Impact of Hypertension and Apolipoprotein E4 on Poststroke Cognition in Subjects ≥75 Years of Age

E. Rowan, PhD; C.M. Morris, PhD; S. Stephens, BSc; C. Ballard, MRC Psych, MD; H. Dickinson, PhD; H. Rao, PhD; B.K. Saxby, BSc; A.T. McLaren, MRCP; R.N. Kalaria, FRC; R.A. Kenny, FRCP

Background and Purpose—The apolipoprotein E4 allele (APOE4) associates with increased dementia risk, and hypertension may associate with mild cognitive deficits. We examined whether nondemented stroke patients with (1) a prestroke history of hypertension and (2) APOE4 were more cognitively impaired at 3 months after stroke.

Methods—A total of 257 participants were genotyped and outcomes from neuropsychological evaluations analyzed using regression.

Results—Total Cambridge Assessment for Mental Disorders in the Elderly (CAMCOG) and speed of working memory significantly associated with hypertension. No outcomes significantly associated with APOE4.

Conclusions—Subjects with prestroke hypertension had more impaired global cognition and slower access to information held in working memory. (Stroke. 2005;36:1864-1868.)

Key Words: cognition ■ hypertension ■ stroke

A n association exists between the apolipoprotein E4 allele (APOE4 gene; apoE protein) and increased risk of cognitive decline and dementia, whereas APOE2 may protect against dementia. Cardiovascular factors increase risk of cognitive decline; however, relationships are unclear between these, vascular dementia (VaD), and genetic factors. A study on Taiwan Chinese subjects did not suggest any association between APOE4 and VaD; however, another indicated that there is an increased risk for VaD in stroke subjects with APOE4.

We reported that in mildly impaired elderly stroke patients, APOE4 was associated with greater cognitive decline between 3 and 15 months after stroke. Recent studies have explored relationships between hypertension and APOE. Significant differences were demonstrated between hypertensives with and without APOE4; APOE4 carriers had higher systolic blood pressure and increased intimal-medial carotid artery thickness, suggesting that APOE4 may trigger susceptibility to hypertension and carotid artery atherosclerosis. Existence of hypertension and APOE4 together may increase susceptibility to white matter lesions. Researchers have questioned whether attentional deficits in hypertensives may be associated with these lesions. Further work demonstrated that working and episodic memory and executive function are impaired in healthy elderly hypertensives compared with normotensives.

Atrial fibrillation (AF) is an independent risk factor for poor cognition in elderly men and pre-stroke dementia. The cognitive effects of diabetes or hypertension have also been investigated; although steeper declines were associated with diabetes than hypertension, decline was greatest in people with both.

Hypertension is a primary risk factor for vascular disease; therefore, in this context, our aim was to investigate whether stroke patients with: (1) a prestroke history of hypertension, (2) APOE4, and (3) hypertension and APOE4 in combination were more cognitively impaired at 3 months after stroke than others. We hypothesized that patients with APOE4 and hypertension would be most impaired. Although our primary outcome was global cognition, we also examined secondary outcomes relevant to vascular cognitive impairment (memory, attention, and executive function) while controlling for age, gender, AF, APOE2, and type 2 diabetes mellitus.

Methods

Local research ethics committees gave approval for the study. A total of 706 stroke patients ≥75 years of age were prescreened consecutively from hospital-based stroke registers in Tyneside and Wearside. After general practitioner approval and explanation and discussion of the study, 355 patients gave written informed consent with assent from next of kin. We excluded those with significant physical illness and disabilities that would preclude neuropsychological testing and dementia, according to Diagnostic and Statistical...
Manual of Mental Disorders, Third Edition (DSM III-R) criteria. Thirty-seven of 77 excluded cases had dementia. Additionally, general practitioners did not give us approval to approach 62 patients, 14 people could not be contacted, and 198 declined participation.

Hospital notes of participants were reviewed for diagnoses of hypertension (a documented history of blood pressure >140/90 mm Hg or treatment of raised blood pressure), AF, and diabetes, documented or treated before stroke. Cases in which hypertension diagnosis was equivocal because of only 1 documented abnormal blood pressure reading or potentially antihypertensive treatment without clear primary indication were not included in the analysis. Participants were invited to donate optional blood samples for APOE genotyping.

The Cambridge Assessment for Mental Disorders in the Elderly (CAMCOG) section B23 and the Cognitive Drug Research (CDR) computerized battery24 were performed at 3 months after stroke. CAMCOG tests global cognition (subscores include memory, orientation, language comprehension, language expression, attention, praxis, calculation, abstract thinking, perception, and executive function). Total CAMCOG score (CAMTOT; maximum 105) was our primary outcome measure because it is effective when applied as a screening instrument for dementia after stroke.25 Memory total (MEMTOT) and executive function subscores were secondary outcome measures. Distributions of outcome measures were examined graphically. Positively skewed measures (PoA and SWM) were log transformed, and negatively skewed ones (CAMTOT and QWM) were subtracted from the maximum possible score then log transformed, giving approximately normal distributions. MEMTOT and executive function were approximately normal.

Outcome measures were related to putative risk factors using forward stepwise regression. Regression results were significant if the P value was <0.05. We intended to consider the interaction between hypertension and APOE4 if both proved to be significantly associated with outcome measure(s). Sensitivity analyses were performed to check the final multivariate models, removing the single most influential observation on the basis of (1) the change in the regression coefficient consequent to the removal of each observation and (2) leverage. The influence of missing data was assessed by assigning participants with missing data the mean values from the appropriate gender and hypertension category. Where the final model included a continuous covariate, residuals were plotted against fitted values and the relevant covariate, and plots were visually assessed for any systematic pattern.

Statistical evaluation was performed using STATA (version 8) and SPSS (version 11).

Results

A total of 257 of 268 genotyped participants had records indicating a definite presence or absence of prestroke hypertension (Table 1).

Clinical and neuroimaging (computed tomography scan) evidence-based diagnoses of stroke were available on 254 of 257

TABLE 1. Characteristics of Participants by Presence/Absence of Hypertension and APOE4

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Whole Group</th>
<th>Hypertension</th>
<th>No Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E4 Present</td>
<td>E4 Absent</td>
<td>E4 Present</td>
</tr>
<tr>
<td>No. of males (%)</td>
<td>135 (53)</td>
<td>14 (35)</td>
<td>54 (50)</td>
</tr>
<tr>
<td>No. (%) of participants with AF*</td>
<td>37 (14)</td>
<td>5 (12)</td>
<td>18 (17)*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20 (8)</td>
<td>3 (7)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>APOE2</td>
<td>43 (17)</td>
<td>7 (17)</td>
<td>19 (18)</td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
<td>80.4 (3.9)</td>
<td>80.2 (2.9)</td>
<td>80.6 (3.8)</td>
</tr>
</tbody>
</table>

*AF was not assessed for 3 participants: 2 in the hypertension/E4 absent group and 1 in the no hypertension/E4 absent group.

Differences between hypertension/APOE4 categories were assessed using χ2 tests of heterogeneity for categorical variables (presence/absence of AF, diabetes mellitus, APOE2) and 1-way ANOVA for age. Association between APOE4 and hypertension was assessed using a χ2 test. Correlations were examined between primary and secondary outcome measures. Distributions of outcome measures were examined graphically. Positively skewed measures (PoA and SWM) were log transformed, and negatively skewed ones (CAMTOT and QWM) were subtracted from the maximum possible score then log transformed, giving approximately normal distributions. MEMTOT and executive function were approximately normal.

Outcome measures were related to putative risk factors using forward stepwise regression. Regression results were significant if the P value was <0.05. We intended to consider the interaction between hypertension and APOE4 if both proved to be significantly associated with outcome measure(s). Sensitivity analyses were performed to check the final multivariate models, removing the single most influential observation on the basis of (1) the change in the regression coefficient consequent to the removal of each observation and (2) leverage. The influence of missing data was assessed by assigning participants with missing data the mean values from the appropriate gender and hypertension category. Where the final model included a continuous covariate, residuals were plotted against fitted values and the relevant covariate, and plots were visually assessed for any systematic pattern.

Statistical evaluation was performed using STATA (version 8) and SPSS (version 11).

Results

A total of 257 of 268 genotyped participants had records indicating a definite presence or absence of prestroke hypertension (Table 1).

Clinical and neuroimaging (computed tomography scan) evidence-based diagnoses of stroke were available on 254 of 257

TABLE 2. Cognitive Performance at 3 Months After Stroke: Mean (SD) of Test Scores

<table>
<thead>
<tr>
<th>Test*</th>
<th>No. Assessed</th>
<th>Hypertension</th>
<th>No Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whole Group</td>
<td>E4 Present</td>
<td>E4 Absent</td>
</tr>
<tr>
<td>CAMTOT</td>
<td>257</td>
<td>86 (9)</td>
<td>83 (9)</td>
</tr>
<tr>
<td>Executive function</td>
<td>257</td>
<td>14 (5)</td>
<td>13 (4)</td>
</tr>
<tr>
<td>MEMTOT</td>
<td>257</td>
<td>21 (3)</td>
<td>21 (3)</td>
</tr>
<tr>
<td>PoA (s)</td>
<td>252</td>
<td>1.8 (0.6)</td>
<td>1.9 (0.6)</td>
</tr>
<tr>
<td>QWM</td>
<td>250</td>
<td>1.4 (0.4)</td>
<td>1.3 (0.4)</td>
</tr>
<tr>
<td>SWM (s)</td>
<td>250</td>
<td>3.5 (2.2)</td>
<td>3.8 (1.5)</td>
</tr>
</tbody>
</table>

*Higher scores on CAMTOT, executive function, MEMTOT, and QWM indicate better performance; lower scores on PoA and SWM indicate better performance.

†Not recorded for 2 participants; ‡not recorded for 1 participant.
participants: 239 had ischemic infarctions, 3 hemorrhagic infarctions, 6 intracerebral hemorrhages, and 6 transient ischemic attacks.

A total of 148 (58%) participants had prestroke hypertension and 66 (26%) APOE4. APOE4 subjects were not at significantly higher risk of hypertension (odds ratio, 1.2; 95% CI, 0.7 to 2.1). Mean age was 80.4 years (range 75 to 92) and did not differ significantly between the 4 hypertension/APOE4 categories. No significant differences existed between the 4 categories in prevalence of AF and diabetes, as well as no differences between participants with and without hypertension in prevalence of E2 alleles. Gender varied significantly: 66% of women but only 50% of men had hypertension ($P=0.014$).

Table 2 shows mean outcome scores. Secondary outcomes significantly correlated with CAMTOT: ($r=0.75$, 0.72, −0.55, 0.31, and −0.41 for executive function, MEMTOT, PoA, QWM, and SWM, respectively).

APOE4 was not significantly associated with outcomes (Table 3), (CAMTOT was 85 and 86 for subjects with and without E4 alleles, respectively); therefore, it was not appropriate to investigate interactions between APOE4 and hypertension. APOE2, AF, and diabetes did not significantly associate with outcomes.

CAMTOT significantly associated with hypertension (mean score was 85 for hypertensives and 87 for normoten-
sives), age, and gender (mean score was 84 for females and 87 for males) in univariate analyses. Women were older than men (mean age 81 and 80 years, respectively), but after allowing for age, gender was no longer significant. The final multivariate model indicated that CAMTOT scores of hypertensives were lower than normotensives and decreased with age. Sensitivity analyses excluding influential participants had little effect on the final model; plots of residuals showed no systematic pattern, indicating that the model was a good fit.

SWM significantly associated with hypertension (mean SWM was 3.8 s in hypertensives and 3.2 s in normotensives), age, and gender (mean SWM was 3.1 s in males and 4.1 s in females) in univariate analysis. However, after allowing for gender, age was no longer significant. Sensitivity analyses (1) excluding influential participants and (2) assigning participants with missing data the mean values from the appropriate gender and hypertension category had little effect on the final model.

PoA significantly associated with hypertension, age, and gender in univariate analyses; however, after allowing for gender, age was no longer significant. People without hypertension had better PoA, and males fared better than females (mean PoA was 2.0 s for females and 1.7 s for males). If the participant with the highest PoA score (a hypertensive woman; 86.5 years of age; PoA 5.1) was excluded, the association between PoA and hypertension was no longer significant. Sensitivity analyses assigning participants with missing data mean values from the appropriate gender and hypertension category had little effect.

Executive function significantly associated with age; for every advancing year, there was a drop of 0.16 points (95% CI: −0.31 to 0.01). Plots of residuals showed no systematic pattern. However, if the oldest participant (92.8 years of age; executive function score 6) was excluded, the association was no longer significant.

MEMTOT significantly associated with age and gender in univariate analyses; however, after allowing for gender, age was no longer significant (MEMTOT was 21 for females and 22 for males). Sensitivity analyses excluding influential participants had little effect. QWM was not significantly associated with any variable.

**Discussion**

APOE4 did not associate with cognition at 3 months after stroke; therefore, in the present study, we were unable to examine interactions between APOE4 and hypertension. However, our results confirm that prestroke hypertension is associated with detrimental poststroke cognitive outcome. Hypertension had adverse effects on CAMTOT and SWM after allowing for independent adverse effects of age and gender, respectively. This is similar to a study comparing untreated elderly hypertensives and normotensives, which revealed that hypertension impairs speed of cognition, executive function, and working memory. Other work demonstrated that subjects with mild late-life cognitive impairment were more likely to have received midlife diagnoses of hypertension than controls.

The CAMCOG appeared to be our most powerful instrument for detecting associations of risk factors with cognition at 3 months. Early impairments experienced by nondemented stroke subjects are often subtle and evident globally rather than at domain levels. Undoubtedly, there was diversity within our group in terms of type and size of strokes that may explain this. CAMTOT encompasses a broad range of cognitive domains; therefore, this may be the reason that it was effective.

Dementia risk in cerebrovascular disease has been associated with white matter changes, and hypertension may be the cause. Two mechanisms have been suggested: hypertension could impair cerebral blood flow or initiate structural changes in arterioles within white matter. MRI studies on a subgroup of our stroke cohort demonstrated that attention and processing speed deficits are significantly associated with white matter hyperintensity volumes in the frontal lobe regions. This supports the theory that cognitive decline/dementia may be minimized by controlling blood pressure earlier in life.

APOE4 did not have significant negative associations with cognition, suggesting that it had little influence on short-term poststroke cognitive function. APOE is involved with lipoprotein metabolism and associated with higher low-density lipoprotein and total cholesterol levels: risk factors for coronary artery disease, cerebrovascular disease, and stroke. Although there is controversy over the mechanisms by which APOE4 contributes to dementia and cognitive impairment, it may increase amyloid-β accumulation and brain cholesterol and influence senile plaque formation. APOE4 may also affect neuronal growth, repair, and oxidation. APOE4 may be a risk factor for dementia only in hypertensive individuals who have not received blood pressure medication. Because 126 of 148 hypertensives in our group were taking medications for hypertension at time of stroke, this could explain our lack of association between APOE4 and cognition. We excluded subjects with dementia, aphasia, serious illnesses, and disabilities at 3 months after stroke, and this may have further reduced our chances of detecting an association. We may not have found a relationship because our cohort was heterogeneous in terms of stroke types, sizes, and locations. Studies are needed to clarify whether APOE influences these features and precisely how they influence cognition. Additionally, our sample size may not provide sufficient statistical power to detect subtle effects of APOE4 at the single, (short-term) 3-month time point. Nevertheless, it is widely accepted that APOE4 is the main genetic risk factor for Alzheimer disease, and previous findings examining rate of CAMCOG change between 3 and 15 months indicate that the influence of APOE4 on poststroke cognition manifests itself in the medium to long term, and therefore should be taken seriously as an indicator for dementia risk.

We found no evidence that APOE4 was a risk factor for the development of prestroke hypertension. There was little difference between groups in the prevalence of ≥1 APOE2 allele, and this was not associated with any outcomes. AF and diabetes were uncommon, and it is not surprising that these variables had no significant associations. Increasing age associated with lower CAMTOT, and this supports findings that dementia prevalence is higher in older stroke survivors. Gender associated with MEMTOT and SWM, females being disadvantaged. Although gender associated with CAMTOT...
in univariate analysis, once age was accounted for, the association was no longer statistically significant.

Summary

Subjects with prestroke hypertension had more impaired global cognition and slower access to information in working memory at 3 months after stroke. We found no significant association between cognitive outcomes and APOE4, and therefore no significant interaction between the effects of APOE4 and hypertension on cognition. Longitudinal studies are required to investigate interactions between APOE4 and hypertension.

Acknowledgments

This work was supported by the Medical Research Council. We would like to thank Cognitive Drug Research Ltd for their technical assistance.

References

Impact of Hypertension and Apolipoprotein E4 on Poststroke Cognition in Subjects >75 Years of Age


Stroke. 2005;36:1864-1868; originally published online July 28, 2005;
doi: 10.1161/01.STR.0000177524.17424.2a
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/36/9/1864

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/