SHORT REPORT

Longitudinal analysis of the effect of apolipoprotein E ε4 and education on cognitive performance in elderly subjects: the PAQUID study

M Winnock, L Letenneur, H Jacqmin-Gadda, J Dallongeville, P Amouyel, J F Dartigues

Background: The apolipoprotein E (apoE) ε4 allele has been shown to be a risk factor for dementia, but it is not clear to what extent apoE affects overall cognitive function in non-demented elderly subjects, or how this risk may be modified by gene–environment interactions.

Objective: To examine changes in cognitive function in elderly people as a function of the apoE ε4 phenotype.

Methods: A community based prospective cohort study of 600 non-demented subjects aged over 65 years living in Gironde (France) was analysed to evaluate change over time (seven years) in scores on the mini-mental state examination (MMSE).

Results: Age at cohort inception was negatively associated with cognitive performance for both ε4 carriers and non-carriers (p < 0.001). The evolution of MMSE scores differed as a function of age: scores remained stable among younger subjects but decreased over time in older subjects. The ε4 allele was shown to be significantly associated with lower cognitive performance at baseline (p = 0.02). The course of cognitive performance during the follow up was the same for both ε4 carriers and non-carriers. Lower educational level was associated with lower cognitive performance at baseline (p < 0.001) and the effect of an ε4 allele on cognitive performance disappeared after adjustment for education. When incident cases of dementia were excluded, the results remained unchanged except for the course of the MMSE scores, which now remained stable over time in the older subjects.

Conclusions: apoE ε4 carriers show decreased MMSE scores compared with ε4 non-carriers, but the effect of apoE on cognition disappears after adjustment for education. Non-demented elderly people maintain a stable cognitive performance regardless of their apoE phenotype.

The association between the ε4 allele of apolipoprotein E (apoE) and the risk of developing Alzheimer’s disease is well established. The presence of one or two ε4 alleles is associated with both familial and sporadic late onset Alzheimer’s disease in most ethnic groups, across all ages, and in both men and women. On the other hand, the presence of the ε2 allele appears to have a protective effect. While there is overall consensus about the role of apoE as a risk factor for Alzheimer’s disease, less is known about the influence of apoE on cognitive function. At present it is not clear whether the presence of the ε4 allele conveys a risk of cognitive impairment in elderly people without dementia.

Several longitudinal studies using the mini-mental state examination (MMSE) have been planned to evaluate progression of cognitive decline in both demented and non-demented individuals. So far these have shown a clear decline in the former and relative stability in the latter.

Our objective in this study was to describe the relation between the presence of the apoE ε4 allele and changes in the MMSE score during a seven year period in a large sample of non-demented elderly people and to examine how environmental factors, such as education, might influence this relation.

METHODS

This study was part of the PAQUID research programme, a prospective cohort study of normal and pathological cerebral aging, composed of a randomly selected sample of non-institutionalised individuals aged 65 years and over living in the southwest of France. The methodology of this study has already been extensively described.

The survey started in 1988, following 2792 subjects who were interviewed at home by trained psychologists at one, three, five, eight, and 10 years after the baseline visit. Our sample comprised of a subgroup of 626 subjects who volunteered to give a blood sample for apoE phenotyping at the first year follow up interview.

Cognitive performance was evaluated at each visit using a comprehensive battery of neuropsychological tests. After the psychometric evaluation, the psychologists systematically completed an evaluation of the DSMIII-R criteria for dementia, and subjects who met these criteria were then seen by a senior neurologist who confirmed the diagnosis of dementia.

The results presented here are based on the MMSE, which is a global mental function screening test. For the analyses we used longitudinal MMSE score data, obtained from the one, three, five, and eight year follow up interviews; the 10 year follow up interview was only used to obtain DSMIII-R data and to establish diagnosis of dementia.

Our objective was to investigate the evolution of cognitive performance in non-demented elderly individuals. Thus in the initial analysis we excluded those subjects with a confirmed diagnosis of dementia at baseline (n = 22), and also at the first year follow up (n = 4), as the blood sample was collected at that time. In a second analysis, we then excluded any subjects in whom a diagnosis of dementia had been made between the three year and the 10 year follow up visits (n = 53). In this way, we were certain that no subjects included in the second analysis had been diagnosed as having dementia in the two year period after the last MMSE score.

The sample for the first analysis comprised 600 subjects and for the second analysis, 547 subjects.

Serum samples were obtained during the first year follow up (1989–90) and frozen until determination of apoE phenotype. Homozygotes and heterozygotes for apoE ε4 were combined and designated as ε4 carriers; other phenotypes were designated as ε4 non-carriers.

Statistical analyses

To study the variables associated with cognitive performance, we used a random effects linear regression model, which takes...
RESULTS
At baseline, the mean (SEM) age of the 600 participants was 73.7 (0.26) years, range 65 to 94. No difference was found between mean ages for ε4 carriers (73.1 (0.53) years, range 65 to 92) and ε4 non-carriers (73.9 (0.29) years, range 65 to 94) (t = 1.37, p = 0.17). There was no difference in sex between ε4 carriers and non-carriers (men: women: carriers: 57:73; non-carriers: 203:267).

The most frequent apoE phenotypes for the group were ε3/ε3 (n = 403), ε3/ε4 (n = 114), and ε2/ε3 (n = 60). Individuals homozygous for the ε4 or ε2 alleles, or with the ε2/ε4 phenotype, were poorly represented (n = 5, 7, and 11, respectively). In our sample, approximately one in five subjects was diagnosed as demented on the one, three, five, eight, and 10 year follow up interviews (B) (95.7%, 508 (84.7%), 457 (76.2%), and 364 (60.7%) completed the MMSE at the one, three, five, and eight year follow up, respectively. Four MMSE measures were available in 332 participants (55.3%), and 116 (19.3%) died during follow up. There were no differences in the response patterns between ε4 carriers and ε4 non-carriers (data not shown).

Results of the linear regressions with random effects for the square root of the number of errors in the mini-mental state examination (MMSE) for non-demented subjects at the one year follow up (A) and after exclusion of those diagnosed as demented on the one, three, five, eight, and 10 year follow up interviews (B)

<table>
<thead>
<tr>
<th>Variable</th>
<th>A (n=600)</th>
<th>B (n=547)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>Age (at baseline)</td>
<td>0.045</td>
<td>0.005</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.025</td>
<td>0.056</td>
</tr>
<tr>
<td>Time</td>
<td>-0.192</td>
<td>0.075</td>
</tr>
<tr>
<td>Age by time</td>
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<td>0.001</td>
</tr>
<tr>
<td>ApoE ε4</td>
<td>0.155</td>
<td>0.068</td>
</tr>
</tbody>
</table>

A negative coefficient indicates an increase in the mean MMSE score.
*SE, standard error.
†Primary school with diploma = no school/primary school without diploma.

A lower educational level was associated with lower performance at baseline (p < 0.0001) (model 2A), but the evolution of cognitive performance was the same over time for all levels of education (education by time, p = 0.14). This effect was the same for ε4 carriers and ε4 non-carriers (apoE ε4 by education, p = 0.26). In contrast, the effect of the presence of an ε4 allele on baseline cognitive performance disappeared when adjusted for education (fig 1B).

When subjects who were diagnosed as demented during the 10 year follow up were excluded from the analyses, the effect of age at baseline upon cognitive performance was still significant (p < 0.0001) (table 1, model 1B) (fig 1B). However, the evolution of cognitive performance over time, denoted as time, became non-significant, meaning that the level of performance remained stable over time. No differential evolution as a function of age at baseline was observed (age by time, p = 0.87). The apoE ε4 allele was still important for cognitive performance, as ε4 carriers had a decreased score at baseline compared with non-carriers (model 1B) (p = 0.018) (fig 1B). Education continued to have a significant effect (p < 0.0001), and the influence of the presence of an ε4 allele again disappeared when adjusted for education (model 2B) (fig 1D). In contrast to model 1B, women showed a better performance at baseline than men (p = 0.03) when cognitive performance was adjusted for education, but the evolution over time was the same for both sexes (sex by time, p = 0.16).

DISCUSSION
Four major conclusions can be drawn from this study. First, the apoE phenotype had a significant effect on cognitive performance of elderly subjects at the baseline level, in that apoE ε4 carriers had a decreased MMSE score compared with non-carriers. Second, the difference between ε4 carriers and non-carriers disappeared after adjustment for education. Third, no global cognitive decline was observed over time in elderly subjects, once those with dementia or impending dementia were excluded from the analysis; the slight decline in cognitive function observed when the analysis included the entire cohort reflected the decline in individuals who were in the early stages of dementia. Finally, the level of global cognitive performance remained stable throughout follow up and was independent of the apoE phenotype, suggesting that this phenotype did not influence cognitive performance over time.

The evolution of MMSE scores depended on the subject's age at entry to the study and on educational level. Interestingly, the effect of apoE ε4 disappeared after taking into account the level of education. In our study, the frequency of subjects with a primary school diploma differed between ε4 carriers and ε4 non-carriers, suggesting that apoE phenotype might influence cognition through the entire life span.
It is possible that certain genetic characteristics might influence both the level of education attained and any later susceptibility to cognitive change. ApoE may influence cognitive function through direct changes in brain morphology in ε4 carriers, and it appears that the biological influence of the apoE genotype may be assessed by differences in cognitive function in clinically healthy people. Education could also exert a direct effect on cognition. Animal studies have shown that environmental experiences can modify brain anatomy and function. Swaab suggested that the activation of nerve cells in people who have completed higher education protects these cells from degeneration, thereby delaying the pathological process that lead to cognitive decline. Along the same lines, it was hypothesised that higher education could also lead to an increased brain reserve capacity, so that other neurons can take over the tasks of ones that have died.

To some degree at least education may be a surrogate for other factors that could influence cognition. The educational classification used in our study was the attainment of a primary school diploma. This is based on linguistic and conceptual abilities, judged by performance in tests of reading, writing, and mathematical problem solving. The number of years of education were not taken into account, only intellectual ability—subjects who fail the examination may subsequently be involved in less demanding cognitive tasks, leading to reduced brain stimulation and thus to a more limited cognitive reserve.

Our data suggest that apoE could play a direct role in cognition since early life by influencing the level of education that could be attained. In support of our data, two recent studies have shown a significant difference in the educational background between apoE ε4 carriers and non-carriers, the former staying in school longer than the latter. The level of education could have a secondary influence on the brain reserve capacity.

A possible limitation of our study is whether the subcohort was a truly representative sample, as it was composed of volunteers from the French PAQUID cohort. However, the frequency of the individual apoE phenotypes observed in our sample was comparable with other published reports.

Figure 1 Graphical representation of the evolution of mean mini-mental state examination scores estimated by linear mixed effects models. Scores estimated are shown for all subjects (A, C) and after exclusion of those diagnosed as demented during the 10 year follow up (B, D), before (A, B) and after (C, D) adjustment for education. ApoE, apolipoprotein E; MMSE, mini-mental state examination.
preclinical Alzheimer’s disease. These aspects will be of particular interest for follow up studies.

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