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Complex dyskinesias in Parkinson patients on levodopa/carbidopa intestinal gel

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ABSTRACT

Background: Levodopa-carbidopa intestinal infusion is an effective treatment for motor fluctuations in Parkinson's disease. However, it has been recently associated with emergent complex/atypical dyskinesias. We sought to characterize patients who developed these dyskinesias after levodopa infusion initiation, and to compare these patients to a control population with conventional motor fluctuations.

Methods: 208 Parkinson's disease patients, treated with levodopa intestinal infusion due to motor fluctuations, were screened for onset and/or worsening of dyskinesias after initiation of levodopa infusion, resistant to the routine titration, and presenting with atypical or unexpected patterns. Patients with extensive follow-up data were enrolled for a longitudinal analysis. Cases were compared to a control sample with conventional motor fluctuations in order to investigate predisposing factors, difference in dyskinesia phenotype, management strategies and dropouts.

Results: Thirty patients out of 208 (14.4%) reported atypical (i.e. long-lasting) biphasic, biphasic-like (i.e. continuous) or mixed (peak-dose and continuous biphasic) dyskinesias after levodopa infusion. They were compared at baseline and follow-up to a sample of 49 patients with conventional motor fluctuations on levodopa infusion. Both groups had similar demographic and clinical features, except the former having higher prevalence of biphasic dyskinesias while on oral therapy. Biphasic-like dyskinesias in nearly half the number of cases improved with increasing the dopaminergic load, while mixed dyskinesias had the worst outcome and highest dropout rate (58%).

Conclusions: Atypical biphasic, biphasic-like and complex dyskinesias could hinder the course of patients treated with levodopa infusion. This study further informs the selection process of advanced therapies, particularly in dyskinetic patients.

1. Introduction

Continuous levodopa carbidopa intestinal gel (LCIG) infusion is a valuable therapy for the treatment of motor fluctuations in Parkinson's disease (PD). Compared to conventional oral levodopa therapy, LCIG has demonstrated a significant reduction of off time and increase of on time without troublesome dyskinesias [1]. The effectiveness of LCIG on troublesome dyskinesias is supported by a post-hoc analysis of two randomized clinical trials and by a single prospective observational trial [2,3]. Conversely, the multicenter study by Sensi et al. [4] lists dyskinesias as a cause of LCIG discontinuation in 6 out of 905 patients, and the figure is even higher in a single-center study by Calandrella et al. [5] (3 out 35 patients), making dyskinesias the second most common cause of LCIG discontinuation.

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Dyskinesias have been traditionally classified according to their motor phenomenology as well as their relationship with levodopa plasma concentrations. There is an association between phenomenology and plasma levels in categorizing the type of dyskinesia. For example, peak-dose dyskinesias occur at levodopa peak plasma concentrations (monophasic) with chorea of the upper trunk, neck and arms whereas biphasic dyskinesias present during the rising and dropping of levodopa plasma levels and involve predominantly legs. Biphasic dyskinesias are also accompanied by repetitive alternating movements (RAMs), pain, dystonia or restlessness [6,7]. Some patients are susceptible to both dyskinetic patterns but experience each at different times [8]. Overall, biphasic dyskinesias are less common and poorly studied: a cross-sectional study in 168 PD patients with dyskinesias estimated their prevalence as 18.4% [9].

Recently, two small series have brought attention to emergent complex dyskinesias related to LCIG treatment [10,11]. Catalán et al. [10] reported two PD patients with LCIG-induced dyskinesias featuring a "new phenotype" characterized by the presence of continuous dyskinesias, which manifested during optimal dopaminergic stimulation and were worse at higher levodopa levels (6.6% of their LCIG cohort). These involuntary movements resembled biphasic dyskinesias from a phenomenological standpoint in that they exhibited variable occurrence of lower limb involvement, restlessness, pain, and dystonia. These dyskinesias should be preferably termed 'biphasic-like' since they do not exhibit the typical temporal pattern. Interestingly, biphasic-like continuous dyskinesias have been previously reported in two of ten patients treated with intravenous continuous infusion of levodopa [12], during 24 h infusions of the dopamine agonist lisuride [13], and in graft-induced dyskinesias [8].

A subsequent report by Meloni et al. [11] described four LCIG patients who developed biphasic dyskinesias that presented after morning dose administration and at night after pump disconnection (12% of LCIG cohort). These dyskinesias are probably similar to biphasic dyskinesias seen in PD patients not treated with LCIG, although it is unclear why they are longer in duration than typically seen in patients treated with oral levodopa (i.e., they are "atypical biphasic dyskinesias").

We sought to characterize patients who developed onset of new troublesome dyskinesias after LCIG initiation. We were particularly interested in patients who did not improve with conventional management strategies and presented atypical phenomenology such as "biphasic-like dyskinesias" during LCIG infusion, prolonged biphasic dyskinesias at pump discontinuation ("atypical biphasic dyskinesias"), and superimposition of peak-dose on biphasic-like dyskinesias ("mixed dyskinesias") (Fig. 1). To this aim, we initially performed a chart review of all LCIG patients seen in four tertiary movement disorder centers to estimate the prevalence of such presentations. In order to identify possible associated factors, we then performed a retrospective longitudinal case-control study on a well characterized sample of LCIG patients who developed these dyskinesias and compared them to a control group of LCIG patients with conventional motor complications (peak-dose dyskinesias and/or transient – usually post-prandial – wearing off symptoms).

2. Methods

2.1. Retrospective cross-sectional survey

We retrospectively reviewed the medical records of 208 idiopathic PD patients from four tertiary movement disorder centers (Fig. 2A, Supplementary Table 1). Clinicians were asked to select cases fulfilling three criteria ("DYSK" group): 1. the onset or worsening of dyskinesias after LCIG initiation, 2. dyskinesias resistant to conventional LCIG titration procedures and management (e.g. LCIG dose adjustments, anti-dyskinetic drugs), and 3. unexpected atypical dyskinetic patterns (i.e. continuous biphasic-like, atypical biphasic dyskinesias upon pump disconnection, and mixed dyskinesias) developed after LCIG. Dyskinesias were clinically classified in keeping with the methods of similar studies [13]. The different possible dyskinesias scenarios are reported in Fig. 1. See supplementary materials for cross-sectional data collection.

2.2. Retrospective longitudinal case-control study

A better-characterized group of 15 DYSK ("bcDYSK") patients followed-up in Rome and Toronto was then taken into account in a retrospective longitudinal case-control study (Fig. 2A). These patients were compared with a control group of 49 LCIG patients with conventional motor fluctuations ("CONV" group, Fig. 1), at three time points: before LCIG initiation, at the end of titration (median time of 4 weeks, after LCIG initiation), and at the latest follow-up visit (median time of 19 months on LCIG). Patients of the bcDYSK group did not differ significantly in terms of age, disease duration, and gender distribution, compared to patients with DYSK patients from the other two centers (data not shown). See supplementary materials for information on group sampling and data collection.

All statistical analyses were performed using R software, version 3.5.2. See supplementary materials for further statistical methodology.

3. Results

3.1. Cross-sectional survey

Out of 208 LCIG patients, a total of 30 cases fulfilling the selection criteria were enrolled (DYSK, 14.4%, Supplementary Table 1). All selected patients presented with biphasic-like dyskinesias during continuous LCIG infusion of which eight cases displayed atypical biphasic dyskinesias at pump disconnection (Videos 1 and 2). In 12 cases (35%), biphasic and peak dose elements were indiscernible and embedded in a mixed phenotype (Fig. 2B, Video 3). Before LCIG, 12 patients (40.0%) had peak-dose dyskinesias, 11 patients (36.7%) had biphasic dyskinesias, and 5 (16.7%) had both peak-dose and biphasic dyskinesias, each presenting separately (i.e., none had history of mixed-dyskinesias).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.11.008.

Dyskinesias worsened after lunch or during the late afternoon in 27 (90%) and 28 (93.3%) patients respectively. The presence of biphasic-like and mixed dyskinesias required multiple management strategies (Supplementary Fig. 1). Dyskinesias worsened when lowering the LCIG maintenance dose in 25 (83.3%) patients and when using extra doses in 13 (43.3%) patients. Clinicians reported an improvement of dyskinesias through strategies aimed at increasing Levodopa Equivalent Daily Dose (LEDD) (27 patients; 90%) [14], such as increasing the continuous dose (27, 90%), and prescribing dopaminergic add-on therapies (i.e. long acting or extra levodopa/carbidopa tablets, dopamine agonists, monoamine-oxidase B or Catechol-O-methyl-transferase inhibitors) (13, 43.3%). In five patients (17.2%), reducing the morning dose to the lowest tolerated level and increasing the continuous dose was reported to improve biphasic-like dyskinesias. In seven patients (23.3%), clinicians managed dyskinesias through infusion breaks during the day or earlier disconnection at night. A 24-h infusion was effective only for a brief period in two cases (6.7%). One patient had subthalamic nucleus deep brain stimulation (STN DBS), which allowed a better control of biphasic dyskinesias and parkinsonism while still on LCIG. Other strategies (alone or in combination) included use of amantadine (5, 16.6%) or educating the patient to perform multiple daily infusion rates (i.e. manual up-titration of the continuous dose after an extra-dose in the afternoon) (11, 37.9%; Supplementary Fig. 1).

Overall, dyskinesia management strategies were defined as "sufficiently effective" or "definitively effective" in 17 patients out of 30 (56.7%) (see supplementary methods for outcome definition). The remaining 13 patients (43.3%) were dissatisfied: six achieved only a

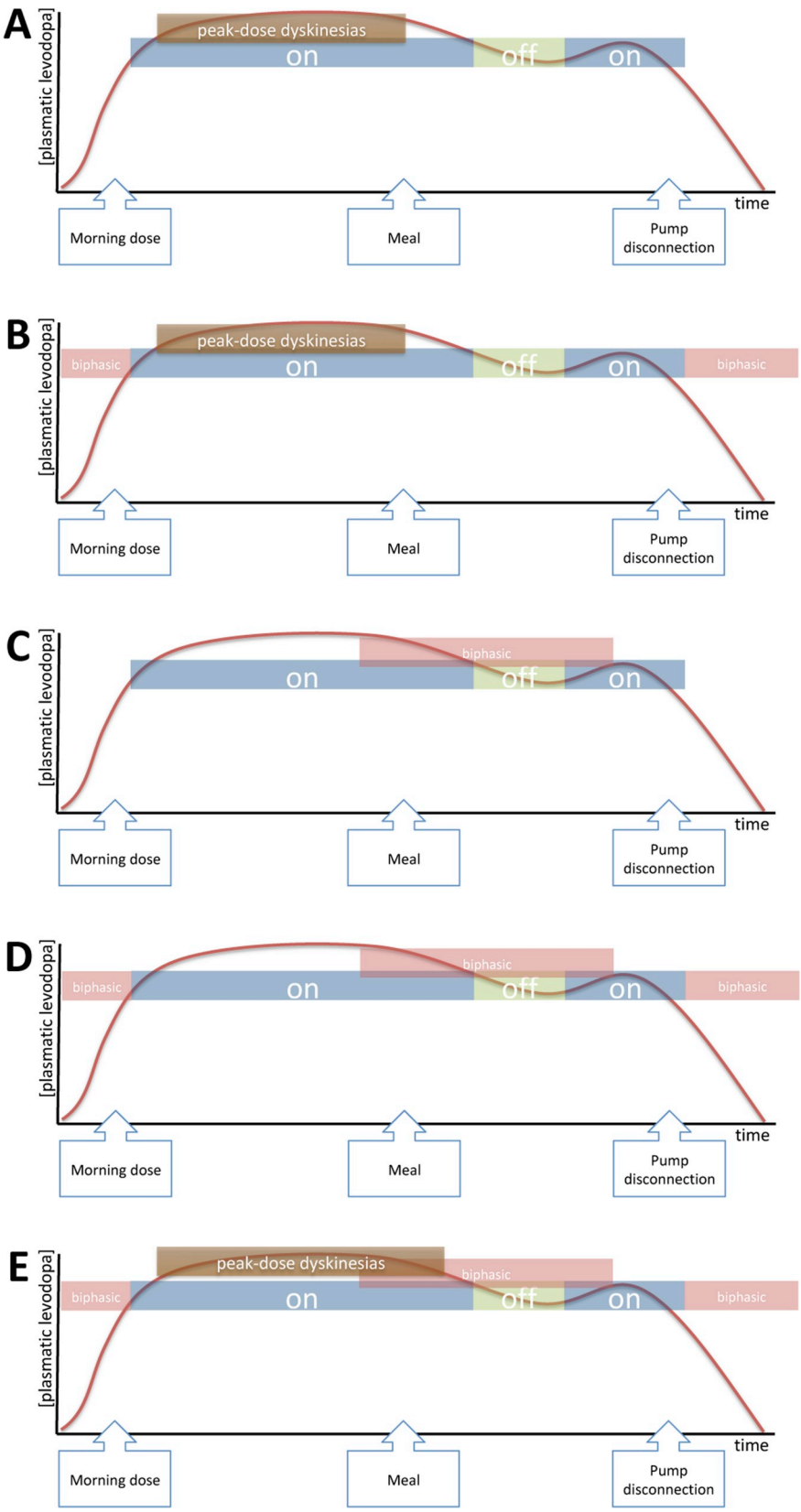

Fig. 1. The possible scenarios of motor complications in LCIG patients. Peak-dose dyskinesias (usually in the morning) with transient PD worsening in the afternoon after a meal (Fig. 1A), seldom accompanied by biphasic dyskinesias at the beginning and end of LCIG administration (Fig. 1B), biphasic-like dyskinesias during ongoing LCIG infusion (Fig. 1C), often accompanied by atypical (i.e. sustained) biphasic dyskinesias at the beginning and end of LCIG administration (Fig. 1D), and combination of biphasic-like, atypical biphasic and peak-dose dyskinesias (Fig. 1E; mixed dyskinesias). In this study we defined patterns A and B as conventional dyskinesias (CONV) and the remaining ones as complex dyskinesias post LCIG initiation (DYSK).

mild/transient improvement but remained on LCIG whereas seven patients discontinued LCIG (23.3%, Fig. 2C). Patients discontinuing LCIG were all classified as having mixed dyskinesias. Four of them reported improvement of dyskinesias and worsening of fluctuations upon LCIG discontinuation, while the remaining three cases were lost at follow-up (Video 3).

Table 1 depicts the comparison between the DYSK and CONV groups: several differences were noted, such as the dyskinesia phenotype presented before (occurrence of biphasic dyskinesias only in DYSK group) and after LCIG, dyskinesia daily course after LCIG and

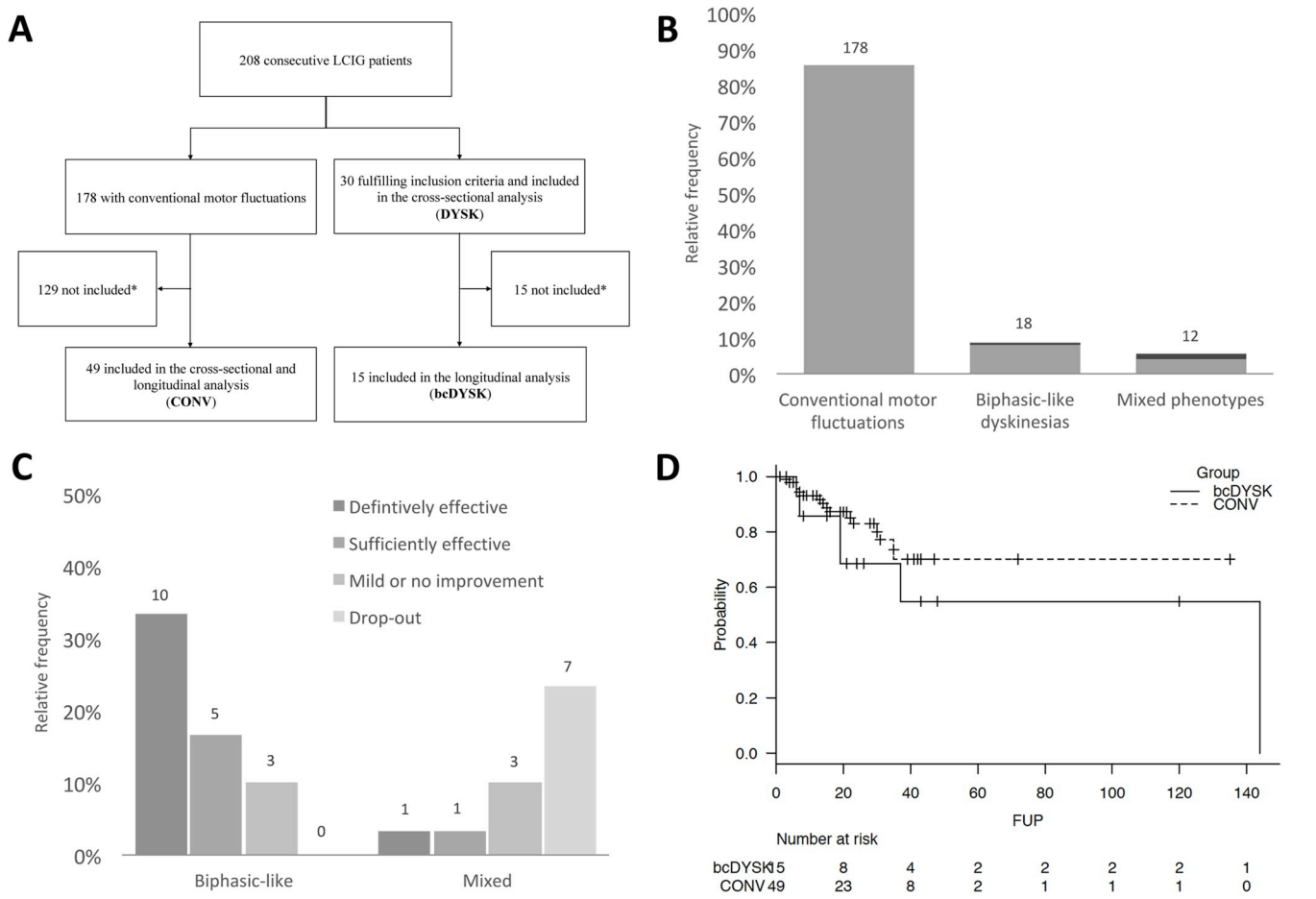

Fig. 2. Study design, cohort stratification, management efficacy and time to dropout analysis. A) *: excluded patients were not followed in Rome or Toronto and/or had insufficient data (see text for details). **B)** Stratification according to dyskinesia phenotype (atypical biphasic dyskinesias in black). **C)** Efficacy of management strategies in DYSK patients. **D)** Survival curves of bcDYSK versus CONV patients.

management strategies. Groups also differed in terms of outcome, which was described as definitively or sufficiently efficacious in 56.6% vs. 91.8% ($p < 0.0001$), and dropout rates due to dyskinesias (20% vs. 2%, $p = 0.020$). Notably no significant difference was found when comparing dropout rates due to all other causes unrelated to dyskinesia (23% vs. 16%, $p = 0.637$).

When comparing patients with biphasic-like dyskinesias ($n = 18$) vs. patients with mixed dyskinesias ($n = 12$) within the DYSK group, we found that the latter were worsened by extra doses more often than biphasic dyskinesias ($p = 0.002$). Furthermore, only patients with biphasic-like dyskinesias improved with continuous dose increases ($p < 0.001$), and overall benefitted more from proposed management strategies than patients with mixed dyskinesias ($p = 0.016$). Supplementary material details management differences between patients with biphasic-like versus mixed dyskinesias. No other clinical or demographic differences were identified (Supplementary Table 2).

3.2. Retrospective longitudinal case-control study

Baseline – CONV ($n = 49$) and bcDYSK ($n = 15$) patients were similar in age, disease duration, sex, BMI, modified Hoehn & Yahr and total LEDD before LCIG initiation. All subjects were on levodopa and only differed in amantadine intake, which was more frequently used in bcDYSK than CONV (26.7% vs. 6.1%; $p = 0.031$). The global severity of motor fluctuations was similar across groups according to UPDRS IV A + B scores ($p = 0.116$). However, UPDRS IV A score (i.e. dyskinesias) was significantly higher in bcDYSK than in the CONV group (5, IQR 3–6.5 vs. 3, IQR 1-5; $p = 0.022$). A previous history of biphasic dyskinesias was only reported in bcDYSK patients (46.7% vs. 0% in the CONV group; $p < 0.001$), while previous history of peak-dose phenotype showed a similar frequency in both groups (100% vs. 61%; $p = 0.328$) (Table 2).

End of titration period – Both groups were similar in total LEDD and distribution of add-on therapies. The bcDYSK group reported higher UPDRS IV A and B scores (UPDRS IV A, 7.5, IQR 6-9 vs. 2, IQR 1-4; $p < 0.001$; UPDRS IV B, 4, IQR 3-4 vs. 3, IQR 2-3, $p = 0.006$), and a larger number of cases with biphasic dyskinesias than the CONV group (80% vs. 2%; $p < 0.001$). After LCIG, only patients in the bcDYSK group presented with mixed dyskinesias ($n = 8$, 53.3%) (Table 2).

Latest follow-up – The follow-up duration of both groups was similar, with a median follow-up time of 19 months (IQR, 8-34). The bcDYSK group presented a higher dropout rate than CONV (42.9% vs. 8.6% due to all causes, $p = 0.035$; 33.3% vs. 2% dropout due to dyskinesias, $p = 0.008$). No differences were found in dropout time between the two groups (Fig. 2D; Log Rank test, $p = 0.345$). The total LEDD and add-on therapies distribution were still similar between groups. BMI showed a linear reduction over time, with no between-group difference at the last follow-up visit. However, BMI was significantly reduced compared to baseline only in the bcDYSK group (24, IQR 21.1–26.2 vs. 22.9, IQR 21-27; $p = 0.043$). Other comparisons are depicted in Table 2.

4. Discussion

In this retrospective study we reviewed the medical records of 208 LCIG patients and found that 14.4% had biphasic-like dyskinesias

Table 1
Demographic and clinical data of DYSK and CONV patients included in the cross-sectional survey.

		DYSK (n = 30)	CONV (n = 49)	p
Demographic and disease features				
Age (years)		68.5 (62, 72.7)	71.00 (46, 84)	.512
Gender (Females)		14 (46.7)	18 (36.7)	.524
Modified Hoehn and Yahr scale	2	2 (6.6)	2 (4.1)	.379
	2.5	10 (33.3)	12 (24.5)	
	3	13 (43.3)	27 (55.1)	
	4	5 (16.6)	8 (16.3)	
Total LEDD before LCIG initiation (mg/day)		1250 (960, 1850)	1165 (858, 1482)	.273
Disease duration at LCIG (years)		10 (8, 13.5)	10 (8, 15)	.611
Dyskinesia phenotype before LCIG initiation				
Biphasic dyskinesias prior to LCIG		16 (53.3)	0	**.000**
Peak dose dyskinesias prior to LCIG		17 (56.6)	30 (61.2)	.864
Dyskinesia phenotype after LCIG titration				
Peak-dose		18 (65.2)	32 (65.3)	.814
Biphasic-like or biphasic		30 (100)	1 (2)	**.000**
Mixed		12 (40)	0	**.000**
Dyskinesias daily course				
Worsening with continuous dose lowering		24 (82.8)	0	**.000**
Worsening with extra-doses		12 (41.4)	32 (65.3)	**.000**
Better with continuous dose increasing		15 (51.7)	0	**.000**
Trigger by morning dose		11 (37.9)	32 (65.3)	**.000**
Worsening during late morning or after lunch		26 (89.6)	0	**.000**
Worsening in the late afternoon		27 (93.1)	9 (18.4)	**.000**
Prominent at pump disconnection		7 (24.1)	1 (2)	**.004**
Management strategies				
Morning dose lowering		5 (17.2)	32 (65.3)	**.000**
Continuous dose increasing		26 (89.6)	0	**.000**
Add-on therapy with DAs, iMAO-B and/or iCOMT		12 (41.4)	11 (22.4)	.158
Use of Amantadine		5 (16.6)	2 (4.8)	.098
Multiple infusion rates		11 (37.9)	1 (2)	**.000**
24-h infusion		2 (6.9)	2 (4.8)	.632
Temporary or early disconnection during the day		6 (20.7)	2 (4.8)	.058
STN DBS		1 (5.6)	0	.379
Outcomes				
Definitively or sufficiently efficacious		17 (56.6)	45 (91.8)	**.000**
Dropout		7 (23.3)	8 (16)	.637
Dropout due to dyskinesias		6 (20)	1 (2)	**.020**

Continuous data are expressed as median (IQR), categorical variables as number of cases (%). Significantly different comparisons are bold-typed. Abbreviations: iCOMT, catechol-o-methyl-transferase inhibitor; iMAO-B, monoamine-oxidase type B inhibitor; IQR, interquartile range; LCIG, levodopa carbidopa intestinal gel; LEDD, levodopa equivalent daily dose; STN DBS, subthalamic nucleus deep brain stimulation.

during continuous LCIG infusion, a figure similar to the 12% reported in another series describing the same problem [11]. In 26.7% of these patients, dyskinesias were accompanied by prolonged and disabling biphasic dyskinesias at pump disconnection and 56.7% of them also featured peak-dose dyskinesias. The combination of biphasic-like and peak-dose dyskinesias (defined here as “mixed dyskinesias”) is a rather unique and disabling condition, leading to LCIG discontinuation in roughly 60% of these cases. Mixed dyskinesias were seen in 5.8% of the entire cohort, similar to the 6.6% reported in another series of LCIG patients [10]. Remarkably, we found that more than half of these PD patients suffered from biphasic dyskinesias while on oral therapies prior to LCIG initiation.

Most DYSK patients in our series had worsening of dyskinesias during the second half of the day. Although we did not measure levodopa plasma levels, we speculated that a drop in levodopa level is the cause of this phenomenon (Fig. 1A). Indeed, a recent report by Thomas et al. [15] suggested that nearly half of LCIG patients have predictable worsening of motor signs in the afternoon due to a reduced treatment effect. In keeping with this hypothesis, the group of patients with only biphasic-like dyskinesias improved after increasing the LEDD using different strategies.

Conceptually, the continuous infusion of levodopa – as obtained with LCIG – should be a valuable strategy to treat biphasic dyskinesias. However, although LCIG has shown to be effective in managing peak-dose dyskinesias [1,2,16], no study has specifically addressed its effect on biphasic dyskinesias. Our data might suggest that LCIG could be of help in managing these dyskinesias when present in isolation (15 out of 18 reported at least a sufficient efficacy, with a median follow-up time of 24 months IQR, 11.5–45.5). We defined these situations ‘biphasic-like’ because of the phenomenology (resembling RAMs) in absence of the typical biphasic temporal pattern. It is conceivable that these patients are being treated with constantly low levodopa levels, which perpetuate RAMs and all other phenomena seen with classic biphasic dyskinesias. “Low-dopa dyskinesias” is indeed another term historically used to describe these dyskinesias [17] and can possibly better describe this phenomenon in LCIG patients. However, we preferred to use ‘biphasic-like’ as most physicians are familiar with this terminology.

An important feature of LCIG-associated biphasic-like dyskinesias is that roughly a quarter of these patients also suffer from prolonged and worsened involuntary movements after pump disconnection. The reason for the prolonged dyskinesias is unknown and has also been rarely reported in PD patients on oral levodopa treatment [18]. Stopping the infusion earlier or multiple times during the day proved beneficial for some patients by providing them with shorter periods of dyskinesias. This observation leads to the hypothesis that the longer the effect of levodopa the longer the involuntary movements upon discontinuation of infusion therapy. This hypothesis – if proven true – would support the notion that the pulsatile dopaminergic stimulation, observed in PD patients on oral levodopa, causes short-lasting but might in fact prevent the occurrence of sustained biphasic dyskinesias.

In line with these considerations, continuous 24h infusion without any breaks would be the best strategy to avoid this problem. Although 24h LCIG infusion has been recently reported as a treatment for dyskinesias [19], in our study we found that this strategy provides only a mild and transient benefit for biphasic-like dyskinesias. This is likely due to the subsequent development of peak-dose dyskinesias (‘mixed phenotype’), which are known to be associated with higher cumulative doses of levodopa [20]. Similarly, in their study Quinn et al. reported that two out of 10 patients undergoing levodopa intravenous infusion developed biphasic-like dyskinesias during ongoing infusion [12]. These dyskinesias were briefly relieved by extra-doses followed by maintenance dose increases, but returned shortly thereafter. Interestingly, and comparable to our findings (see below), these two patients suffered from typical violent biphasic dyskinesias while on oral levodopa therapy, prior to the infusion [12]. The authors concluded that management of biphasic-like dyskinesias by increasing the dopaminergic load contributes to a greater risk of developing complicated dyskinesias in the long term [12]. We think that this is comparable to what happens in our patients with ‘mixed dyskinesias’ (see below).

Intriguingly, choreic dyskinesias also increased in 23 of 34 patients treated with 24 h infusion of lisuride followed for a mean of 20.85 (range 6–45) months and diphasic dyskinesia increased in eight patients leading to treatment discontinuation in two. However, it is unknown if these patients belonged to the group of 14 patients presenting biphasic dyskinesias before lisuride infusion [13].

In their serial positron emission tomography (PET) imaging study, Politis and colleagues observed that LCIG infusion could generate a stable rise in striatal dopamine levels, evidenced by the reduction in striatal [^{11}C]raclopide binding in six advanced PD patients while on LCIG [21]. Although serial PET imaging is a powerful tool for investigating striatal dopamine levels, to date no study has been performed in patients with biphasic-dyskinesias on oral levodopa or after LCIG. Therefore, any discussion about the pathophysiology of biphasic-like and especially mixed phenotype in LCIG patients is merely

Table 2
Baseline and follow-up features obtained of patients analyzed in the Retrospective longitudinal case-control study.

	Baseline data			End of titration			Last follow-up		
	bcDYSK (n = 15)	CONV (n = 49)	p	bcDYSK (n = 15)	CONV (n = 49)	p	bcDYSK (n = 15)	CONV (n = 49)	p
LEDD, other anti-PD drugs									
Total LEDD (mg)	1000 (969, 1833)	1165 (855, 1500)	.950	1287 (1016, 1818)	1136 (1000, 1625)	.762	1382.5 (1004, 1920.5)	1420 (1202, 1729)	.913
LD/CD	15 (100)	15 (100)	–	8 (53.3)	30 (61.2)	.783	7 (58.3)	31 (63.3)	.752
iMAO-B	3 (33.3)	15 (30.6)	.493	6 (6.7)	5 (10.2)	.494	0	6 (12.2)	.202
DA	8 (53.3)	24 (49)	.533	6 (40)	21 (42.9)	1	4 (33.3)	18 (36.7)	.826
iCOMT	3 (20)	15 (30.6)	.566	0	3 (6.1)	.326	0	4 (8.2)	.306
Amantadine	4 (26.7)	3 (6.1)	**.031**	1 (6.7)	5 (10.2)	.212	2 (16.7)	4 (8.2)	.375
Motor complications									
UPDRS IV A + B	9 (6.5, 11)	7.5 (5.2, 9.7)	.116	10.5 (9.7, 13.2)	5 (4, 7)	**.000**	10 (7, 13)	4 (4, 6)	**.000**
UPDRS IV A	5 (3, 6.5)	3 (1, 5)	**.022**	7.5 (6, 9)	2 (1, 4)	**.000**	7 (4.7, 8)	2 (1, 3)	**.000**
UPDRS IV B	4 (3, 5)	4.5 (4, 5)	.361	4 (3, 4)	3 (2, 3)	**.006**	3.5 (2.7, 5)	3 (2, 3)	**.048**
Dyskinesia phenotype									
Peak-dose	15 (100)	30 (61)	.328	12 (80)	32 (65.3)	.440	Unchanged		
Biphasic-like or biphasic	7 (46.7)	0	**.000**	12 (80)	1 (2)	**.000**			
Mixed	0	0	1	8 (53.3)	0	**.000**			

Continuous data are expressed as median (IQR), categorical variables as number of cases (%). Significantly different comparisons are bold-typed. Abbreviations: bcDYSK, better characterized DYSK group; CONV, conventional motor complications group; DA, dopamine agonists; iCOMT, catechol-o-methyl-transferase inhibitor; iMAO-B, monoamine-oxidase type B inhibitor; IQR, interquartile range; LCIG, levodopa carbidopa intestinal gel; LD/CD: levodopa/carbidopa tablets; LEDD, levodopa equivalent daily dose; PD, Parkinson's disease; UPDRS IV, unified Parkinson's disease rating scale part IV.

speculative at the moment.

A small percentage of our LCIG patients (5.8% of the entire cohort) was found to have biphasic-like and peak-dose dyskinesias ('mixed dyskinesias'), which led to LCIG discontinuation in roughly 60% of cases. Interestingly, four patients (out of seven) reported an overall improvement of dyskinesias after LCIG discontinuation.

The pathophysiology of the mixed phenotype of dyskinesias is unknown and has been seen as a completely new phenomenon of LCIG patients [10]. A possible – yet to be verified – hypothesis was proposed by Quinn et al. for their patients with levodopa intravenous infusion (see above) [12]. Supplementary Fig. 2 depicts the possible pathophysiological underpinning of 'mixed dyskinesias' inspired by the works on threshold for levodopa response by Nutt and colleagues [22] and the notion that multiple thresholds might co-exist and overlap in PD patients [23]. It is possible to hypothesize that patients with biphasic dyskinesias before LCIG are at risk of developing biphasic-like dyskinesias during LCIG. This is managed by increasing LEDD, which in turn might predispose them to the development of concomitant peak-dose dyskinesias (mixed phenotype). Future prospective studies are needed to confirm this hypothesis.

Comparisons between groups can shed light on possible mechanisms underlying the complex nature of dyskinesias in LCIG patients. The most prominent difference between groups was the high prevalence of biphasic dyskinesias before LCIG initiation. Analysis of the longitudinal cohort (bcDYSK) confirmed these findings and also showed that CONV patients had less severe dyskinesias at baseline and throughout their follow-up. On the other hand, almost half of DYSK patients did not have biphasic dyskinesias before LCIG initiation, which raises the question whether patients, physicians and assessment tools (e.g. diaries) are always able to identify them [24].

In addition to the well-known limitations of retrospective and open studies, our findings are limited by the lack of patients' plasma levodopa levels, which are however of controversial utility in LCIG patients suffering for dyskinesias [25]. In addition, our study lacks motor diaries, particularly designed to address biphasic dyskinesias. Although we catch data on motor fluctuations changes through the UPDRS IV scale, a more specific assessment tool (e.g. the Unified Dyskinesias Rating Scale) could have given additional useful information. Therefore, our findings rely mainly on clinical observations and questionnaires.

In conclusion, our observations suggest that disabling biphasic-like and mixed dyskinesias could complicate LCIG patients' follow-up. While these dyskinesias bear some phenomenological resemblance to the classic biphasic dyskinesias, the mechanism(s) behind this complication remains unclear. Our study also shows that biphasic-like dyskinesias without the presence of peak-dose dyskinesias are more easily managed, usually by increasing the levodopa load. However, it is possible that these patients will later develop mixed-dyskinesias. The nasojejunal test should also be considered to aid the selection process in these cases, although complex dyskinesias are fully manifested within a timeframe that is often longer than the duration of such test.

Further prospective studies should be designed to investigate why continuous levodopa infusion is more prone to cause these complex dyskinesias. While awaiting these studies, clinician's should investigate patients' dyskinesias carefully in order to inform the selection process of advanced therapies, particularly LCIG therapy for patients with pre-existing biphasic dyskinesias.

Author contribution statement

Conception and design of the study: MM, AF.
Data collection and organization: MM, TN, LdB, YYP, ADS, RA, PM.
Execution and review of the statistical analysis: MM, AF.
Wrote the manuscript: MM, TN, AF.
Review and critique of the manuscript: MM, LdB, YYP, GC, PM, VDL, AF.

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Patient consent for publication

All identifiable subjects present on videos gave consent to be video-recorded for publication both in print and online.

Data statement

Data are available in spreadsheets upon request to the corresponding author.

Ethics approval

The present study has been approved by the local ethic committees.

Declaration of competing interest

Authors deny any competing interest for the present study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.11.008.

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