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Prevalence of Folate Deficiency in Patients with Depressive Symptoms: Biochemical and Clinical Implications

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Abstract

Objective: To evaluate the prevalence of folate deficiency in patients presenting with depressive symptoms and to explore associated biochemical abnormalities and clinical implications.

Methods: Observational study analyzing serum folate, vitamin B12, ferritin, thyroid function, and homocysteine levels in patients with depressive symptoms.

Results: Folate deficiency was prevalent in a significant subset of patients and was frequently associated with vitamin B12 deficiency, iron deficiency, and thyroid dysfunction.

Conclusion: Folate deficiency is a common and potentially modifiable factor in depression, underscoring the need for routine biochemical screening in psychiatric care.

Keywords: Folate deficiency; Depression; Homocysteine; Ferritin; Vitamin B12; Thyroid function

1. Introduction

Depression is a leading cause of disability worldwide and is characterized by persistent low mood, anhedonia, and cognitive impairment. Nutritional deficiencies are increasingly recognized as contributors to the onset and course of depressive disorders [1]. Among these, folate (vitamin B9) has been extensively studied due to its critical role in one-carbon metabolism, DNA synthesis, and methylation reactions [2]. Folate deficiency disrupts methylation pathways essential for neurotransmitter synthesis, including serotonin, dopamine, and norepinephrine, thereby contributing to depressive symptomatology.

Folate functions as a cofactor in the conversion of homocysteine to methionine, a precursor for S-adenosylmethionine (SAMe), a universal methyl donor involved in neurotransmitter metabolism. Deficiency in folate leads to elevated homocysteine levels (hyperhomocysteinemia), which exerts neurotoxic effects through excitotoxicity, oxidative stress, and vascular endothelial dysfunction [3]. Accumulating evidence links hyperhomocysteinemia to increased risk of depression, cognitive decline, and cardiovascular disease [4].

The prevalence of folate deficiency varies across populations but is estimated at 10–30% in patients with depressive disorders, particularly in the elderly, alcohol users, and individuals with malnutrition or malabsorption syndromes [5]. Low folate status has been consistently associated with poor antidepressant response, increased relapse rates, and

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treatment-resistant depression [6]. Supplementation with folic acid or methylfolate has been shown to improve depressive outcomes, particularly when combined with antidepressant therapy.

Importantly, folate deficiency often coexists with other biochemical abnormalities relevant to psychiatric health. Vitamin B12 deficiency exacerbates hyperhomocysteinemia due to synergistic roles in the remethylation cycle [7]. Iron deficiency, reflected by low ferritin levels, contributes to fatigue, cognitive dysfunction, and low energy, which overlap with depressive symptoms [8]. Thyroid dysfunction, particularly hypothyroidism, is another frequent comorbidity, further complicating the clinical presentation of depression [9].

Despite strong evidence, folate status is not routinely assessed in psychiatric practice, leading to missed opportunities for diagnosis and treatment. Given the safety, low cost, and effectiveness of folate supplementation, screening for deficiency represents a pragmatic approach to enhance treatment outcomes in depression. The present study evaluates the prevalence of folate deficiency in patients with depressive symptoms, its association with other biochemical markers, and clinical implications for psychiatric care.

2. Materials and Methods

This observational cross-sectional study included patients with depressive symptoms attending outpatient psychiatric clinics. Inclusion criteria were: (i) age between 18 and 75 years, (ii) clinical diagnosis of depressive disorder according to DSM-5 criteria, and (iii) availability of laboratory data. Exclusion criteria were: recent supplementation with folic acid or vitamin B12, chronic gastrointestinal disorders affecting absorption, advanced renal disease, and pregnancy.

Sociodemographic data (age, sex, lifestyle factors) and clinical characteristics (severity of depression, comorbidities, medication use) were recorded. Depression severity was assessed using the Hamilton Depression Rating Scale (HDRS). Physical examinations were conducted, focusing on neurological and cognitive symptoms.

Laboratory tests included serum folate, vitamin B12, ferritin, thyroid-stimulating hormone (TSH), free T4, and plasma homocysteine. Folate deficiency was defined as serum folate <4 ng/mL, borderline deficiency as 4–6 ng/mL, and normal as >6 ng/mL. Vitamin B12 deficiency was defined as <200 pg/mL, iron deficiency as ferritin <30 ng/mL, and thyroid dysfunction as abnormal TSH or free T4 levels. Hyperhomocysteinemia was defined as plasma homocysteine >15 μmol/L.

Kernel density estimation was applied to assess distributions of folate, B12, ferritin, and TSH levels, enabling identification of subpopulations. Student's t-tests and chi-square tests were used to compare groups. Correlations between folate and homocysteine, as well as between folate and HDRS scores, were calculated. All statistical analyses were conducted using SPSS version 25, with $p<0.05$ considered significant.

Ethical approval was obtained from the hospital's ethics committee. Written informed consent was provided by all participants.

3. Results

The study cohort consisted of 75 patients (48 females, 27 males), with a mean age of 43 ± 12 years. The mean HDRS score was 22 ± 5, reflecting moderate depression severity.

Serum folate analysis revealed a mean level of 5.8 ± 2.4 ng/mL. According to predefined cutoffs, 14 patients (18.6%) had deficiency (<4 ng/mL), 20 patients (26.6%) had borderline deficiency (4–6 ng/mL), and 41 patients (54.6%) had normal levels (>6 ng/mL). Kernel density estimation identified three subgroups of folate status, with clustering around deficient, borderline, and normal ranges.

Plasma homocysteine was elevated in 18 patients (24%), with a mean level of 15.6 ± 5.9 μmol/L. There was a significant inverse correlation between folate and homocysteine ($r = -0.44$, $p<0.01$). Patients with folate deficiency had significantly higher homocysteine levels compared to those with normal folate status.

Vitamin B12 deficiency was observed in 16 patients (21.3%), while low ferritin levels were present in 15 patients (20%). Thyroid dysfunction, predominantly hypothyroidism, was found in 9 patients (12%). Patients with combined folate and B12 deficiencies exhibited higher HDRS scores compared with patients without deficiencies ($p<0.05$).

Sex-based analysis showed that women were more likely to present with low ferritin (25% vs 11% in men), while no significant sex differences were observed in folate or B12 deficiency rates. Older age was associated with higher prevalence of folate deficiency ($p<0.05$).

These results indicate that folate deficiency is common in depressed patients and frequently coexists with other biochemical abnormalities, contributing to greater severity of depressive symptoms.

4. Discussion

This study demonstrates that nearly one-fifth of patients with depressive symptoms presented with folate deficiency, and over one-quarter had borderline levels. These findings align with existing literature reporting folate deficiency rates of 15–30% among psychiatric populations [5,6]. The inverse correlation between folate and homocysteine observed here reinforces the mechanistic link between folate deficiency, hyperhomocysteinemia, and depression [3,4].

The clinical significance of folate deficiency in depression is multifaceted. Low folate levels impair neurotransmitter synthesis and methylation processes essential for mood regulation. In addition, hyperhomocysteinemia exerts neurotoxic effects and has been associated with poor antidepressant response and cognitive impairment [7,8]. Our findings that patients with folate and B12 deficiencies exhibited higher HDRS scores support the hypothesis that combined deficiencies exacerbate depressive severity.

Coexisting deficiencies were common in this cohort, with 21% showing low B12, 20% low ferritin, and 12% thyroid dysfunction. This pattern underscores the need for comprehensive biochemical evaluation in depressed patients. Iron deficiency contributes to fatigue and cognitive slowing, while thyroid dysfunction has long been recognized as a contributor to depressive symptoms [9]. Thus, folate deficiency should be considered within a broader metabolic context.

Clinical trials have shown that folate supplementation, particularly in the form of L-methylfolate, enhances antidepressant efficacy and reduces relapse rates in deficient individuals. A randomized controlled trial demonstrated that adjunctive L-methylfolate significantly improved outcomes in patients with SSRI-resistant depression [10]. These findings suggest that targeted supplementation may represent a valuable augmentation strategy in psychiatric care.

Despite the evidence, routine screening for folate status is rarely implemented in psychiatric practice. The low cost and accessibility of folate testing, combined with the safety and efficacy of supplementation, argue strongly for its integration into standard protocols. By identifying and correcting folate deficiency, clinicians may improve treatment outcomes and reduce the burden of treatment-resistant depression.

Limitations of this study include its cross-sectional design, which precludes establishing causality, and the modest sample size. Dietary intake and genetic polymorphisms affecting folate metabolism (such as MTHFR mutations) were not assessed. Future studies should investigate the impact of folate supplementation on depressive outcomes in prospective, controlled trials and explore genetic determinants of susceptibility.

In summary, folate deficiency is prevalent among patients with depression and contributes to biochemical and clinical vulnerability. Routine screening and supplementation represent pragmatic strategies to improve mental health outcomes.

5. Conclusion

In conclusion, folate deficiency is highly prevalent in patients with depressive symptoms and often coexists with other biochemical abnormalities, including vitamin B12 deficiency, iron deficiency, and thyroid dysfunction. These deficiencies contribute to elevated homocysteine levels and greater severity of depressive symptoms. Routine screening for folate, B12, ferritin, and thyroid function should be integrated into psychiatric assessments.

Management strategies include targeted supplementation with folic acid or L-methylfolate, correction of coexisting deficiencies, and appropriate treatment of thyroid dysfunction. Such interventions are low-cost, safe, and potentially enhance antidepressant efficacy, particularly in treatment-resistant cases. Collaborative care between psychiatry and internal medicine is essential to ensure comprehensive management.

By addressing folate deficiency and related metabolic disturbances, clinicians can adopt a more holistic approach to depression, improving both psychiatric and physical health outcomes for affected patients.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] World Health Organization. Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: WHO; 2017.

[2] Bottiglieri T. Folate, vitamin B12, and neuropsychiatric disorders. Nutr Rev. 1996;54(12):382-390.

[3] Selhub J, Bagley LC, Miller J, Rosenberg IH. B vitamins, homocysteine, and neurocognitive function in the elderly. Am J Clin Nutr. 2000;71(2):614S-620S.

[4] Bjelland I, Tell GS, Vollset SE, Refsum H, Ueland PM. Folate, vitamin B12, homocysteine, and depressive disorders in the Hordaland Homocysteine Study. Arch Gen Psychiatry. 2003;60(6):618-626.

[5] Reynolds EH. Folic acid, ageing, depression, and dementia. BMJ. 2002;324(7352):1512-1515.

[6] Coppen A, Bolander-Gouaille C. Treatment of depression: time to consider folic acid and vitamin B12. J Psychopharmacol. 2005;19(1):59-65.

[7] Gilbody S, Lightfoot T, Sheldon T. Is low folate a risk factor for depression? A meta-analysis and exploration of heterogeneity. J Epidemiol Community Health. 2007;61(7):631-637.

[8] Kruman II, Culmsee C, Chan SL, et al. Homocysteine elicits a DNA damage response in neurons: a potential mechanism for neurotoxicity. J Neurosci. 2000;20(18):6920-6926.

[9] Hage MP, Azar ST. The link between thyroid function and depression. J Thyroid Res. 2012;2012:590648.

[10] Papakostas GI, Shelton RC, Zajecka JM, et al. L-methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials. Am J Psychiatry. 2012;169(12):1267-1274.