Familial Association of Intracranial Aneurysms and Cervical Artery Dissections

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Background and Purpose: The familial occurrence of intracranial aneurysms and cervical artery dissections has been described in different families and supports the hypothesis that a primary arteriopathy may play a role in the pathogenesis of these disorders. Although the basis for this arteriopathy is generally not believed to be similar among cases of intracranial aneurysms and cervical artery dissections, several similarities exist in the epidemiology of these disorders and a common underlying arterial abnormality may be suspected.

Summary of Reports: The medical records of all 175 patients with spontaneous dissections of the cervical arteries who were seen at the Mayo Clinic between 1970 and 1989 were reviewed to identify families in which intracranial aneurysms and cervical dissections coexisted. Three families were identified in which intracranial aneurysms and cervical artery dissections were observed among siblings. These families are described in detail.

Conclusions: The familial occurrence of intracranial aneurysms and cervical artery dissections within the same families provides support to the importance of a common underlying arteriopathy in the pathogenesis of both these disorders. The underlying vascular defect may, at least in some cases, be inherited. (Stroke 1991;22:1426–1430)

Saccular intracranial aneurysms are relatively common acquired lesions of the circle of Willis, with a prevalence of 2.5–5% in autopsy studies. Symptomatic intracranial aneurysms are less frequently diagnosed, and the annual incidence of aneurysmal subarachnoid hemorrhage is approximately 10–20 per 100,000 population.

Spontaneous cervical artery dissections are encountered less commonly than intracranial aneurysms but are regularly recognized as a cause of ischemic cerebrovascular disease in young and middle-aged patients.

A primary structural defect of the arterial wall may be operative in the pathogenesis of both these vascular disorders. The basis for this arteriopathy usually remains elusive and is generally not believed to be similar among cases of intracranial aneurysms and cervical artery dissection. We describe three families in which intracranial aneurysms and cervical artery dissection were observed among siblings.

Case Reports

Family A

The pedigree of Family A is depicted in Figure 1 (left upper panel).

Subject II-5. This 46-year-old woman, the proposita, with a lifelong history of complicated migraine, developed dysphasia, right facial weakness, and right hand clumsiness. There was no history of trauma, and the character of her headaches had not changed appreciably. Head computed tomography (CT) was negative. An angiogram demonstrated a dissection of the left internal carotid artery from just distal to its origin to just proximal to its entry into the carotid canal and a fusiform area of dilatation of the mid-cervical right internal carotid artery consistent with an old healed dissection. She received anticoagulants. Her symptoms resolved over the next several days except for some residual right hand dysfunction that lasted for several months. Repeat angiography 14 months later showed the dissections to have resolved with minimal residual irregularity of the right carotid artery. Both cervical internal carotid arteries were found to be moderately elongated and tortuous. Her warfarin was discontinued.

Subject II-2. This 52-year-old man with a history of common migraine experienced a sudden severe headache, vomited, and lost consciousness. He was taken to a local hospital and was found to be...
comatose. Head CT demonstrated subarachnoid and intraventricular hemorrhage. An angiogram showed a small anterior communicating artery aneurysm. He died shortly thereafter. No autopsy was performed.

Subject II-3. This 43-year-old woman with a history of migraine headaches developed an atypical headache that she described as the most severe that she had had in many years. Several days later she was found unconscious. On examination elsewhere she was comatose, and bilateral fundal hemorrhages were present. Head CT showed a massive subarachnoid hemorrhage with midline shift and herniation. She died shortly thereafter. An autopsy was not performed.

Family B

The pedigree of Family B is depicted in Figure 1 (left lower panel).

Subject II-2. This 48-year-old man, the propositus, developed a left-sided hemiparesis and right-sided pulsatile tinnitus 2 weeks after the onset of a severe right frontotemporal headache. On examination there was left ptosis, mild left hemiparesis, dysarthria, and weakness of the left side of the tongue. Angiography revealed a dissection of the right cervical internal carotid artery and a subcranial dissecting aneurysm of the left internal carotid artery. Anticoagulant therapy was begun, and the patient gradually improved. Six months later there was mild residual left hemiparesis. Repeat angiography showed complete resolution of the right carotid artery dissection, but the left subcranial carotid artery aneurysm had persisted. Anticoagulant therapy was discontinued, and he has had no further cerebral ischemic events.

Subject II-1. This 37-year-old man developed a severe headache and lost consciousness while straining at stool. Three weeks earlier, while hunting, he had suffered a sudden excruciating headache. On examination at another institution, meningeal irritation was noted and subarachnoid hemorrhage was diagnosed by lumbar puncture. An angiogram revealed an irregular saccular aneurysm measuring 14 mm in diameter arising from the suprachinoid portion of the right internal carotid artery and a 6-mm saccular right middle cerebral artery aneurysm. Both aneurysms were clipped, and the patient recovered well from the surgery.

Family C

The pedigree of Family C is depicted in Figure 1 (right upper panel).

Subject II-4. This 46-year-old woman, the proposita, developed left facial pain and left pulsatile tinnitus several days after she hit the vertex of her head against a towel rack. Neurological examination was unremarkable. An angiogram showed an irregularly tapered stenosis of the left cervical internal carotid artery consistent with dissection. The facial pain and tinnitus gradually resolved, but she developed occipital pain and left-sided torticollis 1 year after the incident. She was treated with diazepam, analgesics, and nerve blocks with variable success. Three years after the incident her torticollis began to improve, and it had virtually resolved during the ensuing 4 years.

Subject II-1. This 50-year-old woman presented elsewhere with a 3-year history of episodes of vertigo and loss of consciousness and recent onset of numbness of her right face and upper extremity. Neurological examination was unremarkable except for hyperesthesia on the entire right side and increased deep tendon reflexes on the right. A radioisotope brain scan was essentially normal. Angiography demonstrated an 8×6-mm aneurysm arising from the immediate supraclinoid segment of the left internal carotid artery. The patient refused surgical interven-
tion, and her symptoms gradually resolved. She has remained in good health during 20 years of follow-up.

There was no known consanguinity in the three families, and none of the family members exhibited any obvious clinical features of a generalized connective tissue disorder.

Discussion

The three presently described patients with carotid dissection constitute 1.7% of all 175 patients seen in our institution with spontaneous cervical artery dissection between 1970 and 1989. Five additional patients with cervical artery dissections gave a history of first-degree relatives who had suffered a subarachnoid or “cerebral” hemorrhage at an early age (before age 45 years), but the underlying pathology could not be ascertained.

The pathogenesis of intracranial aneurysms is complex but likely involves both an underlying arterial structural defect in the tunica media or internal elastic lamina and hemodynamic and degenerative factors primarily affecting the internal elastic lamina. Similarly, the pathogenesis of cervical artery dissection is generally believed to involve mechanical factors and an underlying arteriopathy. A genetic predisposition to such a structural weakness of the arterial wall with subsequent intracranial aneurysm formation or cervical artery dissection is mainly supported by the familial occurrence of these arterial disorders and their association with certain inherited connective tissue diseases. The occurrence of intracranial aneurysms within families and among twins has repeatedly been reported.10-13 One recent study concluded that 7% of all intracranial aneurysms may be familial.11 The familial occurrence of spontaneous extracranial carotid artery dissection has been described in two families seen in our institution.14

Ehlers-Danlos syndrome type IV and Marfan’s syndrome are heritable connective tissue diseases associated with intracranial aneurysms as well as cervical artery dissection.15-22 The underlying defect of Ehlers-Danlos syndrome type IV is an abnormality of collagen type III.23 This type of collagen is an important component of distensible tissues that makes up about 40% of arterial walls.24 The underlying defect in Marfan’s syndrome is probably an abnormality of fibrillin, a component of the microfibrillar system.25,26

Collagen type III abnormalities have been reported to be detectable by biochemical analyses in up to 40-50% of otherwise normal patients with ruptured saccular intracranial aneurysms.27,28 Conversely, using similar biochemical techniques, normal collagen type III studies are to be expected in at least half of patients with saccular intracranial aneurysms.27-30 Abnormalities of other components of the extracellular matrix or more subtle collagen type III defects may also be related to a primary arteriopathy underlying the development of saccular intracranial aneurysms.

Collagen type III defects have been suggested to play a role in the pathogenesis of spontaneous cervical artery dissection, although this has not been systematically investigated.19 Collagen type III is one of several constituents of reticular fibers.21 Morphological abnormalities of reticular fibers have been repeatedly observed in cerebral arteries of patients who suffered lethal aneurysmal subarachnoid hemorrhage.32-35 Similar reticular fiber changes have been detected in patients with intracranial dissecting aneurysms36 but, to our knowledge, such changes have not been reported in patients with spontaneous cervical artery dissection.

Fibromuscular dysplasia is a generalized arterial disease of unknown etiology that is associated with both saccular intracranial aneurysms and cervical artery dissection.6,7,37-40 A genetic factor may play a role in the pathogenesis of fibromuscular dysplasia as evidenced by the familial occurrence of the disease in37-40 and its association with human lymphocyte antigen (HLA) DRw6.40 No HLA haplotype is consistently found in an increased frequency in cases of saccular intracranial aneurysms49,45 and, to our knowledge, HLA frequency studies have not been performed in groups of patients with cervical artery dissection.

Several similarities exist in the epidemiology of ruptured intracranial aneurysms and dissection of the cervical arteries. A preponderance of female patients and an average age of affected individuals in the fifth or sixth decade of life is seen in both disorders.7,9,46,47 In contrast to the incidence of aneurysmal subarachnoid hemorrhage, which has been shown to increase with age,34 spontaneous cervical artery dissection is infrequently diagnosed in patients older than 65 years of age. However, angiographic examination is not commonly performed in patients in this age group who present with ischemic cerebrovascular disease, and true incidence figures for cervical artery dissections are not available. In addition, concomitant atherosclerotic changes in the elderly patient may obscure the angiographic detection of arterial dissection. It is likely that spontaneous cervical artery dissection is significantly underdiagnosed in the elderly, although probably not to the extent that the incidence of dissection would show a consistent increase with age, as is the case in aneurysmal subarachnoid hemorrhage.

Precipitating events are regularly noted in both aneurysmal subarachnoid hemorrhage48 and cervical artery dissection.6,49 These events are usually related to hemodynamic and intracranial pressure changes in aneurysmal rupture and to mechanical factors resulting in compression or stretching of the artery in dissection.

Although their significance in the pathogenesis of these disorders is uncertain, reported risk factors for both cervical artery dissection and aneurysmal subarachnoid hemorrhage include arterial hypertension, cigarette smoking, and oral contraceptive use.6,7,30-35 Migraine has been reported to occur in up to 40% of
patients with cervical artery dissection, although this has been less frequent in our experience (approximately 12%). In the first reported family there was a strong familial history of migraine, and the patient with cervical artery dissection as well as her siblings with subarachnoid hemorrhage had suffered from migraine headaches for many years.

Although the occurrence of cervical artery dissection and saccular intracranial aneurysms in the same individual is not particularly common, in a recent study from our institution saccular intracranial aneurysms were detected angiographically in 5.5% of patients with cervical artery dissection compared with 1% in those without dissection.

The pathogenesis of intracranial aneurysms and cervical artery dissection is complex and incompletely understood. The occurrence of both intracranial aneurysms and dissection of the cervical arteries in the same families provides support to the importance of a common underlying primary arteriopathy in the development of these vascular disorders. The underlying vascular defect may, at least in some cases, be inherited. However, if a common underlying arteriopathy does exist in these conditions, the subsequent pathophysiological steps leading to saccular aneurysm formation on the one hand and cervical artery dissection on the other may be quite divergent.

Note added in proof. Following the submission of this manuscript, a fourth family was identified in which cervical artery dissection, aneurysmal subarachnoid hemorrhage, and sudden death at an early age were observed among first-degree relatives.

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