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Speech difficulties in early *de novo* patients with Parkinson's disease

Sotirios Polychronis, MSc,[1]* Flavia Niccolini, MD,[1]* Gennaro Pagano, MD,[1] Tayyabah Yousaf, MSc,[1] and Marios Politis, MD, PhD, FRCP, FEAN[1]

[1]Neurodegeneration Imaging Group, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London, London, United Kingdom

*These authors contributed equally

Address correspondence to: Professor Marios Politis, MD, MSc, PhD, FRCP, FEAN; Neurodegeneration Imaging Group, Maurice Wohl Clinical Neuroscience Institute Institute of Psychiatry, Psychology & Neuroscience (IoPPN), 125 Coldharbour Lane, Camberwell, London, SE5 9NU, Telephone: +44-207-8485682, email: marios.politis@kcl.ac.uk website: http://nig-politis.com/

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Co., F. Hoffman-La Roche, Ltd., GE Healthcare, Genentech, GlaxoSmithKline, Lundbeck, Merck, MesoScale, Piramal, Pfizer and UCB.PPMI. Industry partners are contributing to PPMI through financial and in-kind donations and are playing a lead role in providing feedback on study parameters through the Industry Scientific Advisory Board (ISAB). Through close interaction with the study, the ISAB is positioned to inform the selection and review of potential progression markers that could be used in clinical testing. Mr Polychronis, Dr. Niccolini, Dr. Pagano, Ms Tayyabah Yousaf and Dr. Politis report no disclosures.

Potential Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

ABSTRACT

INTRODUCTION: Speech difficulties are a common debilitating feature of Parkinson's disease and we aimed to investigate whether speech difficulties are associated with striatal dopaminergic deficits and faster disease progression.

METHODS: Using the Parkinson's Progression Markers Initiative database, 143 early *de novo* Parkinson's disease patients with speech difficulties were identified and matched 1:1 with 143 Parkinson's disease patients without speech difficulties for age, disease duration, motor symptoms severity. We investigated differences in clinical features and striatal [^{123}I]FP-CIT single photon emission computed tomography (SPECT) uptake in Parkinson's disease patients with and without speech difficulties. Cox proportional hazards analysis was carried out to investigate whether speech difficulties were predictive of a faster motor progression and cognitive decline.

RESULTS: Speech difficulties were more common in patients with akinetic-rigid motor compared to tremor-dominant phenotype. Parkinson's disease patients with speech difficulties had lower resting tremor (P=0.027), higher autonomic dysfunction (P=0.034) and increased daytime sleepiness (ESS; P=0.048) compared to those without speech difficulties. Parkinson's disease patients with speech difficulties had significant lower [^{123}I]FP-CIT uptake in the striatum (P<0.001), caudate (P=0.003) and putamen (P<0.001) compared to those without speech difficulties. The presence of speech difficulties was a predictor of cognitive decline [Hazard Ratio (HR): 0.341, 95% Confidence Interval (CI): 0.153–0.759; Wald: 6.945; P=0.008), whereas had no influence on motor progression (HR: 0.885, 95% CI: 0.662–1.183; Wald: 0.680; P>0.10).

CONCLUSION: Speech difficulties are associated with greater autonomic dysfunction, excessive daytime sleepiness and striatal dopaminergic deficit, and predictive of faster cognitive decline in early Parkinson's disease.

Keywords: Parkinson's disease; Speech difficulties; Cognitive decline; SPECT.

INTRODUCTION

Speech difficulties are very common and debilitating features of Parkinson's disease (PD) occurring in up to 90% of the patients over the course of the disease, and significantly affecting their social interactions and quality of life[1]. Changes in voice and speech have been reported in early drug-naïve PD patients[2, 3] and even as early as five years prior to PD diagnosis[4]. Speech difficulties in PD, collectively termed as hypokinetic dysarthria, are characterized by reduced voice amplitude, monotone, breathy, hoarse voice quality, and imprecise articulation[5]. It has been suggested that hypokinetic dysarthria is the result of bradykinesia and rigidity of the laryngeal muscles due to dopaminergic deficits[6-8]. However, previous studies investigating the effects dopamine replacement therapy on speech performance in PD yielded inconsistent results showing either no effects of dopamine replacement therapy on speech parameters[8-11], or improvements in speech intelligibility, endurance and pitch variability following levodopa treatment in PD patients[7, 12-15]. Thus, the mechanisms underlying speech abnormalities in PD are still poorly understood and little is known on their prognostic value on PD progression. Here, we investigated whether speech difficulties are associated with presynaptic dopaminergic deficits using [^{123}I]FP-CIT single photon emission computed tomography (SPECT) molecular imaging; and whether speech difficulties are linked to progression of symptoms in early *de novo* PD patients.

METHODS

Participants and clinical evaluation

From the 412 PD patients included in the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data), a total of 353 early *de novo*

PD patients had a complete three-year follow-up and were included in the analysis. All PD patients were recruited between 2010-2015, diagnosed with PD less than two years prior to a screening visit, never treated with dopamine replacement therapy and presented with two among bradykinesia, resting tremor and rigidity or with asymmetric resting tremor/bradykinesia at screening. The diagnosis was confirmed by the presence of dopaminergic deficit at [^{123}I]FP-CIT SPECT imaging.

The presence of speech difficulties was defined according to the Unified PD Rating Scale Part-III (UPDRS-III), Item 3.1 (Speech) ≥ 1. This item is a clinician-based scale consisting of 5 scores, rating between 0 (normal) and 4 (most severe impairment). Using propensity scores, 143 PD patients with speech difficulties were matched 1:1 with 143 PD patients without speech difficulties for age, disease duration, UPDRS-III. All matching variables were balanced after propensity scores.

Motor symptom severity was assessed with the UPDRS-III and staged with the Hoehn and Yahr (H&Y) scale. UPDRS-III score was calculated excluding Item 3.1 (Speech). Each motor domain (bradykinesia, resting tremor, rigidity, postural instability) was calculated using specific UPDRS-III sub-items as follows: bradykinesia (Total score range 0–52) = sum of Item 3.4 finger tapping, item 3.5 hand movements, item 3.6 pronation-supination movements of hands, item 3.7 toe tapping, item 3.8 leg agility, item 3.9 arising from chair, item 3.13 posture and item 3.14 body bradykinesia; rigidity (Total score range 0–20) = sum of Item 3.3 rigidity (neck, upper limbs and lower limbs); resting tremor (total score range 0–

24) = sum of item 3.17 rest tremor amplitude (lip/jaw, upper limbs and lower limbs) and item 3.18 constancy of tremor; axial (total score range 0–12) = sum of item 3.10 gait, item 3.11 freezing of gait and item 3.12 postural stability[16]. UPDRS-II score was calculated excluding Item 2.1 (Speech).

PD motor phenotypes were identified as either tremor-dominant or akinetic-rigid using the numerical ratio, which was derived from a patient's mean tremor score and mean akinetic-rigidity score[17]. Patients with ratio < 0.8 were classified as akinetic-rigidity phenotype, patients with ratio > 1.0 were classified as tremor-dominant phenotype and patients with ratio between 0.8 and 1 were classified as mixed subtype. Non-motor symptoms were assessed using UPDRS-I and the Scale for Outcomes for PD–Autonomic function (SCOPA-AUT). Neuropsychiatric symptoms were assessed with the short version of the 15-item Geriatric Depression Scale (GDS) and the State Trait Anxiety Total scale (STAI). Sleep disorders were assessed with the Epworth Sleeping Scale and REM sleep behavior disorder questionnaire (RBDQ). Cognitive impairment was measured using the Montreal cognitive assessment (MoCA). Olfactory dysfunction was measured by the University of Pennsylvania Smell Identification Test (UPSIT). Disability was estimated using the Modified Schwab & England Activity of Daily Living (ADL).

This study is registered with ClinicalTrials.gov (No: NCT01141023). Each PPMI site has received approval from an ethical committee on human experimentation before the study's initiation. Written informed consent for research was obtained from all individuals participating in the study. The present study was written according to the STROBE guidelines[18].

Dopaminergic imaging

SPECT images were obtained 4±0.5 h after administrating an injection of approximately 185 MBq [^{123}I]FP-CIT. [^{123}I]FP-CIT SPECT scans were analysed following the imaging technical operations manual (http://ppmi-info.org/). Raw SPECT data was acquired into a 128 x 128 matrix stepping each 3 degrees for a total of 120 (or 4 degrees for a total of 90) projections in a window centered on 159±10%KeV. The total scan duration was 30-45 minutes. A Chang 0 attenuation correction was applied using a customised *Mu* determined empirically from the anthropomorphic brain phantom acquired at each site. A standard Gaussian 3D 6.0mm filter was applied to each image volume and then normalised to standard Montreal Neurologic Institute space. Each scan was interpreted by two independent readers who were blinded to the subjects' demographics and characteristics. For quantification, SPECT image volumes were spatially normalized to an Ioflupane template. The eight most prominent axial slices containing striatum were summed and then a standardized volume of interest (VOI) template was applied to this image. VOI analyses were performed on the left and right caudate and putamen with the occipital region serving as a reference tissue. Specific binding ratios (SBR) were calculated as the ratio of the caudate or putamen VOI count density divided by count density of the occipital cortex minus 1. This measure approximates the binding potential, BP_{ND}, when the tracer is in equilibrium at the target site and was previously reported with Ioflupane SPECT[19].

Assessment of motor progression and cognitive decline

Motor progression was defined as a change of one point in the H&Y scale at each follow-up visit. Cognitive decline was defined as MoCA score of ≤22 at the

follow-up visits. Follow-up visits took place in the outpatient unit of the reference hospitals once every 12 months. All early *de novo* PD patients were followed up for a three-year period.

Statistical analysis

Statistical analysis and graph illustration were performed with SPSS (version 20) and GraphPad Prism (version 6.0c) for MAC OS X, respectively. For all variables, variance homogeneity and Gaussianity were tested with Kolmogorov-Smirnov test.

Group comparisons between PD patients with and without speech difficulties were carried out using the Student *t*-test (parametric variables) and Mann-Whitney U test (non-parametric variables) as appropriate. Categorical variables were compared using a χ^2 test, *P*-values for each variable were calculated following Bonferroni's multiple comparisons test. We interrogated correlations between the speech scores and imaging data using Spearman's rank correlation and we applied Bonferroni's multiple comparisons test. To investigate whether speech difficulties were predictive of a faster disease progression and development of cognitive impairment, two Cox proportional hazards analyses were carried out investigating the presence of speech difficulties as predictor of: (1) motor progression; (2) cognitive decline. The analyses have been repeated including age and gender as covariate. The time to occurrence of the first event in a category for a given subject was used in the Cox model. All data are presented as mean ± standard deviation (SD), and the level α was set for all comparisons at $P<0.05$, corrected.

RESULTS

Clinical characteristics

Speech difficulties were more common in *de novo PD* patients with akinetic-rigid motor compared to tremor-dominant phenotype (100/84; 69.9% *vs* 27/43; 18.9%, $P<0.05$).

In order to avoid biases due to motor symptoms severity and disease duration, we performed a case-control analysis matching for age, disease duration and UPDRS-III. With regards to UPDRS-III motor subscores, PD patients with speech difficulties had lower resting tremor ($P=0.027$) and global tremor ($P=0.027$) scores compared to those without speech difficulties. No difference was observed in bradykinesia, rigidity and postural instability subscores between the two groups (all $P>0.10$; Table 1).

Early *de novo* PD patients with speech difficulties had higher autonomic dysfunction ($P=0.034$) and increased daytime sleepiness (ESS; $P=0.048$) compared to patients without speech difficulties. There were no differences in UPDRS-I, UPSIT and RBDQ scores, anxiety/depressive symptoms, cognitive function and ADL between *de novo* PD patients with and without speech difficulties (all $P>0.10$; Table 1).

Imaging assessment: presynaptic dopaminergic function

Early *de novo* PD patients with speech difficulties had lower [^{123}I]FP-CIT uptakes in the striatum ($P<0.001$), caudate ($P=0.003$) and putamen ($P=0.003$) compared to those without speech difficulties (Table 2; Figure 1A and 1C). Worse speech

scores at the UPDRS-III item 3.1 were associated with lower [^{123}I]FP-CIT uptakes in the striatum (r_s=−0.24; P<0.001), caudate (r_s=−0.21; P=0.006) and putamen (r_s=−0.23; P<0.001; Figure 1B).

Motor progression and cognitive decline

Over a period of three years, 151 (42.8%) *de novo* PD patients showed motor progression and 27 (7.6%) of them developed cognitive impairment. Cox proportional hazards analysis showed that the presence of speech difficulties in early *de novo* PD patients predicts cognitive decline at a three-year follow-up [Hazard Ratio (HR): 0.341, 95% Confidence Interval (CI): 0.153–0.759; Wald: 6.945; P=0.008; Figure 2], whereas has no influence on PD motor progression (HR: 0.885, 95% CI: 0.662–1.183; Wald: 0.680; P>0.10). These results were confirmed after the inclusion of age and gender as covariate.

DISCUSSION

Our findings indicate that early *de novo* PD patients with speech difficulties have greater autonomic dysfunction, excessive daytime sleepiness and striatal dopaminergic deficit compared to a cohort of PD patients without speech difficulties independently from disease duration, age and severity of overall motor symptoms. Moreover, the presence of speech difficulties in early *de novo* PD patients is linked to an increased risk of cognitive decline.

We found a 42.8% prevalence of speech difficulties in our cohort of 353 early *de novo* PD patients, in line with previous studies showing that speech difficulties can occur in about 40% of early untreated PD patients[3]. Speech difficulties were more

common in akinetic-rigid PD patients. Increased bradykinesia and rigidity were the motor symptoms specifically associated with speech difficulties suggesting that speech impairment in PD may be linked to bradykinesia and rigidity of laryngeal muscles. A recent study investigating longitudinal changes of speech in 55 early *de novo* PD patients has shown that worse speech performance according to quantitative acoustic vocal evaluation and UPDR-III (Speech) item 3.1 was associated with increased UPDRS-III motor scores and bradykinesia subscores[20]. At follow-up assessment, improvements in speech performance were closely related to dopamine replacement therapy and antiparkinsonian treatment-related improvements in motor symptoms and particularly in bradykinesia subscores[20].

Other studies have found a significant correlation between speech abnormalities and axial symptoms, in particular freezing of gait, in moderate PD patients who were on dopamine replacement therapy[15, 21, 22]. We did not find significant differences in axial subscores between early *de novo* PD patients with and without speech difficulties. This discrepancy may be explained by the different stages of the PD cohorts examined and the presence/absence of dopamine replacement therapy.

We found that early *de novo* PD patients had significant lower striatal [^{123}I]FP-CIT levels compared to those without speech difficulties and that lower striatal presynaptic dopaminergic function was associated with higher speech impairment. To our knowledge, this is the first study showing a link between striatal presynaptic dopaminergic deficits and speech impairment in PD. Previous positron emission tomography (PET)[23-26] and functional magnetic resonance (fMRI)

studies[27, 28] have investigated neuronal substrates of speech difficulties in PD. These neuroimaging studies have shown abnormal activation of the basal ganglia–cerebellum–cortex circuit with altered recruitment of the orofacial motor cortex, supplementary motor cortex, cerebellum and an increased involvement of the premotor and prefrontal cortices in moderate PD patients on dopamine replacement therapy[27, 28]. A recent fMRI study, investigating speech related resting state functional connectivity in the ON and OFF medication states, showed an association between levodopa-induced changes in caudate-dorsolateral prefrontal cortex connectivity and speech improvement in PD patients suggesting a link between dopamine deficits and speech impairment in PD[27].

Among the non-motor symptoms, PD patients with speech difficulties showed worse dysautonomic dysfunction and excessive daytime sleepiness whereas anxiety, depressive symptoms and cognitive function did not differ between the two groups. Interestingly, we found that the presence of speech difficulties was associated with an increased risk of cognitive decline but did not predict motor progression over a three-year follow-up period. Two studies have investigated the role of PD-related speech difficulties in predicting cognitive dysfunction in smaller cohorts of PD patients[29, 30] . Gago and colleagues[29] found that speech impairment progression, as measured by the UPDRS-III (Speech) was the strongest predictor of dementia over a six-year period in 24 early stage PD patients without axial motor impairment at baseline. PD patients with speech difficulties showed more rapid declines at the Mini Mental Status Examination, Clock Drawing, Semantic Verbal Fluency and Block Design neuropsychological tests[29]. Subsequently, a more recent study using quantitative acoustic vocal assessment

showed that variation in the range of the fundamental voice frequency and in specific the speech index of rhythmicity can predict changes in cognitive status as measured by the Addenbrooke's cognitive examination with 73.2% accuracy over a 2-year period[30]. Our study extends previous preliminary observations and provides robust evidence for the link and predictive role of speech impairment in the development of cognitive decline in a very large cohort of early stage patients with PD.

A limitation of our study includes the absence of quantitative acoustic vocal assessment to assess speech difficulties in PD patients. However, the use of the clinician-based scale such as the UPDRS-III (Speech) item 3.1 may provide a simple tool for clinician to follow-up the progression of speech difficulties and monitor closely those PD patients who will be more likely to develop cognitive impairment.

Our findings demonstrate that speech difficulties are associated with higher striatal dopaminergic deficits and worse symptomatology in early PD and are predictive of a faster cognitive decline.

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AUTHORSHIP

S.P. and M.P. conceived the study and conceptualized the experimental design. F.N., and G.P. gave input to experimental design. F.N. and S.P. wrote the first draft and prepared the manuscript. G.P., F.N. and S.P. performed the statistical analysis. F.N., S.P. and T.Y. generated the figures. F.N., M.P., S.P., G.P. interpreted the data. All authors revised and gave input to the manuscript.

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FIGURE LEGEND

Figure 1. Presynaptic dopaminergic deficit in the group of early de novo Parkinson's disease patients with speech difficulties. (A) Box-plot showing decreased [^{123}I]FP-CIT uptakes in the striatum, caudate and putamen of early *de novo* PD patients with speech difficulties. **(B)** Correlations between the degree of speech impairment (UPDRS-III, item 3.1) and [^{123}I]FP-CIT uptake in the striatum (r_s=−0.24; P<0.001), caudate (r_s=−0.21; P=0.006) and putamen (r_s=−0.23; P<0.001) of early *de novo* PD patients; ***P<0.001; **P<0.01. **(C)** [^{123}I]FP-CIT SPECT images in Parkinson's disease patients with and without speech difficulties. (Top) 55-year-old healthy control showing typical [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 3.41) and putamen (SBR: 2.49) (Middle) 55-year-old male without speech difficulties exhibiting slight dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 2.43) and putamen (SBR: 1.19); (Bottom) 55-year-old male with speech difficulties demonstrating larger striatal dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 1.22) and putamen (SBR: 0.455).

Figure 2. Overall survival curves for the development of cognitive impairment regarding to the presence of speech difficulties. Patients with speech difficulties had an increased risk of developing cognitive impairment compared to those without speech difficulties (Log Rank (Mantel-Cox)=7.702; HR: 0.341, 95% CI: 0.153–0.759; Wald: 6.945; P=0.008).