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Vitamin B_6 Level Is Associated with Symptoms of Depression

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Key Words
Vitamin B_6 · Pyridoxal phosphate · Depression

Abstract
Background: A low level of vitamin B_6 might theoretically cause depression as vitamin B_6 is a cofactor in the tryptophan-serotonin pathway. In the present study, we examined the association between depression and the phosphate derivative of vitamin B_6 in plasma, pyridoxal phosphate (PLP). ***Methods:*** In 140 individuals, symptoms of depression were evaluated by the Major Depression Inventory, and biochemical markers of vitamin B deficiency were measured. ***Results:*** We found that 18 (13%) individuals were depressed. A low plasma level of PLP was significantly associated with the depression score ($p = 0.002$). No significant association was found between depression and plasma vitamin B_{12} ($p = 0.13$), plasma methylmalonic acid ($p = 0.67$), erythrocyte folate ($p = 0.77$), and plasma total homocysteine ($p = 0.16$). ***Conclusion:*** Our study suggests that a low level of plasma PLP is associated with symptoms of depression. Randomized trials are now justified and needed in order to examine whether treatment with vitamin B_6 may improve symptoms of depression.

Introduction

Depression is a serious mental disorder associated with an increased morbidity and mortality and is rather frequent with prevalence estimates of moderate to severe depression around 3–5% of the general population. Since the metabolite of vitamin B_6 pyridoxal 5′-phosphate (PLP) is a coenzyme in the tryptophan-serotonin pathway, a lack of vitamin B_6 might theoretically cause depression [1]. This theory is supported by a study reporting that low levels of vitamin B_6 were found in depressed outpatients [2]. However, the few studies investigating the benefit of vitamin B_6 supplementation focus on depression as a part of premenstrual syndrome or the use of oral contraceptives [3].

The aim of the present study was to explore the association between depression examined by the Major Depression Inventory (MDI) [4] and the vitamin B_6 phosphorylated derivative PLP.

Methods

Study Population

Potential participants were identified from a follow-up study of individuals with an increased plasma methylmalonic acid level, as described elsewhere [5]. Amongst these, 140 individuals participated in a randomized trial fulfilling the following inclusion criteria: moderately increased plasma methylmalonic acid level (0.40–

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Table 1. Distribution of the biochemical markers in the study population (n = 140)

Variables	Median	Reference intervals
Pyridoxal phosphate, nmol/l	44 (6–370)	5–80 [22]
Plasma methylmalonic acid, μmol/l	0.52 (0.26–2.00)	0.08–0.28 [23]
Plasma vitamin B_{12}, pmol/l	265 (137–1,348)	200–600
Erythrocyte folate, nmol/l	608 (199–1,685)	>350
Plasma total homocysteine, μmol/l	13 (5–47)	5.8–11.9

Figures in parentheses indicate ranges.

2.00 μmol/l) not followed by vitamin B_{12} treatment, age 18 years or older, and permanent address in the municipality of Aarhus, Denmark [6]. The examinations for the current study were performed prior to intervention. Written informed consent was obtained from all individuals, and the study was approved by the Research Ethics Committee of Aarhus County (1998/4207).

Symptoms of Depression

To investigate symptoms of depression, we used the MDI, a self-rating inventory developed to measure DSM-IV and ICD-10 diagnosis of depression [4]. Functionally the test contains 10 items, which are summed up with a score range from 0 to 50; higher scores indicate more symptoms of depression. Besides using the total score, we scored the MDI according to the ICD-10 algorithm where the presence of at least 2 of the 3 core symptoms (items 1–3) and at least 4 of the other 7 items suggest moderate to severe (major) depression [4]. When using the total score on the MDI to measure severity of depression, a score of 20 equals mild depression and a score of 26 or more equals moderate depression [7].

Laboratory Investigations

The PLP was analyzed by an ion-pair reversed-phase chromatography (HP 1100 system, Hewlett Packard; the software, ChemStation version A.06.03 from Hewlett Packard) as described by Bisp et al. [8]. The analytical imprecision was 15% for PLP concentrations below 25 nmol/l (mean = 20.45 nmol/l, n = 24).

Methylmalonic acid in plasma was measured by stable isotope dilution capillary gas chromatography-mass spectrometry (analytical imprecision <8%) [9]. Plasma total homocysteine was measured by an immunological method employing an IMx (Abbot) equipment (analytical imprecision <5%). Plasma was separated from the blood cells within less than 2 h. Plasma vitamin B_{12} and erythrocyte folate were determined on the ACS:Centaur™ Automated Chemiluminescence System (Bayer A/S) by a competitive protein-binding assay (analytical imprecision <10%). All the reference intervals are indicated in table 1.

Statistical Analysis

The associations between depression score and age and sex were analyzed by linear regression analysis. Linear and logistic regression analyses were used to analyze the associations between depression score and biochemical markers. To fulfill the criteria for Gaussian distribution, data were log-transformed when appropriate. p values below 5% were regarded as statistically significant. Data were analyzed using SPSS 10.0 (SPSS Inc.).

Results

In the study population, the median age was 75 years (range; 19–92 years), and 98 (70%) were women. The distribution of the biochemical markers of the study population is shown in table 1. All of the individuals had normal renal function (median plasma creatinine: 87 μmol/l). The majority (81%) of the study population did not have anemia (median blood hemoglobin; 8.4 mmol/l).

Using the MDI according to the ICD-10 algorithm, 18 (13%) individuals had symptoms of depression: 9 individuals were slightly depressed, 6 were moderately depressed, and 3 individuals were severely depressed. We found an association between old age and high depression score (p = 0.06) and a significant association between sex and depression score (p = 0.03, women having the highest score).

PLP was significantly associated with the MDI (r = –0.25; p = 0.002, adjusted for age and gender; fig. 1). Individuals with PLP below 30 nmol/l (n = 48) had more frequently symptoms of depression than others (p = 0.02; 95% CI = 1.2–9.4, adjusted for age and gender). When we excluded individuals with a depression score of 0 (n = 7), the association between low PLP and high depression score was still significant (r = –28; p = 0.03, adjusted for age and gender).

No significant association was observed between symptoms of depression and the levels of plasma vitamin B_{12} (p = 0.13), plasma methylmalonic acid (p = 0.67), erythrocyte folate (p = 0.77), and plasma total homocysteine (p = 0.16). All analyses were adjusted for age and gender.

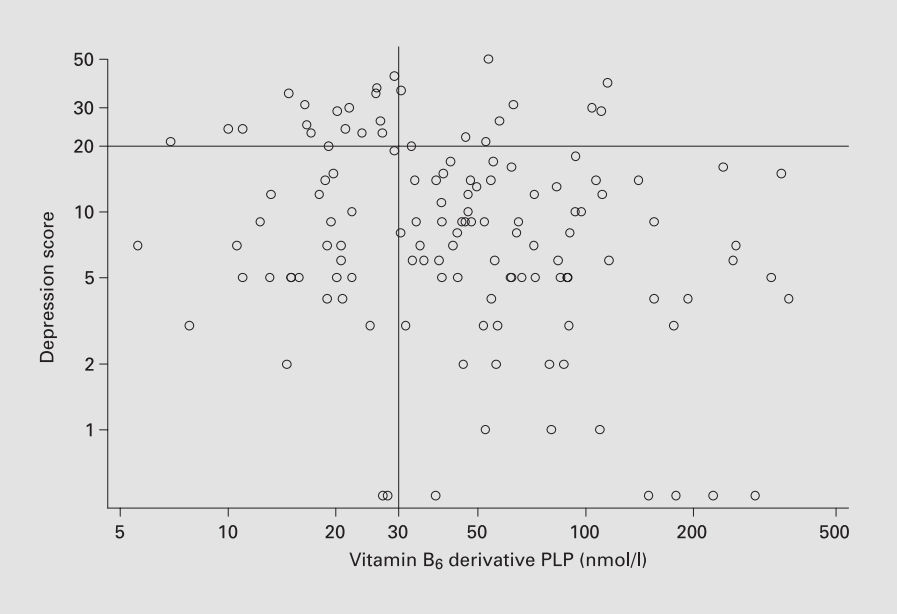

Fig. 1. Association between depression score and the level of the vitamin B_6 derivative PLP. Data were log-transformed. A depression score of 20 or more indicates clinical depression.

Discussion

In the present study population of mainly elderly individuals, we found a significant association between the vitamin B_6 phosphate derivative PLP and symptoms of depression.

Depression has been associated with deficiency of serotonin or the catecholamines [10]. The synthesis of the serotonin and catecholamines is PLP dependent, and for this reason vitamin B_6 has been considered a therapeutic adjunct in a variety of conditions with known or suspected neurotransmitter abnormalities [1]. Besides that, both folate and vitamin B_{12} appear to facilitate monoamine neurotransmitter synthesis, and thus these vitamins are also suggested to play a role in developing depression [11]. These hypotheses have been supported by the fact that some studies have found low B_6 levels [2], folate deficiency [12, 13], and vitamin B_{12} deficiency among depressed patients [14]. However, others have not found an association between vitamin B_6 status and depression [15].

Wyatt et al. [3] summarized the randomized vitamin B_6 intervention studies concerning the premenstrual syndrome and found some improvement after supplementation, supporting the hypothesis that vitamin B_6 supplementation might be beneficial in case of depression. As our results demonstrated a significant association between the vitamin B_6 derivative PLP and symptoms of depression, the present study adds to the evidence supporting this hypothesis.

A number of previous studies have suggested that a lack of one or more of the B vitamins may be related to depression [13, 16–19]. Recently, Penninx et al. [16] have found that individuals with vitamin B_{12} deficiency had a twofold risk of severe depression, and Bottiglieri et al. [19] reported that depressed patients had increased plasma homocysteine. Finally, low folate status was found in depressed individuals in the general US population [13], and the response to antidepressant drugs have been found to be poorer in patients with low folate [20].

Our results agree with other studies not supporting the correlation between vitamin B_{12} levels and depression [17, 21]. Efforts to demonstrate a correlation between low folate levels and more severe depression have yielded mixed results [11], and the present study does not support a clear association between the level of erythrocyte folate and symptoms of depression.

The present study includes mainly elderly individuals, which limits the possibility to generalize the results. Besides that, the study population is quite small, implying that a rather limited number has symptoms of depression.

In spite of the limitations, our results suggest vitamin B_6 to play a role in developing symptoms of depression. The study warrants further work in order to explore how common vitamin B_6 deficiency is amongst depressed

individuals. Even more importantly, randomized controlled trials are justified and needed in order to show whether treatment with vitamin B_6 may improve symptoms of depression among individuals with low levels of vitamin B_6.

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