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Motor asymmetry and neuromelanin imaging: Concordance in Parkinson's disease

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ABSTRACT

Background: The onset of motor symptoms in Parkinson's disease (PD) is characteristically asymmetric and correlates with dopaminergic deficit of contralateral basal ganglia. This study explored the concordance between motor asymmetry and changes of substantia nigra pars compacta (SNc) using neuromelanin-sensitive imaging.
Methods: Forty-four subjects with PD and fifteen healthy controls were included in this study. Clinical laterality (CL) was based on the motor sub scores of the Unified Parkinson's Disease Rating Scale-Part III. All subjects underwent neuromelanin-sensitive imaging and imaging laterality (IL) was based on the differences between contrast ratios of the right and left lateral SNc. Concordance was evaluated by correlating CL and IL.
Results: Motor asymmetry at disease onset was reported in 97.72% of subjects with PD, of which 65.90% reported right-sided onset. Forty-three subjects were right-handed and 68.18% reported onset of symptoms on dominant side. Right CL was observed in 59.09%, left CL in 40.90%, right IL in 11.36% and left IL in 88.63%. Concordance was established in 61.36%, majority of whom had a combination of right CL and left IL. In healthy controls, a significantly lower contrast ratio of the left lateral SNc was also noted.
Conclusions: Handedness may correlate with motor asymmetry and left hemisphere may have a predilection for neurodegeneration. The finding of significant neuronal loss of left SNc in controls warrants further evaluation for better understanding of motor asymmetry in PD. Neuromelanin sensitive imaging can be a useful tool to study the relationship between motor asymmetry and nigrostriatal dysfunction.

1. Introduction

The onset of motor symptoms in Parkinson's disease (PD) is characteristically asymmetric in nature [1] and this asymmetry has been frequently correlated with contralateral basal ganglia dopaminergic deficit [2]. Despite this observation being well established, the precise mechanism determining this asymmetry remains unclear.

Progressive degeneration of the pigmented dopaminergic neurons in the A9 region of the substantia nigra pars compacta (SNc) is considered to be key in the pathogenesis of PD, and preferential degeneration of the lateral ventral tier has been well reported [3,4]. Loss of striatal dopaminergic nerve endings secondary to the loss of ascending nigrostriatal projections is well visualized with imaging techniques such as ^{18}F-dopa positron emission tomography (PET) and dopamine-transporter single-photon emission computed tomography (DAT SPECT). Several studies have explored the relationship of motor asymmetry with contralateral dopaminergic deficit by utilizing the above methods [2,5,6].

Neuromelanin is a by-product of dopamine and noradrenaline metabolism, hence is present in the SNc and locus coeruleus [7]. Depigmentation of these regions secondary to loss of neuromelanin is a conspicuous pathological feature in PD. Neuromelanin-sensitive imaging (NMSI) is a technique first described by Sasaki et al. [8], which permits direct visualization of the neuromelanin in the SNc. Isaias et al. [9], have reported that this method can be used to quantify SN pathology in PD and the results closely correlate with dopaminergic striatal innervation loss evaluated by DAT SPECT.

This study aims to explore the relationship between motor symptom asymmetry and changes in the SNc observed by NMSI, and ascertain the presence of concordance in subjects with PD.

2. Methodology

2.1. Subject recruitment and clinical evaluation

This study was conducted at the Department of Neurology, National

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Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India. Forty-four subjects with PD and 15 age-matched healthy controls were included in this study. Sixteen subjects with PD and the healthy controls have been part of a previous study [10]. Diagnosis of idiopathic PD was based on the United Kingdom Parkinson's Disease Society Brain Bank criteria [11] and confirmed by trained movement disorder specialists (authors-PKP, RY). Subjects with PD and controls included in this study are part of an ongoing study on Parkinson's disease. Only those whose imaging protocols included the NMSI sequence were recruited for the present study. The study was approved by the Institutional Ethics Committee of NIMHANS. All participants in this study provided informed consent prior to recruitment.

Demographic and clinical details such as gender, handedness, age at presentation, age at onset (AAO) of motor symptoms, disease duration, side of onset of first symptom (rest tremor, stiffness or slowness), Unified Parkinson's Disease Rating Scale (UPDRS- III) OFF-state scores, and Hoehn and Yahr (H&Y) stages were recorded. Clinical laterality (CL) was established by measuring the difference between the right and left UPDRS-III sub scores, i.e. question 23 to 26 [12]. A difference of ≥ 1 was considered as CL. A subject with PD was deemed to have either right CL (RLC) or left CL (LCL) based on the side which had a higher score. Handedness was defined as the hand used for writing.

2.2. Imaging protocols

All MRI scans were done in a 3-T Philips Achieva MRI scanner. After the initial localization sequences, high-resolution 3D T1-weighted, anatomical MR images were obtained (repetition time: 26 ms; echo time: 2.2 ms; flip angle: 20°; reconstructed matrix size: 512 × 512; field of view: 180 × 180 × 50 mm; voxel size: 0.9 × 0.9 × 1 mm; number of slices: 50; slice thickness: 1 mm; and acquisition time: 4 min 12.9 s).

The MRIs were retrieved from the archive and screened for gross cortical structural abnormalities by an experienced neuroradiologist (author-JS). Post which the images were set perpendicular to the fourth ventricle floor with coverage between the posterior commissure and inferior border of the pons.

2.3. Data processing

Quantitative analysis of the neuromelanin-sensitive MR images was performed using the image processing software OsiriX (author-SP). The investigator was blinded to clinical laterality at the time of analysis. A section of the midbrain at midpoint of the mammillary body was selected for placement of regions of interest (ROI) [10]. Signal intensities (SI) were measured by placing circular ROI's measuring 10 mm^2 over the lateral part of bilateral SNc, and also anterior to the cerebral aqueduct. Contrast ratios (CRs) of the lateral part of the SNc was calculated based on methodology previously described [10,13]. The following equation was used for calculation of CRs:

$$CR = \frac{SISNL - SIN}{SIN}$$

where SI_{SNL} is the value of the signal intensity (SI) of either the right or left ROI and SI_N is the SI of the region anterior to cerebral aqueduct.

Comparisons between right lateral CR (RLCR) and left lateral CRs (LLCR) of subjects with PD and controls were performed to confirm the presence of significant differences. Imaging laterality (IL) was established by calculating the difference between RLCRs and LLCRs in individual subjects with PD. The side with the lower CR was considered as the lateralized side.

2.4. Statistical analysis

The CL and IL was individually compared to identify subjects with PD with IL contralateral to CL i.e. those with concordance or lack thereof. Based on this, subjects with PD were divided into the following subgroups: (a) Right CL + Left IL (RCL + LIL), (b) RCL + Right IL (RCL + RIL), (c) Left CL + RIL (LCL + RIL) and (d) LCL + LIL. Mean RLCRs and LLCRs for these subgroups were compared using the *t*-test to confirm the contralateral relationship. Additionally, the side of onset was compared with CL and IL and the presence or absence of concordance was correlated with the duration of illness.

Independent *t*-test was used to determine statistical significance; the level of which was set at $p < 0.05$. IBM SPSS Statistics 23.0 was used for statistical analysis.

Table 1
Demographics and clinical characteristics of subjects with PD and controls.

	PD (n = 44)	Controls (n = 15)
Age (years)	58.00 ± 8.66	56.3 ± 8.52
Male: Female	31:13	11:4
Disease duration (years)	6.36 ± 4.05	–
Age at onset (years)	52.00 ± 8.70	–
Initial side of onset of motor symptoms (R: L: B/l)	29:14:1	–
UPDRS-III (OFF-state)	39.00 ± 15.75	–
Hoehn & Yahr stage	2.28 ± 0.63	–

B/l: Bilateral, L: Left, PD: Parkinson's disease, R: Right, UPDRS: Unified Parkinson's disease rating scale.

3. Results

3.1. Demographic and clinical data

Forty-four subjects with PD and 15 healthy controls were included in this study. Demographic and clinical details of subjects with PD and controls are provided in Table 1. The mean age of the subjects with PD was 58.00 ± 8.66 years and there was no age difference in comparison to controls ($p > 0.05$). The mean age at onset (AAO) of motor symptoms was 52.00 ± 8.70 years and the mean disease duration was 6.36 ± 4.05 years. With the exception of one subject with PD, all others including the controls were right-handed.

Motor asymmetry at the onset of illness was observed in 97.72% (n = 43) of subjects with PD, of which 65.90% (n = 29) reported right sided asymmetry and 31.81% (n = 14) reported left sided asymmetry (Fig. 1). Among the right-handed subjects with PD who had an asymmetrical onset, 67.44% (n = 29) reported the first symptom on the right side and 30.23% (n = 13) on their left side. The single left-handed subject with PD reported the first symptom on the left side. Hence, of the 43 subjects with PD, with asymmetrical onset of PD motor symptoms, 68.18% (n = 30) reported the onset of symptoms on the dominant side.

3.2. Clinical and imaging laterality (Fig. 1)

Based on UPDRS-III sub scores, 59.09% (n = 26) of subjects with PD showed RCL and 40.90% (n = 18) had LCL. The difference of UPDRS -III sub scores was 5.94 ± 4.32. Of the 29 subjects with PD who reported right sided asymmetry of motor symptoms at the onset of illness, 79.31% (n = 23) persisted to have RCL while 20.68% (n = 6) had LCL. Similarly, of the 14 subjects with PD who reported left sided asymmetry of motor symptoms at the onset of illness, 78.57% (n = 11) persisted to have LCL while 21.42% (n = 3) developed RCL. One subject with PD who reported no asymmetry at onset, was found to have LCL.

Comparison of the RLCR and LLCRs revealed RIL in 11.36% (n = 5) and LIL in 88.63% (n = 39) of subjects with PD (Fig. 1). Representative neuromelanin sensitive images of controls and subjects with PD are show in Supplementary Fig. 1.

Subjects with PD had significantly lower CRs of both RLCR and LLCR when compared to controls, and the LLCR was also lower than the RLCR (Table 2). A similar finding of significant reduction in the LLCR in