Atherosclerosis and Lipoproteins

Circle of Willis Atherosclerosis Is a Risk Factor for Sporadic Alzheimer’s Disease

Alex E. Roher; Chera Esh; Tyler A. Kokjohn; Walter Kalback; Dean C. Luehrs; James D. Seward; Lucia I. Sue; Thomas G. Beach

Objectives—We conducted a quantitative investigation of brain arterial atherosclerotic damage and its relationship to sporadic Alzheimer’s disease (AD).

Methods and Results—Fifty-four consecutive autopsy cases, 32 AD and 22 nondemented control subjects, were examined to establish the degree of arterial stenosis. Vessel external and lumenal area measurements were taken from 3-mm arterial cross-sections to calculate a stenosis index. AD patient circle of Willis arteries possessed a significant degree of stenosis as a consequence of multiple and severe atherosclerotic lesions. These lesions were significantly more severe in AD cases than in age-matched controls ($P<0.0001$), and the number of stenoses and the index of occlusion ($R=0.67; P<0.00001$) were positively correlated. In addition, the index of stenosis significantly correlated with the following measures of AD neuropathological lesions: total plaque score, neuritic plaque score, neurofibrillary tangle score, Braak stage score, and white matter rarefaction score.

Conclusions—Our study reveals an association between severe circle of Willis atherosclerosis and sporadic AD that should be considered a risk factor for this dementia. These observations strongly suggest that atherosclerosis-induced brain hypoperfusion contributes to the clinical and pathological manifestations of AD. (Arterioscler Thromb Vasc Biol. 2003; 23:2055-2062.)

Key Words: atherosclerosis ■ circle of Willis ■ Alzheimer’s disease ■ brain hypoperfusion

Mounting evidence demonstrates a close relationship between sporadic Alzheimer’s disease (AD) and cardiovascular disease. Critical coronary artery disease, myocardial infarction, cardiac arrest, atherosclerosis of the internal carotid arteries, cardiovascular inflammation, hypertension, hypotension, hypercholesterolemia, hyperhomocysteinemia, and diabetes mellitus have all been clearly documented as significant AD risk factors. Furthermore, individuals with neuropathologically diagnosed AD have higher plasma cholesterol levels than nondemented (ND) control subjects, and AD subjects exhibit positive correlations between brain $A\beta$ n-42 levels and total serum cholesterol, LDL cholesterol, and apolipoprotein (Apo) B-100 and a negative correlation with HDL cholesterol levels. Elevated total and LDL cholesterol have been reported in very old patients with AD. Likewise, in a meta-analysis study, patients with probable or possible early-stage AD were found to possess elevated total cholesterol values compared with a ND population. In addition to the well-established association between vascular disease risk factors and sporadic AD, the present study provides, for the first time, a rigorous and significant neuropathological association between circle of Willis atherosclerosis and sporadic AD.

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Methods

Subjects were voluntary participants in the Brain Donation Program at Sun Health Research Institute (Sun City, Ariz). Rapid autopsies (2.5-hour average postmortem delay) were performed to remove and preserve the brain. All individuals examined were Caucasian. The degree and extent of arterial stenosis was quantified in 54 consecutive autopsy cases, in which neuropathologic examination indicated presence of either AD or normal aging changes only; the latter cases were considered ND controls if the neuropsychologic profile was within normal age limits. The sample subjected to computer-based quantitative analysis contained 22 ND control cases, consisting of 14 women and 8 men with mean ages of 87.1 and 82.6 years, respectively, and 32 AD cases, 18 women and 14 men with mean ages of 84.4 and 86.4 years, respectively. History of cardiovascular disease, in particular the presence or absence of hypertension, myocardial infarction, coronary artery disease, valvular heart disease, disorders of rhythm and conduction, cardiomyopathy, cardiorespiratory failure, and peripher-
al vascular disease, were recorded from the patient’s clinical charts. Demographic and neuropathologic data are illustrated in Table 1.

Neuropathologic Diagnosis and Scoring for AD-Related Pathology

The diagnosis of AD was made according to published consensus criteria developed by the Consortium to Establish a Registry for Alzheimer’s disease (CERAD) and a committee formed by the National Institute on Aging and Reagan Institute (NIA-R).41,42 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.

Two methods were used to obtain senile plaque scores for each brain. The total plaque score was obtained by estimating the density of all plaque types (compact, neuritic, classical, and diffuse) on 40-μm thioflavin-S-stained sections. The diagrams published by CERAD were used to classify plaque density as none, sparse, moderate, or frequent. For statistical purposes, these were assigned the corresponding numerical values 0, 1, 2, and 3. The scores from several brain regions, including frontal, temporal, parietal, hippocampal, and entorhinal areas, were added to give the total plaque score (maximum score, 15). The second method used was the CERAD neuritic plaque score, in which the density of neuritic plaques was assessed in the same manner as for the total plaque score except that only neuritic plaques were scored. The brain regions assessed were limited to the frontal, temporal, parietal, and occipital neocortex regions, and the overall score represented the highest score seen in any area. These scores therefore ranged between 0 and 3.

Neurofibrillary tangle (NFT) density was also scored with 2 different methods. The total NFT score was calculated in the same manner as that described for the total plaque score, and NFT density was also scored using the Braak Stage method.43 A white-matter rarefaction score was obtained for each cerebral lobe (frontal, temporal, parietal, and occipital) by assessing the extent of white matter rarefaction on 40-μm quarter-hemisphere sections stained with H&E. A, Cross-section of an artery free

evaluating the extent of atherosclerosis were visually obvious when the ND and AD groups were compared. Table 1 compares relevant neuropathologic variables in AD (n=32) and ND (n=22) populations that were studied with quantitative methods. A total of 983 vascular sections, 617 AD and 366 ND, were measured to determine the index of stenosis. A significant difference in neuropathology existed between the AD and ND populations (Table 2). In the AD group, there were statistically significant differences between the female and male populations, with the female group more affected than the male group in 3 out of the 5 neuropathological indices of AD severity (Table 2).

Results

We conducted an investigation of brain arterial atherosclerotic damage and its relationship to sporadic AD. As can be seen in Figures 1 and 2, notable differences in the maximal extent of atherosclerosis were visually obvious when the ND and AD groups were compared. Table 1 compares relevant neuropathologic variables in AD (n=32) and ND (n=22) populations that were studied with quantitative methods. A total of 983 vascular sections, 617 AD and 366 ND, were measured to determine the index of stenosis. A significant difference in neuropathology existed between the AD and ND populations (Table 2). In the AD group, there were statistically significant differences between the female and male populations, with the female group more affected than the male group in 3 out of the 5 neuropathological indices of AD severity (Table 2).

**Figure 1.** Micrographs of middle cerebral arteries stained with Mallory’s trichrome method. A, Cross-section of an artery free of atheroma from a 81-year-old ND control individual. There is a distinction between the intima, media, and adventitia. B, Artery from an 80-year-old AD patient containing a large atheroma plaque. Magnification ×25.

### Table 1. Neuropathology Profile of Study Subjects

<table>
<thead>
<tr>
<th>Case ID</th>
<th>Age, y</th>
<th>Weight, g</th>
<th>Braak Score</th>
<th>CERAD Score</th>
<th>White Matter Score</th>
<th>Total Plaque Score</th>
<th>NFT Score</th>
<th>NFT Stage</th>
<th>NP Score</th>
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</thead>
<tbody>
<tr>
<td>Nondemented cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean, female (N=14)</td>
<td>87.1</td>
<td>1110</td>
<td>0.786</td>
<td>5.38</td>
<td>4.23</td>
<td>3.00</td>
<td>0.429</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean, male (N=8)</td>
<td>82.6</td>
<td>1235</td>
<td>0.625</td>
<td>6.97</td>
<td>3.58</td>
<td>2.63</td>
<td>0.375</td>
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<tr>
<td>Mean, total (N=22)</td>
<td>85.5</td>
<td>1155</td>
<td>0.727</td>
<td>5.96</td>
<td>4.00</td>
<td>2.86</td>
<td>0.409</td>
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<td></td>
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<td>Alzheimer’s disease cases</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean, female (N=18)</td>
<td>84.4</td>
<td>952</td>
<td>2.17</td>
<td>12.9</td>
<td>13.6</td>
<td>5.72</td>
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<tr>
<td>Mean, male (N=14)</td>
<td>86.4</td>
<td>1127</td>
<td>1.00</td>
<td>11.7</td>
<td>9.64</td>
<td>4.43</td>
<td>2.50</td>
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<tr>
<td>Mean, total (N=32)</td>
<td>85.2</td>
<td>1028</td>
<td>1.66</td>
<td>12.4</td>
<td>11.9</td>
<td>5.16</td>
<td>2.67</td>
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</table>

**Assessment of Circle of Willis Atherosclerosis**

For quantitative assessment, the circle of Willis was dissected intact at the time of autopsy and fixed in 4% paraformaldehyde. The following arteries were individually studied: right and left vertebral arteries, basilar artery, right and left posterior cerebral arteries (PCAs), right and left posterior communicating arteries (PcomAs), right and left middle cerebral arteries, right and left internal carotid arteries, right and left anterior cerebral arteries (ACAs), and anterior communicating arteries (AcomAs). All arteries were cut into 3-mm lengths, and the cross-sections were examined with a Leica S8APO dissecting microscope to find all areas of appreciable vascular stenosis and photographed with an Optronics Magnafire SP camera (model s99805) and software program (Optronics). Measurements of the vessel external and luminal areas were taken from the photographic record using the calibrated ImagePro Express, version 4.0 software (Media Cybernetics). After all of the arteries of a single case were measured, a stenosis index 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.

**Apolipoprotein E Genotyping**

Genomic DNA was extracted from ~50 mg of cerebellar tissue and subjected to polymerase chain reaction analysis as described.44

**Results**

We conducted an investigation of brain arterial atherosclerotic damage and its relationship to sporadic AD. As can be seen in Figures 1 and 2, notable differences in the maximal extent of atherosclerosis were visually obvious when the ND and AD groups were compared. Table 1 compares relevant neuropathologic variables in AD (n=32) and ND (n=22) populations that were studied with quantitative methods. A total of 983 vascular sections, 617 AD and 366 ND, were measured to determine the index of stenosis. A significant difference in neuropathology existed between the AD and ND populations (Table 2). In the AD group, there were statistically significant differences between the female and male populations, with the female group more affected than the male group in 3 out of the 5 neuropathological indices of AD severity (Table 2).

**Figure 1.** Micrographs of middle cerebral arteries stained with Mallory’s trichrome method. A, Cross-section of an artery free of atheroma from a 81-year-old ND control individual. There is a distinction between the intima, media, and adventitia. B, Artery from an 80-year-old AD patient containing a large atheroma plaque. Magnification ×25.
In the AD group, 87 of 391 (22.25%) examined arteries were more than 80% occluded, whereas only 13 of 277 (4.7%) were as extensively blocked in the ND group (\(P<0.001\)). Furthermore, in the AD cohort, there were 14 arteries with a 100% occlusion (3.6%), whereas in the ND only 4 were observed (1.1%). Overall in the ND control group on a per-case basis, 73% of the subjects had greater than 50% occlusion, 23% of the subjects had greater than 60% occlusion, and none of the subjects had greater than 70% occlusion. In contrast, in the AD group, 97% of the patients had 50% occlusion, 81% of the patients had greater than 60% occlusion, and 38% of the patients had greater than 70% occlusion.

The mean degree of arterial stenosis was determined for each of the circle of Willis arteries, and these results are depicted in Figure 3. A major difference in arterial stenosis degree was evident between the AD and ND groups. The stenosis degree was statistically greater for the AD group in each artery (unpaired, 2-tailed \(t\) tests; \(P<0.0001\)), with the posterior communicating arteries showing the greatest contrast between AD and ND group stenosis percentages.

Figure 4 illustrates the total number of stenoses plotted against the average index of occlusion per each of the investigated circle of Willis and related arteries, which shows a positive correlation between the 2 parameters (\(R=0.67\)). The average number of stenoses found in the ND and AD circle of Willis arterial networks was 19.91 and 30.22, respectively (\(P<0.0001\)). The magnitude of cerebral hypoperfusion is directly proportional to the number of atheroma plaques along the arterial tree and the degree of the stenosis dictated by the size of the remaining arterial lumen.

Important parameters to be considered, in relation to the degree of stenosis of the arteries that supply the brain and global cerebral perfusion, are individual anatomical variations in the circle of Willis. In some instances these variations may provide an additional alternative blood flow routing. However, in most cases they represent a disadvantage because of total vascular absence or vascular hypoplasia that imposes limitations in collateral circulation. Our data revealed that the normal vascular pattern was present in 17 of 32 AD cases and in 13 of 22 ND cases. The observed vascular variations were as follows: triplication of the ACA: AD=1, ND=0; duplication of AcomA: AD=4, ND=1; lack of AcomA: AD=1, ND=1; hypoplasia of a PcomA: AD=5,

<table>
<thead>
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<th>TABLE 2. Statistical Analysis of Study Subjects</th>
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<tr>
<td>Case ID</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>ND/female vs ND/male</td>
</tr>
<tr>
<td>AD/female vs AD/male</td>
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<tr>
<td>AD vs ND</td>
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*Unpaired, 2-tailed \(t\) test and 2-tailed Wilcoxon rank-sum test.
of AD (Figure 5). All correlations were evaluated using Spearman’s rank correlation test. When the average stenosis score (average stenoses of all blood vessels for each case) was compared with the brain total plaque score (sum of plaque scores of all brain regions) (Figure 5A), a positive correlation was evident ($R_s=0.43; P<0.01$), with minimal divergence between sex (men, $R_s=0.45, P<0.05$; women, $R_s=0.42, P<0.05$). Similar correlations were present between average stenosis score and CERAD neuritic plaque score (Figure 5D; men, $R_s=0.58, P=0.01$; women, $R_s=0.59, P<0.01$; men and women, $R_s=0.59, P<0.01$).

The correlation between average arterial stenosis score and total NFT score (Figure 5B) was also positive ($R_s=0.44, P<0.01$). In this instance, however, there were important sex differences (men, $R_s=0.32, P>0.05$; women, $R_s=0.50, P<0.01$), with the female correlation being far more robust. The average arterial stenosis score and Braak stage (Figure 5C) were strongly correlated ($R_s=0.51, P<0.001$) as well, with large differences when the sexes were considered separately (men, $R_s=0.36, P>0.05$; women, $R_s=0.60, P<0.001$). Comparing average stenosis score with the white-matter score (Figure 5E) again showed a positive correlation that was more marked in women than in men (women, $R_s=0.32, P>0.05$; men, $R_s=0.60, P=0.001$; men and women together, $R_s=0.47, P=0.005$). The mean number of stenoses per each artery was calculated and averaged (2.33 for AD and 1.47 for ND; unpaired, 2-tailed t tests, $P=0.004$). Hence, the total number of vascular stenoses in the AD group was always greater than that of the ND group.

There were no statistically significant differences between the ages of the AD and ND populations ($P=0.91$). However, when subdivided by sex, there was a significant difference between the ages of men and women in the ND group (82.6 and 87.1 years, respectively; unpaired, 2-tailed t tests, $P=0.004$). In the AD population, the differences in age
between the male and female groups were not significant (86.4 and 84.4 years, respectively; unpaired, 2-tailed t tests, \( P=0.46 \)).

The Apo E allelic frequencies in the ND group were \( e^2=0.09, e^3=0.73, \) and \( e^4=0.18 \) and for the AD group were \( e^2=0.02, e^3=0.72, \) and \( e^4=0.26 \), respectively. In this study, there was no association between the Apo E genotype and the degree of atherosclerosis in either the AD or ND cohorts. Because the apolipoprotein E \( e^4 \) allele has been associated with increased coronary atherosclerosis, it is possible that the association of circle of Willis atherosclerosis with AD histopathology is secondary to the increased \( e^4 \) allele frequency in the AD group.

Neuropathological examination of the brain coronal sections revealed no statistically significant differences in ischemic stroke numbers between AD (38%) and control individuals (36%). In reference to other cardiovascular pathology, coronary artery disease was 2 times more frequent in AD than ND patients (44% and 23%, respectively). Myocardial infarction was more frequent in AD than in ND (13% and 5%, respectively). In the ND population, there was a higher incidence of valvular heart disease, disorders of rhythm and conduction, and other peripheral vascular diseases than in the AD cohort (5% versus 0%, 45% versus 9%, and 23% versus 3%, respectively). Other cardiovascular pathologies such as hypertension, cardiomyopathy, stroke, and lacunar infarcts and cardiorespiratory failure were not different in frequency between the AD and ND populations.

**Discussion**

The primary goal of this investigation was to quantitatively assess the pathological impact of atherosclerosis and stenosis of the circle of Willis and related arteries in AD and ND individuals and their correlation with the neuropathological lesions of AD. Our observations link for the first time circle of Willis atherosclerosis and AD lesions and dementia, suggesting that cerebral atherosclerosis is a strong contributory factor to sporadic AD pathogenesis. However, because this study was conducted using postmortem AD cases, at this time we do not have data regarding the time course of atherosclerosis development in relation to dementia onset and progression.

Surprisingly, with respect to most parameters, the female sex seemed to have a higher degree of pathological severity. This observation may be related to the higher levels of cholesterol in elderly women relative to men. Serum cholesterol levels may have profound effects on cognitive function. A prior study from our laboratory of 100 individuals revealed a sex-specific relationship between serum cholesterol levels and the prevalence of AD. Female AD subjects had statistically higher total cholesterol, LDL cholesterol, and triglycerides levels than did the controls (unpaired, 2-tailed \( t \) tests, \( P=0.01 \)). For men, however, levels of total cholesterol, LDL cholesterol, and triglycerides were statistically indistinguishable between AD subjects and ND controls (unpaired, 2-tailed \( t \) tests, \( P>0.20 \)) (A.E. Roher, unpublished observations, 2003). In a large group of postmenopausal women, high LDL and total cholesterol levels were statistically linked to lower scores on the most common tests assessing cognitive impairment. Moreover, a reduction in the LDL cholesterol level during the 4-year period of this study was associated with lower odds of cognitive impairment.

Unfortunately, because of the fact that the cases in the present study were nursing-home patients and only largely incomplete and nonsystematic clinical chart data records concerning other cardiovascular risk factors were available (ie, dyslipidemia, homocysteinemia, C-reactive protein, etc), no correlations with these parameters could be established in our study. Future, carefully planned, longitudinal studies will permit the necessary comprehensive clinical, psychometric, and laboratory tests to be implemented as well as the required temporal follow-up of these parameters and permit their correlation with postmortem vascular and neuropathological alterations.

By demonstrating an association between circle of Willis atherosclerosis and sporadic AD, our observations bolster an increasing convergence between clinical evidence and basic science data linking vascular dementia and AD pathophysiology. In support of this linkage, detailed physical and functional examination of transgenic mice overexpressing \( \beta PP/\beta \) has revealed profound cerebrovascular autoregulation impairment. These mice also exhibit endothelial dysfunction that can be reversed by superoxide dismutase activity and decreased neocortical blood flow elicited by somatosensory activation compared with nontransgenic mice.

Circle of Willis arterial stenosis could contribute to AD-associated brain hypoperfusion. Recent investigations conducted with living patients have demonstrated a substantial and widespread pathologic perturbation of brain hemodynamics in patients with AD. MR perfusion and single photon emission computed tomography (SPECT) techniques have clearly revealed decreased cerebral blood flow in AD. Functional MRI has also been used in the evaluation of AD dementia to determine blood volume distribution. A comparison of the dynamic contrast susceptibility observations to fluorodeoxyglucose positron emission tomography in the same patients demonstrated a high degree of concordance. Thus, the decrease in temporoparietal perfusion seen in AD by positron emission tomography–SPECT was also identified by dynamic contrast susceptibility MR. Using a spin-labeling technique, cerebral perfusion was evaluated by MR, revealing a significant hypoperfusion in frontal, temporal, parietal, and cingulate regions in AD.

Our results add to an accumulating mass of evidence that links recognized atherosclerotic disease risk factors and mechanisms with sporadic AD and \( \beta \) dynamics. Individuals carrying the Apo E \( e^4 \) gene allele, a known risk factor for atherosclerosis, are at high risk of developing AD at an earlier age. Cholesterol-fed rabbits exhibit a time-dependent increase in intraneuronal \( \beta \) immunoreactivity, and transgenic \( \beta PP \) mice fed a cholesterol-rich diet develop a faster and significantly more florid amyloid deposition than the nontransgenic littermates. Tissue culture experiments have shown that cholesterol addition increases \( \beta \) production whereas cholesterol depletion reduces \( \beta \) synthesis. Acyl-Coenzyme A cholesterol transferase modulates the generation of \( \beta \). Reducing cholesterol synthesis by inhibiting
hydroxymethyl glutaryl CoA reductase decreases Aβ production in vitro and in vivo.\textsuperscript{65,66}

It has long been thought that cerebral arteriosclerosis has no relationship to AD,\textsuperscript{67,68} leaving plaques and NFT as the only significant pathologic abnormalities. Importantly, earlier studies did not use statistical analysis or quantitative stenosis measurements, relying instead on simple visual assessment and data tabulation. Our quantitatively based comparisons and statistical analyses, however, conclusively demonstrate that circle of Willis arteriosclerosis has a significant statistical association with sporadic AD. What remains to be explained, however, is why some sporadic AD cases have almost normal-appearing blood vessels, with minimal arteriosclerosis. This discordance could be attributable to the etiologic heterogeneity of sporadic AD, with arteriosclerosis playing a role in only a subset of AD cases. Sporadic AD is a terminal neurodegenerative disorder of the brain for which no single pathogenetic explanation has been found. In all probability, sporadic AD is a multifactorial disorder related to the age-associated exponential decay of the brain. Consequently, severe circle of Willis arteriosclerosis and ensuing stenosis may accelerate or worsen AD once it is initiated by pleiotropic pathological processes. Sporadic AD is an emerging disease in the elderly, and it is important to consider recent economic, technological, and medical developments in relation to a potentially evolving AD epidemiology. Over the last century, the mean life expectancy in the United States has dramatically increased from 50 years to \(\approx\)80 years. Indeed, the population in the present study was 85.2 years of age on average. Increased longevity is a critical factor in AD development, but additional changes have significant impact as well. Dietary habits and physical activity patterns have changed with consequent impressive physical manifestations. The National Health and Nutrition Examination Survey reported a dramatic adult obesity prevalence increase between the years 1960 and 2000.\textsuperscript{69,70} Among the elderly adults, the population at highest relative sporadic AD risk, the prevalence of obesity for men and women increased from 8.4% to 35.8% and from 26.2% to 39.6%, respectively. Obesity is a major cause of mortality in the United States, annually accounting for 280,000 deaths,\textsuperscript{71} the larger number of deaths attributed directly to cardiovascular disease. Moreover, \(\approx\)250,000 deaths per year in the United States are attributable to lack of regular physical activity.\textsuperscript{72,73} Increased longevity and high caloric diets coupled with sedentary lifestyles undoubtedly promote weight gain, high LDL cholesterol, and low HDL cholesterol among the elderly and consequent disease conditions, such as arteriosclerosis and, perhaps ultimately, AD.

In summary, we speculate that a probable pathologic consequence associated with extensive and increasing circle of Willis stenosis is an evolving brain hypoperfusion. Amyloid deposition and tau neurofibrillary accumulation, in some sporadic AD cases, may represent the terminal manifestation of a general breakdown in brain energy metabolism. Our results are unambiguous and represent a significant step toward a more complete understanding of sporadic AD pathogenesis. Additional longitudinal studies, combining cardiovascular risk factor measurements with cerebrovascular imaging techniques, will clarify the event sequence underlying our neuropathological observations and the potential role of hypoperfusion in sporadic AD. Atherosclerosis, arterial stenosis, and brain hypoperfusion contribute to the pathology and clinical symptoms of sporadic AD and as such present a potential target for already available therapeutic intervention that may delay the onset of sporadic AD or enhance the quality of life of patients with this dementia.

Acknowledgments

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References


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