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Depressive symptoms, vascular risk factors, and Alzheimer's disease

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Abstract

Background—Depressive symptoms in the elderly are associated with an increased Alzheimer's disease (AD) risk. We sought to determine whether the association between depressive symptoms and AD is explained by a history of vascular risk factors and stroke.

Methods—526 elderly persons from New York City without dementia at baseline were followed for a mean of 5 years. Depressive symptoms were assessed using the 17-item Hamilton Depression Rating Scale (HAM). Incident AD was ascertained using standard criteria. Diabetes, hypertension, heart disease, current smoking and stroke were ascertained by self-report. Proportional hazards regression was used to relate HAM scores to incident AD.

Results—HAM scores were higher in persons with hypertension, heart disease, and stroke, which in turn were related to higher AD risk. AD risk increased with increasing HAM scores as a continuous logarithmically transformed variable (HR for one point increase = 1.4; 95% CI: 1.1,1.8) and as a categorical variable (HR for HAM ≥ 10 = 3.4; 95% CI=1.5,8.1; p for trend = 0.004 with HAM =0 as the reference). These results were virtually unchanged after adjustment for vascular risk factors and stroke, individually (HR for HAM ≥ 10 = 3.4; 95% CI=1.5,8.1; p for trend = 0.004), and in a composite measure (HR for HAM ≥ 10 = 3.0; 95% CI: 1.2,7.8; p for trend = 0.02).

Conclusion—The prospective relation between depressive symptoms and AD is not explained by the a history of vascular risk factors and stroke, suggesting that other mechanisms may account for this association.

Keywords

depressive symptoms; vascular risk factors; stroke; Alzheimer's disease

INTRODUCTION

A third of persons with dementia have depressive symptoms (Lyketsos, Lopez et al. 2002), and the risk of dementia is approximately doubled in the elderly with depressive symptoms (Jorm 2001). Vascular dementia, AD, and depression may present in similar ways (Braaten, Parsons et al. 2006), but depressive symptoms may be more severe in vascular dementia compared to AD (Newman 1999; Simpson, Allen et al. 1999; Park, Lee et al. 2007). However, there is mounting evidence that vascular risk factors and cerebrovascular disease may be important predictors of AD (Breteler 2000; Luchsinger and Mayeux 2004; Luchsinger, Reitz et al. 2005) in addition to depression (Alexopoulos, Meyers et al. 1997) and vascular dementia (Hsiung, Donald et al. 2006). This suggests that vascular and cerebrovascular disease could be the mechanism linking depressive symptoms and AD. However, a recent analysis in the cardiovascular health study showed that the relation between depressive symptoms and mild cognitive impairment, a transitional stage between normal cognition and AD (Petersen 2004), was not explained by underlying vascular disease (Barnes, Alexopoulos et al. 2006). There is a paucity of longitudinal epidemiologic studies examining whether vascular disease explains the association between depressive symptoms and AD. We previously reported that depressive symptoms (Devanand, Sano et al. 1996), vascular risk factors (Luchsinger, Reitz et al. 2005), and stroke (Honig, Tang et al. 2003) are associated with increased AD risk. Our objective was to determine whether vascular risk factors and stroke explain the association between depressive symptoms and AD.

METHODS

Participants and Setting

Participants were enrolled in a cohort study by random sampling of Medicare recipients 65 years or older from northern Manhattan (Washington Heights, Hamilton Heights, Inwood) (Tang, Stern et al. 1998). Participants underwent an in-person interview of general health and function at the time of study entry followed by a standard assessment, including medical history, physical and neurological examination and a neuropsychological battery (Stern, Andrews et al. 1992). Baseline data were collected from 1992 through 1994. Follow-up data were collected at intervals of approximately 18 months. The institutional review board of Columbia-Presbyterian Medical Center approved this study.

The sample for this study included participants without dementia who completed the Hamilton Depression Rating Scale (HAM) with at least one interval of follow-up. Of the 1,128 persons without dementia at baseline and with follow-up (Luchsinger, Reitz et al. 2005), 526 persons received the HAM and comprise the sample for these analyses. The 526 persons were selected based on convenience and the availability of trained staff to do the HAM. Compared to the participants who did not complete the HAM, participants who completed the HAM were younger (75.1 vs. 76.7; $p < 0.001$), had a similar proportion of women (67.7 vs. 70.9%; $p = 0.22$), African Americans (31.2 vs. 34.1%; $p = 0.28$), Hispanics (48.3 vs. 43.4%; $p = 0.09$), and Whites (20.5 vs. 22.5%; $p = 0.39$), a higher prevalence of diabetes (25.7 vs. 20.1%; $p = 0.02$), heart disease (39.7 vs. 28.4; $p < 0.0001$), and stroke (20.3% vs. 11.3%), and a similar prevalence of hypertension (68.8 vs. 67.2%; $p = 0.54$) and current smoking (8.5 vs. 10.1%; $p = 0.35$). The AD conversion rate for the final sample was identical to the original cohort (4 per 100 person-years of follow-up).

Diagnosis of Dementia

Dementia diagnosis was made by consensus based on baseline and follow-up information. Dementia diagnosis was based on DSM-IV criteria (1994) and required evidence of cognitive deficit on the neuropsychological test battery and evidence of impairment in social or occupational function (Clinical Dementia Rating of 1 or more) (Hughes, Berg et al. 1982). AD diagnosis was based on the NINCDS-ADRDA criteria (McKhann, Drachman et al. 1984). Diagnosis of dementia associated with stroke was made when the dementia started within 3 months of the stroke in whom its local effects were thought to be the primary mechanism.

Depressive symptoms

depressive symptoms were assessed using the 17-item Hamilton Depression Rating Scale (HAM) by a trained interviewer (Williams 1988). The validity and reliability of the HAM was established in a subsample of our cohort (Devanand, Sano et al. 1996).

Vascular risk factors and stroke

We included as vascular risk factors those related to higher AD risk (Luchsinger and Mayeux 2004; Luchsinger, Reitz et al. 2005), diabetes mellitus, hypertension, heart disease, and current smoking. Diabetes was defined by self-report at baseline and at each follow-up or by use of diabetes medications. Hypertension was defined by self report or by a systolic blood pressure over 140 mmHg or a diastolic blood pressure over 90 mmHg (Chobanian, Bakris et al. 2003). The results did not change when blood pressure levels were taken into account, and we report results only for hypertension by self-report. Heart disease comprised a history of atrial fibrillation and other arrhythmias, myocardial infarction, congestive heart failure or angina pectoris. Smoking was ascertained by self report and classified as current or ever smoking. These diagnoses have shown a sensitivity and specificity of over 90 percent using medical records as the gold standard (Luchsinger, Reitz et al. 2005). Stroke was defined by World Health Organization criteria (Hatano 1976). Brain imaging was available in 85% of the persons who reported a history of stroke. For secondary analyses we built a composite score of vascular burden by aggregating the presence of risk factors and stroke. For example, if one person had diabetes and hypertension, the score was 2, if only heart disease was present, the score was 1.

Other covariates

Ethnic group was based on self-report using the format of the 1990 census (database 1991) and classified as African American, Hispanic, or White. We examined education as a continuous variable (years of education completed), and as a categorical variable (≤ 6 years of education, 7 - 12 years, 13 - 16 years, and > 16 years). We included ethnic group and education as covariates because Hispanics and African-Americans, and subjects with less education have a higher prevalence of vascular risk factors (Luchsinger 2001), and higher AD risk (Tang, Cross et al. 2001).

APOE genotypes were determined as described by Hixson and Vernier (Hixson and Vernier 1990) with slight modification (Mayeux, Ottman et al. 1995). We classified persons by the presence (homozygous or heterozygous) or absence of the APOE $\epsilon 4$ allele; 126 subjects in the final sample had missing data on APOE genotype.

Statistical Methods

We conducted bivariate analyses comparing all variables between persons with and without dementia using Chi-squared for categorical variables and t-test for continuous variables. We also compared the HAM scores between persons with and without vascular risk factors using t-test. HAM scores were not normally distributed and required logarithmic transformation. Proportional hazards regression (Cox and Oakes 1984) was used in multivariate analyses. We

conducted analyses with the HAM as a continuous variable, and categorized in the following manner: 0, 1-9, > 9, using 0 (persons not reporting any depressive symptom) as the reference. A cutoff of 10 in the HAM is usually used for the diagnosis of depression (Tabert, Liu et al. in press), and we wanted to examine if there was a dose-response relationship between the HAM score and AD. The time-to-event variable was time from HAM administration to incident AD; individuals who did not develop dementia were censored at the last follow-up. Individuals who developed other dementias (e.g. vascular dementia), were censored at the time of diagnosis. We show results for 2 models: one adjusted for age and gender, and another model also adjusting for education, ethnic group, APOE-ε4, diabetes, hypertension, heart disease, current smoking, and stroke. An attenuation of the hazard ratios (HR) in the second model would be interpreted as evidence of mediation of vascular disease in the relation of depression with AD. All analyses were conducted using SAS 9.1 for Windows.

RESULTS

There were 114 cases of AD in 526 participants with a mean follow-up time of 5.1 ± 3.3 years (2,682 person-years); 22.6% of individuals had one follow-up, 17.5% had 2 follow-ups, 9.7% had 3 follow-ups, and the rest (50.2%) had 4 or more follow-ups. The mean age at the time of HAM administration was 75.1 ± 6.4 years; 67.7% of the sample were women, 31.2% were African American, 48.3% were Hispanic, and 20.5% were White. The prevalence of APOE-ε4 was 29.5%. Diabetes was reported by 25.7% of the sample, hypertension by 68.8%, heart disease by 39.7%, current smoking by 8.9%, and stroke by 20.3%. The mean HAM score was 4.6 ± 4.4 ; 13.9 % has a HAM score of 0, 72% had a HAM score between 1 and 9, and 13.9% had a score of 10 or more.

Persons with incident AD were older (Table 1), had less years of education, were more likely to be Hispanic, less likely to be White, more likely to have diabetes, heart disease, stroke, and be current smokers compared to persons without AD. Persons who developed AD also had a higher HAM score before the development of dementia. Diabetes (HR = 1.5; 95% CI: 1.0,2.2), current smoking (HR = 1.9; 95% CI: 1.1,3.4), and stroke (HR = 1.5; 95% CI: 1.0,2.3), but not heart disease and hypertension, were independently associated with a higher AD risk as previously reported in this cohort (Luchsinger and Mayeux 2004). Hypertension, heart disease and stroke were related to higher HAM scores (Table 2), but not diabetes nor current smoking.

HAM as a continuous logarithmically transformed variable was related to higher AD risk (HR for one point increase = 1.4; 95% CI: 1.1,1.8) after adjustment for age and gender. This estimate did not change appreciably after adjustment for vascular risk factors and stroke (HR = 1.3; 95% CI: 1.0,1.7).

Among persons with no depressive symptoms 10.9% converted to AD (table 3), twice as many with 1 to 9 symptoms converted (21.8% vs. 10.9%), and three times as many converted if the HAM ≥ 10 (31.5% vs. 10.9%; global p from chi-square = 0.02).

In multivariate analyses (Table 3) the risk of AD increased with higher HAM scores (HR for HAM ≥ 10 = 3.4; 95% CI=1.5,8.1; p for trend = 0.004). The results were similar when we used a composite score of the presence of vascular risk factors and stroke (HR for HAM ≥ 10 = 3.0; 95% CI: 1.2,7.8; p for trend = 0.02), and when persons with stroke were excluded (HR for HAM ≥ 10 = 2.9; 95% CI: 1.0,9.2; p for trend = 0.06).

DISCUSSION

We found a dose-response association between depressive symptoms and AD risk. A history of cerebrovascular risk factors and stroke did not account for this association.

Patients with major depression have demonstrated high conversion rate to dementia in clinical samples during long term follow-up (Alexopoulos, Meyers et al. 1993). Our group reported the first community-based epidemiological data showing that depressive symptomatology is an antecedent to dementia in the elderly (Devanand, Sano et al. 1996). Numerous studies have reported that depressive symptoms predict incident dementia and cognitive decline (Buntinx, Kester et al. 1996; Dufouil, Fuhrer et al. 1996; Berger, Fratiglioni et al. 1999; Chen, Ganguli et al. 1999; Yaffe, Blackwell et al. 1999; Geerlings, Schoevers et al. 2000; Wilson, Barnes et al. 2002; Green, Cupples et al. 2003; Vinkers, Gussekloo et al. 2004; Mitchell 2005) with little dissenting data (Chen, Ganguli et al. 1999).

Depressive symptoms have been traditionally considered to be more characteristic of vascular cognitive syndromes than AD. It seems clear that cerebrovascular disease disrupts frontal-subcortical pathways causing a frontal syndrome with depressive symptoms and impairment in executive abilities (Pugh and Lipsitz 2002). As reviewed by Alexopoulos et al (Alexopoulos, Schultz et al. 2005), adult depressed patients have low volumes of frontostriatal network structures, including the subgenual anterior cingulate (Drevets, Price et al. 1997), caudate head (Krishnan, McDonald et al. 1992), and the putamen (Husain, McDonald et al. 1991). Elderly depressed patients have low volumes of the anterior cingulate, orbitofrontal cortex, and rectus gyrus (Ballmaier, Toga et al. 2004). Subcortical white matter disease as seen in brain imaging are associated with executive dysfunction (Boone, Miller et al. 1992; Aizenstein, Nebes et al. 2002), a putative clinical feature of frontostriatal dysfunction (Tekin and Cummings 2002). Clearly, disrupted basal ganglia-frontal cortical circuits can lead to depression (Tekin and Cummings 2002; Alexopoulos 2005). Frontal lobe lesions may damage the glutamatergic projections of frontal cortex to striatum, and basal ganglia lesions may damage GABAergic transmission, including in the limbic-striatal pathways. These pathways have been implicated in motivation, psychomotor speed, impaired initiation, memory encoding and retrieval, and visuospatial perception, i.e., cognitive areas beyond executive dysfunction, though associations of these symptoms with lesions in brain imaging is not clear (Krishnan, Hays et al. 1997; Alexopoulos 2002). Vascular dementia, AD, and depression may present in similar ways (Braaten, Parsons et al. 2006), but depressive symptoms seem to be more severe in vascular dementia compared to AD (Newman 1999; Simpson, Allen et al. 1999; Park, Lee et al. 2007) and worsening cerebrovascular disease on MRI is related to onset of dementia in older persons with depression, particularly non- AD dementia (Steffens, Potter et al. 2007). One study showed that depressive symptoms were more prevalent in VD compared to AD, but a history of vascular or cerebrovascular disease was more common in persons with AD with depressive symptomatology compared to those without depressive symptomatology (Bowirrat, Oscar-Berman et al. 2006), supporting our hypothesis. However, one study found no differences between VD and AD in depressive symptomatology (Verhey, Ponds et al. 1995) (Verhey).

Because cerebrovascular disease is increasingly recognized as an important factor in both depression (Alexopoulos, Meyers et al. 1997) and AD (Vermeer, Prins et al. 2003), and cerebrovascular risk factors also predict AD (Breteler 2000; Luchsinger and Mayeux 2004; Luchsinger, Reitz et al. 2005), we postulated that cerebrovascular risk factors and disease was the link between depressive symptoms and AD, which we could support by demonstrating an appreciable attenuation of the relation between depressive symptoms and AD when adjusting for cerebrovascular risk factors and stroke. A putative mechanism in such a relation would have been the disruption of subcortical-frontal pathways and a so-called vascular depression or executive impairment syndrome- as discussed above- co-existing with AD precipitated or caused by cerebrovascular disease. We used a history of vascular risk factors and stroke as a proxy of cerebrovascular disease. We found no evidence that these risk factors and stroke explain the association between depressive symptoms and AD. Our results are consistent with a study in 55 persons showing that cerebral infarctions ascertained at autopsy did not explain

the relation between depressive symptoms and cognitive impairment (Bennett, Wilson et al. 2004). An analysis in 2,220 participants from the Cardiovascular Health Study found that depressive symptoms were associated with a higher prevalence of mild cognitive impairment, a transitional stage between normal cognition and AD (Petersen 2004), independent of vascular disease (Barnes, Alexopoulos et al. 2006), similar to our results. Our results and those of the mentioned studies suggest that depressive symptoms related to cerebrovascular disease may not be the primary mechanism explaining depressive symptoms preceding the diagnosis of AD. Mechanisms other than cerebrovascular disease that could explain the relation of depressive symptoms with AD include a psychological reaction to memory loss, or damage to key catecholaminergic circuits at an early pre-clinical stage of AD. Degenerative processes may lead to dysfunction of limbic structures that increases the vulnerability to depression. In PET studies, a hypermetabolic state of the amygdala is associated with greater depressive symptoms and negative emotions (Drevets 1999; Drevets 2003). Hippocampal atrophy, one of the hallmarks of AD, may be greater in depressed patients and may be associated with chronicity, (Bremner, Narayan et al. 2000; MacQueen, Campbell et al. 2003; Sheline, Gado et al. 2003) and may be a premorbid risk factor for depression (Frodl, Meisenzahl et al. 2002; Campbell and MacQueen 2004; Hastings, Parsey et al. 2004). The CA1 hippocampal region and the subiculum are vulnerable to ischemia (MacQueen, Campbell et al. 2003) and to the effect of hypercortisolemia resulting from stress and chronic medical illness (Miller and O'Callaghan 2003). These factors may underlie the smaller hippocampal volumes seen in elderly depressed patients (Sheline, Gado et al. 2003). Thus, AD and depressive symptoms share pathologic mechanisms beyond the contribution of vascular disease, and this could explain our findings. It is possible that depressive symptoms are part of the AD preclinical syndrome caused by damage in the same structures that explain early memory impairment, such as the hippocampus (Cummings 2004).

We must consider alternative explanations for our finding that a history of vascular disease and stroke did not explain the association between depressive symptoms and incident AD. One is suboptimal ascertainment of vascular risk factors and cerebrovascular disease. We ascertained vascular risk factors and stroke by self-report. We did not have subclinical measures of vascular and cerebrovascular disease burden such as carotid intima-medial thickness, measures of left ventricular hypertrophy, or brain imaging measures of cerebrovascular disease (Reitz, Brickman et al. 2007). In addition, our composite score of vascular history did not take into account the relative weight of each vascular risk factor, nor the duration or severity. This could have resulted in an underestimation of vascular and cerebrovascular burden that could explain our finding that vascular risk and stroke history did not account for the association between depressive symptoms and AD. However, this explanation seems unlikely because vascular risk factors and stroke were both independently related to depressive symptoms and AD. Another potential explanation is bias. Our sample was relatively small and selected from our larger cohort. However, we were able to reproduce the associations from our larger cohort in the smaller analytical sample, which makes selection bias an unlikely explanation for our findings.

Major strengths of our study include assessment of depressing symptoms using a standard valid and reliable tool, AD ascertainment using standard research methods, and its prospective nature. In conclusion, a history of cerebrovascular risk factors or stroke does not seem to account for the relation of depressive symptoms with AD. This suggests that vascular and cerebrovascular disease may not be the primary mechanism relating depressive symptoms to AD. It is possible that depressive symptoms are a result of the same processes that lead to memory impairment in AD, but this requires further study.

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Table 1

Comparison of demographic variables, vascular risk factors, and Hamilton Depression Rating Scale (HAM) score between persons with and without incident Alzheimer's disease. Washington Heights- Inwood Columbia Aging Project 1992-2003.

	No Alzheimer's disease	Alzheimer's disease	p value
Age (years $\pm$ SD)	74.8 $\pm$ 6.6	78.1 $\pm$ 6.6	<0.0001
Gender (%)	272 (67.7)	84 (67.7)	0.99
Education (years $\pm$ SD)	9.0 $\pm$ 4.4	7.3 $\pm$ 4.5	0.0002
African American (%)	120 (29.9)	44 (35.5)	0.24
Hispanic (%)	183 (45.5)	71 (57.3)	0.02
White (%)	99 (24.6)	9 (7.3)	< 0.0001
APOE-ϵ4 (%)	81 (28.0)	36 (33.3)	0.30
Diabetes (%)	92 (22.9)	43 (34.9)	0.009
Hypertension (%)	271 (67.4)	91 (73.4)	0.21
Heart disease (%)	151 (37.6)	58 (46.8)	0.07
Stroke (%)	67 (16.7)	40 (32.2)	0.0002
Current smoking (%)	29 (7.2)	16 (12.9)	0.04
HAM score	4.4 $\pm$ 4.6	5.3 $\pm$ 5.4	0.04

Table 2

Comparison of Hamilton Dementia Rating Scale Scores by the presence of vascular risk factors. Washington Heights-Inwood Columbia Aging Project 1992-2003.

	HAM scores		p value
	Risk factor absent	Risk factor present	
Diabetes	5.4±4.1	5.2±5.1	0.08
Hypertension	3.9±3.8	4.9±4.6	0.01
Heart disease	4.2±4.0	5.3±4.9	0.003
Current smoking	4.7±4.4	4.2±4.0	0.46
Stroke	4.4±4.2	5.3±4.9	0.05

Table 3

Hazard ratios (HR) and 95% confidence intervals relating Hamilton Depression Rating Scale (HAM) scores to incident Alzheimer's disease (AD). Model 1 is adjusted for age and gender. Model 2 is adjusted also for ethnic group, education, APOEε4, diabetes, hypertension, heart disease, current smoking, and stroke. Washington Heights- Inwood Columbia Aging Project 1992-2003.

HAM score	At risk	AD Cases (%)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
0	73	8 (10.9)	1.0	1.0
1-9	380	83 (21.8)	2.4 (1.2,5.1)	2.3 (1.0,5.3)
≥ 10	73	23 (31.5)	3.4 (1.5,8.1)	3.0 (1.2,7.9)
p for trend			0.004	0.03