

Frequency of intracranial hemorrhage as a presenting symptom and subtype analysis: a population-based study of intracranial vascular malformations in Olmsted County, Minnesota

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✓ The purpose of this study was to determine the symptoms at presentation and the incidence of intracranial hemorrhage (ICrH) caused by intracranial vascular malformations (IVMs) in a defined population. The authors used the Mayo Clinic medical records linkage system to detect all cases of IVM among residents of Olmsted County, Minnesota, during the period 1965 through 1992. Forty-eight IVMs were detected over the 27-year period. Twenty-nine of the 48 patients were symptomatic at presentation. The most common presenting symptom was ICrH, which was present in 20 patients, 69% of all symptomatic cases. Sixty-five percent of arteriovenous malformations (AVMs) presented with ICrH. The most common subtype of ICrH was intracerebral hemorrhage, which was found in nine of 20 patients; the second most common subtype was subarachnoid hemorrhage. The peak occurrence of hemorrhage was during the fifth decade of life. The age- and gender-adjusted occurrence of a first ICrH from an IVM among residents of Olmsted County, Minnesota was 0.82 per 100,000 person years (95% confidence interval 0.46–1.19). There was no increase in the detection of IVM-related ICrH throughout the study period. The 30-day mortality rate following ICrH was 17.6% for patients with an AVM and 25% for all patients with IVMs. This study provides unique data on symptoms at presentation and the incidence of ICrH and hemorrhage subtypes from IVMs on a population basis.

KEY WORDS • cerebrovascular malformation • incidence • hemorrhage • arteriovenous malformation • cavernous malformation

INTRACRANIAL hemorrhage (ICrH) is the most common presenting symptom in patients with intracranial arteriovenous malformation (AVM), noted in 20% to 50% of cases.^{6,8,16} The risk of hemorrhage among those presenting with symptoms other than an initial hemorrhage is approximately 2.2% per year, and the mortality rate of patients with an initial hemorrhage is between 10% and 29%.^{4,6,8,16} Other important presenting symptoms include seizures, headaches, progressive neurological deficit, pulsatile tinnitus, and other unrelated symptoms that lead to a fortuitous diagnosis.⁴

Although AVMs are the most common type of intracranial vascular malformations (IVMs) that cause neurological symptoms, other classifications of vascular malformations may lead to neurological disease. Cavernous malformations have been recently recognized as lesions that may potentially cause serious neurological disorders.¹³ The most common presentations of these anomalies include an asymptomatic state, seizures, ICrH, and progressive neurological deficit. The frequency of significant hemorrhage has been considered to be relatively low, although the case series reported have been small, making

natural history data somewhat uncertain. Venous angiomas are the most common IVM detected at autopsy, accounting for 63% of all cerebrovascular malformations. These lesions are typically asymptomatic, although clinically significant hemorrhage is occasionally detected.^{12,15} A dural-based AVM can also cause aggressive neurological symptoms, including ICrH.^{2,5}

Although considerable information is available with regard to the natural history of AVMs, none of these natural history data are available on a population basis. The importance of ICrH as a presenting symptom of all IVM subtypes is only known from referral-based series. Knowing the relative frequency of hemorrhage for each of these lesions on a population basis may aid in characterizing the overall importance of these lesions compared to other central nervous system lesions; may carry implications to selection of patients for vascular malformation treatment trials; and may also impact studies on the natural history of these lesions. In the current paper we report our findings on the incidence and subtypes of ICrH as a presenting symptom for IVMs and IVM subgroups in a defined population.

TABLE 1
Presenting symptoms in 48 patients with an IVM*

Symptom	IVM-Related Symptoms (no. of patients)	Main Symptom at Presentation† (no. of patients)
ICrH	20	20
seizures	6	6
pulsatile tinnitus	2	2
indeterminate focal spells		
due to IVM	1	4
not due to IVM	0	3
nonspecific headache	0	4
migraine headache	0	3
change in consciousness	0	1
no neurological symptoms	19	5

* ICrH = intracranial hemorrhage; IVM = intracranial vascular malformation.

† Includes symptoms unrelated to IVM.

Clinical Material and Methods

Patient Population

The Mayo Clinic medical records linkage system affords the unique opportunity to ascertain virtually all cases with a specific medical diagnosis in a defined population.¹⁰ The medical records of all residents of Olmsted County with a diagnosis of IVM or a diagnosis that could be mistaken for IVM were reviewed for the period 1965 through 1992. Olmsted County residency was confirmed for all appropriate cases. Vascular malformations detected at autopsy or on a radiological imaging study were also reviewed. Verification of patient residency was based on information available from city and county directories, earlier medical records, and, when necessary, direct contact with family members or others to establish when certain street addresses were within the Olmsted County limits. No cases were included in estimates of incidence unless patient residence was established at least 1 year prior to the earliest known symptoms or discovery of the IVM.

Computation of Data

All available radiological imaging, surgical records, and autopsy information was reviewed to categorize patients into an IVM subtype. Major subtypes included AVM, dural AVM, cavernous malformation, and venous angioma.

Information on all identified cases was abstracted, and follow-up contacts with the patients established their current status. For those patients who had died, all available autopsy information and death certificates were reviewed.

All events that were consistent with an ICrH were further characterized by subtype using all available clinical data, radiological imaging studies, surgical records, and autopsy protocol review.

Statistical Analysis

Statistical analyses included calculation of age- and gender-adjusted incidence rates for hemorrhage determined by dividing the number of incidence cases by the proper denominator established from decennial census

TABLE 2
Presenting symptoms of IVMs in 48 patients according to IVM subtype*

Symptom	IVM Subtype (no. of patients)			
	AVM	VA	CM	DAVM
ICrH	17	2	0	1
seizures	5	0	1	0
pulsatile tinnitus	0	0	0	2
indeterminate spells due to IVM	0	0	1	0
none (asymptomatic)	4	12	3	0
total	26	14	5	3

* AVM = arteriovenous malformation; CM = cavernous malformation; DAVM = dural arteriovenous malformation; ICrH = intracranial hemorrhage; IVM = intracranial vascular malformation; VA = venous angioma.

data. Incidence rates were adjusted to the 1980 United States population, and 95% confidence intervals were estimated using Poisson regression. Other confidence intervals reported for proportions are 95% exact confidence intervals (95% CI).

Results

Among the 48 patients with IVMs detected for the period 1965 to 1992, 29 patients were symptomatic. The symptoms detected at presentation are noted in Table 1. The most common presenting symptom was ICrH in 20 patients, which included 42% (95% CI 27.6–56.8) of all patients and 69% (95% CI 49.2–84.7) of all symptomatic patients. Other symptoms leading to diagnosis included seizures in six patients, pulsatile tinnitus in two, and indeterminate focal spells (probable seizures believed to be secondary to the vascular malformation) in one patient. The main symptoms unrelated to IVM at the time of presentation are also listed in Table 1. These include any neurological symptoms that led to the detection of the IVMs, including those that were not likely to have been caused by them.

The characterization of IVM-related symptoms by subtype is presented in Table 2. Of the 26 patients with AVMs, 17 (65%; 95% CI 44.3–82.8) presented with ICrH, five (19%; 95% CI 6.6–39.4) presented with seizures, and four (15%; 95% CI 1.8–42.8) were asymptomatic. One of these asymptomatic cases was diagnosed by magnetic resonance (MR) imaging and arteriography; another had a venous malformation detected on autopsy. There was no evidence of a cavernous malformation associated with the venous malformation, although its presence cannot be excluded with certainty in the first case. There were no instances of progressive neurological deficit, or focal ischemic spells in the distribution of the AVMs over the 27-year period. The venous angiomas usually were asymptomatic lesions detected either at autopsy or on radiological imaging studies performed for some other reason. However, two (14%) of the 14 patients with venous angiomas presented with intracerebral hemorrhage. There were few cavernous malformations or dural AVMs. Most of the cavernous malformations were asymptomatic whereas two of the three patients with dural AVMs presented with pulsatile tinnitus and one with ICrH. Overall,

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TABLE 3
Population-based analysis of ICrH in IVMs*

ICrH Subtype	IVM Subtype (no. of patients)				
	All IVM Subtypes	AVM	VA	CM	DAVM
intracerebral hemorrhage	9	7	2	0	0
subarachnoid hemorrhage	4	4	0	0	0
intraventricular & intracerebral hemorrhage	3	3	0	0	0
intraventricular hemorrhage	2	2	0	0	0
subarachnoid & intracerebral hemorrhage	2	1	0	0	1
total	20	17	2	0	1

* AVM = arteriovenous malformation; CM = cavernous malformation; DAVM = dural arteriovenous malformation; ICrH = intracranial hemorrhage; IVM = intracranial vascular malformation; VA = venous angioma.

twenty (69%) of the 29 patients with symptomatic IVMs presenting during the 27-year period experienced ICrH as the initial symptom.

Results of an analysis of ICrH subtypes among the IVMs diagnosed in Olmsted County from 1965 to 1992 are summarized in Table 3. The most common hemorrhage subtype was intracerebral hemorrhage, which was noted in nine of 20 patients including seven of 17 patients with AVMs. Other hemorrhage subtypes included subarachnoid hemorrhage (four patients), intraventricular hemorrhage (two patients), subarachnoid hemorrhage and intracerebral hemorrhage (two patients), and intraventricular and intracerebral hemorrhage (three patients).

The mean age of patients at first ICrH was 38.7 years, which was slightly younger than the mean age at detection for all IVMs (mean 44.2 years, range 3 to 81 years). The peak occurrence of hemorrhage was during the fifth decade of life, with six hemorrhages; 75% of hemorrhages occurred before the patient reached 50 years of age (Fig. 1). Although a relatively small number of patients presented with symptoms other than hemorrhage, there was no evidence that hemorrhage was a more common presentation in a certain age subgroup.

The age- and gender-adjusted incidence of first ICrH caused by IVM among residents of Olmsted County, Minnesota was 0.82 per 100,000 person years (95% CI 0.46–1.19). Although detection of IVMs increased from 1965 to 1992,³ ICrH events were evenly spread throughout the study period with no increase in detected IVM-related ICrH noted either after the initiation of computerized tomography scanning of the head in 1973 or following the advent of MR imaging technology in the 1980s. The prevalence of a disorder may be defined as the number of persons affected in a specific population at a given time or during a particular time period.¹⁴ Age- and gender-adjusted prevalence for any type of IVM-related ICrH as of January 1, 1990 was 7.50 per 100,000 population (95% CI 2.18–12.81).

Four patients, each with an underlying AVM, experienced a second hemorrhage. The mean time interval from first to second ICrH was 3.6 years. Seven patients died as a result of an ICrH including five patients who died following their first ICrH. One of these deaths occurred following a subarachnoid hemorrhage caused by a dural

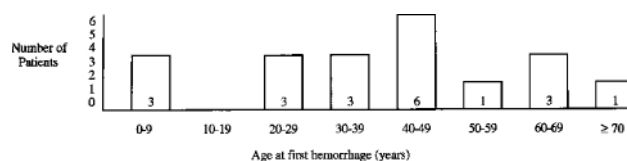


FIG. 1. Bar graph depicting the results of a population-based analysis of age at first intracranial hemorrhage caused by intracranial vascular malformations. The study included 20 patients.

AVM, one after an ICrH from a venous angioma, and the other three after first AVM-related hemorrhages. The 30-day mortality rate following a first ICrH was 17.6% (95% CI 3.8–43.4) for patients with an AVM and 25% (95% CI 8.7–49.1) for all IVMs detected during the 27-year period. The 30-day mortality rate among those experiencing a second hemorrhage was 50% in a small group of only four patients. Seven of the 15 survivors of the initial hemorrhage received immediate surgical intervention following the hemorrhage, including six complete excisions and one partial excision. Long-term freedom from new neurological difficulties occurred in six of the seven patients who underwent surgery; the last patient, who had a partial AVM excision, had a recurrent, fatal hemorrhage 257 days after the initial hemorrhage.

Discussion

Previous referral-based natural history studies of IVMs have reported a 20% to 40% frequency of ICrH as a presenting symptom.^{7,9,11} The frequency of hemorrhage in these studies is biased by the studies' referral nature, including selecting patients who survive to reach the medical center, selecting patients treated at a specific center because of its noted expertise in a subspecialty area, and inability to include patients who have died suddenly. There has never been a population-based study that clarified the importance of ICrH as a presenting symptom. The present data from a defined population agree with the theory that ICrH is the most common presenting symptom. However, these data indicate that ICrH may be a more common presenting symptom than previously reported, with 42% of all patients and 69% of all symptomatic patients presenting with ICrH. If one considers vascular malformation subtypes, the most common type of symptomatic vascular malformation, AVM, presented with hemorrhage in 65% of cases, whereas seizures were a much less common presentation of this anomaly. It is unlikely that any AVMs were missed, given our methods of detecting cases coded according to the clinical record or autopsy protocols. The frequency of hemorrhage among all vascular malformations may be an overestimation because some venous and cavernous malformations may not have been coded on the clinical record or in an autopsy protocol because they were considered by some to be clinically insignificant lesions. In this defined population, which should have been free of referral bias, the peak occurrence of hemorrhage was during the fifth decade of life, and 75% of the hemorrhages occurred before the patients reached 50 years of age. It is important to note that IVMs caused hemorrhages in older age groups, with

20% of the IVM-related hemorrhages reported here occurring in patients over 60 years of age.

The small numbers of patients in each IVM subtype precluded ICrH frequency characterization by any IVM subtype other than AVM. However, it is apparent from this population-based study that venous angioma and dural AVM are potential causes of ICrHs, although this is a relatively uncommon occurrence. The incidence data document the frequency of ICrH caused by IVM in a defined population. The incidence of a first ICrH caused by an IVM among residents of Olmsted County was 0.82 per 100,000 patient years. This may be compared to the incidence of all intracerebral hemorrhages, which was determined to be 15.5 per 100,000 population from 1985 to 1989 in Rochester, Minnesota.³ Prevalence rates provide a better estimate of survivors of IVM-related hemorrhage in the community. As of January 1, 1990, the prevalence rate was 7.5 per 100,000 population (95% CI 2.18–12.81). These survivors of the ICrH are persons likely to be of importance in assessing the public health impact of these lesions in terms of ongoing necessary follow-up examinations, medical care, and lost productivity from ICrH morbidity.

The mortality rate during the first 30 days following an initial AVM-related hemorrhage was 17.6%. This percent is based on the first data available to clarify the short-term mortality rate on a population basis without regard to multiple referral-based biases. Other studies have indicated a short-term mortality of 10% to 29%.^{5-8,11,16}

The frequency of the various types of ICrH categorized by IVM subtype has not been previously studied on a population basis. The data reported here support the contention that AVMs are the most common IVM to cause ICrH, and that the intracerebral area is the most common location for hemorrhage in vascular malformations. However, although others have reported that subarachnoid hemorrhage may rarely occur secondary to AVM,¹ in this series we noted that 24% of the AVM-related hemorrhages were primarily subarachnoid in location. There are a number of implications in the frequency with which IVMs in general, and AVMs in particular, present with intracerebral hemorrhage. The importance of intracerebral hemorrhage at first presentation among AVMs was probably underestimated at the referral centers because of biases discussed previously. The frequency of hemorrhage as a presenting symptom in the current study indicates that this bias may be quite prominent because 65% of patients presented with hemorrhage, and nearly 18% of those patients with hemorrhage caused by AVM died within 30 days. These issues also may impact on inclusion and exclusion criteria for treatment of patients with IVMs. In summary, although IVMs are being detected before ICrH with increasing frequency because of the use of improved radiological imaging studies, hemorrhage is still the most frequent presenting symptom and carries a significant short-term mortality rate.

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