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Atherosclerosis Risk Factors in American Indians With Alzheimer Disease:

Preliminary Findings

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Abstract

Factors predisposing to and associated with atherosclerosis may impact the onset and progression of Alzheimer disease (AD). The high prevalence of atherosclerosis and associated risk factors in American Indians makes them ideal subjects to test this association. We compared frequency of history of hypertension, myocardial infarction, stroke, diabetes, and high cholesterol in 34 American Indians with AD with 34 age-matched American Indian controls, and 34 age-matched whites with probable AD. We also measured waist size, height, and weight, and acquired blood for determination of plasma homocysteine and apolipoprotein E genotype. The 3 groups did not differ significantly in age or sex. History of hypertension and diabetes was significantly more common among American Indian AD patients than Indian controls or whites with AD. The 3 groups did not differ in history of stroke or myocardial infarction. Body mass index was significantly greater in both Indian groups than the white AD group. Plasma homocysteine levels were greater, but not significantly so, in the Indian AD than the Indian control group. Thus, there is preliminary evidence of a modest association between history of hypertension and diabetes and AD in a small sample of American Indians. This suggests that changes in lifestyle factors could influence the expression of AD in American Indians.

Keywords

atherosclerosis; hypertension; diabetes; homocysteine; Alzheimer disease

There is evidence for a relationship between atherosclerosis risk factors, cardiovascular comorbidities, and Alzheimer disease (AD), both in terms of predisposition to developing the disease and influence on its clinical course. An association has been shown between midlife hypertension and later onset of dementia[1] and AD,[2] and AD pathology in brain.[3] Furthermore, treatment of hypertension seems to reduce the risk of subsequent dementia and AD.[4] Type 2 diabetes has also been associated with risk for AD.[5,6] The evidence for

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cardiovascular factors predisposing to AD includes premature presence of senile plaques in persons with coronary artery disease and an association of both senile plaques and neurofibrillary tangles with a history of hypertension.[7] Additionally, large-vessel (but not small vessel) atherosclerosis has been found associated with frequency of neuritic plaques.[8] An autopsy study of persons who met neuropathologic criteria for AD showed that those with infarcts had poorer cognitive function and a higher prevalence of dementia than those without infarcts.[9] By contrast, a retrospective examination of the UT Southwestern Alzheimer's Disease Center database found that the presence of atherosclerotic risk factors and cardiovascular comorbidities and risk factors did not influence rate of AD progression.[10] The relationship of hyperhomocysteinemia to the development of AD is questionable at best,[11] but it has been associated with vascular damage[12] that might hasten the onset and worsen the course of AD. An association has also been shown between increased body weight and the subsequent development of AD,[13] and between the metabolic syndrome (with or without the presence of diabetes) and AD.[14] The relationship between diabetes and AD suggested by epidemiologic evidence[15] has not been confirmed in relation to AD pathology in brain.[16]

In an earlier study, we found that the prevalence of diabetes and hypertension was related significantly to degree of American Indian heritage among American Indians with AD.[17] Among subjects with >50% American Indian heritage, history of diabetes was 50% versus 10% among those with <50% heritage; history of hypertension was 76% versus 46%. The prevalence of diabetes, hypertension, and cardiovascular disease has been increasing rapidly among American Indians;[18–20] these in turn seem partly related to lifestyle factors such as diet and exercise in a vulnerable population. This report contains preliminary data from an ongoing study of risk factors for AD in American Indians.

METHODS

Subjects

For our white AD subjects, we employed the database of the University of Texas (UT) Southwestern Medical Center's Alzheimer's Disease Center, which contains deidentified data from persons diagnosed with probable AD by National Institute of Neurological and Communicative Disorder and Stroke-Alzheimer's Disease and Related Disorder Association (NINCDS-ADRDA) criteria[21] who had given consent for their data to be used for scientific purposes and for whom data were available concerning history of hypertension, diabetes, and high cholesterol. We recruited Indian AD subjects from our American Indian satellite in Talihina, OK. Our control Indian subjects were recruited from among relatives of persons seen at our satellite clinic and also from persons attending health fairs at various locations in Oklahoma; volunteers who completed testing and allowed blood sampling were given a $25 Wal-Mart gift certificate. All Indian AD subjects and their caregivers signed informed consent documents approved by the UT Southwestern Institutional Review Board and the Choctaw nation Institutional Review Board; Indian control subjects also signed informed consent.

Inclusion Criteria

We included Indian probable and possible AD subjects, white probable AD subjects, and Indian controls for whom the following data were available: age, sex, years of education, waist size, height, weight, history of hypertension, diabetes, high cholesterol, myocardial infarction, stroke, alcohol abuse in the previous 5 years, and history of dementia in a first-degree relative. Information concerning AD subjects (eg, history of dementia, hypertension, diabetes, and high cholesterol) was obtained from 3 sources; the patient, a knowledgeable informant (usually a spouse), and the patient's medical record. White AD and Indian control

subjects were matched as closely as possible in age to Indian AD subjects. Certified Degree of American Indian Blood was available for all Indian subjects.

The diagnosis of AD in all subjects was made by experienced neurologists and geriatric psychiatrists based on NINCDS-ADRDA criteria. Routine laboratory testing and brain imaging studies had been performed for all white subjects and for the majority of Indian subjects. To reduce the barrier to successful recruiting, cognitive screening of controls was limited to lack of subjective memory complaint (verified by an informant) and Mini- Mental State Examination (MMSE) score[22] within normal range adjusted for age and education.[23] The additional physical and biologic measures acquired were body mass index (BMI) (as a measure of total body fat), waist size (as an index of visceral or central obesity), height, weight, and blood sampling for plasma homocysteine (HCY) concentration and apolipoprotein E genotyping.

Statistical Methods

For the dichotomous measures, the number (%) for each variable was provided and χ^2 or the Fisher-Freeman-Halton test, as appropriate, were performed to compare the 3 groups on each variable. For the continuous measures, the median (range) is provided and Kruskal-Wallis was performed to compare the 3 groups on each variable except for plasma HCY and % native American heritage, which were compared only between the 2 Indian groups using a Mann-Whitney *U* test. To further examine the relationships in native Americans, Spearman rank order correlations (ρ) were used to compare plasma HCY concentrations to degree of Indian heritage and age in native Americans and a Mann-Whitney *U* test was used to compare median HCY concentrations for males and females. All statistical tests were checked for violations of assumptions. SPSS V15.0 and StatXact V8 (for the Fisher-Freeman-Halton tests) were used for all analyses. Statistical tests were performed using 2-sided tests, and $P<0.05$.

RESULTS

All 3 groups were similar in age, but differed in education ($P<0.001$), white AD subjects had the most education; Indian AD subjects the least (Table 1). The Indian AD and control groups had a median American Indian heritage of 75% (range=3% to 100%). Only 1 Indian AD subjects was diagnosed as possible AD. Only 2 control subjects had a first-degree relative with memory problems whereas there were 10 patients in each of the AD groups with an affected first-degree relative. As seen in Table 2, the groups differed medically only in history of hypertension ($P=0.001$) and history of diabetes ($P=0.015$). For history of hypertension, both Choctaw groups had higher percentages than whites (82.4% and 73.5% vs. 41.2%). History of diabetes was most prevalent in Indian ADs; less so in Indian controls and white ADs (52.9% vs. 35.3% vs. 18.8%). One (2.9%) Indian control and 1 (2.9%) white AD subject had a history of alcohol abuse. Indian control MMSE scores were higher than white AD scores, which were in turn higher than in Indian AD subjects ($P<0.001$). BMI was greatest in Indian controls and least in white AD subjects ($P=0.007$).

We were unable to compare Indian with white HCY levels because we were not able to obtain fasting samples or perform them in the same research laboratory in Dallas. Indian HCY levels were carried out by a commercial laboratory. Plasma HCY concentrations were unrelated to degree of Indian heritage ($\rho= -0.063$, $P=0.626$), were greater in men than in women [median (range) 11.9 (5.42 to 24.0) vs. 11.0 (5.17 to 33.70)], but not significantly ($P=0.137$), and increased significantly with age ($\rho=0.349$, $P<0.001$). HCY values in AD subjects, although 8.8% higher than in controls (12.4 vs. 11.4 μmol/L) were not significantly greater ($P=0.137$) (Table 1).

DISCUSSION

An important shortcoming in studies of the influence of ethnicity on biologic measures is the inexactness of ethnicity, which is usually based on self-designation rather than an objective measure. American Indians have the advantage of a quantitative measure, the Certificate of Degree of American Indian Blood (CDIB), which certifies that an individual has a specific percentage of Indian blood of a federally recognized tribe or tribes.[24] CDIB validity is supported by ascertainment of the au H2 genotype, found only in populations with European ancestry. Henderson et al[25] showed 29% history of tau H2 frequency in whites, 28% in persons claiming <50% Indian heritage, and only 8% in those claiming >50% Indian heritage.

Medical history was confirmed by review of AD patients' charts; we did not review the medical records of Indian AD controls, but did ask if they were taking medication for cholesterol diabetes, or high blood pressure. History of hypertension was used instead of direct blood pressure measurement because of the tendency of blood pressure to normalize with the onset of AD.[26] History of high cholesterol or use of cholesterol-lowering agents was used instead of determining actual cholesterol values because of differences in the use of hypolipidemic agents among both Indians and whites in the populations studied.[17] Differences in education between groups are similar to our previous findings,[23] and partially explain differences in MMSE scores between white and Indian AD subjects. BMI findings suggesting loss of body fat in Indian AD subjects is consistent with the literature showing a tendency to weight loss with onset and progression of AD.[27] The findings of this investigation are limited in several respects, including a biased sample and the inaccuracies of retrospective studies. Our sample is biased in that we are designated as an AD clinic and rarely saw persons in our Dallas or Talihina clinics who had suffered clinically evident strokes. Our study also fails to consider undetected evidence of atherosclerosis, including undocumented myocardial infarction and stroke. Irina et al[28] did not find a relationship of dementia or pathologically confirmed AD with a pathologic cardiovascular index that combined the extent of brain and peripheral atherosclerosis with evidence of cardiovascular lesions and cardiomegaly, but there is still the possibility that undetected strokes might hasten the onset of dementia and the detection of AD.

We continue to increase our sample size (projected N=85 Indian AD subjects, 45 Indian controls, and 85 white controls). We are obtaining brain magnetic resonance imaging studies for a subset of our subjects to compare evidence of cerebrovascular disease as manifest by frank strokes or leukoaraiosis in Indian AD subjects and controls. ApoE genotyping is pending.

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TABLE 1

Quantitative Characteristics of the 3 Groups

	Choctaw AD			Choctaw Control			White AD			Kruskal-Wallis or Mann-Whitney *U*
Variable	**N**	**Median**	**Range**	**N**	**Median**	**Range**	**N**	**Median**	**Range**	***P***
Age	34	78	56–91	34	75.5	64–85	34	76.5	58–88	0.870
Education (y)	34	10	3–13	34	12	7–17	34	13.5	6–20	<0.001
% American Indian	34	72	3–100	34	75	6–100	0			0.960
Mini-Mental state score	30	19	1–28	34	29.5	22–30	34	22	5–30	<0.001
Homocysteine (μmol/L)	28	12.4	8.6–27.1	34	11.4	7.5–28.5	0			0.137
Waist size (inches)	32	34	30–47	34	36	30–52	34	34	27.5–46	0.428
Body mass index (kg/m^2)	31	27.2	18.5–39.5	34	28.6	21.4–39.3	34	24.2	17.9–37.1	0.004

AD indicates Alzheimer disease.

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TABLE 2

Sex and Medical History Characteristics of the 3 Groups*

	Group					
Variable	**Choctaw AD, N (%)**	**Choctaw Control, N (%)**	**White AD, N (%)**	**Total, N (%)**	χ^2	***P***
Female	21 (61.8)	23 (67.6)	14 (41.2)	58 (56.9)	5.36	0.069
History of hypertension	28 (82.4)	25 (73.5)	14 (41.2)	67 (65.7)	14.18	0.001
History of diabetes	18 (52.9)	12 (35.3)	6 (18.8)	36 (36.0)	8.38	0.015
History of high cholesterol	16 (48.5)	14 (41.2)	23 (69.7)	53 (53.0)	5.87	0.053
History of myocardial infarction	3 (8.8)	1 (2.9)	3 (9.4)	7 (7.0)	†	0.126
History of stroke	3 (8.8)	1 (2.9)	3 (9.4)	7 (7.0)	†	0.126

*N and (%) are provided in this table. All χ^2 tests had *df*=2.

†Fisher-Freeman-Halton test.

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