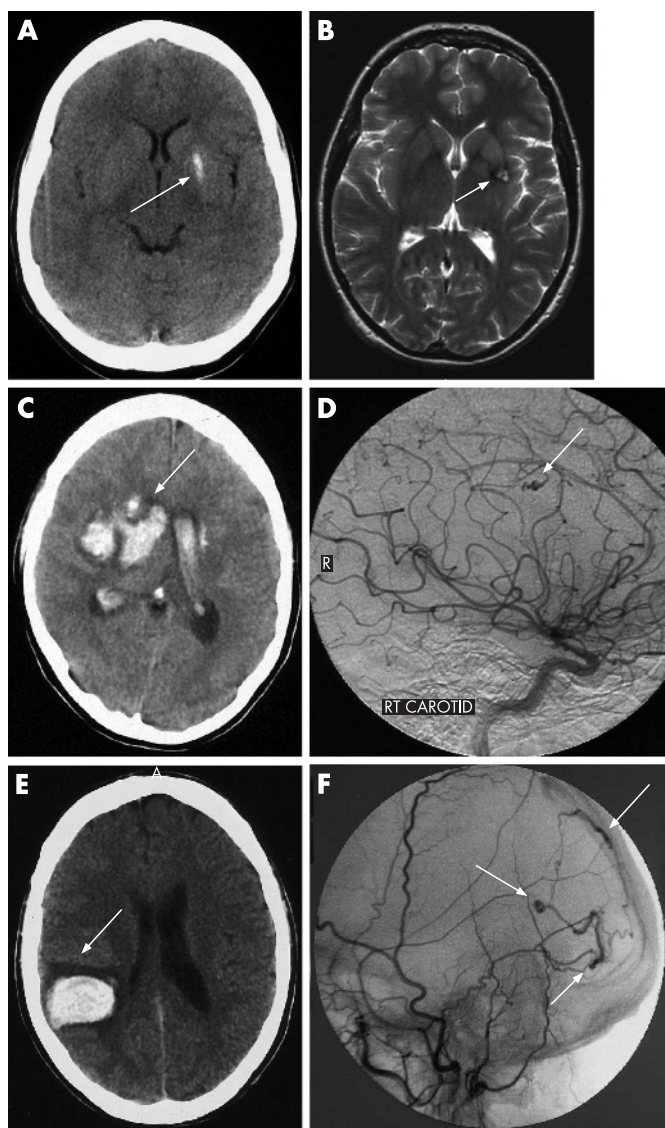


Figure 1 Illustrations of intracerebral haemorrhages due to intracranial vascular malformations: 12.0 cm³ cavernous malformation bleed (A and B), 9.8 cm³ brain arteriovenous malformation irregular bleed (C and D) and 33.6 cm³ dural arteriovenous fistula bleed (E and F).

CM hemispheric haematoma volumes were smaller, and this remained statistically significant (Kruskal–Wallis, $p = 0.0004$).

DISCUSSION

We found that intracranial haemorrhages due to CMs occurred at a younger age and tended to be less disabling at onset than those due to BAVM and DAVF. CMs always caused intracerebral haemorrhages, which were smaller than those due to other IVMs, thereby explaining the difference in their severity at onset.¹⁰ ICHs due to CMs never extended into other brain compartments (unlike half of the ICHs due to BAVM and DAVF). Haematoma volumes of 2.4–12.0 cm³ were found in all IVM types, but volumes of >34 cm³ were only found to be due to BAVM.

This is the first study to compare brain-imaging characteristics of intracranial haemorrhage due to IVMs identified prospectively in the same epoch in the same population. SIVMS is based on a population of roughly five million

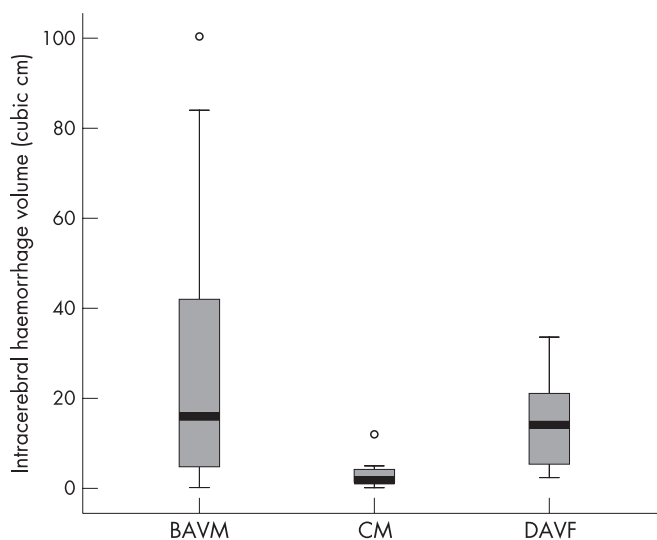


Figure 2 Box plot of the volumes of haematomas among intracranial vascular malformations. Dark lines represent medians, boxes represent interquartile ranges and outliers are indicated by open circles. BAVM: brain arteriovenous malformation; DAVF: dural arteriovenous fistula; CM: cavernous malformation.

Table 3 Characteristics of intracerebral haemorrhages

	BAVM (n = 90)	CM (n = 17)	DAVF (n = 8)	Statistical test
Regular shape (%)	54 (60)	14 (82)	2 (25)	Chi square = 7.6, p = 0.02
Type of ICH				
Pure ICH, n (%)	45 (50)	17 (100)	4 (50)	Fisher's exact test = 18.6, p = 0.006
ICH & IVH & SAH, n (%)	5 (6)	0	1 (12.5)	
ICH & IVH, n (%)	26 (29)	0	1 (12.5)	
ICH & SAH, n (%)	12 (13)	0	1 (12.5)	
ICH & SDH, n (%)	2 (2)	0	1 (12.5)	
Location				
Lobar, n (%)	66 (72)	8 (47)	7 (88)	NS
Deep, n (%)	10 (12)	4 (24)	0	
Posterior fossa, n (%)	14 (16)	5 (29)	1 (12)	
	BAVM (n = 85)	CM (n = 17)	DAVF (n = 8)	
Median width A, cm (IQR)	4 (1 to 8)	2 (1 to 3)	3 (2 to 5)	NS
Median width B, cm (IQR)	2 (1 to 6)	2 (0.3 to 3)	2 (2 to 3)	NS
Median depth C, cm (IQR)	4 (1 to 8)	2 (1 to 4)	3 (2 to 6)	NS
Haematoma volume (cm ³)				
Median (IQR)	16 (5 to 42)	2 (1 to 4)	14 (5 to 22)	Kruskal–Wallis, p < 0.0001
Minimum–maximum	0.2–100	0.2–12	2–34	

BAVM, brain arteriovenous malformation; CM, cavernous malformation; DAVF, dural arteriovenous fistula; ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage; SAH, subarachnoid haemorrhage; SDH, subdural haemorrhage; IQR, interquartile range; NS, not significant.

inhabitants over 5 years, enabling us to find several statistically significant differences between IVM types. However, the number of adults presenting with haemorrhage was relatively small.

The identification of an IVM as a cause of intracranial haemorrhage usually relies on further investigation following the imaging that diagnosed the haemorrhage. Whether and how to further investigate ICH in Scotland is not determined by SIVMS; rather, it is decided on by each patient's clinician in conjunction with a local radiologist. Whether to further investigate intracranial haemorrhage for an underlying IVM—and, if so, what test to use—is not based on firm evidence,¹¹ and is therefore influenced by clinicians' and radiologists' personal beliefs, as well as the availability of diagnostic imaging. This may, therefore, have biased our findings towards the expectations of everyday clinical practice across Scotland: for example, the differences in age at presentation between the IVM types may reflect clinicians' and radiologists' propensity to request and undertake further imaging (table 1). Such biases would be impossible to avoid in any population unless a routine scanning protocol of both MRI and some form of angiography were adopted for every patient with intracranial haemorrhage (although this may happen in some parts of the world, it certainly does not happen in Scotland).

One further limitation of our study was the method of haematoma volume estimation. First, the easy-to-use ABC/2 formula has been validated against a computer-assisted volumetric technique (but not for ICH due to IVMs),⁶ and although ABC/2 has been criticised because of its inapplicability to irregular ICHs,⁷ our conclusions were robust to a sensitivity analysis using the alternative ABC/3 calculation. Second, haematoma volume is known to increase over the first day or two following symptom onset, but there was no difference in delay to imaging between the IVM types (table 2), and we could not explore the influence of imaging timing in the 58% who were scanned on the same date as symptom onset because the time of the scan is not recorded by SIVMS.

There is little research into the patterns of intracranial haemorrhage and volumes of haematomas caused by IVMs, and whether they influence outcome. One small retrospective study at the Mayo Clinic studied the radiological features of intracranial haemorrhages due to IVMs.¹² In view of the small sample size, this study's findings mostly related to BAVMs with a pattern of haemorrhage extension that was similar to the pattern in our study (table 2), but no CM haemorrhages occurred for comparison.¹² In an effort to confirm our observation that no ICH due to CM extended into other cranial compartments, we reviewed the literature on CM haemorrhage.^{13–25} Most studies implied that the pattern of CM bleeding was intracerebral, with no extension into other compartments due to the low pressure at which their bleeds are thought to occur. However, one study described subarachnoid haemorrhage due to CM,²⁵ and another study described the pattern of extension of intracranial haemorrhages due to CMs, and three of seven were purely intraventricular,²¹ preventing a generalisation that CM haemorrhages are always purely intracerebral. No study quantified the volumes of haematomas due to CMs. Only one study has tried to identify distinctive clinical features of people with ICH due to IVMs in comparison to all other causes of ICH; in this retrospective cohort study of members of a health-maintenance organisation in the USA, people with ICH secondary to BAVMs tended to be younger and were more likely to be female, non-smokers with lower blood pressures, lower blood cholesterol and lower white blood cell counts on presentation.²

In conclusion, some characteristics of intracranial haemorrhage appear to differ between IVM types. In our study, patients with a CM presented at a younger age with haematomas of smaller volume and milder clinical severity than other IVM types. Although every haemorrhage from a CM in this study was purely intracerebral, a firm generalisation is precluded by some descriptions of intraventricular and subarachnoid haemorrhage from CMs.^{21–25} The volume of a haematoma could tentatively predict the type of IVM that

might underlie it: we found ICH volumes of 2.4–12.0 cm³ in all IVM types, but volumes of >34 cm³ were only found to be due to BAVM. Therefore, patients with ICH who are suspected of having an IVM may require both angiographic imaging and MRI to identify the underlying cause. Future research should comprehensively investigate the underlying causes of ICH, and explore the best imaging strategies to detect them.

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