

The Presentation and Clinical Course of Intracranial Developmental Venous Anomalies in Adults

A Systematic Review and Prospective, Population-Based Study

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Background and Purpose—Reported risks of hemorrhage from intracranial developmental venous anomalies (DVAs) vary, so we investigated this in a systematic review and population-based study.

Methods—We systematically reviewed the literature (Ovid Medline and Embase to November 7, 2007) and selected studies of ≥ 20 participants with ≥ 1 DVA(s) that described their clinical presentation and/or their clinical course over a specified follow-up period. We also identified every adult first diagnosed with a DVA in Scotland from 1999 to 2003 and followed them in a prospective, population-based study.

Results—Of 2068 articles detected by the literature search, 15 met our inclusion criteria and described clinical presentation, 8 of which also described the clinical course of DVAs. In the 15 studies of 714 people first presenting with a DVA, 61% were incidental findings, the mode of presentation was unclear in 23%, 6% presented with nonhemorrhagic focal neurological deficit, 6% had caused symptomatic hemorrhage, 4% were associated with epileptic seizure, and $<1\%$ were associated with infarction. In studies of the clinical course of 422 people with a DVA, the hemorrhage rate after first presentation ranged from 0% to 1.28% per year. In the population-based study of 93 adults with DVAs, 98% were incidental, 1% presented with symptomatic hemorrhage, and 1% presented with an infarct, but there were no symptomatic hemorrhages or infarcts in 492 person-years of follow-up (0% per person-year; 95% CI, 0% to 0.7%).

Conclusions—Intracranial DVAs have a benign presentation and clinical course. (*Stroke*. 2009;40:00-00.)

Key Words: hemorrhagic ■ intracranial developmental venous anomaly ■ stroke ■ vascular malformations

Intracranial developmental venous anomalies (DVAs), otherwise known as venous malformations or venous angiomas, are assumed to be congenital abnormalities of venous drainage through which blood flows at low velocity. DVAs occur sporadically, perhaps due to ischemia during intrauterine life causing the development of aberrant venous architecture,¹ but they occasionally obey a dominant pattern of inheritance due to a gene mutation on the short arm of chromosome 9, which is thought to alter early venous development.^{2,3} DVAs sometimes coexist with other intracranial vascular malformations, usually cavernous malformations of the brain (CMs).^{4,5}

The detection rate (incidence) of DVAs in population-based studies was 0.41 (95% CI, 0.17 to 0.65) per 100 000 person-years in Olmsted County, Minn,⁶ and 0.43 (95% CI, 0.31 to 0.61) per 100 000 person-years in Scotland,⁷ which is lower than

the incidence of arteriovenous malformations of the brain in these studies. However, one study found DVAs to be the most prevalent intracranial vascular malformation at autopsy.⁸ With the increasing availability and uptake of brain MRI, the DVA detection rate may yet rise.⁹

DVAs appear to be associated with symptoms infrequently and these have usually been due to intracranial hemorrhage or infarction.¹⁰ The frequencies of these manifestations at the time of DVA diagnosis and during untreated follow-up after diagnosis (clinical course) appear to vary between studies. Whether to treat DVAs¹¹ or not^{12–14} is still debated. However, it is generally agreed that resection of a functionally draining DVA carries a high risk of cerebral infarction and consequent morbidity.¹⁴

In view of the uncertainty about DVA prognosis, we systematically reviewed the literature to ascertain the fre-

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quency of intracranial hemorrhage, infarction, and death attributable to DVAs at first presentation and during follow-up. We also sought to confirm or refute the findings of the review in a prospective, population-based study of DVAs.

Materials and Methods

Systematic Review

We systematically reviewed the literature on intracranial DVAs in November 2007 by running electronic search strategies (Supplemental Appendix, available online at <http://stroke.ahajournals.org>) in Ovid Medline (from 1950) and Embase (from 1980). The titles and available abstracts were read to identify studies of ≥ 20 participants with at least one intracranial DVA reporting original data on their clinical presentation and clinical course for objective outcome events over a specified follow-up period. Although a sample size of ≥ 20 participants represents an arbitrary cutoff, this is the minimum number required to reject a null hypothesis (at the $P=0.05$ level) and minimizes the influence of case reports and small case series, which tend to report unusual phenomena. If multiple publications arose from the same cohort, we selected the one with the largest sample size that was most pertinent to this review.

One author (J.M.L.H.) extracted the following data from each included study and crosschecked selected studies with another author (R.A.-S.S.). We derived the mode of clinical presentation for each participant from the published description. When associated CMs were thought to be responsible for the symptoms that led to DVA diagnosis, we regarded these DVAs as asymptomatic. We allocated a primary mode of presentation to each participant if >1 mode had been allocated by the study authors, in the following hierarchical order.

Symptomatic Hemorrhage

Symptomatic hemorrhage has evidence of recent hemorrhage close to the DVA (not due to an associated CM) on radiological or pathological examination, causing a symptomatic neurological event (any of the following: headache, seizures, global neurological deficit, or focal neurological deficit).

Symptomatic Infarction

Symptomatic infarction has radiological or pathological evidence of infarction close to the DVA causing rapidly developing clinical signs of focal or global neurological disturbance lasting ≥ 24 hours.

Nonhemorrhagic Focal Neurological Deficit

Nonhemorrhagic focal neurological deficit is a focal neurological deficit that was anatomically referable to the location of the DVA without radiological or pathological evidence of recent hemorrhage or infarction and that could not be due to an associated CM.

Seizure

A seizure is an epileptic seizure that was anatomically referable to the location of the DVA based on seizure semiology or electroencephalography.

Incidental

We regarded all other modes of presentation as incidental, including headache, asymptomatic hemorrhage, generalized seizure disorders, neurological deficits that were anatomically unrelated to the DVA, and deficits that were attributable to an associated CM.

We classified studies documenting the clinical course of DVAs as prospective, retrospective, or "lifetime" (if they used a retrospective approach to clinical events that occurred during each participant's entire lifetime, ie, from birth until the age reached at the study's end point) or "not specified." We extracted measures of follow-up duration (median or mean, range, and total person-years of follow-up), numbers of objective outcome events during follow-up, and calculated a symptomatic hemorrhage rate per person-year of follow-up with 95% CIs where possible.

Scottish Intracranial Vascular Malformation Study

Participants

The Scottish Intracranial Vascular Malformation Study (SIVMS) is a prospective, population-based cohort study based on an anonymized extract of data from the Scottish Audit of Intracranial Vascular Malformations (SAIVMs, www.saivms.scot.nhs.uk), which identified Scottish residents aged ≥ 16 years at the time they were first diagnosed with any type of intracranial vascular malformation in the years 1999 to 2003.¹⁵ SAIVMs uses multiple, overlapping sources of case ascertainment to identify incident adults and follows up those who do not opt out by medical records surveillance and annual postal questionnaires, which are sent to each adult's general (family) practitioner. In this analysis, we included every adult in SAIVMs first diagnosed with an intracranial DVA during the years 1999 to 2003 and used follow-up data accrued until June 1, 2007. We defined a DVA as an intraparenchymal, purely venous variant of normal intracranial venous drainage, without an arteriovenous shunt, diagnosed by contrast-enhanced CT, MRI, or intra-arterial digital subtraction angiography.¹⁶

Data Collection

J.M.L.H. extracted the primary mode of DVA presentation (incidental, symptomatic hemorrhage, infarction, seizures, and focal neurological deficit [as defined previously]) for each SIVMS participant and double-checked with one of the authors (R.A.-S.S.) in case of doubt. During follow-up (defined as the period from the initial presentation that led to DVA diagnosis until the latest follow-up assessment or death), we specifically looked for the occurrence of any objective outcomes attributable to the DVA.

Ethical Approval

The Multicenter Research Ethics Committee for Scotland approved SIVMS (MREC/98/0/48).

Results

Systematic Review

Characteristics of Studies

The electronic searches yielded 1197 articles from Medline and 871 articles from Embase, of which 21 studies reported results on ≥ 20 participants with ≥ 1 DVA. Six of these studies did not match the selection criteria; one did not contain any information on clinical presentation or clinical course,¹⁷ 4 were earlier, smaller versions of studies included in this systematic review,^{18–21} and one was a precursor of the SIVMS data presented in this article.⁷ The 15 remaining papers,^{11–13,16,22–32} reported on the clinical presentation of DVAs (Table 1), and 8 of these studies also described their clinical course (Table 3).^{12,13,16,22,24,26,28,29} The largest study included 100 participants¹²; 6 (40%) studies of clinical presentation^{12,23–27}; and 3 (38%) studies of clinical course^{12,24,26} included ≥ 50 participants. The proportion of DVAs with associated CMs ranged from 2% to 40% in the 11 papers that reported their occurrence.^{12,13,16,23–26,28–30,32} Radiological methods used to diagnose DVAs varied to such an extent within and between studies that we could not set a diagnostic threshold: methods included CT, CT venography, MRI, MR angiography/venography, intra-arterial digital subtraction angiography, postmortem, or biopsy. Of those studies using a consistent method of diagnosis for all participants, MRI was the most commonly used modality (6 [40%] of all studies).

Table 1. The Clinical Presentation of DVAs in Studies With ≥20 Participants

Study	Participants With ≥1 DVA n	Participants With ≥1 Associated CM n %		Diagnostic Method (Selected Cases in Brackets)	Primary Clinical Mode of Presentation Attributable to DVA								Anatomically Consistent With DVA Location?		
					Incidental		Symptomatic Intracranial Hemorrhage		Epileptic Seizure(s)		Focal Neurological Deficit			Infarction	
					n	(%)	n	(%)	n	(%)	n	(%)		n	(%)
Garner et al ¹²	100	2	(2)	CT and/or MR and/or IADSA	86	(86)	1	(1)	5	(5)	8	(8)	0		Yes
Uchino et al ²³	82	≥10	(≥12)	MR (IADSA)	2	(2)	1*	(1)	Yes
McLaughlin et al ²⁴	80	3	(4)	IADSA or MR	67	(84)	0		4	(5)	9	(11)	0		Yes
Töpper et al ²⁵	67	10	(15)	MR (IADSA)	67	(100)	0		0		0		0		Yes
Naff et al ²⁶	63	8	(13)	MR and/or IADSA	47	(75)	2	(3)	1	(2)	13	(20)	0		Yes
Hendrich et al ²⁷	50	?		CT and CTV (MR, MRA, IADSA)	9†	(18)
Huber et al ²⁸	43	17	(40)	CT and MR and IADSA	40	(93)	0		1	(2)	2	(5)	0		?
Fujii et al ²²	40‡	?		IADSA	19	(47)	15§	(37)	1	(3)	5	(13)	0		?
Buhl et al ¹³	35	4	(11)	MR and MRA (IADSA)	30	(86)	1	(3)	4	(11)	0		0		?
Kovacs et al ²⁹	32¶	2	(6)	MR and MRA	28	(88)	0		3	(9)	0		1	(3)	?
Rigamonti et al ¹⁶	30	2	(7)	CT or MR or IADSA	24	(80)	0		1	(3)	4	(13)	1	(3)	Yes
Vidiri et al ³⁰	29	4	(14)	MR (MRA)	1**	(3)	0		0		Yes
Congia et al ³¹	22	?		MR or MRA	4	(18)	Yes
Malik et al ¹¹	21	?		CT and IADSA	8	(38)	9	(43)	1	(5)	3	(14)	0		Yes
Ostertun et al ³²	20	7	(35)	MRA (and IADSA and/or MR and/or CT)	19	(95)	0		1	(5)	0		0		Yes
Totals	714	≥69	(≥10)	...	435	(61)	40	(6)	27	(4)	44	(6)	2	(0.3)	...
SIVMS	93	19	(20)	CT or MR or IADSA or PM or biopsy	91	(98)	1	(1)	0		0		1	(1)	Yes

*Due to an old hemorrhagic venous infarct due to the DVA.

†Includes one subarachnoid hemorrhage in addition to 8 intraparenchymal hemorrhages.

‡Three of these DVAs had arterial components.

§It was unclear whether all were symptomatic (3 patients had headache as the only symptom). One hemorrhagic DVA had an arterial component.

||We have interpreted “weakness” to mean focal neurological deficit.

¶Every DVA was located in the cerebellum.

**It was unclear whether this was symptomatic.

IADSA indicates intra-arterial digital subtraction angiography; CTV, CT venography; MRA, MR angiography; PM, postmortem.

Clinical Presentation

Fifteen studies reported the clinical presentation of a total of 714 participants (Table 1),^{11–13,16,22–32} of whom at least 10% had an associated CM. Some studies were not generalizable because, for example, they were restricted to cerebellar DVAs²⁹ or included DVAs that had arterial components.²² There were insufficient details in several papers to adequately establish whether the DVA was symptomatic; in one paper, it was unclear whether “weakness” could be classified as focal neurological deficit²²; in some cases, authors were not explicit about whether the hemorrhages were symptomatic, and in others, symptoms may have been related to an associated CM. In other studies, the distinction among prepresentation hemorrhages, presenting symptomatic hemorrhages, and those occurring after diagnosis was not always clear.^{12,13,24} The primary mode of DVA clinical presentation was insufficiently described (“unclear”) for 23% overall; 61% presented with symptoms entirely incidental to their DVA, 6% presented with nonhemorrhagic focal neurological deficit, 6% presented with symptomatic hemorrhage, 4% presented with an

epileptic seizure, and <1% presented with symptomatic infarction (Table 1). Symptomatic hemorrhages were uncommon at presentation overall (6%), and 3 studies—in which 18%,²⁷ 37%,²² and 43%,¹¹ of participants presented with symptomatic hemorrhage—heavily influenced this pooled estimate (Table 1). One of these studies reported a subarachnoid hemorrhage caused by a DVA,²⁷ whereas the other bleeds (including one due to a DVA with an arterial component²²) were intraparenchymal. Two studies found that infratentorial DVAs were more likely to present with intracranial hemorrhage^{22,33}; this association remained when we used all the available data to test it (OR, 2.9; 95% CI, 1.4 to 5.9; Table 2), but the data were heavily influenced by just one study²² whose omission removed any apparent association (OR, 1.4; 95% CI, 0.5 to 3.6).

Clinical Course

Eight studies reported the clinical course of a total of 422 participants with DVAs (Table 3),^{12,13,16,22,24,26,28,29} Only 2 studies were prospective,^{24,26} and the remainder were retro-

Table 2. Exploration of the Association Between DVA Location and Symptomatic Hemorrhage at Presentation

Study	Supratentorial DVAs			Infratentorial DVAs			OR (Infratentorial Versus Supratentorial) (95% CI)	
	Total in Each Study	No. Causing Symptomatic ICH		Total in Each Study	No. Causing Symptomatic ICH			
		n	(%)		n	(%)		
Fujii et al ²²	25	4	(16)	16	11	(69)	11.6 (2.6–52.0)	
Malik et al ¹¹	11	5	(45)	12	4	(33)		
Hendrich et al ^{27*}	36	6	(17)	14	2	(14)		
Naff et al ²⁶	45	1	(2)	18	1	(6)		1.4 (0.5–3.6)
Garner et al ¹²	83	1	(1)	17	0			
Buhl et al ¹³	23	1	(4)	12	0			
Total	223	18	(8)	89	18	(20)	2.9 (1.4–5.9)	
SIVMS	56	0		38	1	(3)	OR incalculable	

*Figures only available for intraparenchymal hemorrhages. ICH indicates intracranial hemorrhage.

spective^{12,16,28,29} or the method of follow-up was not specified^{13,22}; the 3 largest studies also calculated “lifetime” hemorrhage rates.^{12,24,26} The mean length of follow-up ranged from 2.5 to 4.2 years (the median of the available means was 3.6 years). One study quoted neither average nor total person-years of follow-up.²⁸ None of the studies reported cerebral infarction or death attributable to a DVA. Retrospective “lifetime” hemorrhage rates ranged from 0.15% to 0.61% per year, but asymptomatic hemorrhages were included among these.^{24,26} Symptomatic hemorrhages occurred during follow-up in only 2 of the 8 studies (and in both, undocumented CMs may have been the cause^{22,24}); 3 (0.7%) of all

422 participants experienced symptomatic hemorrhage for annualized hemorrhage rates of 0.34% per year²⁴ to 1.28% per year²² in the individual studies (a pooled rate could not be calculated because only 2 studies documented their total person-years of follow-up^{24,26}).

Scottish Intracranial Vascular Malformation Study

Baseline Characteristics

During 1999 to 2003, 94 DVAs were detected in 93 adults in Scotland (49 [53%] women; median age at presentation, 44 years [range, 20 to 93 years]). Most DVAs (n=56 [60%]) were supratentorial, and half of these were in the frontal lobe.

Table 3. The Clinical Course of DVAs in Studies With ≥20 Participants

Study	Study Design	Participants With ≥1 DVA n	Participants With ≥1 Associated CM		Follow-Up Duration Mean Years (Range Years)	Hemorrhage Rate		Infarction n	Death n	
			n	(%)		ICH n (%)	After Presentation Percent/Year (95% CI)			
Garner et al ¹²	Retrospective and lifetime	100	2	(2)	2.5 (?)	0	0	0.22	0	0
McLaughlin et al ²⁴	Prospective and lifetime	80	3	(4)	3.6 (?)	1* (1.3)	0.34 (0.1–1.9)	0.61†	0	0
Naff et al ²⁶	Prospective and lifetime	63	8	(13)	4.2 (1.0–?)	0	0	0.15†	0	0
Huber et al ²⁸	Retrospective	43	17	(40)	? (2.0–10.0)	0	0	...	0	0
Fujii et al ²²	Not specified	40‡	?		3.9 (0.0–16.0)	2§ (5.0)	1.28 (0.4–4.5)	...	0	0
Buhl et al ¹³	Not specified	35	4	(11)	2.8 (0.3–6.0)	0	0	...	0	0
Kovacs et al ²⁹	Retrospective	32¶	2	(6)	3.5 (2.0–9.0)	0	0	...	0	0
Rigamonti et al ¹⁶	Retrospective	29	2	(7)	3.8 (1.5–8.7)	0	0	...	0	0
Totals	...	422	38	(9)	3.5 (0.0–16.0)	3 (0.7)	0	0
SIVMS	Prospective	93	19	(20)	5.3 (0.0–8.8)	0	0 (0–0.7)	...	0	0

*This may have been due to an undocumented CM.

†Rate includes “asymptomatic” hemorrhages.

‡Three DVAs had arterial components.

§Both were recurrent bleeds; it is unclear whether one of these DVAs may have had an arterial component.

||This was calculated based on an estimated total person years of follow-up (157 years) deduced from the mean length of follow-up multiplied by the no. of participants.

¶Every DVA was located in the cerebellum.

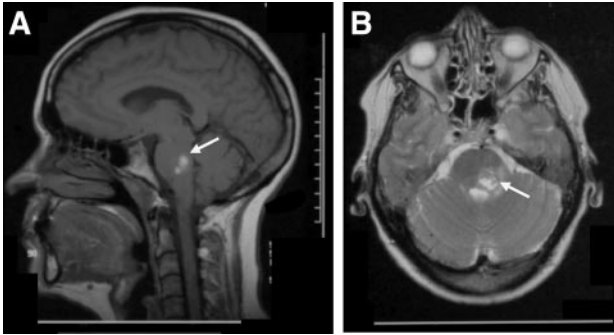


Figure 1. T₁-weighted sagittal (A) and T₂-weighted axial (B) MRI with signal characteristics consistent with methemoglobin due to acute, symptomatic hemorrhage from a pontine developmental venous anomaly.

Most of the infratentorial DVAs were located in the cerebellum (n=31 of 38 [82%]), and the remaining 7 were in the brainstem. The modalities used for DVA diagnosis were MRI (62%), contrast-enhanced CT (29%), intra-arterial digital subtraction angiography (6%), postmortem (2%), and biopsy (1%). Nineteen adults (20%) had ≥ 1 CM in close proximity to the DVA diagnosed by MRI (n=17) or pathological examination (n=2).

Clinical Presentation

Ninety-one of the 93 participants had presented to medical attention with symptoms that appeared to be entirely incidental to the DVA: headache (n=23), neurological symptoms unrelated to a DVA or CM (n=20), nonneurological symptoms (n=14), epileptic seizure(s) (n=10), symptoms attributable to an associated CM (n=7), detected during cancer staging imaging (n=5), unrelated cerebral infarction (n=4), tinnitus (n=4), unrelated intracranial hemorrhage (n=2), and cognitive impairment (n=2). The 2 remaining participants presented with symptoms that appeared to be anatomically referable to their DVA.

A 49-year-old woman (SIVMS ID 292) presented with sudden loss of balance, diminished sensation around her upper lip and nose, left facial weakness, and dyesthesia of her right thigh; MRI with gadolinium contrast administration (Figure 1) revealed a pontine hemorrhage, originally thought to be due to a CM, but surgical evacuation of the hematoma and pathological examination of its contents revealed the cause to be a DVA.

A 59-year-old woman (SIVMS ID 333) presented with sudden-onset ataxia and supranuclear right facial weakness; CT and MRI without intravenous contrast (Figure 2) revealed a right cerebellar infarct in proximity to a cerebellar DVA, which was initially thought to be the cause. However, during follow-up, she sustained further cerebral infarcts in anterior and posterior circulations, thought to be cardioembolic in origin.

Clinical Course

During 492 person-years of follow-up from initial clinical presentation (median, 5.6 years per patient [range, 0 to 8.8 years]), whose completeness was 87% (observed person-time of follow-up as a proportion of potential follow-up time),³⁴

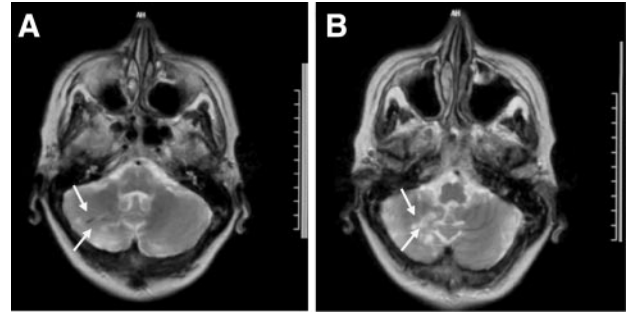


Figure 2. Contiguous sections on T₂-weighted axial MRI illustrating a flow void due to a developmental venous anomaly (A) adjacent to an acute right cerebellar hemisphere infarct (B).

there were no hemorrhages, deaths, or cerebral infarcts attributable to a DVA (0% per year; 95% CI, 0% to 0.7%).

Discussion

This systematic review and prospective population-based study confirm that the presentation and clinical course of DVAs are usually benign.

The systematic review used extensive electronic search strategies, restricted inclusion to studies of ≥ 20 participants in an effort to improve generalizability and precision, and attempted to apply a consistent method of allocating clinical presentation focusing on events that were clearly attributable to a DVA. It was impossible to allocate a mode of presentation to 23% of the participants, but none of them had symptomatic hemorrhage. Although 3 of the 15 published studies reported an unexpectedly high prevalence of intracranial hemorrhage due to DVAs (Table 1),^{11,22,27} their findings may be explained by selection, investigation, and reporting biases (for example, none of them used MRI and consequently did not report whether there were associated CMs and one of them included DVAs with arterial components²²).

Our study is the only prospective population-based analysis of DVAs, uses multiple overlapping sources of case ascertainment in a population of 5.1 million,¹⁵ and has recruited the second largest cohort of DVAs with the longest duration of follow-up (Table 3). Our finding of a benign prognosis is consistent with most of the large, published studies (Table 3), but even then, we are likely have overestimated the severity of DVA prognosis because of the asymptomatic reservoir of DVAs in the population.⁹ It is impossible to rule out a bias toward underreporting of symptomatic DVAs due to the incomplete investigation of intracranial hemorrhage in everyday clinical practice, the occasional difficulty of establishing a DVA diagnosis with certainty (Figure 1), or the obliteration of a DVA by the hemorrhage it caused (although this would not alter the low risk of recurrent hemorrhage because there would be nothing left to bleed from).

Neurological events that have been attributed to DVAs may have been due to venous hypertension,⁵ undetected cavernous malformations,⁵ rare “mechanical” or flow-related complications,¹⁰ or they may have been completely coincidental. There is anecdotal experience in SIVMS of an apparently symptomatic infarct later turning out to be incidental; one patient’s infarct initially appeared to be due to an

anatomically related DVA, but follow-up revealed a different mechanism of infarction to be more likely (Figure 2); another patient presented with adult-onset focal epileptic seizures and an anatomically related DVA was considered as the cause, but at postmortem, a white matter hamartoma was discovered. Furthermore, the prevalences of DVAs and spontaneous intracerebral hemorrhages without an apparent cause (so-called “primary”) make a chance association a possibility.

Summary

Although this systematic review will have been affected by the selection, investigation, and reporting biases in this area of clinical research, its summary data are in agreement with the largest and longest prospective population-based study on DVAs. Solitary DVAs are very rarely associated with symptoms, which may be a chance association. When identified, DVAs appear to have a benign short-term prognosis.

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Disclosures

None.

References

- Saito Y, Kobayashi N. Cerebral venous angiomas: clinical evaluation and possible etiology. *Radiology*. 1981;139:87–94.
- Gallione CJ, Pasyk KA, Boon LM, Lennon F, Johnson DW, Helmbold EA, Markel DS, Vikkula M, Mulliken JB, Warman ML, et al. A gene for familial venous malformations maps to chromosome 9p in a second large kindred. *J Med Genet*. 1995;32:197–199.
- Boon LM, Mulliken JB, Vikkula M, Watkins H, Seidman J, Olsen BR, Warman ML. Assignment of a locus for dominantly inherited venous malformations to chromosome 9p. *Hum Mol Genet*. 1994;3:1583–1587.
- Abdulrauf SI, Kaynar MY, Awad IA. A comparison of the clinical profile of cavernous malformations with and without associated venous malformations. *Neurosurgery*. 1999;44:41–46.
- San Millán Ruiz D, Delavelle J, Yilmaz H, Gailloud P, Piovon E, Bertramello A, Pizzini F, Rüfenacht DA. Parenchymal abnormalities associated with developmental venous anomalies. *Neuroradiology*. 2007;49:987–995.
- Brown RD Jr, Wiebers DO, Torner JC, O’Fallon WM. Incidence and prevalence of intracranial vascular malformations in Olmsted County, Minnesota, 1965 to 1992. *Neurology*. 1996;46:949–952.
- Al-Shahi R, Bhattacharya JJ, Currie DG, Papanastassiou V, Ritchie V, Roberts RC, Sellar RJ, Warlow CP; Scottish Intracranial Vascular Malformation Study Collaborators. Prospective, population-based detection of intracranial vascular malformations in adults: the Scottish Intracranial Vascular Malformation Study (SIVMS). *Stroke*. 2003;34:1163–1169.
- Sarwar M, McCormick WF. Intracerebral venous angioma. Case report and review. *Arch Neurol*. 1978;35:323–325.
- Al-Shahi R, Salman R, Whiteley WN, Warlow C. Screening using whole-body magnetic resonance imaging scanning: who wants an incidentaloma? *J Med Screen*. 2007;14:2–4.
- Pereira VM, Geibprasert S, Krings T, Aurboonyawat T, Ozanne A, Toulgoat F, Pongpech S, Lasjaunias PL. Pathomechanisms of symptomatic developmental venous anomalies. *Stroke*. 2008;39:3201–3215.
- Malik GM, Morgan JK, Boulos RS, Ausman JI. Venous angiomas: an underestimated cause of intracranial hemorrhage. *Surg Neurol*. 1988;30:350–358.
- Garner TB, Del CO Jr, Kelly DL Jr, Laster DW. The natural history of intracranial venous angiomas. *J Neurosurg*. 1991;75:715–722.
- Buhl R, Hempelmann RG, Stark AM, Mehdorn HM. Therapeutical considerations in patients with intracranial venous angiomas. *Eur J Neurol*. 2002;9:165–169.
- Senegor M, Dohrmann GJ, Wollmann RL. Venous angiomas of the posterior fossa should be considered as anomalous venous drainage. *Surg Neurol*. 1983;19:26–32.
- Al-Shahi R, Bhattacharya JJ, Currie DG, Papanastassiou V, Ritchie V, Roberts RC, Sellar RJ, Warlow CP; Scottish Intracranial Vascular Malformation Study Collaborators. Scottish Intracranial Vascular Malformation Study (SIVMS): evaluation of methods, ICD-10 coding, and potential sources of bias in a prospective, population-based cohort [Erratum appears in *Stroke*. 2003;34:1573]. *Stroke*. 2003;34:1156–1162.
- Rigamonti D, Spetzler RF, Medina M, Rigamonti K, Geckle DS, Pappas C. Cerebral venous malformations. *J Neurosurg*. 1990;73:560–564.
- Lee C, Pennington MA, Kenney CM III. MR evaluation of developmental venous anomalies: medullary venous anatomy of venous angiomas. *Am J Neuroradiol*. 1996;17:61–70.
- Huber G, Piepgras U, Henkes H, Faubert C. Venous anomalies of the brain. The clinical significance of the so-called venous angioma [in German]. *Radiologe*. 1991;31:274–282.
- Uchino A, Hasuo K, Matsumoto S, Masuda K. Double cerebral venous angiomas: MRI. *Neuroradiology*. 1995;37:25–28.
- Kitamura K, Fukui M, Oka K, Matsushima T, Hasuo K, Fukushima T, Tomonaga M, Okudera T. Hemangiomas of the central nervous system in Japan: an epidemiological and clinicopathological study with special reference to venous and cavernous malformations. *Neurosurg Rev*. 1986;9:221–231.
- Kondziolka D, Dempsey PK, Lunsford LD. The case for conservative management of venous angiomas. *Can J Neurol Sci*. 1991;18:295–299.
- Fujii K, Matsushima T, Inamura T, Fukui M. Natural history and choice of treatment in forty patients with medullary venous malformation (MVM). *Neurosurg Rev*. 1992;15:13–20.
- Uchino A, Hasuo K, Matsumoto S, Fujii K, Fukui M, Horino K, Tsukamoto Y, Masuda K. Cerebral venous angiomas associated with hemorrhagic lesions. Their MRI manifestations. *Clin Imaging*. 1996;20:157–163.
- McLaughlin MR, Kondziolka D, Flickinger JC, Lunsford S, Lunsford LD. The prospective natural history of cerebral venous malformations. *Neurosurgery*. 1998;43:195–200.
- Topper R, Jurgens E, Reul J, Thron A. Clinical significance of intracranial developmental venous anomalies. *J Neurol Neurosurg Psychiatry*. 1999;67:234–238.
- Naff NJ, Wemmer J, Hoenig-Rigamonti K, Rigamonti DR. A longitudinal study of patients with venous malformations: documentation of a negligible hemorrhage risk and benign natural history. *Neurology*. 1998;50:1709–1714.
- Hendrich B, Hojny A, Kowalewski K, Filarski J, Sasiadek M. The value of CT venography in assessing cerebral venous malformations. *Polish Journal of Radiology*. 2005;70:7–12.
- Huber G, Henkes H, Hermes M, Felber S, Terstegge K, Piepgras U. Regional association of developmental venous anomalies with angiographically occult vascular malformations. *Eur Radiol*. 1996;6:30–37.
- Kovacs T, Osztie E, Bodrogi L, Pajor P, Farsang M, Juhasz C, Szirmai I. Cerebellar developmental venous anomalies with associated vascular pathology. *Br J Neurosurg*. 2007;21:217–223.
- Vidiri A, Crecco M, Floris R, Mastrostefano R, Mattioli M, Squillaci S. Venous angiomas or ‘developmental venous abnormalities’: MR and angio-MR findings, association with cavernous angiomas and review of the literature. *Rivista di Neuroradiologia*. 1996;9:37–46.
- Congia S, Loi F, Cannas A, Vacca M, Borghero G, Mura M, Mascia MM, Manca E, Manca M, Derin M. Cerebral venous angiomas and epilepsy. *Bollettino—Lega Italiana contro l’Epilessia*. 2001;113–114:157–161.
- Ostertun B, Solymosi L. Magnetic resonance angiography of cerebral developmental venous anomalies: its role in differential diagnosis. *Neuroradiology*. 1993;35:97–104.
- Rothfus WE, Albright AL, Casey KF, Latchaw RE, Roppolo HM. Cerebellar venous angioma: ‘benign’ entity? *AJNR Am J Neuroradiol*. 1984;5:61–66.
- Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. *Lancet*. 2002;359:1309–1310.

Supplemental Appendix

Electronic Search Strategies

OID MEDLINE From 1950

1. central nervous system venous angioma/
2. Cerebral Veins/ab, pp [Abnormalities, Physiopathology]
3. *hemangioma/ and *veins/
4. ((vein\$ or venous) adj5 (anomal\$ or angioma\$ or hemangioma\$ or hemangioma\$ or malformation\$ or abnormal\$)).tw.
5. 3 or 4
6. exp brain/ or central nervous system/ or exp cerebral veins/ or exp cerebrovascular disorders/
7. (brain\$ or cerebral or intracerebral or central nervous system or intracranial or cerebellar or intraventricular or supratentorial or medullary or cerebrovascular\$).tw.
8. 6 or 7
9. 5 and 8
10. 1 or 2 or 9
11. limit 10 to humans
12. (exp child/ or exp infant/ or adolescent/) and exp adult/
13. exp child/ or exp infant/ or adolescent/
14. 13 not 12
15. 11 not 14

EMBASE From 1980

1. brain vein/

2. brain hemangioma/ or vein malformation/ or brain malformation/ or cerebrovascular malformation/ or congenital blood vessel malformation/ or central nervous system malformation/
3. 1 and 2
4. (hemangioma/ or angioma/) and brain vein/
5. (*hemangioma/ or *angioma/) and *vein/
6. *vein malformation/
7. ((vein\$ or venous) adj5 (anomal\$ or angioma\$ or hemangioma\$ or hemangioma\$ or malformation\$ or abnormal\$)).tw.
8. 5 or 6 or 7
9. exp brain/ or central nervous system/ or exp cerebrovascular disease/
10. (brain\$ or cerebral or intracerebral or central nervous system or intracranial or cerebellar or intraventricular or supratentorial or medullary or cerebrovascular).tw.
11. 9 or 10
12. 8 and 11
13. 3 or 4 or 12
14. limit 13 to human
15. (exp child/ or exp adolescent/ or newborn/) and (adult/ or middle aged/ or exp aged/)
16. exp child/ or exp adolescent/ or newborn/
17. 16 not 15
18. 14 not 17



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