Apolipoprotein E genotypes and outcome from out of hospital cardiac arrest

W T Longstreth Jr, G D Schellenberg, C E Fahrenbruch, L A Cobb, M K Copass, D S Siscovick

Short Report

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Whether genetic factors influence outcome after cardiac arrest is uncertain. Three alleles of the apolipoprotein E gene (APOE ε2, ε3, and ε4) encode three isoforms of the protein (E2, E3, and E4), which exert differential effects on response of nervous tissue to injury.1 In a study of transgenic mice, APOE ε4 was associated with greater hippocampal damage after global cerebral ischaemia,2 contrary to results in 58 humans who died after surviving a mean of 5.7 days after cardiac arrest.3 In another study of 80 patients admitted after cardiac arrest, having the APOE ε3/ε3 genotype was associated with a better survival and neurological outcome.4 If genetic factors affect outcome after cardiac arrest, they could provide clues about pathophysiology and could suggest novel treatments. We explored associations of genotype with outcome from out of hospital cardiac arrest.

METHODS

As part of another study,5 paramedics in Seattle have collected blood specimens from patients with out of hospital cardiac arrest since 1988. Regardless of the outcome of resuscitation, personnel collected all of the information without knowledge of any clinical information, and was successful in 90.5% of patients: 80.8% for those who died in the field; 93.0% for those who died in hospital; 92.0% for those who survived to hospital discharge; and 87.7% for control subjects. We subsequently reclassified patients based on the most current and accurate information collected by personnel with the prehospital emergency medical system in Seattle (Medic One), as part of continuing efforts to improve the quality of care of these patients. We included those who died in the emergency department with those who died in the field. With this redistribution, APOE genotype was available on: 134 who died in the field, 131 who died in hospital, 198 patients who survived to be discharged from hospital, and 64 control subjects.

We also used this database to obtain information on patients’ age, sex, race (white v other), and initial rhythm (ventricular fibrillation v other). For patients discharged from the hospital, personnel used medical records and telephone follow up to decide survival status at 3 months and recovery of independence at any time by 3 months after the cardiac arrest. Personnel collected all of the information without knowledge of the results of the genotyping.

Outcomes used in this study included: death in the field, death in hospital, survival to discharge from hospital, survival at 3 months, and independence by 3 months. To evaluate associations between these outcomes and genotype, we used logistic regression, with the outcome as the dependent variable and the genotype as the independent variable. In addition to unadjusted models, we also evaluated models adjusted for age, sex, race and initial rhythm. An association was considered significant if the p value for the genotype coefficient in the logistic regression model was <0.05. Race was unknown in three patients. Survival status at 3 months was unknown for 19 patients. In these patients, the independence status at the last contact was used for the status by 3 months. No other variables had missing values, and the maximum number of missing values for any model was 20 patients, occurring in models where the dependent variable was survival at 3 months. Analyses were performed using SPSS statistical software (version 10.0 for Macintosh; SPSS Inc., Chicago, IL, USA). The Human Subjects Review Committee at the University of Washington approved the study.

RESULTS

Characteristics of the study groups are shown in table 1, and the results of the APOE genotyping in the four study groups are shown in table 2. In the unadjusted and adjusted models, having one or two alleles of APOE ε4 was not significantly related to the outcomes examined: having a cardiac arrest v
Table 1 Characteristic of study groups

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>Death in field (n = 134)</th>
<th>Death in hospital (n = 131)</th>
<th>Survival to discharge (n = 198)</th>
<th>Control subjects (n = 64)</th>
<th>Total (n = 527)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean (SD)</td>
<td>66.6 (16.7)</td>
<td>65.5 (15.6)</td>
<td>63.5 (15.4)</td>
<td>58.0 (10.2)</td>
<td>64.1 (15.4)</td>
</tr>
<tr>
<td>Men (%)</td>
<td>92 (69)</td>
<td>97 (74)</td>
<td>155 (78)</td>
<td>50 (78)</td>
<td>394 (75)</td>
</tr>
<tr>
<td>White (%)</td>
<td>111 (84)</td>
<td>106 (82)</td>
<td>164 (83)</td>
<td>61 (95)</td>
<td>442 (84)</td>
</tr>
<tr>
<td>VF (%)</td>
<td>46 (34)</td>
<td>71 (54%)</td>
<td>177 (89)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Values missing for race in three subjects. Otherwise no missing values.
VF, initial rhythm being ventricular fibrillation in those subjects who experienced a cardiac arrest.

Table 2 Apolipoprotein E genotypes and outcome from out of hospital cardiac arrest

<table>
<thead>
<tr>
<th>APOE genotype</th>
<th>Death in field</th>
<th>Death in hospital</th>
<th>Survival to discharge</th>
<th>Control subjects</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>e3/e3</td>
<td>15 (11.2)</td>
<td>11 (8.4)</td>
<td>1 (0.8)</td>
<td>7 (0.9)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>e3/e4</td>
<td>5 (03.7)</td>
<td>1 (00.8)</td>
<td>7 (07.6)</td>
<td>7 (10.9)</td>
<td>48 (09.1)</td>
</tr>
<tr>
<td>e4/e4</td>
<td>87 (64.9)</td>
<td>84 (64.1)</td>
<td>138 (69.7)</td>
<td>41 (64.1)</td>
<td>350 (66.4)</td>
</tr>
<tr>
<td>e4/e3</td>
<td>25 (18.7)</td>
<td>31 (23.7)</td>
<td>43 (21.7)</td>
<td>16 (25.0)</td>
<td>115 (21.8)</td>
</tr>
<tr>
<td>e4/e4</td>
<td>2 (01.5)</td>
<td>4 (03.1)</td>
<td>1 (00.5)</td>
<td>-</td>
<td>7 (01.3)</td>
</tr>
<tr>
<td>Total</td>
<td>134</td>
<td>131</td>
<td>198</td>
<td>64</td>
<td>527</td>
</tr>
</tbody>
</table>

DISCUSSION

How apolipoprotein E genotypes affect outcomes from brain injury is uncertain but seemingly dependent upon the mechanism of injury.1 Detrimental effects of having one or two alleles of APOE e4 have been demonstrated for traumatic brain injury2 and haemorrhagic stroke3–12 but not for ischaemic stroke.11–13 As expected, based on previous studies of hippocampal damage and neurological outcome in patients with cardiac arrest,14–16 we found that having one or two alleles of APOE e4 was not associated with outcome. In this regard, global and focal brain ischaemia are similar. Unlike a previous study,17 we found that APOE e3/e3 genotype was also not significantly associated with any of the outcomes examined. Why the results from the two studies differ is unclear. We examined a larger number and a less select group of patients than in the previous study. Perhaps the results would have differed if we had succeeded in genotyping all the specimens, but the genotyping was performed without any clinical information, making such a bias unlikely. Perhaps more detailed determination of neurological outcome is needed to identify such associations. Even if an association with APOE genotype is lacking, it is likely that other genetic factors that affect the response to global brain ischaemia accompanying cardiac arrest exist. Understanding such genetic factors may hold the key to understanding brain protection and resuscitation.

ACKNOWLEDGEMENTS

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Competing interest: none declared

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REFERENCES


HISTORICAL NOTE

Sir Thomas Clifford Allbutt

Thomas Clifford Allbutt, (b. 20 July 1836; d. 22 February 1925) is of interest to neurologists as the main instigator, along with Gowers, of the routine clinical use of the ophthalmoscope.

He was born in Dewsbury, Yorkshire, the only son of Reverend Thomas Allbutt and his wife Marianne, daughter of Robert Wooler. He was educated at St Peter’s School, York, and Caius College, Cambridge, where he graduated in 1859 with first class honours in the natural sciences tripos. He trained at St George’s Hospital, graduating MB in 1860. After training, Allbutt was appointed in 1864 to the staff of the General Infirmary at Leeds, and lectured on the practice of physic and anatomy at the Yorkshire College. Leeds remained his home for 28 years.

Allbutt was one of the first to employ the ophthalmoscope in Britain; importantly, he extended its use beyond the diagnosis of ocular diseases. Like Gowers, he tried to use funduscopy to show the numerous and important signs (optic atrophy, papilloedema and such) of intracranial disease that the ophthalmoscope could provide. He observed:

‘‘The number of physicians who are working with the ophthalmoscope in England may, I believe, be counted upon the fingers of one hand.‘‘

In 1866, Allbutt invented the conveniently portable 6 inch clinical thermometer, able to record temperature in 5 minutes. It replaced a 12 inch standard model that required 20 minutes. Other studies also led to the improved treatment of arterial diseases when he proved that narrowing of the coronary arteries causes angina.

By 1889, Allbutt had acquired an unrivalled reputation in northern England, but curiously he retired from consulting practice to become a commissioner in lunacy. After 3 years in London, however, he was tempted to the Regius chair of Physic at Cambridge. Election as physician to Addenbrooke’s Hospital followed in 1900; thereafter his work and reputation persisted from Aristotle through the Arab and medieval physicians to the untaught as performance on a musical instrument. In spite, therefore, of the encyclopaedic tradition which has persisted from Aristotle through the Arab and medieval physicians to the untaught as performance on a musical instrument. In spite, therefore, of the encyclopaedic tradition which has persisted from Aristotle through the Arab and medieval physicians to the untaught as performance on a musical instrument. 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