The Prevalence of Alzheimer Neuropathologic Lesions Is Similar in Blacks and Whites

Miguel A. Riudavets, MD, Ana Rubio, MD, PhD, Christopher Cox, PhD, Gay Rudow, BA, David Fowler, MD, and Juan C. Troncoso, MD

Abstract

Alzheimer disease is the most common dementia in older Americans, but its impact on blacks is not clearly understood. We examined prospectively 200 autopsy brains at the Office of the Chief Medical Examiner in Maryland and compared the frequency and severity of Alzheimer lesions in blacks and whites. Histologic sections of the hippocampus and entorhinal and neocortices were immunostained for Aβ and tau proteins. Subjects were genotyped for ApoE. Aβ deposits were rated as none, sparse, moderate, or frequent; tau lesions were rated into 4 groups corresponding to Braak scores; and Aβ angiopathy was classified as present or absent. Outcome scores were treated as ordinal variables and analyzed by proportional odds logistic regression. Aβ plaques were present in 60% of black males, 58% of white males, 74% of black females, and 74% of white females. Tau lesions were present in 96% of black males, 88% of white males, 96% of black females, and 96% of white females. Neither race nor gender was a significant factor in the frequency or severity of Alzheimer lesions, and ApoE4 increased the risk for Alzheimer lesions similarly in blacks and whites.

Key Words: Alzheimer disease, ApoE4, Autopsy, Gender, Prevalence, Race.

INTRODUCTION

Alzheimer disease is the most common dementia in older Americans (1); however, its impact on specific minority groups is not well understood. Studies comparing the clinical incidence of Alzheimer disease between blacks and whites have provided conflicting conclusions. Some studies have found an increased prevalence of dementia in general (2), and of Alzheimer disease in particular, among blacks (3, 4), whereas others have not (5). There are few studies comparing the neuropathology of Alzheimer disease in blacks and whites and all of them are retrospective. In a series of hospital-based autopsies, blacks had more multi-infarct dementia and whites more Alzheimer lesions (6), but in forensic-based autopsies, the prevalence of neuropsychologic lesions of Alzheimer disease was independent of race and gender (7). An increased prevalence of Alzheimer disease in blacks could be attributed to the higher frequency in blacks of the ApoE4 allele (8), a risk factor for Alzheimer disease (9–11). This notion is also controversial, however, because there is no agreement on whether ApoE4 enhances the risk for Alzheimer disease in blacks as it does in whites. Some studies have found that the ApoE4 allele is a risk factor for Alzheimer disease in blacks (12, 13), whereas other investigations have found that the effect is weaker in blacks than in whites (14), and yet other reports indicate there is no effect in blacks (4, 15).

Aware that the discrepancies among clinical studies comparing Alzheimer disease in blacks and whites may reflect ascertainment biases resulting from educational, cultural, and social–economic factors, we compared the prevalence of Alzheimer disease in blacks and whites from a neuropathologic perspective. We examined prospectively a large series of forensic autopsies and asked 2 main questions: 1) Is there a difference in the frequency and severity of Alzheimer disease lesions between blacks and whites? 2) Is there a difference in the effect of the ApoE4 allele on the development of Alzheimer disease lesions between the 2 races?

MATERIALS AND METHODS

Autopsies and Neuropathology

We examined prospectively 200 brains, that is, 50 black males, 50 black females, 50 white males, and 50 white females, from subjects between the ages of 65 and 95 years from consecutive autopsies conducted at the Office of the Chief Medical Examiner of the State of Maryland between 2002 and 2005. The autopsy and brain examination and laboratory testing were performed as required and authorized under the Maryland Post Mortem Commission Act. The Maryland Department of Health and Mental Hygiene Institutional Review Board exempts research on autopsy tissues in which all identifiers are removed.

Race was assigned according to family self-identification. To choose a sample size, we assumed a response rate of 20% in whites. With 100 brains in each group, we had 80%
power to detect a response rate of 37.9% in blacks (relative risk of 2) at the usual 5% level of significance. We anticipated that use of ordinal response scores in addition to a simple binary response would provide additional power. The inclusion of the brains in the study was independent of history of cognitive decline or dementia and of the cause or manner of death. We purposely did not seek or obtain information on clinical or cognitive status. There were 116 complete autopsies and 84 limited to the brain. Brains were weighed and then fixed in formaldehyde (n = 41) or examined in the fresh state (n = 159). All brains were examined by a neuropathologist (AR, MAR, or JCT) (Table 1). Histologic sections of the hippocampus, and entorhinal, middle frontal, middle temporal, and occipital cortices were immunostained for Aβ (6-E-10, Signet Labs, Inc., Dedham, MA; dilution 1:500) and phosphorylated tau protein (PHF-1 clone, a gift from Dr. P. Davies; dilution 1:100). The severity of the Aβ parenchymal deposits (plaques) was rated as none, sparse, moderate, or severe according to The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) guidelines (Fig. 1) (16), and Aβ angiopathy was assessed as present or absent. The severity of tau lesions (neurofibrillary tangles [NFTs]) was rated on tau immunostains into 4 categories corresponding to Braak scores 0, I, and II (transentorhinal), III and IV (limbic), and V and VI (isocortical) (17).

**ApoE Genotyping**

ApoE genotyping was conducted as described by Hixson and Vernier on DNA extracted from brain tissue on 198 subjects (18) (Table 2).

**Statistical Analysis**

The dependent variables Aβ plaque score, Braak score, and Aβ angiopathy were treated as ordinal variables and analyzed using proportional odds logistic regression (19). Aβ plaques were analyzed using CERAD scores (i.e. no Aβ plaques, sparse, moderate, or frequent) and NFTs according to Braak scores (i.e. no tangles, transentorhinal, limbic, or isocortical). Aβ angiopathy was analyzed as present or absent. Independent variables were age, gender, ApoE 4 genotype (positive/negative), and race. The dependent variables were Aβ plaques, NFT, and Aβ angiopathy. Our strategy was to run one (main effects) analysis including all of the previously mentioned independent variables. Because the ages of subjects examined were distributed over a 31-year span, the primary analysis was a logistic regression in which the comparison of the racial groups was adjusted for age. A second analysis was used to test for interaction between ApoE and both race and gender by using 2 2-way and one 3-way interactions. Our main hypothesis was that in the primary analysis, race would be a significant predictor of neuropathologic outcome with blacks having more severe Aβ and tau scores. A second hypothesis was that the race × ApoE interaction would not be statistically significant. In addition, we estimated individual odds ratios and profile likelihood confidence intervals for an ApoE effect in each of the 4 race × gender groups. We also used ordinal logistic regression analysis to examine the effect of manner of death on Aβ and tau lesions. We compared only natural versus nonnatural manner of death because the other categories (undetermined, homicides, and suicides) had very few subjects.

**RESULTS**

Among the 200 subjects, 133 (66.5%) showed Aβ plaques, 67 (67%) in blacks and 66 (66%) in whites. In terms of gender, Aβ plaques were present in 60% of black males, 58% of white males, 74% of black females, and 74% of white females (Figs. 2 and 3). In the primary analysis, both age and ApoE4 were significant predictors of Aβ plaques and Aβ angiopathy (Table 3). Neither race nor gender was a predictor of Aβ plaques (odds ratio [OR], 0.97; confidence interval [CI], 0.55–1.71, p = 0.92 and OR, 1.56, CI, 0.90–2.70, p = 0.11, respectively) or Aβ angiopathy (OR, 1.18; CI, 0.57–2.51, p = 0.65 and OR, 1.62; CI, 0.79–3.40, p = 0.19, respectively). In the secondary analysis for Aβ angiopathy, the ApoE interaction with gender was significant (p = 0.018) and the effect was significant only for males (Table 3).

![FIGURE 1. Cerebral cortex immunostained for Aβ. The panels are representative of the 3 frequency levels of Aβ plaques and their respective mean fractional areas: (A) sparse; (B) moderate; and (C) frequent.](image_url)

**TABLE 1. Demographics and Gross Pathologic Findings**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>White Males</th>
<th>White Females</th>
<th>Black Males</th>
<th>Black Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Age (mean) in years</td>
<td>76.1 ± 7.8</td>
<td>80.5 ± 8.3</td>
<td>73.1 ± 7.3</td>
<td>75.3 ± 7.6</td>
</tr>
<tr>
<td>Manner of death: accident</td>
<td>48%</td>
<td>50%</td>
<td>28%</td>
<td>32%</td>
</tr>
<tr>
<td>Homicide</td>
<td>4%</td>
<td>2%</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Natural</td>
<td>30%</td>
<td>44%</td>
<td>60%</td>
<td>62%</td>
</tr>
<tr>
<td>Suicide</td>
<td>18%</td>
<td>4%</td>
<td>6%</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Brain weight (g)</td>
<td>1350.9 ± 135.6</td>
<td>1169.2 ± 123.7</td>
<td>1279 ± 132.1</td>
<td>1123.8 ± 131.8</td>
</tr>
<tr>
<td>Brain infarcts or lacunes</td>
<td>26%</td>
<td>16%</td>
<td>16%</td>
<td>26%</td>
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</table>
Neurofibrillary tangles were present in 96% of black males, 88% of white males, 96% of black females, and 96% of white females, and age was the only significant predictor in the primary analysis (Table 3). Race (OR, 1.08; CI, 0.62–1.89, p = 0.76), gender (OR, 1.48; CI, 0.86–2.57, p = 0.15), and ApoE4 (Table 2) were not significant for the sample as a whole, and in the secondary analysis, ApoE4 appeared marginally significant only for white females (Table 3).

We detected vascular lesions in 44 (22%) brains in the whole sample (Table 1). Thirteen infarcts (26%) of black females (8 with multiple infarcts, 2 with lacunar infarcts, and 3 with cortical lesions), 9 infarcts (18%) of black males (4 with multiple infarcts, 5 with lacunar infarcts), 9 infarcts (18%) of white females (4 with multiple infarcts, 2 with lacunar infarcts, and 3 with cortical lesions), and 13 infarcts (26%) of white males (6 with multiple infarcts, 3 with lacunar infarcts, and 4 with cortical lesions). Inclusion of the presence or absence of vascular lesions did not modify the outcome of statistical analysis for Aβ lesions or tangles.

Manner of death was not a statistically significant predictor either for Aβ or tau lesions.

**DISCUSSION**

We believe that our sample is representative of the population at large. In Maryland, forensic autopsies are mandated by law and do not require next-of-kin consent. This avoids many of the potential biases that complicate hospital autopsy series, including racial differences in access to medical attention and hospitalization, and attitudes toward disease and autopsy. Other features of our sample design that contributed to minimize potential biases were the inclusion of consecutive autopsies regardless of history of cognitive status, previous diseases, circumstances of death, or the cause or manner of death.

In the present study, age was a highly significant predictive factor for Alzheimer disease lesions, including Aβ angiopathy, in all groups, an observation consistent with clinical and pathologic studies indicating that age is a risk factor for Alzheimer disease (7, 20).

Our results showed that the prevalence of the neuropathologic lesions of Alzheimer disease is independent of gender (Table 3), an outcome consistent with some previous pathologic and clinical studies indicating that gender is not a risk factor (5, 7). It should be noted that some other studies have found that women have a higher risk of developing Alzheimer disease compared with men (21, 22).

The most important observation in our study is that the prevalence of the neuropathologic lesions of Alzheimer disease is independent of race. This finding fails to confirm the hypothesis that blacks tend to have more severe neuropathology scores and is similar to that of a previous neuropathologic series (7), but differs from another study of 144 hospital autopsies, which demonstrated that blacks...
Some population studies have described a higher prevalence of Alzheimer disease in blacks compared with whites (2–4) and in black males compared with white males (22). Other studies, however, have shown no differences in the risk for Alzheimer disease between blacks and whites (5).

The apparent discrepancy between our study, which shows no difference in the prevalence of Alzheimer disease lesions between blacks and whites, and those clinical studies that describe higher frequencies of Alzheimer disease among blacks, may have several explanations. A distinct possibility is that the increased clinical ascertainment of Alzheimer disease among blacks may reflect the inadvertent inclusion of cases with cerebrovascular lesions (23). Blacks are reported to have a higher prevalence of cerebrovascular lesions (24), which may be the cause of dementia (vascular dementia) or contribute to the clinical expression of otherwise subclinical Alzheimer disease lesions (mixed dementia), or vice versa (25). However, when we adjusted for the presence of brain infarcts in relation to Aβ plaques, tau lesions, and Aβ angiopathy, no statistically significant differences were observed.

Another possibility is that the instruments used to assess cognition in blacks are not the most appropriate and could be culturally biased (26, 27). This notion is supported by the observation that elderly blacks, without cognitive impairment or dementia, tend to perform slightly worse than whites in some cognitive tests (28).

We are also aware that Alzheimer disease is a complex disease and that the presence and severity of Aβ and tau lesions may not be the sole determinants of the clinical expression of the disease. It is possible that 2 individuals with comparable Aβ loads in their brains may have different clinical outcomes. These outcomes could be modulated by factors such as local inflammatory response to Aβ deposition (29, 30), serum cholesterol (31), diet (32), chronic use of medications (33), and education (34).

<table>
<thead>
<tr>
<th>Effects as a predictor for</th>
<th>White Males</th>
<th>White Females</th>
<th>Black Males</th>
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<tbody>
<tr>
<td>Aβ plaques</td>
<td>(1.053, 1.092, 1.133) p &lt; 0.001</td>
<td>(1.043, 1.081, 1.121) p &lt; 0.001</td>
<td>(1.007, 1.054, 1.104) p = 0.02</td>
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<tr>
<td>Tau lesions (tangles)</td>
<td>(1.053, 1.092, 1.133) p &lt; 0.001</td>
<td>(1.043, 1.081, 1.121) p &lt; 0.001</td>
<td>(1.007, 1.054, 1.104) p = 0.02</td>
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<td>Aβ angiopathy</td>
<td>(1.053, 1.092, 1.133) p &lt; 0.001</td>
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<td>(1.007, 1.054, 1.104) p = 0.02</td>
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<tr>
<td>ApoE4 as a predictor for</td>
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<tr>
<td>Aβ plaques</td>
<td>(3.299, 6.189, 11.996) p &lt; 0.001</td>
<td>(1.673, 3.749, 23.623)</td>
<td>(2.508, 6.959, 20.154)</td>
<td>(1.784, 5.708, 20.809)</td>
</tr>
<tr>
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<tr>
<td>Aβ angiopathy (by group)</td>
<td>(1.053, 1.092, 1.133) p &lt; 0.001</td>
<td>(1.043, 1.081, 1.121) p &lt; 0.001</td>
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The panel shows 95% confidence intervals (lower limit, odds ratio, upper limit), p values, and estimated relative risk (EE) from proportional odds logistic regression analysis.
The ApoE4 allele is a recognized risk factor for sporadic–late-onset Alzheimer disease, which also influences the age of onset and the severity of Aβ lesions (9, 10, 35–37). According to some clinical studies, the ApoE4 allele is a risk factor for Alzheimer disease in whites but not in blacks (4, 15). However, another study found that the ApoE4 allele is strongly associated with Alzheimer disease in a sample of blacks older than 65 years of age (12). The frequency of the ApoE4 allele in our subjects was within the expected range for both blacks (19.5%) and whites (12.24%) in the general sample (8), but for black females (15%), it was below the previously reported range (38) (Table 2). There were no differences in age among subjects with and without ApoE4 alleles in any of the 4 groups. Our observations indicate that the ApoE4 allele is equally significant as a predictive factor for the development of Aβ plaques in both blacks and whites. The relative risk for developing lesions in carriers of the ApoE4 allele is not significantly different among the 4 groups examined (Table 3). This is consistent with some previous population-based studies that have shown the importance of ApoE4 as a risk factor for Alzheimer disease in the general population (9–11) and for blacks (12, 13).

Our study also indicates that the ApoE4 allele is a significant predictive factor of tau lesions (tangles) in white females (p = 0.03), but in none of the other groups. Previous pathologic studies have shown higher tau lesion scores in ApoE4 carriers in general (35), but no previous analyses by gender or race are available. With regard to Aβ angiopathy, we found that the presence of at least one ApoE4 allele is a significant predictive factor for Aβ angiopathy in black males and white males, but not in females (Table 3). This observation is consistent with previous studies showing that ApoE4 is an important risk factor for Aβ angiopathy in general (39). In our study, the significance is specific for males with ApoE4 and might be explained by a role of sex hormones on the deposition of Aβ in blood vessels; however, previous studies suggest that there is no association between sex hormones and amyloid plaques or cerebral amyloid angiopathy (40).

In conclusion, we found that the frequency and severity of the neuropathologic lesions of Alzheimer disease are similar in blacks and whites and that the ApoE4 allele represents a similar risk factor for Alzheimer disease lesions in both races.

ACKNOWLEDGMENTS

The authors thank Dr. Pamela Talalay for reviewing the manuscript, Dr. Olga Pletnikova and Mrs. Stina Tucker for their support and constructive suggestions, Ms. Jessica Winicki for excellent technical assistance, and Ms. Karen Wall for preparation of the manuscript.

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