Editorial

# Vitamin B12 (cobalamin) and Parkinson's disease

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Vitamin B12 (cobalamin) deficiency has long been associated with neurological impairments, particularly neuropathy, subacute combined degeneration of the spinal cord and mental complications ('megaloblastic madness'). These were initially associated with glossy tongue, premature gray hair and yellow skin, all due to pernicious anemia [1], but have later been associated with vitamin B12 deficiency itself. Until 1988, neurological impairments due to vitamin B12 deficiency were thought to be preceded by macrocytosis or anemia [2]. This dogma was dispelled when a series of patients with neurological impairments and vitamin B12 deficiency (but without anemia or macrocytosis) were successfully treated with vitamin B12 replacement, so now vitamin B12 levels are often checked in the assessment of peripheral neuropathies and other possible vitamin B12-related disorders even when anemia is not present.

The association between vitamin B12 and Parkinson's disease (PD) had been of minor concern until recently. L-DOPA, the most important treatment for PD motor dysfunction, has an effect on vitamin B12 serum levels, which appeared to be minor [3], but reports in the last few years have suggested that peripheral neuropathies are far more common in PD patients than previously thought and that these are often associated with markers of systemic vitamin B12 deficiency. Furthermore, several PD patients treated with continuous duodenal L-DOPA infusion (DLI) have developed neuropathies related to vitamin B12 deficiency [4].

The normal functioning of the nervous system and hematopoietic system requires the water-soluble vitamin B12, which must be ingested, usually in animal protein. All cells in the body use vitamin B12 for DNA synthesis and regulation, fatty acid synthesis and energy production.

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Normally, vitamin B12 is released from food protein via peptic digestion at a low pH. It then binds to R protein, a glycoprotein found in gastric juice and saliva. In the duodenum, this complex is digested by pancreatic proteases. Vitamin B12 is then released and forms a complex with IF, a protein produced by gastric parietal cells. The vitamin B12–IF complex gets absorbed in the ileum, where vitamin B12 is ultimately released. Intestinal absorption of vitamin B12 requires the presence of IF. Vitamin B12 is then used in the conversion of methylmalonyl coenzyme-A to succinyl coenzyme-A, and in the production of tetrahydrofolate and methionine, which are important for methylation reactions in the nervous system [5]. Large amounts of vitamin B12 ingestion are usually well tolerated, as excess amounts are excreted via the kidneys. As opposed to the deficiency states, no adverse effects from vitamin B12 excess have been reported. In deficiency states, serum levels of homocysteine (Hcy) and methylmalonic acid (MMA) rise and are thought to be more reliable indicators of intracellular vitamin B12 status [6]. It is therefore possible for serum vitamin B12 levels to be normal despite a systemic vitamin B12 deficiency indicated by elevated levels of Hcy and MMA.

Vitamin B12 deficiency occurs frequently among elderly patients (10–15% prevalence), but it is often unrecognized due to subtle clinical manifestations. They usually present with cognitive impairment and fatigue, which gets attributed to 'old age' [7]. Wang *et al.* investigated vitamin B12 status in 827 Chinese patients aged 60 years and older who were inpatients at Shanghai Punan Hospital and showed that vitamin B12 deficiency was found in 163 patients (19.71%), especially in older patients [8]. However, all the patients had renal or hepatic failure, making this prevalence nongeneralizable. A study in Australian nursing homes found that 14% of previously untested subjects were vitamin B12 deficient [9]. Elderly patients are more prone to vitamin B12 deficiency either from dietary deficiency, or from malabsorption due to gastric atrophy, other malabsorption syndromes, drug interactions or a combination of these [1]. Vitamin B12 absorption is decreased by acid suppression, so the drugs commonly used in the western countries to prevent gastric reflux must be considered.

Vitamin B12 deficiency causing significant neurological problems is uncommon in the west. Over a 17-year period in two large New York City (NY, USA) hospitals only 143 patients were identified. The syndromes identified were: a combined myelopathy and neuropathy (41%), neuropathy (25%), myelopathy (subacute combined degeneration of the spinal cord; 12%), cognitive impairment (8%) and paresthesias with a normal neurological examination occurring in 14% [10]. A random sample of 1000-community-dwelling individuals aged 75 years or older in the UK revealed that low vitamin B12 levels were associated with a two- to four-fold increased risk for cognitive impairment [7]. No causal implication was suggested and no association between alcohol consumption and vitamin B12 status was found [7].

A large, prospective, population-based cohort study of 5289 people aged 55 years and older (the Rotterdam study) found that there was no association between dietary vitamin B12 and an increased risk of PD [11]. This study did not check serum vitamin B12 levels. Another study of 82 patients with PD found that there was no significant difference in the level of serum vitamin B12 between the PD patients and controls, but Hcy and MMA were not measured [12]. Since vitamin B12 levels can be altered by numerous medical conditions, diet and drugs, which are difficult to control for, as the degree of confounding factors muddles interpretation. However, there has been speculation that Hcy is neurotoxic to dopaminergic cells and may contribute to disease progression [13] and it has been shown that MMA causes striatal degeneration when injected directly into the rat brain [14].

L-DOPA is our most effective treatment for the motor aspects of PD. It is converted to dopamine in the brain, which is broken down by monoamine oxidase and catechol-*O*-methyltransferase (COMT). This requires methylation via *S*-adenosylmethionine, which produces Hcy, utilizing vitamin B12. Hence, increased dopamine secretion leads to vitamin B12 consumption [4,13]. Patients with PD may be predisposed to having a vitamin B12 deficiency for several reasons, including the fact that the majority of PD patients are elderly, many are on gastric acid antagonists and may have atrophic gastritis or malabsorption syndromes. PD also alters diet, and L-DOPA may reduce vitamin B12 levels while increasing Hcy [15]. One study reported similarly elevated levels of Hcy and MMA in 68 patients with

three neurodegenerative disorders (PD, progressive supranuclear palsy or amyotrophic lateral sclerosis) regardless of L-DOPA status [6], suggesting that disparate neurodegenerative disorders may cause this change, perhaps via diet, or low vitamin B12 may be associated with neurodegenerative diseases. In a study comparing Hcy levels in 26 PD patients on L-DOPA, 20 PD patients on L-DOPA plus COMT inhibitors (COMT-I) and 32 controls, elevated Hcy levels were found in subjects on L-DOPA only, while subjects on COMT-I plus L-DOPA had significantly reduced plasma Hcy levels [16]. As noted above, COMT-I should reduce the breakdown of dopamine, thereby reducing the production of Hcy and the decrease in vitamin B12, as was found in this study.

In a 2001 study, 37 randomly chosen PD patients (without neuropathic complaints), were compared with age-matched controls for the presence of neuropathies [17]. Of those 37, 14 PD patients had a neuropathy – a significantly increased number compared with controls. These affected PD patients were then compared with non-PD patients with neuropathies for markers of vitamin B12 deficiency and the PD patients were found to have significantly reduced vitamin B12 levels. Finally, the serum vitamin B12 correlated with the cumulative exposure to L-DOPA [17]. A similar study chose 58 subjects randomly from a PD database and compared them to age- and gender-matched controls. This study also found a marked increase of neuropathy in the PD patients compared with the controls (55 vs 9%), and the PD patients with neuropathy had lower vitamin B12, and higher MMA and Hcy serum levels, as well as a higher cumulative exposure to L-DOPA [18]. These results suggest that PD patients have a considerably higher incidence of neuropathy than an age- and sex-matched cohort, and that this neuropathy may be related to diminished systemic vitamin B12, which itself may be related to L-DOPA intake.

Continuous DLI is a technique for treating PD patients with refractory clinical fluctuations in response to their PD medications ('on–off'). L-DOPA solution is infused at a constant rate directly into the duodenum via an extra-corporeal pump carried by the patient. DLI markedly reduces the fluctuations and the dyskinesias. Published results with DLI appear to equal the results from deep brain stimulation although the two have not been compared head to head. DLI has been available in Europe for many years and is being tested for approval in the USA. There are at least 13 cases described in the literature of neuropathy associated with DLI [4]. These include one case of Guillain–Barré syndrome, two of small-fiber neuropathy and ten of axonal neuropathies. Vitamin B12 was not measured in the Guillain–Barré syndrome case, whereas vitamin B12 was low or borderline in the other 12 cases and Hcy, although not measured in all cases, was high [19,20]. Vitamin B12 supplementation was helpful in some cases, but in other cases the neuropathy stopped progressing despite continuing DLI without vitamin B12 supplementation and another improved simply with stopping the DLI. Any connection between DLI and neuropathy and vitamin B12 thus remains speculative.

We conclude that, while vitamin B12 is crucial for normal function of the nervous system, its specific relationship to PD has yet to be determined. The hypothesis that vitamin B12 deficiency promotes degeneration in PD has only a small amount of data to support it. The observation that L-DOPA reduces vitamin B12 has moderate support but there is only suggestive evidence that this has clinical relevance. Two reports of a marked increase in neuropathy in PD patients require further investigation as these studies indicate that 40–50% of PD patients have unsuspected neuropathies, which may be related to vitamin B12 deficiency and therefore reversible and probably preventable. And finally, there are reports that DLI may be associated with a further increased risk for neuropathy in PD patients. Santos-Garcia *et al.* raise the possibility that "L-DOPA gel infusion may induce a decrease in vitamin B12 levels, leading to peripheral neuropathy" [4]. This issue is currently under investigation in the US trials of DLI [Fernandez H, Pers. Comm.] so that an answer, obtained prospectively, should be available. Until these questions are answered, all PD patients should be assessed for neuropathies and, if present, should be evaluated with respect to vitamin B12, Hcy and MMA levels. Alternatively, all PD patients may be treated with vitamin B12 supplementation as no adverse effects of vitamin B12 excess have been reported.

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