AETIOLOGY

Earlier onset and increased risk of Alzheimer's disease in Down's syndrome was associated with sex and apolipoprotein E genotype

Schupf N, Kapell D, Nighingale B, et al. *Earlier onset of Alzheimer's disease in men with Down syndrome. Neurology* 1998 Apr;50:991-5.

Questions

In adults with Down's syndrome, is sex associated with age at onset or risk of Alzheimer's disease (AD)? Does the apolipoprotein E (APOE) genotype modify the effect of sex on risk of AD?

Design

Cohort analytic study.

Setting

New York, USA.

Participants

A random sample of 174 adults who were 30-70 years of age and had Down's syndrome were identified from the New York State Office of Mental Retardation and Developmental Disabilities registry. 111 adults (mean age 51 y, 55% men) participated in the study.

Assessment of risk factors

APOE genotypes were determined using blood samples. Data on age, sex, race, history of and age at onset of AD, hyperthyroidism, psychiatric disorders, and other conditions leading to dementia were obtained in semistructured interviews.

Main outcome measure

Diagnoses of AD (with other causes of dementia ruled out) by physicians were obtained from medical records. All diagnoses were made without knowledge of APOE genotypes.

Main results

Men with Down's syndrome were more likely to develop AD at an earlier age than women with Down's syndrome (cumulative incidence to age 65 y 79% v 28%). After the results were adjusted for age and level of function, men had a 3-fold greater risk of AD

than did women (table). The presence of an APOE $\epsilon 4$ allele ($\epsilon 3/\epsilon 4$ or $\epsilon 4/\epsilon 4$ genotypes) was associated with an earlier onset of AD (cumulative incidence to age 65 y 79% v 50% for APOE $\epsilon 4$ allele v APOE $\epsilon 3/\epsilon 3$ genotype). Adults with Down's syndrome who had an APOE $\epsilon 2$ allele did not develop AD. After adjusting the results for age and level of function, those who had an APOE $\epsilon 4$ allele had a 4-fold greater risk of AD than did those with the APOE $\epsilon 3/\epsilon 3$ genotype (table). No interaction between sex and APOE genotype existed; the increased risk of AD associated with the APOE $\epsilon 4$ allele was similar for both men and women using people with the APOE $\epsilon 3/\epsilon 3$ genotype as the reference group (table).

Conclusions

In adults with Down's syndrome, a greater risk and earlier onset of Alzheimer's disease (AD) was associated with being male or having an apolipoprotein E (APOE) allele. Those who had an APOE $\epsilon 2$ allele did not develop AD. The APOE genotype did not modify the effect of sex on the risk of AD.

Risk of Alzheimer's disease in adults with Down's syndrome

Risk factors	Relative risk* (95% CI)
Men v women	2.9 (1.01 to 8.4)
APOE $\epsilon 4$ allele v $\epsilon 3/\epsilon 3$	4.1 (1.5 to 11.6)
APOE $\epsilon 4$ allele v $\epsilon 3/\epsilon 3$ in men	3.9 (1.1 to 13.9)
APOE $\epsilon 4$ allele v $\epsilon 3/\epsilon 3$ in women	2.4 (0.4 to 14.9)

*Adjusted for age and level of function.

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Commentary

The study by Schupf *et al* is an important advance in the research on AD in people with Down's syndrome. Their finding that men with Down's syndrome develop earlier onset of AD than women with Down's syndrome differs from findings in the general population. The authors speculate that their findings may be related to sex differences in the hormonal function of adults with Down's syndrome. They further state that these hormonal abnormalities in adults with Down's syndrome (a) appear to progress with age and (b) are more frequent in men with Down's syndrome; older men with Down's syndrome therefore may not benefit from the relative preservation of oestrogen, which is believed to diminish the risk of AD in men in the general population. Further research is needed to test this hypothesis. The question of sex as an independent risk factor

for AD has been controversial in the past.^{1 2} Findings of earlier prevalence studies showed higher rates in women than in men, whereas incident studies showed no relation with sex.

The other main finding of this study is the association between the APOE $\epsilon 4$ allele and an increased risk of AD; in contrast, the presence of APOE $\epsilon 2$ allele was found to be protective. These findings agree with those of previous studies in the general population and in people with Down's syndrome.

Of note, the authors acknowledged the limitation of relying on medical practitioners for the diagnoses of AD. Age and specific prevalence rates of dementia in this population have varied because of selection bias and, more importantly, the use of vague diagnostic criteria rather than formal diagnostic instruments. Better

standards and valid diagnostic schedules for AD are needed specifically for this group. Recently, some researchers have attempted to address this issue by using established diagnostic techniques and criteria that were developed for other groups. For example, the study by Holland *et al* used a modified version of the informant interview of the Cambridge Examination for Mental Disorders of the Elderly (CAM-DEX) and showed face validity for the CAM-DEX tool in this particular population.³

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1 Tang MX, Jacobs D, Stern Y, *et al. Lancet* 1996;348:429-32.

2 Payami H, Zarepari S, Montee KR, *et al. Am J Hum Genet* 1996;58:803-11.

3 Holland AJ, Hon J, Huppert FA, *et al. Br J Psychiatry* 1998;172:493-8.