The Effects of Preexisting Depression on Cerebrovascular Health Outcomes in Geriatric Continuing Care

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Background. Previous studies have investigated depression as the cause and outcome of vascular deficit in elderly persons.

Methods. The authors wanted to determine whether baseline depression is predictive of subsequent cardiovascular events in very elderly persons residing in a continuing care retirement community (n = 181).

Results. Controlling for demographic factors, both depression and the number of cardiovascular risk factors (CVRFs) at baseline were strongly predictive of stroke, whereas only CVRFs strongly predicted myocardial infarctions. Depression accounted for 12% of the variance in stroke incidence, beyond the contribution of CVRFs. Path analysis indicated that depression was also a partial moderator of the effect of CVRFs.

Conclusions. In support of the vascular depression hypothesis, the study findings indicate that, for the oldest old, depression may be a strong predictor of future stroke. The presence of depression in elderly patients should alert physicians to carefully investigate other stroke risk factors and to integrate depression into an overall intervention regimen for reducing patients’ risks for stroke.

One of the key goals of gerontology is to improve satisfaction in late life, by enabling health-care professionals to identify serious conditions and provide early treatment for their patients. One focus has been depression. It has been known for some time that rates of depression are significantly higher in eldercare settings than in the community. For instance, Kramer and associates (1) found a rate of major depression of only 1.3% in the community. In comparison, Rapp and coworkers (2) found that 15.3% of inpatients in a similar sample were depressed, for a rate approximately 10 times higher. This trend has been widely reproduced. Therefore, identifying the causes and consequences of depression is important in improving medical care for elderly persons.

Research has also indicated that depression in elderly people is often related to declines in vascular function. Alexopolous and colleagues (3) defined depression as vascular when it coincided with a history of hypertension or vascular deficit, and they found that this occurs with distinct symptoms, including increased cognitive impairment and disability. Several confirming studies have indicated that elders with cardiovascular risk factors (CVRFs), such as hypertension, are at risk for depression (4,5), and imaging and neuropathologic examinations (6–8) have confirmed a unique physiologic presentation of depression in younger persons, specifically an increased presence of white matter hyperintensities and basal ganglia lesions in conjunction with depression in elderly persons.

Research has also indicated that depression may be conceptualized as both the cause and the result of major health events that are common in elderly individuals. In particular, there has been considerable interest in the link between depression and major cardiovascular events, specifically stroke and myocardial infarction (MI). Everson and colleagues (9) found that the relative risk for death as a result of stroke in depressed patients was 57% to 70% greater than that for nondepressed patients (mean age at baseline, 43.4 years). Wasserthelt-Smoller and colleagues (10) also found increased risks for stroke (6% to 29%) and MI (7% to 20%) in depressed persons (mean age, approximately 70 years). However, Colantino and associates (11) found only a non-significant increase in stroke rate for depressed compared with nondepressed patients (average age, approximately 70 years), and Thomas coworkers (12) found no significant difference in the overall mortality rates for depressed and non-depressed patients (average age, 75 years).

Although the overall rate of stroke is low, one half of all strokes occur in patients older than 75 years (13). Furthermore, previous research into elders’ health outcomes has shown significant differences between the “young-old” (those in their 60s and 70s) and the “old-old” (those older than 80 years). For instance, Hanks and Lichtenberg (14) found that persons older than 70 years showed significantly worse outcomes in rehabilitation, similarly indicating a need to focus screening efforts on this group.

In summary, although previous studies have laid an excellent foundation for understanding the role of depression in stroke outcomes, none of these studies have focused on the oldest old in care settings, the population at greatest risk for depression and stroke. In the current study, we sought to address this gap, considering the oldest old in continuing care. This setting offers two strengths. First, this type of care...
accounts for an increasing portion of eldercare in the United States. Second, members of such a community live independently on entry, with minimal caregiver intervention, suggesting higher functioning and reduced initial comorbidity, creating a baseline that is more representative of the healthy young-old phase, and representing the increasing need for care through follow-up examinations.

To elucidate the relation between vascular deficit and depression, we tested the following hypotheses: (a) that the baseline presence of depression and traditional CVRFs predict cardiovascular events (strokes and MIs) in elders; (b) that, consistent with the vascular depression hypothesis, depression is an early result of the same vascular deficit that leads to cardiovascular events and may therefore serve as a partial mediator between CVRFs and cardiovascular events; and (c) that the impact of baseline depression on stroke incidence is greater than its impact on MI, because depression indicates specific cerebrovascular deficit, whereas MIs may occur when a vascular deficit is localized outside the brain.

METHODS

Participants
Participants in this study consisted of residents in a continuing care retirement community (n = 181) in central Michigan. This facility integrated housing options from independent or assisted living to long-term care. Table 1 summarizes characteristics of the sample, which consisted of mostly female (69.1%), very elderly (M = 83.2 years, SD = 7.1 years), predominantly white (>99%) persons. All residents were admitted to independent living apartments between 1992 and 1996, with many subsequently receiving increased levels of care (n = 68) on average approximately 3 years after admission (M = 35 months, SD = 27.9 months). All participants were examined between 1992 and 2002.

Procedures
Each resident was examined at baseline (admission), and at least once yearly thereafter, by a board-certified geriatrician. Depression was recorded at baseline for many of the residents (n = 126) through administration of the Geriatric Depression Scale (GDS-15) and was also evaluated by physician diagnosis (DSM-III-R criteria). This scale has been extensively validated for use with the elderly population in community, clinical, and eldercare settings (15). In addition, cognitive functioning was assessed at baseline using the Mini-Mental State Examination (data available for 151 residents), with a cutoff score of 24 or better indicating intact functioning.

Cardiovascular risk factors were documented after a physical examination by the attending physician and consisted of hypertension (defined as systolic blood pressure of at least 160 mmHg and diastolic blood pressure of at least 90 mmHg), congestive heart failure, arterial fibrillation, diabetes, hyperlipidemia (defined as a low-density lipoprotein count of at least 150 mg/dL), and smoking (participant report of lifetime history). Although body mass index was calculated, few residents qualified as obese, and so obesity was not included as a CVRF. Using dates of onset, only CVRFs prevalent at admission were included in the analysis. Finally, stroke and MI incidence were documented during the follow-up period, as indicated by physician diagnosis.

Some residents were removed from the sample as a result of missing baseline data: Mini-Mental State Examination (n = 60), GDS (n = 55), or both. One was removed because of prevalent stroke history (none experienced prevalent MI), leaving a total of 110 participants in the reduced sample. The participants were separated into 3 outcome groups: those who experienced a stroke (n = 24), an MI (n = 15), or neither (n = 73). Two residents experienced both events and were included in both of the latter groups.

Statistical Procedures
Pearson correlations were performed to assess the relationship between the predictor variables (demographics, depression, cognitive function, and CVRFs) and the criterion (stroke or MI). The incidence rates for stroke and MI for depressed and nondepressed residents were calculated with the respective 95% confidence intervals.

Binary logistic regressions were performed to model the likelihood of MI and stroke as a function of demographics, cognitive function, CVRFs, and depression. Variables were entered blockwise, with sex, the number of CVRFs, and depression entered in late blocks. All regression analyses were performed using SPSS version 11.5 (SPSS, Chicago, IL). Finally, a path analysis was performed using Amos version 5.0 (SPSS, Chicago, IL) to determine whether depression mediated the relationship between CVRFs and the subsequent incidence of stroke. In this analysis, the number of CVRFs and sex were entered as exogenous variables, and depression and stroke incidence were entered as endogenous variables. Sex was included in the model because of its significant correlation with depression prevalence.

RESULTS
Table 1 summarizes the demographics of the original and reduced samples. Consistent with previous literature, the baseline depression rate was 34.9%, and 82.1% of residents
displayed MMSE scores in the range of intact functioning (defined as a score of 24 or more, with a mean of 26.5 points, $SD = 3.5$ points). A cut score of 6 or more on the GDS-15 was used to indicate depression; when compared with clinical diagnoses, this was found to have a sensitivity of 0.71. The reduced sample ($n = 110$ persons with baseline GDS and MMSE data and no history of stroke or MI at admission) did not differ significantly on any demographic variable, although the average number of CVRFs per participant was higher ($t(289) = 2.206, p < .05$) than in the original sample, as was the nominal incidence rate of strokes ($\chi^2 = 9.491, p < .01$).

Table 2 shows the demographic comparisons of outcome groups. Demographic differences between groups were primarily limited to sex: the stroke group had a significantly higher percentage of women, and the MI group had a significantly lower percentage of women compared with the “neither” group ($\chi^2 = 12.769, p = .002$). Beyond demographics, the stroke group had a higher rate of depression than the MI group, which in turn had a higher rate of depression than the neither group ($\chi^2 = 41.859, p < .001$). A one-way analysis of variance test with post hoc Tukey-HSD assessment indicated that both the stroke and MI groups had significantly greater numbers of CVRFs, but the difference between the 2 groups was not significant ($F = 25.030, p < .001$).

The Pearson correlation test was used to determine the relationships between baseline characteristics and outcomes (Table 3). Although not all variables are truly interval-ratio, this parametric test is sufficiently robust to provide meaningful estimates. In cases below with a substantial deviation (>$5\%$) between the Pearson and Spearman tests, both values are indicated. Although not shown, correlations between CVRFs ranged from $r = .04$ to $r = .45$. The number of CVRFs was strongly positively correlated with baseline depression ($r = .47, p < .001$) and with the likelihood of both stroke ($r = .43, p = .46$; both $p < .001$) and MI ($r = .34, p = .30$; both $p = .001$). However, hypertension was a better predictor of stroke and diabetes was a better predictor of MI than the overall number of CVRFs. Depression at baseline, measured using the GDS, showed strong positive correlation with the likelihood of stroke ($r = .62, p < .001$) but not MI ($r = -.05, p = .594$).

Finally, sex was considerably correlated with depression ($r = -.21, p = .024$) and with the rates of MI ($r = .25, p = .008$) and stroke ($r = -.21, p = .027$), with women being more likely to be depressed at baseline and to experience strokes, and men being more likely to be free of depression at baseline and to experience MI.

The incidence rate of stroke in the depressed group ($58\%$) was significantly higher than in the nondepressed group ($4\%$). In comparison, we found no significant difference in MI rates ($11\%$ vs $15\%$). Table 4 summarizes the incidence rates and shows the associated confidence intervals.

We used logistic regression to determine whether depression was a significant predictor of stroke, once the effect of CVRFs was taken into account (Table 5). Sex was not significant, indicating that traditional physiologic risk factors can explain the difference in stroke rates between men and women in this sample. The number of CVRFs was significant, explaining an additional $15\%$ of variance in stroke incidence beyond demographic factors. However, depression also accounted for a large amount of variance ($12\%$), above and beyond demographics and CVRFs, and reached the highest level of significance ($p < .001$) in the model. For comparison, a similar model of MI incidence was tested; in this model, only the number of CVRFs
Our initial hypotheses were (a) that baseline CVRFs and depression predict cardiovascular events in elderly people; (b) that depression mediates the effect of CVRFs on event likelihood; and (c) that the impact of depression on stroke is stronger than that for MIs. This investigation showed that although both CVRFs and depression are predictive of stroke incidence, only CVRFs are predictive of MIs, partially validating the first hypothesis. Most of the contribution of CVRFs to stroke incidence came through the mediation of depression, a path that did not significantly explain the incidence of MI, validating the second and third hypotheses.

The vascular depression hypothesis states that depression in elderly populations may be attributed frequently to impaired cerebrovascular function (3). Although this may be related to obstructions in the heart or surrounding arteries, which may lead to MI, it is much more directly related to strokes, particularly of the embolism type, which can only arise from preexisting cerebrovascular obstruction. Therefore, the fact that depression often presaged stroke in our participants with vascular burden is consistent with the vascular depression hypothesis, in that vascular depression may be an early adverse effect of the process leading to strokes.

This study is the first, to our knowledge, to present a dramatically increased risk for stroke in depressed elders. Although previous studies have investigated this, they have either failed to find a risk increase or found a considerably smaller increase. One key difference between this study and past studies is age; the current mean age of 83.2 years is more than 10 years older than other reported samples. Previous studies have shown that age is a strong direct predictor of death and also mediates other risk factors (16).

Applications and Future Directions

Our primary conclusion is that, at least in the old-old, depression appears to identify cerebrovascular deficit and predict future stroke. It is not yet clear how the comorbidty of cerebrovascular deficit and depression arises. Although studies have identified white-matter hyperintensities and other lesions, there is no consensus on their origin. One possible source is undiagnosed or underdiagnosed transient ischemic attacks. Although they are traditionally defined by their short nature (all symptoms pass within 1 day) and lack of permanent damage, recent studies have indicated longer-term effects of transient ischemic attacks. Lovett and colleagues (17) found that they significantly predicted subsequent stroke. One possible mechanism is that transient ischemic attacks may only slowly create lesions, which are not reported as a result of the apparent transience of symptoms, but that lead, over time, to vascular depression and stroke.

Our study was limited in several ways. The lack of imaging analysis or post-mortem examination precludes our ability to confirm the definite vascular nature of depression, although the age range and strong relationship to vascular burden make this a reasonable assumption. Furthermore, we are limited by a lack of data on the focal or diffuse nature of the strokes observed, probable thrombotic or embolic nature. A demonstration that vascular depression increases

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**Table 5. Binary Logistic Regression of Stroke Outcome Against Baseline Variables**

<table>
<thead>
<tr>
<th>Block</th>
<th>Variable</th>
<th>β</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>Sig</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Cum. R² (Cox &amp; Snell)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0)</td>
<td>Constant</td>
<td>−1.35</td>
<td>4.69</td>
<td>0.08</td>
<td>1</td>
<td>0.77</td>
<td>1.00</td>
<td></td>
<td>0.00</td>
</tr>
<tr>
<td>(1)</td>
<td>Age at</td>
<td>−0.02</td>
<td>0.05</td>
<td>0.22</td>
<td>1</td>
<td>0.64</td>
<td>0.98</td>
<td>(0.89, 1.08)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>admission, y</td>
<td>−0.14</td>
<td>0.72</td>
<td>0.04</td>
<td>1</td>
<td>0.85</td>
<td>0.87</td>
<td>(0.21, 3.56)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marital status*a</td>
<td>−0.04</td>
<td>0.13</td>
<td>0.96</td>
<td>1</td>
<td>1.01</td>
<td>1.00</td>
<td>(0.78, 1.29)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Level of education, y</td>
<td>0.01</td>
<td>0.03</td>
<td>1.05</td>
<td>1</td>
<td>0.72</td>
<td>0.36</td>
<td>(0.01, 0.75)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Body mass index¹</td>
<td>−0.38</td>
<td>0.06</td>
<td>0.32</td>
<td>1</td>
<td>1.90</td>
<td>0.14</td>
<td>(0.18, 2.54)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High functioning per MMSE²</td>
<td>−0.89</td>
<td>0.87</td>
<td>1.04</td>
<td>1</td>
<td>0.31</td>
<td>0.41</td>
<td>(0.07, 2.26)</td>
<td></td>
</tr>
<tr>
<td>(2)</td>
<td>Sex*</td>
<td>−0.23</td>
<td>0.83</td>
<td>2.18</td>
<td>1</td>
<td>0.14</td>
<td>0.29</td>
<td>(0.06, 1.50)</td>
<td>0.09</td>
</tr>
<tr>
<td>(3)</td>
<td>No. of CVRFs</td>
<td>0.56</td>
<td>0.25</td>
<td>5.21</td>
<td>1</td>
<td>0.02</td>
<td>1.78</td>
<td>(1.09, 2.92)</td>
<td>0.24</td>
</tr>
<tr>
<td>(4)</td>
<td>Depressed per GDS¹</td>
<td>2.90</td>
<td>0.74</td>
<td>15.52</td>
<td>1</td>
<td>1.00</td>
<td>18.17</td>
<td>(4.30, 76.90)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

*Notes: Outcome coded as stroke occurred = 1, *Coded as married = 1, †Coded as impaired functioning = 1 (MMSE < 24); ‡Coded as male = 1; §Coded as depressed (GDS ≥ 6) = 1. SE = standard error; CI = confidence interval; MMSE = Mini-Mental State Examination; CVRF = cardiovascular risk factor; GDS = Geriatric Depression Scale.

(β = .83, p = .001) was significant at the α = .05 level. Depression was not significant (β = −1.08, p = .186). The addition of the depression block in this model had a minimal impact on the R² value, increasing it from .18 to .19.

Finally, we conducted a path analysis to determine whether depression mediated the relationship between CVRFs and the incidence of stroke (Figure 1). CVRFs were predictive of depression, and depression was a strong predictor of incident stroke. Although the relationship between CVRFs and stroke remained statistically significant in this model, the magnitude of this relationship was diminished by the inclusion of depression as a mediator when compared with the bivariate correlation coefficient between CVRFs and stroke (r = .43, p = .46, both p < .001). Therefore, depression partially mediated the relationship between CVRFs and stroke.

**Discussion**

Implications of the Results

Our study was limited in several ways. The lack of imaging analysis or post-mortem examination precludes our ability to confirm the definite vascular nature of depression, although the age range and strong relationship to vascular burden make this a reasonable assumption. Furthermore, we are limited by a lack of data on the focal or diffuse nature of the strokes observed, probable thrombotic or embolic nature. A demonstration that vascular depression increases
the likelihood of embolic strokes to a greater degree than thrombotic strokes would further validate the role of long-term cerebrovascular impairment in depression in elderly persons.

Finally, our study was relatively small and did not examine young-old and old-old participants simultaneously. Although it would be difficult to examine a large group including comparable members of both categories, it would directly demonstrate the dependence of this phenomenon on age.

Although depression does not have adequate predictive power to be a stand-alone diagnostic indicator for increased stroke risk, geriatricians dealing with depressed, elderly patients would be well advised to investigate the possibility of other stroke risk factors and to integrate therapeutic interventions for depression and cardiovascular risk.

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