Beyond Motor Symptoms – Impact of Continuous Dopaminergic Stimulation on Non-motor and Social Aspects of Advanced Parkinson's Disease

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Abstract

Two patient cases are presented here that illustrate the benefits of continuous dopaminergic stimulation on the non-motor symptoms of Parkinson's disease. In both cases, levodopa/carbidopa intestinal gel infusion therapy led to improvements in anxiety, depression, concentration, urge incontinence, sexual function, sleep, vivid dreams and rapid eye movement sleep behaviour disorder, pain, sweating and feelings of self-assuredness. Such improvements have an impact on patients' quality of life and can help their social functioning.

Keywords

Parkinson's disease, levodopa, continuous dopaminergic stimulation, non-motor symptoms, quality of life

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The non-motor symptoms (NMS) of Parkinson's disease (PD) are common and often not fully appreciated. They are sometimes referred to as non-dopaminergic symptoms, which in some cases may be a misnomer. NMS are present at all stages of the disease, and are potentially a major source of disability. Some of these symptoms, such as dementia, delirium, hallucinations, and psychosis, are important factors in PD patients' lives and may lead to institutionalisation. As such, they affect not only the individual but also have a social impact.

It is encouraging that the non-motor features of PD have been incorporated into the American Academy of Neurology (AAN) PD quality measures published in 2010,[1] as healthcare stakeholders use these measures when making decisions on the allocation of healthcare resources. Out of the 10 AAN quality measures, five concern the non-motor features of PD (see *Box 1*).

The following two case reports illustrate the impact of continuous dopaminergic stimulation (CDS) on the NMS and social aspects of PD.

Case Report 1

Patient 1, a 57-year-old male family physician, had been diagnosed with PD at the age of 45. After 12 years of PD, his daily regimen was 800 mg levodopa (spread over seven intakes) plus 100 mg levodopa-benserazide hydrodynamically balanced system (HBS). He also took 200 mg tolcapone (three times a day), 100 mg amantadine (twice daily), 1 mg rasagiline (once daily) and 150 mg venlafaxine (once daily).

The patient's motor complications included troublesome dyskinesias, end-of-dose 'wearing off', unpredictable 'on-off' motor fluctuations, dose failures and delayed 'on'. His non-motor complications comprised depression, free-floating anxiety, concentration problems, sleep dysfunction, autonomic dysfunction (urinary urgency), sensory dysfunction (hyposmia and pain) and sexual dysfunction (erectile dysfunction and libido loss). The patient's family was concerned that he might become dyskinetic or drop into a deep 'off' when he was outside the home. The NMS were also very troublesome for the patient professionally, with his patients beginning to question his competency. The combination of motor and non-motor complications led him to a forced early retirement and the patient's social and family life were adversely affected.

To obtain reimbursement from the Belgian authorities for levodopa/carbidopa intestinal gel (LCIG) infusion, a test week is required. The patient completed a test week in November 2009, and in March 2010 approval was obtained to initiate LCIG infusion therapy. All other Parkinson's medications were stopped. His dosages during the first year of LCIG infusion therapy were fairly stable (see *Table 1*).

After the patient started LCIG infusion therapy, there was an evolution in his clinical motor presentation. His morning 'off' improved and he no longer had unpredictable 'off' or delayed 'on'. The patient had suffered from stuttering in childhood, which had improved when he was a young man but had returned with the onset of PD. It was particularly troublesome during 'off' periods.

Box 1: The Five Non-motor Features of Parkinson's Disease Included in the Parkinson Disease Quality Measures of the American Academy of Neurology

- Psychiatric disorders or disturbances assessment – at least annually
- Cognitive impairment or dysfunction assessment – at least annually
- Querying about symptoms of autonomic dysfunction – at least annually
- Querying about sleep disturbances – at least annually
- Querying about falls – all visits

Adapted from Cheng et al., 2010.[1]

Table 1: Patient 1 – Dosages of Levodopa/Carbidopa Intestinal Gel Infusion Therapy during the First Year

	Levodopa/Carbidopa Intestinal Gel Infusion Dosage		
	Start of Therapy	6 Months	1 Year
Morning dose	3.0 ml	3.0 ml	3.0 ml
Continual dose	1.6 ml/h	1.8 ml/h	1.5 ml/h
Extra dose	1.0 ml	1.0 ml	1.0 ml

Table 2: Patient 1 – Dyskinesia Scores in the Unified Parkinson's Disease Rating Scale at Baseline, 6 Months and 1 Year after Initiating Levodopa/Carbidopa Intestinal Gel Infusion Therapy

	Unified Parkinson's Disease Rating Scale Scores		
	Duration	Disability	Pain
Baseline	3	3	3
6 months	2	1	0
1 year	2	1	0

Table 3: Patient 2 – Dosages of Levodopa/Carbidopa Intestinal Gel Infusion Therapy during the First Year

	Levodopa/Carbidopa Intestinal Gel Infusion Dosage		
	Start of Therapy	6 Months	1 Year
Morning dose	2.5 ml	-	-
Continual dose	1.9 ml/h	2.2 ml/h	2.9 / 2.6 ml/h
Extra dose	1.0 ml	1.0 ml	1.6 ml

After beginning LCIG infusion treatment, he reported that the stuttering improved significantly. The patient's dyskinesia was also improved. One year after initiating LCIG infusion therapy, the duration and disability of dyskinesia were reduced and pain was eliminated (see *Table 2*).

Additionally, there were improvements in a range of NMS (anxiety, depression, urge incontinence, feeling self-assured and sexual dysfunction) and the patient was able to return to work full-time. These were improvements that the patient considered as being the most important in his life.

Case Report 2

Patient 2, a 52-year-old male administrator in health insurance, had been diagnosed with PD at 40 years of age, but the first sign of tremor had actually appeared at the age of 30. After 12 years of PD, his daily regimen included 600 mg levodopa (spread over 12 intakes) plus 100 mg levodopa-benserazide HBS. He also took 200 mg tolcapone (three times daily) and 1 mg pergolide (three times daily). The patient also received 2 mg safinamide (once daily) in a clinical trial.

This patient had troublesome dyskinesias, end-of-dose 'wearing off', unpredictable 'on-off' fluctuations, dose failures and delayed 'on', and painful early morning dystonia. He also suffered from extensive non-motor complications, including depression, anxiety, sleep dysfunction, vivid dreams and rapid eye movement sleep behaviour disorder (RBD), sensory dysfunction (hyposmia and dystonic pain), excessive sweating and sexual dysfunction (erectile dysfunction and libido loss). When away from home, he would often have to call his wife and ask her to pick him up because he was in a deep 'off'. As a result of his motor complications, the patient was forced to work part-time from home, and complained that he was becoming increasingly isolated from society.

The patient completed a test week of LCIG infusion in November 2009, and started the therapy in March 2010. The continual dose of LCIG was slightly increased at six months, from 1.9 to 2.2 ml/h, which was not a concern (see *Table 3*). After six months, the patient did not have a morning dose because he used the pump 24 hours a day. At one year, he was on 2.9 ml/h during the waking day and at midnight, the dose was reduced to 2.6 ml/h. An extra dose of 1.6 ml was used a few times a week, mostly post-prandial.

The patient's motor symptoms improved after beginning LCIG infusion therapy. His morning 'off', unpredictable 'on-off' fluctuations and delayed 'on' were all eliminated. There was substantial improvement in his dyskinesias: their duration was reduced from 2 to 1 as assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) and they were no longer disabling (UPDRS disability score was reduced from 3 to 0). There were also improvements in various NMS (depression, anxiety, concentration, sleep, sexual dysfunction, pain, sweating, and vivid dreams and RBD), and the patient was able to work full-time again.

Non-motor Symptoms in Parkinson's Disease

NMS are recognised as an integral part of PD. However, they remain misdiagnosed and untreated in many patients, which is an issue given that the appearance of non-motor manifestations often represents a milestone in the disease trajectory, and can indicate a worse prognosis and lower quality of life (QoL).

The NMS complex of PD (see *Box 2*) changes over the course of the disease.[2] There is compelling evidence that sleep disturbances (e.g., RBD),[3,4] olfactory dysfunction,[5] depression[6] and constipation[7] precede the development of motor symptoms. The evidence for restless legs syndrome, apathy, anxiety, fatigue and genitourinary dysfunction being pre-clinical features of PD is less strong.[2]

It is increasingly recognised that gait dysfunction, freezing and postural instability are multifactorial, involving an interaction of motor and non-motor mechanisms.[8] Cognition also plays a role in freezing and, as a result of these symptoms, falls are common in advanced Parkinson's disease (APD) and are a leading cause of morbidity and mortality in this population. For example, the frequency of fractures is doubled in PD patients compared with age-matched controls.[9] Falls can also lead to placement in a nursing home.

Box 2: The Non-motor Symptoms of Parkinson's Disease[2]

Neuropsychiatric Symptoms
- Cognitive impairment and dementia
- Apathy, anxiety and panic attacks
- Anhedonia and depression
- Delirium
- Hallucinations, illusions and delusions
- Impulse control disorders
- Dopamine dysregulation syndrome

Sleep Disorders
- Rapid eye movement sleep behaviour disorder
- Excessive daytime sleepiness
- Vivid dreaming
- Insomnia
- Restless legs syndrome and periodic limb movements in sleep
- Sleep-disordered breathing

Autonomic Symptoms
- Orthostatic hypotension (coat-hanger pain and falls)
- Urinary disturbances (frequency, urgency and nocturia)
- Sexual dysfunction
- Hypersexuality
- Paroxysmal sweating
- Seborrhoea
- Xerostomia

Gastrointestinal Symptoms
- Drooling
- Ageusia
- Dysphagia
- Constipation
- Faecal incontinence

Sensory Symptoms
- Pain
- Paraesthesia
- Olfactory disturbances
- Visual disturbances

Miscellaneous
- Fatigue
- Weight changes

The cognitive and neuropsychiatric symptoms of PD can also result in admission to a nursing home. They range from anxiety, apathy and depression to dementia, some of which may be part of the disease process itself, but may also be aggravated by medications and co-morbidities.

These cognitive and neuropsychiatric symptoms could also occur in response to having a chronic progressive illness and, in this context, may be improved by anti-Parkinson's medications, as seen in the two patient cases discussed above. In these two patients, CDS therapy with LCIG infusion also resulted in improvements in other NMS, such as sleep disorders, autonomic symptoms and sensory symptoms.

Prospective Study on Non-motor Symptoms in Parkinson's Disease

In a prospective study on genotype-phenotype correlations in 139 PD patients (mean age 68 years ± 10.4, mean age of disease onset 60.5 years and mean disease duration 7.5 years ± 6.2), our group showed a high prevalence of NMS (the median number of NMS per patient was nine).[10] The most common were urinary urgency, nocturia and sleeping problems. A higher number of reported NMS was associated with a longer disease duration and clinical features that suggested more advanced disease, such as motor fluctuations, dyskinesias, dementia and postural instability. The study results also showed that disease progression, rather than age, was associated with a greater number of reported NMS. Furthermore, our group showed a weak correlation between the number of reported NMS and UPDRS motor score. However, these results are likely confounded by medication use.

Conclusions

NMS are increasingly recognised as sources of disability for many patients with PD, and have a major impact on patients' integration into society. Consequently, these NMS features have been incorporated into the AAN Parkinson Disease Quality Measures,[1] which are used by healthcare stakeholders when making decisions on the allocation of healthcare resources.

The two case reports presented in this article illustrate the impact of CDS treatment in PD. By increasing dopaminergic tone through LCIG infusion treatment, the two patients' motor performance was improved and their NMS were considerably reduced. Thus, CDS therapy has greatly improved these patients' lives and, by allowing them to return to work full-time, has also had an important social impact. ■

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