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SEX DIFFERENCES IN PREDICTORS OF COGNITIVE AND FUNCTIONAL OUTCOMES IN PATIENTS WITH ALZHEIMER'S DISEASE

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CONCLUSIONS

The predictors of cognitive and functional deterioration differed between the sexes. Use of nonsteroidal anti-inflammatory drugs (NSAIDs)/acetylsalicylic acid was a protective factor for better cognitive outcome in women, which suggested that women might have greater cerebral inflammation and additional advantages of treatment with these drugs. Antidepressants in men and solitary living among women were risk factors for more-rapid worsening in instrumental activities of daily living (ADL) and basic ADL (only women living alone), which underlined the risk of apathy and social isolation among those individuals. Cognitive reserve capacity could have a larger impact on Alzheimer's disease (AD) prognosis in women because a higher level of education implied increased cognitive or functional impairment over time. In women, the presence of the apolipoprotein E (APOE) ε4 allele led to lower cognitive performance. These risk factors indicate more hereditary and advanced forms of AD in women. A higher mean dose of cholinesterase inhibitors (ChEI), irrespective of drug agent, was associated with slower cognitive decline in both sexes and lower functional progression rate among men, which might support the better ChEI response among men described previously. The findings stress the importance for clinicians to optimize the ChEI dose in AD regardless of sex to improve therapeutic effectiveness.

BACKGROUND

About two-thirds of patients with AD are women, mostly because of their longer life-span and the higher prevalence of AD among older persons. A more-pronounced association between AD pathology and dementia (faster brain atrophy) and more-rapid cognitive decline have been reported in women.

The AD prognosis might be affected by, e.g., size of cerebral hemispheres, role of sex hormones, cerebro- and cardiovascular comorbidities, psychiatric symptoms, and concomitant medications, which are all influenced by sex differences. A better cognitive response to ChEI was observed in men compared with women. Thus, the predictors (genetic, sociodemographic, and clinical factors) of longitudinal cognitive and functional outcomes including aspects of ChEI treatment (e.g., drug agent, dose) may differ between sexes.

In a study that included both sexes, our group previously found that male sex, older age, absence of the APOE ε4 allele, use of NSAIDs/acetylsalicylic acids, and receiving a higher ChEI dose (regardless of type of drug), were independent predictors for a slower cognitive deterioration. Reports of sex-specific characteristics and effects of ChEIs that might affect the long-term course of AD are scarce. This study aimed to identify sex-specific factors, including aspects of ChEI therapy, that may predict cognitive and functional progression rates in AD.

METHODS

The Swedish Alzheimer Treatment Study (SATS) is a prospective, open, nonrandomized multicenter study for the assessment of longitudinal effectiveness of ChEI therapy in a routine clinical setting. Among the 1,258 outpatients clinically diagnosed with probable or possible AD, 1,021 (367 men and 654 women) had mild-to-moderate AD (Mini-Mental State Examination [MMSE] score, 10–26) at the start of ChEI treatment (baseline) and were included in the current study.

The participants were evaluated using cognitive tests (MMSE and Alzheimer's Disease Assessment Scale–cognitive subscale [ADAS-cog]) and functional capacity scales (Instrumental Activities of Daily Living scale [IADL] and Physical Self-Maintenance Scale [PSMS]) at baseline and every 6 months for 3 years. Mixed, linear, and nonlinear fixed and random coefficient regression models were performed. The dependent variables were the scores (ADAS-cog, IADL, or PSMS) assigned at the second and subsequent visits for each individual.

The following potential predictors were investigated: APOE genotype, solitary living, duration of AD, age at baseline, years of education, type of ChEI, dose of ChEI (mean percentage of the maximum recommended dose, namely 10 mg for donepezil, 12 mg for rivastigmine, and 24 mg for galantamine), specific concomitant medications (antihypertensive/cardiac therapy, antidiabetic drugs, asthma medication, thyroid therapy, lipid-lowering agents, estrogens, NSAIDs/acetylsalicylic acid, antidepressants, antipsychotics, and anxiolytics/sedatives/hypnotics), cognition, IADL, and basic ADL at baseline. In Tables 2–4, β values were unstandardized and are expressed per 1 unit increase for continuous variables and for the condition present in dichotomous variables.

RESULTS

Table 1. Baseline characteristics by sex (n = 1,021)

		Males	Females	*p* value
Number of patients (n/%)		367/36%	654/64%	
APOE genotype				**<0.001**
	Two ε4 alleles	14%	16%	
	One ε4 allele	46%	57%	
Solitary living		15%	46%	**<0.001**
Antihypertensive/cardiac therapy		44%	39%	0.137
Antidiabetics		8%	3%	**0.001**
Asthma medication		4%	5%	0.560
Thyroid therapy		3%	11%	**<0.001**
Lipid-lowering agents		14%	10%	0.122
Estrogens		0%	11%	**<0.001**
NSAIDs/acetylsalicylic acid		34%	28%	**0.029**
Antidepressants		19%	28%	**0.001**
Antipsychotics		3%	6%	0.067
Anxiolytics/sedatives/hypnotics		10%	17%	**0.003**
Mean ± standard deviation				
Estimated age at onset, years		71.8 ± 7.5	72.4 ± 7.2	0.238
Age at first assessment (baseline), years		74.9 ± 7.2	75.4 ± 6.8	0.249
Duration of AD, years		3.1 ± 2.0	3.0 ± 2.1	0.807
Education, years		9.9 ± 2.9	9.2 ± 2.3	**<0.001**
MMSE score (range, 0–30)		21.5 ± 3.7	21.4 ± 3.7	0.637
ADAS-cog score (range, 0–70)		20.9 ± 9.0	20.7 ± 8.9	0.766
IADL score (range, 8–31)		16.7 ± 5.4	15.5 ± 5.4	**0.002**
PSMS score (range, 6–30)		7.5 ± 2.2	7.5 ± 2.3	0.846

Abbreviations: AD, Alzheimer's disease; ADAS-cog, Alzheimer's Disease Assessment Scale–cognitive subscale; 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; ns, not significant; NSAIDs, nonsteroidal anti-inflammatory drugs; PSMS, Physical Self-Maintenance Scale.

Table 2. Factors affecting the long-term outcome with ADAS-cog score as the dependent variable by sex.

	Males			Females		
Percentage of variance accounted for, all fixed terms	54.4%, $p < 0.001$			53.1%, $p < 0.001$		
Significant predictors in final mixed models	**β**	**95% CI**	***p* value**	**β**	**95% CI**	***p* value**
Fixed terms						
Intercept	−7.379	−25.015, 10.256	0.411	6.426	2.719, 10.133	0.001
Time in months from baseline	−0.110	−0.230, 0.010	0.073	−0.532	−0.763, −0.300	<0.001
Time in months from baseline^2			ns	0.004	0.002, 0.006	<0.001
ADAS-cog score at baseline	1.462	0.670, 2.254	<0.001	0.698	0.618, 0.778	<0.001
Time in months x ADAS-cog score at baseline	0.023	0.018, 0.029	<0.001	0.021	0.016, 0.027	<0.001
Background variables:						
APOE ε4 carrier (no = 0, yes = 1)			ns	1.471	0.310, 2.633	0.013
NSAIDs/acetylsalicylic acid (no = 0, yes = 1)			ns	−1.675	−2.812, −0.537	0.004
Age at first assessment, years	0.161	−0.073, 0.396	0.177			ns
Age x ADAS-cog score at baseline	−0.013	−0.024, −0.002	0.019			ns
Education, years			ns	−0.281	−0.534, −0.028	0.030
Time in months x Education, years			ns	0.039	0.020, 0.057	<0.001
IADL score at baseline	0.350	0.194, 0.505	<0.001	0.161	0.043, 0.280	0.008
ChEI dose	−0.048	−0.091, −0.006	0.025	−0.038	−0.067, −0.009	0.010

Better cognitive or IADL abilities at the initiation of ChEI treatment implied a slower cognitive decline over time in both sexes. An interaction effect showed that the difference in cognitive status at baseline between ages was more pronounced among older men (but not women) who were more cognitively impaired. In women, the absence of the APOE ε4 allele or receiving NSAIDs/acetylsalicylic acid therapy were protective factors for a lower rate of cognitive progression. For women, there was a significant interaction effect between time in months and years of education, i.e., a higher level of education implied increased cognitive impairment over time. Men and women who received a higher mean dose of ChEI during the study showed a slower decline in cognitive ability. Solitary living, duration of AD, PSMS score at baseline, specific concomitant medications used at baseline except for NSAIDs/acetylsalicylic acid, and the variable comparing the ChEI agents, were not significant predictors in the models.

Table 3. Factors affecting the long-term outcome with IADL score as the dependent variable by sex.

	Males			Females		
Percentage of variance accounted for, all fixed terms	68.7%, $p < 0.001$			61.4%, $p < 0.001$		
Significant predictors in final mixed models	**β**	**95% CI**	***p* value**	**β**	**95% CI**	***p* value**
Fixed terms						
Intercept	−1.842	−4.771, 1.086	0.217	−2.612	−5.387, 0.164	0.065
Time in months from baseline	0.210	0.188, 0.232	<0.001	0.176	0.080, 0.272	<0.001
IADL score at baseline	1.523	1.184, 1.862	<0.001	1.560	1.268, 1.851	<0.001
IADL score at baseline^2	−0.019	−0.029, −0.009	<0.001	−0.022	−0.031, −0.014	<0.001
Time in months x IADL score at baseline			ns	−0.001	−0.005, 0.003	0.658
Time in months^2 x IADL score at baseline			ns	−0.00008	−0.00014, −0.00002	0.005
Background variables:						
Solitary living (no = 0, yes = 1)			ns	0.559	0.045, 1.072	0.033
Antidepressants, (no = 0, yes = 1)	0.923	0.167, 1.679	0.017			ns
Education, years			ns	−0.082	−0.208, 0.044	0.201
Time in months x education, years			ns	0.012	0.004, 0.020	0.002
ADAS-cog score at baseline	0.046	0.007, 0.085	0.020	0.070	0.036, 0.104	<0.001
ChEI dose	−0.023	−0.040, −0.005	0.011			ns

Patients of both sexes with better cognitive performance at baseline exhibited a more favorable long-term outcome in IADL capacity. The use of antidepressants in men and solitary living in women predicted worsening IADL. For women, there was a significant interaction effect between time in months and years of education, i.e., a higher level of education implied increased functional impairment over time. Men who received higher ChEI doses exhibited lower progression rates in IADL. APOE genotype, age at baseline, duration of AD, specific concomitant medications used at baseline except for antidepressants, and the variable comparing the ChEI agents were not significant predictors in the models.

Table 4. Factors affecting the long-term outcome with PSMS score as the dependent variable by sex.

	Males			Females		
Percentage of variance accounted for, all fixed terms	45.7%, $p < 0.001$			39.0%, $p < 0.001$		
Significant predictors in final mixed models	**β**	**95% CI**	***p* value**	**β**	**95% CI**	***p* value**
Fixed terms						
Intercept	1.734	0.500, 2.969	0.006	2.847	0.903, 4.792	0.004
Time in months from baseline	−0.014	−0.080, 0.053	0.684	0.020	−0.066, 0.105	0.652
PSMS score at baseline	0.669	0.560, 0.778	<0.001	0.454	0.087, 0.822	0.015
PSMS score at baseline^2			ns	0.018	0.001, 0.036	0.039
Time in months x PSMS score at baseline	0.019	0.010, 0.028	<0.001	0.001	−0.008, 0.009	0.866
Time in months^2 x PSMS score at baseline			ns	0.00012	0.00002, 0.00022	0.020
Background variables:						
Solitary living (no = 0, yes = 1)			ns	0.315	0.017, 0.613	0.038
Education, years			ns	−0.057	−0.134, 0.020	0.144
Time in months x education, years			ns	0.007	0.0002, 0.013	0.042
ADAS-cog score at baseline	0.034	0.013, 0.056	0.002	0.026	0.008, 0.044	0.004
ChEI dose	−0.011	−0.022, −0.00006	0.049			ns

Lower cognitive ability at baseline predicted a faster deterioration in basic ADL among both sexes. Women living alone demonstrated poorer prognosis in basic ADL. For women, there was a significant interaction effect between time in months and years of education, i.e., a higher level of education implied increased functional impairment over time. Men who received higher ChEI doses exhibited lower progression rates in basic ADL. APOE genotype, age at baseline, duration of AD, specific concomitant medications used at baseline, and the variable comparing the ChEI agents were not significant predictors in the models.

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