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The Relationship of Cardiovascular Risk Factors to Alzheimer Disease in Choctaw Indians

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Abstract

Objectives—To test the hypothesis that cardiovascular risk factors (CRFs) influence predisposition to and the clinical course of Alzheimer disease (AD), the authors compared Choctaw Indians, a group with known high CRF with white subjects with AD. In addition to CRF history, the authors investigated the frequency of apolipoprotein E4 (apoE4) genotype and plasma homocysteine (HC) levels.

Method—The authors compared 39 Choctaw Indians with AD and 39 Choctaw Indians without AD to 39 white subjects with AD with all groups similar in age. CRF history included diabetes, hypertension, high cholesterol or hypolipidemic agent use, or myocardial infarction. The authors also compared plasma HC concentration and apoE4 allele frequency.

Results—Choctaw subjects with AD differed significantly from white subjects with AD in history of hypertension, diabetes, and in HC values but not from Indians without AD. There was a significantly lower apoE4 allele frequency in Choctaw Indian AD than white subjects with AD, and both AD groups had an affected first degree relative significantly more often than Indian controls. There was no relationship between the number of CRF history and age at onset among Indians or whites, whereas HC concentration was associated with significantly earlier age of onset for Choctaw Indians but not for whites.

Conclusions—This small study suggests that in Choctaw Indians modifiable risk factors may play more of a role in disease pathogenesis than in whites and that nonmodifiable risk factors such as apoE4 may play less of a role.

Keywords

Alzheimer disease; American Indian; cardiovascular risk; homocysteine; apolipoprotein E

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M. Weiner and L. Hynan developed the initial concept, designed the study, and were responsible for the analysis and interpretation of the data. C. Fuller recruited Indian subjects and collected data in the field. H. Rossetti managed the database and prepared the article for submission. K. Womack and R. Rosenberg performed clinical evaluations of Indian AD subjects and contributed to the discussion. Y.-H. Gong, B.-X. Qu, and R. Diaz-Arrastia were responsible for performance and interpretation of apoE genotyping.

Numerous studies have associated cardiovascular risk factors (CRFs) with Alzheimer disease (AD),¹ but these CRF differ among ethnic groups² and may have different influence within each group. For example, American Indians have more CRF (hypertension, elevated cholesterol, diabetes, myocardial infarction, and obesity) than U.S. whites.³ Disparities between whites and African Americans have also been noted, in particular, the higher prevalence of hypertension among African Americans.⁴ In addition, several studies have compared Mexican Americans with white (non-Hispanic) adults and found several higher CRF among Mexican Americans.⁵

We asked for the Certified Degree of Indian Blood (CDIB) for Choctaw subjects to establish degree of Indian heritage. The CDIB, based on records from the tribal rolls, indicates the percentage (e.g., full blood, 50%, and 25%) of American Indian heritage. The CDIB was found in an earlier study to be comparable with genotyping as a means to ascertain American Indian heritage.⁶

We had previously found among Cherokee subjects with AD that greater Indian heritage was associated with reduced risk of AD independent of apolipoprotein E4 (apoE4) genotype (inheritance of the E4 allele is associated with increased risk for AD in many other populations).⁷ In 26 patients with AD, 9 of 17 with Indian heritage <50% had an apoE4 allele, when compared with three of nine in patients with AD with Indian heritage 50%. It had been shown previously in Choctaws that apoE4 status varied inversely with degree of Indian heritage.⁶ In AD cases, apoE4 allele frequency was only 6% in those claiming full-blood status, 33% in the nine persons with 50% Choctaw heritage, and 13% in the eight persons with 50% Choctaw heritage. Thus, it appeared in both Cherokee and Choctaw Indians that apoE4 may play less of a role in the development of AD than in whites, as has been reported for Nigerians.⁸ Whether AD prevalence is lower in U.S. Indian tribes than in whites, as was reported for Cree Indians in Canada,⁹ is unknown.

Postulated modifiable CRF for AD include serum cholesterol concentration. In laboratory animals, diet enrichment with cholesterol increases beta amyloid production, whereas cholesterol depletion inhibits amyloid formation,¹⁰ but it is not clear from epidemiologic studies if treating hypercholesterolemia with statins lowers the incidence of AD.¹¹ Hypercholesterolemia is associated with apoE4 in whites¹² as an independent risk factor for AD.¹³ However, a relationship between AD and nonfasting total cholesterol levels in African Americans independent of apoE4 allele status has been found.¹⁴

Plasma homocysteine (HC) concentration is known to increase with age,¹⁵ and a level >14 $\mu\text{m/L}$ has been suggested as a risk factor for AD.¹⁶ In addition, Type 2 diabetes and hypertension may increase the functional impact of AD pathology.¹⁷ Type 2 diabetes and hypertension are prevalent in American Indians,^{3,18} including Choctaws.¹⁹ If CRF contribute to the clinical manifestation of AD, reducing CRF could delay the onset of symptoms. Thus, detection of risk factors such as CRF and knowledge of their interaction with apoE4 could lead to greater understanding of factors in the clinical development of AD unique to specific ethnic groups.

We proposed to determine whether modifiable CRF history (high cholesterol, diabetes, hypertension, hypolipidemic agent use, or myocardial infarction) differ between Choctaw Indians with and without AD and whites with AD and to determine the relationship of CRF history, apoE4 genotype, and HC levels to age of AD onset.

MATERIALS AND METHODS

Study Subjects

Choctaw Indian subjects with AD and controls were recruited by employees of the Choctaw Nation Health Care Authority (CNHCA) in Talihina, Oklahoma who were funded by grants to UT Southwestern. We asked for the CDIB for Choctaw subjects to establish degree of Indian heritage. The CDIB, based on records from the tribal rolls, indicates the percentage (e.g., full blood, 50%, and 25%) of American Indian heritage. The CDIB was found in an earlier study to be comparable with genotyping as a means to ascertain American Indian heritage.⁶

We used data from persons of Choctaw and other American Indian heritage seen at this site and diagnosed by the UT Southwestern clinical team as probable AD, using National Institute of Neurological and Communicative Disorders and Stroke–AD and Related Disorders Association criteria.²⁰ The diagnostic process included a standardized examination by an experienced neurologist or geriatric psychiatrist (KW, RR, and MW), neuropsychological testing with the CERAD battery²¹ augmented by the Trail Making Test and the Clock-Drawing Test, routine chemistries, serological test for syphilis, and brain computed tomography scan. With the exception of using magnetic resonance imaging brain scans, the same diagnostic procedure is used in Dallas.

We obtained deidentified data on white persons with AD similar in age from the database of the UT Southwestern Alzheimer's Disease Center (ADC), including medical history, plasma HC concentration, and apoE4 status. These individuals had been seen as clinical or research referrals to the ADC.

History of high cholesterol, diabetes, hypertension, hypolipidemic agent use, or myocardial infarction was obtained from the subject and an informant, usually a spouse. Subjects were screened for history of depression or alcohol abuse in the previous 5 years.

The Choctaw Indian subjects without AD were similar in age to Indian subjects with AD. Inclusion criteria were 1) no history of cognitive impairment by an informant, 2) no history of alcohol abuse or mental illness within 5 years, 3) no history of clinical stroke or significant CNS disorder, and 4) Mini-Mental State Examination score above cutoff for age and education.²²

All newly evaluated persons with AD gave informed consent or assent. Subjects with AD and their legal representatives signed informed consent documents approved by the UT Southwestern Institutional Review Board and in the case of Choctaw Indians, the CNHCA Institutional Review Board. Indian normal subjects signed informed consent as well. Hard copies of information were maintained in the files of the UT Southwestern ADC, and

electronically recorded information was kept in the ADC database. The research data collected by the UT Southwestern ADC are maintained by its Database and Statistics Core.

We collected blood from all Choctaw subjects to determine HC concentration and apoE genotype.

HC Methods

Blood for Indian plasma HC determination was collected in EDTA tubes and immediately placed on ice. It was centrifuged cold within 2 hours at the Clinical Laboratory of the CNHCA in Talihina, Oklahoma. Plasma was shipped in refrigerated transport tubes to a commercial laboratory (LabCorp) at which samples were analyzed using methods described elsewhere.²³ HC determinations for whites had been carried out earlier in a Dallas laboratory using a similar method.²⁴

Genotyping Method

Whole blood was used for genotyping white subjects. Blood for genotyping of Indians was initially collected as single drops of blood placed on FTA Microcards (Whatman International) for ease of collecting, shipping, and storage. This method was unsatisfactory, because repeated extractions were needed to elute the small quantity of DNA. Later, whole blood was collected in 5 mL aliquots in EDTA-treated tubes. DNA was extracted in the UT Southwestern Molecular Diagnostics Laboratory. Genotyping was performed in the laboratory of RDA, as described elsewhere.²³ Indian samples were confirmed by the UT Southwestern Sequencing Core.

Statistical Analysis

The primary measures of interest were the CRF history (diabetes, hypertension, high cholesterol/hypolipidemic agent use, or myocardial infarction), plasma HC concentration, apoE4 allele frequency, and age of AD onset. To detect a 20% difference in serum HC between Indians with AD and whites with AD, a minimum of 21 patients per group was needed using a 2-independent samples, two-sided Mann-Whitney U test for $(1 - \beta) = 80\%$ and $\alpha = 0.05$.

Kruskal-Wallis or Mann-Whitney U tests were used to compare groups when the data were continuous; if the Kruskal-Wallis test was significant, a post-hoc nonparametric multiple comparisons test²⁵ was performed. Chi-square test was used to compare groups when the data were dichotomous; when the χ^2 was found significant, a Tukey-type multiple comparison test among proportions was performed.²⁵ Spearman rank order correlations were used to examine associations between pairs of measure. SPSS V16.0.2 or StatXact V8 was used to perform statistical analyses. All statistical tests were two sided, and the p value for significance was 0.05.

RESULTS

We were able to recruit 43 Indian subjects with a diagnosis of probable AD from our satellite clinic. Of these, two dropped out and two others were reclassified diagnostically,

leaving 39 subjects who were as similar in age as possible with 39 of 45 available Indians without AD. We also obtained data from an equal number of age-matched white subjects with AD similar in age from the UT Southwestern ADC database.

Table 1 shows the quantitative characteristics of the three groups. There was no age difference between the three groups, and there was no difference between percentage of Indian heritage for the two Choctaw groups or between onset age for the two AD groups. Using a post-hoc nonparametric multiple comparisons test,²⁵ white subjects with AD had significantly greater education than Indians and significantly lower HC than Indians, whereas Indian subjects with AD and without AD were similar on all these variables.

As indicated in Table 2, there were no significant differences between Choctaws with and without AD in gender, history of high cholesterol, or myocardial infarction; only 9 of the 114 subjects comprising all three groups had a history of myocardial infarction. White subjects with AD had significantly less history of hypertension than Choctaw subjects with AD and without AD (39% versus 82% or 69%) and significantly less history of diabetes than Indian subjects with AD (16% versus 54%). Both white and Indian AD groups had a significantly higher percentage of affected first-degree relatives than the Indian controls (44% or 31% versus 8%).

ApoE4 status was available for 37 Indian subjects with AD and 39 without AD but for only 14 of the white subjects with AD in our database. Using a Tukey-type multiple comparisons test for proportions,²⁵ white patients with AD had a significantly higher proportion of one or more apoE4 alleles than either Choctaw group (78% versus 35%, $Q(3) = 3.93$, $p = 0.05$; 78% versus 21%, $Q(3) = 5.43$, $p = 0.05$). There was a nonsignificant relationship between the number of CRF (history of hypertension, diabetes, high cholesterol, and myocardial infarction) and the number of subjects with one or more apoE4 alleles when white and both Indian groups were combined ($\chi^2_{[4]} = 4.614$, $p = 0.329$).

There was also no relationship between the median number of CRF in comparing Choctaw subjects with AD with Choctaw subjects without AD (Table 1) or between the number of CRF and degree of Indian heritage, but Choctaw subjects with AD had a significantly higher number of CRF than white subjects with AD. There was a nonsignificant relationship between HC levels and number of CRF in whites and Choctaw groups combined. In the white and Indian groups with AD, there was no significant relationship between onset age and number of CRF (Spearman $r(71) = -0.092$, $p = 0.441$). There was a significant relationship between HC concentration and onset age only with Indian subjects with AD (Spearman $r(27) = 0.506$, $p = 0.005$).

DISCUSSION

The number of modifiable CRF was greater in Choctaw Indians with AD than whites with AD. These CRF in Indian AD cases did not differ from Indians without AD and were not significantly associated with degree of Indian heritage. There was a strong relationship between HC levels and number of CRF in all groups. ApoE4 genotype was associated with greater numbers of CRF in whites but not Choctaws.

Both Indian groups differed significantly from white subjects with AD in HC concentration and frequency of hypertension and diabetes but did not differ significantly from each other (Table 2). Although HC assays were performed by similar methods (high performance liquid chromatography), they were performed in different laboratories at different times, introducing a possible source of bias. We reconfirmed earlier findings of significantly lower occurrence of the apoE4 allele in Indian subjects with AD than in whites.^{6,7} Although the number of whites with apoE genotyping was small in this study (N = 14), the percentage of those with one or more E4 alleles was consistent with reports from larger samples, including our own.²⁶ The base rate of E4 alleles in the general American Indian population is not known. As expected, both AD groups had an affected first degree relative significantly more often than did Indians without AD.

The three groups of study participants were selected to be similar in age because increasing age is associated with increasing HC values¹⁵ and declining apoE4 allele frequency.²⁷ Despite reported drops in blood pressure and cholesterol with disease progression, we thought it still appropriate to compare history of hypertension and history of high cholesterol between groups. We confirmed prior findings of decreased apoE4 allele frequency in American Indians.⁶ The 54 subjects with no apoE4 allele had a median 72% Indian heritage, and the 21 subjects with at least one apoE4 allele had a median of 25% Indian heritage (p = 0.05).

Limitations to Generalization of Findings

The dispersion of Choctaw Nation members over a large area of rural Oklahoma (15,000 square miles) made population-based sampling virtually impossible. We were able to obtain subjects with a broad range of Indian heritage but not able to assess life style factors such as diet. Comparison of rural Indians with urban whites may have been confounded by environmental or life style considerations but only persons with Indian heritage are seen in the CNHCA. Our reliance on self-report could have led to an underestimate of CRF. We asked our Indian subjects and their informants whether they had a history of high cholesterol or whether they took medication for high cholesterol but did not detect additional cases of hyperlipidemia in this way. Use of hypolipidemic, antidiabetic, or antihypertensive agents was not available for whites.

All CRFs were given equal weight, but there was no way to determine the severity of each risk factor and to estimate its impact vis-à-vis the other CRFs. There were also differences in the diagnostic process. Magnetic resonance imaging is routinely performed in Dallas but was not available in Talihina, and some vascular pathology may have been missed using only computed tomography scans for Choctaws.

The lower plasma HC concentrations in whites may have been related to more common use of folic acid supplementation among whites. Whites were fasted, and Indians were not, but the proximity of blood sampling to meals does not significantly affect total plasma HC levels.²⁸ Further confounds include the association of higher HC levels in persons with diabetes and hypertension,²⁹ and impaired renal function.³⁰ Diabetes and hypertension were more common in Indians than whites, and it would be fair to assume on this basis that renal insufficiency is also more common among Indians. Additionally, HC elevations have been

linked to alcohol dependence³¹ and depression;³² however, the sample was screened for these risk factors for the 5 years preceding this study.

Stroke risk has been more strongly associated with subjects with AD than normal controls, based on Framingham Stroke Risk scores.³³ Although there is evidence that the presence of factors that might contribute to brain vascular disease might make the functional changes of AD more clinically obvious^{17,34} and might result in earlier clinical onset of illness, we found this to be the case for HC concentration rather than CRF history. This supports our earlier finding in white subjects that history of CRF had no influence on clinical progression and survival time.¹ A possible explanation for these counterintuitive findings is that the presence or absence of these vascular risk factors may be less important than their effects on HC concentration or other endogenous factors.

The most common predisposing factor to late-onset AD, aside from age, is the apoE4 allele. Its relative infrequency among Indian subjects with AD suggests that the apoE4 allele plays less of a role in Choctaw Indians than in whites.

CONCLUSIONS

The relatively low frequency of the apoE4 allele in Choctaw Indian subjects with AD and the association of higher HC levels with earlier onset of disease suggest that modifiable risk factors may be more prevalent in Indians than whites. Although lowering HC levels in subjects with AD using high-dose B vitamins had no therapeutic effect in patients with AD,³⁵ it is possible that lowering HC levels might influence the clinical course of persons at risk for AD.

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TABLE 1
Quantitative Characteristics of American Indians With AD, Indian Controls, and Whites With AD

Variables	Indian AD			Indian Control			White AD			Kruskal-Wallis (χ^2 , <i>df</i>) or Mann-Whitney U (<i>Z</i>), Statistic <i>p</i> (Omnibus)
	N	Median	Range	N	Median	Range	N	Median	Range	
Age	39	78.0	54-91	39	75.0	64-85	39	76.0	58-88	1.046, <i>df</i> = 2, 0.624
Age at onset	38	75.0	48-87	-	-	-	38	73.0	56-84	-0.432, 0.666
Education, years	39	11.0*	3-18	39	12.0*	7-17	39	14.0 [†]	6-20	34.068, <i>df</i> = 2, <0.001
% American Indian	39	50.0	2-100	39	63.0	6-100	-	-	-	-0.204, 0.838
Mini-Mental State Score	35	19.0*	0-28	39	29.0	23-30	39	23.0 [†]	5-30	-2.723, 0.006 [‡]
Homocysteine ($\mu\text{mol/L}$)	30	13.0 [‡]	8.6-27.1	39	11.5	7.6-28.5	37	9.2*	5.2-33.7	16.921, <i>df</i> = 2, <0.001
Number of cardiovascular risk factors	37	2.0 [‡]	0.0-4.0	39	1.0	0.0-3.0	37	1.0*	0.0-4.0	7.310, <i>df</i> = 2, 0.026

* Indicates which groups are significantly different (lower).

[†] Indicates which groups are significantly different (higher).

[‡] Mann-Whitney U test for MMSE scores between Indian and white groups with AD; MMSE in normal range for age and education was an inclusion criteria for Indian controls.

TABLE 2
Gender and Medical History Characteristics of American Indians With AD, Indian Controls, and Whites With AD

Variables	Groups, N (%), 95% CI				χ^2	p (Omnibus)
	Indian AD	Indian Control	White AD	Total N (%), 95% CI		
Female	24 (62), 45%–78%	24 (62), 45%–78%	18 (46), 29%–63%	66 (56), 42%–70%	2.50	0.286
History of hypertension	32 (82), * 69%–95%	27 (69), * 53%–85%	15 (39), † 22%–55%	74 (63), 50%–77%	16.84	<0.001
History of diabetes	21 (54), * 37%–71%	15 (39), * 22%–55%	6 (16), † 3%–29%	42 (37), 23%–50%	11.69	0.003
History of high cholesterol/hypolipidemic agent	17 (46), 29%–63%	16 (41), 24%–58%	25 (64), 48%–80%	58 (50), 36%–65%	4.59	0.101
History of myocardial infarction	3 (8), 0%–18%	2 (5), 0%–13%	4 (11), 0%–22%	9 (8), 0%–16%	0.84	0.656
Affected first degree relative	12 (31), * 15%–47%	3 (8), † 0%–17%	14 (44), * 25%–63%	29 (26), 13%–39%	12.38	0.002
One or more E4 allele [‡]	13 (35), † 18%–52%	8 (21), † 7%–35%	11 (79), * 54%–100%	32 (36), 20%–52%	14.72	0.001

Notes: All χ^2 tests had $df = 2$.

* Indicates which groups are significantly different (higher).

† Indicates which groups are significantly different (lower).

[‡] Allele frequency: Indian AD = 0.1714; Indian control = 0.1081.