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BACKGROUND

- Freezing of gait (FOG) is a common and disabling symptom in advanced Parkinson's disease (PD) [1].
- The pathophysiology of FOG associated with advanced PD remains still incompletely understood. Although both dopaminergic and non-dopaminergic mechanisms are involved, its treatment remains a clinical challenge [2,3].
- Based on the spectrum of response to dopaminergic medications, 4 different types of FOG have been characterized.
 - The most common is **"Off-type" FOG**, which is relieved by dopaminergic medication improving or even disappearing in the "on" state; it is a common manifestation of motor fluctuations associated with low dopaminergic drive
 - "Pseudo-on" type FOG** is present during a seemingly optimal "on" state but improves with stronger dopaminergic stimulation.
 - "Unresponsive" FOG** is defined by the presence of FOG in both "off" and "on" state, and it is not influenced by medication.
 - "True-on" type FOG**, which is absent during "off" periods and it occurs or worsens in the "on" state; this type of FOG is relatively rare [4,5].
- Recently, 2 reports based on small samples, showed that improvement of FOG achieved with intestinal gel delivery might be of a greater magnitude than those obtained with oral medical therapies [6,7].

AIM

to determine whether levodopa-carbidopa-intestinal-gel (LCIG) infusion influences freezing of gait (FOG) in advanced Parkinson disease (PD).

Table 1. Comparison of UPDRS scores before and after LCIG infusion for 32 patients.

| | Baseline | LCIG | P value |
|---------------------------------|----------------|----------------|---------|
| Gender (M/F) | 22/10 | - | - |
| Age at surgery, y | 67.5 ± 6.9 | - | - |
| Disease duration, y | 14.0 ± 4.2 | - | - |
| Motor complications duration, y | 5.8 ± 3.2 | - | - |
| UPDRS I | 4.1 ± 2.4 | - | - |
| UPDRS-II total | | | |
| OFF med | 24.9 ± 5.9 | - | - |
| ON med | 13.3 ± 6.0 | 12.9 ± 6.9 | 0.953 |
| UPDRS-II item 14 - FOG | | | |
| OFF med | 2.6 ± 0.9 | - | - |
| ON med | 0.9 ± 0.8 | 0.6 ± 0.7* | 0.027 |
| UPDRS-III total | | | |
| OFF med | 46.3 ± 10.1 | - | - |
| ON med | 23.5 ± 9.9 | 22.8 ± 13.4 | 0.695 |
| UPDRS-III axial | | | |
| OFF med | 11.7 ± 3.4 | - | - |
| ON med | 9.5 ± 5.0 | 9.3 ± 5.2 | 0.846 |
| UPDRS-IV total | 9.2 ± 2.5 | 6.1 ± 2.5** | 0.001 |
| Dyskinesia duration | 1.8 ± 1.0 | 1.4 ± 0.9* | 0.021 |
| OFF period duration | 2.1 ± 0.5 | 0.8 ± 0.5** | 0.001 |
| Hoehn & Yhar | | | |
| OFF med | 3.5 ± 0.9 | - | - |
| ON med | 2.4 ± 0.9 | 2.8 ± 0.9* | 0.015 |
| Schwab & England | | | |
| OFF med | 46.3 ± 16.0 | - | - |
| ON med | 77.8 ± 15.2 | 66.3 ± 19.1** | 0.001 |
| LEDD | 1454.5 ± 410.9 | 1371.2 ± 314.8 | 0.383 |
| Levodopa at night | 21 (66%) | 24 (75%) | 0.383 |
| DA | 21 (66%) | 10 (31%)** | 0.011 |
| COMT-I | 19 (59%) | 1 (3%)** | 0.001 |
| MAO-I | 5 (16%) | 1 (3%) | 0.201 |
| Amantadine | 7 (22%) | 2 (6%) | 0.190 |
| Quetiapine | 5 (16%) | 14 (44%)* | 0.027 |
| Benzodiazepines | 22 (69%) | 23 (72%) | 0.791 |
| Antidepressants | 8 (25%) | 15 (47%) | 0.068 |

Abbreviations: *: FOG On medications worsened in 3 patients and was unchanged in 17 patients (see text); FOG: freezing of gait; LEDD: levodopa-equivalent daily dose; UPDRS-II: Unified Parkinson's Disease Rating Scale – activities of daily living; UPDRS-III: Unified Parkinson's Disease Rating Scale – motor section. Axial: items speech, arising from a chair, posture, gait and stability.

- Giladi N et al. (1997). *Mov Disord*, 12:302–305
- Amboni M et al. (2010). *Mov Disord*, 25:793–795

METHODS

- We retrospectively evaluated **32 consecutive PD patients** undergoing LCIG infusion (Duodopa ©, AbbVie, North Chicago, IL, USA) and regularly followed at our Centre.
- Each patient signed a written informed consent to participate in the study. The Ethical Committee of the Hospital approved the study protocol.

RESULTS

- Evaluation at baseline and after **2.59±1.12** years (range 0.85 – 4.25 ys).
- During this period a **progression of disease** was evident (H&Y and S&E ON-medication)
- LEDD** did not vary significantly (p=0.383).
- 61% reduction of **daily "off" period duration** (p=0.001)
- 25% reduction in daily **dyskinesia duration** (p=0.021)
- FOG related UPDRS-subscore** varied from **2.6 ± 0.9** in "off" condition to **0.9 ± 0.8** in the "on" condition at baseline and improved further to **0.6 ± 0.7** with LCIG infusion (p=0.027).
- 20 patients (63%)** with **"Pseudo-on" FOG**; FOG during "on" improved in 12 - unchanged in 8.
- 11 patients (34%)** with **"Off-type" FOG**; FOG during "on" condition remained = 0 in 8 and worsened to a value of 1 (rare freezing while walking) in 3 patients.
- 1 patient (3%)** with **"Unresponsive" FOG** was unchanged

CONCLUSIONS

- In this case series we have shown that long-term intestinal levodopa infusion is able to **improve "Pseudo-on" FOG and "Off-type" FOG** in a considerable percentage of cases
- larger perspective studies are advisable to better understand the role of LCIG on this troublesome and challenging clinical condition.

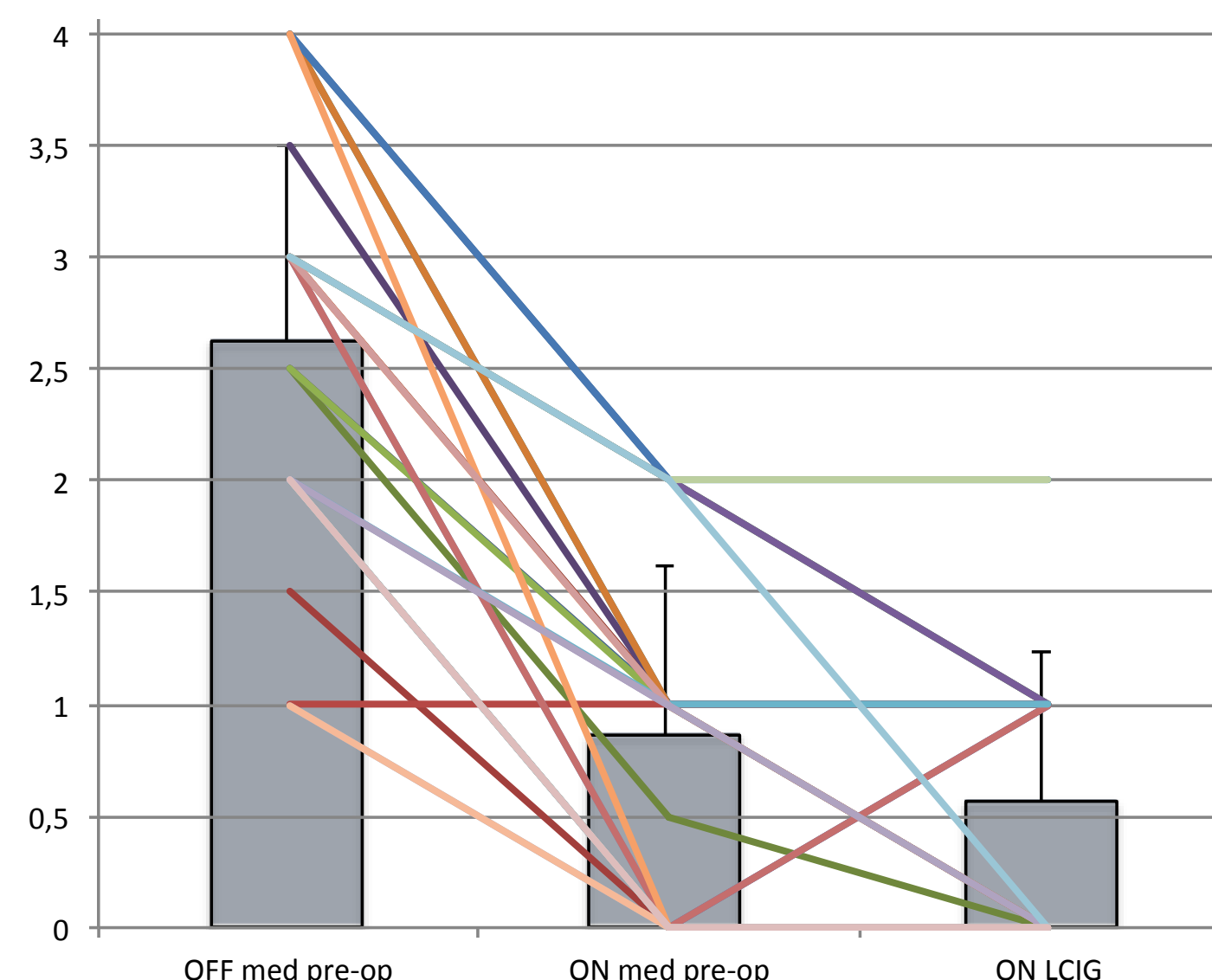


Figure 1. UPDRS item 14 Freezing of Gait.

Table 2. Modifications of different FOG types with LCIG infusion. UPDRS item 14 (subscore for FOG). The score is indicated as the median value and range.

| FoG type | Oral therapy | LCIG infusion | | |
|-----------------------------------|--------------|---------------|-----------|-----------|
| | | LCIG > OT | LCIG = OT | LCIG < OT |
| FoG improvement | | | | |
| Total FoG (N°) | 32 | 12 | 17 | 3 |
| UPDRS item 14 OFF | 2.75 (1-4) | - | - | - |
| UPDRS item 14 ON | 1 (0-2) | 0 (0-1) | 1(0-2) | 1 (1-1) |
| Pseudo-ON type FoG (N°) | 20 | 12 | 8 | - |
| UPDRS item 14 OFF | 3 (2-4) | - | - | - |
| UPDRS item 14 ON | 1 (1-2) | 0 (0-1) | 1 (1-2) | - |
| OFF type FoG (N°) | 11 | - | 8 | 3 |
| UPDRS item 14 OFF | 2 (1-4) | - | - | - |
| UPDRS item 14 ON | 0 (0-0) | - | 0 (0-0) | 1 (1-1) |
| Unresponsive type FoG (N°) | 1 | - | 1 | - |
| UPDRS item 14 OFF | 1 | - | - | - |
| UPDRS item 14 ON | 1 | - | 1 | - |

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