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Successful treatment of levodopa/carbidopa intestinal gel associated 'biphasic-like' dyskinesia with pallidal deep brain stimulation

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This right-handed man was diagnosed with idiopathic Parkinson's disease aged 45 years following presentation with asymmetric rest tremor, anosmia and REM sleep behaviour disorder. Treatment with oral levodopa/carbidopa was successful but, within 3 years, predictable OFF periods and peak-dose dyskinesia emerged. These were adequately managed for the following 17 years with the introduction of rasagiline, rotigotine patch, entacapone and amantadine.

Aged 65 years, persistent motor fluctuations despite optimal medical therapy prompted initiation of levodopa/carbidopa (20/5mg per ml) intestinal gel (LCIG) treatment at 2.8ml/hr, 10 hours per day (0800-2000), with 1ml boluses as needed. Within weeks, new hyperkinetic movements emerged around the time of pump disconnection (see video). These would occur every evening between 7pm and 8pm, and last on average 20 minutes. They persisted despite attempts to reduce or increase the infusion rate, 24hour LCIG infusion or daytime infusion breaks. Their severity and duration correlated with the total daily levodopa dose. For 2 years preceding our review, he had self-isolated in a padded room at 7pm every evening. A functional movement disorder had been considered.

A diagnosis of complex 'biphasic-like' dyskinesia associated with LCIG was made. The patient underwent bilateral pallidal deep brain stimulation (Medtronic Activa PC). Immediate resolution of involuntary movements was observed which persists at 6 months with monopolar stimulation to both deepest contacts at 1.75V, 60μs, 130Hz. He remains on LCIG.

Levodopa-induced dyskinesia (LID) are an almost inescapable complication of chronic levodopa treatment for Parkinson's disease. They affect up to 95% of patients by 15 years, and significantly associate with reduced quality of life[1,2]. LID are most commonly encountered either as 'peak dose' effects, manifesting as choreiform upper limb, neck and trunk movements, or as 'off period' phenomena which are generally dystonic in nature, commonly affecting the feet[3]. Occasionally, 'bi-phasic' dyskinesia, occurring at intermediate levodopa serum levels and manifesting as large amplitude, at times ballistic movements

predominantly of the legs are seen[3]. Randomised controlled trial data supports an anti-dyskinetic effect (increased 'on' time without troublesome dyskinesia) of LCIG infusion therapy[4].

Recently, a novel pattern of dyskinesia has been recognized in 12-14.4% of LCIG treated patients[5,6]. These phenotypically 'complex' dyskinesia generally involve high amplitude, lower limb predominant, often ballistic painful movements, but without the classic biphasic temporal pattern, hence their description as 'biphasic-like'. They commonly emerge in the evening, are frequently prolonged and often refractory to attempts at altering dosage and timing of LCIG infusion. Whether LCIG treatment is itself pathophysiologically implicated in the development of this phenomenon remains unclear. Indeed, these events may simply reflect natural disease progression. Biphasic-like events probably occur in the evening during slow decline in plasma levodopa levels following pump disconnection-this may be aggravated by post-disconnection PEG-J tube flushing, prolonging 'intermediate' serum levodopa levels[6]. This 'association rather than causation' theory is supported by the observation that upon transiently restarting oral levodopa/carbidopa therapy due to PEG-J tube blockage, our patient experienced similar, but much shorter dyskinetic episodes at the end of each dose.

This case highlights a number of important learning points. First, LCIG-associated dyskinesia often exhibits bizarre phenomenology, making them prone to misdiagnosis. Second, these dyskinetic movements often occur in the evening, around the time of pump disconnection (an important clinical clue), probably during the slow decline in serum levodopa levels. Finally, in contrast to the more typical 'peak-dose' and 'off-period' dyskinesia, biphasic and complex LCIG-associated dyskinesia are more challenging to manage using medical therapies. Deep brain stimulation, particularly targeting the posteroventral portion of the globus pallidus internus (GPi) is effective in improving dyskinesia[2]. Moreover, in contrast to the subthalamic nucleus, GPi DBS is better tolerated in patients with pre-existing mild cognitive impairment or gait dysfunction, making it a relatively

forgiving target in advanced PD[2]. This is, to our knowledge, the first case of 'complex' 'biphasic-like' LCIG-associated dyskinesia successfully treated with GPi DBS, the results of which were life-changing.

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3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique

EM: 1A, 1B, 1C, 3A
VL: 1B, 1C, 3B
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Ethical Compliance Statement:

The authors confirm that the approval of an institutional review board was not required for this work. Informed consent from the patient was obtained for publication of this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines

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Video legend:

This video illustrates the large amplitude, lower-limb predominant LCIG-associated dyskinesia prior to pallidal deep brain stimulation, as well as the substantial improvement following the procedure.