Apolipoprotein E genotypes and clinical outcome in Guillain-Barré syndrome

J Pritchard, R A C Hughes, J H Rees, H J Willison, J A R Nicoll

Guillain-Barré syndrome is a peripheral neuropathy in which there is monophasic immune mediated destruction of myelin and axons. There is considerable variability in outcome, for reasons as yet unknown, with some patients showing extensive axonal regeneration and remyelination, whereas others show little recovery. After peripheral nerve injury there is greatly increased production of apolipoprotein E (APOE, gene; apoE, protein) by macrophages. Apolipoprotein E transports lipids to axonal growth cones and Schwann cells to permit axonal growth and remyelination. There is a biologically significant polymorphism in the human APOE gene, with three common alleles, $e_2$, $e_3$, and $e_4$, encoding the respective protein isoforms $E_2$, $E_3$, and $E_4$. The APOE genotype influences various disorders of the central nervous system. For example, possession of $e_4$ is associated with an increased risk of Alzheimer’s disease and a poor outcome after stroke. A logistic regression analysis was undertaken to identify recent Campylobacter jejuni infection. Maximum disability during the acute phase of the disease and outcome at one year was assessed on a disability scale: 0, healthy; 1, minor symptoms or signs and capable of running; 2, able to walk five metres without assistance but unable to run; 3, able to walk five metres with aid; 4, chair bound/bed bound; 5, requiring assisted ventilation for at least part of the day or night; 6, dead. A good outcome was defined as a disability of less than grade 3, a poor outcome by a score of grade 3 or above.

The degree of improvement from maximum disability grade to one year was also assessed, by comparing the number of patients who improved by three grades or more for each genotype.

APOE genotypes were determined from stored DNA samples as previously described. Briefly, the polymorphic fragment of the APOE gene was amplified by polymerase chain reaction (PCR) using standard primers. The PCR products were digested with Hha1. The digestion fragments were separated according to size by polyacrylamide gel electrophoresis, stained with ethidium bromide, and viewed by ultraviolet transillumination.

Statistical analyses were done using the Epi Info 6 (version 6.02) program (WHO, Geneva, 1994) to perform $\chi^2$ tests with Yates’s correction. When numbers were small, Fisher’s exact test was used. Two tailed tests of significance were used throughout. A logistic regression analysis was undertaken to assess the independent effects on outcome of APOE genotype, C jejuni infection, and disease type.

RESULTS

The 91 patients comprised 84 with Guillain-Barré syndrome and seven with its Miller Fisher variant. The average age of onset was 48.6 years (range 4 to 88) and 34% of the patients were female. There was no difference in these baseline characteristics in the patients possessing any APOE2 or any APOE4 allele compared with the whole patient population. Twenty nine patients had neurophysiological evidence of branching, and synaptogenesis, possibly through its role in receptor mediated uptake of lipids to cells. We hypothesised that outcome in Guillain-Barré syndrome is influenced by the APOE genotype. We tested this hypothesis by correlating APOE genotypes with residual disability and degree of improvement assessed one year after presentation.

METHODS

Patients

Ninety one patients with Guillain-Barré syndrome were recruited prospectively from the southeast region of the United Kingdom in 1992 to 1994. Nerve conduction studies were done to classify the disease as demyelinating, predominantly axonal, or demyelinating with superimposed axonal degeneration. Stool was cultured and serum tested to identify recent Campylobacter jejuni infection.

Background: Polymorphism of the gene encoding the cholesterol transport protein apolipoprotein E (APOE, gene; apoE, protein), known to be involved in axonal regeneration and remyelination, influences outcome after a variety of central nervous system disorders. Apolipoprotein E gene polymorphisms could affect recovery from Guillain-Barré syndrome.

Objective: To correlate APOE genotypes with residual disability and degree of improvement in Guillain-Barré syndrome, assessed one year after presentation.

Methods: 91 patients with the syndrome were recruited from southeast England and their APOE genotypes were determined.

Results: There were no clear differences in APOE genotype or allele frequencies when comparing the 91 patients with controls, nor when comparing 81 patients with good outcome and 10 with poor outcome.

Conclusions: APOE genotype did not influence susceptibility to Guillain-Barré syndrome or recovery from it. This may be because our sample size of 91 was not sufficiently large to detect small differences in recovery associated with different APOE genotypes, or because cholesterol transportation is not a crucial rate limiting step in peripheral nerve regeneration.
DISCUSSION

Although Guillain-Barré syndrome has strong associations with antecedent infectious agents including *C jejuni*, *Mycoplasma pneumoniae*, cytomegalovirus, Epstein Barr virus, and possibly *Haemophilus influenzae*, only a small minority of those who experience such infections develop the syndrome. Therefore there must be as yet unidentified host specific factors that determine the onset and course of this disease. Studies of immunogenetic factors in Guillain-Barré syndrome have not consistently implicated a particular gene. In this series, HLA DQB1*03 was more common in patients who had previously had *C jejuni* infection.6

The APOE 3/3 genotype was slightly more common in the patients with Guillain-Barré syndrome than in controls genotyped in the same laboratory, but this difference did not reach statistical significance when the patients were compared with a different control population. The patients were from southeast England while the control samples were from a Scottish population and a mixed population, respectively, which may account for the difference as there is an increase in € frequency with increasing latitude. In order to establish if an increase in APOE 3/3 genotype is a true association of Guillain-Barré syndrome, a larger study with case controls from the same district will be required. The APOE 3/3 genotype has not been associated with other types of neurological disease.

We did not find evidence to support the hypothesis that APOE genotype influences outcome in Guillain-Barré syndrome, either in terms of absolute outcome or in the degree of improvement from the point of maximal disability on a seven point scale. We excluded the four patients who had died from the analysis because death in Guillain-Barré syndrome is usually a result of non-neurological complications. Repeating the analysis including these patients did not alter the conclusions.

Our finding is in contrast with analogous CNS disorders (for example, multiple sclerosis) in which the APOE genotype does appear to have an influence.7 In the CNS, apoE synthesised locally is believed to be the major lipid transport protein. In the peripheral nervous system apoE is involved in recycling of lipids after peripheral nerve injury, both for remyelination and for axonal regeneration. However, other lipoproteins might compensate for isofrom specific differences in apoE function in the peripheral nervous system.

The relatively low prevalence of APOE e2 and e4 alleles means that a study of this size has limited power. In studies of other neurological diseases the APOE genotype induced effects of the magnitude of a 25% reduction in good outcome. This study only had 33% power to detect a true 25% reduction in the proportion of patients with a “good” outcome at one year in those carrying the APOE e4 allele, but did have 96% power to detect a 50% decrease in the proportion of “good” outcome patients. It is thus reasonably certain that differences in outcome in Guillain-Barré syndrome of this order do not exist between those with and without APOE e4 alleles.

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**Table 1** Distribution of APOE genotypes in 91 patients with Guillain-Barré syndrome compared with a Scottish population and a mixed UK/USA population.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>2/2</th>
<th>2/3</th>
<th>3/3</th>
<th>2/4</th>
<th>3/4</th>
<th>4/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>All GBS patients (n=91) (frequency)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Scottish population (n=406) (frequency)</td>
<td>0 (0.000)</td>
<td>5 (0.055)</td>
<td>68 (0.744)</td>
<td>0 (0.000)</td>
<td>17 (0.187)</td>
<td>1 (0.011)</td>
</tr>
<tr>
<td>Mixed population (n=169) (frequency)</td>
<td>4 (0.100)</td>
<td>45 (0.110)</td>
<td>222 (0.550)</td>
<td>13 (0.030)</td>
<td>110 (0.270)</td>
<td>12 (0.030)</td>
</tr>
<tr>
<td>Good outcome GBS patients (n=81) (frequency)</td>
<td>0 (0.000)</td>
<td>5 (0.062)</td>
<td>60 (0.741)</td>
<td>0 (0.000)</td>
<td>15 (0.185)</td>
<td>1 (0.012)</td>
</tr>
<tr>
<td>Poor outcome GBS patients (n=10) (frequency)</td>
<td>0 (0.000)</td>
<td>0 (0.000)</td>
<td>8 (0.800)</td>
<td>0 (0.000)</td>
<td>2 (0.200)</td>
<td>0 (0.000)</td>
</tr>
<tr>
<td>Worst disability of grade 3, 4, or 5 (n=78) (frequency)</td>
<td>0 (0.000)</td>
<td>5 (0.064)</td>
<td>56 (0.718)</td>
<td>0 (0.000)</td>
<td>16 (0.205)</td>
<td>1 (0.013)</td>
</tr>
<tr>
<td>Improved by ≥3 disability grades from grade 3, 4, or 5 (n=51) (frequency)</td>
<td>0 (0.000)</td>
<td>5 (0.098)</td>
<td>34 (0.667)</td>
<td>0 (0.000)</td>
<td>11 (0.216)</td>
<td>1 (0.020)</td>
</tr>
</tbody>
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apoE, apolipoprotein E; APOE, apolipoprotein E; C jejuni, Campylobacter jejuni; GBS, Guillain-Barré syndrome.
REFERENCES