DYLAN WINT, MD
Lou Ruvo Center for Brain Health,
Cleveland Clinic, Las Vegas, NV

Depression: A shared risk factor for cardiovascular and Alzheimer disease

ABSTRACT

Depression has been linked to cardiovascular disease and cognitive impairment, including Alzheimer disease, but the exact nature of the relationship is poorly understood. Although depression seems to progress little after the onset of Alzheimer disease, depression in earlier life increases the risk of dementia and cognitive impairment many years in the future. Depression is also associated with reduced vascular function and is a poorly recognized but significant risk factor for stroke.

The associations among depression, cardiovascular disease, and cognitive impairment are well known. Inflammation is increasingly recognized as playing an important role as well. However, the nature of their relationships and which may actually cause the other is not well understood. This article reviews studies over the past year that link depression with dementia and vascular disease. Desirable directions for future work are also explored.

DEPRESSION AND ALZHEIMER DISEASE

Several studies have shown significant correlations between depression and the risk of developing Alzheimer disease; the frequency of depressive episodes appears to be an important factor. Despite the risk relationship, however, depression and Alzheimer disease may not share a common pathology.

No shared pathology

Wilson and colleagues[1] analyzed data from the Chicago Health and Aging Project, a longitudinal cohort study of risk factors for Alzheimer disease that involved two groups of people aged 65 years and older; one group was composed of people who developed dementia during the study, while the other group had already developed dementia or had some degree of cognitive impairment. The investigators reasoned that if pathologic changes are common to depression and dementia, then there would be evidence of change in depressive symptoms along with the progression of dementia. They found only a barely perceptible increase in depressive symptoms among people who developed Alzheimer disease and concluded that there is no shared pathology between depression and Alzheimer disease.

Degree of depression signals risk

Depression has been associated with nearly double the risk of developing dementia and Alzheimer disease. Saczynski et al[2] evaluated 949 people in the Framingham study, mean age 79 years, using the 60-point Center for Epidemiologic Studies Depression Scale (depression defined as > 16 points). Individuals who had depression at baseline were 1.7 times more likely to develop dementia over the 17-year evaluation period. Results were similar when adjusted for major vascular risk factors (smoking, diabetes, hypertension, and cardiovascular disease). The correlation was slightly lower but still significant when subjects taking antidepressant medications were included in the depressed group.

The study also found a continuous relationship between the level of depression and the likelihood of developing dementia and Alzheimer disease: for every 10-point increase on the depression scale, the risk of developing dementia increased by nearly 50%. This study supports depression as a risk factor for dementia. One could also argue that depression as a simple prodrome to dementia seems unlikely because of the long followup between baseline assessment and the development of dementia.

Multiple episodes of depression increase risk

Dotson et al[3] analyzed data from 1,239 older adults from the Baltimore Longitudinal Study of Aging who

Dr. Wint reported that he has no financial relationships that pose a potential conflict of interest with this article.

This article was developed from an audio transcript of Dr. Wint's lecture at the 2010 Heart-Brain Summit. The transcript was formatted and edited by the *Cleveland Clinic Journal of Medicine* staff for clarity and conciseness, and was then reviewed, revised, and approved by Dr. Wint.

doi:10.3949/ccjm.78.s1.07

did not have depression, dementia, or mild cognitive impairment at baseline. Every 1 to 2 years for about 25 years, cognitive status and mood of the subjects were evaluated. About 10% of the participants developed dementia during the course of the study. Of those who developed dementia, 35% had at least one episode of depression; among those who did not develop dementia, only 23% had a depressive episode. Findings were similar when investigators controlled for vascular risks and vascular dementia.

One episode of depression was associated with an 87% increase in risk of dementia; at least two episodes of depression more than doubled the risk (108%). Overall, each episode of depression conferred an additional 14% risk of developing dementia. Among subjects who had had two or more episodes of depression, the median age of developing dementia was 85 years versus 95 years for those without an episode of depression.

This study had the advantages of being prospective for both depression and dementia and of having a long followup period. A dose-effect relationship was observed, with the "dose" being the number of depressive episodes (rather than severity of depression). Because the definition of a depressive episode included subsyndromal depression (not likely to meet the criteria of clinical depression, but still clinically significant), the findings suggest that even minor depression increases the risk of dementia.

Baseline depression predicts cognitive impairment

Rosenberg et al[4] found depression to be associated with cognitive impairment in their evaluation of 436 women in their 70s; the women, who were participants in the Women's Health and Aging Study, were evaluated for up to 9 years. To be included in the evaluation, subjects needed a Mini-Mental State Examination score of at least 24 points (out of 30 possible) and could not be impaired in more than one basic functional capacity: mobility and exercise tolerance, upper extremity, higher functioning (eg, shopping), and basic self-care). Baseline depressive symptoms were measured using the Geriatric Depression Scale.

Cognitive testing included Hopkins Verbal Learning Tests (for immediate and delayed word recall) and Trail Making Tests (for psychomotor speed and executive functioning). Those who were not impaired (ie, having a cognitive test score below the 10th percentile for age-adjusted norms) were followed with up to six examinations over the next 9 years.

Baseline depression was found to be highly associated with incident impairment in all cognitive areas, especially in executive functioning. For every point increase in the depression scale, a 6% to 7% increase was found in the annual risk of impairment in each cognitive domain.

DEPRESSION AND VASCULAR DISEASE LINKED

It is somewhat easier to assess the relationship between depression and vascular disease than between depression and cognitive impairment because of the availability of objective measures of cardiovascular function.

The International Stroke Study (INTERSTROKE),[5] a case-control study in 22 countries with 3,000 cases of stroke and 3,000 age-, gender-, and ethnicity-matched controls, found nine risk factors that were correlated with 90% of ischemic stroke cases. Depression, with an odds ratio of 1.86, was found to be a more significant risk factor than physical activity, diet, or heavy drinking.

Paranthaman et al[6] evaluated a number of measures of arterial anatomy and function in 25 subjects with depressive disorder and in 21 nondepressed controls (mean age, 72 years). They found that depressed subjects had significantly higher mean carotid intima media thickness, reduced dilation in response to acetylcholine in preconstricted small arteries, and more dilated Virchow-Robin spaces in the basal ganglia observed on magnetic resonance imaging. This study provides evidence that arterial structure and function may mediate the relationship between depression and vascular disease.

FUTURE DIRECTIONS

Future studies into depression as a risk factor should use very well-characterized cohorts that are controlled for blood pressure and other vascular risk factors. Finding biomarkers for depression would be useful, permitting its detection earlier and with more certainty than is now possible. Prospective studies to evaluate the relationship of depression to cognitive impairment and dementia are needed that start earlier than in middle or old age. The key question that needs study is whether treatment of depression can actually change the onset of cognitive impairment, Alzheimer disease, and vascular disease.

REFERENCES

1. **Wilson RS, Hoganson GM, Rajan KB, Barnes LL, Mendes de Leon CF, Evans DA.** Temporal course of depressive symptoms during the development of Alzheimer disease. Neurology 2010; 75:21–26.
2. **Saczynski JS, Beiser A, Seshadri S, Auerbach S, Wolf PA, Au R.** Depressive symptoms and risk of dementia: the Framingham Heart Study. Neurology 2010; 75:35–41.

3. **Dotson VM, Beydoun MA, Zonderman AB.** Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. Neurology 2010; 75:27–34.
4. **Rosenberg PB, Mielke MM, Xue QL, Carlson MC.** Depressive symptoms predict incident cognitive impairment in cognitive healthy older women. Am J Geriatr Psychiatry 2010; 18:204–211.
5. **O'Donnell MJ, Xavier D, Liu L, et al; INTERSTROKE investigators.** Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet 2010; 376:112–123. Epub 2010 Jun 17.
6. **Paranthaman R, Greenstein AS, Burns AS, et al.** Vascular function in older adults with depressive disorder. Biol Psychiatry 2010; 68:133–139.

Correspondence: *Dylan Wint, MD, Lou Ruvo Center for Brain Health, Cleveland Clinic, 888 West Bonneville, Las Vegas, NV 89106; wintd@ccf.org*