Electron Microscopic Studies of Ruptured Arteries in Hypertensive Intracerebral Hemorrhage

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SUMMARY Eleven freshly removed brains and 20 lenticulostriate arteries (collected at emergency surgery for intracerebral hemorrhage) were examined by electron microscopy in a search for the mechanism of arterial rupture in hypertensive intracerebral hemorrhage.

Forty-six of 48 ruptured arteries examined showed severe arteriosclerosis including degenerative changes of the media at or near bifurcations. Atrophy and fragmentation of smooth muscle cells gave them a moth-eaten appearance. Material resembling basement membrane and cell debris was also present in the arterial walls. The above findings were restricted to the middle and distal portions of the perforating arteries. Rupture from a saccular aneurysm was observed in only 2 of the 48 specimens examined. These resembled saccular aneurysms, ultrastructurally. They seemingly formed at a cavity which we strongly felt may have been formed by complete or incomplete subclinical hemorrhages; reabsorption of the hemorrhage from the dissection resulted in the aneurysms seen.

Degeneration of smooth muscle cells may be the result of prolonged tension or spasm of the arterial wall as a result of longstanding hypertension.

LONG-TERM HYPERTENSION enhances intracranial arteriosclerosis and primary intracerebral hemorrhages. How does the progression of arteriosclerosis which induces intimal thickening cause rupture of the arterial wall? This has been an issue of controversy since Charcot’s report in 1868. At present, it is the opinion of the majority that rupture results from a saccular aneurysm (MA) formation secondary to fibrinoid necrosis of the vessel wall. However a few investigators maintain that arterial rupture is due to weakening of the arterial wall by arteriosclerosis.

All the studies in the past were based on the light microscopic examination of paraffin embedded post-mortem specimens without close observation of the ruptured portion. We carried out ultrastructural observations of thin and semi-thin consecutive sections of Epon 812 embedded ruptured arteries obtained from surgical materials collected at emergency surgery for hypertensive intracerebral hemorrhage and from fresh autopsied brains that died of hypertensive intracerebral hemorrhage.

Materials and Methods

Lenticulostriate arteries which appear to be associated with pulsatile hemorrhage or blood clot were examined from patients operated on within 4 hours of their intracerebral bleed. A vessel length of 2 mm was excised from the periphery of the evacuated hematoma and examined. Hemostasis of the remaining portion of the artery was maintained with electrocauclation. The specimens were then immediately fixed with 1.4% isotonic glutaraldehyde in phosphate buffer for 20 minutes. After the fixation, as many specimens as possible of the perforating arteries suspected of rupture were collected from among those pouring into the hemorrhagic site. The lenticulostriate arteries were collected also from the contralateral nonhemorrhagic side. Small temporal cortical branches of the middle cerebral arteries on the hemorrhagic side were also collected as controls.

The collected arteries were observed after Epon 812 embedding. Alternate sections were cut semi-thin and thin. The latter, for electron microscopy, were double-stained with uranyl acetate and lead citrate. Intimal thickening and degeneration of the medial smooth muscle cells were graded 0, 1+, 2+, 3+ and 4+ by assessment of longitudinal semi-thin sections stained with alkaline methylene blue and fuchsin.

Results

Twenty lenticulostriate arteries suspected of rupture were collected from 20 patients at surgery. In 11 out of 20 arterial rupture was identified. Similarly, in 10 of 16 autopsy cases ruptured arteries were found. Each autopsy case disclosed 2 to 11 rupture sites (table 1). In addition, 5 MA’s without rupture were found in 2 cases.

The sex ratio of male to female examined was 16 to 5. The age ranged from 37 to 74 years old. All cases studied had history of hypertension but none had received antihypertensive treatment. All the autopsied cases showed a large hemorrhagic lesion which was the cause of death, and most of the ruptured arteries were of large variety measuring 500–700 μ in diameter. All the ruptured arteries collected from 11 cases at emergency surgery for rather small lateral ganglionic hemorrhages, were smaller measuring less than 300 μ. A positive correlation between the size of the hematoma and the size and number of ruptured arteries was present.

Morphology of Ruptured Arteries

Arterial rupture was found at 11 sites in surgical
TABLE 1  Ruptured Artery and its Size in Each Case

<table>
<thead>
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<th>Age</th>
<th>Sex</th>
<th>Ruptured artery</th>
<th>Size of ruptured artery</th>
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<tr>
<td>37</td>
<td>M</td>
<td>lenticulostriated artery, outer branch</td>
<td>200 μ</td>
</tr>
<tr>
<td>37</td>
<td>M</td>
<td>lenticulostriated artery, outer branch</td>
<td>240</td>
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<tr>
<td>44</td>
<td>M</td>
<td>lenticulostriated artery, outer branch</td>
<td>250</td>
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<td>M</td>
<td>lenticulostriated artery, outer branch</td>
<td>660</td>
</tr>
<tr>
<td>54</td>
<td>F</td>
<td>lenticulostriated artery, outer branch</td>
<td>240</td>
</tr>
<tr>
<td>55</td>
<td>M</td>
<td>lenticulostriated artery, outer branch</td>
<td>160</td>
</tr>
<tr>
<td>55</td>
<td>M</td>
<td>lenticulo striated artery, outer branch</td>
<td>280</td>
</tr>
<tr>
<td>56</td>
<td>F</td>
<td>lenticulo striated artery, outer branch</td>
<td>200</td>
</tr>
<tr>
<td>56</td>
<td>M</td>
<td>lenticulo striated artery, outer branch</td>
<td>240 (MA: 1000* μ)</td>
</tr>
<tr>
<td>57</td>
<td>F</td>
<td>lenticulo striated artery, outer branch</td>
<td>300</td>
</tr>
<tr>
<td>70</td>
<td>M</td>
<td>lenticulo striated artery, outer branch</td>
<td>150</td>
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Autopsied

<table>
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<th>Size of ruptured artery</th>
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<td>37</td>
<td>M</td>
<td>lenticulo striated artery</td>
<td>60~360 μ (8)</td>
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<tr>
<td>41</td>
<td>M</td>
<td>lenticulo striated artery</td>
<td>70~550 (5)</td>
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<tr>
<td>44</td>
<td>M</td>
<td>lenticulo striated artery</td>
<td>80~560 (4)</td>
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<td>45</td>
<td>M</td>
<td>lenticulo striated artery</td>
<td>200~300 (2)</td>
</tr>
<tr>
<td>64</td>
<td>F</td>
<td>thalamoperf. artery</td>
<td>60~240 (4) (MA: 300* μ)</td>
</tr>
<tr>
<td>64</td>
<td>M</td>
<td>lenticulo striated artery</td>
<td>50~400 (3)</td>
</tr>
<tr>
<td>66</td>
<td>F</td>
<td>median artery pons</td>
<td>100~180 (4)</td>
</tr>
<tr>
<td>69</td>
<td>M</td>
<td>lenticulo striated artery</td>
<td>100~700 (4)</td>
</tr>
<tr>
<td>73</td>
<td>M</td>
<td>median artery pons</td>
<td>50~200 (5)</td>
</tr>
<tr>
<td>74</td>
<td>M</td>
<td>thalamoperf. artery</td>
<td>50~250 (11)</td>
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( ) = number of ruptured arteries.
* Diameter of MA.

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materials and at 50 sites in autopsied materials, totaling 61 sites. Of these, rupture from MA was seen at only 2 sites, one each in the surgical and autopsied specimens examined. In the other 59 sites, rupture was at or near bifurcation points (figs. 1 and 2). All the ruptured areas disclosed breakage of the elastic lamina which showed no abnormality electron microscopically (fig. 3). In the arteries with rupture sites, medial degeneration was seen. Intimal thickening measuring 150 μ of various degrees was a common finding in all 11 surgical cases and in the autopsied materials. The medial smooth muscle cells showed irregular atrophy or segmentation with a moth-eaten appearance. The intercellular matrix was widened and replaced by increased amounts of basement membrane-like material as well as granular or vesicular cell debris (fig. 4). The lumen of these arteries was often dilated irrespective of the presence of intimal thickening. In the subendothelium near the rupture sites, neutrophils were sparsely infiltrated. Polymerized fibrin with aggregated platelets covered the surface of some rupture sites (fig. 5).

Some of the ruptured arteries in the autopsied cases

FIGURE 1. Abrupt rupture of a lenticulo striated artery, measuring 720 μ in diameter, at the bifurcation. Arrow indicates severe intimal thickening and medial degeneration, 44 male, autopsied.
FIGURE 2-a. Ruptured artery of a lenticulostriated branch measuring 240 μ in diameter, showing severe intimal thickening and degeneration of media smooth muscle cells. Neutrophils infiltrate in the intima near the ruptured site (↑↑). ↑: original internal elastic lamina, P: Coagulated platelets. 44 y.o., male surgical.

FIGURE 2-b. Ruptured lenticulostriated artery, 660 μ in diameter. An arrow indicates intimal chusion at the bifurcation. 53 y.o., male, surgical.

were nearly normal but they were all small arteries measuring less than 150 μ in diameter (fig. 6). These ruptured arteries without degenerative changes in the media were found only in autopsy cases with large hemorrhages. Secondary rupture was seen in a total of 13 small arteries. Excluding these, there were 36 ruptured arteries in autopsied materials from 10 cases. Of these, 1 case was from MA.

Rupture from MA was also observed in both the surgical and autopsied materials, totalling only 2 cases. The wall of MA at the rupture site was very thin and consisted only of fibrin and mononuclear cells (lymphocytes and macrophages) (fig. 7). The wall of MA was composed of fibrinoid material, insudated plasma proteins, cell debris, lipid particles, lymphocytes, macrophages (some containing lipid), and re-generated endothelial cells partially covering the inner surface (figs. 8 and 9).

Ultrastructural Changes of Lenticulostriate Arteries in Hypertensive Intracerebral Hemorrhage

The lenticulostriate arteries in hypertensive intracerebral hemorrhage showed marked irregular atrophy (moth-eaten appearance) or disappearance of medial smooth muscle cells in the middle and distal portions, i.e. in the basal ganglia of both hemorrhagic and non-hemorrhagic sides (fig. 4). The lenticulostriate arteries in the proximal portion particularly in the portion bifurcating from the middle cerebral artery to the cerebral parenchyma, hardly showed any medial degeneration (fig. 10). In small temporal cortical branches taken as control the media appeared nearly normal. The degeneration of the medial smooth muscle cells in the middle and distal portions of the lenticulostriated arteries showed a closer correlation with long-term hypertension than with aging factors. Lipid deposition of intima (atherosclerotic changes; lipohyalinosis) correlated with aging factors in addition to hypertension. In older patients with intracerebral hemorrhage, even small intracerebral arteries showed progressive atherosclerosis as well as severe medial degeneration.

Complicated pictures of vascular lumen either dilated or stenosed at their branches were also observed in these patients. In the cortical branches used as the control, intimal fibrous thickening gradually advanced with age, but the medial degeneration hardly occurred despite the presence of hypertension and intimal lipid deposition (atherosclerosis) of cortical branches was much milder compared with that in the lenticulostriate arteries (table 2).

Miliary Aneurysm (MA) and Fibrinoid Necrosis

Seven MA’s were found, 2 ruptured and 5 nonruptured. The walls of nonruptured MAs were essentially the same as those of ruptured MAs (fig. 11). In the arterial wall just connected with MA, the subendothelium contained fibrin and plasma insudates and the media demonstrated severe degeneration of smooth muscle cells (fig. 12). Some of the branches of the lenticulostriate arteries with severe atherosclerosis showed slight segmental dilatation with or without disruption of the elastic lamina, and insudation of fibrin in the intima mixed with lipid-laden macrophages (fig. 13).

It may be concluded that a large irregular-shaped MA most likely is a cavity formed by reabsorption of

minimal hemorrhages occurring from rupture of small arteries at bifurcations, and that lipohyalinosis of small arteries is different from MA morphologically.

Discussion

The present study showed that the arteries implicated in primary rupture had arteriosclerosis accompanied by severe degeneration of medial smooth muscle cells and that the arterial rupture occurred at bifurcation sites. Ellis\(^\text{13}\) proposed in 1909 that primary intracerebral hemorrhage is caused by severe atherosclerosis of the brain. Stehbens\(^\text{15}\) and Fisher\(^\text{16}\) also speculated that primary intracerebral hemorrhage is attributed to degenerative or hyalinous changes of intracerebral arteries, but they did not specify whether or not these degenerative changes were the same as atherosclerosis. What they called degenerative or hyalinous changes of the arterial wall was the irregular atrophy (moth-eaten appearance) and disappearance of medial smooth muscle cells that is mentioned above. These changes are not specific to intracerebral arteries having also been observed in arcuate and interlobular arteries of the kidney\(^\text{18}\) and other organ arteries of hypertensive or

FIGURE 5. Ruptured branch of a lenticulostriated artery, 280 \(\mu\) in diameter. Severe atheromatous change is seen at the bifurcation where abrupt breakage is present. 55 male, surgical, P; coagulated platelets.

FIGURE 6. Rupture of a small artery, measured 180 \(\mu\) in diameter, with no degeneration of medial smooth muscle cells. It probably is ruptured secondarily by the tensile strength of rapidly growing hematoma. 37 male, autopsied.
aged patients. However, such severe diffuse changes as observed in the lenticulostriate arteries of hypertensive intracerebral hemorrhages were more characteristic than the others. Moreover, the intracerebral arteries including small arteries and arterioles have the characteristics of being liable to infiltration of lipids and form lipohyalinotic changes. The present study showed that lipohyalinosis ultrastructurally is the same as atherosclerosis appearing in large arteries at the base of the brain.

The irregular atrophy and fragmentation with moth-eaten appearance of medial smooth muscle cells has been produced in experiments of long-term hypertension as well as in repeated vasospasm and stress. It is postulated from these facts that the state of excessive tension or spasm of the vascular wall repeatedly occurring over a long period of time results in degeneration of smooth muscle. Medial degeneration does not occur in the proximal portion of lenticulostriate arteries branching from the middle cerebral artery and entering into the cerebral parenchyma cannot be explained only by the sharp angle at the origin of lenticulostriate arteries, as proposed by some investigators or by the close relation with vasomotor nerves which were similarly distributed in the larger arteries at the base of the brain and in lenticulostriated arteries. Integrated disturbances derived from functional distortion in hypertension as well as from anatomical differences of vessels including innervation may be the causative factors.

It was clarified by the present study that rupture from MA, which has been an issue since it was raised by Charcot, is very low. Shennan supposed that the arteries where MA is formed are generally fine arterial branches and the arteries causing fatal intracerebral hemorrhage are large lenticulostriated arteries. Fisher reported that MA occurred on vessels between 40–160 μ in diameter. In fact in the present study, arteries forming MA were small arteries measuring around 200 μ in diameter, as opposed to the larger arteries measuring 500–800 μ associated with large intracerebral hematomas. Moreover, these ruptured arteries had severe degeneration of medial smooth muscle cells and dilatation of vascular lumen irrespective of the presence of intimal thickening. This may indicate weakening of the vascular wall due to loss of elasticity.

According to most views on the etiology of MA, fibrinoid necrosis in the subendothelium develops gradually into MA with sac-like dilatation. Russell proposed that the combination of age and hypertension produced a degeneration of muscular and elastic elements of cerebral arteries which went on to the formation of multiple MA. However, Elliott attributed MA to dissection of the vascular wall, and Cole and Yates suggested that subclinical rupture of small arteries and re-absorption of hemorrhages form small cystic cavities where MA develops. In view of the findings in our study that the wall of some relatively large irregular shaped MAs were sometimes made only of a very thin layer of fibrin, it is unlikely that MA is a predisposing
state prior to rupture and hemorrhage, thus endorsing the speculation of Cole and Yates. However, some small MAs still retained vascular elements at various parts of the wall, as well as being entirely surrounded by collagen fibres. Therefore, the MA seem to be of two types, i.e., fibrinoid necrosis in the classical way, and post-hemorrhagic absorbed cavity.

The medial degeneration which was the most important finding in ruptured arteries would cause the vascular wall to lose its elasticity and would induce dissec-
tion at the bifurcation which is a highly susceptible site to tensile forces. The various factors such as intravascular pressure, stress forces and size of arteries determine whether complete or incomplete rupture occurs resulting in stroke or small subclinical hemorrhages respectively. Cole and Yates\(^ {31} \) stated that there is a temporal relation between the age at which MAAs appear and the age at which intracerebral hemorrhage occurs. The EM findings and incidental findings of MA in our report do not support the assumption that MAAs are necessarily a predisposing condition for arterial rupture.

The present study suggests that large intracerebral hemorrhages are due to the rupture of large arteries. Multiple ruptured arteries were also observed in cases of large hematomas found at autopsy. Matsuoka\(^ {32} \), pointed out this evidence and considered the presence of simultaneous ruptures from several MAAs (angioneurosis). We believe that a hematoma which is rapidly formed by the rupture of a single vessel gives a variety of tensions to the adjacent arteries, inducing rupture in avalanche fashion of unruptured arteries, thus producing multiple ruptured arteries around the large hematoma. The number of ruptured arteries probably increases as the hemorrhage grows.

There still remains some questions as to how such severe degeneration of medial smooth muscle cells that is not seen in any other organs, occurs at the distal portions of the lenticulostriate arteries and other perfo-

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**Figure 9.** Electron micrograph of miliary aneurysm showing in figure 8. Many neutrophils (N) and macrophage (M) are immigrated into the wall where remarkable deposition of fibrin (F) and plasma protein * E; replaced endothelial cell.

**Figure 10.** A lenticulostriated artery in long-term hypertension -A and -B; distal branches of the same artery distributed in putamen, showing considerable degeneration of medial smooth muscle cells. In addition, photo A consists of severe atherosclerosis showing numerous lipid-laden foam cells in intima. -C; the same artery in the proximal portion in which medial smooth muscle cell is still well preserved. 74 male, autopsied.
TABLE 2  Grade of Arteriosclerosis and Medial Degeneration of the Perforating Arteries and Cortical Arteries. Severe Medial Degeneration Restricts the Perforating Arteries. Arteriosclerosis Increased with Aging is More Advanced in Perforating Arteries than in Cortical Arteries.

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<th>Media degener.</th>
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<th>Media degener.</th>
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<td>3+</td>
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</tr>
<tr>
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<td>M</td>
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</table>

Arteries with hypertension persist, and what is the immediate trigger of arterial rupture.

Although acute inflammatory cell infiltration which is sparsely observed in the subendothelium adjacent to the rupture site is commonly seen in the fresh ruptured artery, such inflammation can subsequently arise after the rupture by an acute traumatic effect or by biochemical attraction of clotting systems. Inflammation is not likely to be a causative phenomena appearing in a mycotic aneurysm or the embolic rupture of an artery.

FIGURE 11. Non ruptured miliary aneurysm, 500 μ in diameter. The wall of the aneurysm consists of dense layers of fibrin and plasma protein admixed with a few hematogenous cells. Endothelial cells are totally replaced on the luminal surface. 64 female, autopsied.

FIGURE 12. A small arterial branch, 180 μ in diameter, connecting a miliary aneurysm shows a large amount of fibrin and plasma protein admixed with lipid particles (↑) in the thickened intima. The media had been severely destroyed. E: endothelial cell. N: neutrophil, EL: internal elastic lamina, A: adventitia, 56 female, surgical.
Figure 13. Fibrin insudation into the atheromatously thickened intima of a small branch, 90 μ in diameter, of lenticulostriated artery. Note lipid-laden foam cells in intima. 64 female, autopsied.

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References
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