Vascular Factors as Predictors of Severe Dementia and Mortality in Alzheimer's Disease

The Cache County Dementia Progression Study

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Abstract

Background. Vascular risk factors, conditions, and treatments may affect Alzheimer's dementia(AD) progression. In the Cache County Study, atrial fibrillation and hypertension were associated with faster AD progression while select antihypertensive and "statin" medications were associated with slower progression. We extend our work to examine whether vascular factors also predict the important clinical outcomes of severe dementia and mortality. ***Methods.*** AD cases (n=335, 66% female), with a mean time between dementia onset and diagnosis of 1.63 (SD=1.25) years were followed up for up to 16 years. Participants were re-examined every 6–18 months on Mini-Mental State (MMSE) & Clinical Dementia Rating (CDR). Severe dementia was defined as MMSE <= 10 or CDR=3. Mortality was monitored through obituaries. History of hypertension, high cholesterol (HC), diabetes, stroke, myocardial infarction (MI), or coronary artery bypass graft (CABG) was obtained by self-report prior to dementia onset or caregiver report thereafter. Anti-hypertensive or statin use was determined at each visit. The association of these predictors with time to severe dementia or death was examined in Cox Regression models, controlling for the following covariates: dementia onset age, duration, gender, APOE, and education. ***Results.*** Mean (SD) age of AD onset was 84.27 (SD=6.39). 79 subjects developed severe dementia while 297 died during observation. In bivariate Cox regression models, MI was associated with a higher hazard of severe dementia (HR=1.61, 95% CI 0.97–2.69) while HC was associated with lower hazard (0.56, 0.35-0.89), although only HC remained significant with the inclusion of covariates. Examination of HC and treatment (HC-no statins, HC-statins vs. neither) revealed reduction in hazard for severe dementia for HC-satins (0.48, 0.25-0.93). Additionally, only HC-statins (0.64, 0.45-0.89) was associated with a lower death hazard. Antihypertensives predicted neither time to severe dementia or death. ***Conclusions.*** We extend our previous finding that statin use in AD and history of HC is associated with slower progression. More research is needed to examine whether medication features (e.g., blood brain barrier penetration) have differential effects.

Introduction

- Little is known about modifiable factors influencing the rate of AD progression, although their identification might identify targets for intervention.
- Previously, in the Cache County Study, we reported that atrial fibrillation and hypertension were associated with faster dementia progression[1]
- Antihypertensive and statin medications were linked with slower decline[1,2]
- In the present analysis, we examine whether vascular factors and their treatments predict clinical outcomes of severe dementia and mortality in AD

Methods

- The Cache Dementia Progression Study[3] is a population-based study of the course of dementia and modifying factors among individuals with *incident* (new onset) dementia, identified in the Cache County Study on Memory in Aging[4]
- 335 cases of dementia were diagnosed with AD by consensus panel. Mean (SD) onset period between dementia onset and diagnosis was 1.63 (1.25) years
- Participants were examined every 6-18 months on Mini-Mental State (MMSE)[5] and the Clinical Dementia Rating[6] (CDR).
- Severe dementia was defined as MMSE <= 10 or CDR=> 3
- Mortality was monitored through local newspaper obituaries
- Vascular factors were determined by self-report prior to the onset of dementia or proxy report thereafter: hypertension, high cholesterol (HC), diabetes, stroke myocardial infarction (MI), and coronary artery bypass graft (CABG).
- Covariates were dementia onset age, duration, gender, presence/absence of APOE E4 allele, and education (less than HS grad/GED vs. other)

Results

Sample Characteristics:

- Most participants were female (66.0%) with mean (sd) age of onset of AD = 84.27 (6.39)
- Severe dementia occurred in 79 subjects at a mean (sd) of 5.4 (2.3) years from dementia onset
- Death occurred in 297 subjects at a mean (se) of 6.33 (0.21) years from dementia onset
- Cox regression examined the association of vascular factors and treatments and survival time to severe dementia and mortality

Table 1. Sample Characteristics of Vascular Factors and Treatments

	Number	Percent
Diabetes	74	22%
Stroke	32	10%
Myocardial Infarction	61	18%
Coronary Artery Bypass Graft	22	7%
High Cholesterol		
No statins	81	24%
Statins	62	19%
Hypertension		
No antihypertensives	26	8%
Antihypertensives	246	74%

Vascular Factors:

- Bivariate Cox regression models showed MI was associated with higher hazard of severe dementia (HR, 95% CI = 1.61, 0.97-2.69) ; HC was associated with lower hazard of severe dementia (HR, 95% CI = 0.56, 0.35-0.89).
- Multivariate models were significant only for HC.

Vascular Treatments:

- In models examining HC group (no HC, HC-no statins, and HC-statins), HC-statins was associated a with lower hazard of severe dementia and death
- A similar grouping of persons with hypertension and medications found no effect for antihypertensive medication use and either clinical outcome

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Figure 1

Kaplan-Meier plots of statins and time to severe dementia and death

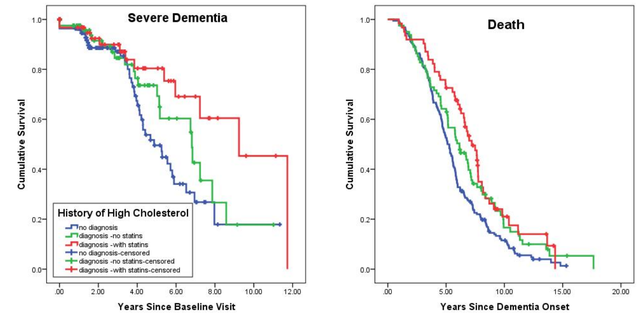

Figure 1 displays the association between high cholesterol groups (no diagnosis, high cholesterol-no statins, and high cholesterol-statins among persons with AD in the Cache County Population

Table 2. Statin Medications and Risk of Severe Dementia or Death

	Severe Dementia			Death		
	Hazard Ratio	P	95% CI	Hazard Ratio	P	95% CI
HC-no statins	0.65	0.11	0.38-1.11	0.84	0.23	0.63-1.17
HC-statins	0.48	0.029	0.25-0.93	0.64	0.008	0.45-0.89
Dementia Duration	1.25	0.006	1.07-1.46	0.80	<0.001	0.72-0.89
Age	1.00	0.86	0.96-1.05	1.09	<0.001	1.07-1.11
< High school	1.99	0.023	1.10-3.59	---	---	---
Female	---	---	---	0.69	0.005	0.54-0.90

Conclusions

- Results are consistent and build on our previous findings that statin medications were associated with slower progression in AD; they do not suggest a role for antihypertensive medications for delaying severe dementia or death in AD
- In view of negative results from randomized controlled trials of statins in the treatment of AD, future work will examine age of use, timing, and duration effects

Citations

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