Folate and vitamin B12 levels in levodopa-treated Parkinson’s disease patients: Their relationship to clinical manifestations, mood and cognition

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Abstract

We tested the hypothesis that mood, clinical manifestations and cognitive impairment of levodopa-treated Parkinson’s disease (PD) patients are associated with vitamin B12 and folate deficiency. To this end, we performed this cross-sectional study by measuring serum folate and vitamin B12 blood levels in 111 consecutive PD patients. Levodopa-treated PD patients showed significantly lower serum levels of folate and vitamin B12 than neurological controls, while depressed patients had significantly lower serum folate levels as compared to non-depressed.

Cognitively impaired PD patients exhibited significantly lower serum vitamin B12 levels as compared to cognitively non-impaired. In conclusion, lower folate levels were associated with depression, while lower vitamin B12 levels were associated with cognitive impairment. The effects of vitamin supplementation merit further attention and investigation.

Keywords: Vitamin B12; Brain lateralization; Cognition; Depression; Folate; Folic acid; Parkinson’s disease

1. Introduction

Parkinsonism is a clinical syndrome characterized by bradykinesia, rigidity and/or tremor at rest. Primarily, it affects elderly individuals and is the second most common neurodegenerative entity next to Alzheimer disease. Parkinsonism is insidious in onset, progressive, and usually affects one side of the body before spreading to the other. The most common form of this nosological entity is idiopathic (primary Parkinsonism, Parkinson’s disease (PD)). A deficit of dopamine in nigrostriatal neurons accounts for most motor symptoms. The most common therapy consists of administering levodopa, a blood brain barrier-penetrating metabolic precursor of dopamine, plus a dopa decarboxylase inhibitor (benzerazide or carvidopa) to prevent its peripheral degradation. There are two major clinical subtypes, depending on motor symptoms: the akinetic dominant and the tremor dominant type of the disease.

Apart from these symptoms, there are some frequently observed non-motor symptoms (e.g. lack of motivation, passivity, dementia and depression) that may in fact be the most disturbing aspects of the disease and a significant co-factor of functional impairment and poor quality of life for these patients [1–3]. Many studies have shown a high frequency of depression in PD patients, which is estimated to be approximately 30–40% [4–6], and is clinically comparable to major depression [7]. The etiology of depression in PD patients is not clear. Some investigators suggest that it is an intrinsic disturbance correlated with neurodegenerative changes of specific cortical and
subcortical pathways observed in these patients [8,9], while the role of homocysteine-related pathways should also be further investigated, as elevated plasma homocysteine levels have been observed both in depression [10,11] and in PD [12–16].

Given that folate and vitamin B12 are both required for the methylation of homocysteine, a deficiency may result in hyperhomocysteinemia, which is related to depression and cognitive impairment. We thus hypothesized a correlation between cognitive impairment and depression of PD patients and their serum folate and/or vitamin B12 levels. We performed this cross-sectional study in order to test this hypothesis.

2. Material and methods

2.1. Study population

Recruited in the study were 111 consecutive right-handed patients with PD (Hoehn and Yahr stage 1: 15 patients, stage 2: 19 patients, stage 3: 35 patients, and stage 4: 42 patients) [17], with 4–17 (mean = 8.4, S.D. = 3.2) years of education, followed during the past 4 years in the Neurological Department of Athens University, Aeginition Hospital. Subjects were treated with levodopa (range of daily dose 375–875 mg, according to their clinical status) for at least 1 year before recruitment. All patients were enrolled in the study during a regular outpatient visit or hospitalization for exacerbation of symptoms. The following patients were excluded from the study: (1) de novo PD patients or patients taking levodopa for less than 1 year, (2) patients taking dopamine agonists (exclusively or as add-on therapy), (3) individuals with vitamin supplementation, (4) patients on antidepressive drugs and, finally, one tested positive for parietal cell antibodies. Ninety-three [55 males, 38 females, 4–17 (mean = 8.2, S.D. = 2.9) years of education] age-matched, right-handed inpatients or outpatients having a variety of neurological diagnoses (10 myopathy, eight myasthenia gravis, seven motor neuron disease, 16 epilepsy, six brain tumors, eight cranial and 10 peripheral nerve disorders, four CNS infections, 16 headache, and eight dizziness) comprised the “neurological control group”. The severity of illnesses varied. Patients with neurological manifestations of vitamin B12 or folate deficiency, any type of dementia, encephalopathy, normal pressure hydrocephalus, depression, and patients on a vitamin supplementation diet were excluded from the control group. Epileptic patients taking antiepileptic drugs were also excluded. The study was approved by the Hospital Ethics Committee, and written, informed consent was obtained from all patients and controls prior to participation in the study.

2.2. Measurements

Non-fasting blood samples were drawn from a peripheral vein and centrifuged within 1 h. Serum folate and vitamin B12 levels were quantified with a paramagnetic particle chemiluminescence immunoassay (Access 2, Immunoassay system, Beckman Coulter, Inc). For folate determination, a competitive-binding receptor assay was used based on a folate-antifolate binding protein pair along with a goat anti-mouse capture antibody coupled to the paramagnetic particles. To determine vitamin B12, a competitive-binding immunoenzymatic assay was used based on an intrinsic–antiintrinsic factor monoclonal mouse antibody pair coupled to paramagnetic particles. Parietal cell antibodies were detected with the use of indirect immunofluorescence on mouse stomach-cell substrate (Inova Diagnostics, Inc., San Diego, USA).

3. Results

Demographic and clinical data as well as mean values of serum vitamin B12 and folate levels of the subject groups who participated in the study are summarized in Table 1. Thirty-one out of 111 PD patients met at least five of the DSM-IV criteria for major depressive episode and these patients were classified as having co-morbid depressive episode. Regarding cognitive performance, 60 patients had an MMSE score ≥26 and 51 had an MMSE score ≤25.

One hundred and eleven out of 125 individuals who fulfilled the inclusion criteria consented to participate in the study, while the remainder rejected psychiatric evaluation and were therefore excluded from the study. During the same period, 49 more levodopa-treated PD patients were also excluded from the study, as five of them had been taking levodopa less than 1 year, two of them had been taking dopamine antagonists as add-on therapy, 30 had been taking antidepressive drugs and, finally, one tested positive for parietal cell antibodies.

3.1. Comparison of serum vitamin B12 and folate levels between PD patients and control groups

In the total group of PD patients, the serum vitamin B12 levels were significantly lower as compared to control subjects (ANOVA, d.f. = 1,202; F = 21.906; p < 0.0000). Serum folate levels were also significantly lower in the
group of PD patients as compared to the group of control subjects (ANOVA, d.f. = 1,202; F = 8.7341; p < 0.003).

3.2. Comparison of serum vitamin B12 and folate levels among subgroups of PD patients and controls

One-way ANOVA among three groups (akinetic, tremor dominant, and control group) for serum vitamin B12 and folate levels showed significant interactions for vitamin B12 levels (d.f. = 2,201; F = 11.008; p < 0.00003) and for folate levels (d.f. = 2,201; F = 5.2604; p < 0.005). Post-hoc analysis revealed: (1) lower vitamin B12 levels for both the akinetic and the tremor dominant groups as compared to controls (Tukey’s p < 0.0010 and p < 0.0001, respectively), while the difference between the akinetic and the tremor dominant groups was not significant. (2) Lower folate levels for the tremor dominant group as compared to the control group (Tukey’s p < 0.003), while the difference between the akinetic and the control group was not significant; the difference between akinetic and tremor dominant group was also not significant.

3.3. Comparison of serum vitamin B12 and folate levels between subgroups of PD patients with and without co-morbid depression and controls

One-way ANOVA among three groups (depressed, non-depressed, and control group) for serum vitamin B12 and folate levels showed significant interactions for vitamin B12-vitamin levels (d.f. = 2,201; F = 11.377; p < 0.00002) and for folate levels (d.f. = 2,201; F = 7.1231; p < 0.001). Post-hoc analysis revealed: (1) lower vitamin B12 levels for both the depressed and the non-depressed groups as compared to controls (Tukey’s p < 0.0003 and p < 0.0002, respectively), while the difference between the depressed and the non-depressed groups was not significant. (2) Lower folate levels for the depressed group as compared to the control group (Tukey’s p < 0.0006), lower folate levels for the depressed as compared to the non-depressed groups (Tukey’s p < 0.05), while the difference between the non-depressed and the control groups was not significant.

3.4. Comparison of serum vitamin B12 and folate levels among subgroups of PD patients and controls according to cognitive impairment

One-way ANOVA among three groups: (1) patients considered cognitively impaired (MMSE<25), (2) patients without cognitive impairment (MMSE>25) and (3) control group, for serum vitamin B12 and folate levels showed significant interaction for vitamin B12 levels (d.f. = 2,201; F = 11.733; p < 0.00002) and for folate levels (d.f. = 2,201; F = 4.3680; p < 0.014). Post-hoc analysis revealed: (1) lower B12-vitamin levels for both the cognitively impaired and the non-impaired groups compared to controls (Tukey’s p < 0.0004 and p < 0.002, respectively), while the difference between the cognitively impaired and the non-impaired groups was significant (p < 0.05). (2) Lower folate levels of both the impaired and the non-impaired groups as compared to controls (Tukey’s p < 0.033 and p < 0.044, respectively).

4. Discussion

The present study shows that levodopa-treated PD patients, as a population, have lower serum folate and vitamin B12 levels as compared to an age-matched group of neurological patients. In most, their serum vitamin B12 and folate levels were within the normal range of values for our laboratory, but they were close to the lower limit and a number of them (20%, approximately) had values below that. The fact of low serum vitamin B12 and folate levels and the relative high percentage of depression and dementia in PD patients prompted us to organize this study. More specifically, our findings showed that lower folate levels were characteristic of PD patients with the tremor dominant form of the disease, as well as of patients with depression. Vitamin B12 levels did not significantly differentiate akinetic from the tremor dominant form or depressed from non-depressed PD patients. Though both groups had vitamin B12 levels significantly lower than controls, in univariate analysis PD patients with cognitive impairment also had a significantly lower level of vitamin B12 than those without.

There are several studies in the literature regarding serum vitamin B12 and folate levels in levodopa-treated PD patients [12,13,15,19–21]. In one, PD patients treated with levodopa + DDC-i plus COMT-i were found to have lower vitamin B12 levels as compared to both levodopa + DDC-i treated PD patients and controls [19], though in another study the same research group reports no difference in vitamin B12 levels between the two groups of PD patients and controls [20]. Regarding serum folate levels, both the above mentioned publications report that levodopa + DDC-i treated patients have lower levels as compared to controls, but in contrast to our findings, they observed that levodopa + DDC-i plus COMT-i treated PD patients have higher levels as compared to both levodopa + DDC-i treated PD patients and controls. O’Sullivan et al. [21] report a decrease in vitamin B12 levels in PD patients after initiation of levodopa therapy—though non-significant—and a small decrease in folate levels.

Miller et al. report a lower but non-statistical decrease in vitamin B12 levels in levodopa-treated patients and no change in folate levels [13], while Carney et al. found lower red cell folate in depressed patients as compared to non-depressed psychiatric patients [22]. We also showed that PD patients with cognitive impairment (MMSE<25) have lower serum vitamin B12 levels when compared to PD patients with normal cognition. On the other hand, we found no significant difference in folate serum levels between cognitively impaired and non-impaired PD patients; although there is evidence that the deterioration of functional and mental capacity in the elderly is...
associated with, or may be caused by, folate deficiency. It has been reported that elderly individuals with an MMSE score greater than 28 have serum and erythrocyte folate levels significantly higher than those with lower scores (MMSE≤27) [23]. Besides, the findings of a recent publication provide evidence that relative folate deficiency may precede Alzheimer disease and vascular dementia [24].

In the present study, we found lower vitamin B12 levels in levodopa-treated PD patients with cognitive impairment and in controls, and this has not been previously reported. This finding should be investigated further. The underlying pathophysiological mechanisms of low serum folate and vitamin B12 levels in PD patients, and the way they influence mood and cognition, are not well understood.

An experimental study suggests that folate deficiency sensitizes mice to neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine-induced PD-like pathology and motor dysfunction [25]. This effect of folate deficiency may be mediated by homocysteine [26], given the inverse relationship between serum folate and homocysteine levels shown by Giles et al. [27]. Levodopa seems to play a role in this, as is concluded in other papers where levodopa-treated PD patients, as our patient population, have plasma homocysteine levels higher than the non-PD and untreated PD patients [28–30].

Some limitations of the present study should be mentioned. One is the choice of the “neurological control group” and the exclusion of controls with neurological manifestations of vitamin B12 or folate deficiency. Another is that our results may suffer from lack of controls for other factors (age, sex, education, comorbidity, depressive state, etc.).

In conclusion, the clinical implication of our findings relates to the importance of determining folate and serum vitamin B12 levels in all levodopa-treated PD patients, mainly because co-existent depression should probably focus clinician attention on the possibility of lower folate levels, though the specific role of folate in the pathophysiology of depression is still under debate. The effects of vitamin supplementation on clinical and psychiatric outcomes in these patients merits further attention and investigation. Well-organized interventional studies may well be worth the effort.

References


