Presence of cardiovascular disease is associated with slower cognitive decline in Alzheimer's disease in the absence of cerebrovascular pathology

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Background

- There has been intense interest in the influence of vascular comorbidities on the pathological processes in Alzheimer's disease (AD).
- While there is substantial evidence that conditions such as diabetes mellitus (DM), hypertension, and dyslipidemia may predispose to the subsequent development of dementia including AD[1,2], the impact of vascular risk factors and comorbid condition such as cardiovascular diseases (comorbid-CVD) on AD progression is still unclear.
- This distinction between effects on the risk for developing dementia versus effects on progression is particularly important as risk factors for AD may be stage specific, and their influence on future outcomes in patients diagnosed with AD should not be inferred.

Objectives

- We aimed to determine the association between individual and combination of vascular risk factors or presence of comorbid CVD at baseline and measured AD progression in an AD center population followed annually.
- We further considered the important influence of prior disease behaviour and the persistence of anti-dementia treatment by the inclusion of the validated measures Pre-progression rate3 and Persistency index4 in the regression analysis.

Methods

Participants

- We conducted an analysis of prospectively collected baseline and follow-up information (n=779) maintained by the Baylor College of Medicine Alzheimer's Disease and Memory Disorders Center (BCM-ADMDC) since 1989. Subjects fulfilled a diagnosis of probable AD according to NINCDS-ADRDA criteria. Those with a known history of cerebrovascular events (cerebral infarctions, hemorrhages or transient ischemic attacks) at the baseline visit were subsequently excluded, as progression of disease maybe dissimilar from the general cohort and would reflect the influence from secondary intracranial pathology.

Vascular risk factors and CVD

- Information regarding vascular comorbidities was recorded at the baseline visit via self- and proxy-report and verified with previous medical reports. We enquired for the presence of the following conditions both ongoing and in the past history: hypertension (HPT), hyperlipidemia (HPL), diabetes mellitus (DM), arrhythmias (defined as significant episodes of bradycardia, tachycardia including atrial fibrillation, and history of pacemaker insertion) and cardiovascular diseases (comorbid CVD) (defined as history of myocardial infarction, angina, congestive heart failure, coronary angioplasty and coronary artery bypass surgery). We did not include examination of medications used for the treatment of these comorbidities in our analyses as we noted inconsistencies between details of treatment and respective comorbidity diagnoses.

Covariates

- Preprogression rate was calculated for each patient based on their performance on the Mini Mental State Examination18 (MMSE) according to the following formula[3,4]:

  (30 - MMSE score [initial]) / physician's estimate of duration [in years])

- The Persistency Index (PI) refers to the ratio of the total years of drug use and total years of disease symptoms (determined by the physician's estimate of duration and extended to the last outcome assessment date), calculated with the following method[5]:

  Total duration of treatment [in years] / total duration of symptoms [in years]

Neuropsychological testing

- Cognitive testing was assessed at baseline and annually by the Mini-Mental State Examination (MMSE) and the Alzheimer disease Assessment Scale-cognition subscale (ADAS-Cog). Global performance was evaluated by the Clinical dementia rating, sum of boxes scale (CDR-SB).

Analysis

- Longitudinal linear regression model was used to examine the impact of comorbidities on the three designated outcome measures. The correlation between two measurements of the same subject is assumed to be proportional to duration of time between these two observations. Using backward elimination, we eliminated the variable with highest p value in each step until only significant variables remained in the model.

Results

Table 1. Baseline characteristics

	Total n	Mean (SD) or n (%)
Demographics		
Age (years)	779	74.7(7.5)
Female sex	779	531(68.2)
Ethnicity	779	
Whites		712 (91.4)
Blacks		59 (7.6)
Others		8 (1.0)
Education	776	13.9 (3.5)
Symptom duration (years)	779	3.9 (2.3)
Average length of follow-up (years)	779	3.9 (2.3)
Persistency of anti-dementia treatment	769	0.19 (0.28)
ApoE	718	262 (36.5)
e4-		456 (63.5)
e4+ (heterozygous and homozygous)		
Cognitive/ global measures		
MMSE	760	20.0 (6.5)
ADAS-Cog	704	23.5 (12.4)
CDR global	767	1.1 (0.7)
CDR-SB	768	6.3 (4.0)
Prevalence of vascular comorbidities		
HPT	776	314 (40.5)
DM	776	75 (9.7)
HPL	776	172 (22.2)
comorbid CVD	775	72 (9.3)
Arrythmias	775	68 (8.8)
Prevalence of multiple comorbidities	778	
0		323 (41.5)
1		304 (39.0)
2		128 (16.5)
3		23 (3.0)

Table 2. Final backward linear regression models of predictors of decline in MMSE

	HPT model Estimate (SE)	DM model Estimate (SE)	HPL model Estimate (SE)	Arrhythmia model Estimate (SE)	Combination model Estimate (SE)	CVD model Estimate (SE)
Time	-2.40 (0.13)*	-2.40 (0.13)*	-2.40 (0.13)*	-2.39 (0.13)*	-2.39 (0.13)*	-2.40 (0.13)*
Time^2	0.09 (0.02)*	0.09 (0.02)*	0.09 (0.02)*	0.09 (0.02)*	0.09 (0.02)*	0.09 (0.02)*
Female Gender	-0.74 (0.36)*	-0.71 (0.36)*		-0.71 (0.36)		
White Race	1.58 (0.65)*	1.48 (0.64)*	1.55 (0.64)*	1.48 (0.64)*	1.68 (0.64)*	1.61 (0.64)*
Age						
Education						
Preprogression rate	-0.32 (0.07)*	-0.32 (0.07)*	-0.33 (0.07)*	-0.32 (0.07)*	-0.34 (0.07)*	-0.33 (0.07)*
Baseline MMSE						
Mild vs moderate/severe	9.40 (0.38)*	9.42 (0.38)*	9.39 (0.38)	9.42 (0.38)*	9.36 (0.39)*	9.39 (0.38)*
Persistency Index						
Cohort						
Hypertension	0.60 (0.34)					
Diabetes		0.22 (0.57)				
Hyperlipidemia			0.55 (0.40)			
Arrhythmia				-0.53 (0.59)		
Combination (0=baseline)						
1 risk factor					0.63 (0.38)	
2 risk factors					0.56 (0.49)	
3 risk factors					0.94 (1.00)	
Comorbid CVD						1.26 (0.59)*

*p<0.05

Table 3. Final backward linear mixed models of predictors of decline in ADAS-Cog

	HPT model Estimate (SE)	DM model Estimate (SE)	HPL model Estimate (SE)	Arrhythmia model Estimate (SE)	Combination model Estimate (SE)	CVD model Estimate (SE)
Time	3.46 (0.15)*	3.45 (0.15)*	3.45 (0.15)*	3.44 (0.15)*	3.45 (0.15)*	3.43 (0.15)*
Time^2						
Gender						
Race	3.91 (1.62)*	3.75 (1.61)*	3.61 (1.60)*	3.95 (1.61)*	4.02 (1.61)*	4.01 (1.60)*
Age						
Education						0.15 (0.08)*
Preprogression rate	0.42 (0.17)	0.41 (0.17)*	0.41 (0.17)*	0.44 (0.17)*	0.43 (0.17)*	0.43 (0.17)*
Baseline MMSE						
Mild vs moderate/severe	-16.99 (0.93)*	-16.99 (0.93)*	-16.90 (0.93)*	-17.21 (0.93)*	-16.84 (0.93)*	-17.10 (0.93)*
Persistency Index						
Cohort	-2.43 (0.80)*	-2.52 (0.80)*	-2.37 (0.81)*	-2.53 (0.81)*	-2.32 (0.81)*	-2.69 (0.81)*
Hypertension	-1.53 (0.82)					
Diabetes		-1.66 (1.38)				
Hyperlipidemia			-1.65 (0.96)			
Arrhythmia				1.83 (1.42)		
Combination (0=baseline)						
1 risk factor					-2.00 (0.90)	
2 risk factors					-2.10 (1.17)	
3 risk factors					-1.49 (2.38)	
Comorbid CVD						-3.62 (1.42)*

*p<0.05

Table 4. Final backward linear mixed models of predictors of decline in CDR-SB

	HPT model Estimate (SE)	DM model Estimate (SE)	HPL model Estimate (SE)	Arrhythmia model Estimate (SE)	Combination model Estimate (SE)	CVD model Estimate (SE)
Time	1.95 (0.11)*	1.95 (0.11)*	1.95 (0.11)*	1.95 (0.11)*	1.94 (0.10)*	1.95 (0.11)*
Time^2	-0.06 (0.02)*	-0.06 (0.02)*	-0.06 (0.02)*	-0.06 (0.02)*	-0.06 (0.02)*	-0.06 (0.02)*
Female gender	0.61 (0.29)*	0.59 (0.30)*		0.59 (0.30)*		
White race	-1.18 (0.52)*	-1.09 (0.52)	-1.15 (0.51)*	-1.09 (0.52)*	1.28 (0.52)*	-1.17 (0.52)*
Age						
Education						
Preprogression rate						
Baseline MMSE						
Mild vs moderate/severe	-5.75 (0.29)*	-5.76 (0.29)*	-5.75 (0.29)*	-5.76 (0.29)*	-5.74 (0.29)*	-5.77 (0.29)*
Persistency Index						
Cohort						
Hypertension	-0.54 (0.28)					
Diabetes		-0.10 (0.46)				
Hyperlipidemia			-0.55 (0.33)			
Arrhythmia				0.59 (0.48)		
Combination (0=baseline)						
1 risk factor					-0.63 (0.31)	
2 risk factors					-0.58 (0.40)	
3 risk factors					-0.43 (0.82)	
Comorbid CVD						-0.56 (0.29)

*p<0.05

- Subjects were predominantly female (68.2%), elderly (age= 74.7±7.6 years) and Caucasian (91.4%). Average follow-up period was 3.9 ±2.3 years.
- Risk factors other than arrhythmias were associated with non-significant trends toward slower decline on all three outcome measures (Table 2-4, higher estimate value on MMSE, lower estimate values on ADAS-Cog and CDR-SB).
- Combination of risk factors similarly display a trend towards slower decline but did not achieve statistical significance (p= 0.32, 0.11, 0.19 for MMSE, ADAS-Cog and CDR-SB respectively).
- Compared to those without the comorbidity, subjects with comorbid CVD performed significantly better on cognitive tests {ADAS-Cog (p=0.01) and MMSE (p=0.03)} but not on the global measure {CDR-SB (p=0.25)}.

Conclusion

- Neither individual vascular risk factors (hypertension, diabetes, hyperlipidemia and arrhythmias), nor their combination were significantly associated with disease progression.
- Presence of comorbid CVD was associated with slower cognitive decline in AD subjects without cerebrovascular disease.
- Possible explanations include a protective effect of treatment for comorbid CVD prior to AD diagnosis, the concomitant treatment of comorbid CVD and AD, or inherent differences in AD progression rate associated with pre-existing comorbid CVD.

References

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