Are Mood Disorders a Stroke Risk Factor?

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A growing body of evidence suggests that biological mechanisms underlie a bidirectional link between depression and many neurological illnesses, and that mood disorders can affect the course of the diseases.1 Depression commonly occurs after a stroke, with an estimated prevalence as high as 30% in the first year after the event.2 It is well known that poststroke depression affects quality of life, functional recovery, cognitive function and health care use in stroke survivors.3 Inversely, does any association exist between a history of a previous affective disorder and future risk of cardiovascular events? Recent prospective studies have shown an association between depression and incidence of hypertension,4,5 coronary heart disease,6,7 and cardiovascular mortality.8–11

In the Multiple Risk Factor Intervention Trial, 12 866 men were followed for 18 years; those with greater depressive symptoms, as measured by the Center for Epidemiologic Studies Depression Scale (CES-D), were associated with a significant higher risk of cardiovascular mortality (hazard ratio = 1.21; 95% CI, 1.03 to 1.41; P < 0.05) and stroke mortality (hazard ratio = 2.03; 95% CI, 1.20 to 3.44; P < 0.01).12 The NHANES I Epidemiologic Study13 showed that individuals reporting 5 or more symptoms of depression at baseline were 50% more likely to die of a stroke-related cause during a 29-year follow-up.

The Baltimore Epidemiologic Catchment Area Study showed that individuals with a history of depressive disorder, measured with the diagnostic interview schedule, were 2.6 times more likely to report stroke.14 Depressive symptoms, measured by the Zung Self-rating Depression Scale, were also associated with an increased incidence of ischemic stroke in a Japanese 10-year follow study.15 Self-reported depression scores significantly predicted stroke in an Australian cohort of people 60 years and older followed for >8 years.16 Significant psychological distress, as measured by the 30-item General Health Questionnaire, was also a predictor of fatal ischemic stroke in the Caerphilly Study (relative risk 3.36; 95% CI, 1.29 to 8.71).17

The study by Salaycik et al18 in this issue of Stroke provides some new insights to the association between mood disorders and risk of ischemic stroke in young and middle-aged people. They conducted a prospective study on 4120 Framingham Heart Study participants, using up to 8 years of follow-up. The CES-D was used to measure depressive symptoms. In this community-based study, depressive symptoms were an independent risk factor for incident stroke/transient ischemic attack in people <65 years. Additionally, the risk of developing stroke/transient ischemic attack was 4.21 times greater in those individuals with symptoms of depression. After adjusting for traditional vascular risk factors (hazard ratio = 3.43; 95% CI, 1.60 to 7.36; P = 0.002) and education (hazard ratio = 4.89, 95% CI, 2.19 to 10.95) similar results were obtained.

Pathogenic Mechanisms

How can we explain this association? Several mechanisms have been proposed to explain the increased risk of cardiovascular disease in depressed patients19–22: (1) sympathoadrenal hyperactivity; (2) diminished heart rate variability; (3) ventricular instability; (4) biological markers, including platelet activation and inflammatory proteins; (5) myocardial ischemia reaction to mental stress. However, the mechanisms by which depressive symptoms may increase the risk of stroke have not been fully elucidated.

It is possible that depressive symptoms may be associated with stroke through the development of hypertension because it has been reported that depressive symptoms predicted later hypertension incidence.4,5 Some authors have considered the association of depressive symptoms and later onset of ischemic stroke an epiphenomenon because late-life depression may have a vascular basis. According to the vascular depression hypothesis, small-vessel disease secondary to hypertension or diabetes may disrupt frontal-subcortical circuits and generate depressive symptoms.23

Depression may also increase the risk of ischemic stroke through increased platelet aggregation.24 Mean plasma levels of platelet factor 4 and β-thromboglobulin were reported to be higher in depressed patients with ischemic heart disease than in nondepressed patients with ischemic heart disease and healthy controls.25 Selective serotonin reuptake inhibitors are known to inhibit platelet activity. Treatment with selective serotonin reuptake inhibitors in depressed postacute coronary syndrome patients has been associated with reductions in platelet/endothelial activation.26

Finally, depressive symptomatology may also be associated with a higher prevalence of other modifiable lifestyle risk factors, such as smoking27 and lower levels of physical activity.28 Behavioral factors, although potential cofounders, do not seem to attenuate the association between depression and stroke incidence.

Methodological issues

Several methodological issues warrant discussion. The question whether depression, depressive symptoms or depressive...
scores on self-rating questionnaires are associated with risk of stroke is clinically relevant. Most studies that analyzed the link between depression and stroke used self-rating scales. Furthermore, they did not confirm the clinical diagnosis of depression by using a psychiatric structured interview or the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. The criteria for the diagnosis of a depressive episode should include at least 2 weeks of depressed mood, loss of interest, or diminished sense of pleasure plus 4 of 7 other features that are sufficient to cause clinically important psychological or physical distress or functional impairment.29

Pre- and poststroke depression are generic terms. For example, differential diagnosis of poststroke depression should include the pseudodepressive manifestations of strategic infarctions (apathy, aprosody, lack of self psychic activation syndrome, pathological crying, and frontal disexecutive syndrome).30 Many epidemiological studies that have focused on depression as a risk factor for stroke only screened “depressive symptoms”. It should be convenient to evaluate a wider spectrum of affective disorders (first major depressive disorder, refractory and chronic depression, atypical depression, bipolar disorder), anxiety disorders and a variety of mental conditions including stress, coping and adjustment reactions, and even subjective emotional well-being. In addition, 10% to 30% of persons with a major depressive episode recover incompletely and have persistent, residual depressive symptoms, called dysthymia. The symptoms of this disorder are similar to those of major depression but last longer and are milder.31

The influence of complications of the mood disorders, such as suicide risk, and important comorbidities, including alcoholism and substance-abuse should be addressed. Other psychosocial factors including social network, psychological status, and personal characteristics may confound the relation between depressive scores and risk of stroke, and should also be analyzed more deeply in further studies.

Psychometric properties of self-rating and/or evaluator-rating scales for depression should be evaluated. Although the CES-D has been the most frequently used self-rating scale and has adequate internal consistency and reliability, other questionnaires have not proven it yet. Briefly, the process of validation and analysis of the metric properties of a self-rating versus evaluator-rating scale should include the following: acceptability (floor and ceiling effects), scaling assumptions (item-total correlation), reliability (internal consistency assessed by using Cronbach’s α; test-retest reliability for individual items assessed by means of weighted κ; test-retest reliability for total scores assessed by means of an intraclass correlation coefficient), construct validity and convergent validity.

Clinical Implications

Which are the clinical implications of an association between mood disorders and stroke incidence in individuals below 65 years? May it be suggested that any reduction in depressive symptoms in those patients at above average stroke risk might potentially result in a corresponding decline in stroke incidence and mortality? Caution is urged because we need to improve and confirm the diagnosis of affective disorders.

Do these data suggest that identification and treatment of depressive symptoms at younger ages may have an impact on the primary prevention of stroke? We need more evidences to propose, as a stroke primary prevention strategy, the prevention and treatment of mood disorders. This situation can be compared with literature regarding poststroke depression therapy because the effectiveness of early initiation of antidepressants in the prevention of poststroke depression is not clear.32 However, the life-long nature of many of the mood disorders, their elevated risk of recurrence and the existence of a wide range of treatments (depression-specific psychotherapies, cognitive therapy and pharmacotherapy), are supporting facts for their prevention, early recognition and treatment.33,34

The results of this interesting study from the Framingham Heart Study investigators raise more questions, and further studies will be necessary to analyze the association between affective disorders and specific ischemic and hemorrhagic stroke subtypes. According to proposed pathogenic mechanisms, an association between mood disorders and atherosclerotic and lacunar stroke subtypes could be hypothesized. Stroke severity, recurrence, mortality, and ethnicity should be studied in specific neuropsychiatric diagnostic categories through standardized measures. The strength of this association among minority populations has not been fully analyzed.

Finally, changes in depression severity over time, rather than baseline depression, might also be predictive of cardiovascular events and should be further evaluated.

Disclosures

None.

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