Statin use and hippocampal volumes in elderly subjects at risk for Alzheimer's disease: A pilot observational study

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Abstract

Statins are investigational therapies for preventing or treating Alzheimer's disease (AD) and mild cognitive impairment (MCI). Hippocampal atrophy is a characteristic feature of MCI and AD.

This study analyzed cross-sectional data from 246 nondemented elderly subjects to test the effect of lipid lowering agent (LLA) therapy on cognition and brain magnetic resonance imaging (MRI) measures of white matter lesions and hippocampal volume. The study also compared rates of hippocampal volume change over two and four years in a smaller subset.

At baseline, LLA users were younger, better educated, more likely to be male, and had higher cognitive scores. Cognitive performance also varied by age and gender, and MRI measures varied by age. After adjusting for these differences, the effect of LLA use on baseline cognition, baseline hippocampal volume, and baseline white matter lesion scores was not significant. The effect of LLA use on hippocampal volume loss at two-year and four-year follow-ups was also not significant.

This study is the first to examine statin effects on brain atrophy measured by MRI. In this cohort, statin use was not associated with rate of change of hippocampal volume. While the study was limited by a relatively small number of statin users, the findings seem consistent with three prior randomized trials that found no cognitive benefits for statins in nondemented subjects. Prospective studies in both nondemented and AD subjects may provide more conclusive answers.

Key words: hippocampal volume, Alzheimer's disease, statin, brain atrophy, lipid lowering agent, mild cognitive impairment

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Introduction

In addition to their beneficial effects on lipids and vascular disease, statins have been reported to increase endothelial nitric oxide synthase (thereby increasing cerebral blood flow) and to potentially have antioxidant, anti-inflammatory, and antiamyloid effects.[1-3] These mechanisms could confer cognitive and antidementia benefits. Observational studies have found statin users to have a lower risk of dementia.[1-3] However, these studies are not fully consistent in the age group that showed benefits, the type of dementia, whether the risk for Alzheimer's disease (AD) was lowered, or whether this effect was related to lipid levels.

While the data are promising, no prospective trials have confirmed the efficacy of any statin for treating or preventing AD. Four published randomized placebo-controlled studies of statins found no benefits over placebo on secondary measures relevant to cognition or function.[3-7] In addition, a recent study of lovastatin in a transgenic animal model of AD (Tg2576 mice) reported that lovastatin lowered plasma cholesterol but enhanced beta-amyloid production and senile plaque deposition in

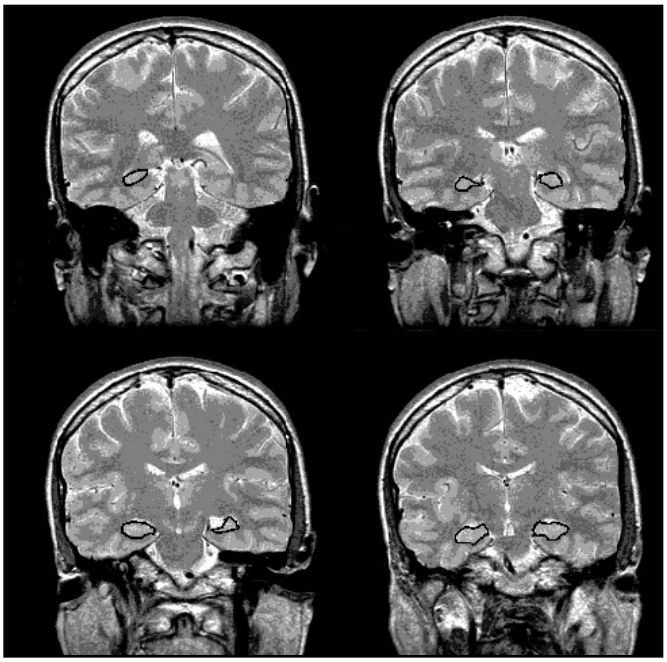

Figure 1. Coronal MRIs are displayed using the GRID program developed by the Duke Neurosychiatric Imaging Research Laboratory. Shown are four slices proceeding from posterior (UL) through anterior (LR). The hippocampus is outlined in each section. The volume of each hippocampus is the sum of the areas of such regions multiplied by the (common) space between slice centers.

the brains of female mice.[8] The apparent discrepancy between observational and randomized study findings suggests the need for further research.

The hippocampus is involved in memory processing, and hippocampal atrophy occurs early in AD.[9] Hippocampal volumes can be reliably measured using magnetic resonance imaging (MRI) and have been proposed as endpoints for AD clinical trials.[9] To our knowledge, there is no prior published study of statin effects on hippocampal atrophy.

Methods

The researchers analyzed data from 246 patients (mean age = 70.7 years, SD = 10, age range = 59 to 96 years) to examine the effect of lipid lowering agent (LLA) therapy on MRI-measured hippocampal volume loss and white matter hyperintensity score. Participants were also involved in a longitudinal study of late-life major depression. The LLA study was approved by the institutional review board, and participants gave written informed consent. At entry, none of the participants met the criteria for dementia (mean Mini-Mental State Exam [MMSE] score = 27.3, SD = 3), although many had mild cognitive deficits. Thirty-five participants (14 percent) were on LLA at baseline, and all but two of them were on statins (i.e., atorvastatin, simvastatin, pravastatin, lovastatin). For change from baseline analyses, LLA nonusers were defined as those who did not use LLA at entry or during their follow-up. Likewise, LLA users were those who used LLA at entry and at every time point studied. All concomitant medications, including antidepressant therapy, were permitted as clinically warranted.

MMSE scores and MRI scans obtained at baseline and at annual follow-up visits were analyzed. Hippocampal volumes (right plus left) were measured from coronal MRIs, as reported previously,[10] and were available only in 147 subjects due to incomplete scans. The MRIs showing the hippocampus are displayed in Figure 1.

The white matter hyperintensity score was obtained using axial brain MRI, as reported previously,[11] and were available in 233 subjects. Consistent with prior reports, the LLA users in this sample tended to differ from non-LLA users in age, gender, and education. Consequently, researchers performed two types of analyses for the longitudinal data. First, researchers analyzed data for all subjects in a generalized linear model (GLM) and adjusted the data statistically to account for the effects of age, gender, and education. Second, since age is a known predictor of cognition and brain atrophy, researchers created and compared matched pairs of LLA users with nonusers. Eleven LLA users (who had follow up MRI data and for whom matched nonusers existed in the database) were matched by age and gender with two separate non-LLA users. The researchers were unable to match perfectly by education because of the logistics of recruitment and sample distribution. The matches were performed blind to cognition scores or MRI data. Researchers then compared rates of change of cognition and hippocampal volume in the 11 LLA users with the 22 LLA nonusers. Statistical analyses were conducted using SAS and consisted of general linear models, chi-square tests, and t-tests.

Results

Baseline hippocampal volume and cognition

At baseline, 35 LLA users tended to be younger (mean ±SD, 66.5 ±6 versus 71.4 ±8 years, $p < 0.0004$), better educated (14.4 ±2 versus 12.9 ±3 years), and more likely to be male (40 percent versus 27 percent, $p < 0.12$) than the 211 nonusers. The effect of LLA use on MMSE was significant before ($F = 8.1$, $p < 0.005$) but not after ($F = 0.46$, $p < 0.51$) adjusting for the effects of age, gender, and education. The mean MMSE score in LLA users

Table 1. Baseline and two-year MRI data in LLA users and nonusers				
	LLA	**Not on LLA**	**t-value**	**p-value**
N	11	22		
Baseline data				
Age (SD)	66 (6)	66 (6)	0.34	0.735
M/F	3/8	6/16	–	1.00
Education (SD)	15.09 (1.64)	14.18 (2.20)	-1.21	0.235
MMSE (SD)	29.45 (0.82)	28.27 (1.91)	2.48	0.019
Left hip. vol.	2.97 (0.194)	2.84 (0.31)	-1.25	0.220
Right hip. vol.	3.06 (0.346)	2.99 (0.31)	-0.57	0.570
Total hip. vol.	6.02 (0.507)	5.83 (0.57)	-0.97	0.341
Change from baseline at two years				
Delta MMSE (SD)	-0.400 (1.430)	0.227 (2.266)	0.80	0.429
Delta left hip. vol.	-0.039 (0.371)	-0.085 (0.380)	-0.33	0.744
Delta right hip. vol.	0.069 (0.336)	-0.073 (0.366)	-1.08	0.289
Delta total hip. vol.	0.030 (0.551)	-0.158 (0.613)	-0.86	0.398

tended to be about one point higher in unadjusted analyses. After adjusting for age, education, and gender the effect of LLA use on MRI-measured white matter hyperintensity score ($F = 0.15$, $p < 0.70$) or hippocampal volume ($F = 0.01$, $p < 0.91$) was not significant.

Change from baseline in hippocampal volume and cognition in matched pairs

The researchers conducted two types of analyses. First, for the overall sample— after adjusting for the effect of age, education, and gender—the effect of LLA use on the two-year rate of hippocampal volume change was not significant ($p > 0.1$). Second, researchers conducted a comparison of matched pairs of LLA users and nonusers. Table 1 depicts the demographic, cognitive, and MRI data of the 11 LLA users and the 22 matched non-LLA users whose longitudinal data were analyzed.

In both groups, mean age was 66 (±6) years, and 83 percent of subjects were women. Despite this matching, at baseline, LLA users had higher MMSE scores than nonusers ($p < 0.01$), and there was a weak trend for education levels to also be higher. There was no difference in baseline hippocampal volume or white matter hyperintensity score. At a two-year follow-up, there were no significant differences between LLA users and nonusers in either rate of change of MMSE scores or rate of change of hippocampal volumes (Table 1). Rates of change also did not differ at the four-year follow-up in a smaller subset of five LLA users compared with 10 matched nonusers ($p > 0.05$).

Discussion

To our knowledge, this is the first report to examine the effects of LLA therapy on hippocampal volume loss in any elderly sample. In this sample, there was no relationship between use of LLA and hippocampal volume at baseline or between LLA use and rate of change of hippocampal volume at two follow-up time points. Baseline MMSE scores were higher in LLA users possibly reflecting either a beneficial effect of LLA on MMSE or the fact that people with higher intelligence or education take LLA earlier in life. The rate of change of MMSE did not differ by LLA use.

The findings regarding cognition appear consistent with six prior randomized studies (in nondemented subjects) of statins or diet in which cognition has been measured. The Heart Protection Study of 20,536 patients (age 40 to 86 years) randomized to simvastatin or placebo for

five years found no significant differences on a brief cognitive test.[4] PROSPER, a randomized study of 5,804 elderly subjects (age 70 to 82 years) followed for 3.2 years, found no significant cognitive differences between pravastatin or placebo, on average.[5] There were also no differences in activities of daily living or incident dementia rates. Another six-month placebo-controlled trial of 209 healthy subjects (age 24 to 60 years) did not find significant cognitive superiority of lovastatin over a placebo.[6] In a randomized placebo-controlled study of 44 persons with AD (age 59 to 77 years), simvastatin did not significantly alter cerebrospinal fluid levels of beta-amyloid (Aß40 or Aß42) in the overall sample but, in post-hoc analyses, had an effect in mild AD.[7] Overall, these studies argue against a positive cognitive benefit for statins and raise the possibility that conclusions of prior observational studies (that statins protect against dementia) may have been biased by other differences between statin users and nonusers. However, it could be argued that existing randomized studies were not specifically designed to test for subtle neuroprotective benefits and did not use sensitive cognitive tools. A recent unpublished pilot randomized trial has reported a beneficial effect for atorvastatin on cognitive progression in AD.[12] To date, no prior study has reported statin effects on brain hippocampal measures in any sample. Since the annual rate of hippocampal decline in AD is much greater than in nondemented subjects, potential neuroprotective effects of statins may be more easily demonstrated in AD samples. Data from ongoing studies will address this issue.

Statin users differ from nonusers in age, gender, and other variables. Because age and gender have meaningful effects on both cognition and MRI measures, researchers in this study used two methods to overcome the bias: 1) they adjusted the model statistically, and 2) they matched each statin user by age and gender with two nonusers.

Limitations

Because of the relatively small numbers of LLA users in the study, limited follow-up data, and nonrandomized observational design the findings should be viewed as preliminary. The MMSE is a brief screening instrument, and more sensitive instruments may yield more conclusive results. The lipid levels of the participants were not included in the study. The participants for this study were selected for a research study of geriatric depression. Since mood complaints coexist commonly with cognitive impairment, and since late-life depression may be a risk factor for dementia,[10] the sample is clinically relevant. There is the possibility of a bias due to effects of antidepressant therapy, although use of antidepressant therapy did not differ by LLA status in the sample. The study pooled all statin users, but there is emerging evidence that statins may differ in their lipophilicity and other effects. There is also evidence that statin effects may vary by genotype.

The study was a pilot. Larger randomized prospective trials of the cognitive and neural effects of various LLAs, including studies testing apolipoprotein E4 allele effects, are warranted and some are already ongoing. The optimal harnessing of potential neural benefits of statins remains a desirable goal.

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