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Short communication

The impact of dysphagia in Parkinson's disease patients treated with levodopa/carbidopa intestinal gel

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ABSTRACT

Background: Dysphagia is common in advanced phases of Parkinson disease (PD), and is a risk factor for aspiration pneumonia. Nonetheless, dysphagia has been poorly investigated in PD patients treated with levodopa-carbidopa intestinal gel (LCIG). We aimed to analyze the impact of dysphagia on mortality in LCIG treated patients and its relationship with other PD disability milestones.

Methods: We retrospectively evaluated 95 consecutive PD patients treated with LCIG. Kaplan-Meier and log-rank test were used to compare mortality in patients with dysphagia from others. Cox regression was used to estimate the impact of dysphagia, age, disease duration, and Hoehn and Yahr (H&Y) on mortality in the entire cohort. Finally, univariate and multivariate regression analyses were used to estimate the association between dysphagia and age, disease duration, H&Y, hallucinations, and dementia.

Results: A significantly higher mortality rate was observed in patients with dysphagia. In the Cox model, dysphagia was the only feature significantly associated with mortality (95%CI 2.780–20.609; $p < 0.001$). Univariate analyses showed a significant correlation between dysphagia and dementia (OR: 0.387; p:0.033), hallucinations (OR: 0.283; p:0.009), and H&Y score (OR: 2.680; $p < 0.001$); in the multivariate analysis, only the H&Y stage was associated with the presence of dysphagia (OR: 2.357; p:0.003).

Conclusion: Dysphagia significantly increased the risk of death in our cohort of LCIG-treated patients, independently from other relevant features such as age, disease duration, dementia, and hallucinations. These findings support the management of this symptom as a priority in the advanced PD stages, even in people treated with LCIG.

1. Introduction

Dysphagia is a detrimental symptom of Parkinson's disease (PD), with a prevalence estimated to be up to 80% during the disease course [1]. Although dysphagia can occur in every disease stage, its frequency increases with disease progression, leading to weight loss, dehydration, malnutrition, limiting social activities for patients and caregivers, and severely affecting quality of life (QoL) [1,2]. Moreover, dysphagia is a significant risk factor for aspiration pneumonia, the first cause of death in PD [2], but systematic longitudinal evaluations of the impact of dysphagia in cohorts of advanced PD patients, especially in those treated with levodopa-carbidopa intestinal gel (LCIG), is still lacking. Pneumonia/respiratory failure as the main cause of death has previously been reported in LCIG-treated patients, supporting a probable indirect association with dysphagia [3]. Importantly, dysphagia is considered one of the disability milestones in PD progression, but the relationship with other milestones as dementia, hallucinations, and postural instability is partly unclear. The possibility of using the already positioned PEG tube for feeding in PD patients treated with LCIG represents a possible advantage for the management of dysphagia and prevention of its complications [4,5].

In this context, the aim of the study was to analyze the impact of

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dysphagia in a large group of advanced PD patients who underwent a PEG-J placement for LCIG infusion, comparing clinical factors, disability, and mortality between those developing and those not developing dysphagia during the time of observation.

2. Methods

We conducted a retrospective observational study including data from patients diagnosed with idiopathic PD [6] treated with LCIG for at least six months in the Movement Disorder Unit of the University of Turin (Italy) and Rome (Sant'Andrea University Hospital, Italy) between 2012 and 2022. All patients were evaluated at a regular interval of about six months during regular follow-up in the outpatient clinics.

Exclusion criteria were: i) presence of dysphagia before LCIG implantation, ii) Hoehn and Yahr (H&Y) score of 5 before LCIG implantation, iii) severe dementia, according to a Mini-Mental State Examination (MMSE) score below 18, iv) discontinuation of LCIG during follow-up, (v) history of stroke or important affection of gastrointestinal systems due to malformation, cancer or previous surgery.

The following data were collected: clinical and demographic features, including age, sex, and disease duration, Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III in the "ON" condition before LCIG implantation and at the last reported visit; medications; total levodopa equivalent daily dose (LEDD); MMSE score; presence of hallucinations; use of antipsychotics drugs at baseline; incidence of institutionalization after LCIG start. A validated formula was used to convert UPDRS into MDS-UPDRS scores, when needed [7].

The presence of dysphagia was defined by a score >1 at item 2.3 of the MDS-UPDRS part II [8,9] after PEG-J implantation for LCIG (or a score >1 at item 7 of the UPDRS). According to the development of dysphagia during follow-up, patients were divided into 2 groups: those who developed dysphagia (LCIG-Dys) and those who did not (LCIG-NDys).

We chose death as the primary outcome measure and H&Y score of 5, the presence of hallucinations (yes or no according to outpatient visit chart review), and a diagnosis of severe dementia (MMSE<16) as secondary outcome measures, to analyze the relationship of dysphagia with mortality and the main disability milestones.

The Local Ethical Committees approved the protocol.

2.1. Statistical analysis

Descriptive statistics were used to summarize numerical data as mean ± SD, and categorical variables as frequencies. The Mann-Whitney *U* test for independent groups was used to assess the difference between LCIG-Dys and LCIG-NDys in terms of age, H&Y, and disease duration. The Chi-square test was used to determine the frequency distribution between the two groups for sex.

Kaplan-Meier survival analysis and log-rank test were used to compare the mortality of patients with or without dysphagia (LCIG-Dys vs. LCIG-NDys). A Cox regression model was used to estimate the influence of the following factors on the mortality of entire cohort of LCIG patients: age, disease duration, H&Y at LCIG implantation, and the development of dysphagia after implantation. Follow-up was calculated for LCIG-Dys since the onset of dysphagia and for LCIG-NDys since the start of LCIG.

Finally, a linear regression analysis was performed to evaluate the association between the presence of dysphagia and the following variables assessed at the last follow-up: age, disease duration, H&Y, presence of hallucinations, and presence of dementia. Univariate regression analyses were performed first, then a multivariate regression analysis model was built with independent variables obtaining a p-value ≤0.1 at the univariate analysis. The significance threshold was set at $\alpha < 0.05$. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 23).

3. Results

From 95 LCIG patients initially screened for the study, a total of 86 patients were included in the analysis according to the inclusion/exclusion criteria. Four patients were excluded for the presence of dysphagia before LCIG started, three for discontinuation of LCIG during follow-up, and two for gastrointestinal comorbidities which led to the placement of a jejunostomy. The demographic and clinical characteristics of included patients are summarized in Table 1. The mean age at LCIG start was 67.7 ± 7.1 years, and the mean disease duration was 13.0 ± 5.1 years. Forty-nine percent of patients (n = 42) developed dysphagia during a mean follow-up since LCIG start of 3 ± 2.2 years. There was no statistically significant difference in age, disease duration, sex, and H&Y score between LCIG-Dys and LCIG-NDys at LCIG start. LCIG-Dys patients developed dysphagia at an average age of 70.5 ± 6.9 years, 15.4 ± 5 years of disease duration, and a mean H&Y stage of 3.

3.1. Analysis of mortality in patients with dysphagia vs. patients without dysphagia

A higher mortality rate was observed at the survival analysis in the LCIG-Dys group (log-rank test $p < 0.001$) (Fig. 1).

According to the Cox regression analysis investigating factors impacting survival in the entire cohort of patients, dysphagia was the only variable significantly associated with mortality, with a Hazard Ratio (HR) of 7.569 (p: <0.001, 95% CI 2.780–20.609) (Supplementary Table 1, Fig. 1).

Table 1
Baseline demographic and clinical features of included patients.

		Overall (N = 86)	LCIG-NDys (N = 44)	LCIG-Dys (N = 42)	P value
Sex	M	58 (67%)	29 (66%)	29 (69%)	.936[b]
	F	28 (33%)	15 (34%)	13 (31%)	
Age at LCIG start (years)		67.7 ± 7.1	67.8 ± 6.9	67.7 ± 7.3	.900[a]
H&Y at LCIG start		3 (2–3)	2.75 (2–3)	3 (2–3)	.213[a]
Disease duration at LCIG start (years)		13.0 ± 5.1	13.4 ± 5.5	12.6 ± 4.6	.845[a]
Follow-up duration		3.01 ± 2.20	3.56 ± 2.54	2.38 ± 1.62	**.016**[a]
LEDD before implantation		1190.76 ± 392.01	1147.62 ± 330.03	1229.89 ± 441.05	0.06[a]
Use of antipsychotic drugs		15 (17.4%)	6 (13.6%)	9 (21.4%)	0.385[b]
Institutionalization		16 (18.6%)	5 (11.3%)	11 (26.2%)	0.06[b]
Age at dysphagia onset (years)		–	–	70.5 ± 6.9	
H&Y at dysphagia onset		–	–	3 (2–4)	
Disease duration at dysphagia onset (years)		–	–	15.4 ± 5.0	
MDS-UPDRS item 2.3 at dysphagia onset		–	–	3.5 (3–4)	

Results are reported as average ± standard deviation *(range)* or absolute values (percentage), as appropriate.
Bold indicates the significant value of p-value: statistical significance.
H&Y: Hoehn and Yahr stage; LCIG: Levodopa-Carbidopa Intestinal Gel; MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale; OR: Odds Ratio; LCIG-Dys: Parkinson's Disease patients with dysphagia; LCIG-NDys: Parkinson's Disease patients without dysphagia, LEDD: Levodopa Equivalent Daily Dose.
[a] Mann-Whitney test.
[b] Chi-square test.

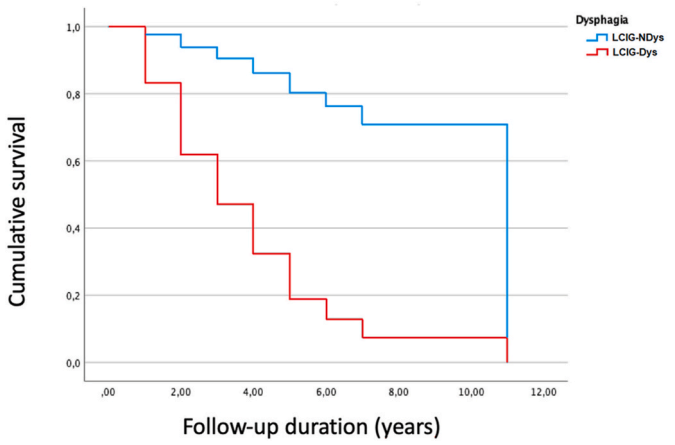

Fig. 1. Survival curves
LCIG-NDys = Patients without dysphagia; LCIG-Dys = Patients with dysphagia.

3.2. Association of dysphagia with clinical-demographic variables and other milestones of disability

Univariate regression analyses showed a significant correlation between dysphagia and dementia (OR: 0.387, p: 0.033), hallucinations (OR: 0.283, p: 0.009), and H&Y score (OR: 2.680, $p < 0.001$). No correlation was found between dysphagia and age and disease duration.

In the multivariate regression analysis, only the H&Y stage survived as a significant variable independently correlated with dysphagia (OR: 2.357, p: 0.003) (Supplementary Table 2).

4. Discussion

We performed a retrospective analysis on the role of dysphagia in advanced PD patients treated with LCIG. While we did not find significant demographic or clinical differences at LCIG start between patients developing or not dysphagia in the following months, the dysphagia group had a significantly higher probability of death during follow-up. Moreover, dysphagia was the only significant predictor of death in our cohort, confirming and highlighting the relevance and impact of this symptom in the advanced disease phases also in a cohort of patients treated with LCIG.

Dysphagia is a common PD symptom causing difficulty in taking drinks, food, and oral medications, resulting in dehydration, malnutrition, and subsequent weight loss, and is strongly associated with dementia, hallucinations, and falls [1,2,9,10]. Overall, dysphagia significantly increases the risk of aspiration pneumonia, which is a leading cause of death in people with PD. However, population studies yielded mixed results on the role of dysphagia on mortality in PD patients. A recent nationwide study estimated that about two-thirds of PD patients die within a year since an episode of aspiration pneumonia, which is in turn due to dysphagia in most cases [11]. Different data arise from a population-based study investigating the early predictors of mortality in PD and parkinsonism with a follow-up of about 10 years in which dysphagia did not resist at the multivariate analysis; however, this second study did not include patients treated with advanced therapies or in the late stage of disease [12].

In our study, we specifically aimed to evaluate the impact of dysphagia on mortality in a population of LCIG-treated PD patients. While we found a high correlation between the presence of dysphagia and mortality, the presence of dysphagia in our cohort showed a significant correlation only with the H&Y disease stage, suggesting a strict relationship with motor disability, while no significant association was found with other disease milestones, such as dementia and hallucinations. Our results are in accordance with those of a recent longitudinal study highlighting the role of dysphagia in predicting disease progression in the late stage of PD [8], with dysphagia found as the only variable significantly predicting the occurrence of hospitalization, H&Y score 5, and death [8]. Interestingly, at the univariate analysis we found an inverse correlation between both dysphagia and dementia and dysphagia and hallucinations, while the presence of dysphagia was associated with higher score of the H&Y. In the multivariate model including dementia, hallucination and H&Y as independent variables, only H&Y stage was associated with the presence of dysphagia indicating the important role of motor disease progression in the development of dysphagia and independently from other non-motor symptoms.

When considering the literature on LCIG-treated patients, dysphagia was under-investigated. In a previous analysis of mortality and its predictors in a cohort of 105 PD patients treated with LCIG for over ten years, cognitive dysfunction emerged as an important mortality predictor [13]. Still, the presence of dysphagia was not systematically analyzed [13]. Another recent study retrospectively analyzed data of safety and mortality in 76 LCIG PD patients; however, dysphagia was not assessed [14].

Noteworthy, recent findings support the hypothesis that LCIG treatment may improve dysphagia by reducing premature bolus spillage and pharyngeal bradykinesia, in accordance with the LCIG's positive effect on other motor functions [4]. The effect of dopaminergic medication on swallowing function is controversial. A trend toward improvement of dysphagia in some PD patients with oral levodopa, subcutaneous apomorphine, or transdermal rotigotine has been observed [1]. Nonetheless, in this study, we did not observe a significant difference in the amount of total dopaminergic therapy between patients developing dysphagia and those who did not.

The main limitations of the study are the retrospective design and the absence of an objective assessment of dysphagia. Furthermore, to select a cohort of advanced PD patients well characterized and systematically followed up over time, we chose a group of patients treated with enteral levodopa infusion, and this could limit the generalizability of the results to all advanced PD patients.

These limitations notwithstanding, we explored for the first time the impact of dysphagia on mortality in a large cohort of advanced PD patients treated with LCIG, confirming its pivotal role as a risk factor for death, which resulted partly unrelated to other PD disabilities milestones. This evidence suggests the importance of prioritizing the management of dysphagia in the advanced stages of the disease, considering that people with PD treated with LCIG have a PEG-J that can be used, in addition to medication administration, for feeding and preserving the airway, particularly during OFF, when dysphagia may be worse. Therefore, early identification of dysphagia is fundamental for correct management, such as adjusting the food and liquid consistency or feeding techniques. When oral nutritional intervention is not effective in preventing dysphagia complications, PEG placement for enteral feeding is recommended [1,4]. The possibility of using the already positioned PEG tube for feeding in PD patients treated with LCIG represents a meaningful and readily achievable intervention for preventing dysphagia complications, which could be reflected positively in outcome measures [4,5]. This possibility has already been proposed by brief reports suggesting potential benefit from the use of the PEG-J tube implanted for LCIG administration also for enteral feeding purposes in PD patients with dysphagia [4,5]. Noteworthy, PD patients candidates for LCIG commonly receive a 15-Fr caliber PEG-J implant, which requires an adaptor to make the gastric port compatible for nutrition tubes. A different PEG available and compatible with 20-Fr caliber should be considered in cases of moderate dysphagia at LCIG start or during one of the routine substitutions [5]. Conversely, no data are available about the different risk of obstruction between the two sizes for enteral nutrition.

We hope this study can raise attention to this severe and dangerous PD symptom, suggesting an accurate screening, especially in frail populations like those of PD patients treated with device-aided therapies.

Author contributions

Domiziana Rinaldi: study conception and design; interpretation of data; drafting the manuscript.

Gabriele Imbalzano: study conception and design; interpretation of data; drafting the manuscript.

Silvia Galli: interpretation of data; drafting the manuscript.

Edoardo Bianchini: acquisition and interpretation of data; revising the manuscript for intellectual content.

Lanfranco De Carolis: interpretation of data; revising the manuscript for intellectual content.

Claudia Ledda: interpretation of data; revising the manuscript for intellectual content.

Maurizio Zibetti: interpretation of data; revising the manuscript for intellectual content.

Leonardo Lopiano: interpretation of data; revising the manuscript for intellectual content.

Francesco Ernesto Pontieri: interpretation of data; revising the manuscript for intellectual content.

Carlo Alberto Artusi: study conception and design; interpretation of data; revising the manuscript for intellectual content.

All the co-authors listed above gave their final approval of this manuscript version.

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Data availability statement

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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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.2023.105368.

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