SHORT REPORT

Apolipoprotein E e4 allele influences aggressive behaviour in Alzheimer's disease

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J Neurol Neurosurg Psychiatry 2004;**75**:1327–1330. doi: 10.1136/jnnp.2003.032276

The rising number of people with cognitive impairment is placing health care budgets under significant strain. Dementia related behavioural change is a major independent risk factor for admission to expensive institutional care, and aggressive symptoms in particular are poorly tolerated by carers and frequently precipitate the collapse of home coping strategies. Aggressive change may result from known genetic risk factors for Alzheimer's disease (AD) and therefore accompany conventional markers such as apolipoprotein E (ApoE). We tested this hypothesis in 400 moderately to severely affected AD patients who were phenotyped for the presence of aggressive or agitated behaviour during the month prior to interview using the Neuropsychiatric Inventory with Caregiver Distress. The proportion of subjects with aggression/agitation in the month prior to interview was 51.8%. A significantly higher frequency of the e4 allele was found in individuals recording aggression/agitation in the month prior to interview ($\chi^2 = 6.69$, df = 2, p = 0.03). The additional risk for aggression/agitation conferred by e4 was also noted when e4 genotypes were compared against non-e4 genotypes ($\chi^2 = 5.45$, df = 1, p = 0.02, OR = 1.60, confidence interval (CI) 1.06 to 2.43). These results indicate that advanced Alzheimer's disease patients are at greater risk of aggressive symptoms because of a genetic weakness in apolipoprotein E.

By 2050, individuals over the age of 60 years are likely to make up about 30% of the population in developed countries.[1] The number of people with cognitive impairment is rising in the same way and the next 30 years will see an anticipated threefold increase in Alzheimer's disease (AD) sufferers in the US alone.[2] These changes are likely to put healthcare budgets under significant strain, especially with regard to the provision of nursing care.[3] Half of all patients diagnosed will need help with personal care, and one third will eventually be institutionalised.[4 5]

Intensive research into the pathophysiology of dementia has failed to identify disease modifying therapeutic agents; however, greater understanding of the components of dementia that finally necessitate admission to residential or nursing home care is also very necessary. Older dementia sufferers living alone, or those with greater functional disability seem more at risk.[6 7] Carer provision and coping skills are also important.[8–10] Other factors such as incontinence or falls will also influence the need for increased supervision and assistance.[11 12]

Dementia related behavioural change is a major independent risk factor for admission to institutional care.[13] Each 1 point increase in the Neuropsychiatric Inventory (NPI) behaviour rating scale costs up to US$400 per year in additional healthcare expense.[14] Aggressive symptoms are common in Alzheimer's disease, are poorly tolerated by carers, and directly contribute to the need for institutionalisation.[15 16] Aggressive behaviours are persistent and affect one fifth to half of all patients in cross sectional surveys.[17 18] They arise more commonly in middle and late phases of the clinical process and correlate with disease severity.[17 19]

It has been suggested that some behaviours result from known genetic risk factors for AD. If this were the case, behavioural symptoms would be seen to accompany conventional markers such as apolipoprotein E (ApoE). The role of ApoE alleles in the aetiology of depression in dementia has been largely negative,[20–26] although it may be wrong to attempt to connect the depressive phenotype that appears relatively early in the dementing process with traditional risk factors for AD. If AD related risk factors do mediate behavioural change then perhaps analysis should be directed at behaviours such as aggression and psychosis, which emerge after a prolonged period of neurodegeneration. The relationship between ApoE and risk of psychosis in AD has been mixed,[27–32] and the relationship between aggression and ApoE has been examined only in the context of mild to moderately demented AD patients.[20 28]

ApoE e4 confers considerable risk for AD and is associated with more rapid progression and greater cortical amyloid burden,[33–37] therefore good theoretical reasons exist for linking ApoE to the emergence of the aggressive phenotype that appears later in the clinical course.

We tested this hypothesis in a large cohort of advanced AD patients who were phenotyped for the presence of aggressive or agitated behaviour during the month prior to interview using the NPI with Caregiver Distress (NPI-D) scale, a validated tool for this research.[38]

METHODS

Ethical approval was obtained from the research ethics committee of Queen's University, Belfast. Informed written consent was obtained from next of kin, and where possible, from patients. Subjects were identified from outpatient memory clinic records based at the Belfast City Hospital Trust, Mater Infirmorum, and Holywell Hospital. Patients fulfilled the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable Alzheimer's disease.[39] Only patients with a carer who had contact at least 3 days a week for at least 3 years were included, to ensure reliability of data.

Abbreviations: AD, Alzheimer's disease; ApoE, apolipoprotein E (ApoE); FAST, Functional Assessment Staging; MMSE, Mini Mental State Examination; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NPI-D, Neuropsychiatric Inventory with Caregiver Distress; SPECT, single photon emission computed tomography

The subjects and main carer were interviewed by means of the Mini Mental State Examination (MMSE),[40] the NPI-D,[38] and Functional Assessment Staging (FAST).[41] Carers were asked for information on family history, personal history of psychiatric illness, and current/previous use of antipsychotic agents or cholinesterase inhibitors.

Genomic DNA was extracted from peripheral blood leukocytes by the salting out method.[42] ApoE genotyping was performed essentially as described.[43] Genotype and allele frequencies were compared by χ^2 analysis, which was also used to test whether the genotype frequencies deviated from the expected Hardy-Weinberg equilibrium. The level of statistical significance was set at $p = 0.05$. The extent of any interaction with previous psychiatric history and previous/current drug use was assessed using a multiple logistic regression model.

RESULTS

The mean (SD) age of participants was 78 (7.5) years, and 65.3% of the 400 participants were female. The average (SD) duration of illness at the point of sampling was 67.9 (41.2) months, and MMSE was 13.1/30 (9.2). The proportion of subjects with aggression/agitation in the month prior to interview was 51.8%. The proportion of participants' recording prior or current use of antipsychotic agents and cholinesterase inhibitors was 9.5% and 62.8% respectively. The relationship between genotypes and alleles of ApoE and baseline variables is shown in table 1. The distribution of genotypes following exclusion of the minor ApoE alleles did not differ significantly from that predicted by the Hardy-Weinberg equilibrium ($\chi^2 = 0.12$, df = 1, $p = 0.72$ when aggression/agitation was present and $\chi^2 = 0.11$, df = 1, $p = 0.724$ when aggression/agitation was absent).

A significantly higher frequency of the e4 allele was found in individuals recording aggression/agitation in the month prior to interview (table 2). The additional risk for aggression/agitation conferred by e4 was also noted when e4 containing genotypes were compared against non-e4 containing genotypes (table 2). Comparison of mean ages in those individuals without aggression/agitation and those with aggression/agitation of recent onset (within and including 24 months duration) were as follows: without aggression/agitation: mean age 78.8 (s.d. 7.4); with aggression/agitation: mean age 76.43 (s.d. 7.3). These differences were significant ($t = 2.77$, df = 294, $p = 0.006$).

Table 2 The ApoE genotype and allele frequencies for 400 AD patients with and without aggression/agitation

	Aggression/agitation			
	Present		Absent	
Genotype/allele	No.	%	No.	%
e2/e2*	2	1.0	3	1.6
e2/e3*	4	2.0	9	4.7
e2/e4*	8	3.8	5	2.6
e3/e3*	76	36.5	86	44.7
e3/e4*	89	42.8	72	37.5
e4/e4*	29	13.9	17	8.9
*$\chi^2 = 7.73$, df = 5, p = 0.17				
e2†	16	3.8	20	5.2
e3†	245	58.9	253	65.9
e4†	155	37.3	111	28.9
†$\chi^2 = 6.69$, df = 2, p = 0.03				
e2/e2+e2/e3+e3/e3‡	82	39.4	98	51.0
e2/e4+e3/e4+e4/e4‡	126	60.6	94	48.0
‡$\chi^2 = 5.45$, df = 1 p = 0.02, OR = 1.60, CI 1.06 to 2.43				

DISCUSSION

Over half our subjects showed aggression/agitation in the month prior to interview, thus confirming the frequent nature of these distressing symptoms, which act to raise the likelihood of carer breakdown and requirement for supervision and institutionalisation.[15 16] This report, in common with all analyses of this type, is limited by the reliability of the carer completing the NPI questionnaire, which operates retrospectively. However, it can be reasonably assumed, given the distressing nature of the symptoms, that carers are unlikely to forget the transition to aggressive or agitated behaviour. Reliability was further improved by excluding patients unable to provide a reliable carer for interview.

To our knowledge, this is the first report to show an increased risk for aggressive/agitated behaviour in advanced AD patients possessing the ApoE e4 allele (OR = 1.60, CI 1.06 to 2.43). Previous negative results may be explained on the basis of sampling error in mild to moderate AD patients.[20 28] ApoE is an accepted risk factor for AD and serves to lower the age of onset.[33 34] ApoE is associated with more rapid progression as measured by single photon emission computed tomography (SPECT) and higher tangle burden in the brain.[35–37 44] The accepted spread of neuropathological damage seen in AD, from the hippocampus to frontal-temporal-parietal regions, may encourage the development of those behavioural symptoms that not only localise regionally within the brain but are dependent on progressive neuronal loss and amyloid deposition away from the mesial temporal lobe. Frontal involvement is the best neuroanatomical correlate for aggression and agitation with secondary disruption of the serotonergic and dopaminergic systems.[45–48] High agitation scores correlate with bilateral orbitofrontal and left anterior cingulated tangle burden,[45] and with left frontotemporal hypoperfusion on SPECT scanning.[46] While overall MMSE scores were similarly low between ApoE genotypes (mean 13.1/30) in our study, the MMSE has little

Table 1 Baseline characteristics according to apoE status

	Genotype					
	2/2	2/3	2/4	3/3	3/4	4/4
Number	5	13	13	162	160	46
Female (%)	60.0	53.8	92.3	63.0	67.7	60.9
Age (years)	75.4	79.2	78.0	78.4	78.2	75.3
Duration/illness	75.6	110.3	81.1	63.6	68.9	62.5
MMSE (/30)	13.6	12.7	7.7	12.6	13.3	15.3
Positive FHx (%)	0	23.1	25.0	15.4	18.2	24.4
Prior psych Hx (%)	0	7.7	23.1	9.3	8.7	10.9
Prior or current use of Cholinesterase inhibitor	80.0	46.2	45.5	62.1	62.9	71.7
Antipsychotic agents	60.0	23.1	63.6	33.1	29.7	20.0

capacity to detect deficits in frontal lobe functioning. Importantly, the mean age of subjects with recent aggressive problems (and therefore less at risk of reporter bias) was significantly lower than the mean age of individuals without reported aggression, thus lending support to the theory that accelerated AD pathology resulting from ApoE e4 inheritance secondarily precipitates behavioural problems such as aggression.

There may be other relevant genetic modalities inducing aggression. Increased risk of aggression in individuals in possession of particular dopamine receptor and serotonin promoter polymorphisms was reported, without examination of the potentially crucial confounding influence of ApoE.[49–52] Investigating genetic risk factors for behavioural symptoms in dementia without accounting for the influence of ApoE is flawed as subclinical features may only become clinically relevant once a required period of neurodegeneration, mediated at least in part by ApoE, occurs.

Neuropsychiatric symptoms of dementia are burdensome for the patient and carer and expensive for healthcare systems. Given the therapeutic opportunity to target non-cognitive decline through improved understanding of ApoE neurobiology,[53] confirmation of these results is required in a longitudinal cohort followed until the late phase of AD.

ACKNOWLEDGEMENTS

Supported by an Alzheimer's Disease Society 3 year project grant (S P McIlroy, A P Passmore) and a British Geriatric Society Senior Registrar startup grant (D Craig).

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Competing interests: none declared

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Received 11 November 2003
Revised 16 December 2003
Accepted 19 December 2003

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