Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2023, Volume 57, no. 4, pages: 401–402
DOI: 10.5603/PJNNS.a2023.0043

ISSN: 0028-3843, e-ISSN: 1897-4260

# Before blaming levodopa/carbidopa intestinal gel for demyelinating polyneuropathy, all differential aetiologies must be ruled out

Josef Finsterer

Neurology & Neurophysiology Centre, Vienna, Austria

**Key words:** polyneuropathy, Parkinson, nerve conduction studies, demyelination, side effect

(*Neurol Neurochir Pol 2023; 57 (2): 401–402*)

## To the Editors

We read with interest the article by Piekarski et al. featuring a 55-year-old male with Parkinson's disease (PD) of 16 years' duration who developed demyelinating polyneuropathy (dPNP) 12 weeks after the initiation of levodopa/carbidopa intestinal gel (LCIG) therapy, which was published alongside a review of 15 cases with LCIG-associated dPNP [1]. It was found that LCIG therapy was discontinued in all 15 cases with LCIG therapy-associated dPNP, and that only in the index patient was LCIG therapy maintained, and that he additionally received intravenous immunoglobulins (IVIGs) [1].

It was concluded that all PD patients scheduled for LCIG therapy should have nerve conduction studies (NCSs) performed prior to initiating LCIG, and that LCIG therapy should not be discontinued if dPNP develops, but should rather be combined with immunosuppressive treatment [1]. This study is compelling, but has limitations that should be discussed.

The main limitation of the case report and review is that alternative aetiologies of dPNP were not adequately ruled out in each of the included cases. Demyelinating large fibre neuropathy is generally due to an immunological disease, such as Guillain–Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), anti-myelin associated protein (MAG) associated neuropathy, nodopathies due to antibodies against neurofascin, POEMS syndrome, connective tissue disease, vasculitis, a hereditary disease such as Charcot-Marie-Tooth (CMT) disease, paraneoplastic conditions (e.g. gammopathies), or neoplastic conditions [2]. To diagnose these conditions, a comprehensive and costly work-up is necessary. However, to remain scientifically sound, all of these differentials must be 'off the table' before a toxic aetiology of dPNP in the enrolled patients can be considered.

A second limitation of the study is that GBS/CIDP following an infection with, or vaccination against, SARS-CoV-2 was not adequately ruled out. Since there is evidence that the virus and the vaccination against it can be complicated by polyradiculitis, and since this patient was reported during the pandemic and had dissociation cyto-albuminique on cerebrospinal fluid (CSF) examination, as did 10 of the 15 patients from the literature, it is crucial that this infectious or immunological cause of dPNP is ruled out.

A strong argument against LCIG therapy as the cause of dPNP in the index patient is that NCSs prior to the onset of LCIG therapy showed a moderate decrease of nerve conduction velocities in sural nerves, severe axonal neuropathy in both peroneal nerves, and mild reduction of conduction velocity and amplitude in both tibial nerves [1]. These results indicate that there was a combined demyelinating and axonal lesion already prior to the initiation of LCIG therapy. Thus, at best, LCIG therapy could have enhanced dPNP, but did not cause it.

We disagree with the statement that nerve conduction velocity in the tibial nerve was "previously intact" [1]. The NCS of the tibial nerves prior to the onset of LCIG therapy

**Address for correspondence:** Josef Finsterer, MD, PhD, Postfach 20, 1180 Vienna, Austria; e-mail: fifigs1@yahoo.de

Received: 30.04.2023 Accepted: 10.05.2023 Early publication date: 19.07.2023

was described as mildly reduced [1]. This discrepancy needs to be resolved.

Another limitation of the study is that the current medication, in addition to LCIG, of the index patient and of the 15 patients from the literature was not provided.

Overall, this interesting study has limitations that put the results and their interpretation into perspective. Addressing these issues would strengthen the conclusions and could improve the status of the study.

Before blaming levodopa/carbidopa intestinal gel for dPNP, alternative aetiologies must be adequately ruled out.

**Conflicts of interest:** *None.*
**Funding:** *None.*

## References

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