PROGNOSIS

Apolipoprotein E ∈4 allele predicted an accelerated rate of cognitive decline in Alzheimer's disease

Craft S, Teri L, Edland SD, et al. ***Accelerated decline in apolipoprotein E-∈4 homozygotes with Alzheimer's disease.*** *Neurology 1998 Jul;**51**:149–53.*

Question
In patients newly diagnosed with Alzheimer's disease (AD), what effect do different apolipoprotein E (APOE) genotypes have on the rate of cognitive decline?

Design
Inception cohort followed up for 1–6 years (mean 2.47 y).

Setting
Health maintenance organisation in Seattle, Washington, USA.

Patients
201 patients who were diagnosed with AD within the previous year based on National Institute of Neurological and Cognitive Disorders and Stroke-Alzheimer's Disease and Related Disorders Association and *DSM-III-R* criteria. Patients with other central nervous system conditions or major psychiatric disorders were excluded.

Assessment of prognostic factors
Patients were grouped according to their APOE genotype: ∈2/3 (n = 14), ∈3/3 (n = 75), ∈3/4 (n = 82), and ∈4/4 (n = 30).

Main outcome measure
Annual rate of cognitive decline assessed by the Dementia Rating Scale (DRS) total scores derived from 5 subscales: attention, memory, initiation and perseveration, conceptualisation, and construction.

Main results
All patients had baseline and ≥1 DRS total score. At the mean DRS score of 105 for this patient sample, the ∈4/4 group had a greater rate of decline than the ∈2/3 group ($p < 0.003$); the differences in rate of decline were less pronounced compared with the ∈3/3 group ($p < 0.076$) and the ∈3/4 group ($p < 0.055$) (table). At a DRS score of 80, the rate of decline in the ∈4/4 group was greater than the ∈2/3 group ($p < 0.001$) and the ∈3/4 group ($p < 0.021$), with a smaller difference compared with the ∈3/3 group ($p < 0.174$) (table). At both cutoff points the rate of decline was slower in the ∈2/3 group than the ∈3/3 and ∈3/4 groups. In addition, older age predicted a slower rate of decline ($p < 0.001$).

Conclusions
Patients newly diagnosed with Alzheimer's disease who were homozygous for the apolipoprotein E ∈4 allele had an increased rate of cognitive decline compared with other genotypes. Patients with the ∈2/3 allele had a slower rate of decline.

Annual rate of cognitive decline among genotype groups at a mean of 2.5 years

DRS score	*Rate of decline (points /y)*			
	∈2/3	∈3/3	∈3/4	∈4/4
105	5.8	9.3	9.6	11.9
80	9.7	18.2	15.8	22.2

DRS = dementia rating scale.

Sources of funding: NIA R01 AG-10880; Alzheimer's Disease Patient Registry; Alzheimer's Association; Department of Veterans Affairs.

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Commentary

The search for biological markers to confirm the clinical diagnosis of AD has been prompted by the assumption that new treatments are most likely to slow or halt disease progression rather than reverse existing damage. Human APOE, previously known for its role in cholesterol transport and plasma lipoprotein metabolism, has emerged as a major genetic risk factor for AD.

The APOE ∈4 allele has been shown to confer an increased risk of AD, occurring in up to 50% of cases.[1] From a clinicopathological viewpoint, the APOE ∈4 allele appears to lower the age of onset of AD and increase the amount of Aβ deposition in the brain.[2] Few studies support the implications of genotype differences in disease severity or rate of decline.[3,4] In that context, this study contributes to knowledge on the molecular genetics of AD.

This study by Craft *et al* includes the largest inception cohort of patients with AD in whom longitudinal data and APOE status have been reported. Another strength of the study is the use of the DRS to measure decline, using its broad range of scores, and therefore avoiding the floor effects of other instruments (eg, Mini Mental State Examination). Furthermore, the study was able to examine the effects of APOE genotype status on disease progression, and detected statistically significant differences in the rate of decline between the ∈4/4 group (fastest) and the ∈2/3 group (slowest), and similar (intermediate) rates for the ∈3/4 and ∈3/3 groups. Finally, the results were robust to the manipulation of age at onset as a covariate or as a correlate of rate of decline.

The study provides further evidence for the hypothesis that APOE plays a mechanistic part in the neuropathologic progression of AD, as well as in its onset. The findings support the previously established clinical utility of APOE testing[5]; and suggest a possible role for APOE testing as a prognostic indicator in some patients presenting with dementia.

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1 Lendon CL, Ashall F, Goate AM. *JAMA* 1997;**227**:825–31.
2 Hyman BT, Gomez-Isla T, Rebeck GW *et al.* *Ann N Y Acad Sci* 1996;**802**:1–5.
3 Soininen HS, Reikkinen PJ Sr. *Trends Neurosci* 1996;**19**:224–8.
4 Growdon JH, Locascio JJ, Corkin S, *et al.* *Neurology* 1996;**47**:444–8.
5 Post SG, Whitehouse PJ, Binstock RH *et al.* *JAMA* 1997;**227**:832–6.

OTHER ARTICLES NOTED

The journals that are reviewed and the criteria for selecting articles from these journals for inclusions in *Evidence-Based Mental Health* are set out in the purpose and procedure in each issue. All articles that meet our criteria in the reviewed journals are cited in *Evidence-Based Mental Health*, but there is not enough space to abstract them all. The following articles passed all criteria but were not abstracted because, in the judgment of the editors, their findings were less widely applicable to clinical practice in the area of mental health.

Therapeutics

Effects of lifestyle activity vs structured aerobic exercise in obese women. A randomized trial. Andersen RE, Wadden TA, Bartlett SJ, *et al. JAMA* 1999 Jan;**281**:335–40.

Low-dose hydrocortisone in chronic fatigue syndrome: a randomised crossover trial. Cleare AJ, Heap E, Malhi GS, *et al. Lancet* 1999 Feb;**353**:455–8.

Intramuscular flunitrazepam versus intramuscular haloperidol in the emergency treatment of aggressive psychotic behavior. Dorevitch A, Katz N, Zemishlany Z, *et al. Am J Psychiatry* 1999 Jan;**156**:142–4.

A placebo-controlled trial of D-Cycloserine added to conventional neuroleptics in patients with schizophrenia. Goff DC, Tsai G, Levitt J, *et al. Arch Gen Psychiatry* 1999 Jan;**56**:21–7.

Olanzapine for schizophrenia. (Cochrane Review, latest version 25 November 1998). Duggan L, Fenton M, Dardennes RM, *et al.* In: *Cochrane Library*. Oxford: Update Software.

Efficacy of high-dose glycine in the treatment of enduring negative symptoms of schizophrenia. Heresco-Levy U, Javitt DC, Ermilov M, *et al. Arch Gen Psychiatry* 1999 Jan;**56**:29–36.

Meta-analysis of benzodiazepine use in the treatment of acute alcohol withdrawal. Holbrook AM, Crowther R, Lotter A, *et al. CMAJ* 1999 Mar 9;**160**:649–55.

Randomised placebo-controlled trial of moclobemide, cognitive-behavioural therapy and their combination in panic disorder with agoraphobia. Loerch B, Graf-Morgenstern M, Hautzinger M, *et al. Br J Psychiatry* 1999 Mar;**174**:205–12.

Effectiveness of behavioral therapy to treat incontinence in homebound older adults. McDowell BJ, Engberg S, Sereika S, *et al. J Am Geriatr Soc* 1999 Mar;**47**:309–18.

Treatment of neuroleptic-induced akathisia with the 5-HT_2 antagonist mianserin. Double-blind, placebo-controlled study. Poyurovsky M, Shardorodsky M, Fuchs C, *et al. Br J Psychiatry* 1999 Mar;**174**:238–42.

Prognosis

The role of the family for behavioral outcome in children and adolescents following traumatic brain injury. Kinsella G, Ong B, Murtagh D, *et al. J Consult Clin Psych* 1999 Feb;**67**:116–23.

Cantabria first-episode schizophrenia study: three year follow-up. Vázquez-Barquero JL, Cuesta MJ, Castanedo SH, *et al. Br J Psychiatry* 1999 Feb;**174**:141–9.

Aetiology

The quantification of mortality resulting from the regular use of illicit opiates. Hulse GK, English DR, Milne E, *et al. Addiction* 1999 Feb;**94**:221–9.

Genetic and environmental contributions to alcohol abuse and dependence in a population-based sample of male twins. Prescott CA, Kendler KS. *Am J Psychiatry* 1999 Jan;**156**:34–40.

Economics

Flumazenil in drug overdose: randomized, placebo-controlled study to assess cost effectiveness. Barnett R, Grace M, Boothe P, *et al. Crit Care Med* 1999 Jan;**27**:78–81.

Correction

In *Evidence-Based Mental Health* May 1999 on page 56 the volume numbers in references 1 and 5 should read 277. The editorial team apologises for the error.