The Smaller Intracerebral Vessels

BY ANNA L. ELLINGTON, M.D.

Abstract:
A pathological study of the smaller intracerebral arteries of 150 to 600 μ was made in 336 cases, ranging in age from 1 day to 96 years. The changes involved the media and adventitia in contradistinction to the large cerebral vessels which showed predominantly intimal changes. The degree of change in the smaller intracerebral arteries was age related but not on a 1:1 basis. A comparison of the degree of change was also made with the large cerebral vessels of the circle of Willis, and although both were age related, they did not appear to be related to each other.

ADDITIONAL KEY WORDS cerebral arteriosclerosis circle of Willis age and smaller intracerebral vessels

Atherosclerosis, as defined by the World Health Organization, "is a variable combination of changes of the intima of arteries (as distinct from arterioles) consisting of the focal accumulation of lipids, complex carbohydrates, blood and blood products, fibrous tissue and calcium deposits and associated with medial changes."

With more advanced changes the lesion is well seen grossly with plaque formation and varying degrees of lumen narrowing. These changes, both gross and microscopic, are easily recognized in the large vessels of the circle of Willis and their branches. However, little attention has been given to the histological appearance of the smaller intracerebral vessels. Baker and Ianone, in a study of the smaller intracerebral vessels of 150 to 500 μ, in 100 cases, stated that these vessels showed changes which are distinctly different from those in the larger vessels. The purpose of this communication is to describe the changes in smaller intracerebral arteries of 150 to 600 μ found in a study of a larger number of cases and to correlate these changes with certain clinical and/or pathological conditions.

Methods
Material was obtained from 345 unselected autopsied cases from the University of Minnesota Hospitals in the years 1960, 1961, and 1962. The age range was 1 day to 96 years with 55% males and 45% females. Sections were taken from the frontal, parietal, and occipital lobes, fixed in formalin, and stained with hematoxylin and eosin, Weigert, and Van Gieson stains. It was arbitrarily decided that at least ten vessels of the stated size be examined in each case.

Because of the possibility that the changes in the pial vessels and those deep in the sulci or parenchyma might differ quantitatively and/or qualitatively, separate grading was done in each location. In the smaller pial and parenchymal vessels, i.e., those of 100 to 600 μ, no difference was noted in 100 cases where ten such vessels in each location were available for study. With this information it was felt that ten vessels of the desired size from either or both locations were adequate. Nine cases were discarded because of the lack of a sufficient number of vessels, and of these, five were under one month of age and all were in the first decade. However, the final 336 cases did include two under the age of one month (one day and three weeks).

Microscopic Examination
The smaller intracerebral vessels belonged to the group classified as muscular arteries and showed three well-defined layers. The intima consisted of an endothelial layer, surrounded by a well-formed, fairly compact internal elastic layer. External to the internal elastic layer and completely surrounding it was the media, composed of muscle fibers which were in layers. The number of intertwining fibers

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were variable, but generally, the width of the media in a given normal vessel was fairly constant throughout the circular diameter of the vessels. Sharp demarcation occurred between the intima and media and also between the media and adventitia. However, the adventitia was the most variable layer, often discernible, if at all, as a few fibrous strands irregularly arranged around the media. A few strands of connective tissue could be detected on careful observation between the muscle fibers (fig. 1).

The changes in the vessels from the above-described normal vessel involved mainly the media and adventitia. The adventitial connective tissue early showed an increase around the entire vessel or only around certain areas. At this time the adventitia and media were still clearly delineated (fig. 2), although strands of connective tissue between the muscle fibers could often be seen without difficulty. As the adventitia increased in thickness and was present around the entire vessel circumference, one of two patterns, as seen in the media, was observed: (1) Frequently, the connective tissue between the muscle fibers was increased throughout the media but, more often in the external layers and the media and adventitia, were no longer clearly delineated (fig. 3). The appearance suggested proliferation of adventitial fibers, which had then invaded and separated the individual muscle fibers. Externally, the adventitia usually maintained its smooth contour. (2) The second pattern, in which there was marked increase of the adventitial layer,
revealed a decrease in the muscle fiber layer which had a compressed appearance. Between the muscle fibers, connective tissue fibers were very few. It was as if the connective tissue fibers had "coalesced," compressing the muscle layer (fig. 4). Whether this increase in connective tissue was due to proliferation of the adventitia alone or in combination with the increase in connective tissue between fibers is not known, but certainly, the microscopic picture suggested that the adventitia played a significant role.

Discussion
The severity of changes in any case may vary not only from section to section, but also in the same section. Generally, it was unusual to find only one vessel with marked increase in the adventitial layer while the remaining vessels showed only a mild increase. The severity of change, however, did appear to increase as the diameter of the vessel decreased. In no case was a vessel seen where the media was entirely replaced by connective tissue. Invariably, a vessel suspected of showing such changes on scanning the slide was found to be smaller than 150 μ. Occasionally, vessels larger than 600 μ showed typical atherosclerotic intimal changes with plaque formation. These changes stood out in marked contrast to the changes seen in smaller vessels.

The intracerebral arteries were graded according to the coding system suggested by

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Grade 1—Mild to marked increase in the thickness of the adventitia only around certain areas of the vessel or around the entire vessel.

Grade 2—Marked increase of the adventitia with replacement of up to two-thirds of the media.

Grade 3—Adventitial increase with fibrous replacement of all or almost all of the media.

Grade 4—Medial hyalinization or adventitial increase that encroaches on the vessel lumen.

In the present series each case was given a number according to the greatest degree of involvement seen. Grade 4 changes were not seen in any of the cases studied.

Results
A comparison of grade with age is shown in table 1, and there was a definite increase in the severity of changes with increasing age. If we consider grades 0 and 1 as representing normal or minimal changes and grades 2 and 3 as representing moderate to severe changes, then significant changes could be seen as early as the second decade. On the other hand, almost one-fourth (23%) of the cases above the eighth decade showed little or no change. Thus, it appears that the changes were not invariably age related and possibly other factors were of importance.
The muscle layer appears as thin rim in grade 3 vessel of 89-year-old female (Van Gieson stain, × 250).

**TABLE 1**
Comparison of Age with Grade in 336 Cases

<table>
<thead>
<tr>
<th>Age</th>
<th>Number of cases</th>
<th>0 (93%)</th>
<th>1 (7%)</th>
<th>2 (15%)</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>40</td>
<td>37</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-19</td>
<td>13</td>
<td>11</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>12</td>
<td>7</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>14</td>
<td>2</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>40</td>
<td>20</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>55</td>
<td>17</td>
<td>16</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>60-69</td>
<td>67</td>
<td>17</td>
<td>12</td>
<td>32</td>
<td>9</td>
</tr>
<tr>
<td>70-79</td>
<td>65</td>
<td>12</td>
<td>15</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>80+</td>
<td>30</td>
<td>3</td>
<td>4</td>
<td>10</td>
<td>13</td>
</tr>
</tbody>
</table>

*No grade 4 changes were seen.

Since complete autopsy reports were available in all cases and complete clinical information was available on most cases, a comparison of changes with certain somatic...
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FIGURE 5
Intracerebral vessel versus circle of Willis scores. (A) Ages 40 to 49, (B) ages 50 to 59, (C) ages 60 to 69, (D) ages 70 to 79.

Diseases was made, including vascular heart disease, malignancies, and hypertension. The category of vascular heart disease included those with (1) heart weight of greater than 450 g but without congenital or acquired valvular disease or (2) heart weight of less than 450 g when there was a definite clinical and/or pathological diagnosis of HCVD and ASHD. The criterion for hypertension was a history of hypertension recorded in the clinical chart. No effort was made to group malignancies, and diagnosis was based solely on pathological information. These included all age groups, but the diagnosis of hypertension or vascular heart disease was not made in the series in any case under 40 years. In table 2 no significant relationship is noted between severity of changes and the somatic diseases listed.

Because the changes seen in the smaller

<table>
<thead>
<tr>
<th>Somatic Diseases</th>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular heart disease</td>
<td></td>
<td>22</td>
<td>16</td>
<td>41</td>
<td>18</td>
<td>97</td>
</tr>
<tr>
<td>Malignancies</td>
<td></td>
<td>50</td>
<td>37</td>
<td>49</td>
<td>23</td>
<td>159</td>
</tr>
</tbody>
</table>

Because the changes seen in the smaller

| Hypertension (ages 40+ yr.) |       | 13  | 5   | 15  | 12  | 45    |
intracerebral vessels were fairly characteristic and strikingly different from those described in the large cerebral vessels at the base of the brain and since the latter have been shown to be age related, the two groups of cerebral vessels were then compared.

The method of grading used for the large vessels at the base of the brain was that suggested by the World Federation of Neurology, and each case was scored according to the method of Resch and Baker. This was done in the three age groups where the number of cases with grading of both groups of vessels was 50 or more and also in the 40 to 49-year group to indicate the changes in the subsequent decades (fig. 5). Hypertension was also noted, although no statement can be made because of the small number in each group. The circle of Willis scores showed an increase with age as did the intracerebral scores, but these did not appear to be related to each other. Although no specific correlation could be made with the presence of hypertension and vessel scores, those with hypertension after the sixth decade did have higher scores in either group of vessels than those without in the same age groups.

Conclusion
1. The smaller intracerebral arterioles, as well as pial vessels, with a diameter of 150 to 600 μ showed changes which were characteristic, involving adventitia and probably secondarily the media, but without intimal changes.
2. These changes did increase in severity with age, significant changes first being seen in the second decade. However, no significant changes were seen in almost one-fourth of the subjects 70 years and above.
3. No correlation was noted between the smaller intracerebral arterioles and the large vessels comprising the circle of Willis.

These findings support those reported earlier by Baker and Iannone.

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