SHORT REPORT

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

Genetic factors may influence outcome from cardiac arrest. In Seattle, WA, paramedics collected blood specimens from patients who had suffered cardiac arrest outside of a medical institution (out of hospital cardiac arrest). We examined associations between apolipoprotein E (APOE) genotype and outcome in 134 who died “in the field”, 131 who died in the hospital, 198 patients who were discharged from hospital alive, and 64 control subjects. APOE genotype was not significantly related to outcome, including being alive at and being independent by 3 months after the arrest. Specifically, having one or two alleles of APOE e4 or having APOE e3/e3 was not related to outcome, even after controlling for age, sex, race, and initial rhythm. We failed to confirm previous studies and found no significant associations between APOE genotype and outcome from out of hospital cardiac arrest.

Whether genetic factors influence outcome after cardiac arrest is uncertain. Three alleles of the apolipoprotein E gene (APOE e2, e3, and e4) 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 e4 was associated with higher hippocampal damage after global cerebral ischaemia,2 contrary to results in 58 humans who died after surviving a cardio-pulmonary arrest.3 In another study of 80 patients who suffered cardiac arrest outside of a medical institution (out of hospital cardiac arrest), we examined associations between apolipoprotein E (APOE) genotype and outcome in 134 who died “in the field”, 131 who died in the hospital, 198 patients who were discharged from hospital alive, and 64 control subjects. APOE genotype was not significantly related to outcome, including being alive at and being independent by 3 months after the arrest. Specifically, having one or two alleles of APOE e4 or having APOE e3/e3 was not related to outcome, even after controlling for age, sex, race, and initial rhythm. We failed to confirm previous studies and found no significant associations between APOE genotype and outcome from out of hospital cardiac arrest.

METHODS

As part of another study, paramedics in Seattle have collected blood specimens from patients with out of hospital cardiac arrest since 1988. Regardless of the outcome of resuscitation, paramedics collect the specimens as soon as possible after return of spontaneous circulation or immediately upon cessation of resuscitative efforts. Blood was collected into tubes containing EDTA, and transported to the Clinical Nutrition Research Laboratory at Harborview Medical Center, where the white blood cells were separated and stored at −70°C. APOE genotyping was attempted on all specimens collected from 1989 to 1995 from patients who had survived to hospital discharge. DNA was prepared from buffy coat preparations by a modification of a salting out procedure. The APOE genotypes were determined using previously described PCR conditions and HhaI restriction digest methods. For comparison, genotyping was also attempted on randomly selected specimens collected in the same time interval from an approximately equal number of patients who died in hospital: about one third this number of patients who died “in the field”; and about one third this number of community control subjects from the study described above. Genotyping was performed 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 pre-hospital 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 e4 was not significantly related to the outcomes examined: having a cardiac arrest v
genetic factors may hold the key to understanding brain accompanying cardiac arrest exist. Understanding such factors that affect the response to global brain ischaemia needed to identify such associations. Even if an association more detailed determination of neurological outcome is clinical information, making such a bias unlikely. Perhaps specimens, but the genotyping was performed without any unclear. We examined a larger number and a less select group examined. Why the results from the two studies differ is also not significantly associated with any of the outcomes independent by 3 months

<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.

**DISCUSSION**

How apolipoprotein E genotypes affect outcomes from brain injury is uncertain but seemingly dependent upon the mechanism of injury. Detrimental effects of having one or two alleles of APOE ε4); for all cardiac arrest patients, being resuscitated and admitted v not (22.2% v 27.5%); surviving to 3 months v not (21.6% v 27.0%); or being independent by 3 months v not (22.6% v 26.1%). Similarly, in the unadjusted and adjusted models, having the APOE ε3/ε3 genotype was not significantly related to the outcomes examined: having a cardiac arrest v being a control (66.7% v 64.1% respectively, having APOE ε3/ε3 genotype); for all cardiac arrest patients, being resuscitated and admitted v not (67.5% v 64.9%); and for patients admitted, surviving to discharge v not (69.7% v 64.1%); surviving to 3 months v not (70.4% v 65.5%); or being independent by 3 months v not (69.0% v 65.8%). Associations with genotypes for survival at and independence by 3 months remained insignificant when only those discharged from the hospital were considered.

**ACKNOWLEDGEMENTS**

The study was possible only because of the outstanding efforts of the firefighters and paramedics of the Seattle Fire Department. We also appreciate the dedicated work of staff of the Medic One Program in determining demographics and outcomes. This study was supported by grants from the National Heart, Lung, and Blood Institute (HL41993 DSS), the National Institute of Aging (PS0 AG05136, GDS), and the Medic One Foundation.

**Authors’ affiliations**

W T Longstreth Jr, C E Fahrenbruch, L A Cobb, M K Copass, D S Siscovick, Departments of Neurology, Epidemiology, and Medicine, Divisions of General Internal Medicine and Cardiology, University of Washington, USA.

G D Schellenberg, Department of Medicine, Division of Gerontology and Geriatric Medicine (Schellenberg), Veterans Affairs Puget Sound Health Care System, Seattle Division, Seattle, WA, USA.

Competing interest: none declared.

Correspondence to: Dr W T Longstreth Jr, Department of Neurology, Box 359775, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104-2420, USA; wlt@u.washington.edu

**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 fundscopy to show the numerous and important signs (optic atrophy, papilloedema and such) of intracranial disease that the ophthalmoscope could provide. He observed:

“It is obvious that the results of such advances prescribe for the clinical physician methods which cannot be pursued without expert assistance; a physician engaged in busy practice cannot himself undertake even the verifications required in the conduct of individual cases. Skill in modern laboratory work is as far out of the reach of 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 schools down to Herbert Spencer, it is forced upon us in our own day that in a pursuit so many sided as medicine, whether in its scientific or in its practical aspect, we have to submit more and more to that division of labour which has been a condition of advance in all other walks of life.”

He received the KCB in 1907 and was made Privy Councillor in 1920.

The many honorary degrees bestowed upon him signify his distinction: Hon DSc Oxon, Manchester, Leeds, Hon LLD Glasgow, McGill, Toronto, St Andrew’s, Durham, Hon MD Dublin.

Allbutt was a student and scholar in both classical and modern medical history. Among his writings was Greek medicine in Rome and other historical essays. His own writing was plain but stylish and he hated the careless or ungrammatical English of some other medical writers.

He was described as sanguine and calm in demeanour, his bearing courtly and aristocratic. It is suggested that the author George Eliot’s character Lydgate in Middlemarch was based on Allbutt, whom Eliot knew in her time in Yorkshire. He married Susan, daughter of Thomas England, a merchant from Headingley, Leeds, in 1869, but they had no children. He died in Cambridge.

---

**References**

1. Allbutt TC. On the use of the ophthalmoscope in diseases of the nervous system and of the kidneys; also in certain other general disorders. London and New York: Macmillan, 1871.