Introduction

Depression is the most common serious psychiatric disorder. Fifteen percent of people will suffer at some point in their lives at least one period of major depression severe enough to require medical help (6). Morbidity associated with depression includes high rates of unemployment, impaired role performance, and poor social or interpersonal functioning (13). Depression has also been associated with 80 percent of suicides in affluent populations (6). Untreated, depression can thus pose a substantial economic, social, and emotional burden on the patient and society.

Traditionally, depression has been treated with psychotherapy, antidepressant drugs, and, in severe cases, electroconvulsive therapy. More recently, however, an association between depression and low levels of the vitamin folate has led to the proposal of folate supplementation as a nutritional therapy for depression. If truly effective, such supplementation would be an ideal therapy or adjuvent therapy for depression, due to its low financial cost and low risk for toxicity or side effects. Thus, given the significant costs of depression, it would be of benefit to examine the potential efficacy of this proposed therapy. It is the purpose of this paper to evaluate the evidence for low folate as a factor in depression, to identify areas in need of further study, and to make recommendations regarding the role of folate supplementation in a therapeutic regimen for depression.

Evidence for the role of folate in depression

In the past ten years, many studies have observed an association between folate deficiency and depression. Depressive symptoms often accompany folate deficiency. Conversely, although vitamin deficiency is rare in the general population of developed countries, folate deficiency has been reported in 15-38% of patients with depression (5,12,14). In addition, depressed patients have been found to exhibit lower serum or RBC folate than normal controls or other psychiatric patients (5), and depressed patients with relatively lower folate levels tend to be rated as more severely depressed (12,19,20). Several studies have countered that spontaneous folate deficiencies among depressed patients may be less common than previously reported (12, 19), but these differences may be accounted for by changes in assay techniques over time and intercontinental dietary differences across patient samples. Thus, the general body of observational studies supports an association, in a subset of depressed patients, between folate deficiency and the onset and severity of their depression.

However, correlation does not prove causation. In clarifying the possible role of folate in the etiology and treatment of depression, it is useful to ask if there exists a plausible mechanism for dietary folate affecting brain function and thus depression. It has been proposed that folate affects the activity of serotonin, a neurotransmitter implicated in mood regulation. In this mechanism, folate acts in the cycle which transfers methyl groups from serine to homocysteine, forming methionine, the immediate precursor of S-adenosylmethionine (SAM), an important methyl donor for many neurochemical reactions, possibly including those involved in serotonin activity (3). In the rat, folate deficiency lowers both brain levels of SAM and serotonin (16), and in the human, folate deficiency lowers CSF levels of SAM and 5-HIAA, a metabolite of serotonin (2); conversely, administration of SAM increases brain serotonin in rats (8) and 5-HIAA in humans (10). Studies involving tryptophan, a serotonin precursor, support the role of

low serotonin levels in effecting depression; acute dietary depletion of tryptophan (ATD) was shown to lower brain serotonin levels and transiently exacerbates symptoms in depressed patients (10). Also, ATD can reverse the therapeutic effects of selective serotonin uptake inhibitors (SSRIs) in depression (9). Finally, a body of literature supports the use of supplementation with L-tryptophan, alone or with SSRIs, in the treatment of depression (11). Taken together, these studies thus implicate folate in a possible etiological mechanism of depression, although further studies are needed to verify this mechanism, and to identify other systems involved and their relation to folate.

The tryptophan studies are especially interesting in that they show that a dietary deficiency can worsen depression and negatively affect its treatment by pharmacological agents, and that dietary tryptophan supplementation can be used as a sole or adjuvent therapy in the treatment of depression. Can dietary folate, implicated in the same mechanism, have similar effects?

Several recent studies have in fact shown that depressed patients with low folate levels may resist treatment by antidepressant medications. In a study of 213 patients with major depressive disorder, those with lower serum folate (SF) levels before treatment with fluoxetine, an SSRI, were less likely to respond to 8 weeks of treatment than patients with normal folate levels; investigators assessing outcome were blind to folate status (12). Another study of 99 patients with major depressive disorder showed that those with lower initial SF were less likely to respond to 5 weeks of treatment with the tricyclic antidepressant desmethylimipramine than those with normal SF (19). These data support an earlier study by Reynolds et al., in which depressed patients with lower serum folate responded less favorably than those with normal SF to antidepressants, tryptophan, or electroconvulsive therapy (18). The new studies also correct some methodological flaws of the Reynolds and earlier studies. For example, such studies often did not control for pretreatment medications, so that folate levels at the beginning of the studies could have already been affected by these medications; the newer studies took care to use unmedicated patients so that baseline folate levels were truly pretreatment. Thus, it appears from these studies that low folate levels may negatively affect the efficacy of antidepressive treatments, suggesting that, if an etiological relation exists, these levels might need to be corrected in some depressed patients in order for other therapies to work optimally.

This seems to be the case upon examining studies of folate supplementation in the treatment of depression. Two earlier studies have shown folate administration to potentiate other treatments. In one double-blind study, patients on long-term lithium therapy treated with folate generally showed more reduction of depressive symptoms than those treated with a placebo (7). Also, in a double-blind, six-month trial of folate-deficient depressed patients who were being treated with tricyclic antidepressants, addition of methylfolate (a form which is actively transported across the blood-brain barrier) was associated with better clinical and social recovery than was addition of a placebo (14). A recent double-blind study by Passeri et al. confirmed these observations. Ninety-six patients with dementia and depression received, in addition to ongoing standard medications, a placebo for two weeks; then, either the antidepressant Trazodone or 50 mg/day of methylfolate was added. Patients in both Tradozone and methylfolate groups who had definite or borderline folate deficiency showed a significantly greater improvement compared to their 2 week recovery with the standard treatment and placebo. This study is especially promising in that normofolatemic patients in the methylfolate group also exhibited significantly better recovery than in the 2-week placebo period (17).

Although the previous studies support the role of folate supplementation in the potentiation of standard antidepressant medications, only one recent study has examined the role of folate supplementation alone in the treatment of depression. Guaraldi et al., in a small (twenty-patient) open-label study, found that over 6 weeks, treatment with 50 mg/day of methylfolate alone was associated with improvement in depressive symptoms in 81% of subjects; only two had been folate-deficient (15).

Application of Research Findings

The data previously described substantiates an association between low folate levels and depression, implicates folate in a possible etiological mechanism for depression, and supports the involvement of folate in treatment outcomes as a sole or adjuvant therapy. When taken as a whole, these data present a cohesive picture of an etiological relationship between folate and depression. Of primary concern to the clinician, however, is the applicability of these results. Should folate be considered as part of a treatment regimen for any particular depressive patient?

First, it should be recognized that although the associations between low folate and depression and low folate and antidepressant response are well-established, well-controlled studies of the direct effects of folate supplementation on depression outcomes are limited in scope and number. To begin with, all studies to date have been performed on adults or elderly adults; younger patient populations and a wider range of age groups in general have not been sampled. Sample sizes themselves have been relatively small as well; none of the studies cited in support of folate supplementation involved over one hundred patients. In addition, no study controlled for chronicity of illness, age of onset of illness, timing of the index depressive episode against the longitudinal course of the illness, or concurrent medical conditions (e.g. dementia in the Passeri study). Thus, the studies supporting folate supplementation as an adjuvant therapy, although apparently valid in themselves, may only be applicable to a small, to-date undefined, subpopulation of depressed patients. In order to expand the generalizability of these data, further studies are needed to correct for the above factors and to examine a broader range of patient populations; such studies could also further the understanding of the exact role of folate in the etiology of depression, and thus understanding of when folate supplementation might be applicable and appropriate. In particular, studies are needed on normofolatemic depressive patients in order to substantiate whether folate levels are continuously related to a range of depressive severity, or if it is the state of folate deficiency that potentially causes depression; this would have obvious implications for treatment recommendations.

In regards to the study by Guaraldi suggesting a role for folate supplementation as a sole therapy for depression, the data can only be seen as preliminary due to its small sample size, open-label nature, and lack of a placebo control. Despite this, and the reservations concerning the generalizability of the other folate supplementation studies, some scientists promote screening depressed patients for low folate levels in order to identify candidates for folate supplementation. Even if the etiological relationship exists, however, such screening may not be accurate. First, it is currently unknown if RBC or serum folate levels reflect bioavailability of folate in the CNS, or if sub-clinical CNS folate deficiencies can be detected by current assays. Also, folate supplementation may not be of benefit if folate deficiencies result from other than dietary causes (e.g. metabolic conditions such as endogenous defects in folate metabolism, malabsorption). In addition, if the patient has a condition that tends to cause folate deficiency but also causes other nutritional, medical, or metabolic disruptions affecting mood (e.g. alcoholism, pregnancy),

supplementation with folate would not be optimally effective in treating the depression itself. Further studies comparing RBC and serum folate levels and measures of depression to thorough evaluations of dietary folate intake, excretion, and turnover as pertains to such conditions, would be illustrative. Combined with additional, more systematic study relating patient subpopulations to the efficacy of folate as an adjuvant or sole therapy for depression, such studies could shed light on the possible indications for folate supplementation in depression.

In consideration of such complexities, and citing the low cost and low risk of oral folate supplementation, some clinicians may support such supplementation for most or all depressed patients. This approach seems reasonable, but there do exist a few cautions. Although folate is in itself nontoxic even at large doses, serotonin excess syndrome due to co-administration of folate with SSRIs (such as displayed by L-tryptophan) has not been disproved. Additionally, folate can mask pernicious anemia, and those patients at risk for vitamin B_{12} deficiency or megaloblastic anemia should undergo the appropriate screening before supplementation with folate doses of over 0.1 mg per day.

In sum, a growing body of evidence supports the potential benefit of folate supplementation therapy in a small subpopulation of depressed patients who exhibit deficiencies in serum or RBC folate levels and/or who are also resistant to treatment with traditional antidepressants. However, it is the judgment of the clinician and involvement of the patient that must determine the applicability of such information to the treatment regimen for that patient, before conclusive research on the role of folate supplementation in the treatment of depression may identify responsive patient subpopulations and delineate treatment protocols.

REFERENCES

1. Benkelfat C, Ellenbogen MA, Dean P, et al. Mood-lowering effect of tryptophan depletion: Enhanced susceptibility in young men at genetic risk for major affective disorders. Arch Gen Psychiatry. 1994:51:687.

2. Botez MI, Young SN, Bachevalier J, et al. Effect of folic acid and vitamin B_{12} deficiencies on 5-hydroxyindoleacetic acid in human cerobrospinal fluid. Ann Neurol. 1982:12:479-484.

3. Bottiglieri T. Folate, vitamin B_{12} and neuropsychiatric disorders. Nutrition Rev. 1996:54:12:382-90.

4. Bottiglieri T, Laundy M, Martin R, et al. S-adenosylmethionine influences monoamine metabolism. Lancet. 1984:ii:224.

5. Carney MWP, Chary TKN, Laundy M, et al. Red cell folate concentrations in psychiatric patients. J Affective Disord. 1990:19:207-13.

6. Clayman CB, ed. American Medical Association Family Medical Guide, 3rd ed. New York: Random House, 1994; 321.

7. Coppen A, Chaudhry S, Swade C. Folic acid enhances lithium prophylaxis. J Affective Disord. 1986:10:9-13.

8. Curcio M, Catto E, Stramentinioli G, Algeri S. Effect of S-adenosyl-L-methionine on serotonin metabolism in rat brain. Prog Neuropsychopharmacol Biol Psychiatry. 1978:2:65-71.

9. Delgado PL, Charney DS, Price JH, et al: Serotonin function and the mechanism of antidepressant action: Reversal of antidepressant induced remission by rapid depletion of plasma tryptophan. Arch Gen Psychiatry. 1990:47:411-418.

10. Delgado PL, Price LH, Miller HL, et al. Serotonin and the neurobiology of depression: Effects of tryptophan depletion in drug-free depressed patients. Arch Gen Psychiatry. 1994:51:865.

11. d'Elia G, Hanson L, Raotma H: L-tryptophan and 5-hydroxytryptophan in the treatment of depression. A review. Acta Psychiatr Scand 1978:239-252.

12. Fava M, Borus JS, Alpert JE, et al. Folate, B_{12}, and homocysteine in major depressive disorder. Am J of Psychiatry. 1997:154:426-8.

13. Friedman A. Social and occupational adjustment in chronic depression. In Kocsis JH and Klein DN,eds. Diagnosis and Treatment of Chronic Depression. New York: Guilford Press, 1995; 89-102.

14. Godfrey PSA, Toone BK, Carney MWP, et al. Enhancement of recovery from psychiatric illness by methylfolate. Lancet. 1990:336:392-95.

15. Guaraldi G, Fava M, Mazzi F, et al. An open trial of methyltetrahydrofolate in elderly depressed patients. Ann Clin Psychiatry. 1993:5:101-6.

16. Ordonez LA, Wurtman RJ. Folic acid deficiency and methyl group metabolism in rat brain: effects of L-dopa. Reversal effect of S-adenosyl-L-methionine. Arch Biochem Biophys. 1974:160:372-376.

17. Passeri M, Cucinotta D, Abate G, et al. Oral 5'methyltetrahydrofolic acid in senile organic mental disorders with depression: results of a double-blind multicenter study. Aging. 1993:1:63-71.

18. Reynolds EH, Preece JM, Bailey J, et al. Folate deficiency in depressive illness. Br J Psychiatry. 1970:117:287-92.

19. Wesson VA, Levitt AJ, Joffe RT. Change in folate status with antidepressant treatment. Psychiatry Research. 1994:53:3:313-22.

20. Wilkinson A, Anderson D, Abou-Saleh M, et al. 5-Methyltetrahydrofolate level in the serum of depressed subjects and its relationship to the outcome of ECT. J Affective Disord. 1994:32:3:163-68.