Atherosclerosis of Cerebral Arteries in Alzheimer Disease

Alex E. Roher, MD, PhD; Chera Esh, BS; Afroza Rahman, PhD; Tyler A. Kokjohn, PhD; Thomas G. Beach, MD, PhD

Abstract—A growing body of evidence suggests that vascular disease underlies Alzheimer dementia. Atherosclerotic lesions in the circle of Willis and large leptomeningeal vessels were quantified and found to correlate with Alzheimer disease (AD) clinical diagnosis and neuropathology. We hypothesize that AD pathology is the complex end result of slowly evolving vascular disease and parenchymal lesions. Confirmation of a central role for vascular pathology in AD will suggest important treatment options and directions for additional interventions to stave off this dementia. (Stroke. 2004;35[suppl I]:2623-2627.)

Key Words: Alzheimer disease ■ atherosclerosis ■ cerebral ischemia ■ circle of Willis

A considerable body of clinical and experimental evidence has demonstrated that cerebral blood flow declines with age and that brain perfusion decreases are significantly greater in Alzheimer disease (AD) patients. 1–3 Epidemiological studies have revealed that many atherosclerotic vascular disease (AVD) risk factors are also AD risk factors. 4,5 Our studies have shown that the degree of atherosclerotic occlusion of the circle of Willis arteries is associated with both AD clinical diagnosis and the prevalence of AD neuropathological lesions at autopsy. 4 We hypothesize that AVD of the circle of Willis and related arteries is a major risk factor for AD development. Evaluation of the circle of Willis and leptomeningeal arterial atherosclerosis may be an effective clinical means to project an individual’s relative risk for developing AD and facilitate prospective identification of patients who would benefit from antiatherosclerotic therapy and changes in lifestyle that may prevent or delay both AVD and AD.

The emergence of AD may be an unintended and unwelcome consequence of medical advances that have greatly extended average life expectancy and cultural changes that continuously alter the dynamics of both our lifestyles and their attendant diseases. Atherosclerosis is considered the archetype of progressive and relentless age-related diseases because, among the elderly, it underlies almost half the deaths in the United States, including those due to coronary heart disease, stroke, and peripheral vascular disease. The inexorable evolution in the physical extent and plaque morbidity of the atherosclerotic lesions with time is complicated by continual reduction in the ability to repair damage inherent in the aging process.

The arteries of the brain originate from the circle of Willis and course through the leptomeninges before entering the brain parenchyma to supply the gray and white matter. Severe AVD of these leptomeningeal vessels is frequently present in AD cases, thus causing brain hypoperfusion conducive to a breakdown in energy metabolism as well as increasing the risk for cerebral infarct and dementia development. The degree of atherosclerotic occlusion of these arteries has never been rigorously measured in AD subjects. In the present study, we document the number and severity of major leptomeningeal arterial stenoses in a group of neuropathologically diagnosed AD cases and compare them with those obtained from a group of elderly nondemented (ND) control individuals. The magnitude of atherosclerotic occlusion of the leptomeningeal arteries is also correlated with the densities of AD neuropathologic lesions and with the degree of AVD of the circle of Willis.

Materials and Methods

Twenty autopsy cases, 10 sporadic AD and 10 ND controls, were investigated to quantify and compare stenoses of the large leptomeningeal arteries. These 20 cases represent a subpopulation of individuals chosen from an initial cohort of 54 consecutive autopsies performed at Sun Health Research Institute (Sun City, Ariz), in which the degree of atherosclerosis of the circle of Willis was investigated. 4 We selected, in both cohorts, those 10 AD and 10 ND cases which appeared by gross visual inspection to be most afflicted with AVD. The Table provides relevant clinical and neuropathological data observed in the populations. An AD diagnosis was made according to published consensus criteria established by the Consortium to Establish a Registry for Alzheimer Disease (CERAD) and by the National Institute on Aging and Reagen Institute (NIA-R). 6,7 Cases were defined as AD if they met CERAD criteria for “definite” or “probable” AD as well as NIA-R criteria for “intermediate” or “high” probability for AD. These individuals were voluntary participants enrolled in our Brain Donation Program. The leptomeningeal membranes carrying the arteries of the convexities of the brain (anterior, middle, and posterior cerebral arteries and their leptomeni-
Inguinal perforating branches) were carefully removed from the surface of the brain, snap frozen and preserved at \(-86^\circ C\). The average delay between death and freezing was 2.5 hours. All subjects were white and were apo E genotyped. The ND cohort was composed of 7 women and 3 men, averaging 87.6 and 84.7 years of age, respectively (combined average age 87 years). The 10 AD individuals, 7 women and 3 men, averaged 89.7 and 83.6 years of age, respectively (combined average age 88 years). There were no significant age differences between the AD and ND populations (unpaired 2-tailed, \(P=0.62\)). Prior to the measuring studies, the leptomeninges were thawed and rinsed several times with cold water (4°C) to remove all traces of entrapped blood, and the large arteries separated from the adjacent leptomeninges. These vessels were fixed with 4% paraformaldehyde for 24 hours, rinsed with phosphate buffered saline and stored at 4°C. The arteries were photographed and a montage of each segment was constructed as shown in Figure 1. Cross-sections of approximately 3 mm were examined with a Leica S8APO dissecting microscope. The areas of appreciable stenosis were photographed with an Optronics Magnafire SP camera (Model s99805) and images processed by the Optronics software program. Measurements of the external and luminal areas were obtained using the calibrated ImagePro Express software (version 4.0, Media Cybernetics). An index of stenosis was calculated for each artery by subtracting the luminal area from the outer area, dividing the difference by the outer area and multiplying the quotient by 100.

### Results

A total of 370 and 236 leptomeningeal arterial sections from the AD and ND control cases, respectively, were measured to establish the corresponding index of stenosis. The results are shown in the Table, which also shows the mean degree of stenosis in the major arteries of the circle of Willis for the same cases measured in a previous study. The percentage of stenosis between the two groups of arteries was similar, with the AD circle of Willis arteries having an average stenosis index of 74% and the corresponding leptomeningeal arteries having an average of 75%. By contrast, the circle of Willis and leptomeningeal arteries in the ND cohort demonstrated a considerably lower index of stenosis (means 55% and 44%, respectively). The differences between AD and ND indices of stenoses were highly significant (\(P<0.00001\)).

All leptomeningeal arteries in the AD cases showed extensive atherosclerotic lesions (Figure 1). Some arterial segments in the AD cases exhibited severe stenotic lesions consisting of long and continuous stretches of atheroma plaque, which in some cases totally occluded the artery lumen (Figure 1). The difference between the AD and ND index of

## Table: Neuropathology Profile of Study Subjects

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>CoW % Stenosis</th>
<th>Lepto % Stenosis</th>
<th>Total No. of Stenoses</th>
<th>Total Plaque Score</th>
<th>NFT Score</th>
<th>WMR Score</th>
<th>Braak Stage</th>
<th>CERAD NP Score</th>
<th>ApoE</th>
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<tr>
<td>79</td>
<td>M *</td>
<td>42%</td>
<td>4</td>
<td>1.80</td>
<td>1.00</td>
<td>1.75</td>
<td>II</td>
<td>0.00</td>
<td>3/3</td>
<td></td>
</tr>
<tr>
<td>88</td>
<td>F</td>
<td>56%</td>
<td>2</td>
<td>0.25</td>
<td>2.00</td>
<td>0.00</td>
<td>II</td>
<td>0.00</td>
<td>3/4</td>
<td></td>
</tr>
<tr>
<td>88</td>
<td>F</td>
<td>52%</td>
<td>43%</td>
<td>0.00</td>
<td>4.50</td>
<td>1.00</td>
<td>IV</td>
<td>0.00</td>
<td>3/3</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>F</td>
<td>42%</td>
<td>41%</td>
<td>6.50</td>
<td>4.50</td>
<td>0.00</td>
<td>III</td>
<td>0.00</td>
<td>3/3</td>
<td></td>
</tr>
<tr>
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<td>43%</td>
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<td>5.00</td>
<td>0.00</td>
<td>III</td>
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<td>3/3</td>
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<tr>
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<td>39%</td>
<td>0.72</td>
<td>4.75</td>
<td>1.00</td>
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<td>2.00</td>
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<tr>
<td>81</td>
<td>M</td>
<td>44%</td>
<td>41%</td>
<td>8.50</td>
<td>7.00</td>
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<td>57%</td>
<td>38%</td>
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<tr>
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<td>55%</td>
<td>44%</td>
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<td>4.00</td>
<td>0.88</td>
<td>II</td>
<td>0.20</td>
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</tr>
</tbody>
</table>

*Severe and patchy atherosclerosis of the circle of Willis (CoW). CoW indicates circle of Willis; Lepto, leptomeningeal vessels; NFT, neurofibrillary tangle; WMR, white matter rarefaction; CERAD, Consortium to Establish a Registry for Alzheimer Disease; NP, neuritic plaque.
stenosis was highly significant \((P<0.00001)\). An important parameter to be considered is the mean number of atherosclerotic stenoses per individual observed in the two cohorts (Table), which was 36 for the AD group and only 2 for the ND group \((P<0.00001)\).

The total plaque score had a mean value of 12.74 for AD and 4.43 for ND controls out of a maximum of 15 points \((P<0.00001)\). The neurofibrillary tangle (NFT) score was elevated in AD (mean=11.95; maximum score=15) relative to the ND group (mean=4.0; \(P<0.00001\)). Likewise, the white matter rarefaction (WMR) in the AD population scored 2.05 out of a maximum value of 3.0 while the same score was 0.88 for the ND group \((P=0.0004)\). In the case of the AD patients, the Braak stage score average number was V (scale from I – VI), whereas in the ND controls the Braak stage score average was III \((P=0.00001)\). Finally, the CERAD neuritic plaque (NP) score for the AD population had an average of 2.90; by contrast the CERAD score for the ND cohort was 0.20 (scale from 0 to 3; \(P<0.00001)\). No association was apparent between the degree of arterial occlusion and apo E genotype. The allelic frequency between the two groups revealed, as expected, that the apo e4 gene was elevated in AD (30%) relative to the apo e4 gene in the ND cohort (15%).

The percentage of arterial stenoses in AD and ND populations also correlated with AD neuropathological lesions. Figure 2 depicts correlations between the percentage of arterial stenosis and the total plaque score (Figure 2A), NFT score (Figure 2B), Braak stage score (Figure 2C), CERAD NP score (Figure 2D), WMR score (Figure 2E) and the total number of stenoses (Figure 2F). Overall, the degree of arterial stenosis and the neuropathological lesions of AD were significantly correlated (see probability values and Rs values in the Table and Figure 2, respectively).

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**Figure 1.** Representative atherosclerotic vascular disease in human leptomeningeal arteries. (A) There is a mild degree of atherosclerosis in a ND individual (Table 1, case 6). There are only 4 arteries with an index of stenosis greater than 60. (B) The atherosclerosis in the AD case 13 is extensive and severe. All 44 cross-sections demonstrated an index of stenosis greater than 63%. Seven sections showed >90% occlusion, 17 were occluded between 80% to 90% and 20 were occluded between 64% to 79%.
The physiological consequences of cardiovascular disease brought about by the aging process on the general health of the individual are devastating, and the brain is no exception to this rule. In the ND population 6 individuals died of cardiorespiratory arrest. Of the remaining 4, two individuals died of cancer and 2 died of renal failure. Among the 20 subjects in this study, 13 were hypertensive (7 AD and 6 ND). Coronary artery disease was present in 6 out of 10 AD patients and in 4 out of 10 ND subjects. Cerebral infarcts or lacunar infarcts or both were present in 7 out of 10 AD individuals and in 4 of the ND subjects. The trend in this small sample suggests that cardiovascular disease is more common in AD than in the ND control group.

**Discussion**

We have determined the extent of atherosclerotic lesions in the large leptomeningeal arteries of AD and ND individuals. Clearly, in those AD subjects with numerous and severe atherosclerotic plaques in the circle of Willis,4 the AVD extended into the large cerebral arteries, further compromising cerebral blood flow and decreasing cerebral perfusion of both gray and white matter. Because AVD is a nearly universal malady among the elderly, some degree of atherosclerosis was also observed in the leptomeningeal vessels of the ND individuals, but to a significantly lesser degree than in AD subjects. Large-scale studies are necessary to more accurately appraise the full impact of AVD in neurodegenerative diseases.

Pathoanatomic observations suggest that cerebral blood flow in AD may be compromised as a result of several types of vascular abnormalities. Aside from atherosclerotic vascular disease, cerebral amyloid angiopathy, arteriosclerosis, infarctions, loss of vascular innervation, capillary endothelial, and basement membrane changes, “string” and “distorted” vessels and vascular atrophy may all contribute to cerebral hypoperfusion. In addition, there is evidence that the blood–brain barrier may be dysfunctional and that the perivascular flow of interstitial fluid may be impaired.10 Vascular pathology and hemodynamic changes may therefore be critical to the initiation and progression of AD.

The recognition of AVD as being responsible for the serious hemodynamic deficits and brain hypoxia/ischemia in the pathogenesis of sporadic AD will focus attention on several treatments already available. Changes in lifestyle such as appropriate exercise and diet modification and the prescription of cholesterol-reducing drugs such as statins (inhibitors of the HMG-CoA reductase) will reduce hyperlipidemia and thus atherosclerosis. Statins have been found to have antiinflammatory activity, which would reduce the incidence of atherosclerosis and perhaps diminish the brain inflammation inherent in AD. In addition, statins are powerful vasodilators because they stimulate the production of endothelial nitric oxide.11 A recent preliminary clinical trial demonstrated that AD patients treated with atorvastatin had a slower disease progression and mood and behavior improvements,12 which could be a result of increased cerebral blood flow. The full recognition of vascular pathology and decreased cerebral blood flow as crucial pathogenetic factors in sporadic AD will stimulate the development of drugs that can prevent or delay the onset of these dementias.

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References
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