Familial intracranial aneurysms and cerebral vascular anomalies

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The author reports a family in which four members had intracranial aneurysms and one additional member was suspect. One member had multiple aneurysms that were successfully treated surgically. Elective angiography on five asymptomatic members of the family disclosed asymptomatic aneurysms in two. In addition, cerebrovascular anomalies were found in many of the family members. The parents of the family were consanguineous. High incidence of these associated anomalies and consanguinity in the parents tend to suggest the hereditary basis of the disease. Banding analysis of chromosomes in three siblings with aneurysms and three siblings without aneurysms was carried out. Elective investigation of the asymptomatic members should be considered where there are already two or more affected in a family. The indications for surgical prophylaxis on asymptomatic aneurysms in other members of the family are discussed.

KEY WORDS • familial aneurysms • cerebrovascular anomalies • consanguinity • chromosomal study • asymptomatic aneurysms • surgical prophylaxis

Although intracranial aneurysms are usually considered congenital in origin, the hereditary basis of the disease is still unsettled. Since Chambers, et al., reported familial incidence of intracranial aneurysms in 1954, there have been 28 reports of similar cases. In many of the reports, however, details such as family size, consanguinity, and the association of other disorders are lacking.

We are documenting a family of 12 members in which intracranial aneurysms were found in four, cerebral hemorrhage in two, and intracranial aneurysm suspected in one. In addition, elective investigation was carried out on asymptomatic members of the family. The purposes of this communication are to present the case studies of this family in which asymptomatic as well as symptomatic members are included, report the associated anomalies found in the cerebrovascular system, and report the results of chromosomal study in six siblings with or without aneurysms. We also discuss the indications for elective investigation on asymptomatic members and surgical prophylaxis on asymptomatic aneurysms found by elective investigation.

Case Reports

Patients with Confirmed Intracranial Aneurysms

Case 1. A 42-year-old housewife was found unconscious and was admitted to a local hospital on May 13, 1974. She was noted to have anisocoria with the left pupil larger than the right, conjugate deviation of the eyes to the right, and prominent stiffness of the neck. She complained of severe
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FIG. 1. Family chart indicating case numbers as reported here. Squares represent males, circles represent females.

FIG. 2. Case 1. Upper Left: Vertebral angiogram, axial view, showing an aneurysm of the left vertebral artery at the junction of the posterior inferior cerebellar artery (PICA) and anomalous termination of the left vertebral artery in the PICA. Upper Right: Right carotid angiogram showing an internal carotid-posterior communicating artery aneurysm. Lower Left: Right carotid angiogram, oblique view, showing a middle cerebral artery aneurysm. A smaller aneurysm just distal to the aneurysm is also shown.
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headache when she regained consciousness 1 hour after admission. Lumbar puncture yielded grossly bloody cerebrospinal fluid (CSF). Three-vessel angiography disclosed multiple intracranial aneurysms. She was subsequently transferred to our neurosurgical department on May 27.

Her previous history disclosed a mild hypertension of 4 years' duration prior to admission. A review of the family history revealed consanguinity in her parents, who were first cousins (Fig. 1). Her brother had died from a ruptured intracranial aneurysm, and her father from a suspected intracranial aneurysm. Two siblings had died from cerebral hemorrhage.

On admission to our hospital, the patient was slightly drowsy and somewhat slow in response. Neurological examination revealed a slightly stiff neck, left abducens palsy, and minimal weakness in the left leg. Muscle stretch reflexes were absent on both sides. Abdominal skin reflexes were decreased on the left. Blood pressure was 114/72. Repeat angiograms revealed multiple saccular aneurysms, and associated cerebral vascular anomalies, namely, anomalous termination of the left vertebral artery in the posterior inferior cerebellar artery (PICA) and the embryonic origin of the posterior cerebral artery (Fig. 2).

On July 3, an aneurysm of the left vertebral artery was clipped. The postoperative course was complicated by meningitis but was otherwise satisfactory, and on September 18 right frontal craniotomy was performed and aneurysms of the right internal carotid-posterior communicating artery (ICA-PCA) and middle cerebral artery (MCA) distal bifurcation were occluded with clips. A sessile aneurysm just distal to the MCA aneurysm was coated with Biobond. On November 1, an aneurysm of the left MCA trifurcation was clipped. The postoperative course was uneventful. The patient was discharged 21 days postoperatively, and 14 months after operation she remains able to do her work without any neurological deficit.

Case 2. The 25-year-old brother of the patient in Case 1 was found dead in bed on the morning of March 3, 1961. Because there had been no previous history of disease and the cause of death could not be determined, an autopsy was performed. According to the autopsy report, there was a ruptured saccular aneurysm of the anterior communicating artery (ACoA) and extensive subarachnoid hemorrhage. The hemorrhage had extended into the right frontal lobe and the lateral and third ventricles.

Suspected Intracranial Aneurysms

Case 3. The 48-year-old father of the patient in Case 1 had a 5-year history of diplopia, anisocoria with the left pupil three times larger than the right, and ptosis on the left. In June, 1950, he was found one morning in coma near his farmhouse. He had not returned home from work on the previous day. A complete hemiplegia was noted on the right. He gradually regained consciousness in a week but incontinence and disorientation persisted. Thirty-five days after the initial hemorrhage, he suddenly died from a second attack. No postmortem examination was done so that the diagnosis was not proved, but apparent third cranial nerve palsy prior to hemorrhage strongly suggests the presence of a ruptured aneurysm of the internal carotid artery (ICA).

Case 4. The 47-year-old elder brother of the patient in Case 1 developed a sudden severe headache accompanied by vomiting, and soon lapsed into coma on September 28, 1974. This was 10 days after the second operation was performed on the patient in Case 1. He was admitted to a local hospital in deep coma with nonreactive pupils. Stiffness of the neck and hyperreflexia were noted. His systolic blood pressure was 230. He had a clonic generalized convulsive seizure lasting 20 minutes and died 7 hours after admission. The possibility of ruptured intracranial aneurysms remains unexplored due to lack of postmortem examination.

Case 5. The 37-year-old younger sister of the patient in Case 1 had a 3-year history of hypertension. She suddenly fell, became comatose, and died 5 minutes later on May 18, 1970. A postmortem examination was not performed, so that the possibility of a ruptured intracranial aneurysm causing the cerebral hemorrhage could not be explored.

Elective Investigation of Siblings

After the sudden death of four family members and the successful surgical treat-
Fig. 3. Case 6. **Upper**: Left carotid angiogram, lateral (left) and oblique views (right), showing an aneurysm at the trifurcation of the middle cerebral artery. **Lower Left**: Right carotid angiogram showing infundibular dilatation of the posterior communicating artery.

**TABLE 1**
*Intracranial aneurysms and cerebral vascular anomalies in this series*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Aneurysm Site</th>
<th>Cerebral Vascular Anomalies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>lt VA-PICA</td>
<td>termination of lt VA in PICA</td>
</tr>
<tr>
<td></td>
<td>rt ICA-PCoA</td>
<td>embryonic origin of lt PCA</td>
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<tr>
<td>1</td>
<td>rt MCA</td>
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<tr>
<td>1</td>
<td>lt MCA</td>
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</tr>
<tr>
<td>2</td>
<td>ACoA</td>
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</tr>
<tr>
<td>3</td>
<td>lt ICA-PCoA</td>
<td>rt infundibular dilatation</td>
</tr>
<tr>
<td>6</td>
<td>lt MCA</td>
<td>termination of rt VA in PICA</td>
</tr>
<tr>
<td></td>
<td>lt ICA-PCoA</td>
<td>embryonic origin of both PCA</td>
</tr>
<tr>
<td>7</td>
<td>rt MCA</td>
<td>duplication of lt SCA</td>
</tr>
<tr>
<td>8</td>
<td>rt ICA-PCoA</td>
<td>termination of rt VA in PICA</td>
</tr>
<tr>
<td>9</td>
<td>rt ICA-PCoA</td>
<td>embryonic origin of rt PCA</td>
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<tr>
<td>10</td>
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<td>rt infundibular dilatation</td>
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<tr>
<td></td>
<td>rt ICA-PCoA</td>
<td>duplication of rt SCA</td>
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</tbody>
</table>

*VA = vertebral artery; PICA = posterior inferior cerebellar artery; ICA-PCoA = internal carotid-posterior communicating artery; MCA = middle cerebral artery; ACoA = anterior communicating artery; PCA = posterior cerebral artery; SCA = superior cerebellar artery.

Elective Angiography

Elective carotid and vertebral angiography was performed on the remaining members of the family. Table 1 lists the aneurysms and cerebral vascular anomalies found in all members of the family who were studied. Two family members who underwent elective angiography were found to be harboring aneurysms.

Case 6. The 47-year-old sister of the patient in Case 1 had a history of hypertension and mild dull headache. Examination revealed a mild hypertension without neurological deficits. Telangiectases were noted on both cheeks, but not elsewhere. She had no history of epistaxis or gastrointestinal bleeding, which are the most common symptoms of patients with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease).
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The routine laboratory data were normal. Left carotid angiography revealed an asymptomatic aneurysm, 2.5 × 3 mm in size, at the trifurcation of the left MCA. Right carotid angiography showed infundibular dilatation of the posterior communicating artery (PCoA) (Fig. 3). A repeat arteriogram was done a year later. There was no evidence of enlargement of the aneurysm.

Case 7. The 33-year-old brother of the patient in Case 1 was first seen on February 27, 1975. Blood pressure was 142/104. No abnormal signs were noted on neurological examination. Skin lesions similar to those in Case 6 were noted on both cheeks. Left carotid angiography disclosed an aneurysm, 3 × 4 mm in size, of the left ICA at the junction of the PCoA (Fig. 4).

In addition, associated anomalies in the cerebrovascular system were also present (Fig. 4). A right retrograde brachial arteriogram revealed anomalous termination of the right vertebral artery in the PICA and the embryonic derivation of the posterior cerebral artery. Left carotid angiogram also showed the embryonic derivation of the left posterior cerebral artery. Left vertebral angiography showed duplication of the left superior cerebellar artery. Repeat angiogram after a year showed the aneurysm unchanged in size.

Chromosomal Study

Banding analysis of chromosomes in three siblings with aneurysms and three siblings without aneurysms revealed no abnormalities in chromosome number or in chromosome structure. C-band analysis of the chromo-
some No. 9 showed three types of centromeric heterochromatin in this family.

Discussion

Review of the literature revealed 46 other families in which more than one member had a proven intracranial aneurysm. Two members were reported affected in 38 families, and more than two members in five families. There is a significant tendency for the onset of symptoms at a younger age in familial cases, with peak incidence in the 30 to 39 year range, compared with non-familial cases, in which peak incidence is seen between 50 and 59 years.

Site distribution of familial aneurysms is given in Fig. 5. The incidence of aneurysms of the ICA (50%) and of the MCA (25.4%) tend to be higher in familial cases, while ACoA aneurysms show a lower incidence (15.8%) (Table 2). No significant difference was noted for the incidence of multiple aneurysms between familial and non-familial cases. It has been reported by several authors that the incidence of anomalies of the circle of Willis is increased in intracranial aneurysm. The incidence of the embryonic origin of the posterior cerebral artery is increased in ICA-PCoA aneurysms. Chambers, et al., described a family in which a member with an ACoA aneurysm had "an anomalous artery, a posterior cerebral branch arising from the internal carotid artery itself." They suggested that the presence of a second anomaly (embryonic origin of the posterior cerebral artery) would tend to support the congenital theory of aneurysm formation.

In our cases four types of anomalies in the cerebrovascular system were confirmed to be present (Table 1): 1) anomalous termination of the vertebral artery in the PICA in four members; 2) embryonic origin of the posterior cerebral artery in eight; 3) infundibular dilatation of the PCoA in three; and 4) duplication of the superior cerebral artery in two.

Krayenbühl and Yaşargil, in reviewing the vertebral angiograms, indicated that the incidence of the anomalous termination of the vertebral artery in the PICA is 0.2%. However, in 1928, Adachi and Hasebe noted this anomaly in eight (9.6%) of 83 autopsied cases. Blackburn observed a 2.3% incidence of this anomaly. The 67% incidence of this anomaly in our cases is significantly high compared with these statistics. In their report on a series of 350 autopsies, Alpers and Berry stated that the posterior cerebral artery preserved its embryonic origin from the ICA in 15% of circles of Willis. Adachi and Hasebe found an embryonic origin of the posterior cerebral artery in 18.1% of their 83 autopsied cases. These statistics are significantly below the incidence in our cases (67%).

Edelsohn, et al., reported a family in which five members had aneurysms and five members had infundibular dilatation. The 50% incidence of infundibular dilatation in our cases is quite high compared with the statistics (6.6%) presented by Saltzman. It is surprising that all members of our family who either had aneurysms or died from cerebral hemorrhage were noted to have telangiectases on both cheeks. The association of these
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relatively rare vascular anomalies strengthens the possibility of hereditary factors in the pathogenesis of intracranial aneurysms. Hypertension has been considered as a size-augmenting factor in the development of sacular aneurysms. The results of the Cooperative Study indicate that 41% of 200 cases of unruptured aneurysms had some degree of hypertension, defined as a systolic blood pressure of greater than 160 mm Hg. This statistic is in accordance with that of familial cases (39.7% of 48 familial cases in which blood pressure observations have been recorded). Three of our five patients with aneurysms are hypertensive.

Beumont, in discussing the pattern of familial aggregation of aneurysms, suggested a simple dominant inheritance. Kak, et al. supported the hypothesis of dominant transmission because of the absence of consanguinity in their familial cases. Bannerman, et al. believed that the pattern of polygenic or multifactorial inheritance might provide the best explanation in some instances. Although no firm conclusion can be reached about the patterns of inheritance, it is suggested from our family data that an autosomal recessive pattern remains a possibility, but an autosomal dominant inheritance seems more likely. Continued study on the children of these siblings would be helpful to reach any conclusion. Three cases of congenital deaf-mutism from the consanguineous marriage are shown in the family chart (Fig. 1). This disorder has been known to be inherited as a simple autosomal recessive in many instances.

There is still a dispute as to whether a relative of a patient with an intracranial aneurysm carries an increased risk of having an asymptomatic aneurysm. Pratt, reviewing the statistics presented by Krayenbühl and Yaşargil and Chakravorty and Gleadhill, stated that “these figures scarcely represented an increased risk to a relative.” McKusick mentioned that there was “at most only a very modest tendency to familial aggregation” and maintained that “particular concern for other members of the family is not warranted.” However, Graf and Kak, et al. indicated that the actual incidence of familial aneurysms was likely to be higher than was hitherto reported.

Edelsohn, et al. first described familial aneurysms in which an asymptomatic aneurysm was found by elective angiography. The author performed elective angiography on five asymptomatic members, and as a result two asymptomatic aneurysms were visualized. These results tend to indicate the increased risk in other members of having asymptomatic aneurysms where there are already two or more people affected in a family.

Crompton suggested from his data on autopsied cases of 289 ruptured aneurysms and 150 unruptured aneurysms that the critical size beyond which aneurysms became unstable and were likely to rupture was an external diameter of 4 mm. However, according to the Cooperative Study, a critical size for ICA-PcoA and ACoA aneurysms is 7 mm, while MCA aneurysms have a smaller critical size.

Moyes reported that eight (27.6%) of 29 patients with untreated aneurysms showed evidence of enlargement or recurrent hemorrhage or both. Mount and Brisman followed 33 patients with at least one asymptomatic aneurysm for 4½ years, and reported enlargement of asymptomatic aneurysms in two cases and subarachnoid hemorrhage in three.

Surgical treatment of multiple intracranial aneurysms has been well documented, but little has been written about incidentally discovered single aneurysms. In 1971, Moyes described surgical treatment of five patients with aneurysms discovered incidentally; there was no death nor significant morbidity. Recently, Jain reported 15 cases of “intact” intracranial aneurysm; 12 of these patients were treated surgically without any operative mortality or morbidity. He recommended that most intact intracranial aneurysms should be treated surgically. In view of these good results, prophylactic surgery on asymptomatic aneurysms in familial cases should be considered when or before these aneurysms reach the critical size.

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References

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