Neuropathological Study of Acute Severe Cerebral Infarction
— Clinical and Experimental Study —

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SUMMARY

The neuropathological findings of acute severe cerebral infarction were analyzed in comparison with four autopsied cases and experimental cerebral infarction in dogs. Four autopsied cases with acute severe cerebral infarction included 1 male and 3 females ranging in age from 57 to 68 years. All patients had histories of hypertension and cardiac disease. Three of the 4 patients died within 7 days after clinical evidence of infarction. In 3 patients, angiography showed an occlusion of internal carotid or middle cerebral artery and a recanalization. A CT-scan was performed on two of these 3 patients and on the one who·survived 22 days. Experimental cerebral infarction was induced in 165 dogs by injecting one or two silicone cylinders through the cervical internal carotid artery. The embolus was found to have obstructed the main trunk of the middle cerebral artery in 102 dogs. And only 47 dogs or 50 per cent, had large hemispheric infarction occupying more than 50 per cent of the hemisphere involving the basal ganglia, cerebral cortex and white matter.

The results obtained were as follows: 1. Pathologic changes of the autopsied and experimental cases resembled each other closely. The gross specimens and histologic sections were reviewed, showing that the massive hemorrhage was localized in the basal ganglia and the petechial hemorrhage in the corticomedullary junction of the infarct affecting the hemisphere in the middle cerebral artery distribution. It is suggested that the massive hemorrhage may be caused by the disruption of the arteriole in the perforating arterial terminal zone, and the petechial hemorrhage by the disruption of the venule in the cortical arterial terminal zone. 2. The CT of the patient with fatal cerebral infarction showed only large low-density area with a negative contrast enhancement which occupied the affected hemisphere almost entirely and which also showed remarkable mass effects. Acute severe cerebral infarcts appeared as low density areas, with lower attenuation values due to the presence of large amounts of edema fluid, therefore the addition of blood in hemorrhagic infarct of the basal ganglia and the corticomedullary junction may be negative on CT scan.

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key words: acute severe cerebral infarction, autopsied cases,
experimental cases, CT findings, pathology

INTRODUCTION

The findings of CT scan and pathological findings on autopsy were investigated in four patients who died of acute severe cerebral infarction; and, further, a study was made by comparing them with the pathological findings obtained from the model dogs with acute large hemispheric infarction.

SUBJECTS AND METHODS

1) Autopsied Cases

The subjects included three females and one male with ages ranging from 57 to 68 years. All the patients were complicated by hypertension, three by atrial fibrillation, one by left ventricular hypertrophy, and they showed suspected embolic cerebral infarction. Hemiplegia or disturbance of consciousness occurred initially in all the patients. Three patients died from day 1 to day 6, and only one died on day 22, which was probably caused by recanalization in the latter period attributable to the administration of a thrombolytic drug. Cerebral angiography was performed on three of the four cases, revealing obstruction of the internal carotid artery in one patient, obstruction of the middle cerebral artery in another, and recanalization in the last one. A CT-scan was performed on three patients (Table 1). Autopsy was performed on all the patients. Horizontal or coronal sections of the brain were prepared, after macroscopic observations, hematoxylin and eosin (HE) stain and

Table 1. Four autopsied cases of acute severe cerebral infarction. CAG= carotid angiography, CT= computerized tomography, F= female, M= male, AF= atrial fibrillation, LVH= left ventricular hypertrophy. R= right, L=left, ICA= internal carotid artery, MCA= middle cerebral artery.

	Case 1	Case 2	Case 3	Case 4
Age, sex	57, F	68, F	59, F	67, M
Hypertension	Yes	Yes	Yes	Yes
Cardiac	AF	AF	AF	LVH
Initial symptoms	R-hemiparesis	L-hemiparesis	L-Hemiplegia	R-Hemiparesis
CAG findings	Occlusion of L-MCA	Occlusion of L-ICA	No	Recanalization
CT examination	Day 3	No	Day 0	Day 22
Day of death	Day 3	Day 1	Day 6	Day 22

specific stain were carried out for light microscopic samples.

2) Experimental Cases

Mongrel adult dogs weighing about 10kg were anesthetized with intravenous Nembutal (20mg/kg), endotracheal intubation was performed, a cervical paramedian incision was made under spontaneous respiration, and 18 G teflon sheath needle (1.4mm in inside diameter, Hakko) was inserted from the right common carotid artery to the internal carotid artery, one or two silicone cylinder (1.1mm in diameter, 8mm in length) were injected, and samples were prepared after 24 hours. For the light microscopic preparation, carbon suspension was rapidly perfused from the beating left ventricle at 120mmHg pressure until a black effluent appeared through the vena cava cannula. The brain was removed and fixed in a 10 per cent formalin for 7 days. The fixed brain was severed into seven coronal or horizontal sections. After macroscopic observations they were embedded in paraffin, and sections 150μ and 15μ in diameter were prepared. The former sections were deparaffined an lucidificated with xylol, and the latter ones were stained with HE. For the electron microscopic preparation, the ultrathin sections were prepared after perfusion fixation and observed by a transmission electron microscope. Apart from this, after perfusion fixation methyl methacrylate resin (Mercox) was infused from the contralateral common carotid artery. Vascular cast specimens and frozen sections were prepared and observed by scanning electron microscope.

RESULT
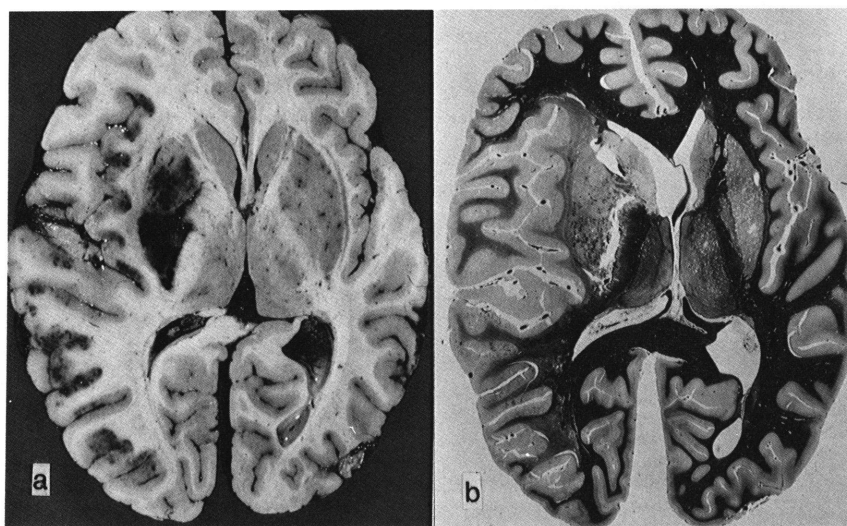
Fig. 1. (a): Brain slice of Case 1 showing confluent petechiae in the corticomedullary junction, caudate nucleus and putamen of infarction affecting the hemisphere in the left middle cerebral artery distribution. (b): The same level of (a) showing poor staining of the white matter in the same region. Note the swelling of the affected hemisphere. Külver-Barvera's stain.

1) Autopsied Cases

The autopsied brains showed exactly the same pathological findings in all the four patients.

Figure 1a shows a cerebral horizontal section from Case 1, where infarction appears extensively in the middle cerebral arterial distribution of the left hemisphere. Of the infarcted lesions, massive hemorrhage was seen in the cerebral basal ganglia, and petechial hemorrhage was seen in the corticomedullary junction. Figure 1b shows a stained myelin sheath of the same section. The infarcted lesion, especially the white matter is faintly stained, markedly swollen, and exhibits a distinct border between the necrosed region and normal region. Figure 2 shows a CT scan of the present patient photographed immediately before his death. It reveals only a low density area extending to the whole area of the middle cerebral arterial distribution in the left hemisphere accompanied by remarkable mass effect. In addition, the contrast enhancement was negative.

2) Experimental Cases

Of the 165 dogs in which embolization was performed with silicone cylinders, the embolization at the proximal portion of the middle cerebral artery could be made in 102, among which infarcted lesion could histologically be proved in 94. Moreover, only 47 dogs or 50 per cent, had large hemispheric infarction occupying more than 50 per cent of hemisphere involving the basal ganglia, cerebral cortex and white matter.[1] Of these 47 dogs, 27 were used for light microscopic preparation and 20 were used for electron microscopic preparation.

Macroscopic findings: Figure 3 shows the horizontal sections of the model with large-sized infarction of the cerebral hemisphere after carbon perfusion. An extensive non-filling area, spreading over 50 per cent of the cerebral hemisphere, involving the basal ganglia, cerebral cortex and white matter, was noted in the region tributed by the middle cerebral artery. Furthermore, of these infarcted lesions, massive extravasation of carbon was seen in the cerebral basal ganglia, and petechial extravasation was seen in the corticomedullary junction.

Light microscopical findings: Figure 4 shows the H.E.-stained specimens. Figure 4-(1) exhibits the contralateral cortex, in which the blood vessels are filled with carbon and nerve cells are normal. Figure 4-(2) exhibits the cortex of an infarcted lesion, in which an edematous change is marked, the blood vessels are only partially filled with carbon, the intravascular spaces are obstructed with erythrocytes, and nerve cells and glia cells are necrosed and have become incrusted. Figure 4-(3) exhibits the corticomedullary junction of the infarcted lesion, in which the following can be noted: petechiae along the border, dilated blood vessels due to being full of erythrocytes, spongy degenerated
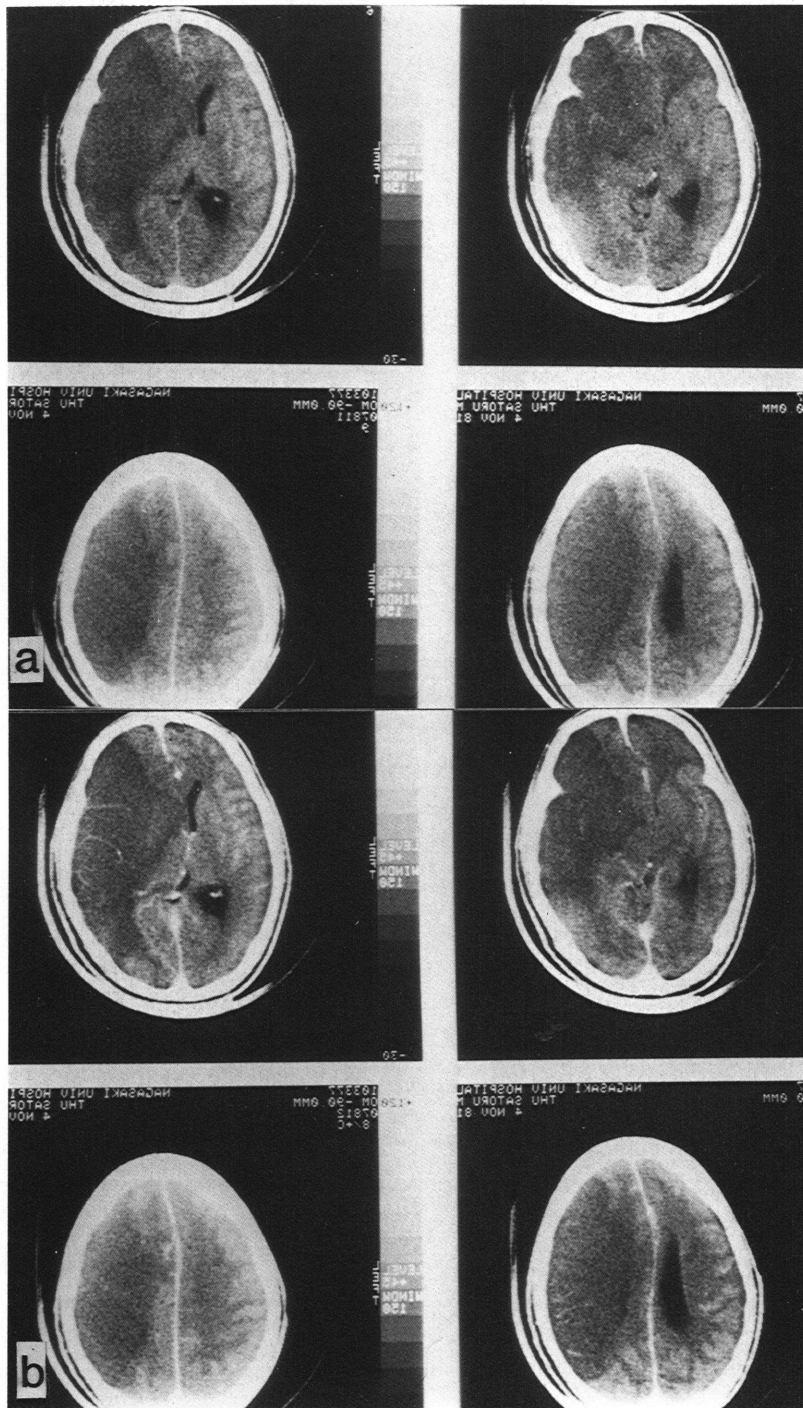
Fig. 2. CT of the same case as Fig. 1 showing only large low-density area and negative contrast enhancement in the left hemisphere with mass effect. (a): precontrast scan, (b): postcontrast scan.
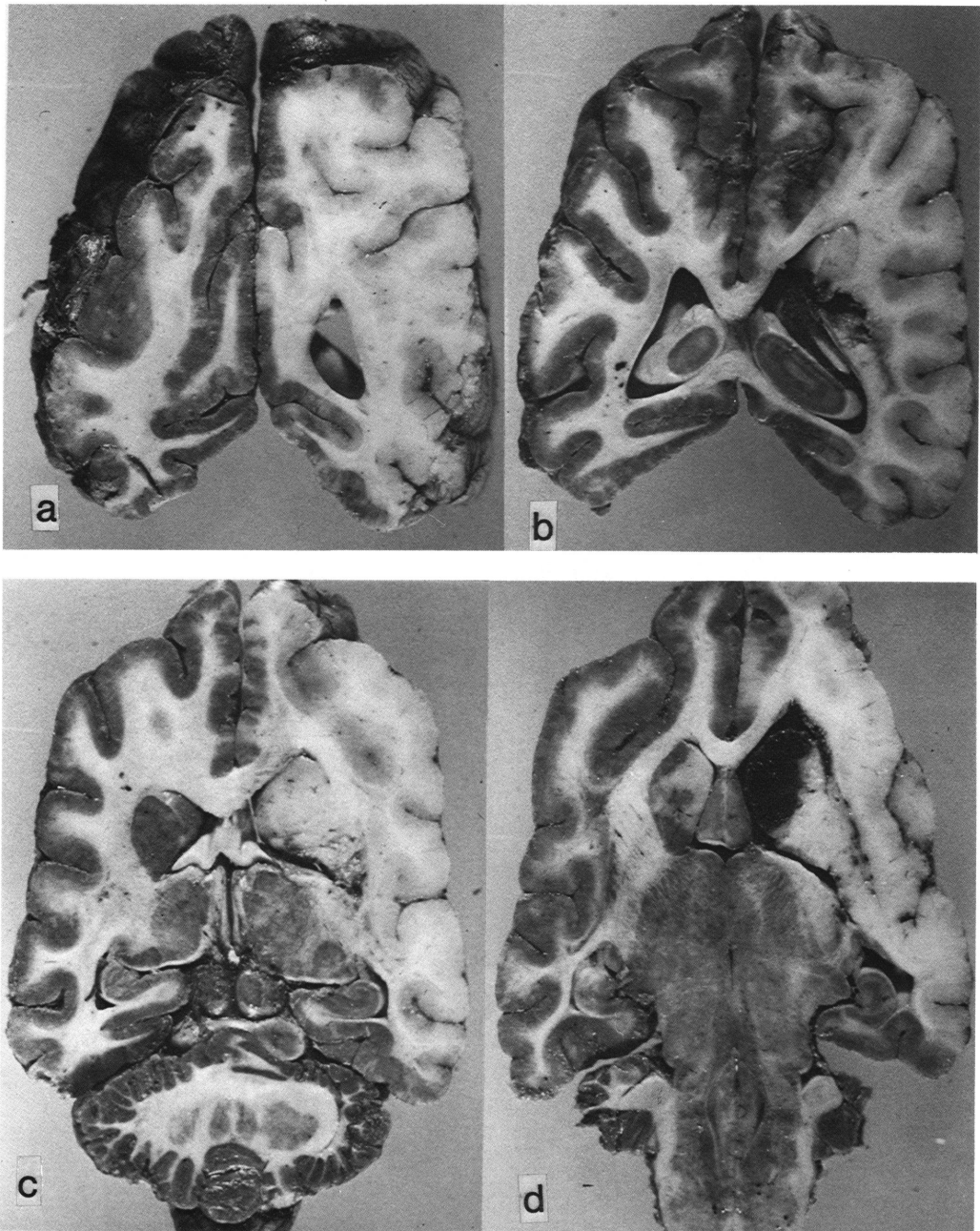
Fig. 3. Brain slices of the dog showing carbon extravasation in the corticomedullary junction, caudate nucleus and putamen of large non-filling area in the right middle cerebral artery distribution.
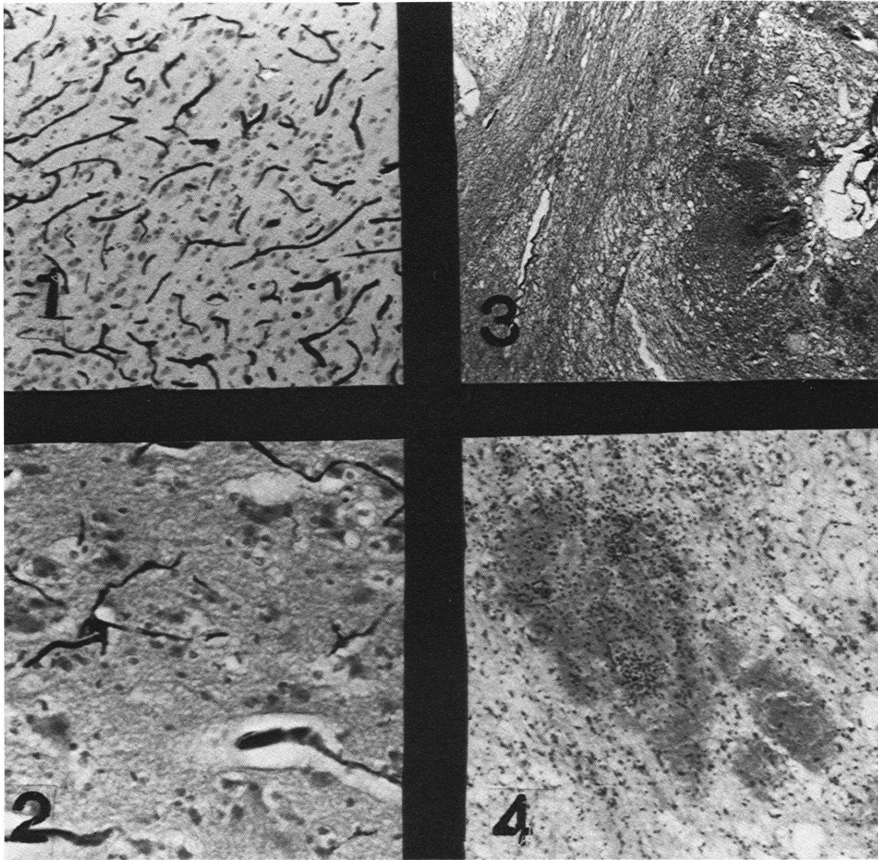
Fig. 4. Histological findings of the cortex on the opposite side $66 \times$(1), and of the cortex $132 \times$(2), corticomedullary junction $33 \times$(3) and basal ganglia $33 \times$(4) on the lesioned side. Hematoxylin and Eosin.

neuropil, and necrosed nerve and glia cells. Figure 4-(4) exhibits the cerebral basal ganglia, with the following: massive hemorrhage around the necrosed blood vessels, spongy degenerated neuropil, and necrosed nerve and glia cells.

Electron microscopical findings: The upper part of Figure 5a shows the vascular cast of a normal dog. Arterioles approximately 50μm in diameter exhibit elastic course branching to three-dimensions and have nuclear indentation and ring-shaped compression on the surface. The lower part of 5a shows the frozen section. Arterioles filled with Mercox, smooth vascular wall, tight perivascular spaces, and flat and smooth neuropils are noted. The ultrathin section as shown in Figure 6a, shows no abnormalities in endothelial cell of capillary, basal lamina and neuropils. The upper part of figure 5b shows the vascular cast of the ischemic cortex. Arterioles lost elasticity and are surrounded by shrunken capillaries. In the lower part of 5b, which is a frozen section, capillaries are shrunken, perivascular
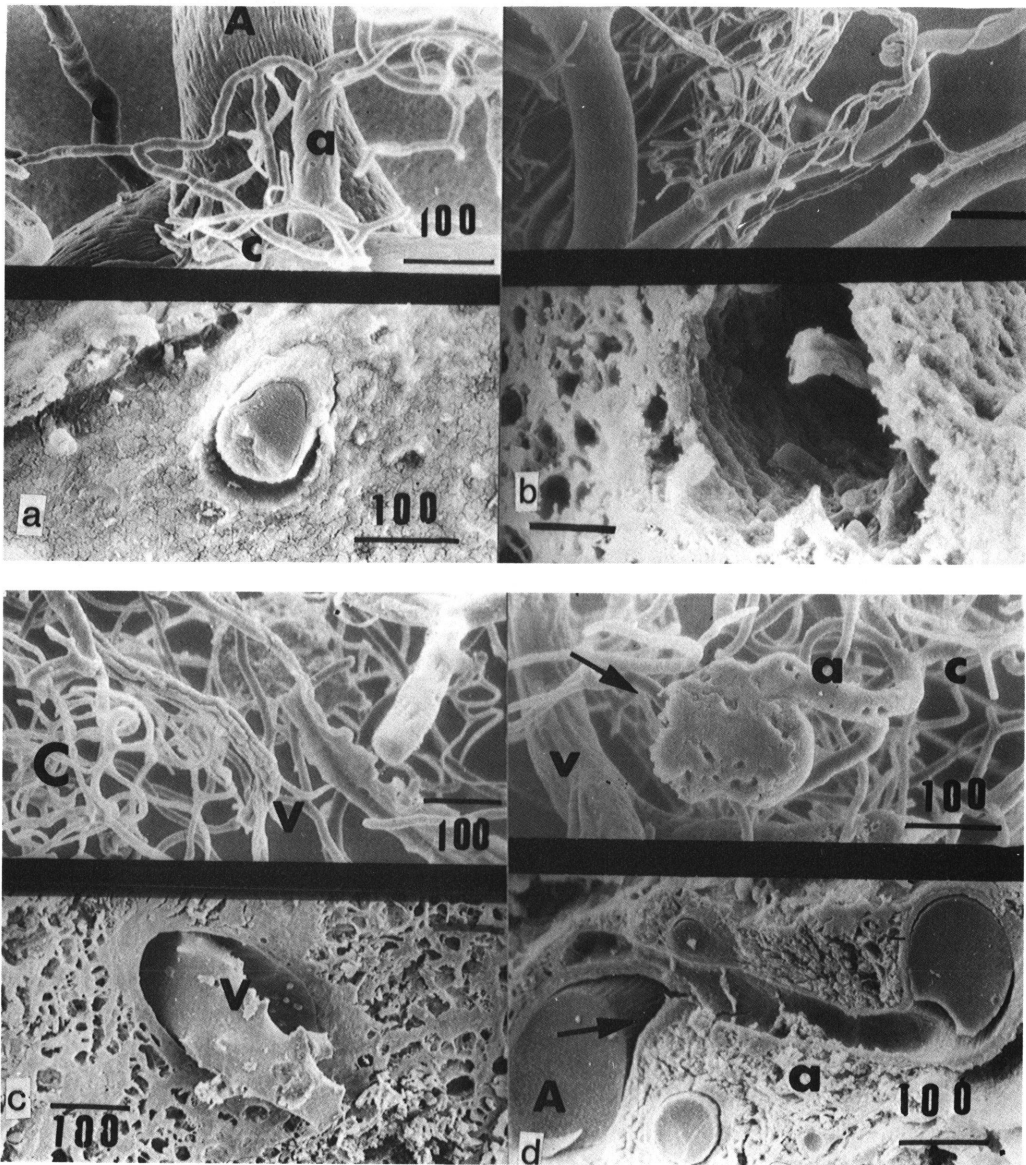
Fig. 5. Electronmicrophotographs of the vascular cast (upper) and cryofracture (lower) showing the artery, arteriole and capillary in the normal canine cerebral cortex (a), shrinkage of the copillary and enlarged pericapillary space in the ischemic cortex (b), leakage of Mercox around venular adventitia in the ischemic corticomedullary junction (c) and aneurysmal dilatation at arteriolar bifurcatio (upper arrow), extravasation of numerous red blood cells and Mercox (lower arrow) in the ischemic basal ganglia (d) at 24 hours. A= artery, a= arteriole, c= capillary, v= venule, Bar= 100μm.

space is enlarged markedly and neuropils contain many vacuoles. Also in Figure 6b, which is an ultrathin section, foldings increase in the luminal surface of capillaries, thinning of walls and vacuolization are partly noted, and edematous fluid is accumulated in the perivascular spaces, containing cell debris and myelin sheaths. Figure 5c shows venules in the corticomedullary junction. Venules are generally shrunken and crumpled, and on the other hand, in some places they are enlarged and even burst, causing leakage of Mercox around its adventitia. The frozen section also exhibits Mercox and few erythrocytes in the perivascular spaces. In Figure 6c, a few erythrocytes are extravasated in th dilated perivascular space. Figure 5d shows arterioles in the cerebral basal ganglia. Aneurysm-like dilatation of Mercox are noted at their bifurcation. In the frozen section Mercox and erthrocytes are massively extravasated, developing a marked perivascular edema. Figure 6d
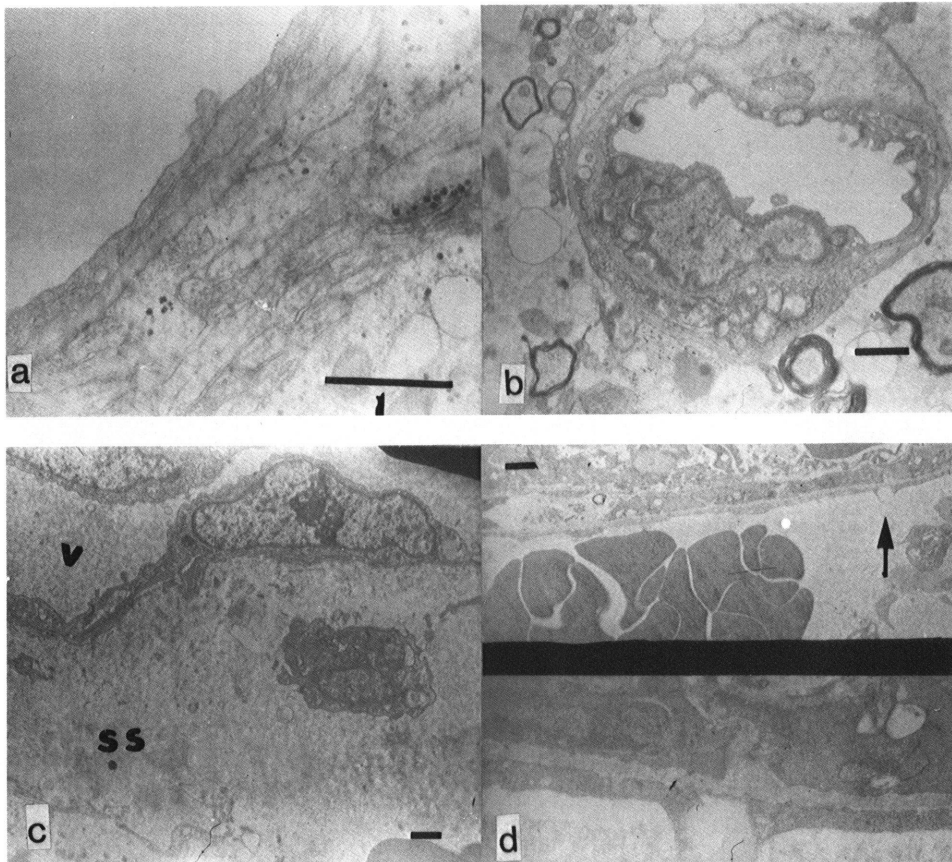
Fig. 6. Electronmicrophotographs of the ultrathin section showing the capillary in the normal canine cerebral cortex (a), surface infolding of the capillary in the ischemic cortex (b), the dilated perivenular space in the ischemic corticomedullary junction (c) and bleb formation of the arteriole (arrow) in the ischemic basal ganglia (d) at 24 hours. V= venule, ss= perivascular space, Bar= 1μm.

shows bleb formation in the endothelial cell and smooth muscles of degenerated arterioles, swelling and breakage in the basal membrane, and enlarged perivascular spaces with numerous erythrocytes and fibrin matrix.

DISCUSSION

The findings on the autopsied brains of the patients with acute severe cerebral infarction were entirely similar to those on the model dogs with large-sized infarction of the cerebral hemisphere. In acute large hemispheric infarction, an extensive infarction was present in the region tributed by the middle cerebral artery with massive hemorrhage in the basal ganglia belonging to the perforating arterial terminal zone and petechial hemorrhage in the corticomedullary junction belonging to the cortical arterial terminal zone.

The occurrences of massive hemorrhage in the cerebral basal ganglia caused by middle cerebral arterial obstruction are occasionally encountered in experimental cases[2-8] and clinical cases.[9-10] Mechanisms for this occurrence are such that, bacause the lenticulostriate arteries are terminal ones and lack anastomosis between the perforating branches, occlusion of this terminal artery can cause not only severe ischemia in the basal ganglia but also necrosis of the arteries. Therefore, if recanalization occurs by new construction of collateral circulation or migration of the embolus, probably disruption of arterioles takes place, resulting in massive hemorrhage. Next, as the authors have already reported,[11] the mechanisms involving petechial hemorrhage occur in the corticomedullary junction in the ischemic lesion are probably as follows: The leptomeningeal arteries have well-developed collateral circulation on the cerebral surface, but they lack anastomoses inside the brain and become terminal arteries, so that ischemia occurs more severely in the subcortex of the brain than on the cortex. The excessive blood flow on the surface overflows into the intact cortical artery not obstructed even by edema in the peri-ischemic region, passes through the arteriovenous shunt[12] at the corticomedully junction and, finally, flows into the venous side, damaging the vascular walls, thus resulting in petechial hemorrhage.

The findings of CT showed only a low-density area accompanied by marked massive effects and extending over the whole area of the middle cerebral arterial distribution, but could not detect, as a high density area on CT, slight hemorrhage in the basal ganglia or corticomedullary junction seen in the autopsied brains, probably because of masking with cerebral edema. It is also suggested that decreased blood flow lessens drastically extravasation of the contrast media, leading to negative contrast enhancement.[13,14]

GARCIA *et al.*'s[15] well-known reports show that cerebral infarction was prepared in monkeys by occlusion of the middle cerebral artery, and a three-zone separation of the histological features is suggested, namely, central, reactive and marginal zone. This

discremination, however, conforms only to anemic infarction occuring at the cortex and sub-cortex in the middle cerebral arterial distribution, and no discription has been given for hemorrhagic lesions in the basal ganglia or corticomedullary junction revealing specific vascular structure. Recently, ASTRUP *et al.*[16] have proposed a concept of ischemic penumbra. In other words, they stress that a half-killed part of the tissue is present in the region around the ischemic lesion like the ring-shaped penumbra surrounding the dense block shadow at the time of a solar eclipse, and that, because this part is recoverable, it is also clinically of importance to recognize the condition of the penumbra. Although the word, "*penumbra*" is of interest as an expression, KAMEYAMA[17] advises that conceptionally it is not new, and these observations had been performed for the cerebral cortex in animal experiments in the past, confirming that, though distribution mechanisms abundant in collateral circulation are common in the cerebral cortex, the same is not true of the basal ganglia and white matter.

Therefore, in cases of acute severe cerebral infarction caused by obstruction in the internal carotid artery or middle cerebral artery, specific vascular structure induces localization of two different lesions: that is, massive hemorrhage in the cerebral basal ganglia of the infarcted hemisphere and petechial hemorrhage in the corticomedullary junction. Consequently, their treatment should be considered very carefully.

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