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The Rate of Change In ADAS-Cog And CDR-SB In MCI Subjects with Women and Men Bias

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Abstract

A greater risk for mild cognitive impairment (MCI), women make up almost two-thirds of Alzheimer's disease (AD) patients in the United States. The higher prevalence of AD in women has been attributed previously to longer female life expectancy or sociocultural detection biases.

Keywords: Mild cognitive impairment; neurobiologic vulnerability; framingham study

Introduction

Although men may have a greater risk for mild cognitive impairment (MCI) [1], women make up almost two-thirds of Alzheimer's disease (AD) patients in the United States [2]. The higher prevalence of AD in women has been attributed previously to longer female life expectancy or sociocultural detection biases, but some recent findings [1], [3], [4], also support an alternate hypothesis that women at risk progress to AD at faster rates than men due to greater neurobiologic vulnerability. The Framingham study found that the age-specific risk of AD was almost twofold greater in women than men (17.2% vs. 9.1% at age 65 years and 28.5% vs. 10.2% at age 75 years) [3]. Holland et al. [4] reported that female gender was associated with a greater rate of cognitive change in MCI subjects than men over a 1-year period, raising further questions about what happens over longer periods.

Studies have also begun to examine underlying reasons for a possible sexual dimorphism in rates of decline. A greater potency of the AD risk associated with the apolipoprotein E4 allele and the brain derived neurotrophic factor (BDNF) Met66 allele has been noted in women [1]. Other theories proposed to explain gender differences include sex hormones (such as estrogen), smaller head size, lower cognitive reserve, lower levels of exercise in women (at least in the United States) and differences in occupational or educational attainment. Gender differences in pathologic vulnerability for AD are supported by studies noting greater annual three-dimensional tensor-based magnetic resonance imaging (MRI) brain atrophy rates in women [4] and a significant association of gender with neuritic plaques and neurofibrillary tangles [5]. In one study, equivalent increases in AD pathology increased the odds of clinical AD by 20-fold for women versus threefold for men. Collectively, these studies argue for more definitive long-term examination of gender differences in MCI rates of progression and pathologic vulnerability.

The aim of this report was to use 8-year longitudinal data on at-risk subjects from a national biomarker study to test the hypothesis that women progress cognitively and functionally at faster rates than men, after covarying for baseline cognition, age, and education. A second aim was to model the long-term trajectories of decline in men versus women to see if the assumptions of linear decline noted by the prior 1-year study held true over a longer period of follow-up. The long-term data allowed us to test for both linear and curvilinear patterns of decline as well as acceleration over time. A third aim was to examine interactions between apolipoprotein E (APOE) genotype and gender on cognitive decline and to see if gender had an effect beyond that conferred by the E4 genotype. Finally, we examined gender differences in the variability of decline in both cognition and function, using instruments widely used in prevention trials.

2. Methods

2.1. Subjects

MCI subjects recruited in Alzheimer's Disease Neuroimaging Initiative-1 (ADNI-1; adni.loni.usc.edu) were used in our analyses. ADNI (ADNI ClinicalTrials.gov identifier: NCT00106899) is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the United States and Canada. ADNI-1 originally recruited 398 MCI subjects who then had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org. Additional details are also provided in the ADNI-1 procedures manual [5], [6].

2.2. Outcome measures

The ADAS-cog 11 is a 70-point scale designed to assess severity of cognitive impairment, and it is commonly used in MCI and Alzheimer's trials. The ADAS-Cog is composed of 11 tasks that assess learning and memory, language production and comprehension, constructional and ideational praxis, and orientation [4]. Higher scores indicate worse performance, as it is scored based on number of errors.

The clinical dementia rating-sum of boxes (CDR-SB), with a range from 0 to 18, is the sum of the ratings for the six domains of the CDR global dementia rating scale. It provides a quantitative assessment of cognitive and functional impairments based on a semi-structured interview of the subject and informant [35]. Higher scores indicate greater impairment.

2.3. Follow-up

ADNI MCI subjects were followed through ADNI-1 and then enrolled in ADNI-2. We compared ADAS-Cog and CDR-SB scores from baseline to end point (using most recent available scores at the time of our data extraction in late 2014) yielding a study duration of up to 8 years (mean duration, 4 years).

In the mentioned model, Ai(t) is the ADAS-Cog value of subject i at time t (in years). Model (2) explains this in terms of μ, the baseline ADAS-Cog value for a 75.1-year-old male with 16 years of education, MMSE of 27 and of APOE ε4 negative. The terms with α are effects of gender, APOE ε4 status, MMSE, age, and years of education on baseline ADAS-Cog values. The terms with β are effects on rates of change and β0 is the baseline rate of change. The terms with γ are effects on curvature and γ0 is the baseline curvature. We include a random effect bi and ri to account for the effect of unmeasured subject factors on the baseline ADAS-Cog value and rate of change, respectively: both are assumed to have a zero mean Gaussian distribution with SD σb. Finally, εit is the measurement error assumed to have an independent zero mean Gaussian distribution with SD σb. Note that the square root transformation was used to obtain approximate Gaussianity of estimated error terms as well as constant variance across fitted values of the response. A similar model was fit for CDR-SB. Model (0.2) was fit by the method of restricted maximum likelihood using the nlme package in the R computing platform (www.r-project.org). In our models, we used the subject's initial MMSE as a covariate to represent baseline cognition; however, gender differences in cognitive decline remained significant when the baseline ADAS-Cog was used as a covariate in the model rather than the MMSE.

3. Results

3.1. Baseline characteristics

Baseline features of the sample are summarized in Table 1. The mean baseline age and educational level in males were statistically higher than those in females (P value for both variables = .03), but the differences were small. There are no significant differences by gender for baseline ADAS, baseline MMSE, number of follow-up visits, or follow-up length.

Higher CDR-SB scores indicate worsening. Solid lines indicate mean ADAS-Cog scores, and dashed lines indicate 95% confidence intervals for these scores. The actual visit date of each subject was used (rather than pooling visits as “annual”) to give a more precise depiction of variability and progression. Abbreviations: CDR-SB, clinical dementia rating-sum of boxes; ADAS-Cog, Alzheimer's disease assessment scale-cognitive subscale.

4. Discussion

This study found a marked gender difference in longitudinal rate of change in ADAS-Cog and CDR-SB in MCI subjects and demonstrates that there is a curvilinear acceleration of rate of change over time (influenced by both gender and APOE ε4 status.) Previously, Holland et al. [6] reported a smaller gender difference in a much shorter (1 year) follow-up study of MCI subjects. We confirm and extend this to a follow-up period of up to 8 years (mean of 4 years). The baseline rate of ADAS change reported in Holland et al (0.49 points/year) was lower than that in our study—likely due to the fact that our much longer follow-up allowed us to quantify a curvilinear acceleration of change over time. The similarity of the gender effect on ADAS-Cog and CDR-SB indicates that women have a faster rate of decline in both cognitive performance and functional status. Our models adjusted for age and APOE ε4, which correlate substantially with risk for amyloid positive status. Gender differences are present in APOE ε4 carriers and noncarriers; however, gender effects appear to be greatest in E4 homozygotes, a group at greatest risk for conversion. Overall, these data confirm and extend prior findings [3], [4] that women with MCI may have a greater vulnerability for cognitive and functional decline.

The strengths of our study include its use of a relatively large baseline sample size (398 MCI subjects recruited nationally), the employment of specific clinical criteria for amnestic MCI with standardized data collection across multiple sites, and relatively long (mean, 4 years) follow-up duration. We focused primarily on MCI subjects originally recruited in ADNI-1 because they had a more traditional form of MCI (i.e. late MCI) whose memory criteria are well established. We did not include any subjects newly recruited in ADNI-Go or ADNI-2 with early MCI because they lacked sufficient long-term follow-up. One potential limitation is that ADNI MCI subjects are not necessarily representative of the population as a whole and as such are more representative of MCI subjects recruited at research centers or those who have been enrolled into secondary prevention trials. Although our mean follow-up time of 4 years is longer than that of others addressing this question, it may still not have been long enough to conclusively test for gender differences in rates of conversion to dementia. The rate of conversion from MCI to dementia was slightly higher among women than men but this was not statistically significant. Subjects who progressed to AD dementia were not excluded. All data points on subjects who entered the study as MCI in ADNI-1 were analyzed.

Despite many candidate drugs being in trials, the causes of AD are not fully known, and uncovering mechanisms underlying gender differences in cognitive progression may yield additional new treatment targets or nonpharmacologic strategies for risk modification and allowing a more personalized intervention. For example, trials of anti-amyloid therapeutics have revealed a greater vulnerability for cerebral adverse events such as amyloid-related imaging abnormalities in E4 carriers and many ongoing studies stratify enrollment by E4 and also use differential treatment dosing by E4. In a similar vein, our findings support a prior call for AD prevention trials to deliberately stratify by sex and have adequate sample size to test for a therapeutic risk-benefit in men and women separately [1]. One could conceivably also have separate thresholds for efficacy. In addition, differences in variability in the rate of change by gender suggest that unequal numbers of males and females may be required to measure the same effect size. Furthermore, the curvilinear acceleration noted in this study suggests that usual statistical approach in trials of linear models may not be optimal to model MCI disease progression over longer periods. The CDR-SB has been suggested as an acceptable single cognitive/functional end point for MCI trials, and our data suggest that lower baseline MMSE, female gender, and APOE ε4 are predictors of faster decline, and sample sizes for various specific effect sizes can be computed using the data. To our knowledge, no prior study has modeled long-term changes in cognition and function in MCI, as well as the effects of covariates, so comprehensively.

5. Conclusions

In conclusion, our results show a robust gender difference in the rate of change in ADAS-Cog and CDR-SB in MCI subjects, with women declining at much higher rates than men. These findings support prior calls [1], [3], [4] to make gender-specific research in AD a priority.

6. References

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