



Acute/subacute demyelinating polyneuropathy in Parkinson's Disease patients on levodopa-carbidopa intestinal gel therapy: systematic review with new case report

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ABSTRACT

Polyneuropathy (PNP) is a known complication of levodopa-carbidopa intestinal gel (LCIG) therapy of advanced Parkinson's Disease (PD). The overall prevalence of PNP in PD is estimated to be 42.1% (as shown in a review by Romagnolo et al. 2018), and the most common type is chronic axonal polyneuropathy. There is a group of acute/subacute onset demyelinating polyneuropathies, which is far less common, although it seems to be an important factor leading to the rapid discontinuation of LCIG treatment. In this systematic review, we present data on demyelinating polyneuropathy with acute/subacute onset; we identified nine papers including prospective assessments and case reports, with detailed information on 15 patients. In all patients, despite treatment with corticosteroids, intravenous immunoglobulins (IVIG) or plasma exchange (PE), the LCIG therapy was terminated. We also present a case of subacute demyelinating polyneuropathy with effective treatment and continuation of LCIG therapy.

Key words: Parkinson's Disease, levodopa-carbidopa intestinal gel, neuropathy, demyelinating polyneuropathy, acute/subacute onset

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Introduction

Parkinson's Disease (PD) is a neurodegenerative, predominantly motor disorder, manifesting with bradykinesia, tremor and rigidity. Nevertheless, it is accompanied by a broad spectrum of non-motor features [1].

Polyneuropathy in PD patients can be related to progression of the PD itself, or it can be medication- (levodopa) induced. It is predominantly of chronic sensory/sensorimotor and axonal type [2–4], and the estimated mean prevalence is 30.2% (12–55%) [5–7]. Polyneuropathy can result in severe instability and repeated falling, and therefore its identification, prevention or treatment would seem to be an important factor contributing to patients' quality of life. In patients with advanced PD undergoing levodopa-carbidopa

intestinal gel (LCIG) therapy, polyneuropathy has been detected with a mean prevalence of 42.1% (13.8% to 100%) [5, 8, 9]. In the literature, a PNP diagnosis has been based on electrophysiological criteria in combination with neurological symptoms and/or validated clinical scales. The most frequent is the sensory/axonal form of neuropathy [5]. However, a substantial number of cases presenting the demyelinating form of polyneuropathy, with acute or subacute onset, have been reported as well [10–13]. The pathophysiology of this group of neuropathies seems to be different, and treatment may require a specific approach.

The aim of this study was to review the literature in order to collect data on acute and subacute demyelinating polyneuropathy during LCIG therapy in advanced PD, accompanied by a new illustrative case report.

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Material and methods

Relevant human studies in the field of PD (MeSH main topic) were searched using the PubMed and Scopus databases up to the end of December 2021 using a variety of combinations of terms used in titles and abstracts: “Duodopa”, “levodopa-carbidopa intestinal gel”, “LCIG”, “levodopa”, “neuropathy”, “polyneuropathy”, “polyradiculoneuropathy”, “Guillain-Barre syndrome”, “GBS”, “chronic inflammatory demyelinating polyradiculoneuropathy”, and “CIDP”. This search was extended to a manual search of references in order to find any papers that did not contain the search terms (and thus could not be detected by established search criteria), but nonetheless contained any information on the problem in question. The inclusion criterion was: any study containing information about patients undergoing LCIG therapy who developed demyelinating polyneuropathy of acute/subacute onset. Acute onset was defined as up to four weeks, and subacute as up to 12 weeks from the onset of symptoms. Our analysis included both publications in which it was possible to perform a detailed analysis of nerve conduction studies (NCS) parameters, and also those where a diagnosis was only based on a patient’s history and clinical examination. Only original papers, systematic reviews and case reports/case series were included. PRISMA guidelines were used, and a flow diagram showing the process of identifying papers is set out at Figure 1 [14]. There were no language limitations, and papers in English and Spanish were included.

Results

Our search using the defined terms from selected databases resulted in the identification of 101 original papers. Subsequently, manual research was conducted — primarily the title research excluded papers that did not concern idiopathic PD or neuropathy as the main topic (excluded n = 47). The next step included manual abstract research in order to identify papers concerning LCIG therapy or papers with detailed information regarding conducted research in the field of neuropathy in PD (excluded n = 26). The remaining papers (n = 28) were manually screened in order to identify cases of acute/subacute demyelinating polyneuropathy with a sufficient amount of detailed information provided.

Ultimately, nine papers were identified (including one in Spanish) — four with prospective assessment [10, 12, 15, 16] and five case reports [11, 13, 17–19]. Publications were identified where such cases were only mentioned (providing an additional 33 cases) without any detailed information, and therefore they were not analysed [20–24]. Finally, the data of 15 patients was collected.

In the selected analysed case series (excluding case reports) from prospective studies, the incidence of demyelinating polyneuropathy was established at 8.9% (i.e. 9/105 pts). The analysed data was grouped into the following categories: demographic data, clinical manifestation and polyneuropathy onset, NCS and laboratory findings, LCIG dose, treatment, and outcome. All cases are presented in Table 1.

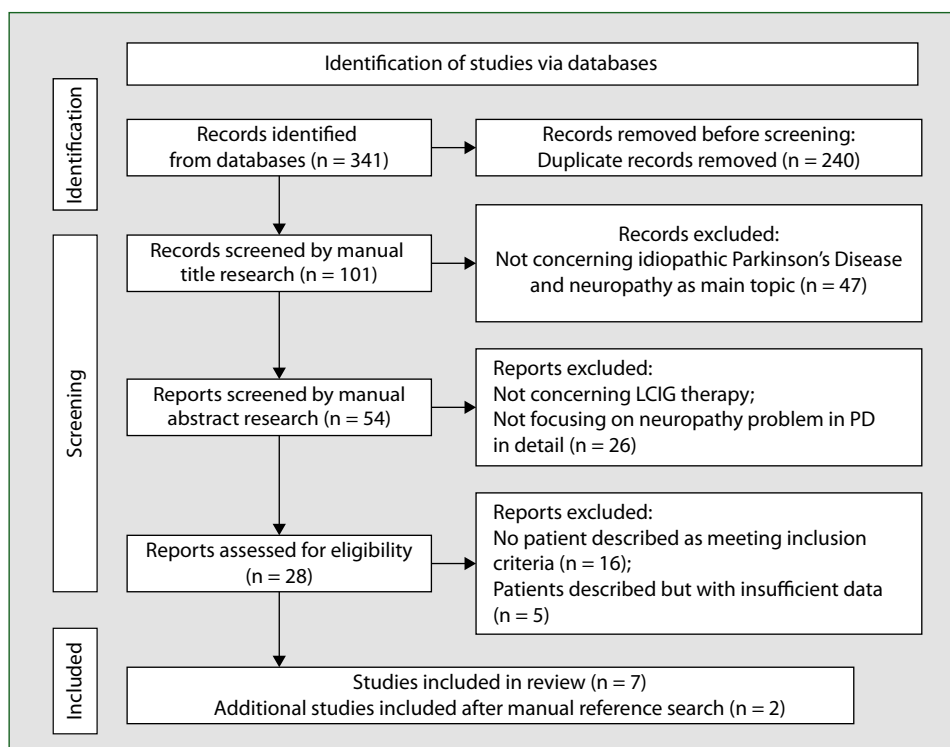


Figure 1. PRISMA flow diagram illustrating data collection process

Table 1. Summary of publications included into systematic review on acute/subacute polyneuropathy during LCIg treatment of advanced Parkinson's Disease

	Preval	PD dur	LEDD	LCIG dur	PNP onset	Diagno sis	Symptoms	Pre NCS	NCS on diag	NCS tol- low up	CSF	Lab	LC IG disc	Treatment	Outcome
Antonini 2007 n = 1/7	14%	Nd	Nd	7 m	1-2 w	GBS	Muscle weakness	Nd	NCS was consistent with GBS	Nd	A-c dis (protein Nd)	Nd	+	PE	"Some benefit"
Kobylecki 2012 n = 2	CR	Nd	1,740-2,240 mg	Nd	6-12 w	Demyelination	Sensory disturbances	Nd	Absent or attenuated sensory responses, reduced motor CVs, F-wave latency prolongation	Nd	No alterations	Hcy ↑ B12 N Nd	+	B12 Suppl	Improved or stabilised
Galazky 2014 n = 1	CR	5 y	2,940 mg	13 m	Sub-acute	GBS/CIDP like	Paresis lower > upper, absent reflexes, sensory disturbances, gait disturbances	Nd	Mixed axonal/demyelinating pattern	CVs improved	A-c dis protein 121 mg/dL	anti GA+ Hcy ↑ (230) B12 ↓ (136) B6 (2) ↓	+	IVIg 90g/3d steroids, PE Suppl Nd IVIg 210 g/7d	Primarily significant deterioration, > 3 m slow recovery
Galazky 2014 n = 1	CR	10 y	1,362 mg	4 m	Nd						A-c dis protein 100 mg/dL	anti GA+	+		
Merola 2014 n = 1/10	10%	Nd	Nd	4 m	Sub-acute	Demyelination	Muscle weakness and sensory disturbances	No alterations	Prolonged DML, MNCB present, CMAP decreased > 30%, reduced CVs	Improvement	No alterations	Hcy N B12 N MMA N Nd	+	Suppl B12 FA	"Partial recovery"
Mancini 2014 n = 4/50	8%	13 y mean	Nd	8 m mean	1 w	Acute inflammatory	Muscle weakness, lack of tendon reflexes, sensory disturbances, inability to walk	Nd	Decrease in motor NCVs < 70%, F-wave latency prolongation	Nd	3/4 A-c dis (Protein Nd) 1/4 Nd	Hcy ↑ vs. no PN B12 ↓ vs. no PN FA ↓ vs. no PN Nd	Nd	Suppl Nd 2/4 IVIG 2/4 steroids Nd	IVIg 1/2 improvement, steroids 1/2 effective, 2/4 died of current diseases
Uncini 2014 n = 1/15	6%	18 y	1,650 mg	4 m	1.5 w	GBS like	Tetraparesis, absent tendon reflexes, sensory disturbances	NCVs normal	Mixed axonal/demyelinating pattern	Improvement	A-c dis protein 148 mg/dL	Hcy N B12 (218) N FA (12.3) N anti GA-	+	Suppl B1, B12, FA PE	Motor recovery in 5 m
Merola 2016 n = 2/23	9%	Nd	Nd	4-6 m	Sub-acute	Nd	Muscle weakness and sensory disturbances	No alterations	Mixed axonal/demyelinating pattern	Improvement	No alterations	Hcy ↑ B12 N FA N Nd	+	Suppl B12, FA	"Progressive recovery"
Pinter 2019 n = 1	CR	10 y	2620 mg	14 m	Nd	CIDP-like	Paraparesis, absent reflexes, sensory disturbances	Nd	"CIDP criteria were met"	Improvement of CMAP and motor CVs	A-c dis Protein 141 mg/dL	Nd	+	IVIg 2 x 35 g every 3 m	Motor recovery in 5 m, sensory symptoms persisted

Table 1 cont. Summary of publications included into systematic review on acute/subacute polyneuropathy during LCIG treatment of advanced Parkinson's Disease

Preval	PD dur	LEDD	LCIG dur	PNP onset	Diagno sis	Symptoms	Pre NCS	NCS on diag	NCS fol- low up	CSF	Lab	LC IG disc	Treatment	Outcome
Rivero de Aguilar 2019	CR	4y	1,520 mg	15 m	8 w	CIDP	Tetraparesis, absent reflexes, sensory disturbances	Nd	Predominantly sensory- motor demyelinating polyneuropathy	A-c dis Protein 51 mg/dL	B12 N FA N Hcy Nd anti GA+	+	IMG2g/kg/5 d, methylpred- nisolone 5 g/5 d	Motor recovery in 6 m
Piekarski 2022	CR	16y	1,720 mg	3 m	12 w	CIDP-like	Tetraparesis, absent reflexes, sensory disturbances	Axonal bilateral lesions of peroneus and suralis	Improve- ment	A-c dis Protein 77 mg/dL	B12 ↓ FA ↓ Hcy ↑	no	Suppl B12, B1, B6, FA IMG 2 g/ /kg/5 d + 1 g/kg/2 d	Progressive motor recovery over following months, sensory symptoms persisted

If no detailed quantitative data was available, "Nd" was used; (+) — performed with positive result; (-) — performed with negative result; ↑ — above normal values; ↓ — below normal values; a-c disc — albuminocytologic dissociation; anti GA — antibodies against gangliosides of many or unspecified type; B6 — vitamin B6 (ng/mL); N > 4.5; B12 — vitamin B12 (pg/mL); N: 191–663; CIDP — chronic inflammatory demyelinating polyneuropathy; CMAP — compound muscle action potential; CR — case report; DML — distal motor latencies; FA — folic acid (pg/mL); N: 3.1–17.5; GBS — Guillain-Barre syndrome; Hcy — homocysteine (umol/l); N: 5–12; IMG — intravenous immunoglobulins; MMA — methylmalonic acid; MNCB — motor nerve conduction block; N — within normal values; NCV — nerve conduction velocity; Nd — no data provided; PE — plasma exchange; Suppl — vitamin supplement

Demographics and clinical manifestations

The most commonly reported symptoms included muscle weakness (tetra- or paraparesis), lack of tendon reflexes, paresthesia, and sensory loss. All of these were present in 11/15 patients, while in two patients only sensory symptoms were present, and for the remaining two there was no detailed information. In only 7/15 cases was detailed demographic data presented, making it impossible to draw unequivocal conclusions. The age of the patients ranged from 48 to 74 years, and the duration of PD was 5–18 years. The onset of polyneuropathy symptoms was on average 8 months (4–15 months) after the initiation of LCIG therapy. Preceding gastrointestinal infection was mentioned in one patient [18], but there was no data available in the remaining cases. Polyneuropathy onset was acute (< 4 weeks) in six cases, subacute (< 12 weeks) in eight cases (but in 5/8 only a descriptive onset was provided), and there was no data in the remaining case.

NCS findings

Due to the heterogeneous and often incomplete NCS data presented, precise interpretation or comparative analysis was impossible. For prospective studies, either only the interpretation of the result [10, 15] or average values [12, 16] are available. Detailed NCS data in the context of a case report was available in 3/5 publications, but in the remaining 2/5 only the descriptive interpretation of the study was available. In most cases, data for the baseline NCS before the diagnosis of polyneuropathy was lacking. Only in one study did we have a complete comparative list of electrophysiological parameters [18], and in two others information was provided that an NCS study had been performed [15, 16]. In the majority of cases, electrophysiological results consisted of a mixed pattern of axonal and demyelinating damage. Only in a few of them, referring to the descriptions provided by authors, were NCS results consistent with GBS/CIDP criteria [10, 13, 25]. Some authors stated that “despite the GBS/CIDP diagnosis, these results did not meet the criteria of acquired inflammatory neuropathy” [13, 18]. Follow up of NCS studies was also only partially conducted (6/9 publications) with more accurate data available only for three of these. In all of the above cases, a gradual improvement of NCV parameters was observed. Therefore, the descriptions of the type of neuropathy in Table 1 are inconsistent and we have adopted the terms used by the authors in the original descriptions (e.g. “demyelinating” “CIDP-like” etc.).

Laboratory findings

Cerebrospinal fluid (CSF) analysis showed elevated protein levels in 10/15 pts — in five cases protein levels ranged from 51 to 128 mg/dL (normal values < 45), and in the remaining five cases there was only albuminocytologic dissociation mentioned, with no quantitative values. In 4/15 patients, protein levels were normal, and in the 15th patient, there was no data at all.

Serum homocysteine was described as elevated in nine patients, (accurate data was presented in three patients and ranged from 8 to 230 $\mu\text{mol/L}$, normal values < 15); in two patients it was within normal values, and in the remaining four there was no data available. Vitamin B12 (B12) level was decreased in six, normal in another six, and in three patients there was no data provided. Other parameters [e.g. folic acid (FA), vitamins B6, B1, methylmalonic acid (MMA)] were scarcely provided and were not included in our analysis. Increased antiganglioside antibodies levels were occasionally reported, and were present in 3/4 patients examined.

Levodopa therapy

The levodopa-equivalent daily dose (LEDD) [26] was available for 7/15 patients on LCIG therapy, and ranged from 1,352 mg/d to 2,940 mg/d (mean 2,010 mg/day), among them three cases were related to 24-hour LCIG infusion. In one prospective study, there was no quantitative data on LEDD, but patients with acute demyelinating polyneuropathy were treated with LEDD 26% higher compared to patients receiving oral therapy [16].

Treatment and outcome

LCIG therapy was discontinued in all cases. The methods of treatment applied are difficult to compare as different combinations of methods have been used for different patients (Tab. 1). Vitamin B-group supplementation (with no exact dose specified) was applied in four patients, combined with IVIG or PE or steroids in six, vitamin supplementation with IVIG or PE and steroids in one, IVIG or PE alone in three, and combined with IVIG and steroids in one case. In all, except for two patients who died due to comorbidities [12], gradual improvements were observed both clinically and electrophysiologically. For six patients detailed follow up NCS parameters were provided, in two patients there was no quantitative data, and in the other seven there was no data at all.

Clinical vignette

We here describe the case of a patient treated in our centre who developed subacute demyelinating polyneuropathy during LCIG therapy. A 66-year-old man with a 16-year history of PD, with no clinical symptoms or signs of peripheral neuropathy at baseline, developed subacute sensory-motor demyelinating polyneuropathy after the 12 weeks from the onset of therapy. There was no data on any infectious disease preceding the onset of symptoms. NCS was performed at baseline (before the initiation of LCIG as a routine procedure in our centre) and showed only a moderate decrease of conduction velocities (CV) in sural nerves with severe axonal neuropathy of both peroneal nerves and a slight decrease of CV and amplitude in both tibial nerves. Twelve weeks after the initiation of LCIG therapy, the patient started to report sensory disturbances — primarily paresthesia in the lower limbs. Over the next 12 weeks, these sensory

symptoms gradually worsened with a decrease of sensation and lower limb weakness. After 12 weeks from the onset of PNP symptoms, he was admitted to hospital. On admission, he presented slight distal weakness of the upper limbs, weakness of the lower limbs significantly influencing gait (walked unassisted), and a lack of tendon reflexes. The LEDD on LCIG was 1,720 mg and this was more than 14% lower compared to the previous oral treatment (LEDD on oral medications before initiating LCIG treatment drugs was 1,980 mg). NCS showed prolonged distal latencies in median and tibial nerves ($L > P$) up to 5.2 ms, with decrease of CV (mean 39.5 m/s) in median and 32.5 m/s in tibial nerves (previously intact) with low frequency of F-wave and prolonged latency up to 69 ms in the left tibial nerve. The sensory responses from both sural nerves were absent, and similarly there were no sensory responses from the left median and ulnar nerves. The CSF examination showed moderately increased protein level (77 mg/dL, $N < 45$), B12 was 156 pg/dL (at baseline 197 pg/dL, $N < 183$), FA decreased to 2.83 ng/mL (at baseline 4.91 ng/mL, $N < 4.5$), and Hcy was above laboratory value $> 50 \mu\text{mol/L}$ (at baseline 33.9 $\mu\text{mol/L}$, $N < 12$). Anti-ganglioside antibodies were not tested. The detailed NCS parameters are presented in Supplemental Table 1, whereas laboratory findings are presented in Supplemental Table 2.

The patient was diagnosed with CIDP-like neuropathy. The LCIG therapy was continued at the same dose of levodopa-carbidopa, vitamin supplementation (B1, B6, B12 and FA), and IVIG (sandoglobulin) was introduced (dosage 2 g per kg of body weight for five days, total dose 150 g, with repeated additional 1 g/kg after two months in two doses). Vitamin supplementation was introduced and primarily conducted in hospital simultaneously with IVIG. The detailed vitamin doses are presented in Supplementary Material 1.

The patient's condition gradually improved, and over the next three months weakness of the lower limbs disappeared with a substantial decrease of sensory disturbances. NCS parameters in motor nerves improved (the first improvement was present one month later), with no improvement in sensory nerves.

Subsequent examinations (the last one 15 months after disease onset) showed still a lack of sensory responses in upper and lower limb nerves: median, ulnar, tibial, sural, but with a persistent improvement of motor responses. Hcy levels had decreased to 15.9 $\mu\text{mol/L}$.

Discussion

The published data on acute/subacute polyneuropathy due to the LCIG therapy is inconsistent and heterogeneous and includes case reports and case series presented both retro- and prospectively (Tab. 1). In the FDA/EMA documents, there is little information about the possible adverse event that is polyneuropathy, with no differentiation made between axonal or demyelination. Apart from warning that precautions should

be taken against PNP, there are no recommendations as to any treatment/prevention approach.

The true prevalence of polyneuropathy (both acute/subacute and chronic) on LCIG therapy is difficult to estimate. Studies that have focused on the assessment of polyneuropathy have shown a prevalence ranging from 13.8% [9] up to 100% [8], while in multicentre studies including large groups of patients (both prospective and retrospective) specifically focusing on effectiveness and an assessment of the safety profile, the incidence of polyneuropathy has ranged from 4.5% [27] to 13% [22].

This difference is most likely due to the usage of more accurate diagnostic tools and specific clinical scales. Polyneuropathy in PD not treated with LCIG is predominantly of chronic sensory and sensorimotor axonal type, and its origin is not fully understood. There are different underlying mechanisms, mainly related to levodopa exposure due to its metabolic pathway and homocysteine formation. B-group vitamins are used as cofactors in this pathway — which may be responsible for a deficiency as an aetiology on the one hand and a neurotoxicity of homocysteine on the other [7, 12, 28–30]. On LCIG treatment, due to intrajejunal delivery, the levodopa bioavailability is higher compared to oral formulations [7, 31], something which makes the mechanism of levodopa-exposure polyneuropathy even more possible. There is also a concept on vitamin malabsorption to be considered due to the presence of levodopa gel in the intestines [32]. Gel formula can also affect gut microbiota leading to a triggering of the autoimmune response [32]. Such concepts are highly speculative, but from our point of view, their occurrence is at least possible.

Acute/subacute demyelinating neuropathy is very rare and may sometimes go unrecognised (i.e. gait deterioration may be attributed to PD progression), and there have only been 15 cases described in detail so far. There are probably more in real life as the inclusion criteria established in this review have potentially excluded many of them. In most cases, muscle weakness is the predominant symptom, with acute or subacute onset and a demyelinating pattern in NCS studies resembling Guillain-Barre syndrome (GBS), or a chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) pattern respectively.

In our new case, it was possible to compare the patient's NCS from baseline assessment at the onset of LCIG therapy, showing this was newly developed demyelinating neuropathy. His relatively fast improvement of motor deficits (and motor NCS) after IGIV treatment (four weeks after initiation) may suggest a demyelinating pattern as well. However, increased homocysteine level along with FA deficiency may suggest an underlying axonal neuropathy which was asymptomatic. Some authors have questioned the demyelinating mechanism in published cases [13, 18]. Unfortunately, due to a lack of sufficient data, in a majority of cases detailed or comparative analysis of NCS parameters is not possible.

Nevertheless, the clinical manifestation of those cases is characteristic for acquired inflammatory polyneuropathies like GBS or CIDP, and such a diagnosis has been made in almost all published cases (Tab. 1). Characteristic (but not specific) for the inflammatory neuropathies are alterations in CSF analysis of albuminocytologic dissociation — in GBS this is present in 75% of patients [33] and in CIDP in up to 90% in a typical pattern [34], but it may be lower (or even absent) in an atypical presentation e.g. Lewis-Sumner Syndrome [35]. In the presented case series, it was detected in 10/15 patients and this may suggest the immunological origin of neuropathy.

Clinical presentations of inflammatory neuropathies may vary significantly — the most characteristic (and most common) is pure symmetric motor demyelinating neuropathy, but there are also sensory and sensorimotor variants with axonal changes in NCS studies or asymmetrical presentation of both GBS and CIDP. Misdiagnosis of CIDP is common and has been reported in up to 50%, mainly in patients with an atypical presentation [36]. There are no diagnostic tools that are 100% specific, and the diagnostic approach must include clinical manifestation, NCS studies and laboratory findings. During LCIG therapy, the presence of percutaneous gastrostomy and the gel formulation of the drug affecting the gut microbiota are suspected to be the crucial factors initiating immunological response [12, 18]. Different types of anti-ganglioside antibodies could be detected in inflammatory neuropathies (GM1, GD1a, GD1b, GT1a, GQ1b, GT1b for GBS and LM1, GM1, GD1b for CIDP) [37, 38]. They were analysed in only 4/15 patients, and in three cases were detected. Therefore, it is difficult to conclude whether the underlying mechanism is of immunological origin, as the majority of case reports do not provide such information. Polyneuropathy occurred within the first 15 months of treatment and in the majority of reported cases was not preceded by an infection. Therefore, one may suspect that it was related to LCIG therapy or that this therapy was an additional factor (e.g. due to possible neurotoxicity of homocysteine) and as in our case polyneuropathy was present (but subclinical) before the LCIG therapy initiation. The baseline NCS were not performed in all presented cases. Another explanation may be a simple coincidence of LCIG therapy and GBS/CIDP, however they are (specifically CIDP) relatively rare conditions, and LCIG treatment is also offered only to a small number of PD patients. Nevertheless, demyelinating pattern in NCS and CSF-protein elevation with clinical motor or sensory/motor neuropathy presentation may suggest its immunological origin.

However, it should be mentioned that B12 deficiency may also present as demyelinating neuropathy with subacute onset. In the largest patient cohort so far, $n = 66$ [39] assessing neurological symptoms in vitamin B12 deficiency, NCS analysis revealed sensory/motor neuropathy which was demyelinating in 11.1%, axonal in 22.2%, and with a mixed pattern in the remaining 66.7%. The onset of symptoms was subacute or chronic symptoms were mainly sensory, but paretic symptoms were observed in four patients (13% with symptoms

of neuropathy). CSF analysis in patients with B12 deficiency shows albuminocytologic dissociation in 65% of cases [40], and therefore may be easily misdiagnosed as GBS/CIDP. Moreover, 44% of patients diagnosed with B12 deficiency with polyneuropathy symptoms had normal B12 levels with abnormal metabolite levels (homocysteine and MMA) [41].

This variable clinical presentation of B12 deficiency polyneuropathy makes the unequivocal interpretation of the neuropathy in LCIG case series even more difficult. Vitamin B12 levels were tested in 12 patients: it was decreased in six (with no accurate values provided), and in the other six was normal.

Concerning the treatment approach, LCIG was discontinued in all cases (except the one case from our centre presented in this paper). However, in one paper (n = 2 patients), LCIG treatment was terminated due to ineffectiveness of immunomodulatory treatment [11].

Supplementation of vitamins has been widely introduced as well as immunomodulatory therapy: steroids, IVIG or PE. This makes impossible the drawing of a simple conclusion on the pathological mechanism of neuropathy. Despite the different combination of treatment approaches, the treatment had a positive effect on disease symptoms in all cases, unfortunately with no data provided on NCS parameters in a majority of reports. In three patients the recovery time was described as 5–6 months, and in 6/15 patients there were performed detailed NCS control examinations, showing gradual improvement.

The authors of the publications analysed in this paper were probably aware of the fact that the NCS criteria [25] for the diagnosis of demyelinating neuropathies were not met in many cases, which is reflected in the usage of terms such as “GBS-like” or “CIDP-like” [11, 18].

In the cases presented above, regarding the clinical manifestation including acute/subacute onset, presence of paresis, laboratory findings and NCS alterations (despite not fulfilling diagnostic criteria in most cases) and the introduction of effective immunomodulatory treatment, it seems that the diagnosis of acquired demyelinating polyneuropathy of immunological origin was justified. Withdrawing LCIG therapy in advanced PD patients may result in a severe deterioration of parkinsonian symptoms. Therefore, such a decision should be made cautiously, and immunotherapy (IVIG, steroids, PE) should be offered before terminating LCIG treatment. The withdrawal of LCIG was common but difficult to understand in terms of patients' improvement on immunological therapies.

Our case report shows that continuation of LCIG therapy may result in long-term benefit, despite the temporal deterioration. The decision to maintain LCIG treatment resulted in a good control of PD motor symptoms and allowed for the introduction of intensive rehabilitation, and our patient was still independent in everyday life.

Due to the high number of neuropathy cases during LCIG treatment, we suggest that NCS studies should be performed

routinely at baseline with control examinations at least every 12 months. In cases with acute/subacute deterioration of gait, and/or motor/sensory deterioration, a NCS examination should be performed on demand. In cases of demyelinating pattern, the proper immunological treatment with IVIG or steroids or PE (there are no recommendations regarding the superiority of one over another) should be offered. We do not recommend the termination of LCIG therapy (as in a majority of the presented cases), as gradual improvements were seen after immunotherapy.

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