The Homocysteine Hypothesis of Depression

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High levels of homocysteine are associated with cerebrovascular disease, monoamine neurotransmitters, and depression of mood. A plausible hypothesis for these associations is that high homocysteine levels cause cerebral vascular disease and neurotransmitter deficiency, which cause depression of mood. The homocysteine depression hypothesis, if true, would mandate inclusions of imaging studies for cerebrovascular disease and measures of homocysteine, folate, and B12 and B6 vitamins in the clinical evaluation of older depressed patients. Longitudinal studies and clinical trials should be designed to challenge the hypothesis.

If depression of mood is in some cases a symptom of disease, knowledge of etiology would lead to prevention and knowledge of pathogenesis would lead to a cure. Although there probably are multiple genetic and environmental causes of depression, we review the evidence here to support one hypothesis or model of depression as a disease. The hypothesis is that genetic and environmental factors elevate homocysteine levels, which cause vascular disease of the brain, and/or transmitter alterations, which cause depression.

Evidence Supporting the Hypothesis

Prevalence of Hyperhomocysteinemia in the Population and in Disease

Homocysteine levels are higher in the elderly and in men (4). In 1,160 adults from the original Framingham Heart Study cohort who had survived to 67 to 96 years of age, a high homocysteine level (>14 µmol/liter) was present in 29.3%. Homocysteine levels were correlated with age and correlated inversely with folate and vitamins B6 and B12 (5). In another study, of women ages 15 to 44, 13% of the sample had elevated total plasma homocysteine concentrations, defined as a concentration ≥10.0 µmol/liter (6).

Some studies find elevated levels of homocysteine in Alzheimer’s disease (7, 8) and cognitive impairment (9), but others do not (10, 11). Hyperhomocysteinemia was also present in 20% of stroke patients but only 2.2% of comparison subjects (odds ratio=5.75; 95% confidence interval [CI]=1.24–53.4, p<0.01) (12).
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Background

We provide background information, recently reviewed by Coppen and Bolander-Gouaille (1), and then review studies supporting the hypothesis. Homocysteine is a sulfurated amino acid derived from ingested methionine found in cheeses, eggs, fish, meat, and poultry. It is directly toxic to neurons and blood vessels and can induce DNA strand breakage, oxidative stress, and apoptosis (2, 3). The methionine-homocysteine metabolic pathway intermediaries are S-adenosylmethionine and S-adenosylhomocysteine. The pathway produces methyl groups required for the synthesis of catecholamines and DNA. This is accomplished by remethylating homocysteine—using B₁₂ and folate as cofactors—back to methionine. Homocysteine is cleared by transulfuration to cysteine and glutathione, an important antioxidant. Transulfuration requires vitamins B₆ and B₁₂.

The components of the homocysteine-methionine cycle, as well as cysteine and glutathione and the enzymes of the pathway, are affected by genetic variation, diet, kidney and gastrointestinal diseases, and prescribed and over-the-counter drugs. Since homocysteine is a sensitive indicator of B vitamin deficiency, an elevated homocysteine level is a marker for a pathogenic process as well as a cause of pathology.

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Samples of geriatric patients have higher levels of homocysteine than do samples of community-dwelling elderly. For example, among patients ages 65 and over who were admitted into an acute care geriatric ward in Northern Italy, 74.2% of men and 68.9% of women had elevated homocysteine levels. Elevated total plasma homocysteine concentrations were associated with older age, male gender, increasing serum creatinine, lower Mini-Mental State Examination score, and disability (4).

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Causes of Hyperhomocysteinemia

Serum levels of homocysteine increase after methionine loading; in dietary deficiency of B12, folate, and B6 (13); and because of renal disease (14, 15) and genetic variation of the enzymes (such as methyl-tetrahydro-folate reductase [MTHFR] and cystathionine beta-synthetase [CBS]) essential for the metabolism of homocysteine. Other causes of hyperhomocysteinemia include gastric atrophy (16), inflammatory bowel disease (17), and laxative use (18), all of which interfere with absorption of nutrients. Anticonvulsants and diuretics elevate homocysteine levels (19).

Homocysteine and Vascular Disease

The association between homocysteine and vascular disease has been documented in studies of genetic variation and from population-based studies of prevalence and incidence. McCully (20) first described the similarity of the homocystinuric vascular lesions to atherosclerosis in two autopsied cases of children with homocystinuria. Furthermore, he showed that the lesions of atherosclerosis could be induced in rabbits by administering either dietary or parenteral methionine or homocysteic acid parenterally. The rabbits died from pulmonary embolism and pulmonary infarct (21).

Genetic Mutations Elevate Homocysteine Levels

Mutations of MTHFR and CBS genes cause a rare recessive genetic disease: homocystinuria. It was first described in 1962 when Carson and Neil, screening urine for amino acid abnormalities in mentally retarded subjects, found four cases of elevated homocysteine levels of 2,000 screened. It was clear from later studies that vascular disease was a regular feature of the phenotype (22). In patients with homocystinuria, the probability of having a clinically detected thromboembolic event by age 15 was 27%, and the probability of not surviving to age 30 was 23% (23). Many mutations have been discovered to cause homocystinuria. Another feature of homocystinuria is the high prevalence of psychiatric disorders. In a study of 63 homocystinuric patients who had been treated with B6, the overall rate of clinically significant psychiatric disorders was 51%, including episodic depression (10%), chronic disorders of behavior (17%), chronic obsessive-compulsive disorder (5%), and personality disorders (19%). The average IQ was 80 (SD=27) (24). In summary, mutations of genes regulating homocysteine metabolism cause mental retardation, vascular brain disease, and psychiatric symptoms.

In addition to the mutations that cause homocystinuria, there are several known allelic variants of the MTHFR gene. Approximately 10% of the population carries the c67TT MTHFR allele, which is associated with elevated homocysteine levels (25). These normal variants increase the risk for myocardial infarction and ischemic stroke, particularly among younger patients and women (26–32). However, two studies showed no association between the c67TT allele and stroke (25, 33).

Interaction of genes and environment were found in a study from Hungary that demonstrated that MTHFR c67TT alleles, when combined with environmental effects, such as drinking or smoking, increased the risk of vascular disease more than the alleles or environmental factors by themselves (34). Many other genes in the methionine pathway are known, but their allelic variants have not yet been explored for clinical associations.

Elevated Homocysteine Levels and Risk

Maternal deficiency of folate and elevated homocysteine levels during pregnancy increase the risk of neural tube defects and possibly schizophrenia (35–37). By 1989, elevated homocysteine was established as an independent risk for vascular disease. Ueland and Refsum (38), distinguished investigators in this area, noted, “Impaired homocysteine metabolism seems to exist in 15–30% of patients with premature cardiovascular disease. Moderate hyperhomocysteinemia is a risk factor for cardiovascular disease, independent of conventional risk factors.”

Results of a recent meta-analysis of prospective studies suggest that lowering the serum homocysteine level by 25% (about 3 µmol/liter) decreases the risk for ischemic heart disease. Reduction of levels reduces the risk of heart disease by 11% and stroke by 19% (16). Another meta-analysis of 72 studies concluded that “lowering homocysteine concentrations by 3 micromol/liter from current levels (achievable by increasing folic acid intake) would reduce the risk of ischemic heart disease by 16%, deep vein thrombosis by 25%, and stroke by 24%” (39).

A dose-response relationship was found in a prospective study in Rotterdam. The risk of stroke and myocardial infarction increased directly with total homocysteine level (6% to 7% for every 1 µmol/liter increase in total homocysteine level) (40, 41). Studies in other countries report the same dose-response relationship between homocysteine and vascular disease (42, 43). Such cross-national studies are important because of regional variations in diet and gene frequencies. In addition to clinically diagnosed stroke, silent brain infarcts, diagnosed by magnetic resonance imaging (MRI), and ischemic white matter disease are also associated with elevated levels of homocysteine (44–46).

Further support for the idea that homocysteine is a cause of vascular disease comes from studies indicating that increasing intake of dietary folate, which effectively lowers homocysteine levels, lowers the risk of ischemic stroke in men (47, 48).

In summary, elevated levels of homocysteine, and in some populations, alleles of the MTHFR genotype, increase the risk for vascular disease of the brain. The proportion of all strokes due to this mechanism is not known but likely varies by age, geographic location, and prevalence of known causes of elevated homocysteine levels.
Results of recent intervention studies designed to lower homocysteine levels are mixed. Although homocysteine levels can be lowered, vascular disease is not prevented (49–53). Explanations for this failure include lack of adequate power and selection criteria, which include cases in which documented vascular disease has already occurred.

Nevertheless, cognitive improvement has been found after homocysteine levels were lowered (54, 55). Depression has been relieved by lowering homocysteine levels with B vitamin supplementation (56).

Stroke As a Cause of Depression

If homocysteine causes vascular disease, is vascular disease then the intermediate cause of hyperhomocysteinemia-related depression? Depression as a specific feature of stroke was first described in a small case-control study using a detailed structured clinical psychiatric interview of patients in a rehabilitation program following stroke and orthopedic conditions. Depression was more often found in stroke patients than in orthopedic patients matched for levels of disability (57). Because the groups were matched for disability, the increased rate of depression in stroke patients could not be attributed only to a psychological reaction to loss of function, i.e., disability. Since then, Robinson (58) and many others have extensively studied poststroke depression. In a review, Robinson noted that “Pooled data from studies conducted throughout the world have found prevalence rates for major depression of 19.3% among hospitalized stroke patients and 23.3% among outpatient samples.” There is evidence that antidepressants improve mood after stroke but no evidence that depression can be prevented (58, 59).

Further evidence of the specificity of depression caused by stroke comes from studies indicating that left hemisphere stroke commonly causes depression. Narushima et al. (60) showed in a meta-analysis that there was a significant inverse correlation between severity of depression and distance of the lesion from the frontal pole among 163 patients who had stroke. Depression was more common in patients with left hemisphere stroke than in orthopedic patients matched for levels of disability (57). Because the groups were matched for disability, the increased rate of depression in stroke patients could not be attributed only to a psychological reaction to loss of function, i.e., disability. Since then, Robinson (58) and many others have extensively studied poststroke depression. In a review, Robinson noted that “Pooled data from studies conducted throughout the world have found prevalence rates for major depression of 19.3% among hospitalized stroke patients and 23.3% among outpatient samples.” There is evidence that antidepressants improve mood after stroke but no evidence that depression can be prevented (58, 59).

Cardiovascular Disease and Depression

Stroke is often associated with heart disease, and depression is a symptom and a risk for heart disease (61). The pathogenesis of depression in heart disease is not known. Possible mechanisms include cerebral infarcts and drugs used to treat depression and heart disease, including diuretics and anticonvulsants (62).

Vascular Disease in Depressed Populations

Several studies indicate that a large proportion of elderly persons with depression also have had either a stroke or other evidence of vascular disease. Many studies find high rates of cerebrovascular disease and white matter lesions on MRI in depressed elderly patients. For example, in a Japanese study in which patients were matched for age, the frequency of silent cerebral infarction varied with both age and the age of depression onset. Among patients over the age of 65 diagnosed with major depression, silent cerebral infarction was observed in 65.9% of those with depression onset before the age of 65 and in 93.7% of those with onset of depression after age 65 (63). In other studies, deep white matter lesions were most common in patients who first presented with depression late in life (64–67). Coffey et al. (68) identified changes in subcortical white matter lesions in 44 of 67 depressed inpatients (66%) referred for ECT. Two autopsy studies demonstrated that the white matter intensities seen in the MRIs of patients with depression were ischemic lesions (69, 70).

Alexopoulos et al. (71) observed a characteristic cognitive pattern in depressed patients with vascular disease. In 1997, he named these cases “vascular depression.” Vascular disease was found in 75 of 139 depressed patients (54%). The vascular group was older and had more hypertension and less family history of depression (72). Furthermore, a severe reduction in mental speed remained after recovery from the depressive episode, which suggested underlying brain disease, such as infarcts (73). Recently, the concept of vascular depression has been challenged (74–76).

Although elderly depressive patients are often the subjects of studies of vascular disease and depression, one study found scan abnormalities associated in children with psychiatric disorders. White matter hyperintensities of 153 child and adolescent psychiatry inpatients were rated on T2-weighted MRI scans. Within the unipolar depression group (N=48), white matter hyperintensities were significantly associated with a higher prevalence of past suicide attempts (p=0.03, Fisher’s exact test) (77). However, in another study, increased rates of white matter hyperintensities were not found in young patients with mood disorders (78).

Several studies have shown that premorbid depression can significantly increase the risk of stroke over the subsequent 10–15 years. Depression has been reported to be a risk for vascular disease in several large population-based prospective studies (e.g., reference 79). However, these studies did not include baseline MRI scans to document the absence of preexisting cerebrovascular disease. In summary, depression occurs frequently after stroke, and high proportions of imaging studies of older depressed patients show infarcts or white matter lesions that indicate the presence of ischemic vascular disease.

Homocysteine and Neurotransmitter Alterations

Homocysteine and stroke might cause depression by alteration of neurotransmitters (80, 81). Evidence for the association between homocysteine and neurotransmitters is found in studies that directly measure neurotransmitter metabolites and in studies demonstrating the antidepressant effects of folate and S-adenosylmethionine, a cofac-
Homocysteine and Depression

The most direct evidence for the association between homocysteine and neurotransmitters is from a study showing that depressed patients with increased total plasma homocysteine levels had significantly lower levels of serum, red cells, and CSF folate, as well as lower levels of CSF S-adenosylmethionine (SAMe). The depressed patients with high total plasma homocysteine levels were also found to have significantly lower mean CSF concentrations of 5-hydroxyindoleacetic acid, homovanillic acid, and 3-methoxy-4-hydroxyphenylglycol (MHPG) (82).

The relationship between homocysteine and neurotransmitters is indirectly suggested by studies showing that mood can be modified by alteration of the homocysteine pathway. S-adenosylmethionine, an intermediary in the homocysteine pathway, has been found to function as an antidepressant. Its effects have been shown to be superior to placebo and comparable to standard tricyclic antidepressants (83, 84). In addition, three randomized trials have suggested supplemental folate as a treatment for depression (85, 86). In a study of depressed patients who had failed to benefit from paroxetine treatment but were currently receiving other treatments, low serum folate levels were found to be associated with poorer response to those treatments (87). Relapse of depression has also been found to be related to folate (88, 89). The improvement in mood following S-adenosylmethionine or supplemental folate administration suggests the involvement of the homocysteine pathway in depression (90).

Direct evidence of the association between homocysteine and neurotransmitter levels comes from studies of Parkinson’s disease. Parkinson’s patients receiving L-dopa, which requires the donation of a methyl group from S-adenosylmethionine to be metabolized, had higher levels of homocysteine than patients not taking L-dopa (91). Use of L-dopa could create a methyl sink, thus preventing the remethylation of homocysteine to methionine with the result of high homocysteine levels. Another potential mechanism for the homocysteine effect on transmitters is by inhibition of the enzyme necessary to catalyze the methylation reactions between the catecholamines and S-adenosylmethionine (SAMe) (92–94).

Association of Homocysteine and Depressive Disorders

The relationship of the homocysteine-methyl donor pathway to depression was noted first by Reynolds and colleagues (95–98) in the 1970s. Subsequent clinical and population-based studies have noted elevated homocysteine levels in depression (82, 99). Associations between homocysteine, folate, B12, and depression vary in particular populations. The Hordaland study of older men and women in Norway found that elevated homocysteine coupled with the T/T allele of MTHFR gene was associated with depression but that folate and B12 without the T/T allele were not associated (100, 101). The Rotterdam study of older men and women found that hyperhomocysteinemia, vitamin B12 deficiency, and—to a lesser extent—folate deficiency were related to depressive disorders (102).

Two studies of special populations did not find that homocysteine was related to depression. The first included women only and found vitamin B12 deficiency to be present in 14.9% of the 478 nondepressed subjects, 17.0% of the 100 mildly depressed subjects, and 27.0% of the 122 severely depressed subjects. No association was found between homocysteine and depression or folate and depression (103). The second was an ethnically diverse U.S. population sample ages 15–39 years. Subjects with any lifetime diagnosis of major depression had serum and red blood cell folate concentrations that were lower than those of subjects who had no history of depression. In this young population, serum homocysteine was not found to be associated with lifetime depression diagnoses (104). Homocysteine, B12, folate, or some combination is related to depression, but age, sex, race, and renal function must be specified. Because there are many types of depression in populations of different ages, as well as many causes for elevated homocysteine, including genetic predisposition and brain disease, samples of randomly selected subjects will be heterogeneous. Therefore, adequate power to demonstrate a specific relationship necessitates large samples.

Conclusions

There is strong published evidence for the association between homocysteine level and depression, vascular disease, and neurotransmitters. More large population-based prospective studies are needed to challenge the idea that elevated homocysteine levels cause vascular disease, which causes depression. Intervention trials are needed to determine whether depression treatment will be enhanced by homocysteine reduction. Since there are many causes of elevated homocysteine levels and probably many causes of depression, prospective and intervention studies must include a large enough sample to ensure adequate power to demonstrate outcome. Subjects included in prevention studies should not have depression, vascular disease, or elevated homocysteine levels at baseline.

If the hypothesis is not rejected by further study, then evaluation of elderly depressed patients should include imaging for vascular disease and measurement of homocysteine, folate, B6, and B12 levels.

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