Arteriolar Tortuosity of the White Matter in Aging and Hypertension. A Microradiographic Study

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Abstract. Previous studies have shown tortuous arteries and arterioles in the brains of older people, but the effects of age and other factors have not been studied. To examine the effects of hypertension, age, sex and race on white matter (WM) arteriolar tortuosity (AT), we performed high-resolution microradiography and morphometry of human brains taken at autopsy from 44 subjects of various ages (range 30–96 years; 31 hypertensives/13 normotensives). About 70% of tortuositities in the WM were found at the gray–white interfaces of the insular region and adjacent subcortical-WM of the inferior frontal and superior temporal gyri. Six morphologic types of tortuous profiles were identified. The number of tortuous profiles increased with age, but not significantly. Hypertension, sex and race had no effect on tortuosity. Our findings also suggest that 1) WM AT is found mostly at the interfaces between gray matter and WM and, therefore, 2) the physical properties of the WM somehow predispose to the development of AT; 3) AT is not associated with tortuosity in the veins; and 4) the location of complex arteriolar coils supports a recent claim that they can be mistaken for the Charcot-Bouchard microaneurysms if injection of contrast media and low-magnification radiography of the brain slices are employed for that purpose.

Key Words: Alkaline phosphatase stain; Arteries; Arterioles; Human brain; Hypertension; Microaneurysms; Microradiography; White matter.

INTRODUCTION

Previous studies of human cadaver brains have shown an array of complex arterial tortuositities (AT) (1–4) which were attributed to aging (3–7) but their exact relationship to age, sex, race and hypertension have not been established. Tortuositities secondary to hypertension are found in other vascular beds (8–10). The functional significance of the AT has also not been determined, but a computer model of blood flow through such arterioles in the subcortical white matter (WM) suggested that AT increases local vascular resistance and that higher pressures than usual may be necessary to keep tortuous vessels open (11).

The present study was designed 1) to document in detail the morphologic features of AT in WM, 2) to document whether veins are involved by tortuosity, and 3) to examine the effects of age, hypertension, sex and race. We did not count the tortuous profiles in the gray matter, since they are much less common, less complex in appearance than the WM tortuositities, and are harder to quantify.

MATERIALS AND METHODS

The brains from 44 patients who died of various causes were obtained at autopsy. Sixteen of the brains were from females; 12 from blacks. Thirty-one of the 44 brains came from hypertensives, the diagnosis having been documented by modified Tracy’s criteria (12–13). Three to six outpatient recordings of blood pressure over 140/100 mm Hg and a written diagnosis of essential hypertension were required for inclusion of a patient in the hypertensive group. In addition, increased heart weight and left ventricular wall thickness without valvular disease and also renal arteriolosclerosis (granular kidneys)—both signs of hypertension—were demonstrated in all the hypertensives at autopsy. The remaining 13 patients served as age-, race- and sex-matched controls. All the hypertensives had been treated with a variety of antihypertensive drugs for essential hypertension for periods ranging from 5–20 years. None had malignant hypertension. One of the hypertensive cases was later excluded because of severe lesions in the area of interest. The patients ranged in age from 30 to 96 years. The brains were obtained between 2 and 24 hours postmortem and were refrigerated for 4 hours to facilitate gross sectioning. A midsagittal cut separated the hemispheres, which were further sectioned coronally. Large blocks of tissue (up to 5 × 5 × 1 cm) were cut out of the coronal slabs. In this study, the block of interest was bounded superiorly by the corona radiata, ventrally by the anterior perforating substance and mid temporal lobe, laterally by the insular cortex and adjoining cortical ribbon of the frontal region, and medially by the lateral and third ventricular surfaces. This block was one of 8–10 blocks obtained from each brain for the study of hypertension-induced changes as part of a different project. This block was preferred because 1) it had a mixture of both cortical and deep gray matter as well as WM of U-fiber, subcortical, deep and commissural regions, and 2) from previous experience we had found that sections from this block uniformly exhibited the greatest number of tortuous profiles among the total number of blocks from each brain.

The tissue block was fixed by immersion in cold, dilute formalin and then dehydrated in a series of alcohols. Next it was embedded in celloidin and sectioned at 100 and 500 μm on a sliding microtome, but only the 500 μm sections, offering a larger...
volume of tissue but too thick for direct light microscopic observations, were used in this study. First, the capillaries, arterioles, and small arteries were stained by the histochemical method for endothelial alkaline phosphatase (11, 16–18) which results in the precipitation of radioopaque lead sulfide in the endothelium. The 500 μm sections were decelloidinized, saturated with mineral oil, pressed and high-resolution contact microradiographs were made as described previously (16).

Line drawings of the microradiographs with internal detail were made at a standard magnification (5.5×) by placing them in the film plane of a photographic enlarger. The nuclear groups and WM tracts were readily discernible at low magnification because of the differences in capillary density. The microradiographs were then examined with the light microscope and all arterial/arteriolar profiles meeting the criteria for tortuosity (see below) were carefully plotted on the enlarged drawings. In this way, both the number and position of all tortuositites were recorded.

Arterioles considered tortuous in this study met the following criteria: (1) they had at least one abrupt change in direction that was not artifactual, i.e. the Virchow-Robin space followed the contour of the tortuosity; (2) they clearly deviated from a “natural” course; and (3) the change of direction was 90° or more within a length about three times the diameter of the vessel.

In most instances it was very clear whether an artery/arteriole met the criteria; however, several measures were taken to ensure reasonably accurate counting of the vessels. First, the plots themselves helped to prevent simple counting errors. Secondly, a pilot study in which 11 cases were counted by three observers showed that interobserver variation of tortuosity counts was negligible. For this reason, the counts for the rest of the study were obtained by one of us, without knowledge of the hypertensive status, age, race and sex.

The area of neuropil containing tortuous profiles in each case was measured from the calibrated plots with a computerized image analyzer (SMI-Microcomp, Atlanta, GA). Assuming a thickness of 500 μm per section, the volume of the neuropil was also calculated and tortuosity expressed as number of profiles per unit area or volume. The latter did not add to the clarity of the results and counts per unit area alone were adopted finally for statistical analyses.

The number of tortuositites for each patient was assumed to follow a Poisson distribution (because it was counted data), and a log-linear model was used to relate the expected number of tortuosities to the patient’s age, hypertensive status, race, and sex. In this way, we adjusted for the effect of each factor against all other factors in the data. An allowance was made for extraneous variation, that is, variation in excess of the usual Poisson dispersion. Significance was evaluated by dividing each effect by its standard error and comparing it to a t-distribution.

RESULTS

Tortuous small arteries and arterioles were found in 38 of the 43 cases. The alkaline phosphatase-negative veins, seen as ghost outlines, showed no tortuosity. Approximately 70% of the tortuous profiles were found in the WM of the external and extreme capsules and in the subcortical region of the insula, and in the subcortical WM of the adjacent cortical ribbon. In many cases, tortuous profiles were also found in the internal capsule, the corona radiata, the anterior commissure and, more rarely, the fornix and stria terminalis. The distribution suggested that tortuosity was more common at gray matter–WM interfaces. In many cases, the number of tortuous profiles in a 500 μm section, especially deep to the insular cortex, was quite impressive. Often arterioles and small arteries run a straight or a slightly wavy course through the cortex but exhibit pronounced tortuosity in transit through the adjacent WM. These vessels arise from medullary and subcortical arterioles and the tortuosities may run for considerable distances. Not all vessels show tortuosity and the fact that affected vessels do not appear shrunk within their Virchow-Robin spaces indicates that they are not artifacts of processing.

High-power photomicrographs of tortuous profiles provide examples of the types of changes seen (Fig. 1). Six basic patterns can be described. The first is a “kink,” a simple acute outward bend that does not otherwise alter the course of the vessel (Fig. 1A). The second is a “simple loop” (Fig. 1B), and the third is a “knot-like” structure (Fig. 1C). In most cases, the vessels appear to be in false knots rather than true knots, a feature revealed by high-power observation.

The remaining three types of tortuosities are more complex and involve a greater length of the vessel. The fourth type of change, the “tight spiral,” is seen only occasionally but is quite distinctive (Fig. 1D). The fifth type is the classic “spiral” or “corkscrew” (Fig. 1E), in which the vessel actually may appear to spiral or may meander back and forth within a single plane, similar to the course of a stream. This type is particularly characteristic of the insular region but occasionally is found elsewhere. The sixth type of change is the “complex” type (Fig. 1F), called the “glomerular loop” by other authors (1, 2, 4). Clearly, there is some gradation between the fifth and sixth types of changes as described here.

Analysis of the profile counts (Table 1) showed that the number of tortuosities increased with increasing age, but not significantly (p = 0.16). Despite this, the direction of the effects was interesting (Fig. 2). There was no significant relationship to hypertension (Table 1), sex and race. White patients had more tortuosities than did black patients, and male patients had more than did female patients.

DISCUSSION

Understanding the causes of WM AT is important because reduction in blood flow through tortuous arterioles could contribute to the overall decrease of cerebral blood flow that accompanies aging (19–21), or to focal abnormalities of the WM such as leuko-araiosis, a common condition seen in computerized tomographic or magnetic resonance images of elderly demented and non-demented subjects (22–28).
Fig. 1. High magnification microradiograph of six basic patterns of tortuous profiles: A) single kink, B) simple loop, C) knot-like structure, D) tight spiral, E) classic spiral, corkscrew or pig-tail, and F) complex type. Bar = 100 μm.
TABLE 1
Percentage of Tortuous Profiles in Six Regions of the Brain*

<table>
<thead>
<tr>
<th>Region</th>
<th>EC/EXC</th>
<th>Corona radiata</th>
<th>Anterior commissure</th>
<th>Internal capsule</th>
<th>Fornix</th>
<th>Stria terminalis</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>69.54 ± 27.12</td>
<td>5.62 ± 8.12</td>
<td>4.62 ± 8.12</td>
<td>15.48 ± 17.58</td>
<td>6.34 ± 9.46</td>
<td>3.69 ± 13.26</td>
</tr>
<tr>
<td>Age &gt; 65 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>66.41 ± 24.00</td>
<td>6.96 ± 7.24</td>
<td>6.62 ± 11.16</td>
<td>16.98 ± 17.70</td>
<td>5.65 ± 8.03</td>
<td>0.73 ± 1.35</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>66.73 ± 37.10</td>
<td>4.22 ± 6.15</td>
<td>3.24 ± 5.21</td>
<td>18.21 ± 20.26</td>
<td>7.84 ± 9.80</td>
<td>0</td>
</tr>
<tr>
<td>Age ≤ 65 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>66.18 ± 28.80</td>
<td>9.55 ± 15.88</td>
<td>5.60 ± 7.80</td>
<td>14.97 ± 17.91</td>
<td>4.85 ± 7.64</td>
<td>1.11 ± 2.72</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>78.32 ± 30.98</td>
<td>0</td>
<td>2.08 ± 4.16</td>
<td>5.55 ± 13.59</td>
<td>0</td>
<td>22.20 ± 38.50</td>
</tr>
</tbody>
</table>

This table shows the percentage of tortuous profiles which were found in each of six selected regions of the brain. The cases were divided into groups based on age and hypertensive status.

*All values are mean ± standard deviation, n = 38; EC = external capsule; EXC = extreme capsule and subcortical fibers of the insula.

The results of this study suggest that the number of WM AT is not increased in hypertensives. This finding is surprising and noteworthy because previous studies of retinal, conjunctival and myocardial vasculature indicated an association between arteriolar tortuosity and hypertension (8–10). In addition, recent work by Baumbach et al (29, 30) on hypertensive rats showed changes in arterial distensibility, and these could conceivably affect tortuosity in some way.

Previous studies claimed that the number of tortuositites was related to age (3, 5, 31–33). In Hassler’s study of a large series of autopsy specimens (31) none were less than 42 years old. The high-resolution microradiography is much more sensitive than the methods employed in the previous studies because one can visualize even 8–10 μm capillaries and at the same time a large area of the brain can be scanned for long distance tracing and counting of the tortuous arteries. The lack of a statistically significant relationship between AT and age in our study simply means that although tortuositites are found in the brains of older subjects, some older subjects may have fewer or more tortuositites than others of same age. Why some individuals are prone to AT needs to be explained. In addition, we do not know exactly why complex AT is so much more common in the WM and can only speculate that physical properties such as parallel orientation of myelinated fibers may somehow predispose to AT. The dense cellularity of the gray matter may prevent AT of the various types and complexity we found in the WM.

One important outcome of the current study is the fairly precise matching of the areas of prevalence of complex tortuositites with that of Charcot-Bouchard microaneurysms by Cole and Yates (34). We have recently suggested that the complex vascular coils in these locations, when filled with radiopaque media and radiographed at low magnifications, can be easily mistaken for Charcot-Bouchard aneurysms (35). The high-resolution microradiography clearly establishes the complex nature of these arteriolar coils and eliminates erroneous interpretation of these coils as microaneurysms.

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