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Association of freezing of gait with nigral iron accumulation in patients with Parkinson's disease

Rajini M. Naduthota[a], Arush Arun Honnedevasthana[e], Abhishek Lenka[a,b], Jitender Saini[c], Sairam Geethanath[e], Rose Dawn Bharath[c], Rita Christopher[d], Ravi Yadav[a], Arun Kumar Gupta[c], Pramod Kumar Pal[a,*]

[a] Department of Neurology, National Institute of Mental Health & Neurosciences, Hosur Road, Bangalore 560029, Karnataka, India
[b] Department of Clinical Neurosciences, National Institute of Mental Health & Neurosciences, Hosur Road, Bangalore 560029, Karnataka, India
[c] Department of Neuroimaging and Interventional Radiology, National Institute of Mental Health & Neurosciences, Hosur Road, Bangalore 560029, Karnataka, India
[d] Department of Neurochemistry, National Institute of Mental Health & Neurosciences, Hosur Road, Bangalore 560029, Karnataka, India
[e] Medical Imaging Research Center, Dayanand Sagar Institutions, Kumara Swamy Layout, Bangalore 560078, India

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ABSTRACT

Background and purpose: The objective of this work was to investigate whether patients with and without freezing of gait (FOG) in Parkinson's disease (PD) have differences in iron accumulation in substantia nigra using R2* relaxometry.

Materials and methods: This study included seventeen PD patients with FOG [FOG (+)], equal number of age and gender matched patients without FOG [FOG (−)] and 34 healthy controls (HC). T2* images were obtained from a 3-Tesla MRI system using multi-echo sequence. R2* values were extracted from Substantia Nigra (SN) and red nucleus and were compared among the three groups and correlated with clinical findings.

Results: R2* values were increased in PD group as a whole compared to HC in rostral and caudal segments of Substantia Nigra pars compacta (SNc) and in Substantia Nigra pars reticulata (SNr) but not in red nucleus. Within PD subgroups, FOG (+) group had increased iron accumulation in SNc compared to FOG (−) and HC. FOG score positively correlated with R2* values in the caudal region of SNc in FOG (+) group.

Conclusions: Our study reveals higher nigral iron content in FOG (+) compared to FOG (−) and HCs. In addition, we observed positive correlation of FOG score with iron accumulation in SNc. Results of this study emphasize possible role of higher nigral iron content in the pathogenesis of FOG in PD.

1. Introduction

Parkinson's disease (PD) is a progressive, neurodegenerative disorder and its cardinal motor symptoms include tremor at rest, rigidity, bradykinesia and postural instability [1]. In addition, several non-motor symptoms such as cognitive impairment, depression, autonomic dysfunction, and sleep disturbances may emerge during the course of the illness [2]. Loss of dopaminergic neurons in substantia nigra (SN) along with accumulation of Lewy bodies in several parts of the brain is the pathological hallmark of PD [3]. Autopsy studies as well as neuroimaging studies have reported greater accumulation of iron in SN of patients with PD compared to healthy controls (HC) [4,5]. It has been speculated that excessive iron accumulation is partially responsible for generation of reactive oxygen species resulting in accelerated loss of dopaminergic neurons in SN in PD [6].

Disturbances of gait and balance are common in patients with PD. Freezing of gait (FOG) is one of the disabling disturbances related to gait characterized by episodic absence or marked reduction of forward progression of feet despite the intention to walk which lasts for a brief duration [7]. Although longer duration, higher stage and increased severity of PD have been reported to have association with FOG, exact neural correlates of FOG still remain elusive [8].

Several studies using advanced structural and functional neuroimaging techniques have attempted to explore the neural correlates of FOG in patients with PD. However, the results have not been uniform enough to draw any conclusive evidence. Studies based on structural neuroimaging have reported abnormalities in white matter tracts in pedunculopontine nucleus, orbitofrontal cortex, primary as well as supplementary motor cortex and widespread grey matter atrophy [9,10]. Functional neuroimaging studies have shown reduced inter-

* Corresponding author.
E-mail address: palpramod@nimhans.ac.in (P.K. Pal).

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hemispheric connectivity and altered functional connectivity in several neural networks including basal ganglia and cognitive networks [11,12].

R2* relaxometry is a noninvasive structural neuroimaging technique, used for the estimation of iron content in the brain [13]. As several studies have emphasized alterations in iron metabolism in patients with PD, R2* relaxometry becomes an important technique for objective quantification of iron deposition in basal ganglia of patients with PD. Most neuroimaging studies using R2* relaxometry [14,15] have reported increased iron level in the basal ganglia, especially in SN in patients with PD compared to HC. However, there is not enough literature on R2* relaxometry based studies in patients with FOG. Currently, there is only one published longitudinal R2* relaxometry study that has explored differential iron accumulation between PD patients with FOG [FOG (+)] and those without FOG [FOG (−)] [16]. As iron deposition in SN is common in PD, comparison of level of iron accumulation in SN of PD patients with and without FOG may provide more insights into the role of iron accumulation in emergence of FOG.

We undertook this study to explore the possibility of differential iron accumulation in patients with and without FOG and HCs using R2* relaxometry.

2. Materials and methods

2.1. Study population

The study population was selected from the Neurology outpatient department and Movement Disorder Clinics of a tertiary care neurological institute. A cohort of 17 (12 men and 5 women) consecutive FOG (+) patients and equal number of age and gender matched FOG (−) patients were recruited for this study. All patients were clinically examined by a single movement disorder neurologist and a diagnosis of clinically probable PD was made as per the UK Parkinson's Disease Society Brain Bank clinical criteria. The base-line demographic and clinical questionnaire included age, gender, age at onset of symptom, the motor score of the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) during best-ON and drug-OFF states, side of initial motor symptom, Hoehn and Yahr stage, Mini Mental State Examination (MMSE), medication details and handedness.

The presence and severity of FOG was assessed by applying the FOG questionnaire [17] to all the patients with PD. PD patients were classified as FOG (+) based on a score of ≥ 1 in the item number-3 of FOG questionnaire or an episode of FOG during clinical evaluation. All the seventeen patients in the FOG (+) group reported episodes of freezing during the OFF-state; in addition, three patients also provided history of freezing occasionally during ON-state. Majority of the patients were part of our published study, which explored the functional neuroimaging correlates of FOG [11]. Thirty-four age and gender matched, right-handed healthy controls (men: 24, women: 10) without any family history of neuropsychiatric illness were recruited from the hospital staff and patient caregivers. Institutional Ethics Committee approved this study and written informed consent was obtained from all the subjects.

2.2. Image acquisition and analysis

2.2.1. Image acquisition parameters

MRI data was acquired on a 3T MRI scanner (Philips Achieva 3T, Philips Medical Systems, Netherlands) using a 32-channel head coil. A multi gradient Fast Field Echo (FFE) sequence was used to estimate the transverse relaxation rate, R2* (R2* = 1/T2*). Five echos with TE ranging from 6.9 to 34.5 ms were obtained with following acquisition parameters: TR/TE1/delta TE (ms) = 39/6.9/6.9, flip angle = 5°, FOV = 100 mm × 100 mm × 96 mm, matrix = 132 × 100, slice thickness = 1.2 mm, total number of images were 192.

2.2.2. Selection of slice and preprocessing

Image processing and analysis were performed using in-house software written in MATLAB (The Math-Works, Inc., Natick, MA, USA) and in ImageJ (http://rsb.info.nih.gov/ij/) software. First, ImageJ was used to locate SN pars reticulata (SNr) and red nucleus. SNr was identified as the hypo-intense band between the ventro-lateral mid brain, whereas the region between SNr and red nucleus was considered as SN pars compacta (SNc) [18]. The prominent slice where red nucleus was clearly visible was labeled as dorsal segment. Subsequently we moved one slice below and labeled as ventral segment as most of the SN is known to present below red nucleus [19]. Dorsal segment was used to draw ROI in red nucleus and ventral segment was used to draw ROI in SNr and SNc.

2.2.3. Data processing and identification of region of interest

In this study, we have employed the curve fitting tool in MATLAB for estimating R2* maps.

The gradient echo (S) images were fit pixel by pixel from a mono-exponential equation:

$$S = S_0 e^{\left(-\frac{TE}{R2^*}\right)}$$

where S_0 and S are base signal intensity and intensities of rest of the images respectively. TE is the echo time and R2* is the relaxometry map obtained from fitting [20].

ROI was drawn manually on the SNr, SNc and red nucleus using MATLAB. As previous studies have documented differential degeneration pattern in SNr and SNc, and within caudal and rostral segments of SNc in PD [21], we drew separate ROIs for each region (Fig. 1). Red nucleus was also examined because of its anatomical proximity to SN. ROIs were drawn manually by tracing the borders in SNr and red nucleus. SNc was divided into rostral and caudal segments as explained by Vaillancourt et al. [21]. Circular ROIs were drawn in both rostral and caudal segments of SNc. Each circular ROI was 10 voxels in diameter, and each voxel was 0.297 mm and total volume of 26.2 mm^3. All the measurements were taken in triplicate and average was taken to avoid intra-rater variability.

2.3. Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (version 20.0, SPSS Inc., Chicago, USA) software. All the results were presented in mean ± SD for clinical parameters. Two-sample independent *t*-test or ANOVA was applied for continuous variables and Chi-square test was applied for comparing categorical variables. Bonferroni correction was applied when ANOVA result was found to be significant. A value of $p < 0.05$ was considered to be statistically significant. Pearson correlation analysis was performed between R2* star relaxometry values and clinical scores. Total SNc and SNr R2* relaxometry values were used for correlation analysis.

3. Results

3.1. Demographic and clinical characteristics

There was no significant difference in age, gender, age at onset of symptoms, duration of illness, UPDRS-III scores during drug-OFF state and MMSE scores between FOG (+) and FOG (−) groups. However, UPDRS-III scores during the best ON state, Hoehn and Yahr score and mean FOG questionnaire scores were more in FOG (+) group. In the overall PD cohort of 34 patients, 23 reported appearance of parkinsonian symptoms first on the right side, 9 on the left side and 2 patients had bilateral appearance of symptoms. Clinical and demographic details are provided in Table 1.