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Speech prosody impairment predicts cognitive decline in Parkinson's disease

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ABSTRACT

Background: Impairment of speech prosody is characteristic for Parkinson's disease (PD) and does not respond well to dopaminergic treatment.
Objectives: We assessed whether baseline acoustic parameters, alone or in combination with other predominantly non-dopaminergic symptoms may predict global cognitive decline as measured by the Addenbrooke's cognitive examination (ACE-R) and/or worsening of cognitive status as assessed by a detailed neuropsychological examination.
Methods: Forty-four consecutive non-depressed PD patients underwent clinical and cognitive testing, and acoustic voice analysis at baseline and at the two-year follow-up. Influence of speech and other clinical parameters on worsening of the ACE-R and of the cognitive status was analyzed using linear and logistic regression.
Results: The cognitive status (classified as normal cognition, mild cognitive impairment and dementia) deteriorated in 25% of patients during the follow-up. The multivariate linear regression model consisted of the variation in range of the fundamental voice frequency (F_0VR) and the REM Sleep Behavioral Disorder Screening Questionnaire (RBDSQ). These parameters explained 37.2% of the variability of the change in ACE-R. The most significant predictors in the univariate logistic regression were the speech index of rhythmicity (SPIR; $p = 0.012$), disease duration ($p = 0.019$), and the RBDSQ ($p = 0.032$). The multivariate regression analysis revealed that SPIR alone led to 73.2% accuracy in predicting a change in cognitive status. Combining SPIR with RBDSQ improved the prediction accuracy of SPIR alone by 7.3%.
Conclusions: Impairment of speech prosody together with symptoms of RBD predicted rapid cognitive decline and worsening of PD cognitive status during a two-year period.

1. Introduction

Early detection of Parkinson's disease (PD) patients who are at risk of dementia (PD-D) is important for managing patient care as well as for clinical trials of preventive drugs. The major risk factors for developing PD-D are higher age, more severe parkinsonism associated with postural instability and gait difficulty, and mild cognitive impairment at the time of evaluation [1]. Many other demographic and clinical features have been assessed as potential risk factors, but the findings have been inconsistent.

Mild cognitive impairment (MCI) is present in about 25% of PD patients and it is characterized by the subjective and objective deterioration of cognitive functions with retention of normal social life and daily functioning [2,3].

Dysprosody seems to be the most characteristic feature of Parkinsonian hypokinetic dysarthria [4] and can be subdivided into

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further dimensions, including speech intensity, pitch variation, speech rate, and regularity. Some acoustic variables reflecting speech prosody seem to correlate with axial non-dopaminergic motor symptoms and seem to reflect the disease progression at later stages better than dopamine-responsive motor symptoms present on extremities [4–7]. Speech prosody impairment in PD does not correlate with limb motor symptoms and does not respond well to either dopaminergic treatment or deep brain stimulation [8,9]. Some authors had hypothesized that pitch and speech rate control were related to non-dopaminergic rather than dopaminergic impairment in PD [4,7]. Speech impairment, as assessed by a subjective evaluation of speech production rated on a 0–4 scale of the Unified Parkinson's Disease Rating Scale, part III (UPDRS III) [10], was an important motor variable related to dementia in a six-year prospective study that followed 24 PD patients without axial motor impairment at baseline [11]. Of note, no studies exist that would specifically address this issue using a detailed acoustic voice analysis in a prospective longitudinal study.

We performed a two-year longitudinal study in consecutive non-depressed patients with mild to moderate PD. We used a detailed cognitive and clinical examination and an acoustic voice analysis in order to assess whether baseline speech prosodic parameters, alone or in combination with other predominantly non-dopaminergic PD symptoms, might predict cognitive decline in this patient group.

2. Methods

Altogether, 50 consecutive non-depressed patients with PD [12] were enrolled in the longitudinal prospective study. For demographic and clinical data, see Tables 1 and 2. None of the patients had a disease affecting the central nervous system other than PD. Following questionnaires and scales were used to evaluate clinical symptoms of PD: Beck Depression Inventory (BDI) [13], Unified Parkinson's Disease Rating Scale, part III: Motor Examination (UPDRS III) [10], non-motor symptoms scale (NMSS30) [14], freezing of gait questionnaire (FOG) [15], REM sleep behavioral disorder screening questionnaire (RBDSQ) [16]. Since the PD phenotype with postural instability and gait difficulty (PIGD) is associated with cognitive decline in PD [1–3] we also identified PD with PIGD [17,18]. All of the assessments were conducted in the ON state on dopaminergic medication. Patients were on levodopa ± dopamine agonist ± COMT (catechol-o-methyl-transferase) inhibitor. None of the patients were on antipsychotic treatment at the time of examination or suffered from hallucinations, illusions, or psychosis. All PD-D patients received cholinesterase inhibitors. The study was approved by the local ethics committee, and all patients signed an informed consent form.

Global cognition was assessed by a neuropsychologist using Addenbrooke's cognitive examination (ACE-R) [19]. In line with other studies [20], we showed that ACE-R can be successfully administered for screening PD-MCI and PD-D [21].

We used the ACE-R as an instrument to examine the magnitude of global cognitive decline during the follow-up period. In addition, based on neuropsychological testing results and the clinician's interview with the patient and a caregiver, the subjects were classified into one of three cognitive categories at baseline and at the follow-up visit: PD with normal cognition (PD-NC), PD with mild cognitive impairment (PD-MCI), and PD dementia (PD-D) according to level II published criteria [1,3]. Both continuous "change in the ACE-R" and categorical "worsening of cognitive status" (YES or NO) were used in our regression models. More specifically, "worsening of cognitive status" referred to either worsening from PD-NC to PD-MCI or worsening from PD-MCI to PD-D. PD-MCI was defined as a cognitive decline reported by the patient, carer, or clinician with a performance of 1.5 standard deviations (SD) below the mean for an age-matched control population on two or more tests from a detailed neuropsychological

Table 1
Demographic and clinical data according to cognitive status change at the follow-up visit (*continuous variables*).

Variable	Total			Stable/improved cognitive status			Cognitive status worsening			p-value
	N	Mean ± SD	Median (min-max)	N	Mean ± SD	Median (min-max)	N	Mean ± SD	Median (min-max)	
Age (years)	44	66.0 ± 6.9	66.0 (49.0–80.0)	33	65.4 ± 6.9	65.0 (49.0–80.0)	11	67.8 ± 7.0	70.0 (54.0–77.0)	0.312
Education (years)	44	13.9 ± 2.7	13.0 (9.0–18.0)	33	14.0 ± 2.7	13.0 (9.0–18.0)	11	13.6 ± 3.0	13.0 (9.0–18.0)	0.682
PD duration (years)	44	7.8 ± 4.7	6.5 (2.0–22.0)	33	6.7 ± 3.5	6.0 (2.0–16.0)	11	11.0 ± 6.4	10.0 (3.0–22.0)	**0.007**
LED (mg/day)	44	1 073.7 ± 581.4	918.8 (150.0–2 185.5)	33	1 042.3 ± 602.3	870.0 (150.0–2 108.3)	11	1 167.7 ± 528.9	931.0 (600.0–2 185.5)	0.542
BDI	38	9.3 ± 5.4	8.5 (3.0–26.0)	28	9.5 ± 5.5	9.0 (3.0–26.0)	10	9.0 ± 5.3	8.0 (3.0–21.0)	0.819
FOG quest.	44	5.8 ± 5.6	4.0 (0.0–18.0)	33	5.2 ± 5.5	2.0 (0.0–18.0)	11	7.6 ± 5.9	7.0 (0.0–18.0)	0.225
NMSS30	44	36.4 ± 22.9	33.5 (2.0–112.0)	33	35.0 ± 21.0	34.0 (2.0–87.0)	11	40.4 ± 28.6	33.0 (12.0–112.0)	0.510
RBDSQ	44	3.5 ± 3.1	3.0 (0.0–13.0)	33	2.9 ± 2.7	2.0 (0.0–13.0)	11	5.5 ± 3.8	5.0 (1.0–12.0)	**0.017**
UPDRS III	44	23.0 ± 11.0	25.0 (5.0–52.0)	33	22.0 ± 10.0	22.0 (5.0–41.0)	11	28.0 ± 13.0	27.0 (5.0–52.0)	0.108
MMSE	44	28.4 ± 1.5	29.0 (24.0–30.0)	33	28.6 ± 1.5	29.0 (24.0–30.0)	11	27.9 ± 1.4	28.0 (26.0–30.0)	0.226
ACE-R 1 - total score (baseline visit)	44	89.0 ± 7.3	90.5 (74.0–100.0)	33	89.9 ± 7.2	92.0 (74.0–100.0)	11	86.4 ± 7.3	88.0 (74.0–97.0)	0.166
ACE-R 2 – total score (follow-up visit)	44	85.2 ± 9.7	87.0 (51.0–97.0)	33	87.4 ± 6.9	88.0 (70.0–97.0)	11	78.6 ± 13.5	79.0 (51.0–96.0)	**0.007**
*E*VR (TSK 5)	44	0.625 ± 0.698	0.383 (0.024–2.962)	33	0.714 ± 0.779	0.385 (0.077–2.962)	11	0.358 ± 0.222	0.251 (0.024–0.753)	0.145
*E*SD (TSK 5)	44	0.076 ± 0.083	0.039 (0.005–0.327)	33	0.087 ± 0.093	0.045 (0.013–0.327)	11	0.043 ± 0.026	0.031 (0.005–0.093)	0.132
F_0VR (TSK 3)	44	136.9 ± 69.9	115.4 (34.7–283.5)	33	131.4 ± 67.0	113.2 (34.7–283.5)	11	153.3 ± 78.9	132.4 (43.1–263.6)	0.373
relF_0SD (TSK 3)	44	0.171 ± 0.089	0.144 (0.071–0.518)	33	0.160 ± 0.088	0.140 (0.071–0.518)	11	0.202 ± 0.087	0.204 (0.090–0.351)	0.174
relF_0VR (TSK 3)	44	0.818 ± 0.451	0.640 (0.273–1.949)	33	0.769 ± 0.431	0.635 (0.273–1.949)	11	0.966 ± 0.499	0.829 (0.389–1.679)	0.213
F_0SD (TSK 3)	44	28.8 ± 14.3	26.7 (9.0–80.0)	33	27.7 ± 14.3	26.1 (9.0–80.0)	11	32.2 ± 14.2	33.4 (12.2–55.2)	0.374
F_0VR (TSK 2)	43	185.3 ± 64.8	205.2 (54.0–290.0)	32	192.6 ± 64.3	209.6 (54.0–290.0)	11	164.4 ± 64.3	155.6 (81.5–261.9)	0.217
relF_0VR (TSK 2)	43	1.137 ± 0.503	1.100 (0.439–2.340)	32	1.139 ± 0.506	1.103 (0.439–2.340)	11	1.131 ± 0.517	0.989 (0.545–2.077)	0.965
SPIR (TSK 4)	41	0.032 ± 0.010	0.033 (0.014–0.053)	31	0.035 ± 0.010	0.034 (0.014–0.053)	10	0.025 ± 0.007	0.025 (0.016–0.035)	**0.005**
F_0VR (TSK 1)	44	287.5 ± 12.6	290.9 (247.8–299.9)	33	288.0 ± 11.5	291.0 (248.7–299.9)	11	285.9 ± 16.1	290.8 (247.8–299.1)	0.624

PD – Parkinson's disease, LED – daily levodopa equivalent dose, BDI – Beck Depression Inventory, FOG – Freezing of Gait, NMSS30 – total score of Non-Motor Symptoms Scale, RBDSQ – REM Sleep Behavior Disorder Screening Questionnaire, UPDRS III – Unified Parkinson's Disease Rating Scale (part III), MMSE – Mini Mental State Examination, ACE-R – Addenbrooke's Cognitive Examination, revised, F_0VR – fundamental frequency variation range, F_0SD – standard deviation of fundamental frequency, relF_0VR – relative fundamental frequency variation range, relF_0SD – relative standard deviation of fundamental frequency, *E*VR – squared energy operator variation range, *E*SD – standard deviation of squared energy operator, SPIR – speech index of rhythmicity.

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