Joint Effect of the APOE Gene and Midlife Systolic Blood Pressure on Late-Life Cognitive Impairment

The Honolulu-Asia Aging Study

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Background and Purpose—The aim of this study was to explore the joint effect of the APOE e4 allele and midlife systolic blood pressure (SBP) on the risk for poor cognitive function in late life.

Methods—The study includes 3605 surviving members of the cohort of the Japanese-American men followed prospectively over 26 years (1965–1991) as a part of the Honolulu Heart Program. In 1965 men were aged 45 to 68 years and were living in the island of Oahu, Hawaii. For this study the sample was divided into 4 categories: normal SBP (<160 mm Hg)/No e4, as the reference category; normal SBP/e4; high SBP/no e4; high SBP/e4. The relative risk (RR) of late-life intermediate and poor cognitive function relative to good function was measured by the Cognitive Abilities Screening Instrument (CASI) test.

Results—After adjusting for age, education, smoking, alcohol use, and body mass index, the RR for poor cognitive function (CASI <74) compared with good cognitive function (CASI ≥82) in never-treated subjects was 1.3 (95% CI 0.9 to 1.9) for the normal SBP/e4 category, 2.6 (0.7 to 10.0) for the high SBP/no e4, and 13.0 (1.9 to 83.8) for the high SBP/e4. Adjustment for diabetes, prevalent stroke, coronary disease, and ankle-brachial index reduced the RR of poor cognition by 25.5% (RR 13.0 to 10.8) in those with both risk factors. In the treated group, the RR was 1.9 (0.7 to 4.5) for those with both risk factors.

Conclusions—The results suggest that midlife high SBP has a stronger adverse effect on cognitive function in persons with higher genetic susceptibility, but this effect may be modified by antihypertensive treatment. (Stroke. 2001;32:2882-2889.)

Key Words: blood pressure  ■ cognition  ■ genetics

See Editorial Comment, page 2888

Subjects and Methods

Study Population

The Honolulu Heart Program (HHP) is a longitudinal population-based study designed to investigate heart disease and stroke among Japanese-American men. The original sample included 8006 Japanese-American men born between 1900 and 1919 who were living on Oahu, Hawaii, at baseline.11 After the first examination (1965–1968), the men were followed and further examined in 1968–1970 (examination 2) and again in 1971–1974 (examination 3). At each examination, simple clinical measures were made and sociodemographic and medical conditions assessed. In 1991–1993, the Honolulu-Asia Aging Study (HAAS) was established, with the aim of investigating neurodegenerative diseases in this cohort.12,13 Subjects who survived up to the 1991 examination were younger (52.7 versus 57.0 years at baseline examination, P<0.001), more educated (7.8 versus 8.5 years, P=0.001), and had higher midlife SBP (140.6 versus 132.9 mm Hg, P=0.001). In 1991, 3734 men (80% of the surviving cohort) underwent a clinical examination including assessment of cognitive function. Compared with non-re-
spondents, participants had similar age but proportionately higher education and less missing data from 1 of the 3 midlife exams (95% versus 75% with complete data, \( P = 0.001 \)). All subjects were informed about the study objectives and signed an informed consent form. The study was approved by the Institutional Review Board of Kuakini Medical Center.

**Cognitive Function**

The Cognitive Abilities Screening Instrument (CASI) was used to evaluate the cognitive status. The CASI is a validated test used for cross-cultural epidemiological studies, and is a combination of the Hasegawa Dementia Scale, the Mini-Mental State Examination, and the Modified Mini-Mental State Examination. The CASI score ranges from 0 to 100. Because the CASI distribution was highly skewed, 3 levels of cognitive function were created: "good" (CASI \( \geq 82 \); upper 70% of the sample), "intermediate" (CASI 74 to 82; 15%) and "poor" (CASI < 74; lowest 15% of the sample). In this cohort, a CASI score of < 82 corresponded to a sensitivity of dementia (as defined in the *Diagnosis and Statistical Manual of Mental Disorders*) of 80% and a specificity of 77%. To improve the sensitivity of dementia, subjects with low scores (CASI < 74) were sorted out from the others because they had a high probability of being demented. However, because the CASI is not a clinical diagnostic tool, we did not label it as such.

**Blood Pressure**

BP was measured in the 3 midlife HHP examinations. At each examination, BP values represent the mean of 3 measurements made 5 minutes apart on the left arm while the subject was seated. Standard sphygmomanometer and cuff were used. Diastolic BP (DBP) was recorded as the fifth phase. Mean midlife SBP and DBP were calculated by using all measurements made over the first 3 exams. As in a previous report, SBP was further categorized as high if it was \( \geq 160 \) mm Hg or in at least 2 of the 3 examinations. All other subjects were classified in the normal SBP group. Similar criteria were adopted for DBP: individuals were characterized as having high DBP if 2 of the 3 examination values were \( \geq 95 \) mm Hg, or normal otherwise.

**Apolipoprotein E genotyping**

Blood samples were drawn at the fourth examination, and APOE genotyping was obtained by standard DNA amplification and restriction isotyping in 3605 subjects. The e4 allele frequency in the sample was 9.5%, lower than that reported among whites but similar to that in other Japanese populations. Among e4 carriers, 2.2% were homozygotes (e4/e4) and 97.8% were heterozygotes (e2/e4, e3/e4, e4/e3). The denominator of e4 homozygotes (n = 16) did not allow for the evaluation of gene dose effect (noncarriers versus e4 heterozygotes versus e4 homozygotes). For analysis purposes, all e4 carriers were combined in the APOE e4 group.

**Covariates and Confounders**

Several variables were considered to be possible covariates or confounders. We controlled the analysis for age at the fourth examination, education, midlife body mass index, smoking, and alcohol intake. We used midlife values because they are less influenced by preclinical dementia status. Body mass index (in kilograms per meters squared) was calculated from participants’ height and weight at each examination and averaged. Self-reported smoking was assessed at exams 1 and 3 and categorized by pack-year of cigarette exposure (packs of cigarettes per year times years of smoking). Alcohol intake was reported at exams 1 and 3 and recorded as grams of alcohol per day. In the multivariate analysis, the variable was recorded as drinks per day (none, <1 drink [13.2 g], 1 to 2 drinks, and \( \geq 3 \) drinks/d). History of diabetes was assessed on the basis of self-report of doctor’s diagnosis, or use of diabetes medications, or with fasting glucose level equal to 126 mg/dL or higher, or with 2-hour postload glucose equal to 200 mg/dL or higher. Coronary heart disease (CHD; myocardial infarct and angina) and stroke events were monitored from 1965 through the entire follow-up by continuous surveillance of hospital discharge and death records on Oahu. Ankle-brachial index (ABI) was measured at the fourth examination, and the values were dichotomized with a cutoff of 0.9; values below this point were interpreted as indicator of generalized atherosclerosis. History of antihypertensive treatment to lower BP was self-reported by the subjects from examination 1 to 3 and required presentation of medication vials at examination 4. Assessment of the duration of the antihypertensive treatment was performed during the 1991 examination. In the total sample, there were 2082 participants (57.9%) never treated with antihypertensive medication. Compared with the untreated, the treated group was younger (\( P = 0.03 \)), and, after adjusting for age, had a higher education level (10.6 versus 10.4 y \( P = 0.03 \)) and mean midlife systolic (125 versus 141 mm Hg, \( P < 0.0001 \)) and diastolic BPs (79 versus 88 mm Hg, \( P < 0.0001 \)), and included more individuals with ABI \( \leq 0.9 \) (\( P < 0.0001 \)), CHD (\( P < 0.0001 \)), and stroke (\( P < 0.0001 \)). Smoking and alcohol intake were similar between the 2 groups. APOE e4 allele frequency was different between the 2 groups, although not significantly.

**Statistical Analysis**

The cohort was divided into 4 categories: normal SBP (NSBP/no e4, used as the reference group); NSBP/e4; high SBP (HSBP/no e4; and HSBP/e4. Similar groups for APOE e4 and DBP were created. However, because no association between e4, DBP, and cognitive impairment was observed, these data are not further discussed. Cohort characteristics were compared across the cognitive function groups and SBP/APOE categories with age- and education-adjusted general linear models for continuous variables and logistic regression models for binary outcomes. A description of sociodemographic and health-related characteristics by cognitive function categories has been previously published. Briefly, subjects with good cognitive function were younger, more educated, had higher ABI and a low prevalence of stroke (\( P = 0.001 \)), while CHD and antihypertensive treatment were similar among the 3 groups of cognitive function.

Logistic regression was used to calculate the estimated relative risk (RR) and the 95% CI of intermediate and poor cognition in relation to good cognition associated with APOE e4 and high SBP. Analysis was adjusted for potential confounders. The cross-product interaction term for APOE and SBP and the 3-way interaction term among APOE, SBP, and hypertension treatment were also tested.

Based on the results of previous studies, which showed a reduction of the risk of low cognitive function and dementia associated with antihypertensive treatment, we considered a priori antihypertensive medication as a possible effect modifier of the association of APOE e4, high SBP and cognitive impairment. Therefore, we performed a stratified analysis. First, we divided the cohort into 2 groups (untreated and treated) and we included all those who were treated before the assessment of cognitive function in the treated group. However, because some of the subjects were treated for only a short period of time, we repeated the analysis, including those who were treated for <3 years prior to 1991 in the untreated group (n = 473). In addition, we checked whether the 2 reference categories (NSBP/no e4) in the treated and untreated strata had a similar risk for poor cognition. Therefore subjects receiving antihypertensive treatment in the reference category (NSBP/no e4) were tested for their risk of intermediate and poor cognitive function compared with the nontreated ones in the same category.

The stratified analyses were adjusted for age and education, smoking, alcohol and body mass index (model 1); and then for diabetes, prevalent stroke, CHD, and ABI (model 2). A value of \( P < 0.05 \) was accepted as statistically significant. All tests were 2-tailed. SAS version 6.12 and STATA version 6.0 were used to perform the statistical analysis.

**Results**

**General Analysis**

In the total sample, 5.9% had a midlife SBP of \( \geq 160 \) mm Hg. Participants in the NSBP/no e4 and NSBP/e4 categories were...
TABLE 1. Characteristics of the HAAS Cohort by APOE ε4 Status and Midlife High SBP Categories

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Normal SBP/No ε4</th>
<th>Normal SBP/ε4</th>
<th>High SBP/No ε4</th>
<th>High SBP/ε4</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=3605</td>
<td>n=2767</td>
<td>n=624</td>
<td>n=169</td>
<td>n=45</td>
<td></td>
</tr>
<tr>
<td>Age, y*</td>
<td>77.7 (4.6)</td>
<td>77.6 (4.5)</td>
<td>77.4 (4.5)</td>
<td>79.8 (5.5)</td>
<td>79.2 (4.5)</td>
</tr>
<tr>
<td>Primary education, %</td>
<td>8.5</td>
<td>8.3</td>
<td>7.8</td>
<td>14.2</td>
<td>8.9</td>
</tr>
<tr>
<td>No antihypertensive treatment, %</td>
<td>57.8</td>
<td>61.4</td>
<td>57.4</td>
<td>12.4</td>
<td>15.6</td>
</tr>
<tr>
<td>Years of antihypertensive treatment</td>
<td>10.8 (9.7)</td>
<td>8.1 (9.5)</td>
<td>8.5 (9.5)</td>
<td>11.04 (11.4)</td>
<td>10.0 (10.2)</td>
</tr>
<tr>
<td>Midlife SBP, mm Hg*</td>
<td>131.8 (17.0)</td>
<td>129.5 (14.4)</td>
<td>129.8 (14.5)</td>
<td>168.2 (12.6)</td>
<td>167.8 (11.7)</td>
</tr>
<tr>
<td>Midlife DBP, mm Hg*</td>
<td>82.5 (9.7)</td>
<td>81.6 (9.0)</td>
<td>82.0 (8.9)</td>
<td>97.3 (10.0)</td>
<td>96.3 (8.5)</td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>23.5 (3.1)</td>
<td>23.4 (3.1)</td>
<td>23.3 (3.2)</td>
<td>23.7 (3.1)</td>
<td>23.7 (3.7)</td>
</tr>
<tr>
<td>ABI=0.9%</td>
<td>13.0</td>
<td>11.9</td>
<td>12.0</td>
<td>30.2</td>
<td>28.9</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>6.2</td>
<td>5.8</td>
<td>5.1</td>
<td>13.6</td>
<td>15.6</td>
</tr>
<tr>
<td>Coronary disease, %</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Probable</td>
<td>13.1</td>
<td>12.6</td>
<td>12.3</td>
<td>21.9</td>
<td>20.0</td>
</tr>
<tr>
<td>Definite</td>
<td>15.9</td>
<td>15.0</td>
<td>17.6</td>
<td>23.7</td>
<td>17.8</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>36.1</td>
<td>35.1</td>
<td>35.3</td>
<td>47.0</td>
<td>64.5</td>
</tr>
<tr>
<td>Nonsmokers, %</td>
<td>36.3</td>
<td>36.6</td>
<td>34.2</td>
<td>37.0</td>
<td>45.4</td>
</tr>
<tr>
<td>Alcohol consumers, %</td>
<td>73.4</td>
<td>72.4</td>
<td>73.1</td>
<td>73.4</td>
<td>73.3</td>
</tr>
<tr>
<td>Alcohol consumption, g/d**</td>
<td>16.2 (22.6)</td>
<td>15.7 (22.4)</td>
<td>16.4 (22.2)</td>
<td>21.2 (25.6)</td>
<td>26.3 (24.5)</td>
</tr>
</tbody>
</table>

CASI categories, %

<table>
<thead>
<tr>
<th></th>
<th>Intermediate (n=586)</th>
<th>Poor (n=539)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal SBP/No ε4</td>
<td>1.0*</td>
<td>1.0*</td>
</tr>
<tr>
<td>Normal SBP/ε4</td>
<td>1.3 (0.9–1.6)</td>
<td>1.3 (0.9–1.7)</td>
</tr>
<tr>
<td>High SBP/No ε4</td>
<td>1.3 (0.8–2.0)</td>
<td>1.8 (1.2–2.9)</td>
</tr>
<tr>
<td>High SBP/ε4</td>
<td>1.2 (0.5–2.8)</td>
<td>2.9 (1.4–6.3)</td>
</tr>
</tbody>
</table>

*Mean (SD).
†P<0.001 by ANOVA, adjusted for age and education.
‡P<0.001 by Mantel-Haenszel χ², adjusted for age and education.
§P<0.05 by ANOVA adjusted for age and education.
Mean alcohol consumption for drinkers only.
Mean time of treatment was calculated only among those who reported being treated up to the fourth exam.

TABLE 2. Relative Risk (95% CI) for Poor Cognitive Function by APOE ε4 Status and midlife high SBP in the Total Sample

<table>
<thead>
<tr>
<th>Cognitive Function</th>
<th>Intermediate (n=586)</th>
<th>Poor (n=539)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal SBP/No ε4</td>
<td>1.0*</td>
<td>1.0*</td>
</tr>
<tr>
<td>Normal SBP/ε4</td>
<td>1.3 (0.9–1.6)</td>
<td>1.3 (0.9–1.7)</td>
</tr>
<tr>
<td>High SBP/No ε4</td>
<td>1.3 (0.8–2.0)</td>
<td>1.8 (1.2–2.9)</td>
</tr>
<tr>
<td>High SBP/ε4</td>
<td>1.2 (0.5–2.8)</td>
<td>2.9 (1.4–6.3)</td>
</tr>
</tbody>
</table>

Cognitive function measured by 100-point CASI test. Good (reference group), CASI≥82; intermediate, 82≤CASI<74; poor, CASI<74.
*Analysis adjusted for age, education, antihypertensive treatment, and duration of the treatment.

younger and less likely to receive antihypertensive medication than those in the other groups (Table 1). Individuals with high SBP alone or with the ε4 allele had a higher prevalence of CHD, stroke, and diabetes and an ABI of ≤0.9 compared with the other 2 groups.

In the total sample, the HSBP/no ε4 category had an increased risk of poor cognitive function compared with the reference group (Table 2). In the HSBP/ε4 category, the estimated RR point estimate for poor cognitive function was slightly higher than expected if the 2 risks were added independently (1.3+2.1=3.4 [baseline risk]=2.4). The analysis was adjusted for age, education, antihypertensive treatment, and duration of the treatment. The ε4 and HSBP interaction term was not significant (P=0.62); however, the 3-way ε4 allele, HSBP, and antihypertensive treatment interaction term reached borderline significance (P=0.09).

Untreated Group

In the NSBP/no ε4 group, those who were treated with antihypertensive medication did not have a different risk of intermediate and poor cognitive function compared with those untreated (age- and education-adjusted RR 1.2 [95% CI 0.9 to 1.4] and RR 0.9 [0.7 to 1.2, respectively]), suggesting that the baseline risk of low cognition for both groups (untreated and treated) was similar.

In the untreated group, the RR of intermediate cognitive function was significantly higher only for ε4 allele carriers (RR 1.4, P=0.025; Table 3). The RR of poor cognition was 13.0 (P=0.009) in the HSBP/ε4 category. Adjustment for diabetes, CHD, stroke, and ABI reduced the RR of poor cognition by 17.0% (RR 13.0 to 10.8) for those with both high SBP and ε4 allele. Hypertension and APOE ε4 alone were not significant. We then included in the untreated group those who were treated for <3 years before the cognitive function assessment. In this group, the RR for intermediate cognitive function was 1.4 (P=0.03) for NSBP/no ε4, 1.9 (P=0.09) for NSBP/ε4, and 1.3 (P=0.70) for HSBP/ε4. The RR for poor cognitive function was 1.4 (P=0.04) for...
Hypertension (HSBP) is a major risk factor for cardiovascular disease (CVD). However, the specific mechanisms linking hypertension to cognitive impairment are not fully understood. Recent studies have suggested that there is a selective mortality among individuals with hypertension and cognitive impairment, possibly due to a genetic predisposition. The aim of this study was to investigate the relationship between midlife hypertension and late-life cognitive impairment, adjusting for known cardiovascular disease risk factors.

Methods:
We conducted a population-based cohort study of 2,860 individuals aged 70-79 years at baseline, with follow-up at ages 75-80 years. Cognitive function was assessed using a 100-point CASI test. Hypertension was defined as systolic blood pressure (SBP) \( \geq 160 \) mm Hg or diastolic blood pressure (DBP) \( \geq 90 \) mm Hg, or use of antihypertensive medication. Adjustments were made for age, sex, education, smoking, alcohol consumption, and body mass index (BMI).

Results:
In the untreated group, the risk for intermediate and poor cognitive function was similar in all the BP and \( \varepsilon4 \) categories (Table 3). After removing from this group those who were treated only for the last 3 years before cognitive assessment, the results for both intermediate and poor cognitive function categories did not change (data not shown).

Discussion:
We found that among individuals never treated for hypertension, \( \varepsilon4 \) carriers with a midlife SBP of \( \geq 160 \) mm Hg had a 10 times greater risk of late-life poor cognitive function than those without the \( \varepsilon4 \) allele and normal SBP. Among those treated with antihypertensive medication, individuals with both \( \varepsilon4 \) and high SBP were not at significantly higher risk for poor cognition than those without the \( \varepsilon4 \) allele.

The present study has several strengths. Data were collected prospectively from 1965 to 1991 on a large, population-based sample. BP was measured in midlife, when the level is less influenced by preclinical disease. However, there are some methodological issues that need to be accounted for when interpreting the results. The sample size of the HSBP/\( \varepsilon4 \) group in the untreated stratum was small, resulting in a wide CI around the estimate. This might explain why the interaction terms were not statistically significant. Possibly, only a few cases explain the results (type I error). The low prevalence of HSBP/\( \varepsilon4 \) individuals may be due to the lower frequency of the \( \varepsilon4 \) allele in the Japanese population compared with other ethnic groups. More likely, it reflects a selective population that was not methodologically studied for those with lower cognitive function.

Several lines of evidence suggest that these findings are biologically plausible. An association of midlife high SBP and cognitive impairment has been shown, and multiple mechanisms linking the 2 traits have been proposed. High BP, including stroke, CHD, and peripheral artery disease, alters cerebral flow autoregulation.29,30 As consequence, transitory conditions of cerebral hypoxia/ischemia can occur, creating impaired cerebral perfusion and asymptomatic depression of oxygenation. Ischemia-related injuries can ultimately lead to clinical and subclinical brain damage, including lacunes and white matter abnormalities on MRI.31

In vivo data indicate that APOE defect mice have twice as much ischemic neuronal damage as wild-type controls after ischemic episodes.32 This neuroprotective function is highly allele specific: APOE \( \varepsilon3 \) seems to promote the repair process and APOE \( \varepsilon4 \) to retard it both in vitro and in vivo.34–37 It is possible that the effect of APOE on cognition is partially due to its modifying the damage created by hypertension. Under this hypothesis, the impact of the hypertension would be much greater among APOE \( \varepsilon4 \) carriers due to their limited capacity to repair neuronal damage. In vivo data indicate that APOE \( \varepsilon4 \) transgenic mice are more susceptible to the effects of the focal and global ischemia compared with the APOE \( \varepsilon3 \) transgenic mice.38,39 APOE \( \varepsilon4 \) is also associated with a lower concentration of plasma apoE protein40 and increased level of cholesterol and atherosclerosis,41 which can interact with hypertension and worsen atherosclerotic conditions. Under specific conditions, hypertensive-induced APOE-deficient

### Table 3. Relative Risk (95% CI) of Cognitive Impairment in HAAS Participants Associated With APOE \( \varepsilon4 \) Status and Midlife High SBP, Stratified by Antihypertensive Treatment

<table>
<thead>
<tr>
<th></th>
<th>Untreated group</th>
<th>Treated Group</th>
<th></th>
<th>Poor (n=330)</th>
<th>Poor (n=209)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermediate (n=328)</td>
<td>Poor (n=209)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal SBP/No ( \varepsilon4 )</td>
<td>1.0</td>
<td>1.0</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Normal SBP/( \varepsilon4 )</td>
<td>1.4 (1.0–2.0)</td>
<td>1.4 (1.0–2.0)</td>
<td>1.3 (0.9–1.9)</td>
<td>1.3 (0.9–1.9)</td>
<td>1.3 (0.9–1.9)</td>
</tr>
<tr>
<td>High SBP/No ( \varepsilon4 )</td>
<td>0.9 (0.2–5.0)</td>
<td>1.0 (0.2–5.3)</td>
<td>2.6 (0.7–10.0)</td>
<td>2.4 (0.6–10.4)</td>
<td></td>
</tr>
<tr>
<td>High SBP/( \varepsilon4 )</td>
<td>...</td>
<td>...</td>
<td>13.0 (1.9–83.8)</td>
<td>10.8 (1.4–83.5)</td>
<td></td>
</tr>
</tbody>
</table>

Cognitive function measured by 100-point CASI test. Good (reference category), CASI=74. Analysis adjusted for age, education, smoking, alcohol, and BMI.

*Analysis adjusted for age, education, smoking, alcohol, and BMI.

†Analysis adjusted for age, education, smoking, alcohol, BMI, diabetes, prevalent stroke and coronary artery disease, and ABI.
mice have shown an increased of atherosclerotic lesions compared with normotensive and wild-type controls. A previous study of dementia in this cohort showed that in this population of Japanese-American men, the risk for the vascular dementia was higher than in those of European ancestry, which suggests that in this population there may be a relatively greater vascular contribution to cognitive impairment than in other groups. The role of an atherosclerosis in the APOE e4–high BP interaction is suggested by the reduction in the RR for poor cognitive function after adjusting for stroke, ABI, and CHD. Therefore, we could interpret model 2 of the analysis as an overadjusted model. SBP and APOE e4 may also interact through the amyloid processing pathways. In an autopsy series based on this cohort, high SBP was associated with the presence of neurofibrillary tangles and neuritic plaques. e4 is associated with a greater β-amyloid deposition and neuritic plaque formation in demented and nondemented individuals. In vitro and in vivo data suggest that β-amyloid has a vasoconstrictive effect on the cerebral microcirculation. This could increase BP levels and exacerbate the insult to the brain created by high SBP. However, given that the BP was measured in midlife, this would imply a very long period of amyloid toxicity.

To date, a limited number of observational studies have examined the interaction between vascular factors, the APOE gene, and cognitive impairment. Two studies have focused specifically on the APOE and BP relationship to cognitive decline. The Zutphen Study tested the risk of cognitive decline in community-dwelling elderly men and found a lower risk of cognitive decline in those with both APOE e4 and hypertension (SBP/DBP ≥140/95 mm Hg or use of antihypertensive medication) compared with those without hypertension. However, BP was measured in late age, concurrent with the first cognitive evaluation. Other studies suggest that concurrently measured BP does not accurately reflect long-term exposure because BP changes with treatment, comorbidity, and possibly incipient dementia. Only one study has examined the long-term effect of midlife BP and the APOE gene on cognitive function. The study showed that the e4 allele and midlife hypertension (SBP/DBP ≥140/90 mm Hg or use of antihypertensive medication) were each associated with a 10-year decline in a neuropsychological test (Digit Symbol Substitution) score, but their combined effect was not greater than expected. However, because the sample was small, the ability to see interactions was low. In addition, in the latter 2 studies, antihypertensive treatment was included as a part of the definition of hypertension.

In the current study, antihypertensive treatment was used as an effect modifier. We found no negative effects of the combination of APOE e4 and HSBP on cognitive function in the treated group. Because the baseline BP and the e4-associated RR were similar in both the treated and untreated groups, this suggests that the potential benefits of the antihypertensive medication may be mediated by a BP-lowering effect. Other studies suggest that antihypertensive treatment may be beneficial in reducing the risk for dementia. A recent study reported a lower incidence of dementia among individuals treated with antihypertensive medication than in untreated subjects; the effect was more evident for APOE e4 carriers. In addition, a randomized trial suggested that antihypertensive treatment may provide some benefits in decreasing the risk for dementia.

However, we cannot rule out several alternative explanations for a difference in effect between the treated and untreated groups. For instance, there may have been selective mortality. Individuals treated with antihypertensive drugs had higher levels of stroke and CHD compared with untreated individuals, and it cannot be excluded that a subset of treated hypertensives at risk for cognitive impairment died prematurely. Although we adjusted for a number of sociodemographic and health-related variables, it is also possible that treated and untreated hypertensive individuals differed by other risk factors not included in the analysis. Ongoing randomized controlled trials on antihypertensive medication and incidence of dementia should be able to examine more fully an interaction with APOE.

In conclusion, this study evaluated the possible synergistic effect of APOE genotype and high midlife SBP on the risk of poor cognitive function among elderly men. The results suggest that the use of antihypertensive medication could potentially reduce this negative outcome, especially for individuals genetically predisposed to higher risk. As life expectancy has increased in the last century, more individuals will reach a very old age and will be at risk both for high SBP and cognitive impairment. If confirmed, the present results may have important preventive public health implications.

Acknowledgments

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Editorial Comment

High Blood Pressure and Apolipoprotein E4: A True Synergistic Effect on Late-Life Cognitive Function

Apolipoprotein E4 (apoE4) allele was shown to be strongly associated with the familial and sporadic forms of Alzheimer’s disease. The apoE4 allele can affect the rate of progression of the disease, the extent of the neuronal cell loss, the accumulation of amyloid plaques, and total beta amyloid production in the brain of AD subjects.1 ApoE4 carrier subjects were also shown to exhibit poor reinnervation and compensatory plasticity in vulnerable brain areas.1,2 Actually, the role of apoE in the maintenance of synaptic integrity and plasticity is so central to brain physiology that the ability of a subject to recover from traumatic brain injuries is highly dependent on apoE4 allele copy number.1 The risk for boxers to develop dementia later in life is conditioned by the presence of the apoE4 allele. Actually, head injury had been considered one of the most reliable environmental risk factor for sporadic AD until it was formally demonstrated that it is the case only for apoE4 carrier subjects.3 ApoE4 is also considered a risk factor for vascular diseases, because it acts as a key modulator of cholesterol transport and homeostasis in periphery. Recently, 2 independent pivotal epidemiological studies examining the effect of the cholesterol-lowering drugs statins on the incidence of AD reported clear protective effects of these agents in a cohort of subjects with varying risk of vascular diseases.4,5 Altogether, these studies suggest a subtle interplay between cardiovascular genetic risk factors and protective agents that modulate the onset and progression of Alzheimer’s disease.

Similarly, the advent of antihypertensive treatment of high systolic blood pressure has certainly brought a significant advance to pharmacological disease prevention. Not only has long-term therapy with these agents revolutionized the prevention and the control of vascular diseases such as stroke, but recent clinical studies clearly indicate a potent reduction of the risk of developing cognitive impairment later in life and, in its extreme form, Alzheimer’s disease.

In the preceding article, Peila and colleagues report the results of a large observational study demonstrating a synergistic association between high systolic blood pressure and the presence of the apoE4 allele on late-life cognitive function in a large cohort of Japanese-American men living in Hawaii. These men have been followed prospectively since 1965, when they were middle aged. If this very important association turns out to be central to the etiopathology of memory disorders such as Alzheimer’s disease or vascular dementia, it could represent an important breakthrough in the search for a medication that could prevent or slow down cognitive impairment due to aging or dementia.

The interaction between high blood pressure in midlife and the apoE4 allele is certainly consistent with the notion of a clear-cut contribution of cardiovascular changes in the pathophysiology of both sporadic Alzheimer’s disease and vascular dementia. However, one must also be careful not to generalize the observation, as it has been shown recently that vascular cognitive impairment without dementia is the most common form of this disease among those aged 65 to 84 years.6

However, for the statistical association to be considered central in the onset of late-life cognitive deficit, we must have evidence of a plausible explanation for the preventive effect and/or a plausible alternative explanation for the statistical association to be ruled out.

One of the most interesting function of apoE in the central nervous system is its central role in the transport and recycling of cholesterol and fatty acids from dead or dying neurons to neurons undergoing terminal sprouting and synaptic remodeling.7 ApoE facilitates the mobilization and redistribution of key lipid molecules in response to damage and neurodegenerative changes in the brain. However, humans, in contrast to all other mammals, are expressing 3 distinct apoE isoforms: apoE2, apoE3, and apoE4. While humans exhibiting the apoE3 and apoE2 alleles appear to exhibit optimal regenerative capacity throughout the brain, subjects carrying 1 or 2 apoE4 alleles demonstrated drastic reduction in regenerative capacity.1,2 One of the obvious consequences of this situation is a marked deterioration of the reinnervation process, with impact on age of onset, age of progression, and recovery period following brain damage or chronic neurodegenerative disease.

Thus, one has to view the injured or diseased brain as a delicate balance between cell loss and compensatory remodeling of surviving neurons. In subjects carrying an apoE4 allele, the ability to remodel its neuronal circuits in response to damage and cell death is drastically reduced and the loss of function is somewhat exacerbated by the virtual absence of compensatory mechanisms. In this context, the report of Peila et al could be viewed as another excellent example of poor compensation in apoE4 carrier, in which the injuries this time are caused by elevated high blood pressure over the course of several years (even decades). This could easily translate into 2 distinct groups of subjects: one group, without the E4 allele (so-called non-E4 subjects), showing normal compensatory remodeling and relatively intact cognitive function at old age or a very late cognitive impairment, and the second group, the apoE4 carriers, exhibiting little or no plasticity in response to the HBP-related damage and a much earlier age of onset for the late-life cognitive impairment. This interpretation of the results is easy to test in the Peila cohort, as one of the central predictions would be the presence of a much higher incidence of the cognitive deficits in non-apoE4 subjects after the age of...
80 years and a much earlier age of onset of the cognitive deficits in apoE4/4 subjects.

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Joint Effect of the APOE Gene and Midlife Systolic Blood Pressure on Late-Life Cognitive Impairment: The Honolulu-Asia Aging Study

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