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Important Link between Dementia Subtype and Apolipoprotein E: a Meta-analysis

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To evaluate the differential diagnostic role of apolipoprotein E (apoE) genotype in dementia, we carried out a meta-analysis of 78 case-control series, including our own new data. The dementia subjects were grouped into Alzheimer's disease (AD) and non-AD. AD patients were subgrouped according to their subtypes, and non-AD patients into vascular dementia (VD), mixed dementia (MD), and non-AD non-VD dementia (NAVD). The apoE allele frequencies and apoE genotype-specific odds ratio (OR) of each group were estimated. The (4 allele frequency was higher in all of the dementia subgroups than in the elderly controls, and the associations with (4 allele were lower in the non-AD (OR 1.8) patients than in the AD (OR 4.2) patients. However, the apoE-related risk alsovaried as a function of the subgroup, in both the AD and non-AD groups; for AD, it was dependent on the subtype of AD (OR 2.3 - 11.3), and higher in late-onset and familial cases than in early-onset and sporadic cases, respectively; among non-AD patients, it was higher in MD (OR 2.6) than in VD (OR 1.3), and intermediate in NAVD (OR 1.9), in which a significant difference was also found between Lewy body dementia (LBD) type (OR 5.1) and non-LBD type (OR 1.3). In conclusion, variability in the apoE-related risk was found in both the AD and non-AD cases, depending on the subgroup. Therefore, precise subgrouping of both AD and non-AD patients should be performed, and this information should taken into consideration when interpreting the results of apoE genotyping.

Key Words: Dementia, alzheimer's disease, apolipoproteins E, meta-analysis

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INTRODUCTION

Many studies suggest that apolipoprotein E (apoE) is associated with an increased risk of Alzheimer's disease (AD), and there is a general consensus that apoE ε4 is a genetic risk factor of AD. However, because AD develops in the absence of the ε4 allele, and many people with the ε4 allele seem to escape from this disease, it is not recommended for use in routine clinical diagnosis, nor should it be used for predictive testing.[1,2] Presently, apoE genotyping is suggested to play a major role in the differential diagnosis of AD from non-AD dementia, such as vascular dementia (VD) and non-AD non-VD dementia (NAVD), in cognitively impaired patients.[3]

However, the role of apoE genotyping in the differential diagnosis of dementia remains unclear, and may have been underestimated for reasons which will be outlined below. In spite of many studies having been done on apoE genotyping in both AD and non-AD dementia, some uncertainty remains concerning the ε4 allele frequencies of patients with non-AD dementia. Moreover, the strength of the association of AD with apoE ε4 allele varies considerably from study to study. These uncertainties limit the role of apoE genotyping in dementia subjects. The strength of the association of AD with the ε4 allele, may depend on the subtype of AD, and that of non-AD with the ε4 allele on the subgroup of non-AD dementia. The usefulness of apoE genotyping may be underestimated when it is crudely applied to differentiate AD from non-AD dementia, and precise subgrouping of both AD and non-AD dementia may be necessary before such

genotyping can play a useful role.

Therefore, we divided both AD and non-AD dementia patients into subgroups and carried out a meta-analysis of published, as well as of our own new data, in order to examine the apoE allele frequency and the apoE-related risk in each dementia subgroup. The results indicated that the apoE ε4 allele frequency was higher and that the ε2 allele frequency was lower in all of the dementia subgroups than in the elderly controls, but that the association between each dementia subgroup and the ε4 allele was different, suggesting the possible role of apoE genotyping in the differential diagnosis of dementia.

MATERIALS AND METHODS

New data

During the period from 1997 to 1999, 174 demented patients were consecutively treated at our hospital. The diagnosis of 'probable AD' was made using the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA),[4] whereas the diagnoses of VD and mixed dementia (MD) were made using the criteria of the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN),[5] and the diagnosis of NAVD was made using their own criteria.[6,7] Neuroimaging and laboratory studies to rule out any other causes of dementia were carried out in all cases. One hundred and sixty-nine age-matched elderly subjects, with 24 points or more on the Mini-Mental State Examination and who showed no evidence of neurological deficit on examination, served as controls. DNA isolated from peripheral blood leukocytes was amplified by PCR along with an upstream primer of 5'-TAAGCTTG GCACGGCTGTCCAAGAA-3' and downstream primer of 5'-ACAGAATTCGCCCCGGCCTGGT ACAC-3'.8 The PCR products were digested with restriction enzyme HhaI, the fragments were separated by electrophoresis on 4% ethidium bromide-containing agarose gel, and DNA fragments were visualized by ultraviolet illumination. ApoE genotypes of the patients and controls were determined in a blinded fashion by scoring a unique combination of fragment sizes.[8]

Meta-analysis

We performed a meta-analysis using previously published information about dementia subtypes and apoE genotypes as well as our own new data. Studies listed on the OVID Medline computer database until Jan 2000 were selected using 'apolipoproteins E' and 'Alzheimer's disease' or 'dementia' as key words. Whenever there was a possibility of two separate publications referring to the same samples, we selected either the one which included the greater number of cases or the one containing the more precise information. Subjects were categorized by a variety of ethnic designations and by clinical or pathologic diagnosis. Caucasian and East Asian patients were classified into separate groups, because of the following reasons; Firstly, there are several reports which indicate that there are differences in apoE allele frequency and in the patterns of association with AD.[9,10] Secondly, the distribution of dementia subgroups may vary according to ethnicity.[11] Lastly, the diagnostic criteria of each dementia subgroup, especially in the case of VD, are different for each ethnic group. Reports involving patients of other ethnicities (Hispanics and Blacks) were excluded from this study, because only a few such reports on non-AD dementia were available.

First, we investigated the association between AD and apoE locus in each subtype of AD. Using an age cut-off of 65 years and based on family history, subjects were separated into sporadic late-onset AD (SLOAD), sporadic early-onset AD (SEOAD), familial late-onset AD (FLOAD) and familial early-onset AD (FEOAD) subgroups. We restricted the FEOAD subgroup to those patients without mutations in the amyloid precursor protein (APP) and presenilin (PS) gene on chromosomes 21, 14, and 1. In this analysis, Caucasians were further divided into two separate groups, Southern European and Northern European/American, because differences in the apoE allele frequency in both elderly control and AD

have been reported.[9,12] We then investigated the apoE-related risk of each subgroup of dementia. Subjects were categorized by a variety of ethnic designations and by clinical or pathologic diagnosis (elderly control, AD or non-AD dementia including VD, MD and NAVD). NAVD was further divided into Lewy body dementia (LBD) type and non-LBD type, because the ε4 allele frequency was reported to be high in LBD.[13]

Statistical analysis was performed by Pearson's Chi-square test to compare the ε4-carrier frequencies by diagnostic category and ethnic group. The influence of the apoE genotype on the odds of developing AD or non-AD was assessed using unconditioned logistic regression with the program SPSS. We estimated the odds ratios (OR) and 95% confidence intervals (CI) associated with the εand ε2 alleles. Those without this allele were used as the respective reference category, without multiplicative assumption. Overall tests of significance and confidence limits were computed in the usual way.[14] A p-value of < 0.05 was considered significant.

RESULTS

New data and studies included in this meta-analysis

The apoE genotype distribution and allele frequencies of our new cases are shown in Table 1. The frequency of the ε4 allele was higher in the AD group (24.6%) and the MD group (22.2%) than in the non-demented elderly control group (10.1%). This was not the case for either the VD group (8.1%) or the NAVD group (11.8%).

Seventy-eight studies, including our new data, were included in this meta-analysis,[13,15-90] and the numbers of patients in each dementia subgroup and apoE allele frequencies are summarized in Table 2. A total 10,654 elderly controls, 7,812 AD patients, and 1,272 patients with non-AD dementia were included; among 19,738 subjects included

Table 1. Our New Data on Age, Sex, and Distribution of ApoE Genotypes and Allele Frequencies in Demented Patients and Elderly Control Subjects

	Elderly controls	Alzheimer's disease	Mixed dementia	Vascular dementia	Non-AD non-VD dementia*
N	169	71	18	68	17
Age (mean±SD)	68 ± 7	73 ± 8	81 ± 5	74 ± 8	77 ± 9
Sex (M:F)	97 : 72	29 : 42 : 00	7 : 11	36 : 32 : 00	12 : 05
Genotype distribution					
ε2 ε2	0	0	0	1	0
ε2 ε3	9	4	3	7	0
ε3 ε3	129	36	8	49	13
ε2 ε4	3	3	0	0	0
ε3 ε4	25	24	6	11	4
ε4 ε4	3	4	1	0	0
Allele frequency (%)					
ε2	3.6	4.9	8.3	6.6	0
ε3	86.3	70.5	69.4	85.3	88.2
ε4	10.1	24.6	22.2	8.1	11.8

*Three cases each of frontotemporal dementia, Lewy body dementia and idiopathic Parkinson's disease with dementia, two cases of other degenerative dementia, and six cases of other dementia.
AD, Alzheimer's disease; VD, vascular dementia.

Table 2. The Apoe Allele Frequencies in Each Subgroup of Dementia and for the Elderly Controls: Meta-analysis of 78 Studies

Grouping	N	ApoE allele frequency (%)		
		ε 2	ε 3	ε 4
Non-demented control				
Clinically diagnosed	10654	7.3	80.4	12.3
Caucasian	5444	8.2	77.6	14.2
Southern European	2963	7.6	81.4	11
East Asian	2247	5.4	85.4	9.2
Pathologic-confirmed	459	7.4	79.5	13.1
Alzheimer's disease				
Clinically diagnosed	7263	3.6	64.3	32.1
(1) Ethnic groups				
Caucasian	3484	3.7	56.9	39.4
Southern European	1811	2.7	67	30.3
East Asian	1470	3.2	70	26.8
(2) Subtypes				
Sporadic late-onset	3505	3.5	65.3	31.2
Familial late-onset[a]	566	3.2	48.9	47.9
Sporadic early-onset	918	4.2	72	23.8
Familial early-onset[b]	231	3.7	59.7	36.6
Pathologic-confirmed	549	4.1	59.7	36.2
Non-AD dementia				
(1) Vascular dementia	786	4.8	79.9	15.3
Caucasian	371	5.7	74.2	20.1
East Asian	415	4.5	82	13.5
(2) Mixed dementia	153	4.9	70.8	24.3
Caucasian	111	5	63.3	31.7
East Asian	42	4.8	76.2	19
(3) Non-AD non-VD dementia	333	7	76.3	16.7
Caucasian	295	8.3	75.2	16.5
East Asian	38	2.6	80.3	17.1
Pathologic-confirmed	141	8.4	65.8	25.8
Non-Lewy body dementia	80	9	71.6	19.4
Lewy body dementia	61	7.6	55.1	37.3

AD, Alzheimer's disease; VD, vascular dementia.
[a]first-degree relatives with dementia ≥ 2.
[b]first-degree relatives with dementia ≥ 2 and no known mutations in the APP and PS gene on chromosome 21, 14, 1.

in this meta-analysis, 77% of the subjects were Caucasian and 23% East Asian.

The association between AD and apoE ε4 allele for each subtype of AD

The association between AD and apoE genotype was evaluated for each subtype of AD. The ApoE allele frequencies and the odds of acquiring AD associated with the carrying one or two ε4 alleles were compared in each group, based on ethnicity and the subtype of AD (Table 2 and Fig. 1A). The relative increase in the frequency of apoE ε4 in the AD group compared with the control group was observed in all subtypes of AD and in all ethnic groups ($p<0.05$). However, significant differences were observed in both the ε4 allele frequency and the OR of AD between the different subtypes of AD ($p<0.01$). The ε4 allele was more prevalent in the late-onset than in the early-onset AD group. Among the patients with late-onset AD, the ε4 allele was more frequent in familial cases (47.9%) than in sporadic cases (31.2%). Among the patients with early-onset AD, the ε4 allele frequency was greater in the FEOAD group (36.6%) than in the SEOAD group (23.8%). We also estimated the OR of AD associated with carrying the ε4 allele in each subtype of AD. It was found to be the highest in the FLOAD group (11.3), the lowest in the SEOAD group (2.3), and intermediate in the FEOAD and SLOAD groups (3.9 and 3.8, respectively). Such findings were consistently observed in all of the ethnicities tested. In all of the groups, based on ethnicity and subtype of AD, the odds of acquiring AD associated with the carrying of two ε4 allele (OR

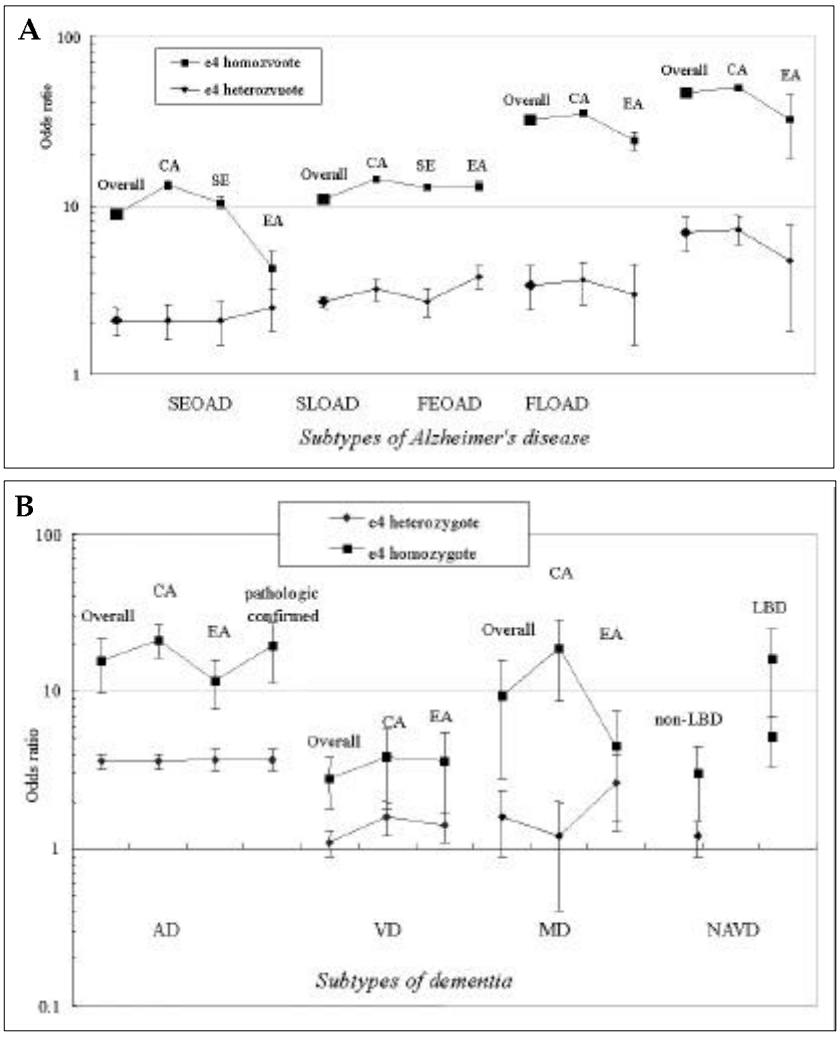

Fig. 1. Odds ratio of each subtype of dementia for each apoE genotype: meta-analysis of 78 studies. (A) Each subty pe of Alzheimer's disease, (B) Each subtype of dementia. CA, Caucasian; SE, Southern European; EA, East Asian. SEOAD, sporadic early-onset cases; SLOAD, sporadic late-onset cases; FEOAD, familial early-onset cases; FLOAD, familial late-onset cases.
AD, Alzheimer's disease; VD, vascular dementia; MD, mixed dementia; NAVD, non-AD non-VD dementia; LBD, Lewy body dementia.

2.1 - 6.9) were 4 - 10 fold higher than those associated with the carrying of only one ε4 allele (8.9 - 46.3), suggesting the existence of a gene-dose effect (Fig. 1A).

Among the 7,812 AD cases, 54% were derived from hospital-based studies, 37% from community-based studies and 8% from pathologic studies. The odds of acquiring AD for an ε4-carrierwere independent of the ascertainment schemes (the sources of the subjects) of the studies: Community-based study (OR 3.9 CI 3.4 - 4.5, $p<0.01$), hospital-based study (OR 4.4 CI 3.9 - 5.2, $p<0.01$), and pathologic study (OR 4.7 CI 3.6 - 6.2, $p<0.01$).

The ApoE ε2 allele was less prevalent in the AD group and significantly associated with a reduced OR for AD in all ethnic groups (OR 0.4 for Caucasian, 0.3 for Southern European and 0.6 for East Asian, $p<0.01$) and all subtypes of AD (OR 0.4 for FLOAD and 0.5 for the others, $p<0.01$).

The association between AD and apoE ε4 allele for each dementia subgroup

The ε4 allele frequencies were also increased in the non-AD dementia group compared with the elderly control group for both the Caucasian and East Asian subjects ($p<0.05$). However, the ε4 allele was less prevalent in the VD (15.3%) and NAVD (16.7%) groups than in the AD (32.6%) or MD (24.3%) groups for both ethnicities (Table 2). The ε2 allele frequency was lower in the demented subjects (3.5% in AD and 4.8-7.0% in non-AD dementia) than in the elderly controls (7.4%), except in the case of the Caucasian NAVD subjects.

The odds of acquiring non-AD dementia associated with the carrying of the ε4 allele were also significantly increased (OR 1.3, CI 1.1 - 1.5 of ε4 heterozygote carrier and OR 3.7, CI 2.6 - 5.2 for ε4 homozygote carrier, $p<0.01$ for both), but to a lesser degree than the AD group (OR 3.1, CI 2.9 - 3.4 of ε4 heterozygote carrier and OR 15.9, CI 13.2 - 19.2 for ε4 homozygote carrier, $p<0.01$ for both). The strength of the association between non-AD dementia and the ε4 allele varied significantly, depending on the subgroup of dementia (Fig. 1B). It was strong in the MD group (OR 2.6, CI 1.7 - 4.0) and weak in the VD group (OR 1.3, CI 1.6). The strength of the association between NAVD and the ε4 allele was intermediate (OR 1.9, CI 1.4 - 2.4), but varied as a function of the type of NAVD; it was strong for the LBD type (OR 5.8, CI 3.4 - 9.7) and weak for the non-LBD type of NAVD (OR 1.3, CI 1.1 - 1.7). As for the ethnicity, the OR associated with the ε4 allele did not differ significantly between the Caucasian and East Asian subjects.

DISCUSSION

The association between AD and apoE ε4 allele for each subtype of AD

Although a plethora of studies have revealed an increased risk of AD for carriers of the apoE ε4 allele, the strength of this association varies considerably from study to study. This variation may be due to differences in the ascertainment of the cases (clinic versus population-based),[82] the diagnostic criteria used, and the limited size of certain studies. However, factors other than selection bias may also be at work. For example, it is well known that the association of apoE ε4 with AD is age- and sex-dependent,[21,91,92] and factors such as ethnicity,[91] serious head injury,[93] smoking,[94] cholesterol level[95] and estrogen[96] may also modify the apoE-related risk.

The association of AD with the ε4 allele may differ depending on the subtypes of AD, and an estimation of the odds of acquiring AD associated with the carrying of the ε4 allele based on a specific AD subtype, rather than that based on age or sex, is required for most practical purposes. However, there are two conflicting results,[97,98] regarding the effects of AD subtype on the association between the apoE genotype and AD. These two studies used different diagnostic criteria of familial AD and did not consider the effect of ethnic variations, thereby introducing selection bias in the estimation of subtype-specific AD-apoE association. Therefore, in the present study we minimized this bias by several means. Firstly, when AD was diagnosed with homogenous diagnostic criteria, the strength of the association between the apoE ε4 allele and AD was found to be independent of the sources of the cases. Sec-

ondly, we included more cases than the previous studies and restricted familial AD cases to those without mutation in the APP and PS genes. Lastly, we individually evaluated the association between subtype of AD and apoE genotype for each ethnicity.

Our results showed a significant variation in the apoE ε4 allele frequencies and ε4 allele associated OR among each subtype of AD. The ε4 allele frequency and ε4 associated OR were high in familial cases and late-onset AD, and the subtype-related trend in the risk of AD among ε4 heterozygote or homozygote carriers showed a consistent pattern for each ethnicity.

Our familial cases without known autosomal dominant mutations exhibited an increased ε4 allele frequency and stronger apoE-AD association than the sporadic cases, suggesting that the apoE ε4 allele played a role in these patients. Although the existence of a first-degree relative with dementia remains one of the most important risk factors for late-onset AD[99], familial cases without mutation in the APP and PS genes did not reveal an obvious pattern of transmission. This might be explained by the fact that the highest apoE ε4-AD association was found in familial AD patients. Several studies suggested the existence of a possible interaction between the apoE genotype and environmental risk factors for AD, including cholesterol and head trauma.[93-96] Such gene-environmental interactions may influence apoE-AD association, especially in sporadic cases. In addition to gene-environmental interactions, numerous studies have been done, which were focused on gene-gene interactions, but no genetic link between apoE polymorphism and the PS-1 gene[32] or APP gene[97] was found, and the question of whether there is any interaction between apoE and the putative susceptibility genes remains controversial.[15,19,26,29,46,50,53,55,86-88]

The association between AD and apoE ε4 allele for each dementia subtype

In reviewing the literature, the ε4 allele frequencies in the case of non-AD dementia is found to be variable and it is still not clear whether the ε4 allele is associated with this type of dementia, because of the small sample sizes of the studies. Our meta-analysis, representing nearly 16,000 apoE alleles of AD and 2,600 apoE alleles of non-AD dementia, demonstrated increased ε4 allele frequencies and a significant association with the ε4 allele in all subgroups of dementia in both Caucasian and East Asian subjects.

However, in the present study, there was a significant difference in the ε4 allele frequency and the apoE-related risk among the subgroups of dementia. Firstly, in our meta-analysis, the ε4 allele frequency was lower in the VD than in the AD group for both Caucasian and East Asian subjects. Demented subjects who carried the ε4 allele had a 3-fold greater probability of acquiring AD than VD. Although different criteria were used for diagnosing VD depending on the ethnicity, this trend was observed in both ethnic groups. Secondly, the ε4 allele frequency of the NAVD subjects was lower than that of the AD subjects for both ethnic groups. The ε4 allele frequency of the NAVD group was lower in the Caucasian than in the East Asian subjects. This might have been due to the difference in the proportion of LBD, which was two times higher in the East Asian than in the Caucasian subjects. The ε4 allele frequency of LBD was previously reported to be high,[13] and this was the case in both the Caucasian and East Asian groups in the present meta-analysis. Therefore, for patients who have been clinically diagnosed as suffering from NAVD are found to have the (4 allele, LBD should be suspected. Lastly, the (4 allele frequency of MD was the highest in the non-AD dementia group. Therefore, for patients who have been clinically diagnosed as suffering from VD are found to have the ε4 allele, MD should be suspected.

ApoE genotyping as a differential diagnostic aid for patients with dementia

ApoE genotyping does not provide sufficient sensitivity or specificity to be used singularly as a diagnostic test for Alzheimer's disease.[100,101] Furthermore, there are some conflicting reports on the role of apoE genotyping and its implication in the differential diagnosis of dementia.[100-102]

However, when used in combination with clinical criteria, it may provide valuable improvement in the differential diagnosis of dementia.[100] In-

deed, several pathologic-confirmed studies suggested that apoE genotyping provides an adjuvant laboratory diagnostic aid which can be used in conjunction with the clinical criteria used in the differentiation of AD from non-AD dementia.[39,100-105] When used with conventional clinical criteria, the presence and absence of the ε4 allele significantly increased diagnostic confidence, by 10 - 30%, in all clinical criteria with varying accuracy of AD and non-AD, respectively.[39,100-105]

The role of apolipoprotein E genotyping in demented subjects may be underestimated

The introduction per se of apoE genotyping to clinical criteria to differentiate AD from non-AD may be insufficient in the differential diagnosis of demented subjects. As shown in Fig. 2, the subtype-related variation in the OR for the AD group (ranging from 2.3 to 11.3) and the subgroup-related variation in the OR for the non-AD dementia group (ranging from 1.3 to 5.8) were greater than the difference in the ORs of the AD (OR 4.2) and non-AD dementia (OR 1.8) groups. Therefore, the clinical criteria used for the differentiation of AD from non-AD dementia may not be sufficient, and the role of apoE genotyping in the differentiation of dementia subtypes may be underestimated. The present results suggest that the AD subtype in clinically diagnosed AD needs to be clearly identified, and that the clinical differentiation of non-AD dementia into those with and without Alzheimer's pathology, such as DLB or MD, should be performed, thereby amplifying the role of apoE genotyping in the differential diagnosis of dementia. When the precise clinical subgrouping of demented subject was performed, the probability of pathologically-confirmed AD may increase or decrease, by more than 10 - 30%, depending on the presence and absence of the ε4 allele, respectively.

To obtain the exact degree of improvement, further pathologic studies, together with clinical information on the dementia subgroup, are required. Until this information is available, a careful history taking to delineate the dementia subtypes should precede the interpretation of the apoE genotype. As for the patients clinically diagnosed as suffering from non-AD dementia, especially in the following two illustrations, ApoE genotyping should be considered; Firstly, those patients who have definitive history of or for whom there is neuroradiological evidence of ischemic lesions, but who experience progressive worsening of cognitive functions; Secondly, those patients with progressive worsening of cognitive

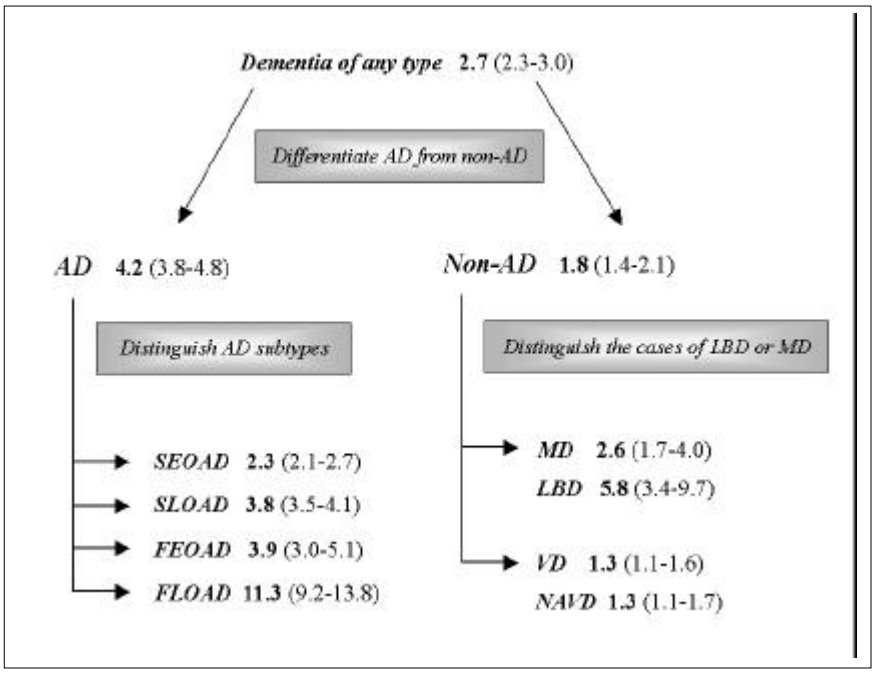

Fig. 2. Variation in the odds ratio for each subtype of dementia associated with the carrying of apoE ε4 in demented subjects. Odds ratio (95% confidence interval) for carrying ε4 allele. AD, Alzheimer's disease; VD, vascular dementia; MD, mixed dementia; LBD, Lewy body dementia.
SEOAD, sporadic early-onset cases; SLOAD, sporadic late-onset cases; FEOAD, familial early-onset cases; FLOAD, familial late-onset cases.

worsening of cognitive functions, but some typical features of LBD. When those patients were ε4 homozygote carriers, one should suspect a possibility of coexisting Alzheimer's pathology, such as MD (OR 9.3, CI 4.1 - 21.0) or LBD (OR 16.0, CI 6.4 - 40.0). As for those patients clinically diagnosed as suffering from AD, the presence of the apoE genotype might have much less diagnostic value in those patients clinically diagnosed as having SEOAD than in those with a family history of dementia or with their onset after they were 65 years-old.

Limitations

The present study has some limitations. Firstly, variations in the odds ratio of AD related to age and gender have been reported,[91] however, we could not use these factors as covariants in calculating the ORs. Therefore, the apoE ε4-associated AD risk was examined in a relatively crude fashion, such as by AD subtype. Secondly, not all of the clinical diagnoses included in this study were confirmed by autopsy, therefore some of them might have been inaccurate. Further studies involving more pathologically confirmed non-AD dementia cases are needed. Lastly, we were not able to estimate the exact extent of the improvement in the predictive value which was provided by both apoE genotyping and precise subgrouping of AD and non-AD dementia. Rather, we were only able to conclude that the differential diagnostic role of apoE genotyping was underestimated by at least 10 - 30%. Most of the pathologic data do not provide any information on the clinical subgrouping of either AD (information about AD subtype) or non-AD dementia (includes the clinical criteria of LBD or MD). Further studies with more precise information on the clinical subgrouping, pathological diagnosis and apoE genotyping may remedy the above mentioned shortcomings.

In conclusion, the apoE ε4 allele is associated with all subtypes of dementia, but the degrees of association are dependent on the subtypes of AD and the subgroups of non-AD dementia. These differences may aid and should be taken into consideration when apoE genotyping is applied in the differential diagnosis of dementia.

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