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Optic nerve integrity as a visuospatial cognitive predictor in Parkinson's disease

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ABSTRACT

Objective: To explore the microstructural integrity of the optic nerve and its role as a cognitive predictor in patients with de novo Parkinson's disease (PD) using diffusion tensor image-based magnetic resonance scans.

Methods: We enrolled 82 patients with de novo PD, 36 patients with drug-induced parkinsonism (DIP), and 36 controls. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) were measured on the mid-portion of the intraorbital optic nerve. Using a multivariate analysis of variance with repeated measures, longitudinal changes in cognitive subscores of a comprehensive neuropsychological test were evaluated in PD patients according to optic nerve integrity.

Results: The mean FA value in PD was significantly lower (0.552 ± 0.103, $p < 0.001$) than that in DIP (0.645 ± 0.099) or the controls (0.689 ± 0.089), whereas the mean ADC value was significantly higher in the PD group compared to the DIP or control group ($p < 0.001$). Optic nerve integrity was not associated with parkinsonian motor severity, striatal dopamine transporter activity, olfaction, or baseline cognitive performance in PD patents. In a longitudinal assessment of cognition in PD, the lower FA group showed significant decline in the performance of Clock Drawing Test ($F = 3.39$, $p = 0.038$), but no significant differences in the other cognitive subsets.

Conclusion: This study demonstrated that microstructural integrity in the optic nerve was distorted in PD patients, and that this nerve integrity might act as a cognitive predictor of visuospatial dysfunction.

Parkinson's disease (PD) is a multi-system disorder that involves the nigrostriatal system as well as cognitive, mood and behavior, autonomic control, and sensory processing systems. Of these, visual processing-associated symptoms are common in patients with PD, in which may span from primary visual dysfunction, such as decreased visual acuity [1], contrast sensitivity [2], and color perception [1] to higher-order dysfunctions including visual perception [3], visual memory [2], or even visual hallucinations [4]. Along with PD pathology-related neurochemical, structural, or functional alterations in the visual association cortex [5], accumulating evidence has suggested that the retina is an important contributor to visual dysfunction in PD. The principal dopaminergic neurons in the retina are A18 amacrine cells, which control dark adaptation, color vision, and spatial contrast sensitivity through interactions between inner and outer plexiform layers [6]. Pathological and in vivo studies have determined that PD patients exhibit retinal dopaminergic cell loss [7] and retinal nerve fiber layer (RNFL) thinning [8]. With regard to cognition, higher-order dysfunctions in visual processing are known to be an indicator of dementia in PD [9] whereas the role of primary visual dysfunction in the cognitive prognosis is unknown.

Diffusion tensor imaging (DTI) has been developed to estimate microstructural integrity in white matter by measuring diffusion tensor, a three-dimensional unit of diffusion. This measure is mainly represented by indices such as fractional anisotropy (FA)

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and mean diffusivity or apparent diffusion coefficient (ADC), which reflect the directionality and magnitude of diffusion of water molecules, respectively. This technology has been widely used to evaluate white matter connectivity in PD and overall white matter involvement in nervous system disorders. In the present study, we examined the microstructural integrity of the optic nerve in de novo PD patients using DTI-based imaging analysis. In addition, we analyzed the association between optic nerve integrity and nigrostriatal dopaminergic and cognitive status to determine whether optic nerve integrity acts as a clinically prognostic marker of PD.

1. Materials and methods

1.1. Subjects and clinical assessment

We retrospectively reviewed medical records from 82 consecutive PD patients who attended the Movement Disorders Clinic at Yonsei University Severance Hospital from January 2009 to June 2013. We also reviewed data collected in our previous studies that received approval from the Institutional Review Board at Yonsei University Severance Hospital; written consent was obtained from all participants. PD diagnosis was determined based on the clinical criteria of the United Kingdom PD Society Brain Bank [10], and all patients with PD were determined to have a drug-naïve de novo status. A total of 36 control subjects neither exhibit any symptoms of neurologic deficits nor profiles of abnormal movements or gait problems were recruited during the same period. The patients with drug-induced parkinsonism (DIP) were determined by the criteria in a previously published study [11], and 36 eligible patients were finally included. Subject that suffered from any neurodegenerative or known ophthalmologic disorders which were identified by medical records and an ophthalmologist, or a self-report of miscellaneous ocular problems (such as visual blurring, ocular pain, visuospatial dysfunction, or visual hallucinations), were excluded from the study. A conventional brain magnetic resonance imaging (MRI) including DTI for all subjects and a [^{18}F] *N*-(3-fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane (^{18}F-FP-CIT) positron emission tomography (PET) scan for entire PD and DIP participants were conducted respectively at their initial evaluation. The Unified PD Rating Scale (UPDRS) part III and the Cross Cultural Smell Identification Test (CCSIT) were completed at initial diagnosis in PD. In study participants, all diagnostic work-up series mentioned above were undertaken in drug naïve status. We received approval from the Institutional Review Board at Yonsei University Severance Hospital, and written consent was obtained from all participants.

1.2. Cognitive assessment

To determine cognitive status in PD, a comprehensive neuropsychological test was performed by an experienced neuropsychologist in all 82 patients with PD. This assessment was conducted at baseline evaluation using the Seoul Neuropsychological Screening Battery (SNSB) [12] and a Korean version of the Mini Mental State Examination (K-MMSE) [13]. The SNSB is composed of various task subsets in five cognitive domains, and we selected representative tasks for each domain as follows: Attention (Stroop color reading); Working memory (Digit span forward and backward); Language (Korean version of the Boston Naming Test); Visuospatial function (Rey Complex Figure Test (RCFT) copying, 10-point Clock Drawing Test (CDT) [14], six-point drawing Interlocking Pentagon [15]); Memory (verbal memory, 20-min delayed recall using the Seoul Verbal Learning Test; visual memory, 20-min delayed recall using the RCFT); and Frontal executive function (semantic and phonemic fluency using the Controlled Oral Word Association Test (COWAT)). Additionally, we analyzed longitudinal changes in cognitive performance according to optic nerve integrity in 45 out of total PD patients whose follow-up SNSB data were available. The baseline demographic and neuropsychological profiles in this subgroup were quite comparable to those in the total PD group (Table e-1).

1.3. MRI acquisition

All scans were performed with a 3T MR imaging (Achieva; Philips Medical Systems, Best, the Netherlands) using a 32-channel sensitivity-encoding head coil. DTI was performed using a single-shot spin-echo EPI. The axial images were obtained parallel to the anterior/posterior commissure line. The parameters for DTI were as follows: FOV = 220 mm, voxel size = 1.72 × 1.72 × 2 mm^3, TE = ~70 ms, TR = ~8000 ms, FA = 90°, slice gap = 0 mm, NEX = 1, b-factor = 600 s/mm^2, non-cardiac gating, and 70 axial slices. We acquired diffusion-weighted images from 32 non-collinear, non-coplanar directions, with a baseline image without diffusion weighting. Total acquisition time was 5 min 45 s. Isotropic fractional anisotropy (FA), trace, and apparent diffusion coefficient (ADC) maps were immediately generated on the console by the chosen software (Packman Tools; Philips Medical Systems).

1.4. Diffusion tensor image analysis

To obtain cross-sectional area measurements of the optic nerves, we made coronal reformatted FA and ADC maps using Aquarius iNtuition software (TeraRecon, Foster City, CA, USA) (Fig. e-1 in supplementary data). Circular regions of interest (ROIs) with a mean diameter of 3.1 mm (range, 2.7–3.3 mm) were manually drawn on the mid-portion of the intraorbital optic nerve on FA and ADC maps. All ROIs were placed strictly within the optic nerve boundary to avoid contamination from adjacent fat or cerebrospinal fluid. The mean FA and ADC values were calculated by averaging the values measured in bilateral optic nerves in all subjects. To confirm the estimate consensus, two board-certified neurologists (J.J.L. and Y.J.L.), with blinded to patient information, separately have conducted measurements of FA and ADC values. The internal consistency (Cronbach's alpha) was demonstrated by inter-rater values of 0.804 for FA and 0.826 for ADC and intra-rater values of 0.886 for FA and 0.878 for ADC.

1.5. ^{18}F-FP-CIT PET acquisition and quantitative analysis

A ^{18}F-FP-CIT PET scan was performed using a GE Discovery STe (DSTE) PET-CT scanner (GE Healthcare Technologies, Milwaukee, WI), which obtained images with a three-dimensional resolution of 2.3 mm at full-width at half-maximum. A 5 mCi (185 MBq) of ^{18}F-FP-CIT was injected intravenously, and images were acquired in three-dimensional mode during a 20-min session that occurred 90 min after contrast injection. The quantitative analyses of the images were carried out according to a previously published procedure [16] and detailed processes are fully described in Supplementary Data.

1.6. Statistical analysis

To assess the demographic characteristics of the subjects, an analysis of variance followed by multiple comparisons was used to compare group differences of continuous variables. The normality of the continuous variables was evaluated using the Kolmogorov–Smirnov test. The χ^2 test was used for categorical variables. The group differences in mean FA and mean ADC were analyzed using