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Rates of Progression in Patients with Alzheimer's Disease Depending on Apolipoprotein E Genotype and Concomitant Medications

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CONCLUSION

Various concomitant medications and comorbidities might affect the cognitive and functional outcomes of Alzheimer's disease (AD) differently depending on apolipoprotein E (APOE) genotype. APOE ε4-carriers, but not non-ε4-carriers, who received lipid-lowering agents showed a slower cognitive decline than nonusers. Because the APOE ε4 allele is known to be associated with higher cholesterol levels and has been implicated in AD-related processes, such as beta-amyloid burden and inflammation, ε4-carriers may benefit more from use of statins. A risk factor for faster cognitive decline among APOE ε4-carriers only was treatment with anxiolytics/sedatives/hypnotics, suggesting that these individuals might be more prone to the related adverse effects. In non-ε4-carriers, neuropsychiatric symptoms were risk factors for faster functional deterioration, particularly in Instrumental Activities of Daily Living (IADL), which is an important measure of independent living.

BACKGROUND

The APOE ε4 allele is associated with higher cholesterol levels, and an increased risk of developing AD and amyloid-related imaging abnormalities after initiation of amyloid-modifying therapies. A worse cognitive response to cholinesterase inhibitor (ChEI) treatment and longitudinal outcome in APOE ε4-carriers has been observed. Based on these clinical findings, cholesterol and the APOE ε4 allele may affect beta-amyloid burden, metabolism, and inflammation in the brain. Younger age at onset and at diagnosis of AD have also been reported in APOE ε4-carriers. Younger persons usually have less comorbidity and fewer concomitant medications that may affect the outcome of AD. This longitudinal study examined potential differences in cognitive and functional progression rates in AD between patients with different APOE genotypes and concomitant medications.

METHODS

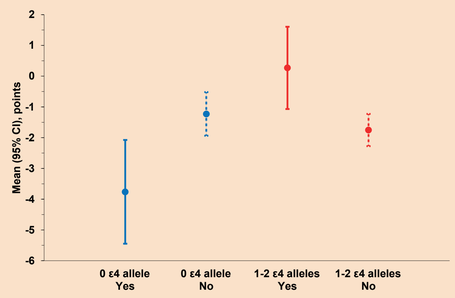
The Swedish Alzheimer Treatment Study (SATS) is a prospective observational clinical practice-based multicenter study for evaluation of long-term effectiveness of ChEI therapy. Here, 999 outpatients (320 APOE non-ε4-carriers and 679 ε4-carriers) clinically diagnosed with mild-to-moderate AD (Mini-Mental State Examination [MMSE] score, 10–26) at the start of ChEI treatment (baseline) were enrolled. Participants were assessed for cognitive (MMSE) and functional performance ([IADL] and Physical Self-Maintenance Scale [PSMS]) at baseline and every 6 months for 3 years. Independent-sample *t* tests were performed to compare the differences between the means obtained for two groups, and χ^2 tests were computed to analyze categorical variables (Table 1). Univariate general linear models were used to investigate whether usage of specific concomitant medications (antihypertensive/cardiac therapy, antidiabetic drugs, asthma medication, thyroid therapy, lipid-lowering agents, estrogens, nonsteroidal anti-inflammatory drugs/acetylsalicylic acid, antidepressants, antipsychotics, and anxiolytics/sedatives/hypnotics) affected the rates of disease progression in patients with or without the APOE ε4 allele. The outcomes were adjusted for sex, age at baseline, years of education, and cognitive and functional abilities at baseline (Figures 1–4).

RESULTS

Table 1. *Baseline characteristics by APOE genotype (n = 999).*

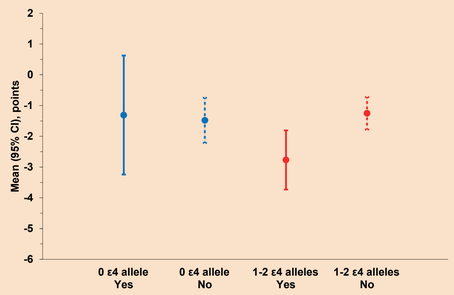
	No APOE ε4 alleles	1 or 2 APOE ε4 alleles	*p* value
Number of patients (*n*/%)	320/32%	679/68%	
Female sex	55%	69%	**<0.001**
Antihypertensive/cardiac therapy	42%	40%	0.494
Antidiabetics	7%	4%	**0.026**
Asthma medication	5%	4%	0.765
Thyroid therapy	8%	8%	0.885
Lipid-lowering agents	10%	13%	0.153
Estrogens	8%	7%	0.612
NSAIDs/acetylsalicylic acid	29%	30%	0.609
Antidepressants	22%	27%	0.115
Antipsychotics	3%	5%	0.149
Anxiolytics/sedatives/hypnotics	13%	15%	0.470
	Mean ± standard deviation		
Estimated age at onset, years	73.7 ± 7.0	71.4 ± 7.4	**<0.001**
Age at first assessment (baseline), years	76.5 ± 6.7	74.5 ± 7.1	**<0.001**
Estimated duration of AD, years	2.9 ± 1.9	3.1 ± 2.1	**0.037**
Education, years	9.2 ± 2.3	9.6 ± 2.6	**0.021**
MMSE score (range, 0–30)	21.2 ± 3.8	21.5 ± 3.7	0.168
IADL score (range, 8–31)	16.5 ± 5.4	15.6 ± 5.5	**0.012**
PSMS score (range, 6–30)	7.9 ± 2.5	7.3 ± 2.1	**<0.001**

Figure 1. *MMSE score, annual change from baseline by interaction of APOE genotype with lipid-lowering agents.*



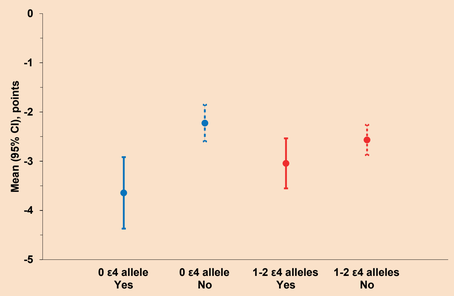
Annual cognitive decline measured by MMSE score was faster in APOE non-ε4-carriers receiving lipid-lowering agents vs. nonusers, mean (95% CI) −3.8 (−5.4, −2.1) vs. −1.2 (−1.9, −0.5) points, ($p = 0.036$). In contrast, cognitive progression rate was slower in ε4-carriers receiving lipid-lowering agents vs. nonusers, 0.3 (−1.1, 1.6) vs. −1.8 (−2.3, −1.2) points, ($p = 0.006$).

Figure 2. *MMSE score, annual change from baseline by interaction of APOE genotype with anxiolytics/sedatives/hypnotics.*



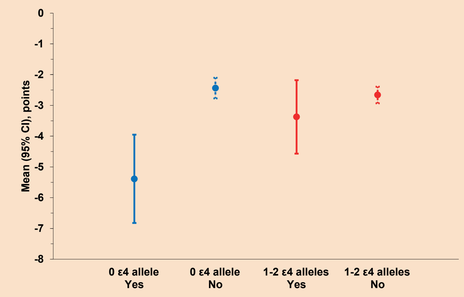
Cognitive decline per year measured by MMSE score was faster in APOE ε4-carriers receiving anxiolytics/sedatives/hypnotics vs. nonusers, mean (95% CI) −2.8 (−3.7, −1.8) vs. −1.3 (−1.8, −0.7) points, ($p = 0.034$); this difference was not found in non-ε4-carriers receiving anxiolytics/sedatives/hypnotics vs. nonusers, −1.3 (−3.2, 0.6) vs. −1.5 (−2.2, −0.7) points, ($p = 0.871$).

Figure 3. *IADL score, annual change from baseline by interaction of APOE genotype with antidepressants.*



A faster annual progression rate in IADL was demonstrated in APOE non-ε4-carriers receiving antidepressants vs. nonusers, mean (95% CI) −3.6 (−4.4, −2.9) vs. −2.2 (−2.6, −1.9) points, ($p < 0.001$); this difference was not observed in ε4-carriers receiving antidepressants vs. nonusers, −3.0 (−3.6, −2.5) vs. −2.6 (−2.9, −2.3) points, ($p = 0.118$). Worsening in basic ADL (PSMS score) per year was also more pronounced in APOE non-ε4-carriers receiving antidepressants vs. nonusers, mean (95% CI) −2.0 (−2.6, −1.4) vs. −1.2 (−1.4, −0.9) points, ($p = 0.012$); this difference was not observed in ε4-carriers receiving antidepressants vs. nonusers, −1.4 (−1.8, −1.1) vs. −1.1 (−1.3, −0.9) points, ($p = 0.101$). Figure not shown.

Figure 4. *IADL score, annual change from baseline by interaction of APOE genotype with antipsychotics.*



APOE non-ε4-carriers receiving antipsychotics had faster annual IADL deterioration vs. nonusers, mean (95% CI) −5.4 (−6.8, −4.0) vs. −2.4 (−2.8, −2.1) points, ($p = 0.003$); this difference was not detected in ε4-carriers receiving antipsychotics vs. nonusers, −3.4 (−4.6, −2.2) vs. −2.7 (−2.9, −2.4) points, ($p = 0.254$).

Abbreviations:
AD, Alzheimer's disease; ADL, activities of daily living; APOE, apolipoprotein E; ChEI, cholinesterase inhibitor; CI, confidence interval; IADL, Instrumental Activities of Daily Living scale; MMSE, Mini-Mental State Examination; NSAIDs, nonsteroidal anti-inflammatory drugs; PSMS, Physical Self-Maintenance Scale.

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