Natural history of intracranial cavernous malformations

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The authors have reviewed the clinical records of 110 patients with intracranial cavernous malformations diagnosed by histological examination and/or magnetic resonance imaging over a mean follow-up period of 4.71 years. These cases were divided, based on their presentation, into a hemorrhage group, a seizure group, and an incidentally diagnosed group. The rate of subsequent symptomatic bleeding was investigated in relation to age at onset, sex, and location of the initial lesion. A high rate of subsequent symptomatic bleeding episodes was found in the hemorrhage group, especially among younger females. The nonhemorrhagic-onset cases had a very low incidence of bleeding. The outcome was generally good, except in patients with lesions in the basal ganglia and brainstem. These findings will be helpful in planning a rational therapeutic strategy for intracranial cavernous malformations.

KEY WORDS • cavernous malformation • hemorrhage • seizure • natural history • outcome

UNTIL recently, intracranial cavernous malformations or cavernous angiomas had been considered relatively rare lesions, accounting for only approximately 5% of angiographically diagnosed and histologically verified vascular malformations. However, McCormick, et al., reported that 16% of intracranial vascular malformations found at autopsy were cavernous and that the majority of them had been “cryptic.” With the advent of magnetic resonance (MR) imaging techniques that render the detection and diagnosis of these lesions easy and accurate, there has been a substantial increase in the number of patients diagnosed with these lesions, which has helped in the investigation of the natural course of this disorder. In this study, we retrospectively reviewed the clinical records of 110 patients with intracranial cavernous malformations to investigate the natural course of these lesions. Special emphasis was placed on the frequency of hemorrhagic episodes, because such information may contribute to the optimum choice of treatment.

Clinical Material and Methods

Since 1970, we have treated 110 patients with intracranial cavernous malformations diagnosed by histological examination and/or MR imaging. In this study, we reviewed their clinical records and divided them into three groups on the basis of the findings at the time of their initial clinical presentation: a hemorrhage group, a seizure group, and an incidental diagnosis group.

The hemorrhage group included patients who experienced the acute or subacute onset of focal neurological deficits or signs of increased intracranial pressure associated with either a fresh clot outside the malformation at the time of operation or evidence on the initial computerized tomography (CT) scan of intralesional or perilesional clot density that decreased in size and density on follow-up CT. Patients who presented with seizures and showed these radiological findings were categorized in the hemorrhage group. Patients with subclinical hemorrhages (incidentally found on radiological examinations) and worsening of neurological signs without radiological evidence were not included in this study. To evaluate the risk of subsequent bleeding, the patients were divided into younger (39 years or under) and older (40 years or over) subgroups, and the lesions were divided by location into frontal lobe, parietal lobe, temporal lobe, occipital lobe, basal ganglia, corpus callosum, brainstem, and cerebellar subgroups. Thalamic lesions were included in the basal ganglia category.

The seizure group included patients who presented with seizures without any radiological evidence of fresh hemorrhage. These lesions were divided by location into the same subgroups. The incidental group included patients with intracranial cavernous malformations as an incidental finding on MR imaging.

In the bleeding risk study, each patient was followed from the time of initial presentation to surgical resection (in the case of single lesions) or until the last contact.
Follow-up data were obtained during hospital visits, by telephone interview, or by letter.

Statistical analysis was performed using the chi-square test for the sex ratio study and the generalized Wilcoxon test for the survival rate from symptomatic bleeding. The intervals between the initial and second bleeding (or the last contact) were analyzed to reveal the risk of undergoing subsequent bleeding, and the intervals between individual bleeding episodes during the follow-up period were also analyzed to reveal the overall tendency of the subgroup to bleed.

Results

Clinical Presentation

Sixty-two cavernous malformation patients presented with hemorrhage and 25 patients with seizures; 23 patients were identified on the basis of incidental findings. The mean follow-up periods, as defined above, were 4.23 years in the hemorrhage group, 7.98 years in the seizure group, and 2.39 years in the incidental group; the longest period was 15 years. Contact with eight of the 110 patients had been lost at the time this study was performed.

Surgical intervention concluded the follow-up period in 41 patients in the hemorrhage-onset group, 12 patients in the seizure group, and three patients in the incidental group after mean follow-up periods of 1.77 years, 5.13 years, and 8 months, respectively.

Patient Age and Sex

Figure 1 shows the age and sex of the patients in each group at the time of the original presentation. The time of magnetic resonance imaging diagnosis is listed for the incidental group. * Females predominant (p < 0.05, chi-square test). ** Males predominant (p < 0.05, chi-square test).

TABLE 1

<table>
<thead>
<tr>
<th>Location of Lesion</th>
<th>Hemorrhage Group</th>
<th>Seizure Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>frontal lobe</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>parietal lobe</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>temporal lobe</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>occipital lobe</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>basal ganglia</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>corpus callosum</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>brainstem</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>cerebellum</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>62</td>
<td>25*</td>
</tr>
</tbody>
</table>

* Five patients had multiple supratentorial lesions and their epileptic focus could not be verified.

Location of Lesions

Table 1 summarizes the location of the lesions responsible for the initial clinical symptoms. Five patients in the seizure group who had multiple supratentorial lesions and whose epileptic foci had not been determined were omitted from the data presented in this table. No symptomatic hemorrhagic lesions were detected in the right temporal area, and no posterior fossa lesions were detected in the seizure group. The number of malformations detected by MR imaging per patient did not differ significantly in the three groups, although hemorrhage from a lesion previ-
Type of Hemorrhage

Most of the hemorrhages consisted of intralesional or perilesional “slow ooze” or “cluster of bleeding sites” that resulted in subacute or stepwise worsening of the neurological signs. Minor neurological deterioration often occurred within several days after obvious hemorrhagic episodes, but radiological examinations usually could not confirm additional bleeding. Overt hemorrhages (dense clots clearly protruding from the malformation) were observed in seven patients, including three patients with intraventricular hemorrhages.

Symptomatic Hemorrhage Rate

Symptomatic hemorrhages were quite rare in the seizure and incidental groups during the follow-up period. Only one bleed occurred (in the seizure group) per 254 patient years (number of patients × number of years followed), yielding a rate of 0.39% per year per patient. In contrast, 27 of the 62 patients in the hemorrhage group experienced a subsequent symptomatic bleed. Twenty-three patients bled from their initial lesion, one patient from a coexisting lesion, and three from both initial and coexisting lesions.

Thirty-six lesions that caused initial symptoms remained clinically silent during the mean follow-up period of 1.92 years, including 10 lesions that were treated by surgery within 1 month. The other 26 initial symptomatic lesions were responsible for 45 subsequent bleeding episodes during a mean follow-up period of 4.77 years. Thus, the incidence of subsequent hemorrhage for these 62 initially bleeding malformations was 22.9% per year per lesion with an average of 3.12 follow-up years. The interval between episodes ranges from days to 7 years.

The incidence of subsequent bleed according to age at onset and sex is shown in Table 2 and according to the location of the lesion in Table 3. Corpus callosum and occipital lesions are excluded because of the small number of cases, and cerebellar lesions are omitted because the mean follow-up period was less than 1 month.

Subsequent bleeding among patients with initial hemorrhagic lesions according to sex and age

<table>
<thead>
<tr>
<th>Sex &amp; Age at Onset</th>
<th>Total Cases</th>
<th>Subsequent Bleed</th>
<th>Mean Follow-Up Time (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Rate/Lesion/Yr</td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>25</td>
<td>8</td>
<td>19.4%</td>
</tr>
<tr>
<td>&lt;40 yrs</td>
<td>12</td>
<td>4</td>
<td>22.0%</td>
</tr>
<tr>
<td>≥40 yrs</td>
<td>13</td>
<td>4</td>
<td>14.8%</td>
</tr>
<tr>
<td>female</td>
<td>37</td>
<td>18</td>
<td>25.2%</td>
</tr>
<tr>
<td>&lt;40 yrs*</td>
<td>20</td>
<td>11</td>
<td>34.4%</td>
</tr>
<tr>
<td>≥40 yrs</td>
<td>17</td>
<td>7</td>
<td>14.4%</td>
</tr>
<tr>
<td>total cases</td>
<td>62</td>
<td>26</td>
<td>22.9%</td>
</tr>
<tr>
<td>&lt;40 yrs†</td>
<td>31</td>
<td>15</td>
<td>29.0%</td>
</tr>
<tr>
<td>≥40 yrs</td>
<td>31</td>
<td>11</td>
<td>14.1%</td>
</tr>
</tbody>
</table>

* Higher risk of second bleeding versus both older groups (p < 0.05) and shorter bleeding intervals versus the older female group (p < 0.05).
† Higher risk of second bleeding versus the older group (p < 0.05).

Subsequent bleeding among patients with hemorrhagic lesions according to location

<table>
<thead>
<tr>
<th>Location</th>
<th>Total Cases</th>
<th>Subsequent Bleed</th>
<th>Mean Follow-Up Time (yrs)</th>
<th>Age at Onset (yrs), Sex (m/f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>frontal lobe</td>
<td>13</td>
<td>4</td>
<td>16.1%</td>
<td>2.39</td>
</tr>
<tr>
<td>parietal lobe</td>
<td>10</td>
<td>5</td>
<td>23.2%</td>
<td>2.15</td>
</tr>
<tr>
<td>temporal lobe</td>
<td>9</td>
<td>3</td>
<td>57.5%</td>
<td>0.58</td>
</tr>
<tr>
<td>basal ganglia</td>
<td>7</td>
<td>2</td>
<td>11.0%</td>
<td>6.51</td>
</tr>
<tr>
<td>brainstem</td>
<td>15</td>
<td>9</td>
<td>21.5%</td>
<td>5.59</td>
</tr>
</tbody>
</table>

Younger female patients presented a higher risk of a second bleed compared to both older groups (p < 0.05). The younger-onset group patients, both male and female, also exhibited a significantly higher risk of a second bleed compared to the older-onset group (p < 0.05). The intervals of individual bleeding episodes in the younger female group were significantly shorter than the intervals in the older female group (p < 0.05). There were no significant differences regarding subsequent bleeding in the other subgroups delineated in Tables 2 and 3. Two young female patients who had been followed for more than 10 years had lesions that seemed to become less symptomatic as they grew older.

Symptomatic bleeding from coexisting malformations in the hemorrhage group was observed in four patients, one episode each, during 262 patient years, yielding a bleeding incidence of 1.5%. This rate was significantly higher than in the nonhemorrhage groups (p < 0.05).

Treatment and Outcome

Hemorrhage Group. Forty-one of the 62 patients in the hemorrhage group underwent surgery. Lesions in the less eloquent cerebral cortex and cerebellum tended to be operated on earlier, with a good outcome. However, recovery from hemorrhages was generally good even when treated conservatively (Table 4). The sole death was attributable to repeated brainstem hemorrhages. The condition of the severely disabled patient with a parietal lesion was affected by multiple coexisting ischemic lesions. The moderate or severe disability of the other 10 patients resulted from recurrent bleeds in six patients, the first bleed in two patients, and operative complications in approaches to thalamic lesions in two patients. All the lesions responsible for disability were in eloquent brain areas. Surgery was not the cause or a contributing factor in the other five disabled patients with surgical treatment.

Nine patients with brainstem lesions whose outcome was excellent or good had four subsequent bleeding episodes during 36.0 patient years, yielding a subsequent bleeding incidence of 11.1%. The mean ages at onset of nondisabled and disabled patients with brainstem lesions were 46.4 years and 22.2 years, respectively. The size of the brainstem malformation or hematoma at the time of initial presentation was less than 1.2 cm in diameter in patients with a good outcome versus more than 1.5 cm in diameter for most disabled patients.

Seizure and Incidental Groups. All of the patients in the nonhemorrhage groups had an excellent outcome. Two
patients with intractable seizures experienced complete remission after surgical extirpation of the responsible lesions.

Discussion

The natural history of cavernous malformations remains largely unexplored. There have been a few reports on this problem, but the tendency toward surgical resection in the early hemorrhagic stage interfered with their investigation. The follow-up period (time to surgical resection or last contact) of the patients with cerebellar lesions in our study was also very short because of a presumption that posterior fossa vascular malformations are more dangerous than supratentorial malformations.

Patients in the hemorrhage group experienced a high rate of subsequent symptomatic bleeding, whereas those in the seizure and incidental groups rarely had episodes of symptomatic hemorrhage. Lobato, et al., reported that episodes of subsequent bleeding from angiographically occult vascular malformations (AOVM), such as cavernous malformation, are more frequent than from angiographically manifest lesions. Tomlinson, et al., stated that symptomatic AOVM are more frequent in young females.

The sex ratio of patients in the incidental group suggests that this type of malformation has a predilection for males, whereas younger women predominated in the hemorrhage group and had a higher rate of subsequent bleeding. In 1993, Robinson and colleagues reported a higher incidence of subsequent bleeding in young-onset and female patients and in 1991, they and Curling, et al., found a very low incidence of bleeding associated with nonhemorrhagic lesions.

We speculate that the patients in the hemorrhage group had a factor or factors that promoted enlargement or bleeding of the malformation, which eventually grew large enough to become symptomatic. Our data indicate that female hormones may be contributing factors. Robinson and coworkers also proposed this hormonal influence.

Conclusions

Female hormonal factors are implicated in the pathogenesis of symptomatic hemorrhage from an intracranial cavernous malformation. The incidence of subsequent symptomatic bleeding, especially in younger females, is high, whereas episodes of bleeding are rare among patients whose initial manifestation was a seizure and patients in whom the lesions are incidental findings. Even when the bleeding episodes are mild, recurrent bleeding in eloquent areas can cause severe neurological deficits.

References


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