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Neurotoxicity of levodopa/carbidopa intestinal gel preparations can cause polyneuropathy in Parkinson's Disease patients

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To the Editors

We were interested to read the article by Havrankova et al. regarding a retrospective multicentre study investigating whether high-dose levodopa/carbidopa intestinal gel (LCIG) is a risk factor for the development of polyneuropathy in Parkinson's Disease (PD) patients [1].

Of the 183 LCIG users, six developed acute polyneuropathy at a mean dose of 3,015 mg/day [1]. A cut-off value of > 2,605 mg/day was found to be a predictor of polyneuropathy [1]. It was concluded that the risk of acute polyneuropathy in PD patients treated with LCIG was associated with an increase in daily levodopa dose of more than 62% [1]. The study is noteworthy, but several points should be discussed.

Firstly, it is questionable whether elevated homocysteine causes polyneuropathy [1]. Homocysteine is one of the 20 amino acids required to build proteins. How can an endogenous molecule that is needed in all cells and circulates throughout the body be neurotoxic? According to this hypothesis, everyone with elevated homocysteine levels should have neuropathy, which is definitely not the case. Although some studies have found a link between hyperhomocysteinaemia and neuropathy [2], other studies have found no such link [3]. Hyperhomocysteinaemia can also be triggered by the use of N_2O [4]. Is there any evidence that LCIG increases intestinal production of N_2O? N_2O is also used as a volatile anaesthetic that has been associated with the development of neuropathy [5].

The second point is that PD patients generally do not develop B6, B12 or folic acid deficiency. If PD patients were generally B12 deficient due to LCIG, these patients would be more likely to suffer from funicular myelosis. Would it be conceivable that it was not LCIG but a reduced appetite or a reduced desire to eat that led to a secondary vitamin deficiency, which could easily be remedied by supplementation of reduced vitamins? A strong argument against secondary vitamin deficiency as a cause of neuropathy in LCIG recipients is that neuropathy occurs in these patients despite prophylactic supplementation with vitamins [6].

The third point is that 'acute polyneuropathy' has been defined as neuropathy occurring within a few days, or at most a few weeks, after the start of LCIG therapy [1]. This definition is imprecise, as for example the onset of neuropathy three months after the start of LCIG therapy would still be classified as 'acute'. In patient 3, the polyneuropathy did not develop until almost a year after the start of LCIG therapy. Such a long latency period does not indicate a causal relationship, and does not fulfill the criteria for acute polyneuropathy.

The fourth point is that the type of neuropathy caused by LCIG was not reported [1]. Was the polyneuropathy of the axonal or demyelinating type, symmetric or asymmetric, length-dependent or length-independent, and did it predominantly affect large or small fibres? Were nerve conduction studies really performed in all included patients, or was polyneuropathy only clinically diagnosed in some of the patients?

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The fifth point is that no genetic studies were performed to determine whether the included patients had evidence of hereditary neuropathy or genetic PD. Patients with PD may also happen to have an additional hereditary disease that manifests phenotypically with neuropathy, or hereditary PD may additionally manifest with neuropathy. In how many of the included patients was the family history positive for polyneuropathy or PD?

The sixth point refers to the statement that polyneuropathy developed *de novo* in 10 patients [1]. How can the authors be sure that the polyneuropathy was not already subclinical? Were nerve conduction studies performed in these 10 patients prior to starting LCIG treatment?

Finally, we would like to know whether Guillain-Barre syndrome (GBS) was excluded in patients 1, 2, 3 and 5 who had quadruparesis.

In summary, it is more likely than hyperhomocysteinaemia, or vitamin deficiency, or immune mechanisms, that neuropathy in LCIG patients is due to neurotoxicity of the jejunal probe material or to molecules in the LCIG mixture other than levodopa or carbidopa.

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