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Morphogenesis of Plasmatic Arterionecrosis as the Cause of Hypertensive Intracerebral Hemorrhage

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Summary. The morphogenesis of the vascular lesions, which were considered to be the immediate cause of hypertensive intracerebral hemorrhage, was morphologically studied in autopsy cases. The direct cause of the hemorrhage was the rupture of the intracerebral microaneuysms resulted from the plasmatic arterionecrosis. The arterionecrosis was predominantly present in the intracerebral arteries of approximately 150 μ diameter, especially in the external branches of the arteriae corporis striati mediae in the putamen, and characterized by medial smooth muscle cell loss, blood plasma insudation in the intima, histolysis of the internal elastic lamina and intimal collagenous fibers, fibrin deposition (fibrinoid degeneration) in the intima, and luminal dilatation. The morphogenesis of the arterionecrosis was the development of histolysis as well as fibrinoid degeneration caused by blood plasma insudation in the wall of the intracerebral arteries with preceding necrosis and loss of medial smooth muscle cells and subsequent fibrous intimal thickening with dilated lumina. Intracerebral microaneurysms were also formed by the plasmatic arterionecrosis in a narrow sense, in which histolysis due to blood plasma insudation had occurred, but fibrin (fibrinoid substance) deposition in the intima had not yet arisen.

There are various views concerning the direct cause of hypertensive intracerebral haemorrhage, suggesting either diapedetic haemorrhage from the minute blood vessels (Rosenblath, 1918; Westphal and Bär, 1926), or venous haemorrhage (Scheinker, 1945), or arterial rupture, and as the cause of the rupture, arteriosclerosis (Rühl, 1927; Zimmerman, 1949), arterionecrosis (Staemmler, 1936; Beitzke, 1937; Spatz, 1939; Matsuoka, 1939) and "miliary aneurysm" (Charcot and Bouchard, 1868) have been considered. The authors have carried out morphological studies in autopsy cases, searching for the vascular lesions directly responsible for the cerebral haemorrhage, and investigated the morphogenesis of the lesions.

Material and Methods

Morphological investigations were done in 91 autopsy cases of hypertensive intracerebral massive hemorrhage (54 males and 37 females, aged 39～85 years), 19 hypertensive cases with softening in the basal ganglia, 13 hypertensives without gross cerebral lesions (over 40 years of age), and 46 normotensives (over 40 years). Cases of malignant hypertension were not included in the material. Many brain tissue blocks, especially those from the basal ganglia, were fixed in a neutral buffered 10% formalin, and some in absolute alcohol. Serial paraffin sections were prepared from them. Massive brain hemorrhages were studied by the following methods in search of the origin of the bleeding: 1) Numerous tissue blocks, 2) blood vessels isolated from the hematomas by pouring a stream of saline solution into them at autopsy or blood vessels dug out from them after fixation, or 3) the interrupted parts of the intracerebral arteries in the postmortem cerebral arteriography were all examined in serial paraffin

sections. Also histological examination was performed in serial paraffin sections of intracerebral microaneurysms, which were found, under a dissecting microscope, in large cleared slices of the brains which received intra-arterial injection of a radiopaque medium at autopsy.

The following modified method of Russell (1963) and Cole and Yates (1967a), which combined cerebral arteriography and brain tissue clearing was used to find out ruptured arteries and intracerebral microaneurysms: At autopsy, 100～300 cc of a 3～5% gelatin-barium sulfate mixture (100 g of barium sulfate in 150 cc), which was warmed to 40～50°C, was injected, under the pressure less than 150 mm Hg, into the bilateral common carotid arteries; then the brain was taken out, and after fixation in a cold 10% formalin, coronal slices 1 cm thick were prepared to be photographed by ultra-soft x-rays. The coronal slices 0.5 cm thick were dehydrated in alcohol and cleared in tetralin.

Stainings Were as Follows. Hematoxylin and eosin, Mallory's collagen stain, Weigert's resorcin fuchsin for elastic fibers, Congo red method for amyloid, phosphotungstic acid hematoxylin, and tryptophane staining (Adams, 1957). The trypsin digestion test (Ooneda *et al.*, 1959) was performed. Moreover, the digestion test with plasmin (fibrinolysin) was done in the following way: Sections from the tissues fixed in absolute alcohol were incubated at 37°C for 12 hours in a chloroform-activated plasmin solution, prepared from dried human blood plasma by the Ratnoff's method (1948) and diluted to 5～10 folds with a saline solution adjusted to pH 7.35 with a M/20 phosphate buffer. The diameter of arteries was measured at the outermost layer of the media.

The brains from cases of cerebral hemorrhage (4 cases) and hypertension (3 cases) within 6 hours after death were fixed in a neutral buffered 10% formalin, and the 0.5 cm thick slices of the putamina in the hemorrhage-free hemispheres were examined under a dissecting microscope to take out small tissue blocks including microaneurysms with hemosiderin deposit in the adventitia. These blocks were washed with a 0.1 M phosphate buffer (pH 7.2) and fixed in a Millonig's 1% osmium tetroxide for 2 hours. After dehydration with ethanol, these specimens were embedded in Epon 812, and ultrathin sections were cut with an ultramicrotome, stained with uranyl acetate in combination with Millonig's lead acetate, and examined and photographed in a JEM-7 electron microscope.

Results

Retrospective Investigation of Direct Cause. Large cerebral hematomas were investigated to find out the origin of haemorrhage, and ruptured blood vessels were discovered in the hematomas. The majority of these vessels were arteries, and the plasmatic arterionecrosis was noticed at the sites of rupture. Arterial rupture was present at 49 sites of 31 out of 91 cases of cerebral haemorrhage, and predominantly in arteries of 100～200 μ in diameter. In 9 cases, one hematoma contained 2～7 arterial ruptures. The plasmatic arterionecrosis was seen at 20 of the 49 sites (41%), but not at the remaining 29. Search for antecedent states of arterial rupture in the intracerebral arteries of hypertensive cases revealed microaneurysms resulted from the plasmatic arterionecrosis, in which the sac wall, consisting of fibrous tissue swollen by blood plasma infiltration and of blood plasma proteins or fibrinoid substance, was disrupted by diapedetic haemorrhage. Parent artery wall that was connected with the aneurysms remained nearly normal. It was therefore considered that after the rupture of the aneurysms, the changed part would have been blown off by the high intraluminal pressure, leaving the arterial wall without changes. Consequently it was presumed that the plasmatic arterionecrosis must have preceded the arterial rupture even at the 29 sites at which the arterionecrosis was not noticed at the time of observation.

The observation of large cleared slices disclosed intracerebral microaneurysms in all cases of cerebral haemorrhage (30 cases), 4 cases (over 56 years of age) of hypertensives (20 cases), and one (64 years) out of 10 normotensives. Usually

7～8 microaneurysms were seen in a case. Histological investigation confirmed all of them to have resulted from the plasmatic arterionecrosis. As for their histological pictures, 206 (77%) out of 269 microaneurysms in 35 cases exhibited the plasmatic arterionecrosis in an ordinary sense, 58 (21%) the fibronodular arterial lesion, that is, the organized plasmatic arterionecrosis with its obliterating thrombus, and 5 (2%) the plasmatic arterionecrosis in a narrow sense.

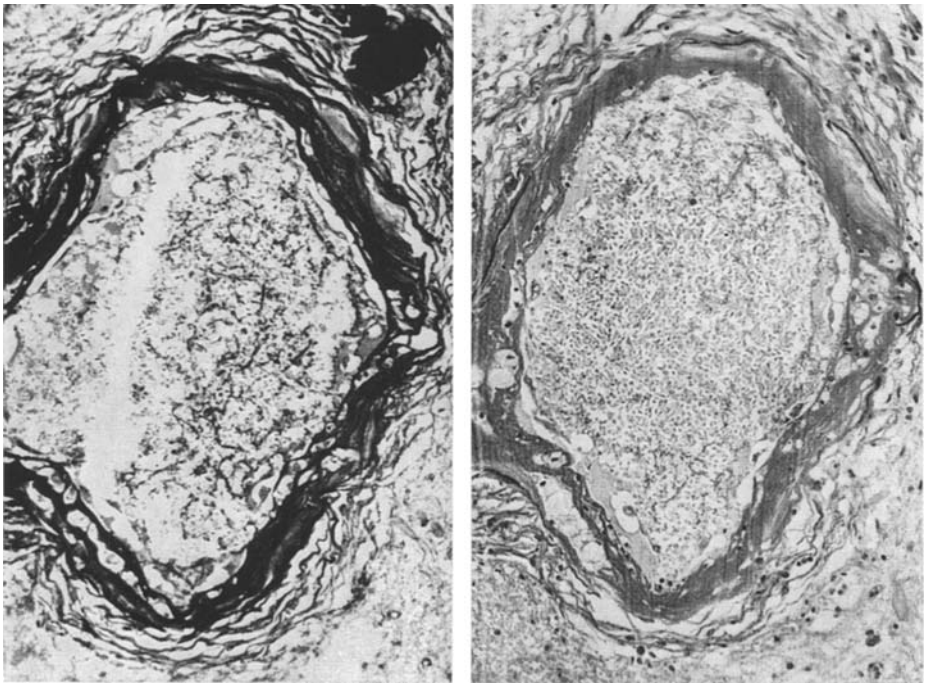
Essential Nature of Plasmatic Arterionecrosis. The plasmatic arterionecrosis was predominantly present in the intracerebral arteries about 150 μ in diameter, especially in the external branches of the arteriae corporis striati mediae (the lateral striate arteries). In the media of the affected arteries, smooth muscle cells had already been lost, and the intima showed some fibrous thickening. In the intima, blood plasma insudation took place, and collagenous fibers in the deep intima were swollen, being decreased in their blue staining with Mallory's stain and frayed into a fibrillar structure. Also the internal elastic lamina was dissolved. The deposition of fibrinoid substance was seen in the middle and inner layer of the intima, and even in its outer layer in severer cases (Fig. 1). Neutrophilic leukocytes and foam cells were frequently observed in the intima. The arterial lumen was dilated, and the arterial wall and its surrounding were sometimes infiltrated with red blood cells. Lymphocytes, large mononuclear cells with or without hemosiderin, and plasma cells were frequently seen infiltrating the periarterial tissue.

In the wall of the intracerebral arteries affected by the arterionecrosis, blood plasma insudation brought about swelling, fraying, fragmentation, and eventually dissolution of the internal elastic lamina and collagenous fibers. Also intimal cells underwent necrosis and subsequently disappeared. Electron microscopically were observed fraying and subsequent dissolution of the internal elastic lamina and collagenous fibers adjacent to the blood plasma infiltration.

The fibrinoid substance in the intima was stained intensely red with hematoxylin and eosin and Mallory's stain, negative in Congo red method, deep blue with phosphotungstic acid hematoxylin, strongly positive with the staining for tryptophane which is contained in fibrin in a high concentration (Adams, 1957), and was digested by trypsin and plasmin (fibrinolysin). Electron microscopically the fibrinoid substance was observed as an electron-dense substance having regular cross-striations with a period of 160～230 Å. From these findings, the fibrinoid substance was believed to be consisted mainly of fibrin.

In 84 of the 91 cases of cerebral hemorrhage, the arterionecrosis was found in the hematomas and their surroundings. Sometimes it showed multiple ocurrence. In 59 of the 91 cases, the arterionecrosis was observed in the arteries of 50～412 μ diameter in the basal ganglia of the hemispheres without haemorrhage, and numbered 166 in total, and was predominantly found in the putamen (61%), followed by the thalamus (21%), caudate nucleus (14%), internal capsule (3%), and pallidum (1%). The arterionecrosis was also observed in 18 of the 19 hypertensive cases with basal ganglionic softening and in 3 of the 13 hypertensive cases without any gross cerebral lesions, all in the arteries of above 50 μ in the basal ganglia. It was not found in any of the 36 normotensives.

Plasmatic arterionecrosis-like lesions with fibrinoid degeneration were noticed in the arterioles and small arteries of the adrenals (9 cases), pancreas (5 cases)



a b

Fig. 1 a and b. Plasmatic arterionecrosis of an arterial branch 210 μ in diameter in the left putamen of a case of left basal ganglionic haemorrhage, male aged 65 years. a Medial muscle cell loss, swelling of collagenous fibers in the deep intima, intimal fibrinoid substance, and luminal dilatation are seen. Mallory's collagen stain. $\times$ 180. b The internal elastic lamina is dissolved. Weigert's resorcin fuchsin. $\times$ 180

and kidneys (5 cases), but not in those of the hearts, in 20 cases of cerebral haemorrhage which showed the arterionecrosis in the intracerebral arteries. These lesions in the extracerebral arteries were different from the intracerebral arterionecrosis, being lower in intensity and smaller in number.

Morphogenesis of Plasmatic Arterionecrosis. In order to elucidate the developmental process of the arterionecrosis, histological observation was made in the lateral striate arteries. At the beginning, medial smooth muscle cells were injured and as the result the lumen became dilated, followed by some intimal thickening with fibrous tissue. In such intima occurred blood plasma insudation, which induced histolysis together with intimal deposition of fibrinoid substance consisting mainly of fibrin. Thus the arterionecrosis was completed. In short, the arterionecrosis consisted of histolysis and fibrinoid degeneration; both of these phenomena were caused by blood plasma insudation; this very phenomenon had occurred in the arteries with preceding medial damage. Hence the arterial lesion can be designated as "plasmatic arterionecrosis". It was accompanied or not accompanied with the deposition of fibrinoid substance in the intima. The former was the plasmatic arterionecrosis in an ordinary sense (Fig. 1), and the

latter in a narrow sense, where the histolysis due to blood plasma insudation occurred. The arterionecrosis in a narrow sense as well as that in an ordinary sense produced intracerebral microaneurysms, which were subject to a diapedetic haemorrhage, eventually leading to the rupture of them.

Sometimes mural thrombi formed in the microaneurysms were covered by endothelial cells and incorporated into the intima. However the major part of the intimal fibrinoid substance seemed to owe its existence to insudation. Microaneurysms occluded by thrombi or the fibronodular arterial lesions resulted from their organization ("derbe fibröse Kugel" of Anders and Eicke, 1939; "Narbenkugel" of Stochdorph and Meessen, 1957) were one of the causes of small infarcts in the basal ganglia (26%).

Smooth muscle cells in the areas of medial damage showed their nuclei swollen or shrunken or lost and their cytoplasm vacuolated, diminished in staining ability or stained intensely red with eosin, thus exhibiting atrophic and regressive changes; they further underwent necrosis and disappeared. The intercellular spaces in these areas were widened and edematous. Finally, the media turned into a somewhat edematous thin tissue without muscle cells. The loss of medial muscle cells in the lateral striate arteries was less marked in their trunks 500～800 μ in diameter, but more marked in their smaller branches 100～200 μ in diameter, especially prominent in somewhat distal segments from the bifurcations with narrowed lumina due to intimal thickening. It was here that the arterionecrosis developed frequently.

In cases of cerebral haemorrhage, the media of the arteries without intimal thickening in the basal ganglia was much thinner than that of the arteries of the same diameter in the kidneys, pancreas and adrenals. The number of medial smooth muscle cells per unit area of the media in the lateral striate arteries 200～500 μ in diameter was, in normotensive cases, greatest in the twenties, and then decreased with aging, remaining almost constant after 50 years of age. In hypertensives, however, the number decreased markedly with aging, especially after 50 years.

Owing to the decrease of medial muscle cells, the lumen became dilated. And then fibrous intimal thickening took place in two types: with dilated lumen, easily inducing blood plasma insudation and subsequent plasmatic arterionecrosis, or with narrowed lumen, hardly inducing these changes.

Discussion

The direct cause of the cerebral haemorrhage is considered to be the rupture of microaneurysms resulted from the plasmatic arterionecrosis in the intracerebral arteries. The arterionecrosis has been given many different names: "Angionekrose" (Westphal and Bär, 1926; Matsuoka, 1939), "Arterionekrose" (Staemmler, 1936; Stochdorph and Meessen, 1957), "Medianekrose" (Nordmann, 1937), "Hyalinose" (Spatz, 1939), hypertensive hyaline arteriolopathy (Scheinker, 1943). "plasmatische Gefäßzerstörung" (Wolff, 1937), "fibrinoide Quellung" (Beitzke, 1937), "fibrinoide Nekrose" (Staemmler, 1936), fibrinoid degeneration (Ooneda *et al.*, 1959), and hypertensive fibrinoid arteritis (Feigin and Prose, 1959).

The results of the present study indicate that the morphogenesis of the arterionecrosis are as follows: In the intracerebral arteries in which medial smooth

muscle cell damage had preceded, blood plasma insudation took place, thus inducing the histolysis of arterial wall and the deposition of fibrin (fibrinoid degeneration). In the development of experimental hypertensive arterial lesions, the necrosis of medial muscle cells was also seen to have preceded blood plasma insudation (Jellinek, 1967; Hüttner *et al.*, 1968). Fibrinoid substance in the arterial intima of hypertensive rats was confirmed to be derived from fibrinogen which insudated abundantly from the arterial lumen (Ooneda *et al.*, 1963, 1965).

The principal causes of the preceding damage of medial smooth muscle cells are considered to be aging and hypertension, both giving considerable influence to the medial tissue which is primarily poor in structure: 1) The intracerebral arteries are characterized by a thinner wall in comparison with the large lumen. Medial muscle cells in the small arteries of the normal brains are less in number than those in the arteries of similar diameter in other parts of the body (Baker, 1937). 2) Number of muscle cells in the media of the lateral striate arteries was decreased with aging, and the decrease was further accelerated by hypertension. 3) Hypertension (Suwa and Takahashi, 1971), overdistention of arterial wall (Giese, 1964) or vasospasm (Westphal and Bär, 1926) due to hypertension. Moreover, disturbance of electrolyte metabolism (Koletsky, 1955) and renal failure (Churg, 1963) are also considered responsible.

The causes of increased permeability, which is responsible for the blood plasma infiltration in the arterial wall, are considered to be as follows: 1) Hypertension (Ooneda *et al.*, 1963), mural overdistention (Giese, 1964) or vasospasm due to hypertension; 2) hemodynamics; 3) medial damage (Linzbach, 1959); 4) hypoxidosis; 5) metabolic disturbance of electrolytes (Koletsky, 1959); 6) permeability factor from the kidneys (Asscher and Anson, 1963); and 7) autoimmunization (Paronetto, 1965). Furthermore, stagnation of transmural blood plasma-stream due to medial damage must be considered (Doerr, 1970).

As for the causes of the histolysis of arterial wall, blood plasma infiltration and its stagnation are considered important (Schürmann and McMahon, 1933; Wolff, 1937). Blood plasma infiltration involves the internal elastic lamina and collagenous fibers, and its stagnation in them causes their swelling, fraying, and disintegration. The following blood-derived enzymes are expected to participate in the histolysis: 1) Elastase from the pancreas (Hall, 1966); and 2) elastase (Janoff and Scherer, 1968) and collagenase (Lazarus *et al.*, 1968), both derived from neutrophilic leukocytes in the intima.

The fibrinoid degeneration, which is the deposition of fibrin, can be considered, like mural thrombi, to have a biological significance of reinforcing the arterial wall that has been affected with marked histolysis. It seems that microneurysms most liable to rupture are those revealing the arterionecrosis with neither thrombosis nor dense deposition of abundant fibrin in the intima. Russell's (1963) view that microaneurysms would rupture before the deposition of abundant fibrin in the intima, was substantiated by the authors' plasmatic arterionecrosis in a narrow sense.

Comparison between the plasmatic arterionecrosis and the atherosclerosis of the intracerebral arteries revealed that the former had a tendency to dilatation and rupture, while the latter was apt to lead to stenosis or occlusion of the lumen. Therefore the latter may result in cerebral infarction but not in cerebral haemor-

rhage. The arterionecrosis is quite different from the scalariform arteriosclerosis (Arab, 1957) and the "drusige Entartung" (Hager, 1968). The "miliary aneurysms" of Charcot and Bouchard (1868) are not true aneurysms, but coagula of extravasated blood (Matsuoka, 1939; Cole and Yates, 1967 b).

It was around the trunks of the lateral striate arteries that lacunes (Zülch, 1961) developed frequently. Here medial damage was mild, and the arterionecrosis was not noticed. Thus the knee-like bend (Zülch, 1961) immediately before the entrance of the arteries into the putamen showed neither plasmatic arterionecrosis nor microaneurysm.

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