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Freezing of gait in early Parkinson's disease: Nigral iron content estimated from magnetic resonance imaging

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ABSTRACT

Purpose: Freezing of gait is a major source of disability associated with the progression of Parkinson's disease (PD). Our objective was to determine whether evolving changes in nigral iron content in association with declining motor function in early PD differentiates subjects who develop freezing from those who do not.
Methods: A cohort of previously untreated individuals with early PD (n = 19) was followed for 36 months clinically and with MRI. The cohort was divided into two groups based on the development of freezing during follow-up. A multiple gradient echo MRI sequence provided an index of basal ganglia iron content.
Results: There were significant baseline differences between those who developed freezing (n = 7) and those who did not (n = 12) in Unified Parkinson's Disease Rating Scale motor scores, time to complete a 14 m walk and timed up and go. There was a significant correlation between the measured change in transverse relaxation in the lateral substantia nigra pars compacta and the change in motor score from baseline to 36 months (p = 0.002). The freezing group showed a greater change in motor score and iron content than did the non-freezing group.
Conclusions: Individuals destined to develop freezing early in PD have more motor impairment at baseline, more rapid deterioration in motor function, and pars compacta changes suggestive of increased iron content in comparison to those who do not.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder. It is both a motor disorder characterized by varying combinations of rest tremor, rigidity, bradykinesia, and gait/balance impairment and a non-motor disorder with features including disturbances of speech, autonomic function, sleep, cognition and mood [1].

The primary change underlying many of the motor features of PD is a gradual loss of dopaminergic neurons projecting from substantia nigra compacta (SNc) to striatum, resulting in decreased striatal dopamine (DA) content. A decrease of ~30% of striatal DA neurons, leading to ~80% decrease in striatal DA precedes the emergence of clinical features of PD, recently reviewed by Burke and O'Malley [2]; motor symptoms then gradually worsen with further dopamine depletion. Lateral SNc neuronal loss has been reported to be particularly correlated with the clinical motor features of PD [3,4]. We have previously shown a significant correlation in early PD between the degree of lateral SNc pathology as indicated by increasing iron content (estimated from MRI) and measures of disease severity that reflect a longitudinal decline in motor function over three years [5].

An important source of disability in PD that emerges and worsens with disease progression is gait impairment, including freezing of gait (FOG) [6]. Freezing of gait refers to a transient reduction or absence of forward progression when there is an intention to walk [6]. It manifests as start hesitation, turning hesitation, target hesitation and open-area hesitation. The unpredictable nature of freezing episodes is associated with increased falls, negatively impacting health-related quality of life. The response of FOG to dopaminergic replacement therapy is variable and complicated. In some individuals, FOG episodes improve with levodopa (OFF freezing) while other episodes (ON freezing) may be resistant to or even exacerbated by the addition of levodopa. Little is known about the pathological substrates underlying this debilitating feature of PD.

While many reports of early PD rely on disease duration to define a group as "early", there is often little attention paid to potential clinical heterogeneity within a cohort with relatively similar disease duration. The primary objective of this study was to determine if changes midbrain pathology, reflected in the MRI estimate of nigral iron content, were associated differently with declining motor function in a cohort

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of previously untreated PD subjects divided into two subgroups: one who developed FOG over three years of follow-up compared to one who did not.

2. Methods

2.1. Subjects

The PD participants presented in this study are part of a larger longitudinal project, other parts of which have been published previously [5,7–9]. We recruited 19 subjects with early, untreated PD from the University of Alberta Movement Disorders Program in Edmonton, Alberta, Canada. All fulfilled standard criteria for a clinical diagnosis of PD [10] as assessed by a movement disorders neurologist (WM). The subjects had participated in a previous study examining presynaptic dopaminergic function measured with dihydrotetrabenazine/PET, and all exhibited striatal PET abnormalities that were consistent with a diagnosis of PD [8]. None of these mildly affected participants required symptomatic treatment with levodopa or other dopaminergic medications at the start of the study. If dopaminergic therapy was initiated for treatment of PD symptoms after baseline assessments, subjects were subsequently examined in the clinically defined "OFF" state, a minimum of 12 h after the last ingestion of dopaminergic medication at subsequent time points in order to obviate the effects of medication on underlying disease state. Assessments were administered by one investigator (MW). A variety of clinical tools were used to assess subjects including the Unified Parkinson's Disease Rating Scale (UPDRS) [11], Mini-Mental State Exam (MMSE) [12], Timed Up and Go [13], 14 m walk (with turn), Berg Balance Test [14] and the Parkinson's Disease Questionnaire (PDQ-39) [15]. The self-reported PDQ-39, assessing eight areas of health and daily activities affecting quality of life, was used to calculate a single index score to give an indication of health-related quality of life. Participants were followed for 36 months with clinical evaluations and MRI scans completed at baseline, 18 and 36 months. Patients were divided into FOG and noFOG groups based on the development of freezing of gait during the 36 month follow-up period. The development of FOG was based on the value of UPDRS II #14 ≥ 1 (rare freezing when walking, may have start hesitation). The study was approved by the Human Research Ethics Board of the University of Alberta and all subjects gave written informed consent.

2.2. MRI data acquisition

MRI data were acquired using a Magnex 3 T research magnet (Magnex Scientific Ltd., Abingdon, U.K.) with actively shielded gradients, controlled with a Surrey Medical Imaging Systems console (Surrey Medical Imaging Systems, Ltd., Guildford, U.K). We used a multiple gradient echo sequence designed for rapid and optimal single-scan mapping of the proton transverse relaxation rate, R_2^* ($R_2^* = 1/T_2^*$), developed by our group [16]. A series of gradient echo images for each slice was acquired at echo times (TE) ranging from 5 ms to 55 ms in 10 ms intervals for a total of six images and a repetition time of 428 ms. With the aid of sagittal gradient echo scout images to guide slice placement, two sets of images were acquired. The first set was comprised of four 5 mm thick slices on a plane at 45° from a plane containing the anterior commissure (AC) and the posterior commissure (PC), as reported previously [5], with the PC placed in the center of the slab of slices. These images provided data for the red nucleus (RN) and substantia nigra (SN). The second set of images consisted of five 5 mm thick slices with the slice plane placed 10° from the plane containing both the AC and PC [5]. This second set provided data for the globus pallidus (GP) and putamen (Pu). The field of view for both sets of images was 300 × 300 mm^2 with 128 × 128 data points acquired and with the matrix subsequently zero-filled to 256 × 256 points for both sets of slices yielding an in-plane resolution of 1.2 × 1.2 mm^2. The total scan time for each participant was approximately 30 min. In order to optimise the reproducibility of voxel placement on follow-up MR scans, the set of scout images for each subject on follow-up scans was compared by visual assessment of anatomical landmarks to those obtained at baseline to ensure identical slice placement on longitudinal studies.

2.3. Image processing and analysis

Image processing and analysis was performed using custom software written in MATLAB (The MathWorks, Inc., Natick, MA). From the series of echo images, R_2^* was determined using a voxel-wise least-squares fit to

$$\ln(M) = (-R_2^*)(TE) + b$$

where M is the signal intensity for a particular voxel in the echo image acquired at TE and b is the intercept. In principle, b = 0 in this relationship; however, it is included to account for experimental variability and improve the fit. Averaged values from selected voxels gave a measure of region specific R_2^* value (s^{-1}). As previously described [5,7], regions-of-interest (ROIs) were drawn on the substantia nigra pars reticulata (SNr), and SNc which were then subdivided into medial and lateral components. The SNr was identified as the band of low signal in the ventrolateral midbrain, while the region between the SNr and the RN was considered to represent the SNc. In the forebrain, ROIs were drawn on the GP and Pu by reference to a standard neuroanatomical atlas. ROI placement on follow-up studies was optimised by direct visual comparison to those placed on baseline images. The individual responsible for ROI analysis (MG) was blinded to the development of FOG to avoid potential bias.

2.4. Statistical methods

Demographic data were compared using t-tests and Fisher exact tests. The R_2^* values were compared between FOG and noFOG subjects using a longitudinal repeated measures analysis of variance in which the within-subject factor was the time point, with three levels (baseline, 18 months, and 36 months), and the between-subject factor was the group, with two levels. For each subject, we obtained a measure of R_2^* change over time by performing a linear regression of R_2^* value versus scan time (baseline, 18, and 36 month) to obtain R_2^* slope (s^{-1}/scan). The R_2^* slope values were then compared to the change clinical measures (month 36 value - baseline value) using linear regression; the Pearson correlation coefficient, r^2, and associated p-value are reported since data were normally distributed. The clinical measures reported include the MMSE, UPDRS III, Timed Up and Go, Berg Balance Test, 14 metre walk and PDQ-39 mobility sub-score. The sequentially rejective Bonferroni correction for multiple comparisons was applied to the p-values. Statistical analysis was performed using IBM SPSS Statistics Version 21.0 for Windows (IBM Corp., Armonk, NY).

3. Results

Baseline demographics are summarized in Table 1. The two groups, i.e. those who developed FOG (n = 7) during 36 months of follow-up and those who did not (noFOG; n = 12), did not differ at baseline with respect to age, disease duration, education or cognitive status (as reflected by the MMSE score), or the PDQ39. There were, however, significant baseline differences between the groups in UPDRS III scores, time to complete a 14 m walk with turn, the Berg Balance Scale and Timed Up and Go.

By month 36, only 6/12 noFOG subjects had initiated dopaminergic therapy while all 7 FOG participants had initiated dopaminergic therapy. The FOG group had a significantly higher levodopa equivalent dose (p = 0.02; Table 2) [17].