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Clinical Study

# Striatal silent lacunar infarction is associated with changes to the substantia nigra in patients with early-stage Parkinson's disease: A diffusion kurtosis imaging study

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ABSTRACT

A recent study has shown that striatal silent infarction may occur secondary to the degeneration of dopaminergic neurons in the substantia nigra (SN) of mice. However, it is uncertain whether this phenomenon occurs in patients with early-stage Parkinson's disease (PD) and can be detected by diffusion kurtosis imaging (DKI). A total of 72 untreated patients with early-stage PD underwent conventional MRI and DKI. Participants were divided into control and striatal silent lacunar infarction (SSLI) groups. The differences in mean kurtosis (MK) values of the SN, Hoehn–Yahr (H–Y) staging, and Unified Parkinson's Disease Rating Scale (UPDRS) III score between groups, were analyzed. Linear regression analysis was used to correlate age, SSLI count, silent lacunar infarction count in other brain areas and age-related white matter change score with MK values of the SN. Spearman correlation coefficient analysis was used to correlate MK values of the SN and SSLI count with H–Y staging and UPDRS III score. There was no significant difference in the severity of disease between two groups; however, MK values of the SN with SSLI present were significantly higher than in SN without SSLI. In addition, SSLI count had linear correlation with MK values of the SN, which had positive correlation with H–Y-staging and UPDRS III score. SSLI is associated with structural changes to the SN in patients with early-stage PD, detectable by DKI, and may aggravate their motor impairments.



## 1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease common in middle-aged and elderly people, in which the main pathological change is selective loss of dopaminergic (DA) neurons in the substantia nigra (SN) [1]. Although PD is a degenerative disease, many researchers believe that vascular factors play an important role in its progression [2]. As most PD patients are older than 50 years and have one or more risk factors for cerebrovascular disease, they are prone to asymptomatic intracranial small vessel occlusion, namely silent lacunar infarction (SLI), of which striatal silent lacunar infarction (SSLI), located in the basal ganglia, is most common.

In recent years, a number of studies on animals and humans have found that symptomatic striatal stroke can result in secondary damage to the SN [3–8]. It is thought that typical symptoms of striatal infarction may induce or aggravate the damage to the closest SN by affecting striatal SN loops [9]. Following this idea, Beatriz and colleagues found that SSLI could also occur secondary to DA neuron degeneration in the SN of mice [10]. However, research into the effect of SSLI on structural change to the SN in PD patients is lacking.

To detect structural changes to the SN in humans, it is necessary to find a safe and sensitive imaging method. Diffusion kurtosis imaging (DKI) is the further extension of diffusion tensor imaging (DTI), suitable for the study of gray matter structures [11], and its main parameter is mean kurtosis (MK). Higher MK values reflect more complex gray matter structures [12]. MK values of the SN have been found significantly higher in patients with PD than in healthy controls [13]. Similar results were also obtained in our recent study [14], indicating that MK values can sensitively reflect structural changes to the SN. Thus, the purpose of this study was to investigate the relationship between SSLI and MK values of SN in

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early-stage PD patients, to reveal whether SSLI is associated with structural changes to the SN.

## 2. Methods

### 2.1. Patients

The examinations in this study were performed with the understanding and written consent of each participant, with the approval of a local ethics committee. From January 2014 to December 2014, 74 inpatients first diagnosed with early PD and no history of stroke, attending the Department of Neurology at the First People's Hospital of Foshan, were recruited. Two subjects were excluded because of incomplete DKI.

The inclusion criteria were as follows: >50 years of age; met the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria; and Hoehn and Yahr (H–Y) staging 1–2. The exclusion criteria were as follows: secondary Parkinson syndrome or Parkinsonism-plus; cardiac insufficiency or severe hepatic and renal impairment; communication barrier; unable to complete MRI; or poor compliance.

Demographics, including age, gender, education level, and occupation, were obtained from participants and recorded. Subjects underwent comprehensive neurological examination. The onset, disease duration, and evolution of the disease were elicited in detail. H–Y staging and the motor section of the Unified Parkinson's Disease Rating Scale III (UPDRS III) [15,16] were used to evaluate the severity of motor impairment.

### 2.2. Imaging data acquisition

Participants underwent MR examination using a 3.0 T superconducting magnetic resonance instrument (GE Signa EXCITE, GE Medical System, USA) with 8-channel phased array coil. T1-weighted MRI, T2-weighted MRI, fluid-attenuated inversion recovery (FLAIR) MRI, and diffusion-weighted imaging, were used to exclude secondary Parkinson's syndrome caused by severe vascular disease, trauma, encephalitis, or multi-system atrophy. Age-related white matter change scores (ARWMCs) were used to evaluate the severity of white matter degeneration in a total of 10 regions of each participant, including bilateral frontal regions, bilateral parietal occipital regions, bilateral temporal regions, bilateral scene regions and bilateral basal ganglia, according to T1-weighted RMI, T2-weighted MRI, and FLAIR MRI (Table 1) [17]. The total ARWMC score was between 0 and 30. Lacunar infarctions with diameter of 3–15 mm in the striatum and other regions were counted according to recently published neuroimaging standards for research into small vessel disease [18].

DKI was obtained using an echo-planar imaging technique with the following scanning parameters: repetition time/echo time, 6500/73.3 ms; motion probing gradients, 25 directions; b values, 0, 1000 and 2000 s/mm$^2$; field of view, 240 mm$^2$; matrix size, 128$^2$; slice thickness, 5.0 mm with 0 mm interslice gaps; and one excitation. Image processing operations were performed with an 4.5 work station function tool software. Regions of interest (ROIs) were drawn independently in the rostral, middle, and caudal SN bilaterally by two of the investigators, using the diffusion tensor imaging method [19].

**Table 1**
Age-related white matter change scores rating scale for MRI

| | Frontal, parieto-occipital, temporal, infratentorial/cerebellum | Basal ganglia |
|---|---|---|
| 0 | No lesions (including symmetrical, well-defined caps or bands) | No lesions |
| 1 | No lesions (including symmetrical, well-defined caps or bands) | One focal lesion (diameter ⩾5 mm) |
| 2 | Beginning confluence of lesions | Confluent lesions |
| 3 | Diffuse involvement of the entire region, with or without involvement of U fibers | Confluent lesions |

White matter changes on MRI were defined as bright lesions 5 mm on T2-weighted MRI or fluid-attenuated inversion recovery MRI. Left and right hemispheres were rated separately.

### 2.3. Experimental protocol

Participants were divided into two groups: a control group consisting of PD patients without SSLI, and a group consisting of PD patients with one or more SSLI.

### 2.4. Statistical analysis

The Statistical Package for the Social Sciences version 13.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. Student *t* test was used to compare age, gender, MK values of the SN, disease duration, H–Y staging, UPDRS III scores, SLI count in other brain areas, and ARWMC scores between the two groups. Chi-square test was used to compare gender differences between groups. Linear regression analyses (enter method) were carried out to correlate age, SSLI (or SSLI count), SLI count in other brain areas, and ARWMC scores with MK values in the SN as the dependent variable and the other four factors as independent variables. Spearman correlation analyses between MK values of the SN and H–Y-staging or UPDRS score were performed to associate MK correction values of the SN with the severity of motor impairment. The MK correction values were the average of MK values for bilateral rostral, middle, and caudal SN.

## 3. Results

### 3.1. General characteristics of study participants

The 72 PD patients were divided into two groups: control group, comprising 38 patients (52.78%) and SSLI group, comprising 34 patients (47.22%). MK values of the SN for the SSLI group was significantly higher than that of the control group ($t = 4.851$, $P < 0.001$), with no significant differences in age ($t = 0.430$, $P = 0.669$), gender ($\chi^2 = 0.019$, $P = 0.891$), disease duration ($t = 0.106$, $P = 0.916$), H–Y staging ($t = 0.883$, $P = 0.380$) and UPDRS score ($t = 0.483$, $P = 0.631$) between the two groups (Table 2).

### 3.2. Comparison of silent lacunar infarction count in other brain areas and Age-related white matter change score between control and striatal silent lacunar infarction groups

SSLI count in the SSLI group was 2.29 ± 0.91. SLI count for other brain areas in the SSLI group (2.71 ± 2.36) was higher than that in the control group (0.79 ± 1.30) ($t = 4.207$, $P < 0.001$). ARWMC score

**Table 2**
General characteristics of study participants

| | SSLI group | Control group | *P* |
|---|---|---|---|
| Gender (M/F) | 12/22 | 14/24 | 0.891 |
| Age (years) | 66.83 ± 5.41 | 66.08 ± 6.77 | 0.669 |
| MK values in the SN | 1.095 ± 0.056 | 1.039 ± 0.038 | <0.001* |
| Duration (months) | 13.41 ± 5.785 | 13.58 ± 7.579 | 0.916 |
| H–Y staging | 1.71 ± 0.304 | 1.63 ± 0.397 | 0.380 |
| UPDRS III score | 15.18 ± 3.927 | 14.74 ± 3.790 | 0.631 |

* $P < 0.05$ was considered statistically significant.
H–Y = Hoehn–Yahr, MK = mean kurtosis, SN = substantia nigra, SSLI = striatal silent lacunar infarction, UPDRS III = Unified Parkinson's Disease Rating Scale III.