Pathological Studies on the Intracerebral and Retinal Arteries in Cerebrovascular and Noncerebrovascular Diseases

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Abstract:
Histological examinations of the intracerebral and retinal arteries were performed in patients who had cerebrovascular disease and in those cases who did not. Fibrinoid degeneration, fibrous nodule, and splitting, which are most frequently found in putamen, thalamus and pons, are thought to be the main changes in cerebral hemorrhage and infarction. Fibrous and fibro-hyalinoid thickenings of the retinal arteries were found mainly in the neighboring region of the optic disk, which reflects the changes of the intracerebral arteries. Hyalinoid thickening was found in the ora serrata, which does not reflect the changes of the intracerebral arteries.

Our results suggest that patients with these retinal artery changes in the region near the optic disk, if moderate to severe, have an increased risk of having or incurring cerebral hemorrhage and infarction, but the arterial changes in the ora serrata do not always indicate risk of cerebral hemorrhage and infarction.

Additional Key Words
- cerebral hemorrhage
- fibrinoid degeneration
- cerebral infarction
- splitting
- fibrous nodule
- putamen
- thalamus
- hypertension
- atherosclerosis
- pons
- other

The significance of the changes of the retinal arteries in various disorders, particularly cerebrovascular diseases, has been of interest to physicians, and controversy exists as to whether the degenerative changes of the intracerebral arteries are parallel to those of the retinal arteries. Several attempts have been made to show the relationship between the changes of these arteries.1-5 However, the comparative analyses of the changes between intracerebral and retinal arteries were not sufficient.

The purpose of this paper is to describe the intracerebral and retinal vascular changes in various types of cerebrovascular diseases (CVD) in the Japanese and the relationship of various degenerative changes between intracerebral and retinal arteries.

Methods
Histological examinations were performed in 22 patients with cerebrovascular diseases. Of these, 11 patients (age range: 37 to 76 years with an average of 58 years) had cerebral hemorrhage. There were eight cases with cerebral infarction (age range: 62 to 85 years with an average of 73 years). The remaining three cases had subarachnoid hemorrhage, their ages being 29, 68 and 75 years. An additional 21 cases without cerebrovascular diseases (non-CVD) were studied (age range: 21 to 69 years with an average of 49 years). An age-matched control study was performed in 12 cases (cerebral hemorrhage in nine, and cerebral infarction in three) with an age range from 37 to 68 years (average of 57 years), and in 12 non-CVD cases, ranging in age from 37 to 69 years (average of 57 years).

In each case 15 samples were taken of the basal ganglia at levels through the mamillary bodies and the tuber cinereum, including the globus pallidus, caudate nucleus, internal capsule, thalamus and putamen; the frontal, parietal and temporal lobes, including the motor and sensory cortices, were also sampled. The occipital lobes with the visual cortices, the cerebellum with the dentate nucleus, the pons through the locus ceruleus, and the eyes also were included. Both sides of each paired structure were examined. All blocks of the brains were embedded in paraffin, and all blocks of the eyes in celloidin. The sections were stained with hematoxylin and eosin, elastica van Gieson, PAS and Mallory's Azan stain. A minimum of 100 serial sections of each eye and a minimum of 30 serial sections of each brain sample were examined.

The severity of each degenerative change of the intracerebral and retinal arteries was recorded as none (−), mild (+) = mild localized change in the vessel wall, moderate (++) = moderate change in the localized or entire vessel wall, or severe (+++) = severe change in the entire vessel wall.

Results
Major degenerative changes of the intracerebral arteries were fibrinoid degeneration with or without aneurysmal dilatation (fig. 1), fibrous nodule (organized microaneurysm, the lumen obliterated by a thrombus or fibrous connective tissue, fig. 2), splitting

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Intracerebral artery with fibrinoid degeneration and perivascular cell infiltration. Thalamus. Hematoxylin and eosin, X 340.

(Fußsplitterung) with or without foam cell formation (fig. 3), intimal fibrous thickening (fig. 4), fibro-hyalinoid thickening, and calcification. Changes of the retinal arteries were fibrinoid degeneration, fibrous thickening (fig. 5), fibro-hyalinoid thickening, and hyalinoid thickening (fig. 6).

CHANGES IN THE INTRACEREBRAL ARTERIES (TABLES 1 and 2)

Fresh fibrinoid degeneration of the intracerebral arteries was found in 10 of 11 cases with cerebral hemorrhage and six of eight cases with cerebral infarction. This was not seen in subarachnoid hemorrhage and non-CVD cases, which is a significant difference (P < 0.001). In a case of cerebral hemorrhage without fibrinoid degeneration of the intracerebral arteries, hemorrhage was localized only in the white matter of the left temporal lobe. Arteries with fibrinoid degeneration often showed microaneurysm dilatation (fig. 7) and fibrous nodule formation (fig. 2). Occasionally, rupture of the part of the arteries with fibrinoid degeneration was observed (fig. 8). The arteries with fibrinoid degeneration ranged in size from 50 μ to 300 μ. Fibrous nodule formation, seen in arteries ranging in size from about 400 μ to 1,000 μ, was present in 6 of 11 cases with cerebral hemorrhage and three of eight cases with cerebral infarction. Eight of nine cases with fibrous nodules also had fibrinoid degeneration. This was not seen in subarachnoid hemorrhage and non-CVD cases. The difference between CVD cases, except for subarachnoid...
hemorrhage, and non-CVD cases was significant (P < 0.01). Splitting of the intracerebral arteries was seen in 7 of 11 cases with cerebral hemorrhage, six of eight cases with cerebral infarction, one of three cases with subarachnoid hemorrhage, and only 1 of 21 non-CVD cases. The difference between CVD and non-CVD cases is significant (P < 0.01), except for subarachnoid hemorrhage. Intimal fibrous thickening was seen in all cases with cerebral hemorrhage and infarction, two of three cases with subarachnoid hemorrhage, and 13 of 21 non-CVD cases. The difference in this factor between CVD and non-CVD cases is not significant (P > 0.05). Moderate to severe intimal fibrous thickening was found in 10 of 11 cases with cerebral hemorrhage, all eight cases with cerebral infarction, and 1 of 21 non-CVD cases, but similar changes were not found in cases with subarachnoid hemorrhage. The difference between CVD cases, except for subarachnoid hemorrhage, and non-CVD cases is significant (P < 0.01). Fibro-hyalinoid thickening was found in all cases with cerebral hemorrhage and infarction, two of three cases with subarachnoid hemorrhage, and 11 of 21 non-CVD cases. Except for subarachnoid hemorrhage, the difference between the CVD cases and non-CVD cases is significant (P < 0.05). Calcification of the intracerebral arteries was found in 6 of 11 cases with cerebral hemorrhage, four of eight cases with cerebral infarction, one of three cases with subarachnoid hemorrhage and 10 of 21 non-CVD cases. The
difference in calcification between the CVD and non-CVD cases is not significant (P > 0.5).

There was no relationship to age in the frequency and severity of intimal fibrous and fibro-hyalinoid thickenings and calcification in non-CVD cases.

The sites of predilection of fibrinoid degeneration, fibrous nodule and splitting were in the putamen, thalamus and pons; those of intimal fibrous thickening in the putamen, thalamus, caudate nucleus, pons, etc.; those of fibro-hyalinoid thickening in the pallidum, cerebral cortices, etc.; and those of calcification exclusively in the pallidum (table 2).

CHANGES IN THE RETINAL ARTERIES (TABLE 3)
Fibrinoid degeneration of the retinal arteries was seen in only 3 of 22 CVD cases, that is, two cases with cerebral hemorrhage and one case with cerebral infarction. These three cases also had fibrinoid degeneration of the intracerebral arteries. No fibrinoid degeneration was found in non-CVD cases. Fibrous and/or fibro-hyalinoid thickenings, which were seen mainly in the neighboring region of the optic disk, were found in 12 of 21 non-CVD cases, and the frequency of these changes showed no relationship to age. Fibrous and/or fibro-hyalinoid thickenings were found in all 11 cases with cerebral hemorrhage (P < 0.05), which is significant, and in all eight cases with cerebral infarction (0.1 > P > 0.05), which is not significant, in comparison to non-CVD cases. Moderate to severe fibrous and/or fibro-hyalinoid thickenings were found in 3 of 21 non-CVD cases, 6 of 11 cases with cerebral hemorrhage, and five of eight cases with cerebral infarction, which is a significant difference between CVD and non-CVD cases (P < 0.05). Hyalinoid thickening, which was seen in the ora serrata retinae, was found in 10 of 21 non-CVD cases, 7 of 11 cases with cerebral hemorrhage, and four of eight cases with cerebral infarction, which is a nonsignificant difference between CVD and non-CVD cases (P > 0.5). Fibrous and/or fibro-hyalinoid thickenings and hyalinoid thickening were seen in two cases and two of three cases with subarachnoid hemorrhage, respectively.

RELATIONSHIP OF THE DEGENERATIVE CHANGES BETWEEN THE INTRACEREBRAL AND RETINAL ARTERIES (TABLE 4)
Fibrous and Fibro-hyalinoid Degeneration of the Retinal Arteries and Changes of the Intracerebral Arteries
In 33 cases with fibrous and/or fibro-hyalinoid thickening of the retinal arteries, 15 cases (45.5%) had

| TABLE 2
The Sites of Predilection of the Intracerebral Artery Changes |
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sites of brain</td>
</tr>
<tr>
<td>Putamen</td>
</tr>
<tr>
<td>Thalamus</td>
</tr>
<tr>
<td>Caudate nucleus</td>
</tr>
<tr>
<td>Pallidum</td>
</tr>
<tr>
<td>Internal capsule</td>
</tr>
<tr>
<td>Frontal lobe</td>
</tr>
<tr>
<td>Parietal lobe</td>
</tr>
<tr>
<td>Temporal lobe</td>
</tr>
<tr>
<td>Occipital lobe</td>
</tr>
<tr>
<td>Cerebellum</td>
</tr>
<tr>
<td>Pons</td>
</tr>
</tbody>
</table>

A numeral shows the number of cases.
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### TABLE 3

<table>
<thead>
<tr>
<th>Retinal artery changes</th>
<th>Cerebral hemorrhage</th>
<th>Cerebral infarction</th>
<th>Non-CVD cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>X²-distribution</td>
<td></td>
</tr>
<tr>
<td>Fibrinoid degeneration</td>
<td>2/11</td>
<td>&gt;0.2</td>
<td></td>
</tr>
<tr>
<td>Fibrous nodule formation</td>
<td>11/11</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Moderate to severe fibrous and/or fibro-hyalinoid thickenings</td>
<td>6/11</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Hyalinoid thickening</td>
<td>7/11</td>
<td>&gt;0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;0.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There are significant differences in the presence of fibrinoid degeneration (P < 0.05), fibrous nodules (P < 0.05), splitting (P < 0.05), intimal fibrous thickening (P < 0.05), and fibro-hyalinoid thickening (P < 0.05) in the intracerebral arteries between groups with and without fibrinoid degeneration of the retinal arteries. However, there is no significant difference in the presence of calcification of the intracerebral arteries between both groups (P > 0.2).

### Hyalinoid Thickening of the Retinal Arteries and Changes of the Intracerebral Arteries

In 19 cases without hyalinoid thickening of the retinal arteries, six cases (31.6%) had fibrinoid degeneration in the intracerebral arteries, five (26.3%) had fibrous nodules, seven (36.8%) had splitting, 12 (63.2%) had fibro-hyalinoid thickening, 14 (73.7%) had intimal fibrous thickening, and seven (36.8%) had calcification.

In 24 cases with hyalinoid thickening of the retina, nine cases (37.5%) had fibrinoid degeneration in the intracerebral arteries, four (16.7%) had fibrous nodules, eight (33.3%) had splitting, 20 (83.3%) had fibro-hyalinoid thickening, and 14 (58.3%) had intimal fibrous thickening, and 14 (58.3%) had calcification.

Between groups with and without hyalinoid thickening of the retinal arteries, there is no significant difference in the presence of degenerative changes of the intracerebral arteries, such as fibrinoid degeneration, fibrous nodules, splitting, intimal fibrous and fibro-hyalinoid thickening and calcification (P > 0.5).

### AGE-MATCHED CONTROL STUDY IN CVD AND NON-CVD CASES

Fibrinoid degeneration of the intracerebral arteries was found in 11 of 12 CVD cases, fibrous nodules in five cases, and splitting in nine. On the other hand, none of 12 non-CVD cases had fibrinoid degeneration, fibrous nodules, or splitting. There was a significant difference in the frequency of fibrinoid degeneration (P < 0.01), fibrous nodules (P < 0.05), and splitting (P < 0.01). Intimal fibrous and fibro-hyalinoid thickenings of the intracerebral arteries were seen in all 12 CVD cases and 8 of 12 non-CVD cases, which is a nonsignificant difference (P > 0.13). Moderate to severe intimal fibrous and fibro-hyalinoid thickenings

### TABLE 4

<table>
<thead>
<tr>
<th>Retinal artery changes</th>
<th>No. of cases</th>
<th>P</th>
<th>No. of cases</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinoid degeneration</td>
<td>15/33</td>
<td>&lt;0.05</td>
<td>9/24</td>
<td>6/19</td>
</tr>
<tr>
<td>Fibrous nodule formation</td>
<td>9/33</td>
<td>&lt;0.05</td>
<td>4/24</td>
<td>5/19</td>
</tr>
<tr>
<td>Splitting</td>
<td>15/33</td>
<td>&lt;0.05</td>
<td>8/24</td>
<td>7/19</td>
</tr>
<tr>
<td>Intimal fibrous thickening</td>
<td>29/33</td>
<td>&lt;0.05</td>
<td>20/24</td>
<td>14/19</td>
</tr>
<tr>
<td>Fibro-hyalinoid thickening</td>
<td>28/33</td>
<td>&lt;0.05</td>
<td>20/24</td>
<td>12/19</td>
</tr>
<tr>
<td>Calcification</td>
<td>17/33</td>
<td>&gt;0.2</td>
<td>14/24</td>
<td>7/19</td>
</tr>
</tbody>
</table>

P: Chi-square distribution.
of the intracerebral arteries were seen in 11 of 12 CVD cases, while moderate to severe intimal fibrous and fibro-hyalinoid thickenings were found in only one case and 4 of 12 non-CVD cases, respectively. This is a significant difference (intimal fibrous thickening, \( P < 0.01 \); fibro-hyalinoid thickening, \( P < 0.05 \)).

Calcification of the intracerebral arteries was seen in 7 of 12 CVD cases and 5 of 12 non-CVD cases, which showed no significant difference between these groups (\( P > 0.2 \)). Fibrous and/or fibro-hyalinoid thickenings of the retinal arteries were seen in all 12 CVD cases and 7 of 12 non-CVD cases, which revealed no significant difference between these groups (\( P = 0.06 \)). Moderate to severe fibrous and fibro-hyalinoid thickenings of the retinal arteries were seen in only 1 of 12 non-CVD cases and 7 of 12 CVD cases, which showed a significant difference (\( P < 0.05 \)). Hyalinoid thickening of the retinal arteries was found in 7 of 12 non-CVD cases and 6 of 12 CVD cases, which showed no significant difference between these groups (\( P > 0.3 \)).

Discussion

Many authors have reported that fibrinoid degeneration, fibrous nodules and splitting are found most frequently in the basal ganglia, particularly in the putamen,\(^{6-13}\) where cerebral hemorrhage and infarction are seen most frequently.\(^{14-17}\) Fibrinoid degeneration and fibrous nodules of the intracerebral arteries were not found in non-CVD cases, and only in those cases with cerebral hemorrhage and infarction. Splitting of the intracerebral arteries, which caused narrowing of the arterial lumen, was seen in only 1 of 21 non-CVD cases and in about half of the CVD cases. Our studies also showed that the sites of predilection of fibrinoid degeneration, fibrous nodules, and splitting in the intracerebral arteries are in the putamen, thalamus and pons, and the arteries with fibrinoid degeneration develop microaneurysms which are thought to rupture or convert to fibrous nodules, as described by others.\(^{6-13}\) These results suggest that in the intracerebral arteries, fibrinoid degeneration, fibrous nodules, and splitting are the main causes of cerebral hemorrhage and infarction, as suggested by other studies.\(^{6-13}\)

The appearance and severity of intimal fibrous and fibro-hyalinoid thickenings did not increase with age in non-CVD cases. All cerebral hemorrhage and infarction cases had intimal fibrous and fibro-hyalinoid thickenings of the intracerebral arteries, and about two-thirds of the cases with subarachnoid hemorrhage and the non-CVD cases also had these changes. No significant difference in the appearance of intimal fibrous and fibro-hyalinoid thickenings was seen, but there was a significant difference in that of moderate to severe intimal fibrous and fibro-hyalinoid thickenings when cerebral hemorrhage and infarction cases and non-CVD cases were compared. This suggests that intimal fibrous and fibro-hyalinoid thickenings as a whole are not closely related to the aging process and the development of CVD, but moderate to severe thickenings (the pathological changes of the arteries) are related to the development of CVD. Calcification was most frequently found in the pallidum, which is not the site of predilection of cerebral hemorrhage and infarction, and there is no significant difference in the frequency of this arterial change between cerebral hemorrhage and infarction cases and non-CVD cases. This change, therefore, is probably not one of the main changes in cerebral hemorrhage and infarction.

Fibrous and fibro-hyalinoid thickenings of the retinal arteries were found mainly in the neighboring region of the optic disk, while arterial changes in the ora serrata (the marginal area of the retina) consisted of hyalinoid thickening. Several studies were done to clarify the correlation between the changes of the intracerebral arteries and those of the retinal arteries.\(^1,4\) Rintelen\(^1\) and Alpers et al.\(^2\) reported that the arteriosclerotic changes of the retinal arteries do not reflect those of the intracerebral arteries, while Lund and Peters\(^1\) reported that the arteriosclerotic changes of the intracerebral arteries paralleled those of the retinal arteries in 82% of their cases. However, in these previous studies, the arterial changes in the brain were compared with those of the retina without differentiation between the various types of arterial changes.

The three cases with fibrinoid degeneration of the retinal arteries had cerebral hemorrhage or infarction, and also had fibrinoid degeneration of the intracerebral arteries. All CVD cases had fibrous and fibro-hyalinoid thickenings in the retinal arteries. Cases without fibrous and/or fibro-hyalinoid thickenings of the retinal arteries had neither fibrinoid degeneration, fibrous nodules nor splitting, which are thought to be the main changes in cerebral hemorrhage and infarction. Half of these cases had only mild intimal fibrous thickening with no moderate to severe changes in the intracerebral arteries. This suggests less risk in the development of cerebral hemorrhage and infarction in those cases without these changes in the retinal arteries.

There was no significant difference in the presence of the degenerative changes of the intracerebral arteries between groups with and without hyalinoid thickening of the retinal arteries. There was no significant difference in the presence of hyalinoid thickening of the retinal arteries between CVD and non-CVD cases. According to these results, hyalinoid thickening in the ora serrata does not necessarily indicate the presence of arterial changes in the brain (the risk of the development of CVD).

There was no significant difference in the frequency of fibrous and/or fibro-hyalinoid thickenings of the retinal arteries between CVD and non-CVD cases in an age-matched control study (\( P = 0.06 \)). The number of cases was probably too small for valid statistical
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analysis. However, there was a significant relationship between the presence of fibrinoid degeneration, fibrous nodules, splitting, intimal fibrous and fibro-hyalinoid thickenings in the intracerebral arteries and the presence of fibrous and/or fibro-hyalinoid thickenings of the retinal arteries near the optic disk. There also was a significant difference in the presence of moderate to severe fibrous and/or fibro-hyalinoid thickenings of the retinal arteries between cerebral hemorrhage and infarction cases and non-CVD cases. These facts suggest that the arterial changes in the region near the optic disk reflect the changes of the intracerebral arteries. Patients with these retinal artery changes, if moderate to severe, have an increased risk of having or incurring cerebral hemorrhage and infarction, but the arterial changes in the ora serrata do not always indicate risk of CVD.

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References

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