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, 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, 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 not12–14 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-
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.

### 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.saiivms.scot.nhs.uk), which identified Scottish residents aged \( \geq 16 \) years at the time they were first diagnosed with any type of intracranial vascular malformation in the years 1999 to 2003.\(^\text{15}\) 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.\(^\text{16}\)

#### Data Collection

J.M.L.H. extracted the primary mode of DVA presentation (incident, symptomatic hemorrhage, infarction, seizures, and focal neurological deficit, or focal neurological deficit).

### 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 \( \geq 20 \) participants with \( \geq 1 \) DVA. Six of these studies did not match the selection criteria; one did not contain any information on clinical presentation or clinical course.\(^\text{17} \) 4 were earlier, smaller versions of studies included in this systematic review,\(^\text{18–21} \) and one was a precursor of the SIVMS data presented in this article.\(^\text{7} \) The 15 remaining papers,\(^\text{11–13,16,22–32} \) reported on the clinical presentation of DVAs (Table 1), and 8 of these studies also described their clinical course (Table 3).\(^\text{12,13,16,22,24,26,28,29} \) The largest study included 100 participants\(^\text{12} \) (6 [40%] studies of clinical presentation\(^\text{12,23–27} \); and 3 [38%] studies of clinical course\(^\text{12,24,26} \) included \( \geq 50 \) participants. The proportion of DVAs with associated CMs ranged from 2% to 40% in the 11 papers that reported their occurrence.\(^\text{12,13,16,23–26,28–30,32} \) 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).
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 hemorrhage22,33; 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-
spective, or the method of follow-up was not specified; the 3 largest studies also calculated “lifetime” hemorrhage rates. 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. 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. Symptomatic hemorrhages occurred during follow-up in only 2 of the 8 studies (and in both, undocumented CMs may have been the cause); 3 (0.7%) of all 422 participants experienced symptomatic hemorrhage for annualized hemorrhage rates of 0.34% per year to 1.28% per year in the individual studies (a pooled rate could not be calculated because only 2 studies documented their total person-years of follow-up).

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]).

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Supratentorial DVAs</th>
<th>Infratentorial DVAs</th>
<th>OR (Infratentorial Versus Supratentorial) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total in Each Study</td>
<td>No. Causing Symptomatic ICH</td>
<td>Total in Each Study</td>
</tr>
<tr>
<td>Fujii et al22</td>
<td>25</td>
<td>4 (16)</td>
<td>16</td>
</tr>
<tr>
<td>Malik et al11</td>
<td>11</td>
<td>5 (45)</td>
<td>12</td>
</tr>
<tr>
<td>Hendrich et al27*</td>
<td>36</td>
<td>6 (17)</td>
<td>14</td>
</tr>
<tr>
<td>Naff et al26</td>
<td>45</td>
<td>1 (2)</td>
<td>18</td>
</tr>
<tr>
<td>Garner et al12</td>
<td>83</td>
<td>1 (1)</td>
<td>17</td>
</tr>
<tr>
<td>Buhl et al13</td>
<td>23</td>
<td>1 (4)</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>223</td>
<td>18 (8)</td>
<td>89</td>
</tr>
<tr>
<td>SIVMS</td>
<td>56</td>
<td>0</td>
<td>38</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants With ≥1 DVA n (Participants With ≥1 Associated CM n [%])</th>
<th>Follow-Up Duration Mean Years (Range Years)</th>
<th>ICH After Presentation n [%] (95% CI)</th>
<th>Hemorrhage Rate</th>
<th>Infarction n</th>
<th>Death n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garner et al12</td>
<td>Retrospective and lifetime 100 2 (2) 2.5 (? 0 0 0.22 0 0</td>
<td>McLaughlin et al24 Prospective and lifetime 80 3 (4) 3.6 (7) 1* (1.3) 0.34 (0.1–1.9) 0.61† 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naff et al26</td>
<td>Prospective and lifetime 63 8 (13) 4.2 (1.0–7) 0 0 0.15† 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huber et al28</td>
<td>Retrospective 43 17 (40) 7 (2.0–10.0) 0 0 . . . 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fujii et al27</td>
<td>Not specified 40† 7 3.9 (0.0–16.0) 2§ (5.0) 1.28 (0.4–4.5) 0 0 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buhl et al13</td>
<td>Not specified 35 4 (11) 2.8 (0.3–6.0) 0 0 . . . 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kovacs et al28</td>
<td>Retrospective 32¶ 2 (6) 3.5 (2.0–9.0) 0 0 . . . 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rigamonti et al16</td>
<td>Retrospective 29 2 (7) 3.8 (1.5–8.7) 0 0 . . . 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>. . . 422 38 (9) 3.5 (0.0–16.0) 3 (0.7) . . . 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIVMS</td>
<td>Prospective 93 19 (20) 5.3 (0.0–8.8) 0 0 (0–0.7) . . . 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*This may have been due to an undocumented CM.
†Rate includes “asymptomatic” hemorrhages.
‡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.
§Both were recurrent bleeds; it is unclear whether one of these DVAs may have had an arterial component.
Most of the infratentorial DVAs were located in the cerebelum (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 dysesthesia 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 due to a CM. 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), 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.

Acknowledgments

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Disclosures

None.

References

Supplemental Appendix

Electronic Search Strategies

OVID 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 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 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