

Speech and voice response to levodopa in late-stage Parkinson's Disease patients: report from an acute levodopa challenge

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BACKGROUND

- Parkinson's disease (PD) patients are affected by hypokinetic dysarthria, characterized by hypophonia and dysprosody, which worsens with disease progression.
- Speech disorders affect nearly 90% of PD patients and have a negative impact on quality of life.
- Levodopa's (L-dopa) effect on quality of speech is inconclusive; no data are currently available for late-stage PD (LSPD).

OBJECTIVE

To assess the modifications of speech and voice in LSPD following an acute L-dopa challenge.

METHODS

❖ LSPD patients (Schwab and England <50/Hoehn Yahr >3 [MED ON]) performed several vocal tasks before and after an acute L-dopa challenge with a supramaximal dose (150%);

❖ The following was assessed during MED OFF and MED ON: a) **respiratory support for speech** (time duration of vowel /a/ prolongation); b) **voice quality** (fundamental frequency [F0]); c) **voice stability** (pitch break time, and jitter); d) **voice variability** (standard deviation [SD] of speaking F0 during sentences [Sentence F0SD]); e) **speech rate** (syllables/sec); f) motor performance (**MDS-UPDRS-III**) and **AIMSm**.

❖ All voice samples were recorded and analyzed by a **speech and language therapist** blinded to patients' therapeutic condition using **Praat 5.1 software**.

Patients data	LSPD (n= 24)	LSPD MALE (n=14)	LSPD FEMALE (n=10)	p - value
Age (yrs)	79 [71.5-81.7]	77.5 [70.7-81.2]	79 [73.5-85]	ns
Age at disease onset (yrs)	64.5 [54.5-69.5]	62.5 [55-67]	65 [51.5-71.5]	ns
Disease duration	14.5 [11-15.7]	13.5 [8.7-17]	15 [11.7-17.2]	ns
Education (yrs)	4 [4-11]	4 [4-12]	5 [4-10.5]	ns
S&E (ON/OFF)	40/35 [40-40.7 / 22.5-40]	40/30 [40-40 / 40-40]	40/30 [27-50 / 17.5-50]	ns
HY (ON/OFF)	4 [2-4] / 4 [2-4.75]	3 [2-4] / 3 [2-4]	4 [4-5] / 4 [4-5]	ns
PDD (n (%))	14 (58%)	10 (71%)	4 (40%)	ns
MMSE	22.5 [21.2-25]	22.5 [22-24.2]	22.5 [16-27.2]	ns
MMSE (demented/non-demented)	22 [17-23.7] / 25 [23-26.7]	22 [21.7-24.2] / 23 [22.2-25.2]	17 [13-19.5] / 27 [25-28.5]	ns
LEDD (mg)	1037 [902-1272]	1100 [990-1303]	905 [742-1257]	ns
MDS-UPDRS-II	31 [27-38]	32 [29.2 - 38.5]	30 [20.5-38]	ns
MDS-UPDRS-III (MED ON/MED OFF)	50 [40-54]/64 [52-77]	50 [42.5-55.2]/61 [53-76]	50 [37.5-62.5]/64 [48-79.5]	ns
Axial sign (MED ON/MED OFF)	8 [6-13] / 10 [7-13]	8 [6-13] / 10 [7-13.2]	8 [6.5-12] / 10 [7-13.5]	ns
MDS-UPDRS-IV	4 [2-9.5]	5 [2-8.5]	4 [0-11.2]	ns

Table 1. Demographic and clinical features. Values are presented as median [IQR, 25th-75th percentile] if no otherwise specified; ns: not significant. LEDD: L-dopa equivalent daily dose; PDD: Parkinson's disease with dementia; MMSE: mini mental state examination. S&E: Schwab and England score; HY: Hoehn Yahr Stage; ns: non-significant; P value is the results for male vs. female scores' comparison.

	PD Patients (N=24)	Normal value
Respiratory support for speech	5.8 [4.4-11.5.8]	22.97 (1.1) ^
Vowel duration (sec)		
Voice stability		
Pitch break time (sec)	1.24 [0.2-2.6.1]	NA*
Jitter (%)	0.8 [0.5-1.1]	≤ 0.5-1%
Voice variability F ₀ SD (Hz)	2.4 [1.6-4]	2-4Hz
Voice quality (Hz) - F ₀	MALE (N=14) FEMALE (N=10)	MALE FEMALE
	125 [104-152] 202 [160-226.8]	128 (36)** 198 (44)**

Table 2. Baseline speech and voice characteristics. Values for LSPD patients are presented as median [IQR, 25th-75th percentile]. Values for healthy subjects are presented as mean (SD), as reported in literature (Maslan J. et al., 2011; Barkana BD & Zhou JA, 2015, Colton & Casper, 1996; Titze IR, 1993). F0: fundamental frequency; F0SD: fundamental frequency standard deviation; NA*: not available (healthy voices should have no trouble in maintaining voicing during a sustained vowel. This is 0% of voice breaks. No standard values are available). ^: normal value for vowel duration are referred to a healthy population aged between 71 and 80 years old. **: normal value for voice quality are referred to a healthy population aged between 55 and 80 years old.

	LSPD patients (N= 24)		p - value
	MED OFF	MED ON	
MDS-UPDRS-III	64 [52-77]	50 [40-54]	<0.001
Speech	2 [1-3]	2 [1-3]	0.83
Freezing of gait	3 [1-4]	2 [0-3]	<0.05 (0.01)
Postural Stability	3 [2-4]	3 [2-3]	<0.05 (0.014)
Gait	3 [2-4]	3 [2-3]	<0.05 (0.01)
Axial Signs	10 [7-13]	8 [6-13]	<0.05 (0.01)
HY	4 [2-4.75]	4 [2-4]	0.7
mAIMS	0	1 [0-6.75]	0.04
Voice Respiratory support for speech			
Vowel duration (sec)	5.8 [4.4-11.5]	7 [3.6-10.6]	0.6
Voice stability			
Pitch break time	1.2 [0.2-2.6]	0.8 [0.07-2.5]	0.9
Jitter	0.8 [0.5-1.1]	0.7 [0.4-1]	0.5
Voice quality F ₀	154 [123-209]	162 [147-203]	0.2
Voice variability SentenceFoSD	31 [19-51]	29 [20-40]	0.5
Speech rate	5 [3.6-5.6]	5 [4.2-5.7]	0.2

Table 3. L-dopa challenge test. Values are presented as median [IQR, 25th-75th percentile]. Statistical significant results are in bold. Axial Signs: sum of item 3.1, 3.10-3.12 of the MDS-UPDRS-III. P - value is the results of MED OFF versus MED ON scores. mAIMS: Modified Abnormal Involuntary Movement Scale.

RESULTS

Patients

- 24/27 (14 men) LSPD patients succeeded in performing voice tasks;
- Median age and disease duration of patients was 79 [IQR: 71.5-81.7] and 14.5 [IQR: 11-15.7] years, respectively;
- There were no differences in demographic or clinical variables between men and women (Table 1).

Baseline voice and speech characteristics

- In MED OFF, **respiratory breath support and pitch break** time of LSPD patients were worse than the normative values of non-parkinsonian (Table 2).
- Mean **jitter** values were in the normal range (Table 2), although results were borderline for men and SD showed a tendency for higher values.
- FOSD was in the normal range (Table 2). However, due to the low level of cooperation of LSPD patients, we adopted an 8-word (14 syllables) declarative sentence (syntactically simple) that in European Portuguese is expected to have a low level of voice variability compared to complex sentences or text reading, which are normally used for this task

Voice features and PD severity

- A correlation was found between **disease duration and voice quality** (R=0.51; p=0.013) and **speech rate** (R= -0.55; p=0.008).
- Motor impairment (**MDS-UPDRS-III**) had a moderate significant correlation with **respiratory support for speech** (R= -0.43; p=0.045) and **pitch break time** (R= -0.565; p=0.006).

L-dopa challenge test

- L-dopa significantly improved MDS-UPDRS-III score (20%; IQR: 11.5%-32%);
- Sub-analysis of MDS-UPDRS-III scores for axial signs showed a significant median improvement after L-dopa intake for all the sub-items, except speech;
- **None of voice and speech variables changed significantly after L-dopa intake as assessed by automatic analysis** (Table 3).
- Equally, separate analysis of non-demented and demented patients showed no modification of speech and voice variables following L-dopa intake.

CONCLUSION

- ❖ Speech is severely affected among LSPD patients.
- ❖ **No effect of L-dopa** was found on speech and voice by means of both automated analysis and clinical evaluation, although patients had a moderate positive motor response, even present for some axial signs, with the exception of speech.
- ❖ Our findings highlight the need to **assess the efficacy and applicability of alternative non-dopaminergic/non-pharmacologic** treatments to specifically target and improve communication of LSPD patients.