Clinicopathological Study of Intracranial Fusiform and Dolichoectatic Aneurysms
Insight on the Mechanism of Growth

Hirofumi Nakatomi, MD; Hiromu Segawa, MD; Atsushi Kurata, MD; Yoshiaki Shiokawa, MD; Kazuya Nagata, MD; Hiroyasu Kamiiyama, MD; Keisuke Ueki, MD; Takaaki Kirino, MD

Background and Purpose—Intracranial fusiform aneurysms can be divided into 2 clinically different subtypes: acute dissecting aneurysms and chronic fusiform or dolichoectatic aneurysms. Of these 2, the natural history and growth mechanism of chronic fusiform aneurysms remains unknown.

Methods—A consecutive series of 16 patients with chronic fusiform aneurysms was studied retrospectively to clarify patient clinical and neuroradiological features. Aneurysm tissues were obtained from 8 cases and were examined to identify histological features that could correspond to the radiological findings.

Results—Four histological features were found: (1) fragmentation of internal elastic lamina (IEL), (2) neoangiogenesis within the thickened intima, (3) intramural hemorrhage (IMH) and thrombus formation, and (4) repetitive intramural hemorrhages from the newly formed vessels within thrombus. IEL fragmentation was found in all cases, which suggests that this change may be one of the earliest processes of aneurysm formation. MRI or CT detected IMH, and marked contrast enhancement of the inside of the aneurysm wall (CEI) on MRI corresponded well with intimal thickening. Eight of 9 symptomatic cases but none of 7 asymptomatic cases presented with both radiological features.

Conclusions—Data suggest that chronic fusiform aneurysms are progressive lesions that start with IEL fragmentation. Formation of IMH seems to be a critical event necessary for lesions to become symptomatic and progress, and this can be monitored on MRI. Knowledge of this possible mechanism of progression and corresponding MRI characteristics could help determine timing of surgical intervention. (Stroke. 2000;31:896-900.)

Key Words: aneurysm, dolichoectatic, fusiform, giant, growth substances

Fusiform cerebral aneurysms are relatively uncommon lesions compared with saccular cerebral aneurysms1–5 and can be divided into 2 clinical subcategories on the basis of their clinical course. One type is acute dissecting aneurysm, which usually causes subarachnoid hemorrhage (SAH) or cerebral ischemia and more frequently involves the vertebrobasilar circulation. The primary cause of this lesion is considered to be an acute disruption of the internal elastic lamina (IEL), which leads to intramural hemorrhage (IMH), with or without luminal connection.6,7 The natural course of acute dissecting aneurysms has been documented fairly well.8,9 Another subcategory, chronic fusiform aneurysms, show relatively slow growth but may lead to serious complications as they progress. Several studies have indicated that these aneurysms might form a spectrum of vascular abnormalities that ranges from small, asymptomatic fusiform aneurysms to symptomatic, giant so-called dolichoectatic aneurysms.3–5 However, mechanisms of progression within this spectrum remain unclear. The present study presents a detailed analysis of 16 consecutive cases of chronic fusiform aneurysms that includes 8 cases from which we obtained aneurysm tissues at surgery or autopsy. To gain insight into how these lesions progress and become symptomatic, we performed a comparative analysis of serial imaging studies and histological findings.

Subjects and Methods
From April 1983 to December 1998, we treated 16 patients with chronic fusiform aneurysms. Imaging studies on all cases included cerebral angiography, CT scan, and MRI. All cases had 2 features on cerebral angiography that we chose as criteria for chronic fusiform aneurysms: (1) fusiform arterial ectasia at a nonbranching site of the intracranial cerebral arteries and (2) no obvious atherosclerotic changes found in other intracranial arteries. Dissecting aneurysms that showed typical “pearl–and-string” sign or clear double lumen on cerebral angiography were excluded; we saw 52 such typical dissecting aneurysms during the study period.

Medical records, including all imaging studies, were reviewed. Follow-up MRI was obtained at least every 12 months in all cases except for in 1 patient who died at an acute stage. As previously
Aneurysm tissues were obtained during surgery in 2 cases and by autopsy in 6. For histological examination, tissues were fixed in 10% formalin and embedded in paraffin. Tissue sections (4 μm each) were made and stained with hematoxylin and eosin, elastica–van Gieson, and Masson’s trichrome stains. For immunohistochemistry, a polyclonal antibody for factor VIII–related antigen (Dako Corp) was used as a primary antibody at 1:1500 dilution, and the Elite ABC kit (Vecstein Laboratory) with nickel enhancement was used for coloring reaction; manufacturer’s protocols were followed. Degree of intimal hyperplasia or of recanalizing vessel formation in the thrombus was evaluated on axial sections and was rated on the basis of the ratio of the area occupied by these vessel lumen relative to the whole circumference of the vessel: none, <15%; slight, 15% to 30%; moderate, 30% to 50%; and severe, >50%. Degree of neoangiogenic vessel formation within the hyperplastic intima or of recanalizing vessel formation in the thrombus was evaluated on axial sections and was rated on the basis of the ratio of the area occupied by these vessel lumen relative to the whole area of the aneurysm wall: none, <15%; slight, 15% to 30%; moderate, 30% to 50%; and severe, >50%. Degree of IMH and luminal thrombus formation were also assessed on axial sections and were rated on the basis of the ratio of the area occupied by the hemorrhage or thrombus to the whole area of the aneurysm: none, <15%; slight, 15% to 30%; moderate, 30% to 50%; and severe, >50%. Degree of intimal hyperplasia was rated as the ratio of intimal thickness to the whole wall thickness: none, <15%; slight, 15% to 30%; moderate, 30% to 50%; and severe, >50%.

**Results**

**Clinical Manifestations**

Age of the 16 patients ranged from 42 to 65 years (median, 53.7 years). The study group included 8 men and 8 women. Follow-up periods ranged from 12 days to 16 years (median, 4 years). Aneurysms were located in the anterior circulation in 10 cases: internal carotid artery (ICA) in 5 and middle cerebral artery (MCA) in 5. Posterior circulation was affected in 6 cases: basilar artery in 2, vertebral artery in 2, posterior communicating artery in 1, and anterior inferior cerebellar artery in 1. Nine cases were symptomatic, with initial manifestations caused by ischemic strokes in 2, hemorrhagic stroke in 1, and compression of surrounding neural structures in 6 (progressive ophthalmoplegia in 1, dysarthria in 1, progressive hemi-paresis in 3, and progressive dizziness in 1). All the ischemic strokes were probably from occlusion of perforating arteries that arose from the aneurysm. The remaining 7 cases were found incidentally on MRI obtained for reasons unrelated to aneurysm.

**Management and Outcomes**

Of the 9 symptomatic patients, 3 underwent proximal occlusion of the parent artery (2 of these 3 in combination with high-flow bypass with a radial artery graft). All 3 patients recovered uneventfully from surgery. One patient had bypass surgery distal to the aneurysm, but the aneurysm progressed and eventually caused visual loss due to compression of the optic nerve. Clip reconstruction was attempted in 1 case, but the patient developed cerebellomedullary infarction after surgery and died. Four patients were followed without surgical treatment. Of those, 2 eventually suffered an aneurysm rupture and died (cases 14 and 16), 1 died of ischemic heart disease, and the remaining patient had deterioration of brain stem function because of mass effect by the aneurysm.

All 7 asymptomatic cases were initially followed conservatively. Two of these died of nonneurological causes: aortic dissection in 1 and panperitonitis in the other. Two patients underwent clip reconstruction 6 and 12 months after diagnosis, at each patient’s request for surgical treatment. No surgical complications occurred.

**MRI Findings**

IMH was observed at initial examination in 8 of 9 symptomatic cases. CEI was found in all cases (Figures 1B and 1D). On serial MRIs, these symptomatic aneurysms showed gradual enlargement in all cases with IMH. On the other hand, 6 of 7 asymptomatic aneurysms showed neither IMH nor CEI at initial examination and did not show enlargement on serial examinations. However, in 1 case, CEI already was evident at initial MRI (Figure 1B). Notably, all 8 aneurysms with IMH were >20 mm in diameter, and all 10 aneurysms with CEI were >12 mm in diameter. We did not notice any difference in degree of tortuosity or irregularity of unaffected arteries of studied patients compared with those of the general population in a similar age range. A summary of the MRI findings is presented in the Table 1.

**Histological Examination of Aneurysms**

Four characteristic features were noticed: (1) IEL fragmentation and intimal hyperplasia; (2) neoangiogenesis in the thickened intima; (3) IMH and luminal thrombosis; and (4) recanalizing vessel formation in the thrombus. Fragmentation of the IEL and intimal hyperplasia were found in all cases, but extent of IEL fragmentation was more prominent in larger or symptomatic aneurysms (Figures 1E through –1H). In addition, degeneration of the media was also noticed universally. Neoangiogenic vessel formation within the thickened intima was observed in 5 of 8 cases (Figures 1F and 2C) and 4 of them accompanied IMH (Figures 1G, 1H, and 2A). Immunohistochemistry for factor VIII–related antigen strongly immunolabeled the endothelial cells of the neoangiogenic vessels, which confirmed the vascular origin of these structures. IMH consisted of fresh IMHs around the neoangiogenic vessels and generally coexisted with old, laminated thrombus. Old thrombus constituted the largest portion of the aneurysms in most cases and occasionally contained recanalizing vessels (Figure 1G, 1H, 2B, and 2D).

When the MRI features of the 8 cases were compared with histological findings, CEI was associated with existence of neoangiogenic vessels within the thickened intima: all 5 cases with intimal neoangiogenesis but none of the 3 cases without neoangiogenesis showed CEI on MRI. MRI detected IMH in all 3 cases with histologically confirmed IMH. Similar to the relationship between MRI findings and size of the aneurysm, good correlation existed between the histological features and the size of the aneurysms: IMH was seen exclusively in aneurysms >28 mm in diameter, and neoangiogenesis was seen exclusively in aneurysms >12 mm in diameter. Results of the histological examination are also summarized in the Table.

**Discussion**

Data given in the present article demonstrate characteristic histological features of chronic fusiform aneurysms, and these histological findings are closely associated with size of
Figure 1. Neuroradiological imagings of representative cases (A through D) with corresponding histology (E through H). Case 3 (A and E), (A) Cerebral angiogram demonstrates relatively small right MCA fusiform aneurysm (8 mm diameter). E, Histology (by van Gieson stain) shows fragmentation of IEL (*) and intimal thickening but no neoangiogenesis. Case 7 (B and F), (B) T1-weighted MRI enhanced on coronal view shows 12-mm fusiform aneurysm of left IC. Marked enhancement of aneurysm wall (arrowhead) is present, but no IMH is seen. F, Histology (van Gieson) reveals IEL fragmentation (*) and intimal thickening accompanied by moderate degree of recanalizing vessel formation (arrowheads). Case 11 (C and G), (C) Nonenhanced T1-weighted MRI shows axial section of 28-mm dolichoectatic aneurysm of right vertebral artery with IMH (arrow). G, Histology (van Gieson) of resected aneurysm reveals marked IEL fragmentation and degeneration (*) and intimal thickening (small arrow) that contains thrombus from old and fresh IMH (large arrow). Case 14 (D and H), (D) T1-weighted MRI without (left) and with (right) gadolinium injection demonstrates advanced-stage dolichoectatic aneurysm of basilar artery, 32-mm diameter. IMH shows slightly high intensity with patchy, laminated enhancement (arrowheads), whereas an area around the recent IMH is markedly enhanced, which indicates neovascularization (arrowheads). H, Histology of aneurysm at autopsy after fatal rupture shows multiple dissection within thickened intima and severely fragmented IEL (*) as well as formation of vasa vaso-rum within the adventitia (van Gieson). All bars indicate 400 μm.
the aneurysm. Universal histological features were fragmentation of IEL and intimal hyperplasia. Therefore, these 2 changes are probably among the earliest processes of chronic fusiform aneurysm formation. Neoangiogenesis within hyperplastic intima was the next most common finding, which corresponded well to CEI observed on MRI. Notably, this plastic intima was the next most common finding, which may correspond well to CEI observed on MRI. Notably, this plastic intima was the next most common finding, which probably among the earliest processes of chronic fusiform aneurysm formation.

Some of the histological features described in our series are similar to atherosclerotic changes, but our observations indicate the causes of fusiform aneurysm may be different from those of atherosclerosis. Recanalizing vessels in a thickened intima, which occasionally cause bleeding, are also found in atherosclerotic arteries at an advanced stage. Disruption or fragmentation of the IEL is found also in atherosclerosis, but not at an early stage of the disease. In atherosclerosis, early changes include intimal cell proliferation around lipid deposits and duplication or thinning of IEL, neither of which was observed in our cases. Therefore, the most prominent difference between atherosclerosis and fusiform aneurysms seems to be at the initial step of the disease: lipid deposition in atherosclerosis and IEL fragmentation in fusiform aneurysms. Therefore, it is likely that the primary abnormality in fusiform aneurysms could lie in the IEL. In support of this notion, 2 of the present cases were similar to those of patients with Ehlers-Danlos syndrome, a systemic disease related to an abnormality in collagen, which is a key component of the IEL.

Data presented in the present study suggest a possible mechanism for progression of chronic fusiform aneurysms, a stepwise progression: (1) The earliest detectable change seems to be IEL fragmentation, almost immediately followed by intimal hyperplasia, possibly as a normal reaction to the damage. (2) When intimal thickening reaches a certain level, neovascularization within the thickened intima occurs. (3) New vessels within the intima then

---

**Clinical Summary of 16 Patients With Fusiform and Dolichoectatic Aneurysms**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y</th>
<th>Sex</th>
<th>Location</th>
<th>Presentation</th>
<th>MRI</th>
<th>Final Aneurysm Maximum Diameter, mm</th>
<th>Histological Findings; CEI and Intimal Hyperplasia</th>
<th>Neoangiogenesis in Thickened Intima</th>
<th>Mural Hemorrhage and Luminal Thrombus Formation</th>
<th>Recanalizing Vessel Formation in Thrombus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CEI</td>
<td>IMH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>41</td>
<td>M</td>
<td>Rt AICA</td>
<td>Incidental</td>
<td>(−)</td>
<td>(−) 5</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>F</td>
<td>Rt MCA</td>
<td>Incidental</td>
<td>(−)</td>
<td>(−) 8</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>M</td>
<td>Rt MCA</td>
<td>Incidental</td>
<td>(−)</td>
<td>(−) 8</td>
<td>(+)</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>4*</td>
<td>50</td>
<td>F</td>
<td>Rt ICA</td>
<td>Incidental</td>
<td>(−)</td>
<td>(−) 8</td>
<td>(+)</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>5</td>
<td>53</td>
<td>F</td>
<td>Lt ICA</td>
<td>Incidental</td>
<td>(−)</td>
<td>(−) 10</td>
<td>(+)</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>6*</td>
<td>67</td>
<td>M</td>
<td>Rt ICA</td>
<td>Incidental</td>
<td>(−)</td>
<td>(−) 12</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>7†</td>
<td>61</td>
<td>M</td>
<td>Lt ICA-MCA</td>
<td>Incidental</td>
<td>(+)</td>
<td>(−) 12</td>
<td>(+)</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>Symptomatic group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>57</td>
<td>M</td>
<td>VBJ</td>
<td>Dysarthria</td>
<td>(+)</td>
<td>(−) 12</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>9</td>
<td>49</td>
<td>F</td>
<td>Rt VA</td>
<td>Progressive dizziness</td>
<td>(+)</td>
<td>(+) 20†</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>10</td>
<td>45</td>
<td>F</td>
<td>Lt Pcom</td>
<td>Stroke</td>
<td>(+)</td>
<td>(+) 25†</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>11†</td>
<td>61</td>
<td>M</td>
<td>Lt VA</td>
<td>Progressive rt hemiparesis</td>
<td>(+)</td>
<td>(+) 28‡</td>
<td>(++)</td>
<td>(+)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>12</td>
<td>42</td>
<td>F</td>
<td>Lt ICA</td>
<td>Progressive ophthalmoplegia</td>
<td>(+)</td>
<td>(+) 25‡</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>13</td>
<td>64</td>
<td>F</td>
<td>Rt MCA</td>
<td>Progressive left hemiparesis</td>
<td>(+)</td>
<td>(+) 28‡</td>
<td>(++)</td>
<td>(+)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>14</td>
<td>64</td>
<td>M</td>
<td>BA</td>
<td>Stroke</td>
<td>(+)</td>
<td>(+) 32‡</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>15</td>
<td>58</td>
<td>M</td>
<td>Lt MCA</td>
<td>Hemorrhagic stroke</td>
<td>(+)</td>
<td>(+) 70‡</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>16</td>
<td>65</td>
<td>F</td>
<td>Rt MCA</td>
<td>Progressive right hemiparesis</td>
<td>(+)</td>
<td>(+) 70‡</td>
<td>(++)</td>
<td>(−)</td>
<td>(−)</td>
<td>(−)</td>
</tr>
</tbody>
</table>

---

**Notes:**
- Rt or rt indicates right; AICA, anterior inferior cerebellar artery; (−), none; (+), moderate; Lt, left; (++) severe; VBJ, vertebrobasilar junction; VA, vertebral artery; Pcom, posterior communicating artery; BA, basilar artery.
- *Positive history of hypertension.
- †Previously diagnosed Ehlers-Danlos patients.
- ‡Aneurysm growth in each patient during follow-up period.
- Data presented in the present study suggest a possible mechanism for progression of chronic fusiform aneurysms, a stepwise progression: (1) The earliest detectable change seems to be IEL fragmentation, almost immediately followed by intimal hyperplasia, possibly as a normal reaction to the damage. (2) When intimal thickening reaches a certain level, neovascularization within the thickened intima occurs. (3) New vessels within the intima then
cause bleeding and IMH. (4) Repeated recanalization of thrombus and further bleeding from those vessels lead to rapid growth. Among those steps, IMH seems to be the most critical event, because it apparently forces the aneurysms to progress and, in most cases, become fatal. Although further studies are needed to confirm this hypothesis, knowledge of this possible mechanism of progression and of corresponding MRI characteristics could help to determine the timing of surgical intervention. Specifically, a surgical intervention to decrease the risk of IMH should be considered when CEI is detected on MRI, because this probably indicates neovascularization in thickened intima, which could herald IMH and rapid aneurysm growth. Once IMH occurs, further progression seems to be inevitable. In our series, 6 cases were treated surgically: 3 underwent parent artery occlusion and 3 had clip reconstruction of the parent artery. The aneurysms disappeared in all 6 cases, and no recurrences have been observed. In contrast, 4 patients with IMH who were observed without surgical intervention or with only a distal bypass showed aneurysm growth without exception. Therefore, appropriate surgical procedures should help patients by preventing progression of the aneurysms.

With wider availability of high-resolution MRI, we are now able to diagnose various previously undetectable vascular lesions and are likely to encounter more cases of asymptomatic fusiform aneurysms. The data and hypothesis presented in the present article could be helpful for establishment of management policy for such lesions. These data also indicate the need for further studies to establish the natural course of chronic fusiform aneurysms.

References
Clinicopathological Study of Intracranial Fusiform and Dolichoectatic Aneurysms: Insight on the Mechanism of Growth
Hirofumi Nakatomi, Hiromu Segawa, Atsushi Kurata, Yoshiaki Shiokawa, Kazuya Nagata, Hiroyasu Kamiyama, Keisuke Ueki and Takaaki Kirino

Stroke. 2000;31:896-900
doi: 10.1161/01.STR.31.4.896

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/31/4/896

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/