TWO CASES OF AXONAL POLYNEUROPATHY ASSOCIATED WITH LCIG THERAPY IN PARKINSON'S DISEASE AND LITERATURE INTEGRATION

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ABSTRACT

Background: Peripheral neuropathy is increasingly recognised in Parkinson's disease (PD), particularly in patients receiving levodopa–carbidopa intestinal gel (LCIG). While most cases are chronic and slowly progressive, acute and subacute neuropathies with variable pathophysiology have also been reported. **Objective:** To describe two cases of advanced PD complicated by severe polyneuropathy during LCIG therapy, and to contextualise their clinical and electrophysiological findings within current literature. **Methods:** We conducted a detailed clinical assessment, laboratory evaluation, nerve conduction studies (NCS), and electromyography (EMG) in two male patients with advanced PD treated with LCIG. Relevant laboratory and nutritional factors were also examined. **Results:** Both patients developed severe sensorimotor axonal polyneuropathy. Case 1, a 67-year-old man, exhibited chronic axonal damage with reinnervation in the context of folate deficiency, systemic illness, and renal impairment. Case 2, a 70-year-old man, presented with active denervation and sensory ataxia, associated with mild vitamin B12 deficiency, weight loss, and renal dysfunction. Both received intravenous immunoglobulin (IVIG) with partial clinical improvement. **Conclusion:** LCIG-associated neuropathy is heterogeneous, encompassing both chronic compensated forms and more aggressive phenotypes with ongoing denervation. Multiple mechanisms—including high levodopa exposure, vitamin depletion, malnutrition, renal impairment, and possible immune factors—may converge in its pathogenesis. These cases emphasise the importance of early prophylactic vitamin supplementation, regular metabolic and neurophysiological monitoring, and timely recognition of both acute and chronic forms to optimise outcomes in LCIG-treated patients.

Keywords: Parkinson's disease; levodopa–carbidopa intestinal gel; polyneuropathy; vitamin deficiency

ΔΥΟ ΠΕΡΙΠΤΩΣΕΙΣ ΑΞΟΝΙΚΗΣ ΠΟΛΥΝΕΥΡΟΠΑΘΕΙΑΣ ΣΧΕΤΙΖΟΜΕΝΗΣ ΜΕ ΤΗΝ ΘΕΡΑΠΕΙΑ ΜΕ ΕΝΤΕΡΙΚΗ ΓΕΛΗ ΛΕΒΟΝΤΟΠΑ/ΚΑΡΒΙΝΤΟΠΑ ΣΤΗΝ ΝΟΣΟ PARKINSON ΚΑΙ ΑΝΑΣΚΟΠΗΣΗ ΤΗΣ ΒΙΒΛΙΟΓΡΑΦΙΑΣ

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ΠΕΡΙΛΗΨΗ

Εισαγωγή: Η περιφερική νευροπάθεια αναγνωρίζεται ολοένα και συχνότερα στη νόσο Πάρκινσον (PD), ιδιαίτερα σε ασθενείς που λαμβάνουν εντερική γέλη λεβοντόπα–καρβιντόπα (LCIG). Αν και οι περισσότερες περιπτώσεις είναι χρόνιες και εξελίσσονται αργά, έχουν επίσης αναφερθεί οξείες και υποξείες νευροπάθειες με ποικίλη παθοφυσιολογία. **Σκοπός:** Η περιγραφή δύο περιστατικών προχωρημένης PD που παρουσίασαν σοβαρή πολυνευροπάθεια κατά τη διάρκεια θεραπείας με LCIG, καθώς και η ερμηνεία των κλινικών και ηλεκτροφυσιολογικών ευρημάτων τους στο πλαίσιο της υπάρχουσας βιβλιογραφίας. **Μέθοδοι:** Διενεργήσαμε λεπτομερή κλινική αξιολόγηση, εργαστηριακό έλεγχο, ηλεκτρονευρογράφημα (NCS) και ηλεκτρομυογράφημα (EMG) σε δύο άνδρες ασθενείς με προχωρημένη PD υπό θεραπεία LCIG. Εξετάστηκαν επίσης

σχετικοί εργαστηριακοί και διατροφικοί παράγοντες. **Αποτελέσματα:** Και οι δύο ασθενείς εμφάνισαν σοβαρή αισθητικοκινητική αξονική πολυνευροπάθεια. Το Περιστατικό 1, άνδρας 67 ετών, παρουσίασε χρόνια αξονική βλάβη με επανανεύρωση, στο πλαίσιο έλλειψης φυλλικού οξέος, συστηματικής νόσου και νεφρικής δυσλειτουργίας. Το Περιστατικό 2, άνδρας 70 ετών, παρουσίασε ενεργό απονεύρωση και αισθητική αταξία, συνδεόμενη με ήπια έλλειψη βιταμίνης Β12, απώλεια βάρους και νεφρική δυσλειτουργία. Και οι δύο έλαβαν ενδοφλέβια ανοσοσφαιρίνη (IVIG) με μερική κλινική βελτίωση. **Συμπεράσματα:** Η νευροπάθεια που σχετίζεται με LCIG είναι ετερογενής, περιλαμβάνοντας τόσο χρόνιες, αντιρροπούμενες μορφές όσο και πιο επιθετικούς φαινότυπους με ενεργό απονεύρωση. Πολλαπλοί μηχανισμοί-συμπεριλαμβανομένης της υψηλής έκθεσης σε λεβοντόπα, της έλλειψης βιταμινών, του υποσιτισμού, της νεφρικής δυσλειτουργίας και πιθανών ανοσολογικών παραγόντων-μπορεί να συμβάλλουν στην παθογένειά της. Τα περιστατικά αυτά υπογραμμίζουν τη σημασία της πρώιμης προφυλακτικής συμπληρωματικής χορήγησης βιταμινών, της τακτικής μεταβολικής και ηλεκτροφυσιολογικής παρακολούθησης, και της έγκαιρης αναγνώρισης τόσο των οξέων όσο και των χρόνιων μορφών για τη βελτιστοποίηση των αποτελεσμάτων σε ασθενείς υπό θεραπεία LCIG.

Λέξεις-κλειδιά: Νόσος Πάρκινσον, εντερική γέλη λεβοντόπα–καρβιντόπα, πολυνευροπάθεια, έλλειψη βιταμινών

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder defined by motor symptoms such as bradykinesia, tremor, and rigidity, but it is increasingly recognised as a systemic condition with multisystem involvement. Among its non-motor manifestations, gastrointestinal dysfunction is particularly relevant, not only because of its impact on quality of life, but also because of its role in levodopa absorption and treatment response.[1]

In recent years, peripheral polyneuropathy have emerged as important complications in advanced PD, especially in patients treated with levodopa–carbidopa intestinal gel (LCIG). While the reported prevalence varies, observational studies suggest that neuropathy occurs in 10–15% of LCIG-treated patients, with both symptomatic and subclinical cases identified on electrophysiological testing.[2,10] Two main phenotypes have been described: a chronic, slowly progressive axonal sensorimotor neuropathy, and an acute or subacute form, sometimes resembling Guillain–Barré syndrome or chronic inflammatory demyelinating polyneuropathy (CIDP).[6,9,11]

The pathophysiology of LCIG-associated neuropathy is multifactorial. High-dose levodopa metabolism increases homocysteine levels via catechol-O-methyltransferase activity, leading to functional deficiencies of vitamin B12, folate, and pyridoxine, and accumulation of methylmalonic acid.[9,14] Malnutrition, significant weight loss, and renal dysfunction may exacerbate this vulnerability.[10] In addition, immune-mediated mechanisms have been proposed, with some patients showing albumino-cytological dissociation, antiganglioside antibodies, and partial response to intravenous immunoglobulin (IVIG).[1,6,11] Finally, small fibre neuropathy has been demonstrated early after LCIG initiation, even in the absence of large fibre involvement, underscoring the potential for early subclinical nerve damage.[5]

Preventive strategies focus on vitamin supplementation and systematic monitoring. Several prospective studies have shown that early and continuous administration of cobalamin, folate, and pyridoxine reduces the incidence of acute and subacute neuropathies, although chronic progression may still occur.[4,16] Regular surveillance of body weight, homocysteine, methylmalonic acid, vitamin levels, and serial neurophysiological studies are increasingly recommended to detect neuropathy at an early stage.[2,10]

Despite accumulating evidence, the true incidence, risk factors, and natural history of LCIG-related neuropathy remain incompletely understood, and clinical practice varies widely across centres. In this report, we present two patients with advanced PD who developed severe sensorimotor polyneuropathy during LCIG therapy, illustrating the clinical heterogeneity of this complication and discussing the findings in light of current literature.

CASE 1

A 67-year-old man with an 18-year history of PD developed motor fluctuations, hallucinations, and orthostatic hypotension after 10 years of disease, with poor response to oral levodopa therapy. LCIG was initiated at 1910 mg/day, later escalated to 24-hour infusion 2645 mg/day. Seven months later, he reported glove-and-stocking paraesthesias and B12 supplement oral therapy was initiated.

Two months later, he experienced a generalised seizure and systemic deterioration with hepatic and renal failure, empyema, pneumothorax, weight loss, and prolonged immobility. On admission, he showed diffuse muscle atrophy, distal weakness (lower > upper limbs), absent reflexes, and loss of vibration and proprioception.

Laboratory tests showed anaemia, folate deficiency (1.8 ng/ml), with elevated vitamin B12 levels (>1800 pg/ml). Autoimmune and paraneoplastic screening were negative; CSF revealed mildly elevated protein (62 mg/dl). Steroid therapy was ineffective, while IVIG provided only mild motor improvement.

Electrophysiology demonstrated a severe axonal sensorimotor polyneuropathy with chronic denervation and reinnervation changes. Despite persistent sensory deficits, strength was relatively preserved, though he became wheelchair dependent, due to osteoporotic fractures as well. LCIG infusion continues to 2248 mg/day until present day.

CASE 2

A 70-year-old man with a 13-year history of PD, complicated by motor fluctuations and painful dystonia, underwent LCIG initiation with infusion at 1878 mg/day. His course was complicated by ~15 kg weight loss, episodes of epigastric discomfort, and acute renal dysfunction, while in the past 8 months he remained mainly bedridden, due to knee arthritis and consequent arthroplasty and adoption of genu varus.

By 2024 and within weeks, he developed fine motor impairment and pseudoathetosis of the hands, distal weakness, and gait inability. On examination, there was atrophy of the right quadriceps and gastrocnemius, distal upper limb weakness, absent lower limb reflexes, glove-and-stocking sensory loss, and severe sensory ataxia.

Laboratory studies revealed anaemia, renal impairment, and low vitamin B12 (237 pg/ml). CSF protein was elevated (87 mg/dl). He was treated with IVIG, with partial sensory and motor improvement, and started on B12 and folic acid supplementation.

NCS showed severe length-dependent axonal sensorimotor polyneuropathy with possible superimposed right median nerve entrapment. EMG confirmed chronic neurogenic changes with active denervation. He remains on LCIG with periodic IVIG therapy and vitamin supplementation.

Table 1 is indicating electrophysiological findings of the two patients.

DISCUSSION

Polyneuropathy is a well-documented but underrecognised complication of LCIG therapy in advanced Parkinson's disease. The two cases presented here illustrate its heterogeneity, with one patient developing a slowly progressive, predominantly axonal neuropathy characterised by chronic denervation and reinnervation, and the other presenting with a more aggressive course marked by active denervation and sensory ataxia, probably indicating an immune-mediated course of disease. These different trajectories underscore the clinical spectrum of LCIG-associated neuropathy, which has been repeatedly observed in both prospective studies and case reports.[2,6,7,9]

The epidemiology of LCIG-associated neuropathy is variable, with prevalence estimates ranging from 13% to as high as 25%, depending on study design and diagnostic methods.[2,7,10] In general Parkinson's cohorts, neuropathy is present in approximately 10–15%, but it appears far more frequent in patients treated with LCIG, suggesting that both cumulative levodopa exposure and pharmacokinetic factors associated with continuous intestinal infusion contribute to its development.[13-15] Most cases are chronic axonal polyneuropathies, although acute or subacute forms have been described, some of which resemble Guillain–Barré syndrome or chronic inflammatory demyelinating polyneuropathy.[6,8,9,11] Havránková and colleagues recently reported that acute polyneuropathy occurred in up to 11% of patients on LCIG, particularly at daily levodopa doses exceeding 2600 mg daily.[3] Case 1 patient received high levodopa doses within this risk range, which likely contributed to the severity of his neuropathy.

The mechanisms underlying LCIG-related neuropathy are multifactorial. The most consistent explanation centres on levodopa metabolism via catechol-O-methyltransferase, which generates homocysteine. When homocysteine is not effectively metabolised, due to relative deficiencies of vitamin B12, folate, or pyridoxine, it accumulates and exerts direct neurotoxic effects through oxidative stress, mitochondrial dysfunction, and impaired methylation pathways[9,14]

Table 1. Electrophysiological findings.

Patient	Age	NCS Findings	EMG Findings	Final Interpretation
Case 1	67	Severe reduction/absence of sensory and motor responses, consistent with axonal sensorimotor polyneuropathy	Chronic denervation with polyphasic motor unit potentials and reinnervation	Chronic severe axonal sensorimotor polyneuropathy with reinnervation
Case 2	70	Severe reduction/absence of responses; very low amplitudes; possible compressive lesion of right median nerve	Chronic neurogenic changes with fibrillations and positive sharp waves; active denervation	Severe length-dependent axonal sensorimotor polyneuropathy with active denervation

In keeping with this mechanism, both of our patients had vitamin abnormalities: folate deficiency in the first and low vitamin B12 levels in the second. Numerous studies have confirmed the depletion of B vitamins in LCIG-treated patients and linked these deficiencies to both biochemical alterations, such as elevated methylmalonic acid, and clinical neuropathy.[4,15,16] Pyridoxine depletion, in particular, has been correlated with higher levodopa doses.[14]

Nutritional factors also play an important role. Weight loss has been consistently associated with neuropathy severity in LCIG patients, with those losing more than 10% of body weight demonstrating significantly higher rates of polyneuropathy.[10] Both of our patients experienced notable weight loss during treatment, which likely exacerbated their vulnerability. Renal dysfunction, which was present in both cases, may further impair clearance of homocysteine and related metabolites, amplifying their neurotoxic potential. These observations reinforce that neuropathy in this setting is not merely a pharmacological complication but rather the product of a complex interaction between drug metabolism, immune pattern, nutritional status, and systemic comorbidities.

An additional dimension is the role of small fibre pathology. Devigili et al. demonstrated that small fibre neuropathy can occur early during LCIG treatment, sometimes within months, even in the absence of large fibre involvement.[5] This supports a stepwise model, in which small fibre damage precedes the emergence of clinically significant large fibre polyneuropathy. The early paraesthesias and painful dysesthesias reported by both of our patients may reflect such early small fibre involvement.

Although metabolic and nutritional mechanisms predominate, immune-mediated contributions have been described. Several reports have documented cases with albumino-cytological dissociation, antiganglioside antibodies, or rapid deterioration suggestive of a dysimmune process.[1,6,11] Some patients improved with immunomodulatory therapies, such as intravenous immunoglobulin or corticosteroids.[1,6] In our series, both patients received IVIG and experienced partial improvement, supporting the possibility that immune mechanisms may contribute in a subset of cases. Uncini and colleagues have proposed that acute, subacute, and chronic forms of LCIG-associated neuropathy may represent a continuum of related mechanisms, rather than entirely distinct entities.[9]

Electrophysiological findings in our cases further illustrate the heterogeneity of this condition. The first patient showed severe axonal loss with evidence of reinnervation, consistent with long-standing compensated neuropathy. The second patient, by contrast, exhibited active denervation, indicative of a more aggressive and multifactorial process. Such variability has been reported across different series, with both pure axonal and mixed axonal–demyelinating patterns observed.[6-8,12] These findings emphasise the need for comprehensive and repeated neurophysiological assessments, as single-point studies may underestimate the evolving nature of the neuropathy.

Management of LCIG-associated neuropathy remains challenging. Vitamin supplementation is currently the cornerstone of prevention. Several studies have shown that early and continuous supplementation with cobalamin, folate, and pyridoxine reduces the risk of acute neuropathy and helps stabilise neurophysiological findings, although chronic progression may still occur in approximately one-fifth of patients.[4,16] Our cases highlight the limitations of delayed supplementation, as both patients began vitamin therapy only after the onset of neurological symptoms. Other strategies, such as the use of COMT inhibitors to reduce homocysteine generation, have been proposed, although robust clinical evidence is still lacking.[14] For patients with rapidly progressive neuropathy, immunotherapy with IVIG or corticosteroids may be considered, although responses are often incomplete.[1,6] Finally, in the most severe cases, dose reduction or discontinuation of LCIG may be necessary, particularly when high doses of levodopa are being administered.[3]

Taken together, our cases and the existing literature highlight several clinical implications. All patients being considered for LCIG should undergo a baseline evaluation including vitamin levels, homocysteine, methylmalonic acid, renal function, and neurophysiological studies.[9,16] Prophylactic vitamin supplementation should be started at the initiation of LCIG, irrespective of baseline levels, as preventive therapy is superior to corrective therapy after symptoms emerge.[4,16] Longitudinal monitoring should include regular assessments of weight, renal function, vitamin status, and electrophysiological testing.[2,10] Emerging tools, such as quantitative sensory testing, skin biopsy, or corneal confocal microscopy, may allow earlier detection of small fibre neuropathy before irreversible large fibre damage occurs.[5] Clinicians should also maintain a high index of suspicion for immune-mediated contributions in rapidly progressive or atypical presentations, and consider immunotherapy in selected cases.[1,6,9]

The future management of LCIG-associated neuropathy will depend on refining prevention strategies and improving early detection. Multicentre prospective studies are needed to define optimal supplementation regimens, clarify the role of COMT inhibition or other metabolic modulators, and establish the utility of small fibre biomarkers.[9,16] Further work is also required to distinguish metabolic, nutritional, and immune contributions to this complication, as

treatment approaches may differ depending on the dominant mechanism.

In summary, the two cases described here exemplify the heterogeneous clinical and electrophysiological presentations of LCIG-associated polyneuropathy. They highlight the multifactorial pathogenesis of this condition, in which high levodopa exposure, vitamin depletion, nutritional compromise, renal dysfunction, and immune factors all play a role. Most importantly, they underscore the necessity of preventive supplementation, systematic monitoring, and early recognition, which remain the most effective strategies for safeguarding neurological outcomes in patients treated with duodenal levodopa infusion. Larger prospective studies are needed to clarify the interplay between levodopa dose, nutritional status, systemic illness, and immune-mediated mechanisms. Standardised supplementation protocols and neurophysiological monitoring should be integrated into LCIG programs to minimise morbidity.

CONCLUSION

Polyneuropathy is a clinically significant complication of advanced PD and LCIG therapy. The two cases presented illustrate heterogeneous presentations, from chronic reinnervation to active denervation with entrapment neuropathy. Preventive supplementation, vigilant monitoring, and early recognition are essential to improve outcomes in this vulnerable population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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