The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow-up assessment

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The authors have updated a series of 166 prospectively followed unoperated symptomatic patients with arteriovenous malformations (AVM's) of the brain. Follow-up data were obtained for 160 (96%) of the original population, with a mean follow-up period of 23.7 years. The rate of major rebleeding was 4.0% per year, and the mortality rate was 1.0% per year. At follow-up review, 23% of the series were dead from AVM hemorrhage. The combined rate of major morbidity and mortality was 2.7% per year. These annual rates remained essentially constant over the entire period of the study. There was no difference in the incidence of rebleeding or death regardless of presentation with or without evidence of hemorrhage. The mean interval between initial presentation and subsequent hemorrhage was 7.7 years.

Key Words • arteriovenous malformation • natural history • rebleeding

The controversy surrounding the indications for therapeutic intervention in the management of arteriovenous malformations (AVM's) of the brain is fueled by a lack of clear understanding regarding their natural history. Early excessively pessimistic opinions on the clinical course of untreated malformations were not borne out by subsequent studies. Unfortunately, the natural history studies reported to date have been limited by small sample size, short inconsistent follow-up studies, and selection bias of the available study population.

We have updated a prospective series of symptomatic unoperated patients. This series has been followed by a group at Helsinki University and was initially reported in 1965 by TroupP. During the time of our study enrollment (1942 through 1975), Helsinki University was the neurosurgical referral center for over 90% of such lesions in the entire Finnish population. Our report reviews nearly a quarter-century of follow-up information for this population.

Clinical Material and Methods

During this study enrollment, 262 patients with angiographically confirmed AVM's of the brain were evaluated. Of these, 168 (64%) had no therapeutic intervention and were prospectively followed; 94 (36%) had some form of surgical intervention and were excluded from the study. Random assignment by the treating physician appears to be the primary determinant for placement in the "natural history" versus "intervention" groups. Figure 1 demonstrates no clear hemispheric or lobar predominance in either group. Despite this random-appearing selection process and distribution, patients with a large or deeply located lesion near eloquent cortex were more often referred to the natural history group.

Patients were enrolled in the study before computerized tomography (CT) was available for diagnosis. Hemorrhage was defined by the presence of a fixed neurological deficit, mass effect on radiographic studies, subarachnoid hemorrhage, or the clinical history of a sudden severe headache.

All patient charts were relocated for the study. Translators were employed to code essential chart data. This careful revalidation of the original population information disclosed two patients who had died at presentation and were erroneously included in the original series. These patients were excluded, leaving 166 patients in the study.

Patients were located by hospital records, by local physicians, and ultimately by income tax authorities. Readmissions, hemorrhage occurrence, and deaths were all reviewed and documented from hospital records.
Follow-up data were obtained primarily by a mailed questionnaire. After initial contact, follow-up correspondence was sent as needed. Additional information was obtained on some patients by telephone interview, correspondence with family or local physicians, and/or personal interviews.

Of the 166 patients, natural history data were obtained on 163 (98%). While many patients had multiple hemorrhagic events, only three (1.8%) underwent surgical or other intervention during the course of the study. These patients were excluded from the study in order to provide a more homogeneous group of patients upon which comparisons and conclusions could be made. This left 160 patients for evaluation: 96% of the original population. The mean follow-up time for this group was 23.7 years (ranging from 12 to 45 years). The majority of these patients (77%) were followed for more than 20 years.

The series was then analyzed as a whole and in three subgroups. The subgroups were defined by their presenting symptom and evidence of hemorrhage at or prior to presentation. The first subgroup was composed of 114 patients who presented with hemorrhage. The second subgroup was composed of 38 patients who presented with a seizure disorder but no history or evidence of hemorrhage. The third subgroup was composed of eight patients who had headaches, asymptomatic bruits, or other vague neurological complaints but no evidence of hemorrhage.

The complexity of this study required a variety of methods for analysis. As essentially the entire population of Finland with known symptomatic AVM was included in this study, epidemiological methods of analysis were used. Yearly rates of events were calculated based on person-years of observation. When the study group was compared with the general population, the difference-of-proportions formula was used to establish significance. Significance was defined as p < 0.05.

Such epidemiological data are truly referable to populations rather than individuals; however, this type of analysis is commonly used in medicine to make inferences as to the clinical course of individuals. Caution must be used in using such data for the calculation of incidence and prevalence. During the early period of study enrollment, the availability of angiography facilities was limited and the threshold of referral was high.

**Results**

**Patient Characteristics**

The population consisted of 99 males and 67 females, giving a 3:2 male preponderance. Despite this, we found no difference in the clinical course between men and women. The mean age at presentation was 33.7 years (ranging from 10 to 70 years). Among the 160 patients with sufficient follow-up data for inclusion in this study, the initial event in 71% was a hemorrhage; 24% presented with seizures and no evidence of hemorrhage; and 5% presented with headaches, asymptomatic bruits, or other vague neurological complaints but no evidence of hemorrhage.

**Follow-Up Findings**

**Hemorrhage.** After study enrollment, 64 (40%) of the 160 patients had at least one major hemorrhage in the follow-up period. The number of subsequent hemorrhages varied from one to as many as 12 in one patient. There were a total of 147 new hemorrhagic events in the population, resulting in a yearly bleed rate of 4.0%. The mean time interval between the patients’ presenting event and subsequent hemorrhage was 7.7 years (ranging from 6 weeks to 22 years). This interval did not significantly vary between the three subgroups.

When the subgroups were analyzed separately, there was no significant difference in the rate of hemorrhage (Table 1). We analyzed the frequency of new hemorrh-
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**TABLE 1**

<table>
<thead>
<tr>
<th>Presentation</th>
<th>No. of Cases</th>
<th>Annual Rate of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hemorrhage</td>
</tr>
<tr>
<td>hemorrhage</td>
<td>114</td>
<td>3.9</td>
</tr>
<tr>
<td>seizure</td>
<td>38</td>
<td>4.3</td>
</tr>
<tr>
<td>other</td>
<td>8</td>
<td>3.9</td>
</tr>
<tr>
<td>totals</td>
<td>160</td>
<td>4.0</td>
</tr>
</tbody>
</table>

* Data are given as a percentage of the entire patient population.

**TABLE 2**

Deaths identified at follow-up review among 160 natural history group patients

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>intracranial hemorrhage</td>
<td>37</td>
</tr>
<tr>
<td>other known causes</td>
<td>30</td>
</tr>
<tr>
<td>unknown</td>
<td>2</td>
</tr>
<tr>
<td>totals</td>
<td>69</td>
</tr>
</tbody>
</table>

The yearly mortality rate was 1.0% per year. There was no significant difference in the annual death rate between subgroups (Table 1). The number of deaths due to AVM hemorrhage were reviewed in 5-year intervals and appeared to be relatively constant over the entire length of the study (Fig. 2).

**Discussion**

Finland is a nation ideally suited to studies of the natural history of disease. A relative geographic and linguistic isolation blends with a unifying culture to conform the Finnish population into an extremely stable group. This stability combined with the centralization of medical care and meticulous record-keeping allow a unique study opportunity. We were able to follow the entire Finnish population with known symptomatic unoperated AVM's for a mean of 23.7 years. This study is not free of surgical selection bias. Of the possible population of 262 patients, only 64% were untreated. Still, this is a smaller bias of the study population than is typically obtainable. This percentage of unoperated cases appears to be sufficiently
large and representative to allow inferences regarding the natural history of all such patients with symptomatic lesions.3

This study found no difference in the natural history of symptomatic patients with or without evidence of hemorrhage historically or at presentation. However, it was begun in the pre-CT era, as is true of any long-term prospective study at this time.4-8,12-16 The accuracy of the division of these populations into subgroups with hemorrhagic and nonhemorrhagic presentations is no doubt limited by some error. Despite this, we must recognize that even current diagnostic tests are not free of error in regard to the diagnosis of hemorrhage from an AVM. In view of this, we believe that the analysis of these subgroups provides valuable insights.

The results of this study indicate that the further subclassification of symptomatic patients with cerebral AVM's of the brain is arbitrary in regard to outcome or management. All symptomatic patients share the same clinical course and risk regardless of their manner of presentation.

We consider that our 4.0% annual rate of bleeding is a conservative figure despite being higher than the 2% to 3% incidence reported previously.3,8,9,17 The long distance to travel for referral through the harsh Finnish winter no doubt kept some patients with minor bleeds from being evaluated in Helsinki. These same referral thresholds would also effect the per-bleed morbidity rates but not the yearly rate of hemorrhage resulting in major morbidity and death, occurrences which were sufficiently severe to merit referral. The higher bleed rate in this series relates to the length and completeness of follow-up review in a well-defined centrally cared-for population. Additionally, the mean interval of 7.7 years between hemorrhagic events is as long or longer than the mean follow-up periods of almost all other studies.3,5-7 These factors undoubtedly contributed to the previous underestimation of the incidence of recurrent hemorrhage. The 7.7-year interval between events also clearly points out that, unlike aneurysms, the risk of rebleeding associated with AVM's is not immediate. There is time to consider the increasingly complex therapeutic alternatives available, either singly or in combination.

The incidence of morbidity and mortality from AVM hemorrhage reveals some important relationships. At follow-up review, 34% of the original population had incurred major morbidity or death from a new hemorrhage. Among the patients who hemorrhaged after study enrollment, 85% eventually suffered a new deficit or death.

Over 50% of all deaths were due to AVM hemorrhage (23% of the total population). The mean patient age at death from AVM hemorrhage was 15 years less than that of patients dying from causes other than AVM hemorrhage. It was also striking that the population not dying from AVM hemorrhage itself had a significantly increased disability and lower life expectancy than the general Finnish population.2 This may be due in part to a number of the patients with AVM-related morbidity, which detracted from their general health and overall life expectancy.

Morbidity in the group presenting with hemorrhage was higher than that in the other two subgroups. We hold that this reflects additive injury incurred and superimposed on neurological impairment from previous hemorrhages. Presumably, prior damage limits the reserve to accommodate new injury from subsequent hemorrhagic events. This may also explain that while the rate of hemorrhage declined by nearly 50% after the 20-year follow-up mark, there was no such decline in the rate of death.

The rate of both hemorrhage and death remained constant over the entire length of the study. This implies that these patients remain at risk for hemorrhage and consequent death for their entire lives, and contradicts previous opinion.3,5 These conclusions and data are only applicable to symptomatic patients. Still, we hope this study will provide a better yardstick against which clinical studies and therapeutic indications may be measured. We await future studies of asymptomatic patients for comparison.1

Conclusions

The population described here has provided a unique opportunity to better define the natural history of cerebral AVM. This prospective natural-history study of symptomatic unoperated patients with AVM had a mean follow-up period of 23.7 years and has disclosed the following:

1. The annual rebleed rate of 4.0% did not vary, regardless of the manner of presentation. This rate of hemorrhage remained constant for over 20 years of follow-up review.
2. The annual mortality rate of 1.0% did not vary, regardless of the manner of presentation. This rate of death remained constant over the entire length of the study. Hence, 23% of the population died as a direct result of AVM hemorrhage.
3. The combined incidence of major morbidity and mortality of 2.7% remained constant over the entire 23.7-year follow-up period. In total, 34% of the population (85% of those who bled) suffered major morbidity or death. While mortality rates were not increased in the subgroup presenting with hemorrhage, the incidence of subsequently acquired morbidity was higher.
4. The mean interval between hemorrhagic events was 7.7 years.
5. The clinical course of all symptomatic patients with AVM's of the brain is the same regardless of the manner of presentation.

References

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Manuscript received July 7, 1989. Accepted in final form February 15, 1990. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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