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Orofacial Strength and Voice Quality as Outcome of Levodopa Challenge Test in Parkinson Disease

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Objective: To assess the usefulness of orofacial strength and voice quality as assessment of response to levodopa challenge test (LCT) used in the diagnosis of early idiopathic Parkinson disease (IPD).

Study Design: Controlled Prospective Study.

Methods: From January 2014 to April 2019, patients with early IPD and healthy individuals were recruited and evaluated for clinical findings (Hoehn and Yahr scale; Unified Parkinson's Disease Rating Scale); Voice Handicap Index (VHI); grade of dysphonia, roughness, breathiness, asthenia, and strain and instability (GRBASI); maximal phonation time; phonation quotient; acoustic parameters; and orofacial muscle strength Oral Performance Instrument (IOPI; IOPI Medical, Woodinville, WA, USA) t) at baseline and 45 minutes after the levodopa intake (LCT).

Results: A total of 32 IPD patients and 20 healthy individuals completed the study. Healthy individuals exhibited better VHI, grade of dysphonia, breathiness, asthenia, strain, instability, and acoustic measurements (noise-related, tremor, F0 short- and mid-term and intensity short-term parameters) than healthy subjects. The mean values of muscle strength of lips, cheeks, fundamental frequency (F0), highest F0, and shimmer significantly improved from pre- to post-LCT in IPD patients. Healthy individuals did not exhibit significant changes of orofacial strength and voice quality assessment from pre- to post-LCT. Significant associations were found between clinical, orofacial strength, and some aerodynamic and acoustic measurements.

Conclusion: Orofacial strength and acoustic voice quality measurements may be used as objective outcomes of the LCT responsiveness in patients with early IPD.

Key Words: Parkinson, voice, strength, muscle, movement, speech, acoustic, aerodynamic, levodopa.

Level of Evidence: 3A.

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INTRODUCTION

Parkinson disease is the second most common neurodegenerative disorder, accounting for 2% to 3% of the U.S. population aged > 65 years.[1] The majority of cases are idiopathic Parkinson disease (IPD). Currently, the IPD diagnosis is mainly based on the clinical examination of patients who present muscle rigidity, tremors, and alterations in speech and gait.[1] According to some reports, 60% to 90% of patients have subtle voice and speech impairments at the time of diagnosis.[2–4] In practice, the clinical diagnosis is often challenging in the onset of the disease, when motor features are subtle.[5] For these doubtful cases, the neurologist may make an acute levodopa challenge test (LCT), which consists of the administration of a standardized dose of levodopa and the objectification of the reduction of the motor symptoms, for example, rigidity, bradykinesia, and resting tremor.[5,6] The nonresponder patients to LCT may benefit from additional examinations for supporting the diagnosis (DatSCAN). The clinical examination from pre- to post-LCT is usually made by a neurologist, who assesses the improvement of clinical findings according to his experience. The subjectivity of the assessment of the LCT response led some authors to use more objective approaches such as speech,[7] acoustic, or aerodynamic measurements.[8–11] However, none of these studies have included a control group with healthy subjects receiving levodopa. The inclusion of a control group makes sense according to the possible modulation of motor cortex excitability and muscle strength by levodopa in healthy individuals.[12] In that way, note that levodopa has recently been used in placebo/controlled trials and seems to be safe in healthy individuals.[13,14]

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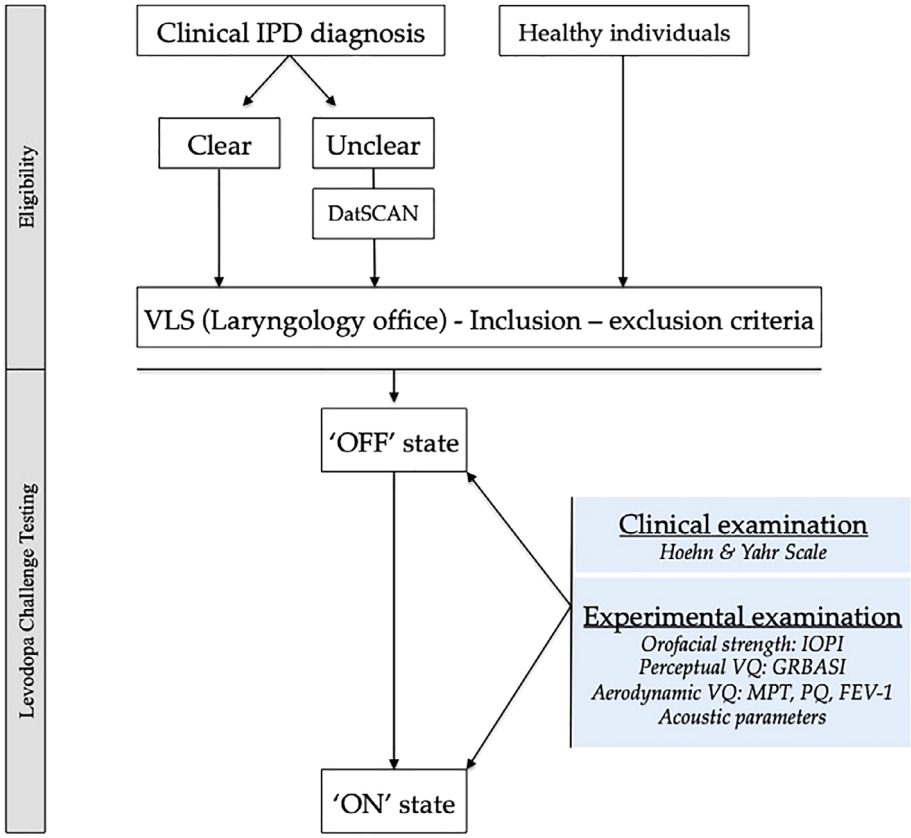

Fig. 1. Chart flow of the study. FEV-1 = forced expiratory volume in 1s; GRBASI = grade of dysphonia, roughness, breathiness, asthenia, strain, instability; IOPI = Iowa Oral Performance Instrument; IPD = idiopathic Parkinson disease; MPT = maximal phonation time; PQ = phonatory quotient; VLS = videolaryngostroboscopy; VQ = voice quality. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

The aim of this study is to investigate the evolution of orofacial strength and subjective, aerodynamic, and acoustic voice quality from pre- to post-LCT in patients with early IPD and in healthy individuals.

MATERIALS AND METHODS

Ethical Considerations

The local ethics committee approved the study protocol (ref. A2014/001). Patients and healthy individuals were invited to participate, and informed consent was obtained.

Subjects and Setting

From January 2014 to April 2019, a total of 34 patients with early IPD were prospectively recruited at the Neurology Departments of the EpiCURA hospital network (Baudour and Ath hospitals, Belgium, Baudour, Ath.). The diagnosis of IPD was made by an experienced neurologist on the basis of the clinical examination, LCT, and in doubtful cases, realization of a DatSCAN. The control group was composed of 20 healthy individuals matched for age and sex ratio. Healthy subjects were recruited in the investigator caregivers and in the University of Mons staff (UMons, Mons, Belgium).

Prior to their inclusion, an experienced otolaryngologist examined patients and healthy individuals through videolaryngostroboscopic (StrobeLED-CLL-S1, Olympus Corporation, Hamburg, Germany) to exclude some vocal fold abnormalities. The white balance was systematically realized before laryngeal examination. The following parameters have been considered for the vocal fold examination: vocal fold aspect, vocal fold mobility, symmetry, mucosa wave, regularity/uniformity, and amplitude.

In the same vein, the following comorbidities that may impact voice and speech qualities were excluded: psychiatric illness; smoker; alcohol dependence; upper respiratory tract infection within the last month; untreated laryngopharyngeal reflux

TABLE I.
Characteristics of Parkinson Patients and Healthy Individuals.

	Parkinson (N = 32)		Healthy (N = 20)		
Characteristics	m ± SD	Range	m ± SD	Range	*P* Value
Age					
Mean ± SD	69.4 ± 10.7	40–84	67.2 ± 10.8	41–82	.323
Gender					
Male	23	72%	16	75%	.514
Female	9	28%	4	25%	
BMI	27.7 ± 4.8		27.5 ± 4.8		.749
Clinical characteristics					
Hoehn and Yahr scale	2.8 ± 0.9		0.8 ± 0.7		.001
UPDRS	40.6 ± 15.0		—		—

BMI = body mass index; m = mean; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.

TABLE II.
Orofacial Strength and Voice Quality Characteristics of Study Groups.

Characteristics	NV	Parkinson (N = 32)	Healthy (N = 20)	*P* Value
Orofacial strength (IOPI)				
Tongue	+	39.2 ± 15.6	45.6 ± 9.0	.276
Lips	+	21.0 ± 10.0	26.2 ± 9.5	.080
Right cheek	+	21.5 ± 7.2	23.9 ± 8.1	.219
Left cheek	+	19.9 ± 7.2	24.4 ± 8.3	.028
Voice quality (subjective)				
Voice Handicap Index	–	19.5 ± 17.5	1.9 ± 3.7	.001
Grade of dysphonia	–	1.5 ± 0.6	0.4 ± 0.5	.001
Roughness	–	0.6 ± 0.6	0.5 ± 0.5	.839
Breathiness	–	1.1 ± 0.8	0.1 ± 0.3	.002
Asthenia	–	1.1 ± 0.8	0.4 ± 0.7	.040
Strain	–	1.2 ± 0.8	0.1 ± 0.3	.001
Instability	–	1.8 ± 0.9	0.1 ± 0.3	.001
Voice quality (objective)				
Aerodynamic measurements				
Maximum phonation time	+	11.7 ± 6.0	14.7 ± 8.0	.110
Vital capacity	+	2,852.6 ± 681.4	3,243.5 ± 986.9	.068
Phonatory quotient	–	340.9 ± 288.6	263.1 ± 164.6	.652
Forced expiratory volume 1s	+	2,206.3 ± 785.6	2,458.0 ± 978.7	.352
Main acoustic parameters				
Fundamental frequency				
F0	–*	128.3 ± 28.6	112.9 ± 24.3	.035
Fhi	+	156.9 ± 40.4	165.9 ± 113.1	.137
Fl0	–	111.5 ± 26.2	99.4 ± 23.4	.035
F0 short-term perturbation cues				
Jitt	–	3.3 ± 4.7	1.6 ± 1.2	.026
RAP	–	2.0 ± 3.1	0.9 ± 0.7	.024
PPQ	–	1.9 ± 2.2	0.9 ± 0.8	.023
sPPQ	–	2.5 ± 1.9	1.9 ± 1.8	.071
F0 mid-term perturbation cues				
PFR	–	6.7 ± 3.7	7.4 ± 8.4	.150
SD	–	7.0 ± 7.1	5.7 ± 8.7	.022
vF0	–	5.2 ± 5.0	4.5 ± 6.0	.084
Intensity short-term perturbation cues				
Shim	–	10.1 ± 9.4	6.8 ± 3.4	.029
APQ	–	7.8 ± 5.5	5.5 ± 2.7	.025
sAPQ	–	11.0 ± 3.1	9.9 ± 3.7	.214
Intensity mid-term perturbation cues				
vAm	–	23.0 ± 9.1	22.1 ± 10.3	.598
Noise-related measurements				
VTI	–	0.06 ± 0.02	0.04 ± 0.01	.023
SPI	+	17.4 ± 11.0	23.9 ± 12.6	.023
NHR	–	0.2 ± 0.1	0.1 ± 0.0	.003
Tremor parameters				
Fatr	–	3.4 ± 0.8	2.7 ± 1.5	.006
Fftr	–	3.6 ± 1.0	3.3 ± 1.5	.880
ATRI	–	6.2 ± 3.1	4.5 ± 3.1	.029
FTRI	–	0.9 ± 0.5	1.0 ± 1.8	.042

For each measurement, the direction of improvement is mentioned as + when the improvement consists of an increases of the value or as – when the improvement consists of a decrease of the measure.

*F0 should be higher in normal female and lower in normal male. Regarding the high prevalence of males in both groups, we considered a lower F0 as better.

APQ = amplitude perturbation quotient; ATRI = Amplitude Tremor Intensity Index; F0 = fundamental frequency; Fl0 = lowest F0; Fhi = Highest F0; Fatr = amplitude tremor frequency; Fftr = fundamental frequency tremor; FTRI = Fo-Tremor Intensity Index; IOPI = Iowa Oral Performance Index; Jitt = jitter percent; NHR = noise harmonic ratio; NV = normal values; PFR = phonatory fundamental frequency range; PPQ = pitch perturbation quotient; RAP = relative average perturbation; sAPQ = smoothed amplitude perturbation quotient; Shim = shimmer percent; sPPQ = smoothed pitch perturbation quotient; SD = standard deviation of F0; SPI = solft phonation index; vAm = peak-to-peak amplitude variation; vF0 = fundamental frequency variation; VTI = voice turbulence index.

disease; previous history of neck surgery or trauma; benign vocal fold lesions; malignancy; history of ear, nose, and throat radiotherapy; and active seasonal allergies or asthma.

Levodopa Challenge Test

Patients and healthy individuals received a standardized dose of levodopa (375 mg) for performing clinical, orofacial strength, and voice quality assessments and, once the diagnosis was confirmed, they were treated by conventional medical treatment of IPD (Fig. 1).

Clinical, Orofacial Strength, and Voice Quality Evaluations

Patients and healthy individuals were assessed before (time [t] 0) and 45 minutes after the levodopa intake (t1). The patient staging was made at baseline through the Unified Parkinson's Disease Rating Scale (UPDRS). whereas the neurologist assessed the clinical stabilization with Hoehn and Yahr scale at t0 and t1.

The muscle strength of tongue, lips, and cheeks, all involved in speech, was determined from pre- to post-LCT with Iowa Oral Performance Instrument (IOPI; IOPI Medical, Woodinville, WA, USA).

The subjective voice quality was assessed with Voice Handicap Index (VHI) (t0) and grade, roughness, breathiness, asthenia, strain, and instability (GRBASI) (blinded assessment by an experienced speech therapist at t0 and t1). To validate the perceptual evaluations, the speech therapist performed the evaluations on voice recordings (balanced text and sustained vowel /a/) respecting a test–re-test procedure that exhibited good intrarater

TABLE III.
Orofacial Strength and Voice Quality Changes in Parkinson Patients from Pre- to Post-Levodopa Challenge Testing.

Outcomes	NV	t0	t1	*P* Value
Orofacial strength (IOPI)				
Tongue	+	39.2 ± 15.6	41.3 ± 14.6	.100
Lips	+	21.0 ± 10.0	24.8 ± 9.1	.008
Right cheek	+	21.5 ± 7.2	24.4 ± 7.9	.001
Left cheek	+	19.9 ± 7.2	22.8 ± 7.8	.027
Voice quality (subjective)				
Grade of dysphonia	–	1.5 ± 0.6	1.2 ± 0.5	.059
Roughness	–	0.6 ± 0.6	0.7 ± 0.7	.564
Breathiness	–	1.1 ± 0.8	0.7 ± 0.6	.011
Asthenia	–	1.1 ± 0.8	0.5 ± 0.6	.001
Strain	–	1.2 ± 0.8	0.8 ± 0.8	.034
Instability	–	1.8 ± 0.9	1.0 ± 0.9	.012
Voice quality (objective)				
Aerodynamic measurements				
Maximum phonation time	+	11.7 ± 6.0	11.5 ± 6.4	.172
Vital capacity	+	2,852.6 ± 681.4	2,872.0 ± 817.3	.879
Phonatory quotient	–	340.9 ± 288.6	288.8 ± 170.9	.211
Forced expiratory volume 1s	+	2,206.3 ± 785.6	2,305.2 ± 707.2	.071
Main acoustic parameters				
Fundamental frequency				
F0	–*	128.3 ± 28.9	130.5 ± 29.9	.028
Fhi	+	156.9 ± 40.4	178.9 ± 72.4	.048
Fl0	–	111.5 ± 26.2	111.2 ± 21.3	.315
F0 short-term perturbation cues				
Jitt	–	3.3 ± 4.7	2.4 ± 2.0	.206
RAP	–	2.0 ± 3.1	1.4 ± 1.1	.256
PPQ	–	1.9 ± 2.2	1.5 ± 1.2	.256
sPPQ	–	2.5 ± 1.9	2.6 ± 2.3	.991
F0 mid-term perturbation cues				
PFR	–	6.7 ± 3.7	8.0 ± 5.5	.255
STD	–	7.0 ± 7.1	7.4 ± 7.8	.538
vF0	–	5.2 ± 5.0	5.2 ± 4.6	.905
Intensity short-term perturbation cues				
Shim	–	10.1 ± 9.4	8.1 ± 3.5	.043
APQ	–	7.8 ± 5.5	6.7 ± 2.5	.074
sAPQ	–	11.0 ± 3.1	10.5 ± 3.3	.144
Intensity mid-term perturbation cue				
vAm	–	23.0 ± 9.1	23.4 ± 11.8	.417
Noise-related measurements				
VTI	–	0.06 ± 0.02	0.05 ± 0.02	.524
SPI	+	17.4 ± 11.0	16.7 ± 8.9	.940
NHR	–	0.2 ± 0.1	0.2 ± 0.1	.352
Tremor parameters				
Fatr	–	3.4 ± 0.8	3.9 ± 1.1	.078
Fftr	–	3.6 ± 1.0	3.9 ± 1.1	.336
ATRI	–	6.2 ± 3.1	6.8 ± 4.8	.770
FTRI	–	0.9 ± 0.5	1.0 ± 0.6	.738

(Continues)

TABLE III.
Continued

For each measurement, the direction of improvement is mentioned as + when the improvement consists of an increases of the value or as – when the improvement consists of a decrease of the measure.

*F0 should be higher in normal female and lower in normal male. Regarding the high prevalence of males in both groups, we considered a lower F0 as better.

APQ = amplitude perturbation quotient; ATRI = Amplitude Tremor Intensity Index; F0 = fundamental frequency; Fatr = Amplitude Tremor Frequency; Fftr = Fundamental Frequency Tremor; FTRI=Fo-Tremor Intensity Index; IOPI = Iowa Oral Performance Index; Jitt = jitter percent; NHR = noise harmonic ratio; NV = normal values; PFR = phonatory fundamental frequency range; PPQ = pitch perturbation quotient; RAP = relative average perturbation; sAPQ = smoothed amplitude perturbation quotient; Shim = shimmer percent; sPPQ = smoothed pitch perturbation quotient; STD = standard deviation of F0; vAm = peak-to-peak amplitude variation; vF0 = fundamental frequency variation.

reliability (Spearman correlation coefficient > 0.600 for all GRBASI items).

The objective voice quality assessments consisted of acoustic and aerodynamic measurements. Maximum phonation time (MPT), forced expiratory volume in 1s (FEV1), and phonatory quotient (PQ) were measured using a calibrated spirometer (Spiro-USB100; Medical Electronic Construction, Brussels, Belgium). The PQ consists of the ratio between vital capacity (mL) and MPT (s). Subjects were asked to produce the vowel /a/ three times at a distance of 30 cm from the microphone (Sony PCM-D50; Brussels, Belgium) in a sound-treated room. We used MDVP software, version 2012 (KayPentax, Montvale, New Jersey, USA) to measure acoustic parameters, including fundamental frequency (F0), standard deviation (SD) of F0, fundamental frequency variation (vF0), jitter percent (Jitt), relative average perturbation (RAP), pitch perturbation quotient (PPQ), smoothed pitch perturbation quotient (sPPQ), phonatory fundamental frequency range (PFR), shimmer percent (Shim), amplitude perturbation quotient (APQ), smoothed amplitude perturbation quotient (sAPQ), peak-to-peak amplitude variation (vAm), and noise harmonic ratio (NHR). To these usual parameters, we also measured the following voice tremor indexes: Fo-Tremor Intensity Index (FTRI), Amplitude Tremor Intensity Index (ATRI), amplitude tremor frequency (Fatr), and fundamental frequency tremor (Fftr). The acoustic parameters were determined for the entire signal of the three sustained vowel productions (with the exclusion of the first and the last second because of their instability). Moreover, a study of relationships between Hoehn and Yahr scale, UPDRS, IOPI data, VHI, and objective voice quality measurements have been conducted.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences for Windows (SPSS version 22.0; IBM Corp. Armonk, NY). According to the distribution of data, the comparison of the mean values of orofacial strength and aerodynamic and acoustic measurements along the LCT were made with the Wilcoxon signed-rank test. The comparison between groups (t0) was made through Mann–Whitney U test. The association

TABLE IV.
Orofacial Strength and Voice Quality Changes in Healthy Individuals from Pre- to Post-Levodopa Challenge Testing.

Outcomes	NV	t0	t1	*P* Value
Orofacial strength (IOPI)				
Tongue	+	45.6 ± 9.0	46.9 ± 9.0	.234
Lips	+	26.2 ± 9.5	26.1 ± 9.3	.905
Right cheek	+	23.9 ± 8.1	23.6 ± 7.8	.627
Left cheek	+	24.4 ± 8.3	26.2 ± 7.2	.076
Voice quality (subjective)				
Grade of dysphonia	–	0.4 ± 0.5	0.4 ± 0.5	.990
Roughness	–	0.5 ± 0.5	0.6 ± 0.5	.564
Breathiness	–	0.1 ± 0.3	0.3 ± 0.7	.157
Asthenia	–	0.4 ± 0.7	0.3 ± 0.5	.317
Strain	–	0.1 ± 0.3	0.1 ± 0.3	.990
Instability	–	0.1 ± 0.3	0.2 ± 0.4	.317
Voice quality (objective)				
Aerodynamic measurements				
Maximum phonation time	+	14.7 ± 8.0	14.7 ± 8.0	.970
Vital capacity	+	3,243.5 ± 986.9	3,243.5 ± 986.9	.478
Phonatory quotient	–	263.1 ± 164.6	263.1 ± 154.6	.841
Forced expiratory volume 1s	+	2,458.0 ± 978.7	2,554.0 ± 1,042.2	.169
Main acoustic parameters				
Fundamental frequency				
F0	–*	112.9 ± 24.3	120.7 ± 27.6	.247
Fhi	+	165.9 ± 113.1	178.9 ± 72.4	.940
Fl0	–	99.4 ± 23.4	107.8 ± 26.2	.108
F0 short-term perturbation cues				
Jitt	–	1.6 ± 1.2	1.8 ± 1.4	.455
RAP	–	0.9 ± 0.7	1.0 ± 0.8	.502
PPQ	–	0.9 ± 0.8	1.1 ± 0.9	.478
sPPQ	–	1.9 ± 1.8	1.9 ± 1.6	.654
F0 mid-term perturbation cues				
PFR	–	7.4 ± 8.4	6.2 ± 5.5	.445
STD	–	5.7 ± 8.7	4.9 ± 6.4	.391
vF0	–	4.5 ± 6.0	3.9 ± 4.2	.709
Intensity short-term perturbation cues				
Shim	–	6.8 ± 3.4	6.5 ± 4.1	.332
APQ	–	5.5 ± 2.7	5.3 ± 3.3	.370
sAPQ	–	9.9 ± 3.7	9.1 ± 4.0	.204
Intensity mid-term perturbation cue				
vAm	–	22.1 ± 10.3	21.1 ± 10.8	.232
Noise-related measurements				
VTI	–	0.04 ± 0.01	0.05 ± 0.01	.271
SPI	+	23.9 ± 12.6	23.3 ± 11.3	.970
NHR	–	0.1 ± 0.0	0.2 ± 0.1	.467
Tremor parameters				
Fatr	–	2.7 ± 1.5	2.8 ± 1.2	.370
Fftr	–	3.3 ± 1.5	3.7 ± 1.5	.117
ATRI	–	4.5 ± 3.1	3.9 ± 2.9	.709
FTRI	–	1.0 ± 1.8	0.8 ± 0.5	.709

For each measurement, the direction of improvement is mentioned as + when the improvement consists of an increases of the value or as – when the improvement consists of a decrease of the measure.

*F0 should be higher in normal female and lower in normal male. Regarding the high prevalence of males in both groups, we considered a lower F0 as better.

APQ = amplitude perturbation quotient; ATRI = Amplitude Tremor Intensity Index; F0 = fundamental frequency; Fl0 = lowest F0; Fhi = Highest F0; Fatr = amplitude tremor frequency; Fftr = fundamental frequency tremor; FTRI = Fo-Tremor Intensity Index; IOPI = Iowa Oral Performance Index; Jitt = jitter percent; NHR = noise harmonic ratio; NV = normal values; PFR = phonatory fundamental frequency range; PPQ = pitch perturbation quotient; RAP = relative average perturbation; sAPQ = smoothed amplitude perturbation quotient; Shim = shimmer percent; sPPQ = smoothed pitch perturbation quotient; SPI = solft phonation index; STD = standard deviation of F0; vAm = peak-to-peak amplitude variation; vF0 = fundamental frequency variation; VTI = voice turbulence index.

between clinical, voice, and speech data was studied through linear multiple regression. A level of significance of .05 was adopted.

RESULTS

A total of 32 IPD patients and 20 healthy individuals were included. Two patients were excluded due to differential diagnoses (Parkinson-plus disease). The mean age of IPD patients and healthy individuals was 69.4 ± 10.7 (40–84) and 67.2 ± 10.8 (41–82), respectively. Cohorts were comparable regarding age, sex ratio, and body mass index (Table I). At baseline, the mean Hoehn and Yahr score of IPD patients was 2.8 ± 0.9 and significantly improved from pre- to post-LCT to 0.8 ± 0.7. The mean t0 UPDRS was 40.6 ± 15.0. The videolaryngostroboscopy (VLS) was unremarkable in the majority of subjects. Three IPD patients had the following VLS abnormalities: mucosal wave amplitude reduction (N = 1), supraglottal strain (ventricular band contraction, N = 1), and glottal insufficiency (N = 1).

Baseline Differences Between IPD Patients and Healthy Individuals

The mean values of tongue, lips, and right cheek muscle strengths were lower in IPD patients than in healthy individuals, but only the mean values of left cheek muscle strength exhibited significant differences between groups. About voice quality, both subjective (GRBASI) and objective (F0, Flo, Jitt, RAP, PPQ, SD, Shim, APQ, VTI, SPI, NHR, Fatr, ATRI, FTRI) voice quality assessments were significantly better in healthy subjects compared to IPD patients (Table II).

Pre- to Post-LCT Orofacial Strength and Voice Quality Evaluations

IOPI measurements reported a significant improvement of lips and cheek muscle strengths from pre- to post-LCT in IPD patients. The mean scores of breathiness, asthenia, strain, and instability significantly decreased from t0 to t1. There was no significant improvement of aerodynamic measurements. The mean values of F0, Fhi, and Shim significantly improved from pre- to post-LCT (Table III).

IOPI measurements, perceptual voice quality, and acoustic and aerodynamic assessments did not significantly change from pre- to post-LCT in healthy individuals (Table IV).

Relevant Associations Between Clinical, Orofacial Strength, and Voice Quality Evaluations

Potential associations have been investigated at baseline in IPD patients. Significant positive association was identified between the clinical state (UPDRS) and the VHI score ($P = .007$). Negative associations were found between the grade of dysphonia and the following evaluations: tongue muscle strength ($P = .042$), vital capacity ($P = .023$), and FEV1 ($P = .029$). There were positive significant associations between F0 and the following aerodynamic measurements: MPT ($P = .013$) and PQ ($P = .001$). The association between MPT and vAm (intensity mid-term perturbation parameter) was significantly negative ($P = .011$).

DISCUSSION

The symptoms of IPD are quite similar to those of other neurological conditions, and approximately 5% to 10% of IPD patients are misdiagnosed.[6,15] The misdiagnosis of IPD may be related to the phenotypic heterogeneity in both the disease and the levodopa responsiveness, as well as the subjectivity of the diagnosis approach, which is still based on the neurologist clinical examination.[15] Thus, over the past decades, an increasing number of studies have been conducted for investigating the reliability of some objective approaches evaluating the motor changes of IPD from pre- to post-LCT, for example, speech and voice quality measurements.[4,8–11,16]

The first part of the study reports that early-stage IPD patients have both subjective and objective voice quality impairments compared to healthy individuals. From an objective standpoint, healthy individuals exhibited better values of noise-related, tremor, F0 short- and mid-term, and intensity short-term parameters than IPD patients. The IPD deterioration of these acoustic measurements may be explained by the impairment of the contraction of adductor, abductor, and tensor laryngeal muscles during the phonation. The perturbation of the laryngeal muscle contraction leads to modifications of the biomechanical properties of both the cover and the body of the vocal cords, which is characterized by short- and mid-term F0 and intensity parameter perturbations.[17] In the same vein, the impairment of some parameters evaluating the voice tremor (Fatr, ATRI, and FTRI) would be related to the occurrence of tremor in the muscle contraction, which is detected by the acoustic analysis. The higher F0 of IPD patients may be explained by a disruption of the muscle balance between the thyroarytenoid (vocal) and the cricoarytenoid muscles; the latter being more powerful than the vocal muscle[18] and less impacted by the early neuromuscular degeneration. Similar results were partly found in studies that investigated the voice quality in early-stage IPD patients and healthy individuals.[19] Precisely, Holmes et al. reported better values of jitter and some F0 parameters in healthy subjects compared to IPD patients, corroborating our results.[19] Note that these authors measured the acoustic parameters through a different method than our own, which may significantly impact the results of the acoustic analyses.[20]

These changes in the vibration process of the vocal cover are still subtle, and they may not be systematically seen in the VLS examination of early-stage IPD patients in comparison with patients with mid- to long history of the disease.[21,22] The lack of sensitivity of the VLS examination in patients with early-stage IPD strengthens the interest of acoustic measurements in the detection of early voice quality disorder.

The linear regression analysis exhibited some associations between aerodynamic and acoustic measurements in IPD patients. The relationship between aerodynamic and acoustic measurements in not new because they directly or indirectly evaluate the same thing: the phonation process. There was no association between voice quality and IOPI evaluations, which supports the well-known heterogeneity in the neuromuscular deterioration of the various muscle groups.[6]

In the second part of the study, we demonstrated that the orofacial strength and some acoustic parameters may be useful for assessing the responsiveness of LCT and, indirectly, may be used for the IPD diagnosis. Precisely, the smooth musculature (cheeks and lips) exhibited better (significant) improvements from pre- to post-LCT than the tongue musculature that did not significantly improve. The useful of IOPI measurements for speech quality assessment has previously been reported in a small number of studies, but no prior study has used it in the Parkinson disease.[23,24] The results of the present study confirm those of a preliminary study that we have conducted on 20 IPD patients.[16] In this study, we demonstrated the useful of voice and muscular strength measurements as outcomes of the levodopa efficacy in IPD patients. However, the low number of patients and the lack of healthy controls limited us to drawn conclusion.

The results of the second part of this study show that perceptual and acoustic voice quality assessments may be useful for the assessment of the levodopa responsiveness. Our enthusiasm for the perceptual voice quality evaluations is, however, limited because the results of these analyses strongly depend of the experience of the rater.[16,25] In addition, the analyses have to be performed in a blind manner to avoid evaluation bias, which complicates their use in clinical practice. Acoustically, shimmer and some F0-related acoustic parameters

significantly improved from pre- to post-LCT, suggesting an improvement of the laryngeal muscle function. In clinical practice, both neurologists and laryngologists often reported that patients with early IPD often have voice loudness impairments. Shimmer is an acoustic measurement of the short-term intensity perturbation of the voice quality. Interestingly, in a recent systematic review of studies assessing voice quality changes over the LCT, shimmer has been identified as the best acoustic parameter for exhibiting the laryngeal muscle improvement from pre- to post-LCT.[4] Thus, the realization of the acoustic measurements is easy and reliable in laryngology office.

The improvement of F0-related acoustic parameters from pre- to post-LCT corroborates the observations of many studies conducted over the past decade.[9–11,26] However, it is important to specify that none of these studies included IPD patients at the diagnosis time, limiting the comparison with our results. From a pathophysiological standpoint, as found for shimmer, the improvement of F0-related acoustic parameters may be due to the improvement of the function of the following laryngeal muscles: cricoarytenoid, thyroarytenoid, and posterior cricoarytenoid muscles (vertical fibers). Overall, the comparison with the studies available in the literature must be cautious because the IPD is characterized by a phenotypic heterogeneity in both the clinical presentation and the responsiveness to levodopa.[6] Thus, the potential discrepancies between studies would be due to differences in the patient profile (e.g., stage, axial vs. lateral disease, comorbidities), which may continuously limit the comparison between studies.

In clinical practice, we have realized that the conduct of this study substantially helped our neurologist to make the IPD diagnosis, especially in patients with unusual disease-presentation. Indeed, beyond the neurological examination and the walking test, IOPI and acoustic measurements provided objective evaluations of muscular strength along the LCT. The value of this approach for the IPD diagnosis is strengthened by the lack of significant changes in healthy individuals from pre- to post-LCT.

The composition of a control group is the main strength of this study because it has been suggested that the administration of levodopa in healthy subjects would be susceptible to impact the motor cortex excitability[12] and the related muscle strength. To our knowledge, no similar controlled study has previously been conducted. However, our control group is small, which is due to the difficulty of convincing healthy individuals to take levodopa.

The main limitations of the present study are the lack of consideration of voice intensity, the low number of patients, and the lack of investigation of the predictive values of both orofacial and voice quality responses to LCT on the sustained, long-term dopaminergic therapeutic response once the patients are stabilized.[27] Such investigations would make sense regarding recent preliminary studies, suggesting that the orofacial and the laryngeal motor benefits of the intake of the standardized dose of levodopa (LCT) may be lost when the patient is stabilized.[16]

CONCLUSION

The use of orofacial muscular strength and acoustic measurements may be an interesting objective approach to evaluate the levodopa responsiveness of patients with early IPD. These findings are strengthened by the lack of changes of orofacial muscular strength and acoustic measurements in healthy subjects from pre- to post-LCT. Future controlled studies with larger groups of patients and healthy individuals are needed to validate the useful of orofacial and voice quality measurements in the establishment of IPD diagnosis through LCT.

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