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ApoE Genotype and Family History in Patients With Dementia and Cognitively Intact Spousal Controls

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Objective: To test that a positive family history and ApoE ε4 genotype are prevalent among dementia patients with onset before 70 years of age compared with healthy spousal controls. *Methods:* A total of 210 patients with dementia and 82 spousal control participants. Neuropsychiatric examination, Consortium to establish a registry on Alzheimer's disease test battery, Clock-drawing Test, and ApoE genotyping were performed in patients and controls. *Results:* Of the 131 patients with Alzheimer dementia, 25 were homozygous for Apo ε4. Among dementia patients with a positive family history (n = 83), homozygosity for the Apo ε4 genotype was found in 19 (22.9%). A positive family history was highest among Apo ε4 homozygous Alzheimer dementia patients (72.0%) and lowest among the cognitively normal spousal controls (9.3%). *Conclusions:* In our sample of patients with Alzheimer dementia, approximately 3 of 4 (72.0%) were homozygous for the genotype Apo ε4 when they had a positive family history.

Keywords: dementia; Alzheimer's disease; ApoE; family history

Introduction

Apo ε4 and familial aggregation of dementia are major risk factors for dementia.[1-6] A dose-related effect of the Apo ε4 allele has been suggested for Alzheimer's disease (AD).[7,8]

No general agreement exists regarding what constitutes early-onset versus late-onset AD. Various investigators have used 60, 65, or 70 years as an arbitrary age limit. Most would agree that onset before age 60 is early and onset after age 70 is late.[9] Others emphasize that the late-onset form of AD is assumed to be multifactorial, whereas the early-onset form appears to be closely linked to genetic causes.[10] We chose the age of onset dementia before age 70 because it is known that only a few percentage of patients develop dementia before age 70. This makes a high genetic component more likely. A very late age of onset would make a multifactorial cause of the dementia more probable.

Concerning the impact of a positive family history on the risk of developing dementia before age 70, 1 study examined the family history of 198 AD patients with age of onset before 70 and 198 controls. A positive family history was found in 48% of cases and in 10% of controls. ApoE genotyping was not done in this study.[11]

It has not been studied so far what percentage of patients with onset of dementia before age 70 carry the Apo ε4 genotype. We tested the hypothesis that a positive family history and Apo ε4 are more prevalent among dementia patients with onset before 70 years of age compared with healthy spousal controls.

Methods

The study was approved by the ethics committee of the Regensburg University medical school. Family history data of 210 clinically diagnosed dementia patients with age of onset ≤70 and cognitively normal spousal control participants were collected

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Table 1. Characteristics of Patients With Dementia[a]

	E2/E2	E2/E3	E3/E3	E2/E4	E3/E4	E4/E4	Total
Number of patients	1	14	75	25	66	29	210
Diagnosis							
Alzheimer's disease (AD)	1	7	33	19	46	25	131
Vascular dementia (VD)	0	1	10	0	8	0	19
Frontotemporal dementia (FTD)	0	6	15	1	6	0	28
Lewy body dementia (DLB)	0	0	3	0	3	0	6
Mixed dementia (AD and VD)	0	0	4	4	3	4	15
Multisystem atrophy	0	0	1	1	0	0	2
Parkinson disease dementia	0	0	8	0	0	0	8
Olivopontocerebellar atrophy	0	0	1	0	0	0	1
Family history, number of patients							
Positive	1	3	20	13	27	19	83
Negative	0	11	55	12	39	10	127

[a] Further details are available on request from the corresponding author.

Table 2. Characteristics of Control Participants[a]

	E2/E2	E2/E3	E3/E3	E2/E4	E3/E4	E4/E4	Total
Number of control participants	0	12	33	1	8	0	54
Family history, number of patients							
Positive	0	1	4	0	0	0	5
Negative	0	11	29	1	8	0	49

[a] Further details are available on request from the corresponding author.

(Tables 1 and 2). Physical and neuropsychiatric examination followed. The neuropsychological assessment comprised the Consortium to establish a registry on Alzheimer disease (CERAD) test battery and the Clock-drawing Test. Mild cognitive impairment (MCI) was defined as probands with *z* scores below −1.5 in 1 or more CERAD subtests, despite normal Mini-Mental State Examination (MMSE) scores.[12] Alzheimer disease was defined by using the *International Classification of Diseases, Tenth Edition* (*ICD-10*), the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*), and the criteria of the National Institute of Neurologic and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). Vascular dementia (VD) was ascertained by using *ICD-10, DSM-IV*, the criteria of the National Institute of Neurological Disorders and Stroke—Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN), and the criteria of Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC). The scales of Hachinski and Rosen helped to distinguish between AD and VD. The diagnosis of mixed dementia was based on a consensus of these criteria. The Lund-Manchester and MC Keith criteria as well as the Frontal Behavioural Inventory (FBI) were used to diagnose frontotemporal dementia (FTD). Lewy body dementia (LBD) was defined by using the McKeith criteria.

ApoE genotyping was performed with the LightCycler real-time polymerase chain reaction (PCR) technology on genomic DNA isolated from whole EDTA-blood and a commercially available kit (LightCycler ApoE Mutation Detection Kit from Roche Diagnostics GmbH, Mannheim, Germany) allowing the analysis of the amino acid positions 112 and 158 in the ApoE protein.

Creatinine, electrolytes, aspartate aminotransferase (AST)/alanine aminotransferase (ALT), g-glutamyl transpeptidase (gGT)l, lipid profile, complete blood count, thyroid hormones, folate, vitamin B12, homocystein and HbA1c were also ascertained.

Results

Among the 210 dementia cases, 131 had AD and 15 had a mixed dementia (AD and VD). A majority of 128 of the dementia patients were widowed, divorced, or single. The control group consisted of 82 spouses with MMSE score $\geq$ 27. Consortium to establish a registry on Alzheimer disease examination showed 13 control participants to be affected by MCI

defined as above. Fifteen control participants with MMSE scores ≥ 27 refused to complete CERAD testing. These control probands were excluded from our analysis. Hence, the small number of 54 control participants.

Apo ε4 homozygous dementia patients suffered from AD (n = 25) or mixed dementia (n=4). Mean age at onset among Apo ε4 heterozygotes was 64.8 ± 5.2 years. It was 63.5 ± 6.4 years for Apo ε4 homozygotes. Mean age at onset in all patients with dementia was 62.6 ± 7.5 years. The mean age at testing of the cognitively intact spousal controls was 65.6 ± 8.5 years. Average age at examination of the 210 patients with dementia was 67.3 ± 7.7 years.

A positive family history was defined as at least one first- or second-degree relative affected by dementia. A positive family history of dementia was present in 43.2% for Apo ε4 heterozyous dementia patients (AD and other dementia patients combined) and in 65.5% for Apo ε4 homozygous dementia patients (AD and other dementia patients combined).

The overall proportion of probands with AD (n = 131) and a positive family history was 44.3% (n = 58). It was lowest among AD participants without Apo ε4 (30.9%) and increased for Apo ε4 heterozygotes (45.1%). A positive family history was highest among Apo ε4 homozygotes (72.0%). Only 9.3% (n = 5) of the controls (n = 54) reported a relative suffering from dementia.

Discussion

The primary aim of our study was to explore the relationship between Apo ε4 and familial history among dementia patients with onset until 70 years of age. Contrarily to other studies, spousal controls were screened by the CERAD test battery. The MMSE is insufficient to diagnose early cognitive difficulties. Earlier studies might not have detected probands with MCI among their normal controls examined only by the MMSE. Our rigorous definition of cognitively normal controls and exclusion of spousal controls with MCI might explain the low percentage of positive family history among cognitively intact controls. Additionally, the low prevalence of a positive family in controls may be partly attributed to recall bias.

The risk of dementia increases significantly by the number of Apo ε4 alleles.[7,8] Patients with dementia were twice as often heterozygous for the Apo ε4 genotype compared with controls. Thus, our results agree with those of Rippon et al (2006), who obtained a nearly 2-fold increased risk (1.7) of AD for Apo ε4 heterozygotes. The risk for Apo ε4 homozygotes was 2.3.[13]

Our data strengthen the hypothesis that Apo ε4 exerts its maximal effect before age 70 years.[14] In our study, probands homozygous for Apo ε4 also had a lower age at onset (63.5 ± 6.4 years) than individuals heterozygous for Apo ε4 allele (64.8 ± 5.2 years). The proportion of dementia patients with a family history of dementia rose according to the number of Apo ε4 alleles. Regardless of the dementia type, family history of dementia was present in 29.9% of dementia patients without Apo ε4 and increased to 43.2% and 65.5% for Apo ε4 heterozygotes and homozygotes, respectively. In patients with AD, the association between Apo ε4 and family history was even more intriguing. The proportion of AD participants without Apo ε4 and a positive family history was 30.9%, whereas for Apo ε4 homozygotes it rose to 72.0%. In cognitively intact spousal controls, a positive family was documented in 9.3%. None of the control group was homozygous for Apo ε4. Thirteen of the spousal controls had to be excluded because of CERAD test results consistent with the diagnosis of MCI. Two of these MCI probands with a normal MMSE score ≥ 27 were homozygous for Apo ε4. Clinically these 13 probands had not complained about cognitive impairment. The categorization as MCI was solely based on the cutoff $z \leq -1.5$. This again is an arbitrarily chosen cutoff. Nevertheless, using the CERAD and a z score defines MCI more accurately than the MMSE.

Our results will need to be repeated in a larger sample using the same rigorous definition of cognitively intact spousal control probands. The MMSE alone was found to be insufficient to define a normal control sample.

In our sample of patients with AD, approximately 3 of 4 (72.0%) were homozygous for the genotype Apo ε4 when they had a positive family history. Our results highlight the contribution of Apo ε4 to familial aggregation among younger persons with AD.

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