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MOVEMENT DISORDERS - SHORT COMMUNICATION

Malnutritional neuropathy under intestinal levodopa infusion

Fabian Klostermann · Constanze Jugel · Thomas Müller · Frank Marzinzik

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Abstract Levodopa/Carbidopa intestinal gel infusion (LCIG) for Parkinson's disease is under debate to provoke polyneuropathy (PNP). In our cohort of 20 thus treated patients, two developed debilitating axonal PNP with deficient pyridoxin and folate levels, and marginal cobalamin. Homocysteine was highly elevated. The neuropathies responded to vitamin replacement. We assume that LCIG can provoke PNP most likely of malnutritional origin. To avoid this side effect, the assessment of predisposing factors before treatment as well as neurophysiological and laboratory screenings appear necessary.

Keywords Parkinson's disease · Intestinal levodopa infusion · Polyneuropathy

Introduction

Levodopa (LD) replacement is the core principle in the treatment of Parkinson's disease (PD). The major disadvantage of LD therapy is, however, the development of instability of its actions in the long run, resulting in wearing off, dyskinesias or unpredictable motor fluctuations of PD patients (Oertel et al. 2006). In these clinical situations, relatively continuous dopaminergic stimulation can be realised with a pump system for intestinal LD/Carbidopa gel infusion (LCIG). Through a tube within a percutaneous endoscopic gastrostomy (PEG), the respective gel formulation is brought to the locus of LD absorption in the upper jejunum, to avoid swings of drug bioavailability due to irregular gastric emptying (Nyholm et al. 2005). In doing so, formerly often complex polypharmacy of PD patients can mostly be reduced to a monotherapy.

Next to the beneficial effects of this treatment on fluctuations, few cases of neuropathic syndromes have been reported as a possible sequel of LCIG treatment (Antonini et al. 2007, Manca et al. 2009, Urban et al. 2010). In this regard, we consider it important to communicate further histories of two patients (out of 20 treated patients at our centre), who developed uncommon and severe polyneuropathy (PNP) in the context of an otherwise effective LCIG treatment.

Patients

The first patient is a 75-year-old man, first diagnosed with Parkinson's disease in 1993. Under the treatment with LD in different combinations with cabergolide, rotigotine, amantadine and Catechol-*O*-methyltransferase (COMT) inhibitors, he developed severe on–off fluctuations. In 2008, this prompted LCIG treatment as a replacement of 900 mg oral LD and further drugs, equivalent to 1,100 mg LD. Consequently, off-time was satisfactorily reduced, leaving him mainly slightly hyperkinetic. Few weeks after treatment start, however, the patient began to lose weight (coming from normal levels) and concomitantly noticed numbness and tingling of the hands, legs and feet. At the follow-up visit 12 weeks after LCIG initiation, the weight loss was 7 kg and gait impairment due to distally distributed paraparesis decreased his previously normal walking

F. Klostermann (✉) · C. Jugel · F. Marzinzik
Deptartment of Neurology, CBF, Charité-University Medicine Berlin, Hindenburdamm 30, 12203 Berlin, Germany
e-mail: fabian.klostermann@charite.de

T. Müller
St. Joseph Hospital, Berlin Weissensee, Germany

distance to 100 m. Further, hand and finger functions were slightly paretic.

The second patient is a 61-year-old man who had been treated for Parkinson's disease since 1990, with different combinations of LD, dopamine agonists, amantadine, selegiline and acetylcholine antagonists. LCIG was started for severe fluctuations in early 2010, replacing drugs equivalent to 3,800 mg LD of which 800 mg were given as LD. As a result, the patient was almost constantly in a slightly hyperkinetic on-condition, but few weeks after therapy start, he began to notice tingling of the hands and feet. Four months later, weakness and numbness progressed over 3 weeks, until he was severely gait-impaired with paretic hip and foot drop. Further, up to this moment he had lost 10 kg of previously normal weight, ever since remaining on that level.

Both patients had been free of polyneuropathic symptoms before LCIG treatment.

Results

Laboratory and neurophysiological findings were strikingly parallel in both patients. Neurography proved severe axonal damage with an average decrease of tibial and peroneal motor compound nerve action potentials (cNAP) down to 15 and 10%, respectively, of the lower cut-off for normal values. Sensory potentials were lost whether after stimulation of upper or lower extremity nerves. Electromyography of distal leg muscles revealed distinct spontaneous activity as correlate of acute denervation. Nerve biopsy was declined by both patients.

Laboratory work-up proved deficient vitamin B_6 (pyridoxine) and folate concentrations, whereas vitamin B_{12} (cobalamin) was relatively low, but still within the normal range. Total plasma homocysteine was 3-and 5-fold elevated, respectively. Finally, high cerebrospinal fluid (CSF) protein concentrations with normal CSF cell count were identified. Further abnormalities in metabolic, immunological or infectious parameters were not obtained. Table 1 summarises the main results.

In the extensive diagnostic work-up of the weight loss, a Forrest III duodenal ulcer and a *Helicobacter pylori* (HP) gastritis (which previously was asymptomatic) were found in the first patient. The ulcer had to be closed surgically and the gastritis was successfully treated by HP eradication. However, this had no influence on the clinical progress of neuropathic symptoms and up to date, the patient lost further 2 kg, despite exclusion of underlying consumptive disease.

In response to this, vitamin B_6, B_{12} and folate replacement was started and maintained ever since. In the second patient, the high LD dose was additionally reduced to 2,800 mg per day and treatment was combined with five times 200 mg entacapone. In both patients, weakness slowly disappeared over several months, but numbness and tingling sensations remained largely unchanged. Neurophysiological parameters partially recovered in that motor potentials, increased by factor two (remaining substandard) and in the second patient, low amplitude sensory cNAPs are recordable again.

Discussion

These histories are communicated, since they appear to reflect still under-recognised neuropathogenic actions of the relatively recently introduced LCIG treatment (Duodopa®). The cases are also reported in view of recent similar cases (Manca et al. 2009; Urban et al. 2010), of importance with respect to the concept of neuropathy in LCIG-treated PD patients.

At first, the clinical presentation in both patients was reminiscent of chronic inflammatory neuropathy (CIP),

Table 1 Summary of the results

Test/parameter	Normal values for test/parameter	Patient 1[a]	Patient 2[a]
Vitamin B_6	(>5 μg/l)	2.5 (low)	2.2 (low)
Folate	(3–20.5 μg/l)	2.8 (low)	2.9 (low)
Vitamin B_{12}	(189–883 ng/l)	223 (marginal)	198 (marginal)
THcys	(<16 μmol/l)	52 (high)	79 (high)
CSF protein	(<50 mg/l)	77 (high)	90 (high)
Motor cNAP	(>3 mV)	0.4 (low)	0.3 (low)
Sensory cNAP	(>10 μV)	Absent	Absent
EMG		Acute denervation	Acute denervation

tHcys total plasma homocysteine, *CSF* cerebrospinal fluid *cNAP* compound nerve action potential (patient values: averages after tibial and peroneal motor stimulation/sensory: after sural, peronaeus superficialis stimulation), *EMG* electromyography

[a] Patient values in the reference units as indicated in column 2

with subacute evolution of symmetrically distributed sensorimotor deficits along with elevated CSF proteins. On the plateau, which lasted for weeks (case 2) to months (case 1), the patients developed severe gait impairment. However, after this phase, symptoms slowly regressed towards a residual level with stable sensory deficits.

In the given context, we consider unlikely that classic CIP or Guillain–Barré syndrome account for the reported abnormalities. As in previous cases, neuropathic symptoms developed shortly after LCIG initiation in both patients (Antonini et al. 2007; Manca et al. 2009; Urban et al. 2010). Also in line to what has been reported (Urban et al. 2010), nerve damage was mainly axonal which is possible in autoimmune neuropathy, but less common than predominant demyelinisation. Anti-ganglioside antibodies, associated with autoimmune neuropathies, as well as typical infections before PNP onset, were absent. Interestingly, the patients shared (3- to 5-fold) increased homocysteine levels as well as vitamin B_6 and folate deficiency together with marginal vitamin B_{12}, as previously described in LCIG-treated patients (Urban et al. 2010). Unfortunately, nerve biopsy, which might have delineated further parallels, was declined by both patients.

Indeed, neurophysiological signs of neuropathy have been described in about ten percent of patients with oral LD therapies (Toth et al. 2008). In this regard, it is of conceptual interest that LD administration is known to elevate homocysteine levels as a by-product of the metabolization to 3-*O*-methyldopa by COMT. Homocysteine, which recently has been shown to be massively elevated in LCIG-treated PD patients (Müller et al. 2011), is under a cloud of provoking vascular as well as neuronal damage and its removal is, in turn, vitamin B and folate dependent (Müller et al. 2004), so that deficiency of the latter agents is critical in hyperhomocysteinemia. Further, vitamin B_6 and B_{12} deficiency (with B_{12} even at lower normal levels) can itself underlie neuropathy (Aita and Calame 1972; Dellon et al. 2001; Saperstein et al. 2003). The reason for low vitamin B_6 and folate levels in LD-treated subjects is unknown, but next to enhanced demands in the metabolism of LD, intestinal malabsorption in the specific case of the jejunal infusion of the highly viscous LD/Carbidopa gel, is certainly a candidate mechanism, particularly in the light of the weight loss in both patients (Heiser et al. 2004; Weber et al. 1990; it remains open if in the first patient duodenal ulcer, probably on the basis of HP colonisation together with local irritation by the jejunal tube had furthered this problem, but note that restoration neither ameliorated PNP nor weight loss). In this regard, it is worthwhile noticing that vitamin B_6 deficiency with similar neuropathic syndromes has been observed after surgery of the upper jejunum (Aasheim et al. 2008; Juhasz-Pocsine et al. 2007). Further, malnutritional neuropathies after bariatric surgery (with a parallel weight loss and hypovitaminosis as in the present cases) did go along with elevated levels of CSF protein concentrations of uncertain origin (a potential explanation being aseptic neuroinflammation due to accumulating neurotoxic metabolites, Thaisetthawatkul et al. 2004). Indeed, the reported neuropathies seemed to respond to vitamin B and/or folate treatment, after which both patients recovered from weakness (but hardly from sensory deficits).

Altogether, these and previous reports suggest that although PNP seldom becomes a relevant problem under oral PD medication, it can be a severe side effect of LCIG treatment. Reasons for this might be the administration of high dose LD as monotherapy, possibly mediating the accumulation or high steady-state levels of neurotoxic metabolites, and/or malnutrition due to the intestinal route of drug application. As long as predisposing factors for PNP development under LCIG remain obscure, therapy standards should be urgently defined and at least comprise the exclusion of gastrointestinal abnormality as well as baseline and follow-up screenings for neuropathy and vitamin levels.

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