Cerebral Hemorrhage in Experimental Renal Hypertension

Masao Ikeda, M.D., Jun Fujii, M.D., Fujio Terasawa, M.D., Saichi Hosoda, M.D., Hiroshi Kurihara, M.D., and Shin-ichi Kimata, M.D.

Cerebral hemorrhages are one of the most important causes of death in hypertensive subjects in Japan. Throughout the world, however, there have been a few studies of the pathogenesis of cerebral hemorrhages. In this paper, cerebral hemorrhages were produced by experimental renal hypertension. The fibrinoid necrosis of the small arteries and arterioles in the brain seemed to be the primary pathogenetic vascular lesion for cerebral hemorrhages. The fibrinoid necrosis of the cerebral vessels appeared to be one of manifestations of the generalized vascular lesions in the whole body. A high blood pressure augmented the incidence of cerebral hemorrhages. Occurrence of the fibrinoid necrosis and high blood pressure, however, are considered to be due to two different factors.

In the numerous studies of experimental renal hypertension which have appeared since the first report by Goldblatt in 1934, interest has been directed toward the mechanism of the occurrence of hypertension as well as its sustaining factor. Few studies have been focussed on cerebral hemorrhage in experimental hypertension, although vascular lesions in experimental hypertension have been extensively studied. In several investigations of cerebral hemorrhage in experimental hypertension and in human necropsies, in Japan as well as in the western countries, fibrinoid necrosis of the small arteries and arterioles in the brain was considered to be the primary vascular lesion which caused the cerebral hemorrhage.

This study was conducted to elucidate the pathogenesis of cerebral hemorrhage related to hypertension and of the fibrinoid necrosis of small arteries and arterioles.

Methods

Renal hypertension was produced in rabbits (weighing about 2 Kg.) by a modification of Goldblatt's method. By applying a silver clamp shown in Fig. 1, narrowing of the main renal arteries was produced on one side, and then 2 or

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3 weeks later on the other side. In the first group of experiments, a clamp with a luminal diameter of 0.7–0.8 mm. was used on one side and then clamps of 0.9–1.0 mm. on the other side. In the second group, a clamp with a luminal diameter of 0.8 mm. was used on one side and then clamps of 1.0–1.1 mm. on the other side. In the third group, one kidney was extirpated in the first procedure and then the renal artery of the other side was narrowed by a clamp with a luminal diameter of 1.1 mm.

All animals were autopsied after spontaneous death. The organs and vascular system in the whole body were examined macroscopically and histologically by hematoxylin-eosin, Azan and elastica trichrom stains.

Results

(1) Incidence of cerebral hemorrhages (Table I)

In the experiments of the first group with moderate narrowing of the renal arteries, cerebral hemorrhages were observed in 14 of 28 animals (50%). In the experiments of the second group with a lesser degree of narrowing of the renal arteries, cerebral hemorrhages were observed in 13 cases of 36 animals (36.2%). In the experiments of the third group with renal extirpation on one side and narrowing of the renal artery on the other side, cerebral hemor-

<table>
<thead>
<tr>
<th>Constriction of Renal Arteries</th>
<th>No. of Cases</th>
<th>Brain Hemorrhage</th>
</tr>
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<tbody>
<tr>
<td>R: 0.7–0.8 mm.</td>
<td>28 Cases</td>
<td>14 Cases (50.0%)</td>
</tr>
<tr>
<td>L: 0.9–1.0 mm.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R: 0.8 mm.</td>
<td>36 Cases</td>
<td>13 Cases (36.2%)</td>
</tr>
<tr>
<td>L: 1.0–1.1 mm.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral Nephrectomy +1.1 mm.</td>
<td>10 Cases</td>
<td>4 Cases (40.0%)</td>
</tr>
<tr>
<td>Total No. of Cases</td>
<td>74 Cases</td>
<td>31 Cases (41.9%)</td>
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</table>
Table II. Visceral Hemorrhages in Goldblatt's Rabbits

<table>
<thead>
<tr>
<th></th>
<th>Brain Hemorrhage (+)</th>
<th>Brain Hemorrhage (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>31 Cases</td>
<td>43 Cases</td>
</tr>
<tr>
<td>Stomach</td>
<td>13 Cases (42.0%)</td>
<td>22 Cases (51.2%)</td>
</tr>
<tr>
<td>Intestine</td>
<td>27 Cases (87.2%)</td>
<td>23 Cases (53.5%)</td>
</tr>
<tr>
<td>Heart</td>
<td>3 Cases (9.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Urinary Bladder</td>
<td>9 Cases (29.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Adrenal Gland</td>
<td>11 Cases (35.5%)</td>
<td>2 Cases (4.7%)</td>
</tr>
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</table>

Hemorrhages were observed in 4 of 10 cases. To sum up these 3 groups of experiments, the incidence of cerebral hemorrhages was 41.9% or 31 out of 74 animals. Spotty bleedings were not considered as cerebral hemorrhages.

Fig. 2 shows one of the experiments, with a massive hemorrhage in the cerebral parenchyma penetrating into the ventricle. The animal died 35 days after the application of the clamp on the renal arteries. The blood pressure was 210 mm.Hg.

(2) Cerebral hemorrhages and hemorrhages in other organs (Table II)

Hemorrhage in organs other than the brain was not infrequent in the cases with cerebral hemorrhages and was found even in cases without cerebral hemorrhages.

(3) Cerebral hemorrhages and blood pressure (Fig. 3) (Table III)

The animals which developed cerebral hemorrhages died mostly within 50 days after the final operation. The longest survival was 389 days. These animals showed a minimal, moderate or marked elevation of the systemic blood pressure. The incidence of cerebral hemorrhages was more frequent in the group showing hypertension above 130 mm.Hg than in the group with
blood pressure below 130 mm.Hg. The incidence of gastrointestinal hemorrhages, however, was not different in the 2 groups.

(4) Cerebral hemorrhages and fibrinoid necrosis of the small arteries and arterioles in the brain and other organs (Table IV)

Fibrinoid necrosis of the small arteries and arterioles in the brain was demonstrated in 20 of 21 cases with cerebral hemorrhage. In these cases, fibrinoid necrosis was also frequent in other organs: the gastrointestinal tracts, heart, liver and suprarenal gland.

Table III. Blood Pressure and Brain Hemorrhage

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>&lt;129 mm. Hg</th>
<th>33 Cases</th>
<th>&gt;130 mm. Hg</th>
<th>41 Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain Hemorrhage</td>
<td>9 Cases (27.2%)</td>
<td></td>
<td>22 Cases (53.6%)</td>
<td></td>
</tr>
<tr>
<td>Gastric Hemorrhage</td>
<td>16 Cases (48.5%)</td>
<td></td>
<td>19 Cases (46.4%)</td>
<td></td>
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<tr>
<td>Intestinal Hemorrhage</td>
<td>22 Cases (66.7%)</td>
<td></td>
<td>28 Cases (68.4%)</td>
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</tbody>
</table>

(* p < 0.02)

Table IV. Brain Hemorrhage and Arterial Fibrinoid Necrosis (F.N.)

<table>
<thead>
<tr>
<th>F.N.</th>
<th>Brain Hemorrhage (+) 21 Cases</th>
<th>Brain Hemorrhage (-) 19 Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>20 Cases (95.2%)</td>
<td>8 Cases (42.1%)</td>
</tr>
<tr>
<td>G-I Tract</td>
<td>20 Cases (95.2%)</td>
<td>10 Cases (52.6%)</td>
</tr>
<tr>
<td>Heart</td>
<td>10 Cases (47.6%)</td>
<td>8 Cases (42.1%)</td>
</tr>
<tr>
<td>Liver</td>
<td>9 Cases (42.8%)</td>
<td>6 Cases (31.6%)</td>
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</table>
Fibrinoid necrosis was also frequently observed in the small arteries and arterioles in the brain and other organs, even in cases without cerebral hemorrhage.

Fig. 4 shows fibrinoid necrosis of the meningeal small artery in an animal with massive cerebral hemorrhage. Fibrinoid substance is deposited in the wall of the vessel, destroying the normal structure (elastica trichrom stain).

Fig. 5 shows fibrinoid necrosis of the arterioles in the right ventricle of the heart.

Fig. 6 shows fibrinoid necrosis and dilation of a small artery in the brain, giving the appearance of a pseudoaneurysm. The animal showed hemorrhages in the cerebral parenchyma as well as in the gastrointestinal tracts and bladder. The animal died 398 days after the operation. The blood pressure reached the maximum level of 168 mm Hg.

Fig. 7 shows fibrinoid necrosis of the small artery of the ileum in the animal shown in Fig. 5.
(5) Blood pressure and fibrinoid necrosis of the small arteries and arterioles (Table V)

Similar incidences of fibrinoid necrosis were noted between the markedly hypertensive group (above 130 mm.Hg) and slightly hypertensive or normotensive group (below 130 mm.Hg) in the small arteries and arterioles in the brain, gastrointestinal tract, heart and liver.

**DISCUSSION**

Cerebral hemorrhage is one of the most important causes of death in hypertensive patients in Japan. Throughout the world, however, there have been only a few studies of the pathogenesis of cerebral hemorrhages. Among the experimental studies of cerebral hemorrhage, Winternitz (1941) produced cerebral hemorrhage by injecting the extract of testis in bilaterally nephrectomized dogs. In experimental renal hypertension, several investigations observed cerebral hemorrhages. Necrotizing changes of the arterioles were considered the primary lesion which subsequently led to cerebral hemorrhage in human hypertension. Matsuoka and Okinaka et al. clearly demonstrated this sequence of events in experimental hypertension as well as in autopsied material of human hypertensives.

In experimental renal hypertension, there has been a discrepancy between the incidence of fibrinoid necrosis in the small arteries and arterioles and the degree of elevation of the blood pressure. This discrepancy might be due to the difference in the grade of the narrowing of the renal arteries, or to the presence of 2 independent factors which separately caused the fibrinoid necrosis and the high blood pressure. We have chosen the shape of the clamp in order to regulate the grade of narrowing of renal arteries with good reproducibility. Moderate narrowing of the renal arteries seemed to be important in the development of cerebral hemorrhage. Cerebral hemorrhage was frequent in the markedly hypertensive animals. The high blood pressure...
seemed to accelerate the rupture of the small arteries with fibrinoid necrosis
and to augment the incidence of cerebral hemorrhages.

The fact that fibrinoid necrosis occurred in the vessels in the brain as well
as in other organs might indicate that fibrinoid necrosis in the brain represents
one of the manifestations of generalized and systemic vascular lesion in the
whole body. The incidence of fibrinoid necrosis of the vessels was fairly
frequent in animals without cerebral hemorrhages but not quite as frequent as
in animals with cerebral hemorrhages. Moreover, the appearance of fibrinoid
necrosis seems to be independent of the grade of high blood pressure. These
findings suggest that the primary factor responsible for cerebral hemorrhage
is the fibrinoid necrosis in the small arteries and arterioles in the brain and not
the high blood pressure itself, although hypertension may accelerate the rupture
of the vessels with the fibrinoid necrosis.

As a matter of fact, the occurrence of fibrinoid necrosis seems to be inter-
mittent for the following reasons. In a long-lived animal with a high blood
pressure, lesions of fibrinoid necrosis were found in both the acute and chronic
forms, some of which seemed to shift to hyalinization. The incidence of fibrin-
od necrosis appears to be higher in animals which died spontaneously than
in animals which were killed artificially.

Some investigators have suggested that the fibrinoid necrosis might be
a secondary phenomenon, caused by high blood pressure,14), 15) especially high
diastolic pressure. Our data have failed to support this concept and strongly
indicates the independence of these 2 changes. It is most likely that 2
separate factors produce the fibrinoid necrosis and the high blood pressure
independently, although the cause of the fibrinoid necrosis of the vessels is
still obscure.

Summary

Using rabbits, massive cerebral hemorrhages were produced in 31 of 74
animals (41.9%) which underwent Goldblatt's type of experimental renal
hypertension.

Fibrinoid necrosis of the small arteries and arterioles in the brain was
observed in the animals with and without cerebral hemorrhages. Fibrinoid
necrosis of the cerebral vessels seems to be the primary pathogenetic vascular
lesion for cerebral hemorrhages and for rupture of the cerebral vessels with
fibrinoid necrosis which rupture caused massive cerebral hemorrhages. Fibrin-
od necrosis of the cerebral vessels appeared to be one of the manifestations
of the generalized vascular lesions in the whole body.

High blood pressure augmented the incidence of cerebral hemorrhages.
Fibrinoid necrosis of the vessels in the brain and other organs, however, was frequently observed in slightly hypertensive as well as in markedly hypertensive animals. Therefore, the occurrence of fibrinoid necrosis and high blood pressure are considered to be due to 2 different factors.

ACKNOWLEDGMENT

We wish to express our sincere gratitude to Prof. Emeritus S. Okinaka and to Prof. K. Nakao, the director of the Third Department of Internal Medicine, University of Tokyo, for their guidance and encouragement. We are also indebted to Dr. F. Amako, the Head of Yokufukai Hospital for the Aged.

REFERENCES