Parkinson disease, L-dopa, and neuropathy
Did we miss something?

Is it conceivable that for 40 years we have overlooked an insidious long-term levodopa treatment adverse effect, such as neuropathy, in idiopathic Parkinson disease (IPD)? In this issue of Neurology®, Rajabally and Martey1 take up the already controversial question, recently mooted by Toth et al.,2 of the increased prevalence of neuropathy in chronic levodopa-treated IPD and its potential but tenuous link to elevated plasma levels of homocysteine (Hcy) and methylmalonic acid (MMA) and to reduced vitamin B12 levels. Even though the role of levodopa in neuropathy is still hypothetical, the clinical relevance is evident, as sensory neuropathy may contribute to impaired balance and neuropathic pain in advanced IPD. Furthermore, vitamin B12 deficiency and increased Hcy and MMA levels can be easily determined in blood, suggesting that neuropathy as a treatment-related complication may be prevented or treated by vitamin B12 and folate supplementation.

But what evidence do we have to direct our clinical care efforts? Patients with IPD, particularly those with long-term levodopa treatment, may more frequently develop a neuropathy. In the cross-sectional case-control studies of Toth et al.3 and Rajabally and Martey,1 neuropathy, mostly axonal, was found clinically or electrically in 32 out of 55 (55%) and 14 out of 37 (37.8%) patients with IPD aged around 68 years with a disease duration of 6 to 9 years, compared to 8% to 9% in matched controls (a rate expected for this age range). Most study participants (3/4) were considered symptomatic in both studies, but to what extent this affected their functional status or well-being was not stated. Both studies involved a limited number of patients and were hospital-based, rather than community-based, so there was probably a selection bias. Furthermore, the use of a more selective neuropathy screening tool and a more complete electrophysiologic assessment would have been useful to characterize fully the frequency and nature of neuropathy in the study of Rajabally and Martey.1 Conversely, no neuropathy associated with IPD has been identified by the French pharmacovigilance network3 or in clinical trials involving more than 12,000 levodopa-treated patients.4 However, the latter studies likely suffered from underreporting and selection bias. Thus, to date, there is no convincing epidemiologic evidence of an increased prevalence or incidence of neuropathy in IPD, and if otherwise, to what extent levodopa may be linked to neuropathy.

There is some evidence that acute or chronic levodopa intake in IPD increases plasma Hcy and MMA plasmatic levels, which vary across published studies.5 Levodopa is catabolized by methylation (through catechol-O-methyltransferase [COMT]), drains methyl reservoirs, and also lowers S-adenosylmethionine (SAM), which is equilibrated with S-adenosylmethionine-Hcy (SAH) via methionine synthetase (which requires vitamin B12 and methyltetrahydrofolate to function).6 Demethylation of SAM forms SAH, which is immediately converted in Hcy.6 Patients with IPD treated with levodopa thus seem to have lower plasmatic B12 but higher Hcy and MMA levels.6 Much has been written about the link between chronic hypercystinemia and the increased risk of vascular disease and dementia, but few data to date suggest that this might be the case in IPD.7 Interestingly, folate or vitamin B12 can help to lower Hcy levels in IPD, the role of COMT inhibitors being more controversial.8

Regarding peripheral nerve disease, there are data suggesting a causal role of these metabolic abnormalities, but no definitive pathophysiologic data. An indirect association has been proposed between a levodopa-induced rise in Hcy and signs of neuropathy; and between levodopa exposure, MMA elevation, and sensorimotor neuropathy in IPD.6 The relationship between vitamin B12 deficiency and elevated Hcy and MMA in levodopa-treated IPD is even more elusive. Vitamin B12 deficiency is a well-known cause of neuropathy but also of multifaceted nervous system disorders, and is quite frequent in the

See page XXX

From Bordeaux University (F.T., G.L.M.), Bordeaux; CHU de Bordeaux (F.T., G.L.M.), Hôpital Haut-Lévêque, Pessac; Institut des Maladies Neurodégénératives (F.T.), CNRS UMR 5293, Bordeaux; and Institut François Magendie (G.L.M.), INSERM 862, Bordeaux, France.

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elderly. Some case reports described severe life-threatening vitamin B\textsubscript{12}–responsive neuropathies following gastroduodenal levodopa (duodopa) infusion in patients with IPD with an already poor nutritional status. Decreased or low-normal B\textsubscript{12} levels have been described in IPD with neuropathy and patients may be stabilized by supplementation by IM cobalamin in some cases. In addition, Rajabally and Martey found a correlation between cumulative levodopa exposure and neuropathic severity. Vitamin B\textsubscript{12} deficiency explained more cases of neuropathy in IPD than in other neuropathic patients, even though B\textsubscript{12} rates were only slightly decreased and Hcy and MMA were not measured.

In view of these data, we now need well-designed unselected population-based investigations and at best prospective epidemiologic studies, as well as experimental and clinical/electrophysiologic studies either demonstrating or refuting a direct causative link between levodopa exposure in IPD, neuropathy, and vitamin B\textsubscript{12} deficiency or increased Hcy and MMA.

Meanwhile, what should we do in our everyday approach to IPD? According to Rajabally and Martey, the wisest thing would be to perform systematic serial clinical assessment for neuropathy in IPD treated with levodopa on a long-term basis, and to perform a classic workup including vitamin B\textsubscript{12} and Hcy and MMA levels in patients with confirmed neuropathy. Finally, for those with either a B\textsubscript{12} decrease (<300 ng/L) or Hcy or MMA increases, it might be judicious to offer systematic B\textsubscript{12} or folate supplementation.

**AUTHOR CONTRIBUTIONS**

Dr. Tison: drafting/revising the manuscript, analysis and interpretation of the data, and acquisition of data. Dr. Le Masson: drafting/revising the manuscript, analysis and interpretation of the data.

**DISCLOSURE**

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**REFERENCES**