SHORT REPORT

Case control study of diffusion tensor imaging in Parkinson's disease

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J Neurol Neurosurg Psychiatry 2007;**78**:1383–1386. doi: 10.1136/jnnp.2007.121525

Background: Preliminary work has shown that diffusion tensor MRI (DTI) may contribute to the diagnosis of Parkinson's disease (PD).

Objectives: We conducted a large, prospective, case control study to determine: (1) if fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values on DTI in the basal ganglia and substantia nigra are different between patients with PD and healthy controls; and (2) the predictive value of these parameters and their clinical utility.

Methods: DTI imaging was carried out in patients with PD and controls. FA and ADC values were obtained from various brain structures on the DTI scan using the diffusion tensor taskcard. The structures studied were: caudate, putamen, globus pallidus, thalamus and substantia nigra.

Results: 151 subjects (73 PD patients, 41 men, 32 women; mean age 63.6 years) and 78 age and sex matched control subjects were studied. The FA value of the substantia nigra in patients with PD was lower compared with controls (0.403 vs 0.415; p = 0.001). However, no significant differences were demonstrated for FA or ADC values of other structures. Multiple regression analysis revealed that the clinical severity of PD correlated inversely with the FA value in the substantia nigra in patients with PD (regression coefficient −0.019). No single FA value had both a high positive and negative predictive power for PD.

Conclusions: We demonstrated in a large, prospective, case control study that the FA value in the substantia nigra on DTI was lower in PD compared with healthy controls, and correlated inversely with the clinical severity of PD. Further longitudinal studies would be helpful to assess the clinical utility of serial FA measurements of the substantia nigra in objective quantification of disease progression and monitoring of the therapeutic response.

The diagnosis of Parkinson's disease (PD) is usually made clinically, based on the presence of rest tremor, bradykinesia and rigidity.[1 2] However, in select cases, the diagnosis may not be clear, especially in patients without tremor. Large community based studies have also shown that there is considerable difficulty in diagnosing parkinsonism or PD among elderly subjects in clinical practice.[3 4] Subtle signs of parkinsonism can be detected on clinical examination in approximately 30% of apparently healthy community based elderly cohorts.[4–6]

Diffusion tensor imaging (DTI) is an MRI technique that can indirectly evaluate the integrity of white matter tracts by measuring water diffusion and its directionality in three dimensions.[7] The magnitude (diffusivity) and directionality (anisotropy) of water molecular displacement by diffusion in the brain can be quantified by the apparent diffusion coefficient (ADC) and fractional anisotropy (FA), respectively.[8–15] Studies have revealed age related declines in white matter FA of normal healthy adults in whom volume loss may not even be evident.[12 15 16] DTI changes have also been reported in structures with relatively low inherent anisotropy, such as the thalamus and putamen.[11 12 17]

A small pilot study reported lower FA values in the nigrostriatal projection of patients with PD.[18] Another group showed that ADC values in the basal ganglia and substantia nigra were no different between patients with PD and controls.[19 20] To our knowledge, correlation of FA and ADC values on DTI with clinical severity, and determination of positive and negative predictive values of DTI parameters have not been demonstrated for PD. Hence, we conducted a large, prospective, case control study to determine the clinical utility of FA and ADC values on DTI in distinguishing patients with PD from healthy controls.

METHODS

Study subjects

Consecutive patients diagnosed as having PD in a tertiary referral centre were prospectively recruited from 2005 to 2006. The diagnosis of PD was made based on the UK PD Brain Bank clinical criteria by a neurologist specialising in PD. Controls were healthy volunteers with no evidence of PD, recruited over the same period. For every PD patient, we looked for a control of similar age (+ 5 years) and gender. We also collected information on age, gender, age of onset of disease, family history, severity of PD (Hoehn and Yahr scale (H&Y)) and dose of levodopa (mg/day). A total of 100 patients with PD were screened, of whom 27 were excluded because of severe immobility (H&Y stage 5), contraindications to MRI, inability to give consent because of dementia or other severely debilitating diseases, or unwilling to participate in the study. Our study received approval from the institutional ethics committee, and all study subjects gave written informed consent.

MR imaging

MR scans were performed on a 1.5 T Scanner (Siemens Avanto, Erlangen, Germany) using a circular polarised head coil (details of the image acquisition are described in the supplementary file; the supplementary file can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental).

Image analysis

FA and ADC values were obtained from various brain structures on the DTI scan using the diffusion tensor taskcard (Massachusetts General Hospital, Boston, USA). The structures studied were: caudate, putamen, globus pallidus, thalamus and

Abbreviations: ADC, apparent diffusion coefficient; DTI, diffusion tensor imaging; FA, fractional anisotropy; H&Y, Hoehn and Yahr staging; PD, Parkinson's disease; ROI, region of interest

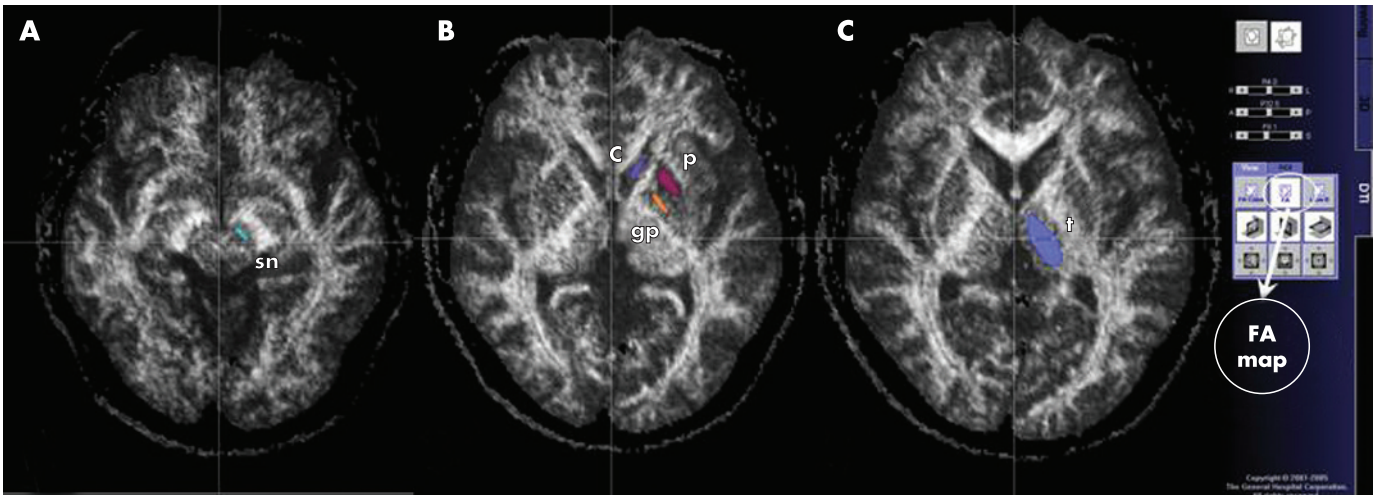

Figure 1 Regions of interest of gray matter structures: (A) substantia nigra (sn), (B) caudate (c), putamen (p), globus pallidus (gp) and (C) thalamus (t), drawn on axial diffusion tensor DTI MR images (4300/90) on the fractional anisotropy map. Regions of interests were analysed on both the right and left sides.

substantia nigra. Regions of interest (ROIs) of size 40 mm^3 were drawn in the substantia nigra (fig 1), which was found between the red nucleus and the crural fibres of the cerebral peduncle at the same level in all subjects.[21–23] ROIs were drawn in the caudate (120 mm^3), putamen (230 mm^3) and globus pallidus (86 mm^3) on the section one slice above the anterior commissure, and in the thalamus (689 mm^3) on the next superior section (fig 1) (details of the image analysis are described in the supplementary file; the supplementary file can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental).

Statistical analysis

Statistical analyses were carried out using SPSS software (details of the analysis are described in the supplementary file; the supplementary file can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental).

RESULTS

A total of 151 (73 PD and 78 controls) subjects were studied. The two groups were matched for age and gender (summarised in the supplementary file, table A; the supplementary file can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental). Median FA and ADC values for each of the brain regions in PD and controls are summarised in table 1. Specifically, the FA value of the substantia nigra in patients with PD was lower compared with controls (0.403 (range 0.314–0.488) vs 0.415 (0.347–0.487); $p = 0.001$) (fig 2, see supplementary file; the supplementary file can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental). However, no significant difference was demonstrated for the caudate, putamen, globus pallidus or thalamus between the two groups. For the ADC, there was a trend towards a higher value in the substantia nigra of PD compared with controls (7.342 vs 7.157; $p = 0.13$). Likewise, no significant difference was found in the ADC values from other brain regions between the two groups. The interclass correlation coefficient values for inter-rater and intra-rater variability for both FA and ADC values were good, ranging from 0.81 to 0.99.

Multiple regression analysis was performed for DTI parameters from the substantia nigra in patients with PD. This revealed that clinical severity, as measured by the H&Y scale, correlated inversely with the FA value (regression coefficient −0.019, 95% CI −0.037 to −0.002). However, there was no significant correlation between FA value and age of onset, gender or levodopa dose. There was also no correlation between ADC values and any of these clinical factors.

Receiver operating characteristic curve analysis showed the area under the curve was modest at 0.653 (95% CI 0.565 to 0.74;

Table 1 Fractional anisotropy and apparent diffusion coefficient values in patients with Parkinson's disease and in controls

	PD	Controls	p Value
Fractional anisotropy			
Caudate	0.259 (0.172, 0.356)	0.251 (0.180, 0.364)	0.121
Globus pallidus	0.334 (0.273, 0.525)	0.335 (0.266, 0.510)	0.990
Putamen	0.262 (0.166, 0.358)	0.255 (0.193, 0.442)	0.056
Substantia nigra	0.403 (0.314, 0.488)	0.415 (0.347, 0.487)	0.001*
Thalamus	0.333 (0.268, 0.417)	0.328 (0.259, 0.419)	0.601
Apparent diffusion coefficient			
Caudate	6.961 (6.061, 8.111)	6.989 (5.766, 8.404	0.664
Globus pallidus	6.570 (4.060, 8.488)	6.482 (4.686, 7.860)	0.438
Putamen	6.658 (5.965, 8.789)	6.700 (4.846, 8.840)	0.953
Substantia nigra	7.342 (5.965, 8.661)	7.157 (6.385, 8.573)	0.131
Thalamus	7.375 (6.589, 8.849)	7.369 (6.553, 9.022)	0.907

PD, Parkinson's disease.
Values are median (range).
*$p<0.05$.

p = 0.001) (fig 3, see supplementary file; the supplementary file can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental). There was no specific FA value which gave both a high sensitivity and specificity (see table B in the supplementary file; the supplementary file can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental).

DISCUSSION

We have adopted a simple and practical approach to drawing the ROI, which could easily be implemented in any clinical radiological setting, with good reproducibility (inter-rater and intra-rater consensus for both FA and ADC measurements were high). The reproducibility of the previous pilot study using more complex methodology was not available.[18] Our study demonstrated a lower FA value in the substantia nigra in patients with PD compared with controls. However, no statistically significant differences were seen in the other regions.

Our results support post-mortem findings that the substantia nigra is the most severely affected primary site of pathology in this condition.[1 2] In the late stages of PD, secondary degeneration may be present in the basal ganglia and extrastriatal regions. The absence of DTI differences in the basal ganglia structures between our study groups could be partly due to the exclusion of the most severe PD cases from the study (those who were severely immobile or demented). Interestingly, the FA values in the substantia nigra were higher than those of the thalamus, which was also the finding of Yoshikawa and colleagues,[18] wherein detailed tracing and drawing of multiple ROIs along a postulated nigrostriatal pathway was employed.

Our ADC values were similar in patients with PD and controls, although there was a trend towards a higher value in the substantia nigra in PD. Some DTI studies have suggested that FA is more sensitive to alterations in microstructural integrity than ADC. In addition, we only used 2 *b* values in the measurement of ADC. Schocke and colleagues[20] found increased putamen diffusivity in 11 patients with multiple system atrophy (parkinsonian variant) compared with 17 patients with PD and 10 controls. Their study also revealed no difference in ADC values in the basal ganglia and substantia nigra between PD and controls.

While the biophysical basis of a deceased FA value in relation to neurodegenerative disorders (decrease in number or density of axons, reduced axonal myelination or orientational coherence of the fibre tract) has not been fully clarified, it is likely that change in FA value corresponds to neuronal loss. Supporting this is our finding in the linear multivariate analysis which showed an inverse correlation between clinical severity (H&Y staging) and the FA value in patients with PD. Our findings suggest that FA measurements of the substantia nigra could serve as a marker for disease progression and therapeutic response.

To assess the potential utility of the FA values we acquired from our study cohort in clinical practice, we evaluated the sensitivity, specificity, and positive and negative predictive values using receiver operating characteristic curve analysis. While the median FA value was lower in PD, there was considerable overlap of FA values between patients and controls (fig 2, supplementary file; the supplementary file can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental). The area under the curve was modest (fig 3, supplementary file; the supplementary file can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental), suggesting that the discriminative property of the FA value as a sole diagnostic tool in PD may not be robust enough. These data suggest that no single FA value in the substantia nigra could be used with absolute certainty for both screening and diagnosis of PD.

There are some inherent limitations in our study. The cross sectional design did not allow us to measure FA values serially for individual subjects in a longitudinal manner. Ideally, a prospective study to measure FA values at fixed time points over a period of a few years would generate a set of data for the rate of decline of the FA value in PD and healthy controls. This information could be a useful quantitative and objective reference when monitoring patients' responses to neuroprotective or therapeutic clinical trials. We did not include other neurodegenerative diseases with parkinsonism in our study and hence our findings could not be generalised beyond our two study groups. Thus we cannot comment on whether a low FA value could help differentiate between PD and other causes of parkinsonism.

In conclusion, we have demonstrated in a large, prospective, case control study that the FA value in the substantia nigra on DTI was lower in PD compared with healthy controls, and correlated inversely with the clinical severity of PD. Because of the overlap of FA values between PD and controls, no single FA value had both a high positive and negative predictive power. Further longitudinal studies would be helpful to assess the clinical utility of serial FA measurement of the substantia nigra as an objective quantitative measure of disease progression and therapeutic response.

ACKNOWLEDGEMENTS

This work was supported by a grant from the National Medical Research Council (NMRC/0760). The authors acknowledge the Massachusetts General Hospital, Boston, USA, for the license to use the diffusion tensor taskcard, and Siemens Medical Solutions for facilitating the software transfer.

The supplementary file can be viewed on the *J Neurol Neurosurg Psychiatry* website at http://www.jnnp.com/supplemental.

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Competing interests: None.

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Received 27 March 2007
Revised 1 June 2007
Accepted 18 June 2007
Published Online First 5 July 2007

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